Cutaneous drug rashes

Adverse drug reactions are a frequent, preventable cause of morbidity and mortality (National Institute for Health and Care Excellence, 2012). Financially, the cost of adverse drug reactions to the taxpayer has been estimated at approximately £380 million a year in NHS England alone (National Institute for Health and Care Excellence, 2012). Cutaneous drug reactions are one of the most common manifestations of drug therapy, with an overall incidence of 2–3% and 1 in 1000 of all hospitalized patients developing severe cutaneous adverse reactions to drugs (Bastuji-Garin et al, 1993; Nayak and Acharjya, 2008). Most drug eruptions are mild, self-limiting and resolve with removal of the offending agent. Severe cutaneous adverse reactions, although rare, are more concerning because of systemic involvement. Mortality rates may reach as high as 20–30% for the most severe cases. Early recognition of those at risk, familiarity with the clinical features and prompt withdrawal of the causative agent is vital to patient prognosis. This article provides a stepwise approach to the assessment, diagnosis and management of cutaneous drug reactions, focussing in particular on severe cutaneous adverse reactions.

Causative drugs

Numerous drugs have been linked to the development of cutaneous drug reactions. *Table 1* gives an overview of common groups (Lee and Thomson, 2006). Although identifying the causative agent is fundamental to management strategies, this is not always feasible. Patients with multiple comorbidities will have a plethora of medications in their history. In these situations the possible association of each drug with the presenting severe cutaneous adverse reaction must be considered in light of the evidence in the literature (Nayak and Acharjya, 2008). There may be cases where medications have to be withdrawn one by one while closely observing cutaneous disease progression. In others it may not be possible to withdraw the offending medication. The latter cases are extremely challenging to manage.

Dr Naveed Ijaz *is Core Medical Trainee,* **Dr Emma McMullen** *is Consultant Dermatologist and* **Dr Mini Singh** *is Senior Lecturer and Honorary Consultant Dermatologist at The Dermatology Centre, Salford Royal NHS Trust, Salford M6 8HD*

Correspondence to: Dr M Singh (Minal.Singh@manchester.ac.uk)

Classification of cutaneous drug reactions

A number of systems attempt to quantify the nature of cutaneous drug reactions. The most well known of these is the Gell and Coombs classification which defines the immune mechanisms behind the clinical symptoms of drug hypersensitivity (Nayak and Acharjya, 2008). Categorizing cutaneous drug eruptions in this way guides management and informs future risk of recurrence in a given individual. A simple way of approaching cutaneous drug reactions is to classify them as either pharmacological, i.e. directly related to the mechanism of action of the drug, or immunoallergic (*Table 2*) (Gell and Coombs, 1963). Pharmacological reactions are predictable, dose related and listed in common reference manuals such as the British National Formulary. Immunoallergic reactions are less easily defined and include all severe cutaneous adverse reactions: this article will focus on them.

Risk factors

There are some patient factors which predispose individuals to immunoallergic cutaneous drug reactions. Those with atopy are more prone to IgE-mediated urticarial rashes, viral infection (consider HIV in particular), female gender, genetic polymorphism (e.g. HLA type B*1502 in carbamazepine-induced toxic epidermal necrolysis), connective tissue disorders and solid organ cancers (Bastuji-Garin et al, 1993).

Table 1. Common drugs implicated in the development of cutaneous drug eruptions

Group	Drug
Antiepileptics	Phenytoin, carbamazepine, lamotrigine
B-lactam antibiotics	Penicillins, cephalosporins
Macrolides	Erythromycin, clarithromycin
Antifungals	Fluconazole
Antiretrovirals	Abacavir, nevirapine
Non-steroidal anti-inflammatory drugs	
Others	Allupurinol, trimethoprim, oral hypoglycaemics, antihypertensives

Table 2. Categorizing cutaneous drug reactions

Pharmacological	Often predictable, related to over dosage, cumulative or delayed toxicity, adverse effects
	Drug–drug interactions
	Can be unpredictable: idiosyncratic
Immunoallergic (type I–IV reactions)	Mediated by IgE: urticaria or anaphylactic shock
	Circulating immune complexes: vasculitis, serum sickness
	Lymphocyte mediated: exanthema, photosensitivity, fixed drug eruption
	Fas/Fas ligand-induced apoptosis: Stevens–Johnson syndrome, toxic epidermal necrolysis

