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Dermatological complications of critical care

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Learning objectives

By reading this article you should be able to:

- Describe classical patterns of cutaneous drug reactions.
- Identify potential causative agents that need to be withdrawn.
- Engage with multidisciplinary staff to help with the management of conditions such as intertrigo and pressure sores.
- Recognise the importance of maintaining an intact skin barrier.

Key points

- Dermatological complications of critical care are common but not usually life-threatening.
- New skin rashes should be taken very seriously in critically unwell patients receiving multiple, newly introduced drug treatments.
- The most important step in reducing morbidity and mortality in severe drug reactions is the cessation of the causative agent.
- A number of dermatological conditions can arise during a critical care admission including pressure sores, intertrigo and symmetrical peripheral gangrene, all of which may be associated with significant morbidity.

Dermatological complications occur in up to 10% of patients admitted to critical care.[1] These may be relatively benign in nature, such as intertrigo, but can also be associated with serious morbidity and mortality. As with any skin condition, a methodical approach to its diagnosis should be used including a review of the history of the rash including events leading up to the development as well as a thorough examination. Specialist input may be required from dermatologists and tissue viability teams to ensure appropriate management is started and to enable follow-up as required. This input should be sought at any stage where the diagnosis or management plan is not clear or has become more complex, such as with a superadded infection.

Drug eruptions

Mild drug eruptions

Adverse cutaneous drug reactions or drug eruptions occur in 2–3% of patients in hospital.[2] A drug-induced reaction should be considered in any patient who is taking new medication and subsequently develops a cutaneous eruption. Approximately 90% of adverse drug reactions present with a classical morbilliform (measles-like) or maculopapular rash (Fig. 1); this is usually widespread and symmetrical, and occurs between 4 to 14 days after commencing the causative agent. Most reactions are mild and resolve when the drug is stopped.[2]

The aetiology of drug eruptions is complex; it may be caused by an immune reaction (immediate or delayed), pseudo-allergy (i.e. an urticarial reaction secondary to mast cell degranulation seen with opioids or non-steroidal anti-inflammatory drugs (NSAIDs)) or a predictable dose-related response. Whilst most

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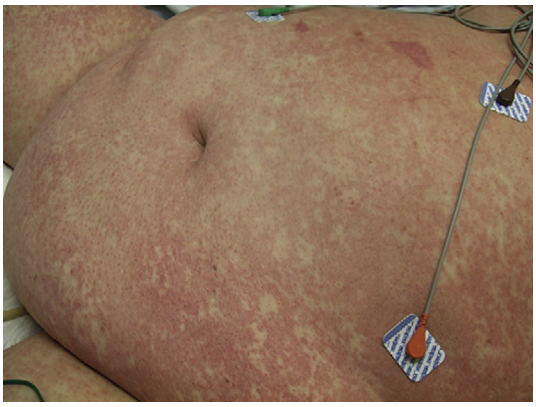

Fig 1 Morbilliform drug rash.

often morbilliform in nature, the eruption can mimic a wide range of dermatoses with varying morphologies including urticarial, pustular and bullous rashes.

Whilst any drug could potentially cause a cutaneous reaction, antibiotics, NSAIDs and antiepileptics are the most commonly implicated. It can be difficult however to identify the causative agent following a drug eruption in a patient in critical care because multiple drugs are often used and there is a time delay between giving the drug and the development of signs and symptoms. Skin prick or patch tests can be performed to identify certain drugs such as the penicillins or anticonvulsants, but may be difficult to interpret in the context of critical illness. Table 1 lists the classical clinical patterns seen in drug reactions and their likely causative agents.

The most important step in reducing morbidity and mortality for all drug reactions is withdrawal of the causative agent. Mild eruptions can be treated with topical corticosteroids, emollients and antihistamines as required under the direction of a dermatologist.

