Cutaneous drug reactions in intensive care

Rashes are common on the wards and in intensive care, and can be the cause of the admission, an extension of an underlying pathology or a side effect of a drug. This review discusses the frequency and causes of these drug rashes, whether they are benign or life threatening, and looks at how to identify and manage them.

Adverse drug reactions are common in intensive care, with rates up to 35% (Park et al, 2013). A significant proportion of these are rashes. It is estimated that rashes caused by drug reactions occur in 10% of patients in intensive care (Campos-Fernández et al, 2005). Dermatological conditions account for 0.47% of all intensive care admissions (George et al, 2008) and 'acute skin failure' constitutes less than 15% of these. Acute skin failure includes conditions such as toxic epidermal necrolysis and exfoliative dermatitis which may be drug-induced. They have a high intensive care and hospital mortality at 35% and 47% respectively.

It is common that a rash will develop on the intensive care unit as a side effect of therapy for the critical illness. The list of side effects on any drug information leaflet almost always includes a rash. Two large studies performed in the 1970s and 1980s assessed the frequency of adverse drug reactions (including rashes) in more than 50 000 people: Boston Collaborative Drug Surveillance Program and the Berne/St Gallen Comprehensive Hospital Drug Monitoring Program. These and other large retrospective studies have provided an indication of the frequency of cutaneous drug reactions (*Table 1*). Drugs that appear to be least likely to result in a cutaneous reaction are listed in *Table 2*.

Polypharmacy can also result in a number of pharmacodynamic and pharmacokinetic interactions. These interactions may increase the incidence of cutaneous adverse effects. This was noticed in the 1980s when administering amoxicillin or ampicillin in the presence of allopurinol doubled the incidence of a cutaneous reaction (Jick and Porter, 1981). Another example is the increased incidence of toxic epidermal necrolysis with the co-prescription of lamotrigine and valproate (Messenheimer et al, 1998).

Alternatively the rash could be an extension of the admission pathology (for example a vasculitic or paraneoplastic phenomenon). Certain medical complexes have well-recognized rashes such as graft *vs* host disease or following immune reconstitution inflammatory syndrome after starting antiretroviral therapy.

The complexity of the intensive care environment is a problematic place in which to develop a rash. Polypharmacy, organ failure and relative immune deficiency are all present, which makes it difficult to definitely diagnose a drug rash. Polypharmacy makes diagnosing any culprit drug harder, meaning a number of drugs may need to be stopped together, some of which

Table 1. Approximate frequency of cutaneous drug reactions

Drug	Approximate frequency*
Amoxicillin, ampicillin	4–8%
Allopurinol	5–7%
Co-trimoxazole	2–4%
Fluoroquinolones	1.5%
Cephalosporins	1.5%
Gentamicin	1%
Non-steroidal anti-inflammatory drugs	0.7%
Carbamazepine, phenytoin, lamotrigine	13%

*The frequency is only a guide as different rates are taken from different studies and different population. From Bigby et al (1986), Hunziker et al (1997), Tennis and Stern (1997)

Table 2. Drugs very rarely associated with cutaneous drug reactions

Digoxin
Paracetamol, aspirin
Tetracycline (except photosensitivity)
Prochlorperazine (Stemetil)
Spironolactone
Prednisolone, hydrocortisone
Ferrous sulphate
Nitroglycerin, isosorbide
Insulin
Aminophylline
Warfarin

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will have limited acceptable alternatives. In intensive care, choosing which drugs to omit and which to continue involves an appreciation of the probability that a particular drug is involved, knowledge of the drug alternatives and a bedside risk–benefit analysis. Dermatological input is crucial in serious cutaneous drug reactions, but is also of benefit for other rashes or where the diagnosis is unclear.