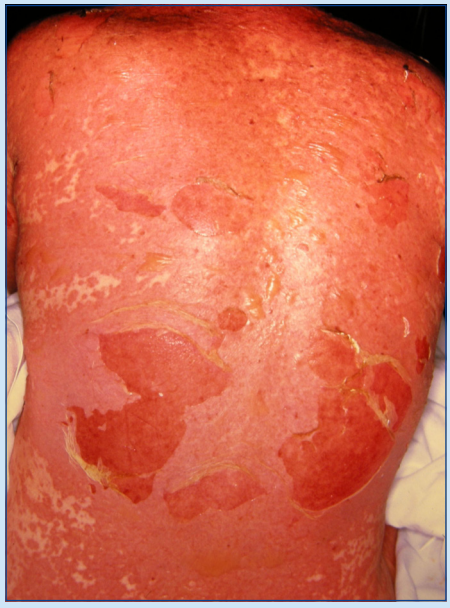
Common cutaneous drug eruptions

Morbilliform or maculo-papular eruptions are the most commonly encountered cutaneous drug rash, closely followed by urticarial eruptions (Nayak and Acharjya, 2008; Ziemer, 2014). They typically occur 4–14 days after the initiation of a drug affecting the trunk and extremities with preservation of the mucous membranes. Rarely, morbilliform eruptions may precede the development of more severe cutaneous reactions. In most cases, advising patients to seek medical attention if the eruption does not improve or progresses within a week is sufficient. Management involves immediate withdrawal of the offending agent (*Table 1*); however, in cases where this is not possible, patients should be closely monitored. Potent topical steroids together with antihistamines form the mainstay of treatment, their use governed by clinical judgement (Valliant, 2000).

Severe cutaneous adverse reactions

Severe cutaneous adverse reactions encompass a variety of dermatological emergencies. The most commonly encountered are toxic epidermal necrolysis (*Figure 1*), Stevens–Johnson syndrome, erythema multiforme major, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome), erythroderma (also known as exfoliative dermatitis) and acute generalized exanthematous pustulosis (Grover, 2011).

Figure 1. Toxic epidermal necrolysis.



Stevens–Johnson syndrome and toxic epidermal necrolysis

Stevens–Johnson syndrome and toxic epidermal necrolysis are two variants within the same spectrum of severe cutaneous adverse reactions (Bachot and Roujeau, 2003). These conditions can affect any age: the mean age of onset for Stevens–Johnson syndrome is between 25 and 47 years, while for toxic epidermal necrolysis it is between 46 and 63 years (Nirken et al, 2010). Both involve truncal, acral sites and one or more mucosal surfaces. A clinically useful classification system to aid diagnosis is described in *Table 3* by Bastuji-Garin et al (1993). In severe cases ocular (scarring), respiratory (acute respiratory distress syndrome) or gastrointestinal (bleeding) complications may result (Nirken et al, 2010; Yang et al, 2013).

Erythema multiforme minor *vs* erythema multiforme major

It is worth noting the inclusion of erythema multiforme major (bullous type) in the classification described above (*Table 3*). The definition of erythema multiforme major *vs* minor is confusing, not least within the literature (Bastuji-Garin et al, 1993, Roujeau, 1994; Tomasini et al, 2014). Both are cited as being predominantly post viral or bacterial infections (herpes simplex or mycoplasma pneumonia) (Bastuji-Garin et al, 1993). Both can cause systemic upset: the former as a result of cutaneous involvement, the latter as a result of the underlying viral infection. Erythema multiforme minor has more benign features with typical target lesions localized peripherally and no or single mucosal involvement (Verma et al, 2012). Many authors argue that the most important feature is prognosis, as erythema multiforme minor has no morbidity or mortality associated with it (Roujeau, 1994; Nayak and Archariya, 2008). As a consequence diagnosis is often confirmed retrospectively.

Drug rash with eosinophilia and systemic symptoms (DRESS) syndrome

The DRESS syndrome (also known as drug-induced hypersensitivity syndrome) is a dermatological emergency characterized by multi-organ involvement. The incidence is approximately 1 in 1000 to 1 in 10 000 drug exposures (Kaswala, 2013). DRESS usually begins 2–8 weeks, occasionally up to 12 weeks or more, after initiation of therapy (Cacoub et al, 2011). The condition is characterized by a morbilliform or erythrodermic rash. The cutaneous eruption can be mistaken for erythroderma, Stevens–Johnson syndrome or toxic epidermal necrolysis. Diagnostic criteria for this condition are three or more of the following:

- Acute drug rash with facial swelling
- Fever >38°C
- Lymphadenopathy
- Systemic involvement: hepatitis with raised aspartate aminotransferase level (commonest), interstitial nephritis, arthritis, interstitial pneumonitis and/or carditis
- Eosinophilia with or without abnormal lymphocytes.