Table 1 Classical clinical patterns of drug reactions and their common causative agents

Drug-induced exanthems (including symmetrical drug-related and flexural exanthema (SDRIFE))	Allopurinol Aminopenicillins Cephalosporins Antiepileptic agents Sulphonamides
Urticaria/angioedema	Non-steroidal anti-inflammatory drugs (NSAIDs) Angiotensin converting enzyme (ACE) inhibitors Antibiotics, especially penicillin and teicoplanin.
Cutaneous small vessel vasculitis	Antibiotics Diuretics NSAIDS Anticonvulsants Antipsychotics TNF-α inhibitors Rituximab IFN-β
Erythroderma/Exfoliative dermatitis	Sulphonamides Chloroquine Penicillin Phenytoin Carbamazepine Allopurinol Isoniazid
Stevens-Johnson syndrome and toxic epidermal necrolysis	Sulphonamides Anticonvulsants Oxicam-type NSAIDs Allopurinol Nevirapine
Drug reaction with eosinophilia and systemic symptoms (DRESS)	Anticonvulsants (mainly carbamazepine, phenobarbital, phenytoin, lamotrigine and sodium valproate) Allopurinol Sulphonamides and dapsone
Acute generalised exanthematous pustulosis (AGEP)	Aminopenicillins Hydroxychloroquine Sulphonamides Terbinafine Diltiazem

Table 2 Warning signs and symptoms of severe cutaneous drug reaction

Immediate symptoms
Widespread rash
Mucosal involvement
Fever >39◦C
Lymphadenopathy
Fatigue; arthralgia; sore throat
Abnormal liver or kidney function tests.
Eosinophil count > 1x 10^9 L^{-1}
Positive Nikolsky's sign (The application of lateral mechanical pressure on the skin causing blistering caused by dislodgement of the upper from the lower epidermis)

Severe drug reactions

Whilst most drug eruptions may be mild in nature, severe cutaneous adverse reactions (SCAR) such as drug rash, eosinophilia and systemic systems (DRESS), Steven Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) may be life threatening, and represent the most severe end of a drug reaction.[2] There should be a high index of suspicion of a severe drug reaction for patients who develop a typical widespread rash with multisystem involvement including fever, mucosal involvement and/or liver and renal impairment. These conditions have been discussed recently in part 1 of this article series.[3]

The broad principles of treatment for such conditions involves immediate cessation of the suspected drug, involvement of dermatology specialists for specific treatment options and supportive care for ensuing organ dysfunction. The indicators that a reaction is severe are listed in Table 2.[4]

Acute generalised exanthematous pustulosis

Acute generalised exanthematous pustulosis (AGEP) is a rare reaction in which there is widespread erythema in the folds of the skin, trunk and extremities, with the development of sterile, non-follicular pustules (Fig. 2). Over 90% of AGEP is drug related, particularly due to the beta-lactam antibiotics. It may be accompanied with fever and neutrophilia, but it is usually self-limiting once the causative drug is stopped.

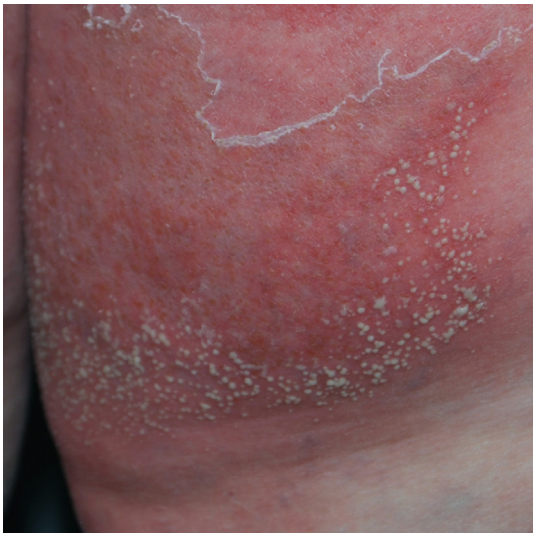

Fig 2 Acute generalised exanthematous pustulosis.

Approximately 17% of patients have some involvement of other organs, usually with mild derangement of liver enzymes and increased serum creatinine. Mortality is less than 5% in AGEP. When death does occur, it is typically a result of multiple organ dysfunction and disseminated intravascular coagulation.[5]

Common causative drugs are listed in Table 1. If there is no resolution within 15 days of drug withdrawal, the diagnosis should be questioned. Because of its self-limiting nature, systemic therapy with steroids is rarely required, however topical steroids may be used after consultation with a dermatologist.[6]

Cutaneous small vessel vasculitis

Cutaneous small vessel vasculitis (CSVV) affects arterioles and venules and presents with purpura and petechiae that can form haemorrhagic bullae (Fig. 3). It can be primary or

