
Abstract

Four types of hypersensitivities may be distinguished. Type I, or immediate hypersensitivity, occurs within about 30 min, is IgE antibody-mediated, and the allergic signs and symptoms are triggered by cross-linking of mast cell-bound IgE which leads to mast cell degranulation and release of inflammatory mediators. Drugs well known to cause type I reactions include β -lactams, neuromuscular blockers, and some NSAIDs. Anaphylactoid reactions may mimic the signs and symptoms of anaphylaxis but, unlike the latter reactions, anaphylactoid reactions are not immune-mediated. Clinical manifestations of anaphylaxis include erythema, urticaria, angioedema, bronchospasm, and cardiovascular collapse. Urticaria is often associated with angioedema and anaphylaxis. ACE inhibitors are responsible for one in six hospital admissions for angioedema. Types II and III hypersensitivities are known as antibody-dependent cytotoxic and immune complex-mediated hypersensitivities, respectively. Examples of drug-induced type II reactions are hemolytic anemia, thrombocytopenia, and granulocytopenia. A serum sickness-like reaction is the prototype type III drug hypersensitivity. Type IV drug hypersensitivities are mediated by antigen-specific T cells. Reactions occur 48–72 h after antigen exposure and are therefore referred to as delayed. Examples of delayed cutaneous reactions include allergic contact dermatitis, psoriasis, FDE, AGEP, DRESS, SJS, and TEN.

2.1 Hypersensitivity: The Early Years—From Koch to Gell and Coombs

The phenomena that constitute the basis of hypersensitivity reactions were discovered, and studies initiated, in the approximately 20-year period between Robert Koch's demonstration of a delayed hypersensitivity reaction to the tubercle bacillus in 1882 and the demonstrations of anaphylactic, Arthus, and serum sickness reactions in the first decade of the twentieth century. Having discovered the tubercle bacillus, Koch showed that the delayed inflammatory response to an intradermal injection of the organism could indicate previous exposure to *Mycobacterium tuberculosis* in an asymptomatic person. This response became known as the tuberculin reaction and, as the Mantoux test, is recognized today as the classical and best known example of a delayed hypersensitivity reaction. Continuing studies initiated with P. Portier in 1902, Charles Richet by 1907 had shown that numerous proteins in small doses could provoke not "phylaxis" or protection, but "anti-protection" or what he termed "anaphylaxis," and this state could be passively transferred to a normal animal by serum. In the first demonstration of the reaction which came to bear his name, N.M. Arthus in 1903 produced erythematous and edematous reactions in rabbits after repeated injections of horse serum, and in 1906, von Pirquet and Béla Schick demonstrated the immune complex-mediated serum sickness reaction (see Sects. 2.2.3 and 3.8) so named because it sometimes occurred following the administration of antisera prepared in horses (e.g., anti-pneumococcal antisera). Despite Landsteiner's initial conviction that cell-bound antibody was the cause of contact sensitivity, Chase's experiments in 1941–1942 transferring "sticky," unclarified peritoneal exudate from guinea pigs sensitized by hapten–stromata conjugate with Freund's complete adjuvant led to the discovery that viable cells from the peritoneum, lymph nodes, and spleen-mediated contact sensitivity and tuberculin reactivity. It was then a further 21 years before Gell and Coombs produced

their classification of hypersensitivity reactions based on the immune mechanisms underlying the different reactions, that is, the latency of reactions, humoral or cellular involvement, complement involvement, and pathophysiological consequences for the host.

2.2 Classification of Hypersensitivity Reactions

A number of arguments have been voiced over the years against the Gell and Coombs classification and published criticisms include its alleged too narrow focus on the deleterious consequences to the host, that some antigens such as drugs do not fit well into the categories, and that the classification scheme should be simplified to pseudo-allergic, antibody-mediated, and cell-mediated reactions. More recently, subdivisions have been suggested for type IV reactions. We believe that the existing classification has deficiencies but, with mechanism-based categories, it remains, overall, the simplest, most valid, and most logical way of distinguishing the host's immune sensitivities. Four types of hypersensitivity reactions, designated types I, II, III, and IV, are distinguished.

2.2.1 Type I Hypersensitivity

Type I hypersensitivity is also known as immediate, or sometimes anaphylactic, hypersensitivity. Responses usually occur within 30–60 min but can be extremely quick (within minutes) and dramatic as in anaphylaxis. In some cases a late onset reaction may occur about 3 or 4 h after allergen exposure and the immediate reaction. This late phase reaction generally peaks at about 6–12 h and subsides at about 24 h (see Sect. 3.3). Immediate reactions can affect a single organ such as the skin (urticaria, eczema), eyes (conjunctivitis), nasopharynx (allergic rhinitis), mucosa of mouth/throat/tongue (angioedema), bronchopulmonary tissue (asthma), and gastrointestinal tract (gastroenteritis) or multiple organs (anaphylaxis), causing symptoms ranging from minor itching and inflammation to death.

Immediate hypersensitivity is mediated by IgE antibodies interacting with mast cells and basophils (Sect. 3.2) and with eosinophils, platelets, and neutrophils amplifying the response. IgE antibodies bind to their complementary FcεRI receptors on mast cells via their Cε3 region leaving both antibody combining sites free to interact with the complementary allergenic determinants. This interaction causes cross-linking of the cell-bound antibodies leading to degranulation of the anchoring mast cells and release of the variety of preformed, and then newly formed, mediators of inflammation and hypersensitivity.

Drugs well known for causing type I allergic reactions include penicillins, cephalosporins, quinolones, chlorhexidine, neuromuscular blocking drugs, some nonsteroidal anti-inflammatory drugs (NSAIDs) such as pyrazolones, trimethoprim, sulfamethoxazole, proton pump inhibitors, heparin, insulin, *L*-asparaginase, etanercept, and chimeric human–animal monoclonal antibodies used for therapy, but it is uncommon to find a drug at least moderately used that has not provoked an anaphylactic reaction in at least one rare individual.

2.2.1.1 Anaphylaxis to Drugs

It seems that every new drug administered to humans has the potential to provoke an anaphylactic response, and the likelihood of such a response therefore increases with increased administration. Unfortunately, while the signs and symptoms of what is commonly termed “anaphylactic shock” seem clear enough, incidences of anaphylaxis in different countries and to different drugs, as well as the terminology used for reactions is often far from consistent.

