INTRODUCTION

Blisters (definition: an elevated cutaneous lesion filled with clear fluid) have very many potential causes, and as always a good history (including drug history), and examination are essential. Consider the age of the patient, previous medical history, the site/distribution and duration of the blisters, whether localised or generalised, and whether associated with any systemic symptoms. Examine the mucous membranes in addition to the skin.

Whatever the cause in general:

- Small blisters can be left intact.
- Drainage of large painful blisters to allow the roof of the blister to adhere to the base provides relief of symptoms and optimises healing. In some cases this will also limit the expansion and therefore ultimate size of the blister.
- If the blister has burst and the roof torn away, the wound should be treated with a non-adherent dressing and protective padding
- Widespread blistering can be associated with considerable morbidity and in some cases even mortality. All cases of extensive blistering require admission and a dermatological referral.

Causes of blistering include:

- Infection eg. herpes simplex, varicella/zoster, hand, foot and mouth disease bullous impetigo and Staphylococcal Scalded Skin Syndrome.
- Drug-induced blistering (see section on drug eruptions).
- Erythema multiforme/Stevens-Johnson Syndrome/TEN (see separate section).
- Eczema and Contact Dermatitis.
- Immunobullous disorders eg. bullous pemphigoid, pemphigus, dermatitis herpetiformis, linear IgA disease, pemphigoid gestationis.
- Physical causes eg friction, thermal and chemical burns.
- Miscellaneous causes of blistering include insect bite reactions, blistering associated with acute exacerbation of oedema, and metabolic causes eg. Porphyria cutanea tarda.

INFECTIVE CAUSES OF BLISTERING

Primary infections with Herpes simplex virus produce symptoms within 3 to 7 days of exposure. There may be a prodrome of malaise, fever and lymphadenopathy. The lesions are typically grouped, sometimes umbilicated, vesicles on an erythematous base. The mouth and lips are most commonly affected in orolabial herpes. Primary infection often presents as a gingivostomatitis in children and is associated with a pharyngitis and mononucleosis-like syndrome in young adults. Primary genital herpes infection can present with an excruciatingly painful balanitis, vulvitis, or vaginitis. Severe infections with HSV can occur in immunocompromised patients. Individuals (usually children) with atopic eczema can develop the widely disseminated lesions of eczema herpeticum.
• Eczema herpeticum requires admission, iv/oral anti-virals and dermatology referral.
• For orolabial infection topical aciclovir plus oral anti-viral agent if severe.
• For the treatment of primary and recurrent genital herpes, oral antivirals are the treatment of choice.

**VARICELLA/ZOSTER**
See section on Herpes zoster (Shingles)

*Bullous impetigo* starts as small vesicles on the face, trunk, buttocks, perineum or extremities. These rapidly enlarge to flaccid transparent bullae up to 5 cm in diameter. The blisters are very superficial and rupture easily leaving erosions. Can occur at any age, but most common in childhood, especially in neonates. Bullous impetigo is always caused by Staph aureus, usually phage II, type 71.

• Local care – cleaning of the skin and removal of crusts.
• For localized disease topical Mupirocin 2% ointment.
• Widespread cases oral antibiotics.

**Staphylococcal Scalded Skin Syndrome**
SSSS is part of a spectrum of staphylococcal toxin-mediated infections which includes bullous impetigo and toxic shock syndrome. It is primarily a disease of children less than 6 years old. There is often a prodrome of malaise, fever, irritability, and severe tenderness of the skin. SSSS starts as erythema followed by the development of flaccid bullae within the superficial epidermis and then desquamation. The diagnosis is mainly clinical. The early pre-exfoliative stage of SSSS can resemble Kawasaki’s disease, a viral exanthem, toxic shock syndrome, a drug reaction, GVHD, and a sunburn reaction, but the rapid progression to exfoliation excludes these conditions.

• Admission and parental anti-staphylococcal antibiotics (eg. Flucloxacillin).
• Moist denuded areas should be lubricated with a bland emollient (eg. a mixture of 50% white soft paraffin and 50% liquid paraffin).
• Isolate affected newborns from other neonates.

**HAND, FOOT, AND MOUTH DISEASE**
Characterised by tiny blisters on the inside of the mouth, palms and soles. Rash lasts for 7 – 10 days, and there may be associated systemic symptoms. Commonly caused by coxsackie virus A16 (enterovirus). Young children most often affected but can be seen in adults.