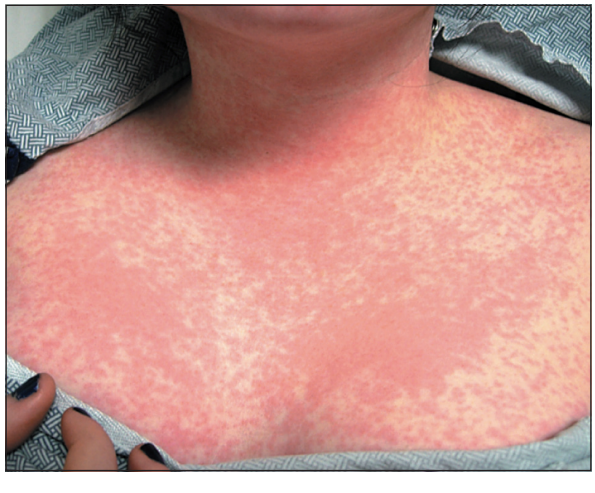
Erythematous rashes in intensive care

Red rashes are a common clinical problem both in intensive care and elsewhere in the hospital. Distinguishing a red rash that is caused by a drug from one caused by an infection is difficult. The timings of drug initiation, rash development and the response to drug withdrawal are helpful but by no means diagnostic. Testing for a drug allergy is possible but may yield false positives and negatives and is not advisable when there has been a severe reaction (see below). The erythematous rash can have various manifestations.

Exanthematous rash

These are widespread (often symmetrical) erythematous or red-pink maculopapular lesions and are also referred to as morbilliform (*Figure 1*). The incidence is estimated at 60–95% of cutaneous drug reactions. They depict a rash that has both small flat and raised areas of redness. The eruption often starts on the trunk and affects the extremities. The face and mucous membranes are often unaffected. The lesions feel warm, and an awake patient may develop pruritis. This commonly occurs 3–7 days after starting the offending drug, although presentations up to 21 days are possible. If the drug is continued the rash may develop into erythroderma (a widespread confluent erythema) or exfoliative dermatitis (erythroderma with desquamation). Exanthematous rashes do not inevitably develop into exfoliative dermatitis, and there are many reports of the rash disappearing despite continued therapy. Erythroderma and exfoliative dermatitis carry the serious risks of hypothermia, dehydration and electrolyte imbalance.

Figure 1. Exanthematous drug reaction demonstrating plaques and papules (predominantly in the neck region) that are beginning to coalesce.



Identifying the rash and discontinuing the correct drug is the most important step in preventing further consequences. Pruritic patients can benefit from an antihistamine. The more frequent precipitants of an exanthematous rash in intensive care are shown in *Table 3*. Other causes of an exanthematous rash such as infections like measles, rubella and parvovirus or developing graft *vs* host disease should be considered under appropriate clinical circumstances.

Urticaria

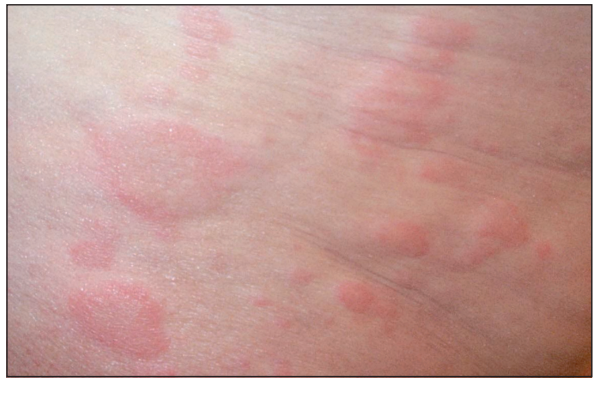
This is the second most common form of drug rash. This rash is usually related to an allergic reaction, and is characterized by transient raised blotches or weals sometimes with a paler centre as a result of a vascular reaction in the upper dermis (*Figure 2*). It usually occurs within 24 hours of exposure. Once the drug is withdrawn the rash usually recedes over the next 24–48 hours although it can take longer. Urticaria can be mediated by IgE reactions, activation of complement, or alterations in the balance of arachidonic acid metabolism. Other pathologies are often associated with urticaria such as anaphylaxis, anaphylactoid reactions, angio-oedema and serum sickness.

Table 3. Common intensive care drugs associated with exanthematous drug reactions

Penicillins and cephalosporins
Gentamicin
Erythromycin
Amphotericin
Co-trimoxazole
Carbamazepine, phenytoin, lamotrigine
Frusemide, thiazides
Allopurinol
Barbiturates
Tricyclic antidepressants and selective serotonin-reuptake inhibitors

Adapted from Degner et al (2004), Stern (2012)

Figure 2. Urticated lesions showing central pallor.