2.2.1.1.1 Terminology

For many years, two terms, “anaphylaxis” and “anaphylactoid,” have been used to describe relatively rare reactions that have features commonly associated with severe immediate, often life-threatening, allergic reactions. These two terms are distinguished by the underlying mechanisms of the reactions. The term anaphylaxis is used by many for an immune IgE antibody-mediated, systemic immediate type I hypersensitivity reaction, often occurring within seconds or minutes,

involving the release of potent allergic and inflammatory mediators from mast cells and basophils and producing at least some of the signs and symptoms of severe immediate reactions such as cardiovascular symptoms (tachycardia, hypotension, cardiovascular collapse), respiratory involvement (dyspnea, bronchospasm, wheeze), gastrointestinal symptoms (nausea, vomiting, abdominal pain), and cutaneous manifestations (urticaria, angioedema, erythema, pruritus). With the knowledge that some agents induce anaphylaxis via an IgG antibody-mediated mechanism, for example, as occurs in some responses to dextrans (and an IgG-mediated pathway to anaphylaxis is known in some laboratory animals such as mice), the wording “IgE antibody-mediated” in the definition above is more correctly replaced by, simply, “antibody-mediated.” The term anaphylactoid is used for reactions that may show clinically similar or even identical signs and symptoms but where no immune-mediated mechanism can be shown, for example, reactions caused by direct mast cell degranulation induced by drugs such as vancomycin, opioids, or contrast media.

In 1998 in the USA, a Joint Task Force on Practice Parameters for Allergy and Immunology defined anaphylaxis as an “immediate systemic reaction caused by rapid, IgE-mediated immune release of potent mediators from tissue mast cells and peripheral basophils.” Anaphylactoid reactions were seen as mechanistically different and said to “mimic signs and symptoms of anaphylaxis, but are caused by non-IgE-mediated release of potent mediators from mast cells and basophils.” By 2004 when the National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) cosponsored a symposium on the definition and management of anaphylaxis, the existing mechanistic definition of anaphylaxis was judged to be “of marginal utility” to the physician and other health care personnel when faced with “the variable constellation of signs and symptoms of this disorder.” In a second symposium in 2005 the NIAID and FAAN brought together allergists, immunologists, pediatricians, emergency and intensive care physicians, internists, and pathologists

together with representatives from the professional bodies in Canada, Europe, and Australia to (among other aims) work toward a universally accepted definition of anaphylaxis and establish clinical criteria to accurately identify cases of anaphylaxis. The definition of anaphylaxis that emerged from this gathering was: "Anaphylaxis is a severe, potentially fatal, systemic allergic reaction that occurs suddenly after contact with an allergy-causing substance." For a definition that would be useful to both the medical and lay communities, anaphylaxis was defined as "a serious allergic reaction that is rapid in onset and may cause death." For the researcher, and those practicing clinical medicine but perhaps not for the layman, it is hard to see how these definitions are an improvement or more useful than the former ones.

As mentioned in Chap. 1, in 2003, the Nomenclature Review Committee of the World Allergy Organization (WAO) defined anaphylaxis (which they referred to as an "umbrella term") as "a severe, life-threatening generalized or systemic hypersensitivity reaction." It was further stated that "the term *allergic anaphylaxis* should be used when the reaction is mediated by an immunological mechanism, e.g., IgE, IgG, and immune complex complement related" and, "an anaphylactic reaction mediated by IgE antibodies, such as peanut-induced food anaphylaxis, may be referred to as *IgE-mediated allergic anaphylaxis*." Lastly, "anaphylaxis from whatever nonimmunologic cause should be referred to as *nonallergic anaphylaxis*." As with the WAO suggested changes to the definition of hypersensitivity and introduction of the term "non-allergic hypersensitivity," (see Chap. 1, Sect. 1.1.2), the proposed definition of anaphylaxis is not only unnecessary but inadequate and the distinction of anaphylaxis into "IgE-mediated allergic" and "nonallergic" is needlessly complicating, cumbersome, and redundant. To move away from a mechanistic definition in defining anaphylaxis for professionally trained workers in medicine and science in an age when scientific progress is influencing clinical medicine to an unprecedented extent, seems to be a step backward. There seems to be much to gain by encouraging physicians to

think more mechanistically of their art. If anaphylaxis is defined in terms of being a systemic, rapidly proceeding, immune-based immediate reaction involving potent mediators released from mast cells and basophils and producing a range of clearly defined profound clinical effects, the addition of descriptors such as "allergic," "IgE-mediated allergic," and "nonallergic" to the word anaphylaxis becomes completely unnecessary. Anaphylaxis has, over many years, come to be known as an allergic reaction mediated by IgE. Hence, the terms "allergic anaphylaxis," "IgE-mediated allergic anaphylaxis" and "nonallergic anaphylaxis" each have added words that are redundant or are a contradiction in terms. It then follows that "anaphylactoid" is a suitable and convenient term to cover those immediate systemic reactions that mimic anaphylaxis but are not immune-mediated and, with the stipulations and distinctions outlined above in mind, reactions will be referred to either as anaphylactic or anaphylactoid throughout this book.

2.2.1.1.2 Incidence of Anaphylaxis

The incidence of all causes of anaphylaxis in Western countries is estimated to be from about 8 to 50 per 100,000 persons per year with 3–4 % hospitalized and a lifetime prevalence of 0.05–2 %. In one retrospective Danish study of anaphylaxis over a 13-year period outside hospital in a catchment area of 48,000 subjects, an incidence of 3.2 cases per 100,000 persons per year was found. Of the 20 cases of anaphylaxis identified, seven were provoked by oral penicillin and three by oral aspirin, indicating that anaphylaxis to penicillin in the non-hospital environment was more common than thought. A retrospective population-based cohort study of 1,255 US residents in one county over a 5-year period revealed an incidence of anaphylaxis of 30 per 100,000 persons per year with an average annual incidence rate of 21 per 100,000 person-years. Drugs, along with foods and insect stings, were the main causes. In a prospective study of 432 Australian patients, medication was the cause in 8.3 % of cases. Minimum occurrence and incidence of new cases were estimated to be 12.6 and 9.9 episodes per 100,000 patient-years,

respectively. An analysis of anaphylaxis admissions to UK critical care units between 2005 and 2009 revealed 1,269 adult and 81 pediatric admissions representing 0.3 % of admissions to adult units and 0.1 % of admissions to pediatric units. The data showed that hospital admission rates for anaphylaxis have increased sevenfold in the last two decades and the absolute numbers of both adults and children rose year-on-year. The authors remarked that drug-triggered reactions are more common in older people and concluded that each UK critical care unit is likely to see at least one anaphylaxis case per year.

