Belinda Welsh
MBBS, MMed, FACD, is consultant dermatologist, St Vincent's Hospital, Melbourne and Sunbury Dermatology and Skin Cancer Clinic, Sunbury, Victoria. drbwelsh@bigpond.net.au

Blistering skin conditions

Background
Blistering of the skin can be due to a number of diverse aetiologies. Pattern and distribution of blisters can be helpful in diagnosis but usually biopsy is required for histopathology and immunofluoresence to make an accurate diagnosis.

Objective
This article outlines the clinical and pathological features of blistering skin conditions with a particular focus on bullous impetigo, dermatitis herpetiformis, bullous pemphigoid and porphyria cutanea tarda.

Discussion
Infections, contact reactions and drug eruptions should always be considered. Occasionally blistering may represent a cutaneous manifestation of a metabolic disease such as porphyria. Although rare, it is important to be aware of the autoimmune group of blistering diseases, as if unrecognised and untreated, they can lead to significant morbidity and mortality. Early referral to a dermatologist is important as management of blistering skin conditions can be challenging.

Blistering of the skin is a reaction pattern to a diverse group of aetiologic triggers and can be classified as either:

- **immunobullous (*Table 1*), or**
- **nonimmunobullous (*Table 2*).**

Separation of the skin layers leading to acquired blistering can occur due to loss of cohesion of cells:

- **within the epidermis (*Figure 1*)**
- **between the epidermis and dermis (basement membrane zone) (*Figure 2*), or**
- **in the uppermost layers of the dermis.**

This distinction forms the histologic basis of diagnosing many of the different blistering diseases. Clinical patterns may also be helpful and are listed in *Table 3*. Important features include:

- location of the blisters (*Figure 3, 4*)
- the presence or absence of mucosal involvement, and
- whether the blisters are tense and intact, or fragile resulting in erosions and crusting (*Figure 5*).

Generally however, diagnosis relies on biopsy for histopathology and immunofluoresence to make an accurate diagnosis.

Overall, the immunobullous diseases are rare (*Table 1*); although awareness is important as delayed diagnosis can lead to significant morbidity and mortality. Most patients will require referral to a dermatologist as diagnosis and management can be challenging.

If you see a patient with blisters it is worth asking yourself:

- Could this be an infection?
- Could this be due to a topical contact reaction or drug eruption?
- Could this be a primary skin disease with:
  a) blisters as a secondary phenomenon (due to inflammation), ie. the small blisters of hand eczema seen in pomphylox?
  b) blistering due to an autoimmune mechanism (immunobullous)?
- Could this be due to an underlying systemic disease or process?

Table 3 provides a guide to the features of the blistering disorders,

with bullous impetigo, dermatitis herpetiformis, bullous pemphigoid and porphyria cutanea tarda discussed in more detail.

Bullous impetigo

The bullous form of impetigo is always caused by coagulase positive *Staphylococcus aureus*, which causes separation of the epidermis by exotoxin production. It is seen most frequently on the face (around the mouth and nose) or at a site of trauma (*Figure 6*). The blisters tend to rupture easily leaving crusted edges and honey coloured crusts. Fever may be present but regional lymphadenopathy is uncommon.

It is important to confirm the diagnosis by skin swab to define the infective organism and establish antibiotic sensitivity.

Topical treatment is important. It is essential to gently remove the crusts – which harbor bacteria – with regular, gentle soaks. This can be done with gauze soaked in saline or aluminium acetate 13% (Burow) solution diluted 1:20 with water, or potassium permanganate (Condy crystals) 0.1% solution diluted 1:10 with water. For very mild infections, mupirocin 2% ointment topically three times per day may be sufficient. For severe infections, widespread or recurrent oral antibiotics are needed, generally either di/flucloxacillin or cephalexin (depending on sensitivities). There is often an associated infective dermatitis, so a mild topical corticosteroid such as 1% hydrocortisone twice per day can be useful.[1]

Because of the contagious nature of impetigo, children should not return to day care or school before the lesions clear. As infection is transmitted by direct contact and by fomites, including hygiene items, clothing and toys, parents and carers must know how to avoid infection, ie. by encouraging good hygiene and hand washing. Impetigo tends to occur in mini epidemics, especially within families where nasal carriage of pathogens is common. If impetigo is recurrent or resistant, suspect chronic nasal carriage of *S. aureus*. If nose and or perineal swabs are positive (depending on the location of the impetigo), it is worth treating both the patient and their family with intranasal mupirocin up each nostril three times per day for 5 days.