Urticaria is managed by stopping the causative drug and initiating antihistamines. Any associated serious pathology should clearly be treated. Drugs that more commonly cause urticaria are listed in *Table 4*.

Erythema multiforme

Erythema multiforme, as the name suggests, describes red skin eruptions in a variety of different patterns. Classically, erythema multiforme affects the extremities more than the body. Target lesions are characteristic, and there may be associated blistering (*Figure 3*). Only 20% of erythema multiforme eruptions are caused by drugs, infections being a far more common aetiology. The most common infection causing erythema multiforme is herpes simplex type 1, the virus responsible for cold sores. Other more frequently occurring infectious causes include *Mycoplasma pneumoniae*, parapoxvirus, herpes varicella zoster and adenovirus. If a drug is the cause, the rash usually appears 4–21 days after initiation. Diagnosing and stopping the drug is usually sufficient and important, as continuing any causative drug could precipitate Stevens–Johnson syndrome or toxic epidermal necrolysis (see below).

Drug reaction with eosinophilia and systemic symptoms

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a potentially severe multisystem disease, which usually develops 2 weeks after initiation of the offending drug. Delayed onset up to 8 weeks has been documented. It often starts with pyrexia and an exanthemous rash on the face, around the eyes and over the body. The mucous membranes are often spared. Lymphadenopathy may be apparent. The rash may progress over a week to a widespread erythema or exfoliative dermatitis. An eosinophilia (>1.5x10^9/litre) or atypical lymphocytes can be present in the blood (*Figure 4*). Any other organ can demonstrate dysfunction, although more commonly hepatitis (>80% of cases), nephritis and thrombocytopenia can develop. Pneumonitis and pericarditis can also occur. Drugs classically involved are listed in *Table 5*.

Table 4. Common intensive care drugs associated with urticaria

Penicillins, cephalosporins
Tetracyclines
Sulphonamides
Phenytoin, carbamazepine, lamotrigine
Vancomycin
Aspirin or non-steroidal anti-inflammatory drugs
Angiotensin-converting enzyme inhibitors
Monoclonal antibodies

Adapted from Shipley and Ormerod (2001)

Diagnosis can sometimes be difficult as a result of the extended time between starting the drug and the condition developing. Cessation of appropriate drugs, supportive care and organ support is required and high doses of corticosteroids are often started although the evidence for this treatment is limited. Steroids should be weaned off gradually as flares of DRESS can occur following too rapid withdrawal. Mortality is estimated at 10% and is from complications such as exfoliative dermatitis, hepatitis, pneumonitis or nephritis. Patch testing later is not recommended, and allergy should be assumed. Drugs in similar classes can also induce DRESS and should be avoided.

Figure 3. Targetoid lesions of erythema multiforme present on the leg of an infant.

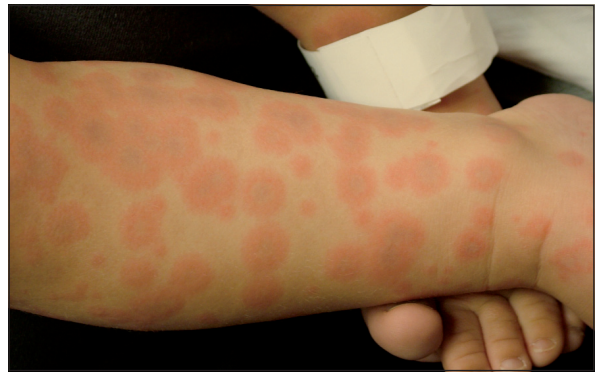


Figure 4. Widespread erythematous skin rash with papules seen in drug reaction with eosinophilia and systemic symptoms.