A large proportion of anaphylactic reactions is due to drugs. In hospitalized patients the prevalence is said to be 3 in 10,000 with deaths occurring in 3–9 % of patients. The overall incidence and the mortality of anaphylaxis induced by drugs are not known but figures are available for some individual drugs or groups of drugs in some localities. Most data over the years for incidences of anaphylaxis to a single drug (or group of drugs) have been for penicillins with published estimates of approximately one reaction for every 10,000 prescriptions and 15–40 reactions per 100,000 persons. During the 1960s and 1970s penicillins were often claimed to be the most common cause of drug-induced anaphylaxis in the US and that may still be the case today. Reactions to contrast media and blood-volume replacement fluids have been reported in one of every 600 and 400 persons, respectively, receiving the drugs. More detail of incidences of anaphylaxis to other drugs are to be found in the chapters on the different drug groups. In a population-based case-cohort study in The Netherlands, a drug was found to be the causative agent in 107 of 252 cases of suspected anaphylaxis classified as “causal relationship certain” or “causal relationship probable.” Of the 107 cases, 19 % were caused by the NSAID glafenine, 11 % by amoxicillin, 7 % for each of diclofenac and acetaminophen and 6 % for propyphenazone. In fact, at least 42.6 % of the 107 cases of possible/probable cases of anaphylaxis were due to a NSAID (27 miscellaneous drugs each causing one reaction were not named). Perhaps the most reliable data available on incidences of drug-

induced anaphylaxis are the figures for drugs used perioperatively. Published incidences of anaphylactic and anaphylactoid reactions include 1 in 5,000–13,000 for Australia, 1 in 1,250–5,000 for New Zealand, 1 in 3,500 for England, 1 in 5,000 in Thailand, and 1 in 4,600 in France. By far the biggest contributor to anaphylaxis alone (that is, with anaphylactoid reactions not involved) during anesthesia is the group of neuromuscular blocking drugs. Reported incidences to these drugs are 1 in 10,000–20,000 Australia, 1 in 5,500 France, 1 in 5,200 Norway, 1 in 10,263 Spain, 1 in 5,500 Thailand and approximately 500 cases per year in the UK. Of the drugs implicated in anaphylaxis, the most complete and reliable data on incidences of reactions are those obtained from studies of perioperative anaphylaxis in Australia and France. A breakdown of the main drugs responsible for anaphylaxis during anesthesia in Australia and France shows the following incidences of reactions (as percentages, Australian figures first): neuromuscular blockers 61.9, 58.1; induction agents 10.4, 2.3; antibiotics 8.6, 12.9; colloids 4.6, 3.4; opioids 2.6, 1.7 (see also Table 7.1).

2.2.1.1.3 Clinical Features of Drug-Induced Anaphylactic Reactions

In the Dutch study discussed above in which 43 different drugs were implicated in causing at least one anaphylactic reaction, the main symptoms seen in the patients admitted to hospitals were (in decreasing order of occurrence) erythema, angioedema, hypotension, bronchospasm, pruritus, urticaria, nausea/vomiting, tachycardia, loss of consciousness, diarrhea, upper airways symptoms, conjunctivitis, laryngeal edema, abdominal pain, and bradycardia. Erythema was seen in 57 % of patients, angioedema in 51 %, hypotension in 36 %, bronchospasm and pruritus in 35 %, urticaria in 31 %, tachycardia in 19 %, and bradycardia in 4 %. For drug-induced anaphylactic and anaphylactoid reactions, however, it is the perioperative data accumulated over many years by Fisher and Baldo in Australia and by the Laxenaire and Mertes groups in France (see Fig. 7.2) that is the most informative. As emphasized by the former workers, the list of

Table 2.1 Clinical features in 315 patients with life-threatening anaphylaxis to anesthetic drugs

Clinical features	Total		Worst feature		Sole feature	
	Number	%	Number	%	Number	%
Cardiovascular collapse	283	89.8	251	79.7	33	10.5
Bronchospasm						
Severe	52	16.5	52	16.5	10	3.2
Transient	50	15.9				
Angioedema	73	23.2	4	1.3	4	1.3
Urticaria	43	13.7				
Rash	42	13.3				
Erythema	151	47.9				
Gastrointestinal symptoms	30	9.5				
Pulmonary edema	11	3.5	3	1.0	1	0.3
Generalized edema	15	4.8				

Other major common features: vomiting, diarrhea, laryngeal edema

Uncommon major features: cardiac failure, disseminated intravascular coagulation, hemoptysis, melena

Minor features: rash, flush, rhinitis, cough, lacrimation, urticaria, pruritus, aura, conjunctivitis

Late features: headache, thromboembolism, edema, wound hematoma, vaginal discharge

Data adapted from Fisher M, Baldo BA. *Eur J Anaesthesiol* 1994;11:263 and *Med J Aust* 1988;149:43

complete signs and symptoms (Table 2.1) does not appear in every patient; cardiovascular collapse is the most common symptom and usually the worst; in addition to cardiovascular collapse there is usually at least one other sign; asthmatic patients who experience anaphylaxis usually get bronchospasm; and a transient bronchospasm or difficulty in inflating the lungs is often seen as the first sign of a reaction. Note that when the problem of lung inflation persists, it is often the most difficult feature to reverse. Cardiovascular collapse, the most common life-threatening feature, is due to vasodilation and the pooling of peripheral blood which reduces the venous return and the cardiac output. Whether the heart is a target organ in anaphylaxis in humans as it is in some other animals is still not clear. Cardiac failure occurs in anaphylactic patients with cardiac disease but rarely in patients with normal cardiac function. Table 2.1 indicates that when bronchospasm is severe, it is usually the worst feature and the sole feature in about 20 % of the cases. Bronchospasm may be critical since the high pressures needed for inflation reduce venous return and may increase ventricular compliance. Angioedema, which involves the head, neck, and upper airways, usually progresses slowly and it is therefore prudent to observe the patient for at

least 12 h. Gastrointestinal symptoms include severe abdominal pain, vomiting, diarrhea, hematemesis, and melena and last up to 6 h. Non-cardiogenic pulmonary edema, which occasionally occurs as a single clinical feature of anaphylaxis and is a common postmortem finding in resultant deaths, has been reported as a sole delayed reaction to protamine after cardiac bypass surgery.

