Drug fever and DRESS syndrome

Febrile drug reactions are under-recognized and challenging to diagnose with possible major implications for treatment and, in the case of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome, significant mortality. This review presents an illustrative case and describes the pathophysiology, diagnosis and management.

Case History

A 48-year-old man sustained a displaced fracture of the left radius and ulna, managed by open reduction and internal fixation, with subsequent uneventful early recovery. On clinic review 3 weeks later, however, his wound was painful and erythematous with purulent discharge, culture of which yielded meticillin-resistant *Staphylococcus aureus* (MRSA). He was re-admitted, commenced on intravenous teicoplanin, and the wound washed out and debrided. Inflammatory markers at this stage were unremarkable (*Figure 1*).

Over the next week the wound dehisced, and further washout and debridement was performed. Biopsy of the ulna confirmed MRSA osteomyelitis, and teicoplanin was continued for a further 4 weeks during which time he remained apyrexial. At this stage there was further clinical deterioration. The arm became increasingly painful in association with the development of intermittent fevers to 39°C. He returned to theatre for removal of metalwork and attachment of an external fixator. Over the next week, repeated blood and urine cultures, chest radiographs, abdominal ultrasound, and transthoracic and transoesophageal echocardiograms were all unremarkable.

The pyrexia continued and, in view of the multiple negative cultures, a diagnosis of drug fever was considered. On a single occasion, however, fever was accompanied by an episode of hypotension, and his antibiotics were switched to ceftazidime (discontinued after 48 hours) and vancomycin to cover the possibility of occult sepsis. Following this change, the patient did not defervesce and instead developed rigors, along with a widespread urticarial rash, marked facial oedema and bilateral axillary lymphadenopathy. This clinical worsening was accompanied by a rising C-reactive protein level, a new pronounced eosinophilia (peak 5.54 x 10^9/litre) and increasingly deranged liver function tests (peak alanine transaminase 420 IU/litre, alkaline phosphatase = 968 IU/litre) (*Figure 1*); renal function remained normal. Further blood cultures were negative, and the diagnosis was revised to drug reaction with eosinophilia and systemic symptoms (DRESS). In view of the known osteomyelitis, glycopeptides were substituted with linezolid, and antihistamines and prednisolone 60 mg daily initiated for 7 days. This led to rapid and complete resolution of all symptoms, and the fevers abated. He was discharged and remains well 4 months later off antibiotics, with satisfactory wound healing.

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Adverse drug reactions are common causes of morbidity and occasionally mortality (Kongkaew et al, 2008). It is not widely appreciated that drugs may cause febrile reactions, which in the case of antimicrobial agents can be challenging to differentiate from pyrexia caused by the underlying infection. This results in substantial diagnostic and treatment dilemmas. This article presents a case and literature review to illustrate this scenario, and steps to achieve resolution.

The clinical challenge

The case history demonstrates a challenging clinical problem, in which a patient with a potentially severe infection develops a fever that may be attributable to use of antimicrobial medication. The decision to persevere with or discontinue antibiotics is far from trivial, and may be disastrous if the wrong conclusion is drawn. Understanding the clinical presentation of such drug reactions aids early recognition and guides the decision-making process.

Figure 2 illustrates the causes of febrile and cutaneous drug reactions. Glycopeptide antibiotics, as in this case, are common culprits. Teicoplanin and vancomycin are active against Gram-positive bacteria, including meticillin-resistant species (Bibler et al, 1987; Stille et al, 1988; Livornese et al, 1993). They have similar efficacy, although the adverse effect profile of teicoplanin is favourable (Smith et al, 1989b; Charbonneau et al, 1994; Neville et al, 1995; Wood, 1996). Vancomycin is more nephrotoxic and rapid infusion can directly induce histamine release causing 'red man' syndrome (erythema, pruritus and flushing of the upper torso); this is exceptional with teicoplanin (Dubettier et al, 1991; Polk, 1991; Wilson, 1998). Allergic cross-reactions can occur between the two glycopeptides (McElrath et al, 1986; Grek at al, 1991), but are unusual (Smith et al, 1989a; Hung et al, 2009).