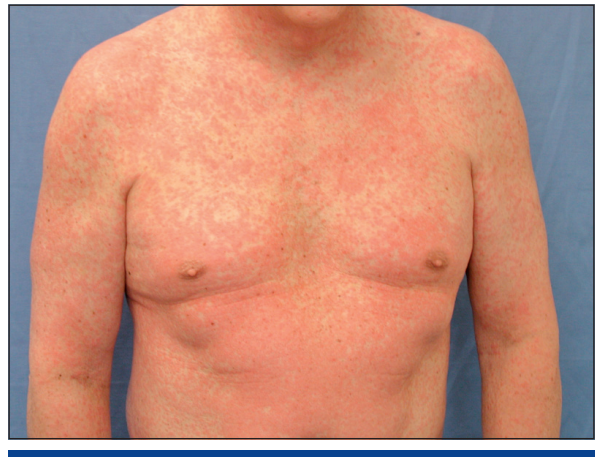


Table 5. Intensive care drugs associated with drug reaction with eosinophilia and systemic symptoms

Lamotrigine, phenytoin, carbamazepine, phenobarbital
Sulphonamides
Allopurinol
Diltiazem
Non-steroidal anti-inflammatory drugs (oxicams)
Atenolol

Blistering rashes in intensive care

Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome and toxic epidermal necrolysis are severe cutaneous conditions that are almost exclusively caused by drugs (Auquier-Dunant et al, 2002). Drugs more commonly implicated in Stevens–Johnson syndrome or toxic epidermal necrolysis are listed in *Table 6*. There can be typical target lesions like in erythema multiforme, although there are often more atypical and flatter lesions that are less well demarcated. There is often a predominance of these lesions on the trunk and affecting the oral mucosa, conjunctiva and genitalia. There is blistering associated with some lesions which are positive for Nikolsky's sign (ready removal of the epidermis on tangential pressure) (*Figure 5*). Currently, differentiating between Stevens–Johnson syndrome and toxic epidermal necrolysis depends on the extent of blistering. Cases in which <10% of lesions blister are considered Stevens–Johnson syndrome, those in which >30% blister are considered toxic epidermal necrolysis, and those in between these amounts are termed Stevens–Johnson syndrome–toxic epidermal necrolysis overlap.

Severe toxic epidermal necrolysis can affect other mucosal surfaces such as nasopharyngeal, bronchial and oesophageal. It can also cause liver dysfunction, nephritis and affect other organs. Managing these patients is akin to managing severe burns. This is a medical emergency and requires resuscitation using the ABC approach. An airway specialist should be involved early to protect the airway and breathing. Further circulatory support should be initiated under expert guidance in intensive care or a specialist unit.

Treatment is largely supportive (Mockenhaupt, 2009). Fluid balance, electrolyte, temperature control, pain control, nutritional support and close surveillance for secondary infection are all important. Caring for the damaged skin is complex and should be guided by an expert. It may include antiseptic solutions (0.5% silver nitrate or 0.05% chlorhexidine), covering any exposed dermis with a wound dressing that promotes healing, humidity, sterility and is non-adhesive. Biological, biosynthetic or completely synthetic dressings are often used in severe cases to cover the significant areas of epidermal loss. Antiseptic oral rinses for oral mucosa, dexpanthenol-based ointments for the lips, and antiseptic creams for genital areas are required.

Ocular involvement needs daily review from an ophthalmologist, antiseptic or antibiotic eye drops up to 2-hourly, and watching for developing synechiae or symblepharon. Synechia is a condition where the iris adheres to either the cornea (anterior synechia) or lens (posterior synechia). It will manifest as a misshapen irregular pupil and is easiest to diagnose with an ophthalmoscope. Untreated it can result in glaucoma and blindness. Symblepharon is adherence of the eyelid and corneal conjunctiva. If left unchecked, this can result in entropion or other eyelid abnormalities.

Mortality ranges from 5% for Stevens–Johnson syndrome to 40% severe toxic epidermal necrolysis. Attempts at immunomodulation (steroids and other immunosuppressive drugs) have been trialled as has intravenous immunoglobulin; all without success. Follow-up patch testing is generally not recommended.