2.2.1.1.4 Clinical Grading System for Anaphylaxis

Definitions of anaphylaxis vary, sometimes making it difficult to interpret and compare clinical findings. Classification of anaphylactic reactions on the bases of clinical features observed and their severity is obviously needed, but there has been no uniformity or agreement on the relevance and importance of the parameters to be included in any grading system. Some grading systems are simple descriptions of common and/or important symptoms while others are based on statistical analyses of individual reaction features, sums of allotted scores, the appearance of “two or more” clinical features, or cardiovascular compromise. From case records of over 1,100 acute generalized hypersensitivity reactions, logistic regression analyses of associations between reaction features and hypotension and hypoxia were used to con-

Table 2.2 Grading system for hypersensitivity reactions including anaphylaxis

Grade	Broad clinical features	Defining symptoms and signs
1 MILD	Cutaneous and subcutaneous only	Generalized erythema, periorbital edema, urticaria, or angioedema
2 MODERATE	Cardiovascular, respiratory, or gastrointestinal involvement	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness, diaphoresis, chest or throat tightness, or abdominal pain
3 SEVERE	Hypoxia, hypotension, or neurologic compromise	Cyanosis or $\text{SpO}_2 \leq 92\%$ at any stage, hypotension (systolic BP < 90 mmHg in adults), confusion, collapse, loss of consciousness, or incontinence

Adapted from Brown SGA. Clinical features and severity grading of anaphylaxis. *J Allergy Clin Immunol* 2004;114:317 with kind permission from Elsevier Limited

struct a grading system suitable for defining reaction severity in clinical and research settings. Three grades that correlated with epinephrine usage, mild, moderate, and severe (Table 2.2), were discerned from the clinical features of confusion, collapse, unconsciousness, incontinence, diaphoresis, vomiting, presyncope, dyspnea, stridor, wheeze, and nausea, all of which were associated with documented hypotension and hypoxia. The clinical features in the moderate and severe grades fit in with a definition of anaphylaxis. A major difference between this and other grading systems is the identified importance of gastrointestinal symptoms. A possible limitation of this study and its conclusions is that clinical assessments were undertaken by emergency medicine clinicians rather than allergists, so confirmatory skin and IgE antibody tests are lacking.

2.2.1.2 Urticaria and Angioedema

Urticaria or hives, the second most common cutaneous reaction induced by drugs after exanthematous reactions, occurs often in association with angioedema, in cases of anaphylaxis and in serum sickness. Virtually any drug can cause urticaria. Hives are generally raised, circumscribed, erythematous papules and plaques (Fig. 2.1) with a central area of pallor, often round in shape and of variable size. Erythematous areas may be smooth surfaced, patchy, or confluent and generalized (Fig. 2.2). Outbreaks that may occur anywhere on the skin are extremely pruritic and transient, usually appearing within 36 h of drug exposure and resolving without sequelae within 24 h. On rechallenge with drug, lesions may appear within minutes. Lesions that persist lon-



Fig. 2.1 A case of severe generalized chronic urticaria and nonlife-threatening angioedema unresponsive to antihistamines. From Fox R, Lieberman P, Blaiss M. Centralized urticarial and angioedema and angioedema of the face. *Atlas of allergic diseases*; 2002;IS:08. With kind permission from Springer Science+Business Media B.V

ger than 24 h and which are painful, burning, or leave bruising and/or pigmentation changes may indicate urticarial vasculitis. Acute urticaria that is more common in children, may appear early after exposure (perhaps minutes) and can last several weeks; chronic urticaria, more common in adults, occurs in episodes that last longer than 6 weeks. Drugs are only infrequently implicated in cases of chronic urticaria and, in fact, no external agent or disease state has been implicated in 80–90 % of patients with chronic urticaria. The incidence of chronic urticaria is said to be as high as 1 % in the USA and several other countries, but the figure is likely to be closer to about 0.1–0.3 %. The mechanisms involved in the



Fig. 2.2 An example of generalized urticaria (hives) showing smooth, erythematous, and pruritic confluent papules and plaques. Aspirin and other nonsteroidal anti-inflammatory drugs are a frequent cause of hives but virtually any drug can precipitate the condition. From Anderson J, Lieberman P, Blaiss M. Allergic drug reactions. Atlas of allergic diseases; 2002;IS:26. With kind permission from Springer Science+Business Media B.V

spectrum of urticarial reactions are reviewed in Sect. 3.2.8. Drugs implicated in reactions include those that provoke type I IgE-mediated reactions (e.g., β -lactams, other antibiotics, antimicrobials such as sulfonamides and trimethoprim, neuromuscular blockers, pyrazolones); direct mast cell degranulation (e.g., opioids, contrast media, vancomycin, quinine, pentamidine, atropine); drugs that promote or exacerbate urticaria due to their pharmacological effects on metabolic pathways (angiotensin-converting enzyme [ACE] inhibitors, e.g., captopril, enalapril, lisinopril; NSAIDs, e.g., aspirin, indomethacin, ibuprofen); drugs involved in type III immune complex formation as in serum sickness (e.g., amoxicillin, cefaclor, ciprofloxacin, monoclonal antibodies); excipients, preservatives, coloring agents, antioxidants (e.g., benzoic acid, sulfites, tartrazine, butylated hydroxytoluene). Note that evidence for adverse effects, including the induction of urticaria, is often lacking for implicated agents in the latter group.