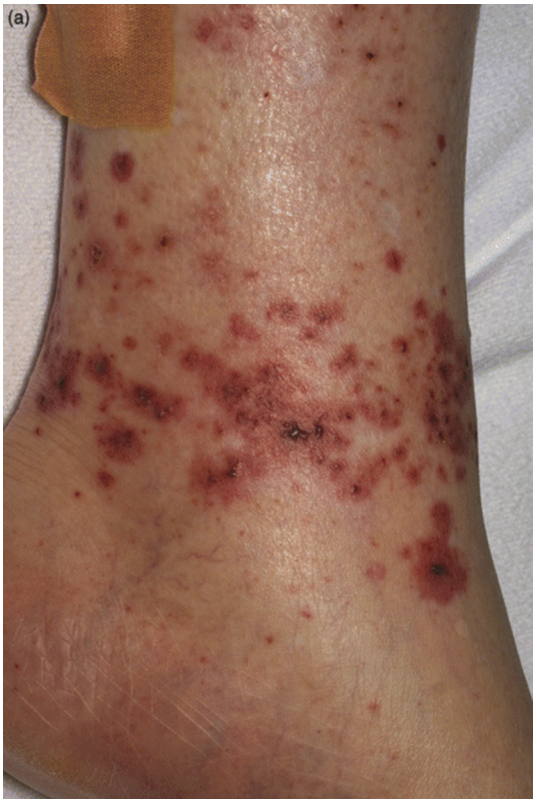

Fig 3 Cutaneous small vessel vasculitis.

idiopathic in nature or secondary to drugs (Table 1), infections (hepatitis viruses, HIV or chronic bacterial infection) or a disease process such as cancer. It is important to exclude systemic vasculitis, which can occur in a small number of patients with concomitant signs of alveolar haemorrhage, glomerulonephritis or visceral organ ischaemia. Complications of CSVV include ulceration, wound infection and cellulitis. Management involves discontinuing the trigger, treating infection, compression of affected limbs and dressing of ulcerations. Most cases resolve within weeks to months. Immunosuppressants can be considered in patients with evidence of acute vasculitis and ulceration or in those with relapsing disease.[7]

Intertrigo

Intertrigo, or intertriginous dermatitis, is a condition in which skin folds become inflamed, tender and erythematous leading to fissuring and peeling (Fig. 4). It can be infective and/or inflammatory in origin. Environmental factors contributing to the process include increased moisture levels, a lack of ventilation to the skin fold and rubbing of opposing skin causing skin damage. Risk factors include obesity, immobility, diabetes mellitus and immunosuppression. The resulting skin breakdown can then be an entry point for secondary fungal and bacterial infections. Indicators of secondary infection are foul odour, satellite papules and pustules, plaques or abscesses.[8]

Daily cleansing and drying of the patient's skin folds along with the use of barrier creams or talc can help to prevent intertrigo. Liberal application of emollients and pastes can be used to reduce friction and irritation. If there is an underlying inflammatory dermatosis contributing to the problem e.g. flexural psoriasis (psoriasis affecting skin folds or creases), a topical steroid agent may be indicated. Topical antifungal or antibacterial creams can be considered to treat potential infection. Systemic antimicrobials should be used when there is evidence of bacterial growth from a culture and if the condition is not resolving.[8]

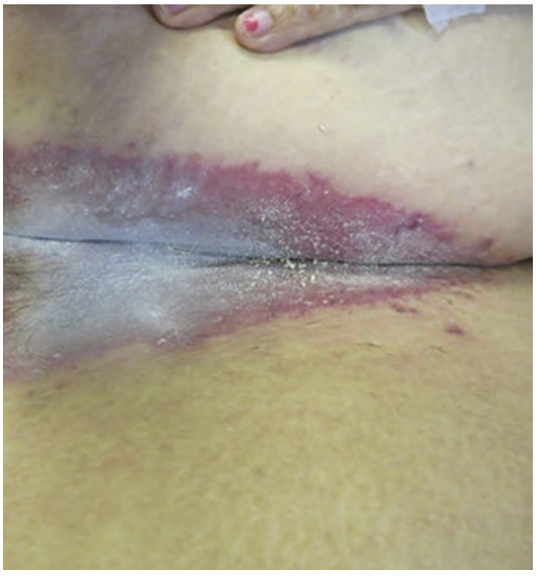

Fig 4 Intertrigo.