Practice tip

If persistent and located around the buttocks and groin (*Figure 3*), consider linear IgA disease (chronic bullous disease of childhood).

Dermatitis herpetiformis

Dermatitis herpetiformis (DH) is an uncommon, autoimmune blistering disorder associated with a gluten sensitive enteropathy. Onset is usually in the second to fourth decade of life.

Dermatitis herpetiformis has recently been proposed as a cutaneous manifestation of asymptomatic to mild coeliac disease. A genetic predisposition to the development of gluten sensitivity underlies the disease. In patients with DH, 10–15% of first degree relatives will have DH or coeliac disease.[2] It has been hypothesised that DH is the result of an immunologic response to chronic stimulation of the gut mucosa by dietary gluten. It has recently been suggested that epidermal transglutaminase is the auto-antigen of DH.

Table 1. Immunobullous diseases

Intraepidermal blistering diseases – the Pemphigus group

- *Pemphigus vulgaris*
- *Pemphigus foliaceus*
- IgA pemphigus (subcorneal pustular dermatosis type)
- paraneoplastic pemphigus

Subepidermal blistering diseases – the Pemphigoid group

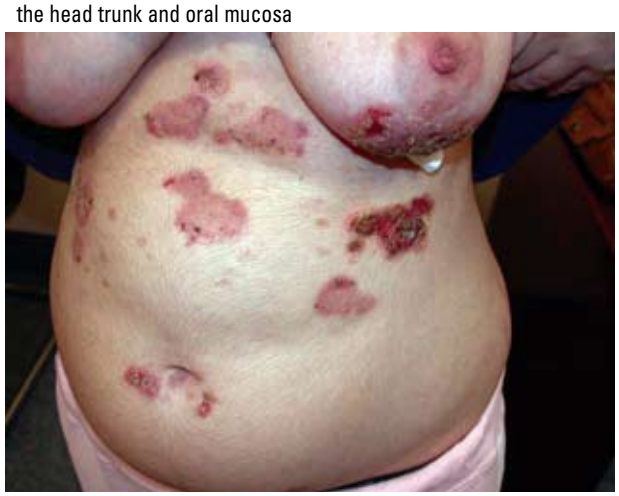
- bullous pemphigoid
- mucous membrane (cicatricial) pemphigoid
- pemphigoid (herpes) gestationis
- linear IgA disease (chronic bullous disease of childhood)
- dermatitis herpetiformis
- epidermolysis bullosa acquisita
- bullous systemic lupus erythematosus

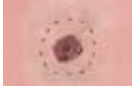
Table 2. Causes of nonimmunobullous blistering

Infection		Viral – herpes simplex, varicella zoster Bacterial – bullous impetigo, bullous erysipelas Fungal – tinea (dermatophyte infection)
Medications		Including photosensitive drug eruptions
Immunological		TEN/SJS/EM/vasculitis*
Infiltrates	Cellular	Sweet syndrome (neutrophils) Mastocytosis (mast cells)
	Noncellular	Amyloidosis
Inflammatory skin disease		Eczema (pompholyx), lichen planus, lichen sclerosus
Metabolic		Porphyria cutanea tarda, renal failure, diabetes

* Toxic epidermal necrolysis/Stevens-Johnston syndrome/erythema multiforme these may be triggered by drugs

Figure 1. Epidermal blistering. Due to the split occurring in the epidermis intact blisters are often not seen in Pemphigus vulgaris. It more commonly presents with nonhealing crusting and erosions on the head trunk and oral mucosa





Typically, patients present with intensely itchy, grouped papules and urticarial plaques. Vesicles are often excoriated to erosions by the time of physical examination and are located on the extensor surfaces of the elbows, knees, buttocks and lower back (*Figure 5*). Patients may have associated worsening of disease with dietary intake of gluten, although many do not report any gastrointestinal (GI) symptoms until prompted.