Angioedema (Quincke's edema), which is seen less often than urticaria but often accompanies it, is a vascular reaction resulting in swelling of the face (Fig. 2.3) around the mouth, in the mucosa of the mouth, throat and tongue, eyelids, genitalia, and occasionally involving the hands and elsewhere (Fig. 2.1). Swelling, which can be itchy and painful, is the result of increased permeability and



Fig. 2.3 Angioedema of the face showing non-pruritic swelling of the cutaneous tissues with some erythema. Angioedema persists longer than urticaria due to the accumulated fluid in the tissues. From Fox R, Lieberman P, Blaiss M. Centralized urticarial and angioedema and angioedema of the face. Atlas of allergic diseases; 2002;IS:08. With kind permission from Springer Science+Business Media B.V

leakage of fluid which produces edema of the submucosal tissues, deep dermis, and subcutaneous tissues. As a result of compression of nerves, patients may experience decreased sensation in the affected areas. In severe reactions involving the airways, stridor, gasping, and wheezing may indicate the need for tracheal intubation. As with urticaria, angioedema is often an IgE antibody-mediated reaction to a drug and one of its main causes is the ACE inhibitor group of drugs which induce reactions with an incidence of 0.1–0.5 %. For black Americans and Afro-Caribbeans this incidence is three times higher. ACE inhibitors are the responsible agents for approximately one in six patients admitted to hospital for treatment of angioedema. It is thought the drugs increase bradykinin levels in peripheral tissues, and this leads to the rapid fluid accumulation

seen in angioedema (Sect. 3.2.8.5.2). Angioedema to ACE inhibitors usually occurs within the first week of treatment and the drug should be withdrawn immediately in the patients who experience a reaction. Aspirin and other NSAIDs are other common causes of angioedema generally involving the face. Responses to the NSAIDs may be complex with mixed cutaneous and respiratory symptoms (Sect. 9.5.2).

Unlike the other types of hypersensitivity caused by antibodies, namely types II and III, only a proportion of the population, the so-called atopics, have a predisposition to developing a type I hypersensitivity reaction when exposed to the allergen in question. Atopy may have a genetic component but type II and III reactions like, for example, penicillin-induced hemolytic anemia and serum sickness, may occur in all individuals, and this may result without a prior sensitization phase.

2.2.2 Type II Hypersensitivity

Type II hypersensitivity, also known as cytotoxic hypersensitivity and antibody-dependent cytotoxicity, causes reactions that are serious and potentially life-threatening. A number of different organs and tissues may be affected with the involvement of multiple underlying mechanisms. The antigens involved are often endogenous but drugs can attach to cell membranes provoking drug-induced immune hemolytic anemia, thrombocytopenia, and granulocytopenia, all examples of type II reactions. Reaction times can range from minutes to hours; IgM or IgG antibodies mediate the reactions and in antibody-dependent cellular cytotoxicity, target cells coated with antibody are killed by a non-phagocytic process involving Fc receptor-bound leukocytes (NK cells, monocytes, neutrophils, and eosinophils). Drug-induced hemolytic anemias with IgG antibodies and complement-mediated cytotoxicity (or an autoantibody) implicated may occur after treatment with penicillins, quinidine, α -methyl dopa, and some cephalosporins. In the penicillin-induced condition, an atypical anti-penicillin antibody (perhaps with drug-surface protein spec-

ificity) appears to be involved. Drug-induced thrombocytopenia with quinine, quinidine, propylthiouracil, gold salts, acetaminophen, vancomycin, and sulfonamides in immune complexes adsorbed onto platelet membranes is well documented. Other mechanisms are also operative in immune-mediated thrombocytopenia. Cytotoxic antibodies to pyrazolone drugs, thiouracil, sulfonamides, anticonvulsives, and phenothiazines may produce granulocytopenia by the destruction of peripheral neutrophils. For more detail, including mechanisms, of each of these reactions, the reader is referred to Chap. 3, Sect. 3.7.

2.2.3 Type III Hypersensitivity

Type III hypersensitivity, also called immune complex hypersensitivity, is mediated by soluble immune complexes of antigen with antibodies mostly of the IgG class but sometimes IgM. Deposition of immune complexes in tissues results in a tissue reaction initiated by complement activation that may lead to mast cell degranulation, leukocyte chemotaxis, and inflammation induced by the cell influx. After exposure, reactions may develop over a period of about 3–10 h against antigens that can be endogenous as in DNA/anti-DNA/complement deposits in the kidneys of patients with systemic lupus erythematosus or, more often, exogenous as in the Arthus reaction in rabbits to intradermal injection of soluble antigen or intrapulmonary Arthus-like reactions in humans to inhaled antigen associated with farmer's lung and extrinsic allergic alveolitis. Other exogenous antigens eliciting type III responses include those from organisms such as filarial worms, dengue virus, and microbial antigens abruptly released following chemotherapy in patients with high antibody levels. More importantly for our purposes are type III reactions with drug involvement where examples include erythema nodosum leprosum in the skin of leprosy patients treated with dapsone, the Jarisch–Herxheimer reaction in syphilitic patients treated with penicillins, and serum sickness-like reactions caused by a number of different drugs including penicillins, cephalosporins, sulfonamides, ciprofloxacin,

tetracycline, lincomycin, NSAIDs, carbamazepine, phenytoin, allopurinol, thiouracil, propanolol, griseofulvin, captopril, gold salts, barbiturates, and monoclonal antibodies.

For a description of the immunological events central to the mechanism of serum sickness, see Sect. 3.8. As well as the most common cause of classical serum sickness reactions, namely equine antiserum given as an antitoxin, other foreign proteins such as vaccines, anti-lymphocyte globulins, streptokinase, and hymenoptera venoms have also been implicated in reactions. Drugs can cause a reaction that is clinically similar to the protein-induced condition although nonprotein antigens generally do not induce the response. Symptoms typically show up 6–21 days after drug administration and are similar to those seen in the classical reaction. Lymphadenopathy is common and fever, one of the earliest signs of serum sickness, tends to persist throughout the illness. Note, however, that lymphadenopathy has not been reported in penicillin-induced serum sickness. Cutaneous symptoms occur in up to 95 % of patients with urticarial and morbilliform eruptions being the most common and erythema and petechiae sometimes appearing. Angioedema may be seen and arthritis or arthralgia and gastrointestinal symptoms of cramping, nausea, vomiting, or diarrhea occur in up to 67 % of patients. Joints (knee, ankle, shoulder, elbow, wrist, spine, jaw) may be severely affected; respiratory symptoms and splenomegaly occurs; and hepatomegaly, peripheral neuropathies, encephalomyelitis, and pericarditis have been reported. With few if any laboratory-detected changes to help with the diagnosis, serum sickness-like reactions, as with classic serum sickness, tend to be diagnosed clinically. Although the drug-induced reaction can be severe, most are mild and usually resolve spontaneously within a few days or weeks after discontinuing the drug. True incidences of the reaction to various drugs are not known although amoxicillin and amoxicillin–clavulanic acid were involved in 18 % of serum sickness-like reactions examined in a pediatric emergency department, and there are numerous reports implicating cefaclor in children. Serum sickness-like reactions