Other blistering drug rashes in intensive care

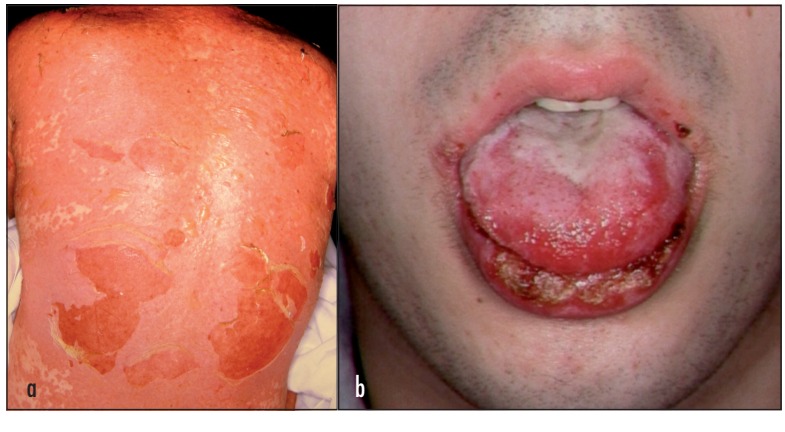
Drug-induced pemphigus, drug-induced pemphigoid or linear IgA disease are other causes of blistering drug rashes. Drug-induced pemphigus and pemphigoid are similar to their namesakes, and are more often associated with drugs used outside the intensive care unit. Pemphigus usually occurs in patients between the ages of 30–60 years, with females being more commonly affected. It is caused by an immune reaction where IgG autoantibodies bind to keratinocytes causing superficial blistering that leads to erosions of the skin. This may be triggered by a number of factors including stress, hormones and pregnancy, tumours, ultraviolet light and some drugs. Those that been associated include penicillamine, captopril and rifampicin. Unfortunately removing the trigger does not usually resolve the disease. Management involves the use of corticosteroids

Table 6. Intensive care drugs more commonly associated with Stevens–Johnson syndrome or toxic epidermal necrolysis

Lamotrigine, phenytoin, carbamazepine, phenobarbital
Sulphonamides
Tetracyclines
Non-steroidal anti-inflammatory drugs (oxicams)
Allopurinol
Penicillins
H_2 antagonists
Nevirapine

Adapted from Mockenhaupt (2009)

Figure 5. a. Extensive blistering and loss of epidermis seen in toxic epidermal necrolysis. b. Mucosal involvement seen in Stevens–Johnson syndrome or toxic epidermal necrolysis.



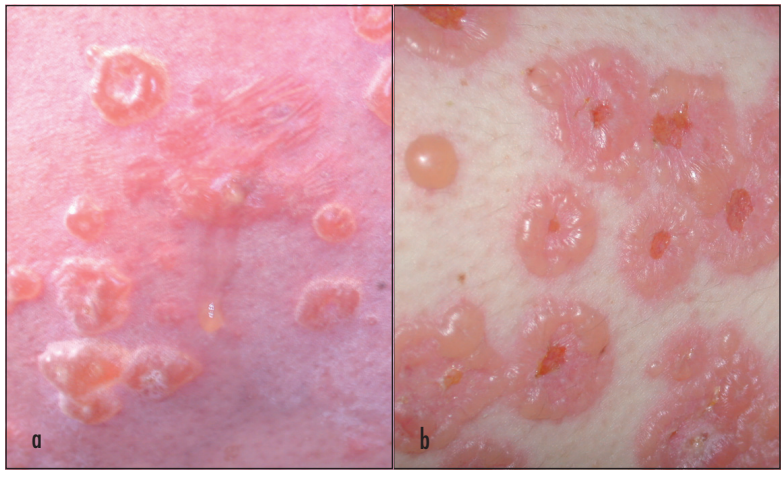
and if this fails then intravenous immunoglobulin and other steroid-sparing immunosuppressive agents such as aziathioprine.

Pemphigoid occurs in an older age group, usually in those over 60 years of age, and equally affects males and females. The immune reaction and IgG deposition takes place further down into the skin between the junction of the dermis and epidermis which produces a more tense blister that is less likely to erode. The triggers are the same as for pemphigus although non-steroidal anti-inflammatory drugs have also been implicated. Treatment can be with potent topical steroids but usually oral corticosteroids are required. They may be required from 6 weeks to 4 years in duration.