In this case, the diagnosis was originally felt to be an isolated drug fever. In retrospect, the early derangement of the liver function tests suggests that the unifying diagnosis from the start was a developing drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome in which diagnostic features took time to manifest. This distinction is far from trivial, as there is significant mortality associated with DRESS but not drug fever alone. The two syndromes are here discussed and contrasted, as their precipitants and clinical features overlap but complications and management differ substantially.

Drug fever

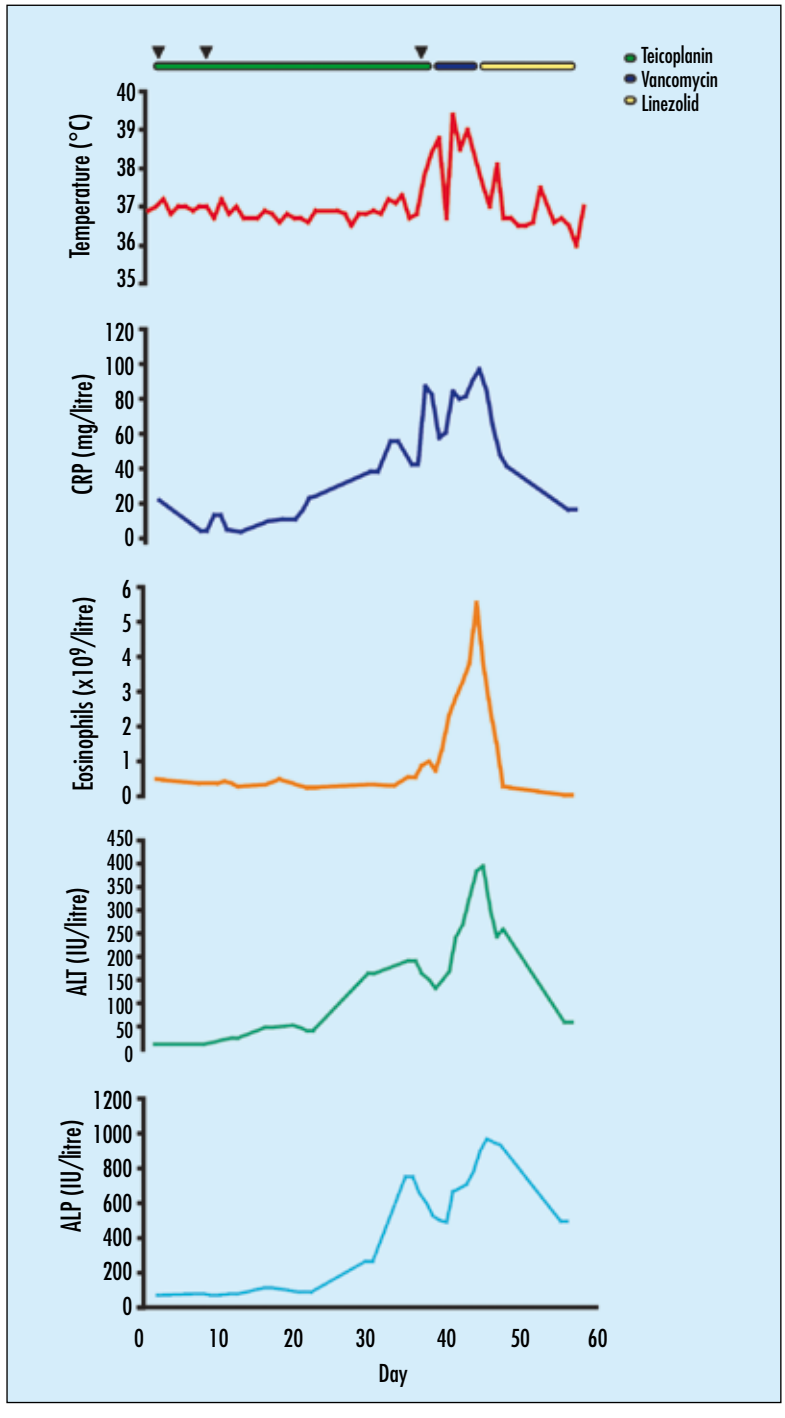
'Drug fever' is a well-recognized clinical phenomenon, whereby provision of a medication elicits a pyrexial response that remits following its discontinuation. The mechanism is poorly understood, and there are no clear risk factors that predict its development. In general, thermoregulation is controlled by the pre-optic area of the anterior hypothalamus. The thermoregulatory set-point can be elevated by interleukin-1 (secretion of which is induced by exogenous pyrogens), eicosanoids and catecholamines (Dinarello, 1999; Blatteis, 2006; Hodges and Johnson, 2009). Secondary changes in peripheral vascular tone, muscle activity, metabolic activity and behaviour then act to adjust core body temperature. Drugs may interfere at any of these stages (Lipsky and Hirschmann, 1981; Patel and Gallagher, 2010); for example, thyroxine elevates basal metabolic rate, adrenaline increases muscle activity and induces peripheral vasoconstriction, and tricyclic antidepressants inhibit sweat gland secretion through anticholinergic action. The spectrum of drug administration-related febrile reactions is summarized in *Figure 2*.