Common drugs leading to DRESS include allopurinol, sulphonamides and antiepileptic drugs; co-infection with human herpes virus can also increase the susceptibility of developing the condition (Burge and Wallis, 2010; Cacoub et al, 2011).

Table 3. The five categories of the Stevens–Johnson syndrome/toxic epidermal necrolysis spectrum proposed by Bastuji-Garin et al (1993)

Severe acute drug reaction	Detachment	Features of rash
Bullous erythema multiforme major	<10% body surface area	and localized typical (three distinct zones of colour) or atypical target lesions
Stevens–Johnson syndrome	<10% body surface area	and widespread erythema or purpuric macules or flat atypical targets
Stevens–Johnson syndrome/ toxic epidermal necrolysis overlap	10–30%	Widespread purpuric macules or atypical targets
Toxic epidermal necrolysis with spots	>30%	Widespread purpuric macules or atypical targets
Toxic epidermal necrolysis without spots	>30%	With large epidermal sheets

Erythroderma

This is a clinical description rather than a diagnosis, characterized by widespread erythema affecting over 90% of the body surface area (Burge and Wallis, 2010). Hepatosplenomegaly, lymphadenopathy, peripheral oedema and high output cardiac failure are potential complications. If a known underlying dermatological condition is not present drug eruption should be high on the differential list (e.g. atopic dermatitis, psoriasis and cutaneous T cell lymphoma). Common drug causes include: sulphonamides, penicillin, isoniazid, antimalarials, allopurinol, phenytoin, omeprazole, captopril and vancomycin (Burge and Wallis, 2010).

Acute generalized exanthematous pustulosis

Cases of acute generalized exanthematous pustulosis are in the region of 1–5/million/year worldwide. It is characterized by an acute (<48 hours) erythema associated with confluent pustules primarily involving the flexor surfaces and skin folds (*Figures 2a* and *b*). In addition, patients have a fever, a burning sensation to the skin, neutrophilia and generalized oedema mainly affecting the face. There is also a risk of visceral involvement with renal failure and hepatitis. Topical or oral steroids may be used in mild to severe cases respectively. Antihistamines are not useful in relieving skin itch. Many cases are self limiting, with full resolution of symptoms in within 14 days.

Approaching the patient

Clinical assessment

The most essential approach to patients is having a high level of suspicion of a possible cutaneous drug reaction. In every patient presenting with a new rash without prior history of skin disease a cutaneous drug reaction should be considered. The next step is to take a detailed history to discover the offending agent (*Table 4*). This may include communication with primary care physicians, recent admissions to hospital in other units and even contacting community pharmacists. Expending every effort to accurately document the exposure to any drug will significantly aid the hunt for the causative agent.

Management of severe cutaneous adverse reactions

The management of severe cutaneous adverse reactions can be split up into general and specific measures. The advice of a specialist (dermatology, plastics, ophthalmology) input should be sought early to guide appropriate medical and nursing management.

General

1. A thorough history and examination (*Table 5*). Clinicians should document a timeline, showing the date the rash began and all the drugs delivered in the days or weeks before its onset
2. Examining the mucosal surfaces for involvement, being alert to the possibility of a severe cutaneous adverse reaction
3. Gain venous access and take bloods for a full blood count, urea and electrolytes, liver function, C-reactive protein and blood cultures
4. Skin biopsies may be performed to exclude differential diagnoses
5. Support failing skin functions (see below)
6. Supportive measures for immobilized patients (e.g. subcutaneous low molecular weight heparin)
7. Prevent sepsis (the commonest cause of mortality) with daily skin swabs and vigilance, particularly at sites of venous access.

Supporting skin functions

It is vital to reduce complications by:

1. Manage thermoregulation in a temperature-controlled side room
2. Carefully monitor fluid balance with commencement of intravenous fluids and catheterization if appropriate. Fluid requirements can be up to 6 litres a day
3. Reintroduce a skin barrier through application of 50% white soft paraffin in liquid paraffin
4. Protect mucosal surfaces (catheterization, ophthalmology input, antiseptic mouthwashes).