are said to make up 4 % of all adverse drug reactions to amoxicillin. Hypersensitivity vasculitis is another example of a type III hypersensitivity response that may be induced by drugs. Drugs most commonly implicated include β -lactams, cotrimoxazole, NSAIDs and some monoclonal antibodies (see Chap. 11, Fig. 11.1).

2.2.4 Delayed-Type (Type IV) Hypersensitivity

Unlike types I, II, and III hypersensitivities that proceed with the involvement of antibodies, type IV hypersensitivity reactions are cell-mediated, in particular, by antigen-specific effector T cells. The term “delayed” refers to the cellular response that generally becomes apparent 48–72 h after antigen exposure and distinguishes the response from type I or immediate reactions that often appear within minutes and peak in a matter of minutes or just a few hours. Type IV hypersensitivity is not represented by a single reaction. Rather, it is a number of related responses seen in a variety of reactions that may have beneficial or undesirable consequences for the host and which, at first sight, do not seem to have a lot in common except for their cellular immune base. Apart from the prototypic tuberculin test, these different reactions include cellular responses to intracellular pathogens such as mycobacteria, fungi, and parasites; graft rejection; graft versus host reactions; granulomatous inflammation as occurs in Crohn’s disease and sarcoidosis; tumor immunity; some autoimmune reactions; and in contact allergy and allergic contact dermatitis. Other infectious diseases in which type IV reactions play a part include leprosy, histoplasmosis, toxoplasmosis, blastomycosis, and leishmaniasis. A well-known example of allergic contact dermatitis is the reaction provoked by the lipid-soluble chemicals, mixed pentadecacatechols in urushiol oil present in plants of the *Rhus* genus, namely, poison ivy, poison oak, and poison sumac. After crossing the cell membrane, the catechol derivatives interact with intracellular proteins before binding with MHC (major histocompatibility

complex) class I molecules. These modified peptides are recognized by CD8+ T cells which respond with the secretion of cytokines such as IFN- γ and cell destruction.

In some classifications, type IV reactions are subdivided into three categories based on the time of onset, the clinical manifestations, and the cells involved. The main features of the different categories in one such classification include:

1. Tuberculin type reaction (seen as local induration): antigen presented intradermally; reaction time 48–72 h; cells involved, lymphocytes, monocytes, and macrophages
2. Contact type reaction (seen as eczema): cutaneous contact (e.g., with chemicals, poison ivy, nickel); reaction time 48–72 h; cells involved, lymphocytes, macrophages
3. Granulomatous type reaction (as in leprosy): antigen persists in the host; reaction time 21–28 days; cells involved, macrophages, epitheloid, and giant cells

Another subdivision of type IV hypersensitivity reactions has categories distinguished by the effector cells and mediators involved together with the resulting associated cutaneous reactions. Four subdivisions are defined: type IVa, mediated by monocytes with IFN- γ as dominant cytokine; type IVb, mediated by eosinophils with IL-5 and IL-4 involvement; type IVc, mediated by T cells with perforin and granzyme B as important effector molecules; and type IVd, mediated by neutrophils with IL-8 involvement. Representative skin reactions for the so-called types IVa, b, c, and d are, respectively, maculopapular rash, maculopapular rash with eosinophilia, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).

It should be remembered that for delayed, type IV cutaneous allergic drug reactions (and sometimes for type I reactions as well), the allergic response is generally heterogeneous with overlapping reactions and with the involvement of different effector cells including various T cells with separate functions. Naturally, this heterogeneity affects the clinical picture and adds to the difficulties of the clinician in coming to a confident diagnostic conclusion.

Table 2.3 presents a side-by-side summary of all four hypersensitivities according to the Gell and Coombs classification viewed from the perspective of the responses to drugs in humans.

Delayed cutaneous hypersensitivity reactions to drugs generally begin from about 7 to 21 days after contact with the drug. Subsequent reactions may appear only 1 or 2 days after reexposure. Identification and specificity of the drug is established from oral challenge studies, patch tests, and intradermal tests read after a delay of at least 48 h. Different T cell subsets with their individual profiles of cytokines and chemokines are associated with different skin hypersensitivity reactions although there is often overlapping cytokine involvement.

Summarized descriptions of the most important immune-mediated delayed cutaneous adverse drug reactions follow. Readers should refer to Sect. 3.6.3 for details of the mechanisms involved in these reactions.

2.2.4.1 Allergic Contact Dermatitis

Contact hypersensitivity may result from sensitization to chemicals such as chromates and picryl chloride in industrial settings; from chemicals such as *p*-phenylenediamine in hair dyes; nickel in jewelry, glasses, and devices (Fig. 2.4); urushiol in *Rhus* plants; and drugs such as neomycin (Sect. 6.1.5.1; Fig. 6.7) and bacitracin (Sect. 6.1.5.2) used in topical applications. Contact dermatitis is the most common occupational disease although it should be remembered that not all contact dermatitis has an immune basis; some irritants such as detergents, solvents, acids, and alkalis may provoke irritant contact dermatitis. Allergic contact dermatitis may appear at any age. The time between the initial exposure to the offending agent and the development of skin sensitivity may only be 2–3 days while the interval between exposure and the first symptoms may be as early as 12 h but is usually closer to 48 h. The reaction is generally confined to the contact site but generalized reactions may occur. When the face is involved, swelling of the eyelids is common. Other skin sites may become involved by the patient touching other areas of skin after touching the