Drug-induced linear IgA disease starts within 1–2 weeks of commencing the causative drug. Tense blisters begin to appear on the limbs and body. It can involve the palms and occasionally the mucous membranes (*Figure 6*). Cessation of the offending drug and supportive care should result in resolution within a further 2 weeks. Vancomycin is the most common agent associated with this condition.

Another potentially blistering drug allergy is a fixed drug eruption (*Figure 7*). A localized area of redness and blistering may occur, especially on the hands, feet or genital areas. It is termed 'fixed' since the reaction occurs at the same site every time the offending drug is taken. If this is the patient's first encounter with the drug it may take 1–2 weeks to develop. Repeat exposures develop more quickly at the same location. Resolution on stopping the drug takes a further few weeks but may leave areas of hyperpigmentation. Antibiotics are the commonest causes, notably sulphonamides and tetracyclines. There are usually no systemic symptoms associated with this eruption. Follow up can include patch testing of the affected skin. Avoidance of the offending drug and related drugs is usually sufficient, and patients make an uneventful recovery.

Figure 6. a. In linear IgA disease clear round target-like blisters are seen on a background of erythematous skin. b. When these resolve new blisters occur around the edge, this is known as the 'string of pearl' sign.



Pustular rashes in intensive care

Acute development of a widespread pustular rash is most likely to be acute generalized exanthematous pustulosis. The other differential diagnosis is pustular psoriasis and should be considered in those with a history of psoriasis.

Acute generalized exanthematous pustulosis

This is the rapid development of sterile pustules on top of erythematous skin over a period of hours (*Figure 8*). It typically starts on the face or in the skin creases and spreads over the body. It usually does not involve mucous membranes. It may be associated with a fever, but the patient does not usually become any more unwell. A smear of the pustules should be taken, which will demonstrate neutrophils, but will otherwise be sterile. It is estimated that between 50% and 90% of acute generalized exanthematous pustulosis are thought to be the result of a drug reaction (Stern, 2012).

The rash will appear within 3 days and, provided the causative agent is stopped, will heal over 1–2 weeks with desquamation. Cessation of the correct drug is the only

Figure 7. Annular scaly hyperpigmented plaque that is seen in a lesion representing a fixed drug eruption.

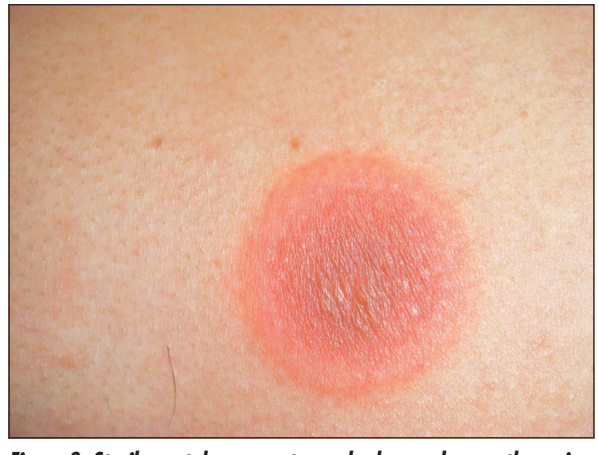
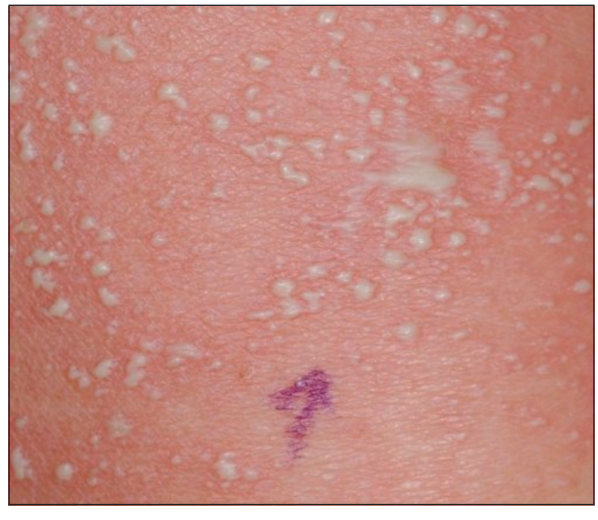