Drug fever is particularly associated with use of antibiotics, especially β-lactams. Antineoplastic agents, anticonvulsants and antidysrhythmic drugs are also commonly implicated (Mackowiak and LeMaistre, 1987; Patel and Gallagher, 2010). The overall incidence of drug fever with teicoplanin is not known, but estimated at approximately 5% (Stille et al, 1988; Livornese et al, 1993; Wilson, 1998). In the UK, post-marketing surveillance has identified 36 cases of pyrexia formally reported with teicoplanin since 1990 (CSM Drug Analysis Prints, 2010), although this will be a substantial underestimate of the true frequency.

The diagnostic challenge, particularly in the context of antibiotics, is whether pyrexia results from persistence of the underlying infection and therefore reflects treatment failure, or from the drug itself. With the former, appropriate action is to repeat cultures, check sensitivities and consider changing antimicrobial agents; for the latter, the current agent should usually be discontinued or substituted. The consequences of misattribution are substantial and potentially catastrophic. Ascribing fever to a drug reaction in the presence of systemic infection may obviously be disastrous, but there are also significant sequelae with the inverse scenario. In patients with drug fever, hospital stay is prolonged by an average of 8.7 days, with associated excess of radiological studies, courses of antibiotics and glucocorticoids, and blood cultures (Mackowiak, 1987). An analysis performed in 1986 concluded that delayed diagnosis of drug fever cost an average of $493 (£313) per patient in diagnostic procedures alone (Harris and Holdsambeck, 1986); adjusted for inflation to 2011, this figure exceeds $803 (£740) per patient.

Drug fever is essentially a diagnosis of exclusion as no definitive test exists, although a number of features may be suggestive (*Figure 3*). Re-challenge has been generally discouraged, although concerns about detrimental outcomes are not clearly substantiated by clinical experience (Mackowiak, 1987). Various fever patterns may be seen, and rigors are common. The classical picture,

Figure 1. Patient temperature and blood tests over the course of the admission. Fever developed after 1 month of teicoplanin, and continued with associated eosinophilia and severely deranged liver function tests after substitution with vancomycin. These resolved on discontinuation of glycopeptides. Timings of surgical interventions are indicated (arrowheads). Laboratory reference ranges: C-reactive protein (CRP)=0–5 mg/litre; eosinophils=0.04–0.4x10^9/litre; alanine transaminase (ALT)=5–50 IU/litre; alkaline phosphatase (ALP)=40–165 IU/litre.



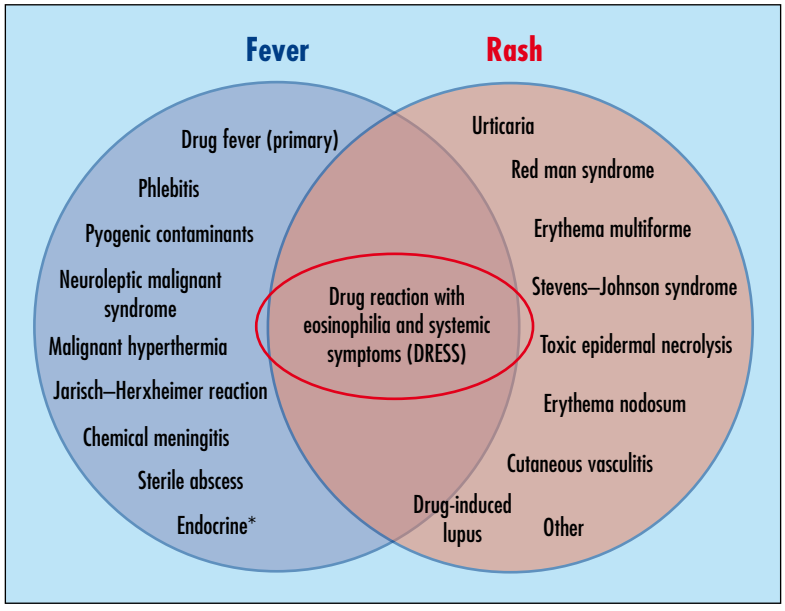


Figure 2. Febrile and cutaneous adverse reactions associated with drug administration. *Endocrine causes include thyroxine (increases basal metabolic rate) and adrenergic agonists or sympathomimetics (increase muscle activity).