Diagnosis requires routine skin biopsy of a representative lesion, which classically shows neutrophil micro-abcesses within the papillary dermis. A second biopsy of adjacent normal skin for direct immunofluorescence displays deposition of immunoglobulin A (IgA) in a granular pattern in the upper papillary dermis.[3] Although most patients have no bowel related symptoms, more than 90% have an associated gluten sensitive enteropathy upon endoscopic examination.[4]

The mainstays of treatment are dapsone and a life long gluten free diet. Following glucose-6-phosphate dehydrogenase screening, the drug of choice is dapsone 100 mg/day. A dramatic clinical response is seen usually within 4–5 days. Once control is obtained, dapsone can be weaned over 4–6 months to maintain the patient on the lowest dose of drug required for control of lesions. Although most patients require 50–150 mg/day, some are controlled on significantly lower doses (eg. dapsone 25 mg/week). Haemolysis is the main side effect of dapsone therapy. A gluten free diet takes 6 months to be effective and to allow reduction or discontinuation of medication.

Gluten is a protein present in grasses of the species Triticeae, which includes barley, rye, and wheat. Rice and oats belong to different species and are generally well tolerated. Strict compliance with a gluten free diet results in normalisation of the small bowel mucosal changes and control of the cutaneous manifestations of DH in most patients.

Practice tip

Initially patients may need referral to a dermatologist, gastroenterologist and dietician. Patients with DH are at increased risk of developing lymphoma of the GI tract.[5] A gluten free diet will help prevent this complication.

Table 3. Distinguishing features of blistering skin disorders

	Pemphigus vulgaris	Bullous pemphigoid	Linear IgA disease	Mucous membrane pemphigoid	Epidermolysis bullosa aquisita	Pemphigoid (herpes) gestationis
Cutaneous lesions	• Crusted, eroded lesions • Occasional intact blister	• Large tense bullae • Urticarial patches and plaques	Small vesicles and/or large bullae	• Crusted erosions on the skin • Scarring alopecia • Oral blisters/ erosions	• Can mimic bullous pemphigoid or cicatricial pemphigoid • Skin fragility • Scarring milia formation	• Small vesicles and blisters • Urticarial patches/ plaques • Intensely itchy • Late pregnancy and immediately postpartum
Distribution	• Scalp • Face • Upper torso	• Trunk • Extremities • Flexures	• Groin • Buttocks • Trunk • Extremities	• Scalp/head and neck • Upper trunk	Sites prone to friction trauma, especially hands and feet	Begins in periumbilical region Palms/soles
Mucosal involvement	Common	Uncommon	Occasional	Common on eyes, mouth, genitals	Variable	Rare
Histology	Intra epidermal loss of cell-cell adhesion of keratinocytes	Subepidermal bullae with eosinophils	Subepidermal bullae with neutrophilic infiltrate	Subepidermal blister with mixed infiltrate	Subepidermal split with variable inflammatory infiltrate	Subepidermal split (similar to bullous pemphigoid)
Direct immunofluoresence	IgG antibodies to desmosomes between keratinocytes	Linear IgG and C3 at basement membrane zone (BMZ)	Linear IgA and C3 at BMZ	Linear IgG and C3 along BMZ	IgG deposits along BMZ (especially on dermal side)	C3 along BMZ
Drug triggers to consider	• Thiol group • Amoxycillin • Ampicillin • Captopril • Cephalosporins • Penicillin	• Sulphur containing drugs • Frusemide (most common) • Amoxicillin • Ampicillin • Penicillin • Beta blockers	• Vancomycin • Diclofenac • Lithium • Phenytoin • Captopril • Amiodarone • Amoxicillin	• Practalol • Clonidine	No	No Spontaneous resolution over weeks to months following delivery

Bullous pemphigoid

Bullous pemphigoid (BP) is a chronic, autoimmune, subepidermal, blistering skin disease that rarely involves the mucous membranes. Bullous pemphigoid is characterised by the presence of immunoglobulin G (IgG) autoantibodies specific for the skin basement membrane. The binding of antibodies at the basement membrane activates complement and inflammatory mediators.