• There is no specific treatment.

**ECZEMA AND CONTACT DERMATITIS**
Pompholyx is a form of eczema of the palms and soles in which oedema fluid accumulates to form visible vesicles or bullae. Because of the thick epidermis at these sites the blisters tend to become larger than at other sites before
bursting. Pompholyx can occur at any age, but onset before ten years is unusual. An attack of pompholyx is characterised by intense pruritus, and the sudden onset of clear deep-seated vesicles which may become confluent and form large bullae especially on the soles of the feet. Occasionally secondary bacterial infection can occur with the formation of pustules and lymphangitis spreading up the arm.

Pompholyx is often a constitutional form of eczema, but can sometimes be due to contact dermatitis or a reactive process due to fungal infection of the feet. The diagnosis is essentially clinical. Immunobullous disorders (see below) occasionally present with blisters on the palms which mimic pompholyx.

- For acute pompholyx hands and feet should be soaked twice daily in a solution of potassium permanganate diluted 1:8000.
- After soaking and drying the skin apply a potent or superpotent topical steroid (eg. Dermovate ointment), followed by cotton gloves for the hands, cotton bandages for the feet.
- Treat secondary bacterial infection with oral antibiotics.
- Refer to Dermatology for ongoing care and investigation of any underlying cause. Can usually be managed as an out-patient.

**ACUTE CONTACT DERMATITIS**

Occasionally patients with an acute contact dermatitis (particularly an allergic contact dermatitis) can present with severe blistering. The diagnosis is usually obvious from the history eg. a severe reaction on the face after use of a hair dye containing paraphenylene diamine.

- Very severe reactions may require systemic steroids (eg. Prednisolone 30mg daily) and/or admission.
- For less severe reactions topical potent steroid (eg. Betnovate ointment).
- Refer Dermatology for on-going care and further investigation.

**IMMUNOBULLOUS DISEASES**

All patients with suspected immunobullous disorders should be referred to Dermatology.

Bullous pemphigoid is the most common immunobullous disease, typically presenting in the elderly with a generalised pruritic bullous eruption. The relative risk for patients over 90 years of age is approximately 300x greater than for those of 60 years or younger. The disease can however affect younger patients, and rarely even children. The sub-epidermal blisters are tense, up to several centimetres in diameter, contain a clear fluid and may persist for several days, leaving crusted and eroded areas. The lesions are frequently distributed symmetrically, and they predominate on the flexural aspects of the limbs, lower trunk, and abdomen. Involvement of the oral cavity in 10-30% of patients, other mucosal surfaces more rarely affected.

Bullous pemphigoid may be drug-induced eg. Furosemide.
Patients with widespread blistering require admission, and an urgent dermatology referral. The diagnosis is confirmed by a skin biopsy for histology and immunofluorescence.

Treatment should start before the diagnosis is confirmed.

Topical and systemic steroids are the mainstays of treatment.

- For localised BP very potent topical steroid (eg. Dermovate ointment) bd
- For more widespread disease in addition to topical steroids give oral Prednisolone:
  - 20mg/day or 0.3mg/kg/day in mild disease
  - 40mg/day or 0.6mg/kg/day in moderate disease
  - 50 – 70mg/day or 0.75 - 1.0mg/kg/day in severe disease

**GENERAL MEASURES**

Large bullae should be popped but not de-roofed.

Dress the limbs with paste bandages (eg Steripaste) applied over the Dermovate ointment.

Apply non-adherent dressings such as Atrauman over the Dermovate-treated blisters/erosions on the trunk.

**PEMPHIGUS**

Mean age of onset 50 – 60 years

The skin lesions are flaccid, thin-walled easily ruptured blisters. They can appear anywhere on the skin surface, and arise either in normal looking skin or erythematous bases. The fluid within the intra-epidermal blisters is initially clear, but may become haemorrhagic, turbid, or even seropurulent. The blisters are fragile and rupture to form painful erosions that ooze and bleed easily. These erosions often attain a large size and may become generalized. Without appropriate treatment, pemphigus vulgaris can be fatal because a large area of the skin loses its barrier function, leading to the loss of body fluids and/or secondary bacterial infection.


**TREATMENT**

- Oral Prednisolone 60mg/day or 1mg/kg/day.
- Topical treatment and general measures as bullous pemphigoid (above).
- Urgent dermatology opinion.