which may occur in up to 70%, is of low-grade fever at the time of onset followed by high and unremitting, or hectic, pyrexias that persist until drug withdrawal when they rapidly subside (de-challenge) (Mackowiak, 1987). No single pattern is diagnostic, and the presentation may be extrinsically modified by antipyretic medications or active cooling measures. The median time from initiation of the offending agent to onset of fever is 7–10 days (Lipsky and Hirschmann, 1981; Tabor, 1986), but is highly variable (Patel and Gallagher, 2010). It appears to differ between drug classes, with short lag times observed with antimicrobial or antineoplastic drugs (onset often within 1 week), whereas drug fever caused by cardiac or anti-inflammatory drugs frequently occurs after 1 month of use (Mackowiak and LeMaistre, 1987). Patients often appear 'inappropriately well', with a relative bradycardia given the magnitude of fever (Lipsky and Hirschmann, 1981).

Laboratory findings are non-specific. A leukocytosis, and in particular a mild eosinophilia, are sometimes seen. Erythrocyte sedimentation rate and C-reactive protein may be modestly raised, and a high lactate dehydrogenase level is observed in approximately 50% of patients (Patel and Gallagher, 2010). The acute phase reactants, however, are usually disproportionately low relative to the degree of fever compared to that seen with bacterial infection, and such discordance should prompt consideration of the diagnosis of drug fever. The inflammatory marker pro-calcitonin has been investigated as a means of differentiating infectious from non-infectious causes of pyrexia, but data supporting this are insufficiently robust (de Bont et al, 2000; Massaro et al, 2007).

The most appropriate course of action when drug fever is considered probable is to discontinue the offending agent and institute an alternative if required. In the rare circumstances where this is not possible, general antipyretic measures are appropriate, with close vigilance to ensure that any new intervening cause of fever such as worsening infection is not masked. Where the diagnosis is questionable and persistent infection still possible, the septic screen should be repeated and serial blood cultures performed, both before and after discontinuing antibiotics.

Drug reaction with eosinophilia and systemic symptoms (DRESS)

DRESS syndrome is a rare but severe hypersensitivity reaction (Kardaun et al, 2007; Ben M'Rad et al, 2009), the cardinal features of which are shown in *Figure 4*. It is one of the three main systemic cutaneous adverse reactions associated with mortality, the others being Stevens–Johnson syndrome or toxic epidermal necrolysis, and acute generalized exanthematous pustulosis. The incidence is approximately 1 per 10 000 drug exposures, and is higher in patients with underlying immunocompromise (Coopman et al, 1993); possible explanations for this include slow acetylator phenotypes, impaired detoxification mechanisms or reactivation of human herpesvirus-6 (Descamps et al, 2001; Tamagawa-Mineoka et al, 2007; Walsh and Creamer, 2010).

DRESS is most frequently of late onset, occurring 3–8 weeks following drug exposure but onset can range from 3–76 days (Chen et al, 2010). This potentially very

Figure 3. Features suggestive of a diagnosis of drug fever. None are diagnostic.

Clues to drug fever
- Typically early onset (7–10 days)
- Unremitting pyrexia
- Multiple negative blood cultures
- Patient appears 'inappropriately well'
- Relative bradycardia for degree of pyrexia
- C-reactive protein level disproportionately low
- Remits on drug withdrawal

Figure 4. Diagnostic features of drug reaction with eosinophilia and system symptoms (DRESS) syndrome. Note that the absence of any component does not exclude the diagnosis. Adapted from Kardaun et al (2008).