Table 2.3 Hypersensitivities to drugs according to the Gell and Coombs classification^a

Type of hypersensitivity	I	II	III	IV
Other designations	Immediate; anaphylactic	Cytotoxic	Immune complex	Delayed; cell-mediated; T cell mediated
Time for reaction to reach maximum	Seconds to 30 min ^b	Hours (~1 day)	3–10 h	24–72 h
Immune reactant(s)	IgE antibody	IgG (and IgM) antibodies	IgG antibody (and/or IgM)	Th1, Th2 and/or Th17 cells Cytotoxic lymphocytes
Effector mechanism	Mast cell and basophil activation	Complement fixation Phagocytes, NK cells (Fc receptor cells)	Complement Phagocytes	Macrophage activation Cytotoxic lymphocytes Eosinophil activation
Intradermal response to antigen	Wheal and flare	Lysis and necrosis	Erythema and edema	Erythema and induration
Histology	Degranulated mast cells; Cellular infiltrates including neutrophils ^b	Immunofluorescence shows antibody, complement, neutrophils	Acute inflammatory reaction; Mainly neutrophils	Perivascular inflammation; Mainly mononuclear cells
Sensitivity transferred by	Serum IgE antibody	Serum antibody	Serum antibody	Lymphoid cells
Examples of disease states	Erythema; urticaria; angioedema; respiratory symptoms; GI symptoms; anaphylaxis	Drug-induced hemolytic anemia, thrombocytopenia, agranulocytosis (immune form)	Serum sickness; Drug-induced vasculitis	Allergic contact dermatitis; Psoriasis; Maculopapular exanthema; AGEP; FDE; DRESS; SJS; TEN; EM
Drugs implicated	β-Lactams; other antibacterials; NMBDs; some NSAIDs; quinolones; mAbs; proton pump inhib's	β-Lactams; quinine; quinidine; sulfonamides; NSAIDs; procainamide; gold; carbamazepine; propylthiouracil; ticlopidine	β-Lactams; ciprofloxacin; sulfonamides; lincomycin; tetracycline; NSAIDs; carbamazepine; allopurinol; gold; methyldopa; mAbs	NSAIDs; β-lactams; other antibiotics; anti-convulsants; antimalarials; local anesthetics; barbiturates; quinolones; dapsone

^aCoombs RRA, Gell PGH. In: Gell PGH et al. (eds.) *Clinical Aspects of Immunology*. Oxford: Blackwells. 1975, p. 761–81

^bLate reaction may occur ~3–4 h after immediate reaction, peak at ~12 h and subside by ~24 h

AGEP acute generalized exanthematous pustulosis, *DRESS* drug reaction with eosinophilia and systemic symptoms, *EM* erythema multiforme, *FDE* fixed drug eruption, *mAbs* monoclonal antibodies, *NMBDs* neuromuscular blocking drugs, *NSAIDs* nonsteroidal anti-inflammatory drugs, *SJS* Stevens–Johnson syndrome, *TEN* toxic epidermal necrolysis

affected area. The skin may be red, swollen, and show blistering or be dry and bumpy but in the active stage, the skin usually shows redness, with raised areas and blisters (Fig. 2.5).

2.2.4.2 Psoriasis

Psoriasis is a chronic, immune-mediated inflammatory skin disease with a prevalence generally stated to be around 2 % but, depending on the population, this figure can range from zero in Samoa to as high as 4.8 % in the USA (US range 0.6–4.8 %). Ethnicity appears to be involved, for example, American blacks show a prevalence of only 0.45–0.7 % and, likewise, there appears to be

a genetic predisposition to psoriasis illustrated by a concordance rate of 70 % in monozygotic twins and prevalences of 50 % and 16 % respectively when both parents or only one has psoriasis. Several genetic susceptibility loci have been reported, particularly the so-called psoriasis susceptibility 1 (PSORS1) locus on chromosome 6 which appears to be associated with up to 50 % of cases of psoriasis. As well as drugs, psoriasis may be triggered by smoking, alcohol, and withdrawal of systemic or topical corticosteroids. One study showed 23 % of patients were taking more than three medications and 11 % of these were taking more than ten medications. The clinical



Fig. 2.4 Allergic nickel contact dermatitis caused by (a) reading glasses and (b) a multifunction key on a cell phone. From Veien NK, in: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. *Contact Dermatitis*. 5th ed. Berlin: Springer-Verlag; 2011. With kind permission from Springer Science+Business Media



Fig. 2.5 Acute allergic contact dermatitis to the topical antiviral tromantadine hydrochloride showing blistering. From Brandão FM, in: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. *Contact Dermatitis*. 5th ed. Berlin: Springer-Verlag; 2011. With kind permission from Springer Science+Business Media

presentation of the disease is, typically, sharply demarcated erythematous papules and rounded plaques covered by silvery micaceous scales most commonly on the scalp, elbows, umbilicus, lumbar region, and knees (Fig. 2.6). Lesions of psoriasis vulgaris may show small pustules but various forms of pustular psoriasis including generalized and localized variants have been described. Both the more common vulgar form and the pustular form may progress to psoriatic erythroderma affecting the whole body. Fingernails and toenails can also be affected in all types of psoriasis.

A relationship between psoriasis and certain drugs is well recognized. The authors of one study, for example, suggested that acute generalized exanthematous pustulosis (AGEP) is a cutaneous reaction pattern that might be favored by a “psoriatic background,” and medications could be responsible for psoriasis in up to 83 % of cases. Drugs can affect psoriasis in a number of ways—they may induce the disease, cause skin eruptions, induce lesions in previously unaffected skin in patients with psoriasis, and induce a form of psoriasis that is resistant to treatment. Drugs that provoke psoriasis can be divided into two categories—drugs that induce psoriasis but withdrawal of the drug stops further progression of the disease and drugs that aggravate psoriasis but the disease still progresses even after drug withdrawal. Lithium, β -blockers, and synthetic anti-malarials are the drugs most commonly mentioned in triggering or worsening psoriasis, but there are many other drugs that have been implicated either as inducers of the disease or for provoking eruptions. In the former case, the list includes acetazolamide, aminoglutethimide, amiodarone, amoxicillin, ampicillin, aspirin, chloroquine, cimetidine, corticosteroids, cyclosporin, diclofenac, diltiazem, hydroxychloroquine, indomethacin, lithium, methicillin, propranolol, and terbinafine. According to Litt (2006), there are at least 125 different drugs known to be responsible for the eruption or induction of psoriasis. Psoriatic eruptions occur in 3.4–45 % of patients treated with lithium. The mechanism is currently believed to be by inhibition of the intracellular release of calcium as a result of lithium-induced