Specific

Stevens–Johnson syndrome or toxic epidermal necrolysis

Ideally patients should be admitted to a burns unit, high dependency unit, and intensive care unit or dermatology unit where specialist nurses are available to attend to the patient's increased needs. No attempt should be made to debride the wounds as the epidermis acts as a natural dressing. Treatment with systemic agents should only be determined by dermatologists and experts in severe drug reactions.

Prognosis in Stevens–Johnson syndrome or toxic epidermal necrolysis is guided by the SCORTEN score. Seven independent risk factors are applied to assess the severity of the patient's condition. Mortality rates

Figure 2. a. Widespread erythema in acute generalized exanthematous pustulosis. b. Pustules on a background of erythema in acute generalized exanthematous pustulosis.

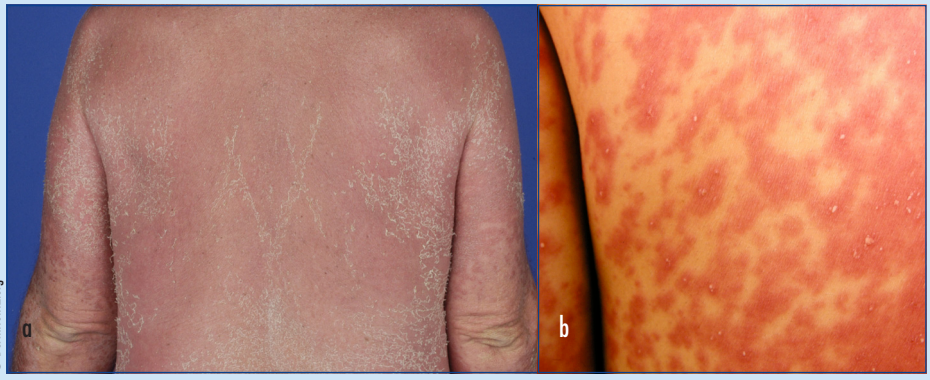


Table 4. Chasing the culprit drug

General medical history
Detailed list of every medication including dosages, start dates, any recent increase in dosages
Enquiry into over the counter medications, herbal remedies, homeopathic treatments
Any history of adverse drug reactions and the nature of these reactions (any skin involvement)
Any concomitant risk factors
Family history of adverse reactions and the nature of these
Environmental or occupational exposure to agents

can be up to 90% in those who score five or more, or as little as 3% in those with one risk factor (Yang et al, 2013).

DRESS syndrome

Oral steroids at a dose of 0.8–1 mg/kg body weight or alternatively intravenous methylprednisolone are recommended treatment options (Lee and Thomson, 2006; Yang et al, 2013). Interestingly, a genetic predisposition to the condition has been reported, so first degree relatives should be counselled about an increased risk of the condition. Mortality is predicted at 10% dependent on whether or not patients progress to liver failure (Kaswala, 2013).

Erythroderma and acute generalized exanthematous pustulosis

General supportive measures are paramount in managing these conditions. Topical steroids may be considered, systemic steroids are often not required if the offending drug is withdrawn. Erythroderma secondary to drugs usually resolves after 2–6 weeks. Fatal cases of acute generalized exanthematous pustulosis usually occur in the elderly and those with multiple comorbidities (Yang et al, 2013).

Conclusions

Clinicians should attempt to make a prompt and accurate diagnosis in cases of a suspected drug rash through thorough history taking. Removal of the offending agent is the cornerstone to managing these conditions and preventing significant morbidity and mortality. BJHM