Drug reaction with eosinophilia and system symptoms (DRESS) syndrome
- Typically late onset (3–8 weeks)
- Fever
- Acute skin eruption
- Eosinophilia
- Lymphadenopathy at two or more sites
- Visceral involvement

delayed reaction may make the clinician overlook the diagnosis of DRESS, as the 'culprit' drug may have been administered and apparently tolerated for some time. Antibiotics are the most common culprits; vancomycin is particularly implicated but it has also been reported following ceftriaxone, rifampin, ciprofloxacin and linezolid (Roujeau and Stern, 1994; Peyriere et al, 2006; Savard et al, 2009; Jeung et al, 2010). Allopurinol, anticonvulsants (especially phenytoin) and antiretrovirals are also established causative agents for DRESS.

No features have been identified that predict susceptibility or severity of the reaction. Unlike drug fever, which follows a relatively benign course, DRESS can be life-threatening with the potential to flare and deteriorate rapidly.

Fever is present in approximately 90% of patients and lymphadenopathy in one third; this may be local or generalized, and no particular distribution is diagnostic. Although a dermatosis is usual (present in at least 70%), its extent varies and the syndrome is not defined or restricted by its morphology. That said, in most cases the rash is a diffuse urticarial or morbilliform eruption, followed in some by desquamation or blister formation. Dermatological review will usually be appropriate, and skin biopsy shows lymphocytic or eosinophilic perivascular inflammation, dyskeratosis and basal vacuolization. There is commonly a prodrome of generalized pruritus and facial oedema, and peri-orbital swelling is highly suggestive (Jeung et al, 2010). Half have mucosal involvement, typically limited to mild erythema of the conjunctivae or oropharynx, although mucosal erosions rarely can develop. Mucosal and cutaneous erosions may mimic Stevens–Johnson syndrome (Ben M'Rad et al, 2009), which can usually be distinguished by the characteristic target-like plaques in addition to the signs of widespread cutaneous and mucosal necrosis, including dusky colour, bullae, erosions and a positive Nikolsky sign (Wolf et al, 2005). Of note, the systemic findings of DRESS, with all the related morbidity and mortality, can rarely occur in a patient with the eruption of Stevens–Johnson syndrome (Teraki et al, 2010).

Haematological abnormalities include lymphocytosis (25% of patients), lymphopaenia (45%), lymphocyte atypia (60%), eosinophilia (50%) and thrombocytopaenia (25%) (Jeung et al, 2010). The C-reactive protein level and erythrocyte sedimentation rate are typically elevated, but as with drug fever neither these nor serum pro-calcitonin are reliable indicators in differentiating from infection (Bonaci-Nikolic et al, 2009). Deranged liver function tests are common and renal failure may develop. Visceral involvement can include hepatitis (50%), interstitial nephritis (20%), pneumonitis (20%) and myocarditis (20%); thyroiditis, colitis, and acalculous cholecystitis or cholangitis occur rarely (Ben M'Rad et al, 2009).

Most patients respond to discontinuation of the causative agent alongside oral corticosteroids (prednisolone 0.5–1 mg/kg/day), although severe cases require intravenous methylprednisolone (Tas and Simonart, 2003). Mortality can be as high as 10%, resulting from fulminant hepatic or renal failure, pneumonitis, or myocarditis causing cardiogenic shock or fatal dysrhythmias (Tas and Simonart, 2003; Mennicke et al, 2009; Chen et al, 2010). Poor outcome tends to be associated with late recognition of the syndrome and therefore, although rare, this mandates early consideration of the diagnosis with prompt investigation and institution of appropriate management if confirmed.

Conclusions

Drug fever and DRESS syndrome are challenging clinical entities to recognize and treat with confidence. Misdiagnosis carries substantial risks, particularly in patients in whom an immunosuppressive strategy is contemplated. A cautious approach is advocated, with an extensive search for infection before the diagnosis is made, and careful monitoring afterwards. Formal reporting of cases will increase awareness and allow more accurate calculations of incidence to be determined. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Suspect drug fever in patients with persistent pyrexia who are otherwise well.
- Repeat a thorough septic screen before stopping antibiotics.
- Regularly review the need for ongoing medication; discontinue if possible.
- Monitor patients closely with repeated inflammatory markers and blood cultures if antibiotics are withdrawn.
- Drug reaction with eosinophilia and system symptoms (DRESS) syndrome may occur weeks after exposure. It can be severe and life-threatening and therefore requires prompt action if suspected.

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