Miliaria

Miliaria, also known as sweat or heat rash, is caused by the obstruction of eccrine sweat gland ducts (Fig. 5). Miliaria rubra is the most common type of miliaria and results in red, non-follicular papules or vesicles. It is seen in those who are exposed to a hot and humid environment such as a tropical climate or in critical care when pyrexia, occlusion of skin with dressings or clothing and prolonged bed rest contributes to blockage of the ducts in the epidermis. The rash is generally erythematous and itchy and tends to be found on the trunk, neck and flexures.

Miliaria is a benign condition and usually resolves with cooling of the patient and environment, exposing skin to air where possible and treating fever with antipyretics. Emollients and topical steroids can be considered as well as antimicrobials for secondary bacterial infection.[9]

Pressure ulcers

Acute skin failure (ASF) in the setting of critical illness is defined as an event in which the skin and underlying tissue die as a result of hypoperfusion concurrent with severe dysfunction or failure of other organ systems.[10]

The skin is the largest organ of the body and receives up to one third of the circulating blood volume; it is therefore vulnerable during critical illness when the circulation is compromised. Skin failure may occur at certain anatomical sites in the first instance, for example points of pressure, resulting in the development of a pressure ulcer.

When an area of skin receives an impaired blood supply due to increased pressure on that area, the blood flow is compromised, and the integrity of the skin becomes at risk. Areas often affected are those over a bony prominence such as the sacrum, calcaneus and ischium, as well as where medical devices contact or enter the skin. Critically ill patients are particularly at risk due to prolonged immobility, poor microvascular circulation and concomitant nutritional deficiency. Contributing factors are excessive moisture where the skin is in contact with urine, sweat or blood.

Pressure ulcers can be graded in terms of severity and range from mild skin erythema to necrosis and ischaemia of deep tissues including muscle and bone (Table 3).[11]

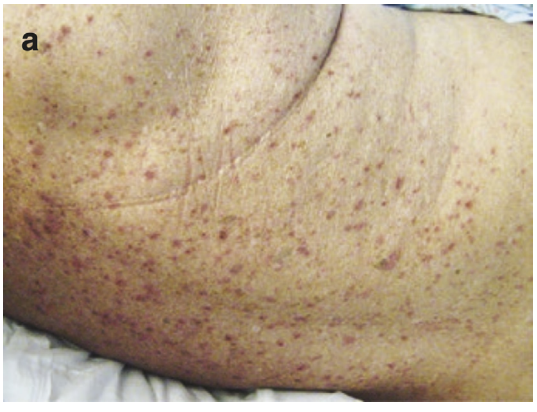

Fig 5 Miliaria.

Table 3 European Pressure Ulcer Advisory Panel classification of pressure ulcers

Grade 1	Intact skin with non-blanchable redness of a localised area usually over a bony prominence. May be painful or itchy
Grade 2	A shallow open ulcer with a red pink wound bed. May also present as an intact or open blister.
Grade 3	Full thickness tissue loss. Subcutaneous fat may be visible, but bone, tendon or muscle are not exposed.
Grade 4	Full thickness tissue loss with exposed bone, tendon or muscle.

Treatment of pressure ulcers can be difficult once the skin integrity has broken, and so interventions aimed at prevention are vital. High-risk patients such as those in critical care should be assessed for their risk of ulceration using validated scoring systems including the Waterlow or Braden Scores, and managed accordingly. Regular skin assessment should be performed with repositioning of the patient at least every 4 hours. Redistributing mattresses and padded materials to relieve pressure on bony prominences should be used where possible and inadequate nutrition addressed with supplementation. Maintaining skin hygiene is imperative.

Attention should be paid to medical devices to ensure that they are not exerting external pressure on the skin. Antiembolic stockings; cervical collars; tracheal tubes; nasogastric tubes; face masks for non-invasive ventilation; faecal management systems; nasal cannulae; pulse oximetry probes; intra-arterial and urinary catheters have all been reported to cause pressure ulceration.[12]

Treatment begins with removing the pressure source from the skin. If the skin is still intact the ulcer will usually heal by itself. Once the skin has broken, the management becomes more complicated. The area must be protected to allow the ulcer to heal, which can be problematic depending on the site. Dressings should be used that promote a warm, moist healing environment. Systemic antibiotics may be required if there is clinical evidence of systemic sepsis, spreading cellulitis or underlying osteomyelitis. High grade or non-healing ulcers should be reviewed by specialist tissue viability and surgical teams to assess the need for negative pressure therapy and/or surgical debridement.[13]

