

may sometimes happen in previously sensitized patients and take the form of urticaria, but laryngeal edema may also ensue (Idsøe *et al.*, 1972). Accelerated reactions may also result in anaphylaxis and may be fatal. These reactions are also mediated by IgE antibodies (Lin, 1992). The treatment of anaphylaxis was recently reviewed by the Lieberman *et al.* (2015) on behalf of the American Academy of Allergy, Asthma and Immunology (AAAAI) and should be referred to for the management of serious immediate hypersensitivity. In general, treatment of anaphylaxis should include immediate i.m. administration of 500–1000 µg (0.5–1.0 ml of a 1:1000 solution) of adrenaline (epinephrine), which is repeated every 5 minutes until improvement occurs (Leading Article, 1981; Sullivan, 1982; Australasian Society of Clinical Immunology and Allergy, 2016; Lieberman *et al.*, 2015). Intramuscular injection is preferred because absorption of adrenaline from subcutaneous injection is too slow. Penicillinase has no place in the emergency treatment of anaphylactic reactions. It rapidly breaks down circulating Pen G, but probably has no effect on preformed antigen–antibody complexes; also penicillinase itself may provoke sensitivity reactions (Idsøe *et al.*, 1968).

CYTOTOXIC AND IMMUNE COMPLEX-MEDIATED REACTIONS

Cytotoxic reactions are defined as Type BII- and BIII-mediated reactions (Pichler, 2007), which can occur in approximately 2% of patients treated with Pen G (Polk, 1982). While these were previously thought to appear 7–10 days after primary administration of Pen G, they can in fact be accelerated and occur on rare occasions within 5–72 hours of administration (Pichler, 2007). In the case of serum sickness, circulating immune complexes are produced after exposure to Pen G, the formation of which is possible because intravascular antigen is still present when antibody is first produced (Parker, 1975). Serum sickness is characterized by fever, malaise, urticaria, joint pains, lymphadenopathy, and occasionally angioneurotic edema. Erythema nodosum is a less common manifestation. Drug fever may be the sole manifestation of Pen G-induced serum sickness (Young *et al.*, 1982a). However, some authors consider that the mechanisms by which drugs induce fever have not been well delineated and that this reaction may not have an allergic basis (Mackowiak and Le Maistre, 1987). Serum sickness is usually not serious, and it subsides when Pen G is withdrawn. Antihistamines are helpful, but in severe cases corticosteroids are necessary.

Cytotoxic reactions can occur from 5 hours to more than 72 hours postexposure and are typically associated with hemolytic anaemia and thrombocytopenia (Pichler, 2007). While no formal testing platform exists for this, drug-specific antiplatelet antibodies can be looked for. The mechanism is believed to be hapten-induced antibody production for both Pen G and Pen V (Arnold *et al.*, 2013). Penicillin can form a covalent bond with proteins on the surface of red blood cells and platelets, resulting in immune hemolytic anaemia and, less commonly, thrombocytopenia (Garratty, 1993; Salamon *et al.*, 1984).

T-CELL-MEDIATED REACTIONS

T-cell-mediated reactions against Pen G and Pen V are classified as Type BIV. These have been further subdivided based on the predominant cellular mechanism, which has been discussed previously (Pichler, 2007). Penicillin has been implicated in T-cell-mediated contact dermatitis, fixed-drug eruptions (FDE), maculopapular exanthems (MPE), drug-induced liver injury (DILI), acute interstitial nephritis (AIN), and severe cutaneous adverse reactions (SCAR). SCAR syndromes include drug reaction with eosinophilia and systemic symptoms (DRESS), acute generalized exanthematous pustulosis (AGEP), Stevens–Johnson Syndrome (SJS), and toxic epidermal necrolysis (TEN). Recent studies indicate that antibiotics are implicated in 50% of SCAR and other T-cell-mediated cutaneous adverse drug reactions, with penicillin commonly being blamed (Forman *et al.*, 2002; Lin *et al.*, 2014; Su and Aw, 2014; Trubiano *et al.*, 2016a). While penicillin MPE is also frequently reported in children, very few cases prove to be reproducible on oral penicillin challenge (Caubet *et al.*, 2015; Vezir *et al.*, 2016), and likely reflect direct viral infections or virus–drug interactions. Contact reactions can result from topical Pen G application or exposure to Pen G aerosol; it is an occupational disease of nurses and other healthcare workers. Reports of penicillin-related T-cell-mediated reactions are likely to become less frequent as broader-spectrum penicillins, aminopenicillins, and other beta-lactams, are employed more commonly.

LOCAL REACTIONS

Swelling and redness at the site of Pen G injections may occur. A careful clinical history still remains the main indicator of possible reactors to Pen G. Idsøe *et al.* (1968) analyzed 151 deaths due to Pen G reported from 1951 to 1965; 38 subjects had a history of previous reaction, and in 74 others the previous drug history was not recorded. Some authors have previously considered that patients with a history of asthma, hay fever, and other allergies are more likely to react to Pen G (Smith, 1974), but subsequently no correlation has been noted between these issues and with a family or personal history of other allergies (Horowitz, 1975). In any case, a theoretical increased risk of Pen G reactions in patients with other allergies appears outdated, and the drug may be given to them whenever it is indicated.

TESTING FOR IMMUNE-MEDIATED PENICILLIN ALLERGY

Previously, routine testing for sensitive individuals before Pen G administration was not practicable. However, with the increasing emergence of multiresistant pathogens and relatively few new antibiotics being developed, the option of formal testing for allergy to beta-lactams (and other agents)—so-called allergy de-labeling—is gaining favor, especially in high-risk patients (Trubiano and Phillips, 2013; Trubiano *et al.*, 2015; Trubiano *et al.*, 2016b). Former suggestions that skin tests using Pen G as an antigen were inadvisable (even in small