Figure 2. Subepidermal blistering of linear IgA disease

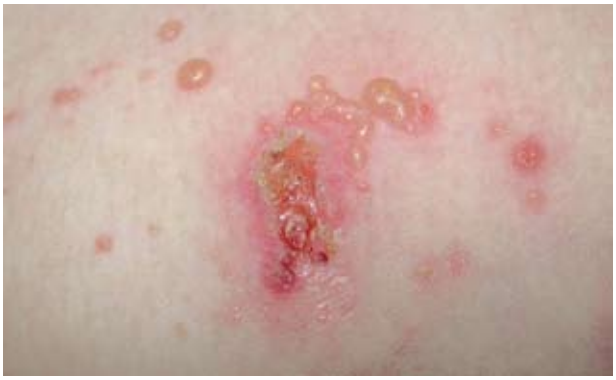


Figure 3. Blistering around the buttocks and groin is a site of predilection for linear IgA disease, particularly in children

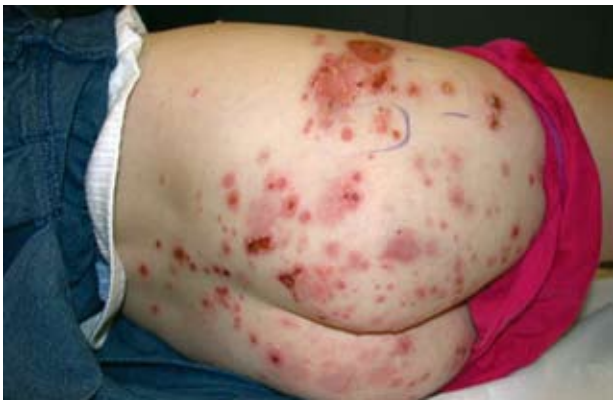
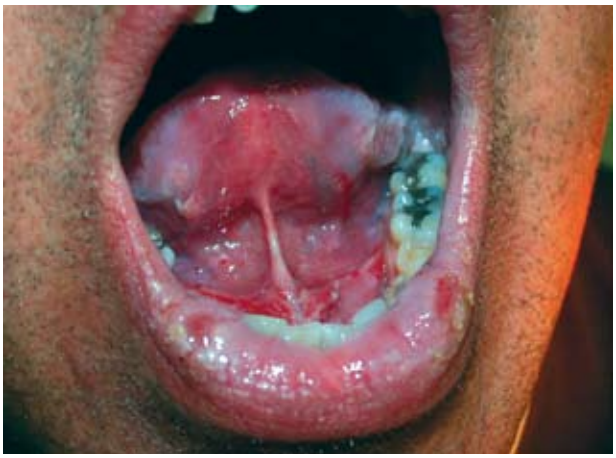


Figure 4. Oral mucosal erosions and blisters, especially common in Pemphigus vulgaris, requiring biopsy for diagnosis



Although BP is uncommon, it is the most common subepidermal autoimmune blistering disease. Incidence is equal in both genders, and childhood disease can occur. The generalised bullous form is the most common presentation.

Onset may be either subacute or acute, with widespread tense blisters (*Figure 1*). Significant itch is frequently present. Tense blisters arise on any part of the skin surface, with a predilection on the flexural areas. Blisters can occur on normal appearing, as well as erythematous, skin surfaces.

It is important to recognise that some patients with BP initially present with persistent urticarial lesions that subsequently convert to blisters. However, urticarial lesions may be the sole manifestation of the disease, often delaying the diagnosis if a biopsy is not done.

Drugs associated with triggering BP include: frusemide, ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDs), captopril, penicillamine, and antibiotics.[6]

Skin biopsy is required to confirm the diagnosis. A 3 mm punch biopsy (in formalin for H+E staining) of the edge of a blister is ideal. A second biopsy of adjacent noninflamed skin in saline soaked gauze is necessary for direct immunofluorescence. The skin is stained looking for deposition of antibodies and complement at the basement membrane zone. This must be sent to a laboratory within 4 hours.

In most patients who are treated, BP remits within 1.5 to 5 years. Because the average age at onset is about 65 years, comorbid conditions are common, making these patients more vulnerable to the adverse effects of corticosteroids and immunosuppressive agents.

For localised disease, strong topical corticosteroid treatment may achieve disease control or topical steroids plus a systemic anti-inflammatory (doxycycline/minocycline 100–200 mg/day and nicotinamide [vitamin B3] 500 mg three times per day) may be sufficient.[7] Oral steroid doses can be kept relatively low, ie. 40–60 mg tapering slowing after 2–3 weeks. Then, over the next 2–3 months, reduce prednisone to 10–20 mg/day. Once dosing is down to 10 mg/day, reduce by 1 mg/month. For patients treated with systemic corticosteroid for more than 1 month, a combined supplement of calcium and vitamin D should be instituted to prevent osteoporosis. Bone mineral density testing should be considered early in the course of treatment, as often long term corticosteroid use is required.