**PEMPHIGOID GESTATIONIS (PG)**

PG classically presents during late pregnancy with the abrupt onset of intensely itchy urticarial lesions on the trunk. This rapidly progresses to a generalized pemphigoid-like eruption, sparing only the face, mucous
membranes, palms and soles. There is an increased risk of prematurity and small for dates babies, and the newborn baby can develop blisters. Patients can present in the post-partum period. The main differential diagnoses are pruritic urticarial papules and plaques of pregnancy, and drug eruptions.

- Patients with widespread blistering require admission.
- Systemic steroids remain the cornerstone of therapy.
- Most patients respond to 0.5 mg/kg of Prednisolone.
- General measures as for pemphigoid/pemphigus (above).
- Patient should be referred for dermatology and obstetric opinions.

**DERMATITIS HERPETIFORMIS AND LINEAR IGA DISEASE**

*Dermatitis Herpetiformis* (DH) is a rare, intensely itchy condition affecting all ages, although in the UK it usually presents in young and middle aged adults with a slight male preponderance. All patients have an underlying gluten sensitive enteropathy which may be asymptomatic. The distribution of lesions is very characteristic, with grouped blisters (the grouping of the blisters resembling that seen in herpes simplex hence herpetiformis) on the extensor aspects of the elbows, forearms and knees, the buttocks, shoulders, face and scalp. The differential diagnosis includes erythema multiforme, linear IgA disease, bullous lupus erythematosus and bullous pemphigoid. The diagnosis is confirmed by skin biopsy for histology and immunofluorescence.

- Refer for Dermatology opinion. Patients do not usually require admission.
- In most patients Dapsone and a gluten free diet

*Linear IgA disease* produces a bullous eruption which may clinically resemble DH or bullous pemphigoid. Some patients have expanding annular plaques with blisters at the edge. Affects children and adults. Linear IgA disease can be drug-induced (eg Vancomycin). The diagnosis is confirmed by skin biopsy for histology and direct immunofluorescence.

- If blistering is extensive require admission and urgent dermatology referral
- General measures as for pemphigoid/pemphigus (above).
- Most patients respond to Sulphapyridine/Dapsone

**BLISTERS ASSOCIATED WITH ODEMA**

Blisters associated with an exacerbation of chronic oedema are not uncommon, particularly on the lower legs of elderly and immobile patients. The tense blisters are non-inflammatory and surrounded by oedematous skin. Oedema develops when the capillary filtration rate exceeds lymphatic drainage. This can be due to heart failure, renal disease, hepatic disease, hypoalbuminaemia, venous disease/occlusion, drugs (eg. calcium channel blockers). Blisters can also occur with acute exacerbations of lymphoedema.

Blistering in the setting of acute oedema is usually clinically obvious. These blisters resolve rapidly when the cause of the oedema is successfully treated.
Elevation and compressive bandages are helpful
Treat underlying cause of oedema

**BULLOUS INSECT BITE REACTIONS**
Insect bites usually appear as intensely itchy erythematous papules or nodules. They are usually grouped, typically in a linear arrangement. Most lesions are the result of an individual immune response to insect antigens introduced by the bite. Bullous insect bite reactions are common especially in children. Flea bites are the most likely to cause blisters especially on the legs. The presence of intense pruritus and lesion distribution usually suggests the diagnosis. However these reactions can mimic bullous pemphigoid, erythema multiforme, bullous impetigo, or eczema.

- Most patients with bullous insect bites can be managed with drainage of blisters, topical steroids, antihistamines for relief of pruritus.
- In the most severe reactions a short course of systemic steroids may be necessary

**FRICTION BLISTERS**
Friction blisters typically occur on the palm, sole, heel, or dorsum of the fingers, and usually do not occur on thin or lax skin. Diagnosis is usually self-evident, but occasionally bullous insect bite reactions and other bullous diseases can be confused with friction blisters. The blisters seen in patients comatose from neurological lesions or drug overdose can clinically resemble those caused by friction.

- Small blisters can be left intact.
- For large painful blisters drainage to allow the roof of the blister to adhere to the base provides relief of symptoms and optimises healing.
- If the blister has burst and the roof torn away, the wound should be treated with a non-adherent dressing and protective padding
- Uncomplicated blisters heal rapidly.

For thermal and chemical burns see section on burns.