Figures 1, 2a *and* 2b *are reproduced with permission from DermNet NZ.*
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Bachot N, Roujeau JC (2003) Differential diagnosis of severe cutaneous drug eruptions. *Am J Clin Dermatol* **4**(8): 561–72
Bastuji-Garin S, Rzany B, Stern RS, Shear NH, Naldi L, Roujeau JC (1993) Clinical classification of cases of toxic epidermal necrolysis, Stevens-Johnson syndrome, and erythema multiforme. *Arch Dermatol* **129**(1): 92–6
Burge S, Wallis D (2010) *Oxford Handbook of Medical Dermatology.* 1st edn. Oxford University Press, Oxford
Cacoub P, Musette P, Descamps V, Meyer O, Speirs C, Finzi L, Roujeau JC (2011) The DRESS syndrome: A literature review. *Am J Med* **124**(7): 588–97 (doi: 10.1016/j.amjmed.2011.01.017)
Gell PGH, Coombs RRA (1963) The classification of allergic reactions underlying disease. In: Coombs RRA, Gell PGH, eds. *Clinical Aspects of Immunology.* Blackwell Science, Oxford
Grover S (2011) Severe cutaneous adverse reactions. *Indian J Dermatol* **77**(1): 3–6 (doi: 10.4103/0378-6323.74963)
Kaswala DH (2013) Drug rash with eosinophillia and systemic symptoms syndrome due to anti TB medication. *J Family Med Prim Care* **2**(1): 83–5 (doi: 10.4103/2249-4863.109958)
Lee A, Thomson J (2006) *Adverse Drug Reactions.* 2nd edn. Pharmaceutical Press, Glasgow
National Institute for Health and Care Excellence (2012) Adverse Drug Reactions. http://cks.nice.org.uk/adverse-drug-reactions#!backgroundsub:2 (accessed 4 January 2015)
Nayak S, Acharjya B (2008) Adverse cutaneous drug reaction. *Indian J Dermatol* **53**(1): 2–8 (doi: 10.4103/0019-5154.39732)
Nirken MH, High WA, Adkinson, NF, Levy ML, Ofori AO (2010) Stevens-Johnson syndrome and toxic epidermal necrolysis: Clinical manifestations; pathogenesis; and diagnosis. http://nihlibrary.ors.nih.gov/jw/POC/USJS.htm (accessed 4 September 2014)
Roujeau JC (1994) What is going on in erythema multiforme? *Dermatology* **188**: 249–50
Tomasini C, Derlino F, Quaglino P, Caproni M, Borroni G (2014) From erythema multiforme to toxic epidermal necrolysis. Same spectrum or different diseases? *G Ital Dermatol Venereol* **149**(2): 243–61
Vaillant L (2000) Mechanisms of cutaneous drug reactions. *Rev Prat* **50**(12): 1294–9
Verma R, Vasudevan B, Pragasam V (2012) Severe cutaneous adverse drug reactions. *MJAFI* **69**(4): 375–83 (doi: 10.1016/j.mjafi.2013.01.007)
Yang MS Kang MG, Jung JW, Song WJ, Kang HR, Cho SH, Min KU (2013) Clinical features and prognostic factors in severe cutaneous drug reactions. *Int Arch Allergy Immunol* **162**(4): 346–54 (doi: 10.1159/000354918)
Ziemer M (2014) Cutaneous drug reactions of the delayed type. *The Dermatologist* **65**(5): 397–408 (doi: 10.1007/s00105-013-2696-9)

KEY POINTS

- Cutaneous drug reactions are the most commonly reported adverse reactions in drug therapy.
- A cutaneous drug eruption should be considered in patients with no prior skin disease presenting with a rash.
- A detailed and accurate recording of the drug history is the single most important aid to identification of the causative agent and prognosis.
- Although rare, severe cutaneous adverse reactions have high mortality rates. Early diagnosis is key to positive outcomes in patients.
- Mainstay of management is cessation of offending agent and supportive care for skin failure.

Table 5. Key features of severe cutaneous adverse reactions

Cutaneous reaction	Erythema multiforme major	Stevens–Johnson syndrome or toxic epidermal necrolysis	DRESS	Erythroderma	Acute generalized exanthematous pustulosis
Onset	3–14 days	1–3 weeks	2–8 weeks, rarely >12 weeks	<1 week	<48 hours
Fever >40°C	No but low grade fever can be present	Yes	Yes	Yes	Yes
Clinical features	Erythematous raised papular target lesions, affecting limbs and trunk, can be bullous. At least one mucosal surface involved, no facial swelling	Acute blistering, positive epidermal detachment: <10% Stevens–Johnson syndrome, 10–30% overlap, >30% toxic epidermal necrolysis, mucosal involvement ++	Morbilliform or erythrodermic rash, facial swelling, lymphadenopathy, eosinophilia, visceral involvement	Widespread, desquamating. >90% of body surface area involved. Lymphadenopathy, organomegaly	Erythematous, confluent pustules involving flexor surfaces and skin folds. Neutrophilia Facial swelling
Aetiology	Infections: herpes simplex virus, mycoplasma	Drugs: sulfonamides, NSAIDs, antiepileptics, allopurinol	Drugs: anticonvulsants, sulfonamides	Drugs: sulfonamides, penicillins, antimalarials	Drugs: penicillins/beta lactams, tetracyclines

DRESS = drug rash with eosinophilia and systemic symptoms; NSAID = non-steroidal anti-inflammatory drugs