For more severe cases, systemic steroids along with immunosuppressives (eg. azathioprine, methotrexate, mycophenolate mofetil, cyclosporine or intravenous immunoglobulin) may be needed to control the disease.[8] More recently, the anti-CD20 antibody (rituximab), which is relatively specific in targeting the antibody producing B cells, has shown promise in recalcitrant cases.[9]

Most patients require therapy for 6 months to 4 years, after which many experience long term remission of the disease.

Practice tip

Other bullous diseases such as epidermolysis bullosa acquisita, erythema multiforme, and bullous drug eruptions may clinically resemble pemphigoid and may explain atypical therapeutic responses.

Porphyria cutanea tarda

Porphyria cutanea tarda encompasses a group of disorders in which activity of the haem synthetic enzyme uroporphyrinogen decarboxylase is deficient.[10] Porphyria cutanea tarda is the most common porphyria and includes familial and acquired types that may occur in individuals with a genetic predisposition (sporadic porphyria cutanea tarda), after exposure to hepatotoxins, or rarely in the context of hepatic tumours.

Figure 5. Excoriated papules on the elbows in dermatitis herpetiformis. Blisters are fragile and often not seen intact

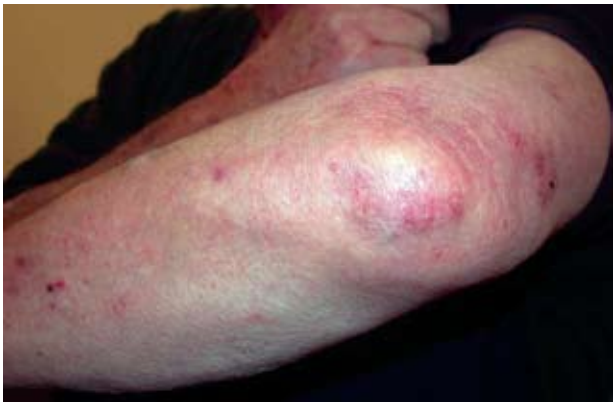


Figure 6. Bullous impetigo

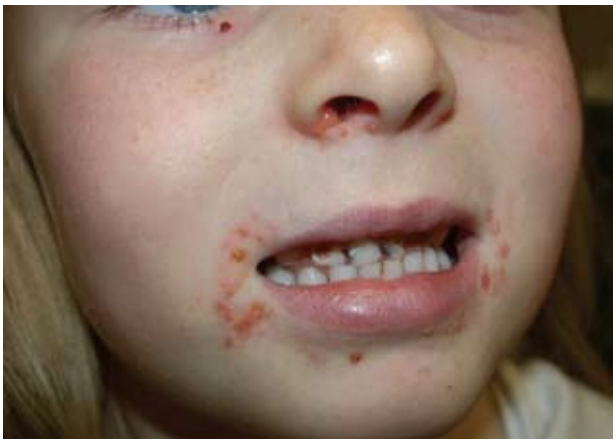
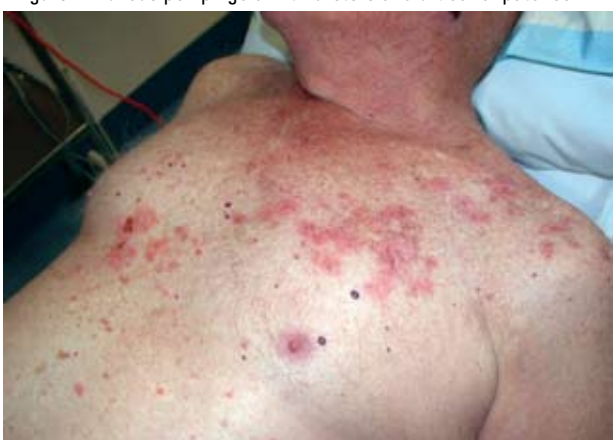


Figure 7. Bullous pemphigoid with blisters and urticarial patches



Some patients are heterozygote for haemochromatosis. It occurs in both genders and the sporadic form typically manifests in adulthood.

Uroporphyrinogen decarboxylase activity is reduced by hepatotoxins and the metabolic products preceding it in the haem pathway become elevated. These porphyrins are reddish pigments that accumulate in the liver and disseminated in plasma to other organs, including the skin. Porphyrins are photoactive molecules that efficiently absorb energy in the visible light spectrum. Photo-excited porphyrins in the skin mediate oxidative damage causing cutaneous lesions.