Figure 8. Sterile pustules present on a background or erythema in acute generalized exanthematous pustulosis.



therapy required other than moisturising during the desquamation stage. The condition is not serious and the patient can be reassured. It may resemble pustular psoriasis, and a prior history of psoriasis places the patient at a slightly higher risk of developing generalized pustulosis. The more common precipitants of acute generalized exanthematous pustulosis in intensive care are shown in *Table 7*.

Purpuric rashes in intensive care

Purpuric rashes are concerning in intensive care as they can be related to serious and deteriorating pathology such as severe sepsis, meningococcal disease or bone marrow failure (*Figure 9*). A combination of thrombocytopenia, platelet dysfunction, coagulopathy and microcirculatory dysfunction will induce purpuric rashes. Several drugs can cause purpuric rashes by inducing a vasculitis. The rash will usually be a mixture of macules, erythematous papules and purpuric lesions. Differentiating a drug-induced vasculitis from one driven by a malignant, autoimmune or infective process can be difficult, and clinical probabilities will have to be judged. The diagnosis is made when withdrawal of the drug results in prompt resolution of the vasculitis. Drug-induced vasculitis can be a multisystem disease leading to multiorgan dysfunction. It is often caused by beta-lactam antibiotics, sulphonamides, erythromycin, carbamazepine, frusemide and thiazides.

Testing for a drug allergy and desensitization

The British Society for Allergy and Clinical Immunology provides guidance as to follow-up requirements of a drug rash (Mirakian et al, 2008).

Potential initial investigations

Initial measurements of sequential serum tryptase and serum-specific IgE is only potentially useful in anaphylactic or anaphylactoid scenarios. Urticaria on its own would not warrant these measurements. A skin biopsy is rarely done for a presumed drug rash. However, if there is diagnostic doubt, and an underlying infective or systemic process could be to blame, then a biopsy may help.

Table 7. Intensive care drugs more commonly associated with acute generalized exanthematous pustulosis

Penicillins, cephalosporins
Tetracyclines
Carbamazepine
Calcium channel-blockers
Quinolones
Macrolides

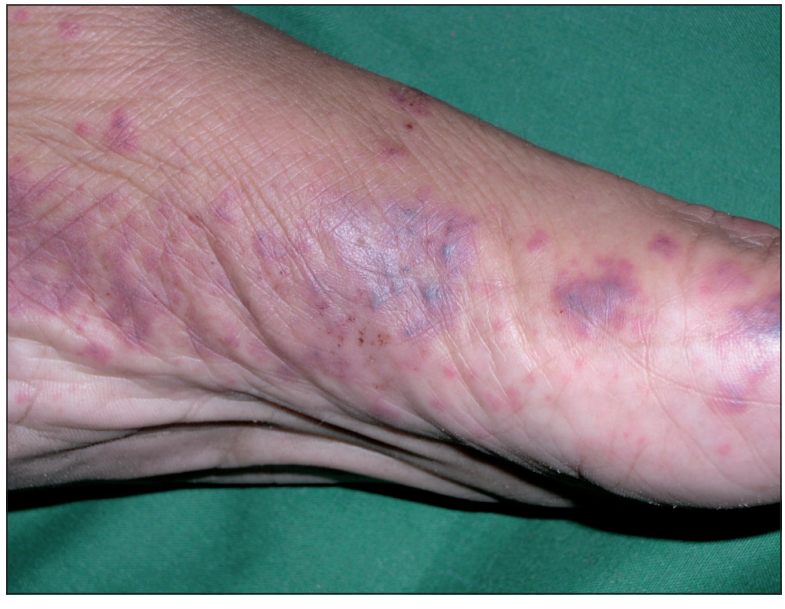
Follow-up testing

Testing following resolution of the rash and resolution of the underling critical illness can be done. Unfortunately, many of these tests have significant false negative and positive results. Therefore, when dealing with potentially life-threatening drug eruptions, clinical suspicion (i.e. pre-test probability) often outweighs the test results and so determines clinical practise.