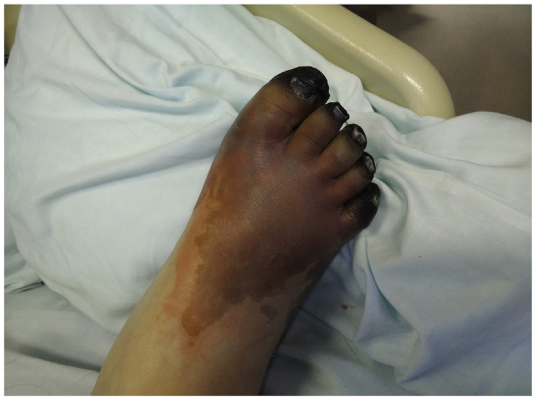

Fig 6 Gangrene to distal digits.

Symmetrical peripheral gangrene and purpura fulminans

Symmetrical peripheral gangrene is defined as distal ischaemic damage in two or more extremities, without large vessel obstruction or vasculitis (Fig. 6). It is sometimes referred to as purpura fulminans as it almost always occurs in patients with disseminated intravascular coagulation in the context of septic shock and high doses of vasopressor drugs.[14]

Reversal of the underlying aetiology, often sepsis, is the mainstay of treatment. If possible, vasoconstrictor doses should be reduced. There is very limited evidence for any specific therapies being beneficial; i.v. vasodilators such as epoprostenol and anticoagulants such as heparin may be useful.[15]

Amputation and skin grafting should be delayed until full demarcation of the necrotic area has occurred, and the patient's condition has improved. The gangrenous areas should be monitored closely during this period as this classically dry gangrene can become wet gangrene if it becomes infected. If infection does occur, then antimicrobial treatment will be required along with the consideration of earlier surgical intervention.

Extravasation injuries

Extravasation is the accidental injection or leakage of fluid into the subcutaneous or perivascular tissues.[15] The damage that may be caused can range from minor, such as localised swelling and oedema, to severe including necrosis and tissue loss, scarring and contractures and ultimately amputation. Patients in critical care are at increased risk of this occurring due to a number of factors including:

- the patient being sedated and therefore not being able to describe sensations of pain;
- poor nutrition and skin that is subsequently at risk of complications;
- the need for continuous and multiple infusions;
- drugs that can cause local damage such as:
  - vasoconstrictors
  - hyperosmolar agents (calcium, magnesium sulphate, total parenteral nutrition, sodium bicarbonate, potassium chloride)
  - acids or alkalis (amiodarone, erythromycin, phenytoin, vancomycin).[15]

Detection of an inadvertent extravasation may begin with pain around the injection site if the patient is able to sense and communicate this. Swelling caused by accumulation of fluids, blanching resulting from increased tissue pressure secondary to the fluid volume, or vasoconstriction from the fluid content may then occur, with subsequent erythema or blistering developing shortly after.[16]

Prompt cessation of the infusion is imperative if extravasation is suspected. If possible, the fluid should be aspirated from the cannula and it be left in place until advice is sought regarding further treatment. The extravasation border should be marked and photographed, and the limb elevated to promote venous drainage. Heat can be used to increase local vasodilation to improve local drug reabsorption. Should the extravasation involve a high-risk agent, referral to a plastic surgeon for specialist advice and treatment should be considered; saline washout of the affected area; or liposuction can be performed to reduce tissue injury. All events and the subsequent management should be well documented in the patient's notes and follow-up arranged to review the progress of the injury.[16]

Summary

Whilst admission to critical care can be lifesaving, it can also be associated with a number of secondary conditions associated with such a stay including dermatological sequalae. A rash in a critically unwell patient is not unusual but must be assessed promptly and managed appropriately to avoid further complication. If a drug eruption is suspected, potential causative agents should be stopped immediately. Meticulous care of the skin should be taken to attempt to avoid burdensome dermatological complications such as pressure sores, miliaria and intertrigo. Whilst not always avoidable, it is vital to be aware of these conditions and try to mitigate against their development.

MCQs

The associated MCQs (to support CME/CPD activity) will be accessible at www.bjaed.org/cme/home by subscribers to BJA Education.

Declaration of interests

The authors declare that they have no conflicts of interest.

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