A history of exposure to environmental inducers (eg. ethanol, oestrogens, hepatitis, human immunodeficiency virus [HIV], iron overload) can be often elicited. Patients often do not realise the role of sunlight exposure in the subsequent appearance of lesions.

The most common photocutaneous manifestations are due to increased mechanical fragility after sunlight exposure; typically erosions and blisters on the backs of the hands that form painful indolent sores that heal slowly, with milia, dyspigmentation and scarring (*Figure 8*). Other common features of porphyria cutanea tarda include hypertrichosis around the temples and cheeks, scleroderma-like plaques that may develop dystrophic calcification, and excretion of discoloured urine that resembles port wine or tea due to the porphyrin pigments present.

Diagnosis requires samples of blood, urine and faeces for porphyrin levels. Urinary porphyrin levels are abnormally high and the faecal isocoproporphyrin is characteristically elevated. Erythrocyte porphyrin levels are in the reference range.

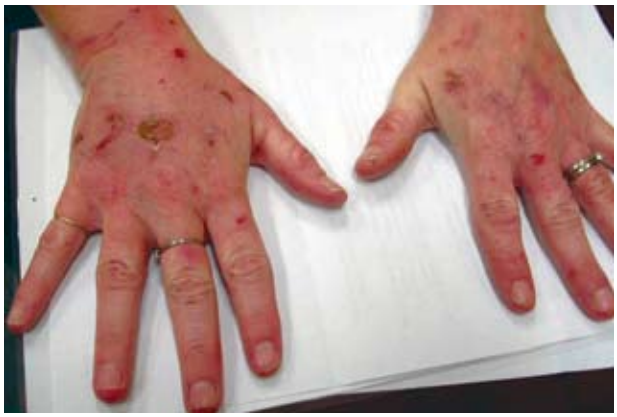
Skin biopsy findings by light microscopy and direct immunofluorescence techniques are not unequivocally diagnostic. Fresh blisters show subepidermal bullae with minimal dermal inflammatory infiltrate and dermal papillae protruding upward into the blister cavity (festooning).

A thorough evaluation requires determination of the haematologic and iron profile, including serum ferritin level, liver function profile, and screening for hepatitis viruses and HIV. Assessment of haemochromatosis genes may be informative. Alpha-fetoprotein presence in serum is useful to screen for hepatocellular carcinoma.

Patients need to avoid sun exposure where possible (protective clothing is preferable to sunscreen) and sunscreens need to be reflective (titanium or zinc oxide) so as to block visible light. Alcohol, oestrogens and other hepatotoxins also need to be eliminated.

Therapeutic phlebotomy probably works by increasing the consumption of iron and porphyrins in the production of new haemoglobin. The goal of therapy is to reduce serum ferritin levels to the lower limit of the reference range.[11] Venesections are generally scheduled every 2–3 weeks, as tolerated by the patient. Clinical remission may not be complete until several weeks to months after biochemical remission has been reached. In patients in whom phlebotomy is not convenient or is contraindicated, and in those who have relatively mild iron overload, oral chloroquine phosphate (77.5 mg twice per week) or hydroxychloroquine sulfate (200 mg 2–3 times per week) is often effective.[12–14] Larger doses can cause severe

Figure 8. This type of skin fragility and poor healing can be seen in both epidermolysis bullous acquisita (pictured) and porphyria cutanea tarda



hepatotoxicity (even low dose regimens require careful monitoring). Oral chloroquine phosphate works by increasing urinary porphyrin excretion. For patients with porphyria cutanea tarda who are anaemic due to other chronic diseases (eg. renal failure, HIV), human recombinant erythropoietin can be used to stimulate erythropoiesis.[15]

Practice tip

Other porphyrias or photo-aggravated bullous dermatoses can manifest with clinical features indistinguishable from those of porphyria cutanea tarda (*Figure 8*). Failure to obtain sufficient biochemical confirmation of the diagnosis can lead to inappropriate treatment. Drugs such as NSAIDs, tetracyclines and frusomide can cause a similar clinical picture on photo-exposed sites (pseudoporphyria).

Conflict of interest: none declared.

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AFP CORRESPONDENCE afp@racgp.org.au