Skin prick testing involves placing diluted allergen into the epidermis. Intradermal tests are similar in nature but the allergen is placed into the dermis. Intradermal testing is more sensitive, less specific and is more likely to trigger a systemic response. A reaction will take place within 15 minutes and is used to provide supporting evidence for an IgE-mediated condition. There is a high false positive and negative rate. For example a drug metabolite could have induced the allergy, resulting in a false negative. Certain drugs (such as atracurium) will induce a direct histamine release making a false positive more likely. Unfortunately, because of the inaccuracies of the test, the polypharmacy and organ dysfunction in intensive care, there is limited use of either test outside of follow up for anaphylaxis and anaphylactoid reactions.

Patch testing involves placing potential allergens on an aluminium disc attached with hypoallergenic tape to a patient's back for 48 hours to detect delayed hypersensitivity responses. False negatives do occur, for example as a result of poor skin penetration. Sensitivity is reported to be between 11 and 43%. Some guidelines do not recommend patch testing following severe cutaneous conditions. The British Society for Allergy and Clinical Immunology suggests that patch testing can be helpful in highly selected severe cases. In these cases patch testing can be very time consuming as the test must start at very low concentrations.

Figure 9. Purpuric lesions on the foot of a patient with drug-induced vasculitis.



A provocation test with a specific drug may be done if the other investigations have been negative and the diagnosis is still in doubt. Obviously it is not a test to be done when the previous administration resulted in a serious skin reaction, and many argue that clinical suspicion should take priority.

Desensitization

Desensitization is only a potentially suitable therapy for IgE-mediated conditions where the allergen is unavoidable. It has no real role in drug anaphylaxis as drug avoidance is a more pragmatic policy. Other mechanisms of severe cutaneous drug reaction are not amenable to this mode of therapy.

Conclusions

Cutaneous drug reactions can be the reason for admission to intensive care, or an unwanted side effect of an intensive care therapy. As an admission criterion, 'acute skin failure' secondary to drugs is very rare, but has a high mortality (47% hospital mortality). Toxic epidermal necrolysis is the most common severe cutaneous drug reaction. Other concerning cutaneous drug manifestations are DRESS, acute generalized exanthematous pustulosis and the generalized blistering skin conditions. The drugs involved in many of these conditions are very similar: antibiotics, antiepileptics, diuretics and cardiac medications. Many of these drugs are used frequently in intensive care, and often together. These severe cutaneous conditions can have long-term sequelae. Severe blistering conditions can heal with significant scarring, while Stevens–Johnson syndrome or toxic epidermal necrolysis can result in permanent ocular damage or blindness. DRESS can leave residual organ dysfunction.

Non-life-threatening red rashes are a frequent adverse drug side effect on intensive care. Exanthematous and urticaria are the most common descriptions. Erythema multiforme is sometimes seen. Early detection of a new rash on intensive care is essential to ensure timely withdrawal of the drug(s) and replacement with an alternative. Expert advice on further management should be sought. This will minimize the chances of an inconvenient 'mild' drug reaction developing into one of the more serious conditions such as exfoliative dermatitis or Stevens–Johnson syndrome. Taking a photograph of the rash can help track the rash and with the subsequent diagnosis. It is also important to have a list of medications and their initiation timings. In follow-up clinics, various skin testing can be performed on the less severe cutaneous reactions, however, they are of limited reliability and clinical suspicions heavily influence subsequent management strategies. **BJHM**

KEY POINTS

- Severe cutaneous drug reactions are a rare cause of intensive care admission, but have a high mortality.
- The incidence of cutaneous drug reactions in intensive care is approximately 10%. Polypharmacy, organ dysfunction and altered immune function all contribute to this high incidence.
- Exanthematous and urticarial drug rashes are the most common presentations.
- Widespread erythema, blistering, pustular and purpuric rashes are all indicative of a potentially serious drug reaction.
- Early diagnosis and removal of the offending drug(s) is most important. Photographs can aid in tracking and retrospective diagnosis.

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Conflict of interest: none.

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