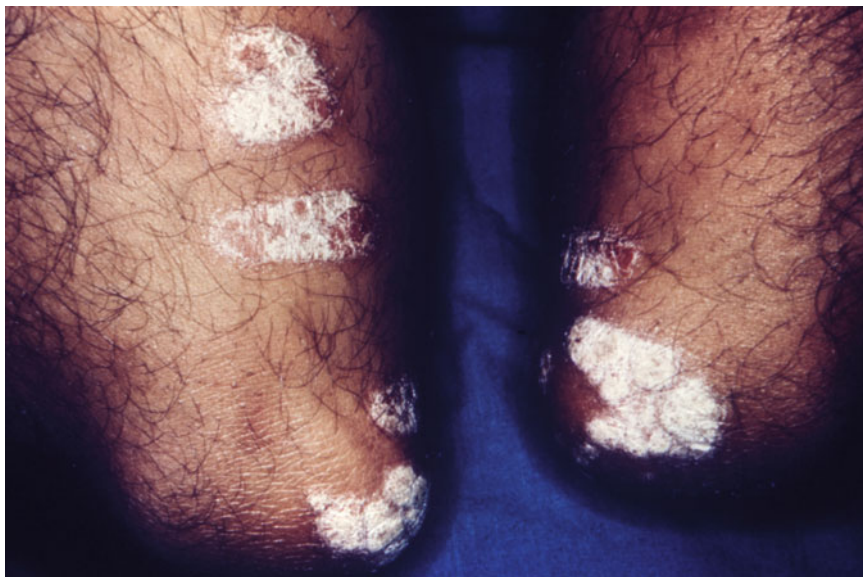


Fig. 2.6 Psoriasis of the elbows showing irregular red patches covered by dry, scaly hyperkeratotic stratum cor-

neum (image by courtesy of the Center for Disease Control and Richard S. Hibbets)

depletion of inositol monophosphatase. Supporting this is the beneficial effect of inositol supplementation in lithium-provoked psoriasis. The administration of the antimalarials chloroquine and hydroxychloroquine to patients with psoriasis is considered to be contraindicated by some. Exacerbation of psoriatic lesions and the induction of the disease have been found after use of these drugs and chloroquine has been implicated in resistance to treatment when given as an antimalarial. Clinical improvement is seen after withdrawal of β -blockers in cases where the drugs have induced or exacerbated psoriasis. The reactions to β -blockers usually manifest 1–18 months after initiation of therapy although, because of some histological findings and clinical features (such as absence of elbow and knee involvement and lesions that are less thick and scaly), some believe that the condition induced by these drugs is not true psoriasis. The mechanism underlying the reactions induced by β -blockers is thought to involve blockade of epidermal β_2 receptors, which leads to decreased cAMP levels in the epidermis and ultimately keratinocyte hyper-proliferation. NSAIDs, many

of which are available over the counter, are frequently used by patients with psoriasis or psoriatic arthritis, but it has been claimed that the NSAIDs are the most common cause of both the induction and exacerbation of psoriasis. Naproxen in particular has been implicated. NSAIDs exhibit a short latency period of only about 1.6 weeks. Leukotrienes, which increase due to NSAID-induced redirection of the arachidonic acid prostanoid pathway to the lipoxigenase pathway (see Chap. 9. Sects. 9.4.1 and 9.5.2.1.2), are thought to aggravate psoriasis. Other drugs for which there is enough data to be sure that they are a significant problem for psoriasis include ACE inhibitors, amiodarone, benzodiazepines, cimetidine, clonidine, digoxin, fluoxetine, gemfibrozil, gold, interferons, quinidine, and tumor necrosis factor. ACE inhibitors appear to be a problem in patients over 50 years of age.

Although the treatment and management of drug reactions are beyond the scope of this book, it is worth noting that a number of biological agents are currently being used either in the clinic or experimentally to treat psoriasis. These include etanercept, a fusion protein inhibitor of tumor

necrosis factor (see Sect. 11.2), and the chimeric and human monoclonal antibodies adalimumab, brodalumab, infliximab, ixekizumab, and ustekinumab (Sect. 11.1).

2.2.4.3 Maculopapular Exanthema

Maculopapular exanthema, also called morbilliform drug reaction, morbilliform exanthem, and maculopapular drug eruption, is the most frequently seen pattern of drug-induced skin eruption. Clinical presentation is diverse and can vary from an erythematous rash mimicking a viral or bacterial exanthem to generalized symmetric eruptions of both isolated and confluent erythematous plaques. These often start on the trunk and then spread to the extremities and neck without involvement of the mucosa. The pink to red macules or papules tend to blanch when pressed and purple, non-blanchable spots (purpura) may appear on the lower legs. Reactions appear 7–14 days after exposure to drug but after only 1 or 2 days in already sensitized patients. Reactions usually tend to progress over a few days before regressing over a 2-week period often with accompanying desquamation. This may be the course of events even if the drug has been withdrawn. Reactions may be associated with a mild fever and itch. Histologically, lymphocytes are seen in papillary dermis and at the junction of the dermis and epidermis while degenerated, necrotic and some dyskeratotic keratinocytes and spongiosis are visible in early lesions. Maculopapular exanthema can be caused by a wide variety of drugs. Those commonly implicated are chiefly antibiotics, especially aminopenicillins (Fig. 2.7) and cephalosporins, but also sulfonamides, anticonvulsants like carbamazepine, allopurinol, and NSAIDs.

2.2.4.4 Acute Generalized Exanthematous Pustulosis

AGEP, also termed toxic pustuloderma and pustular drug eruption, is induced in 90 % of cases by drugs and characterized by fever and acute non-follicular pustular eruptions that overlay erythrodermic skin. The incidence of the disease is said to be about three to five cases per million per year with a mortality rate of about 5 %. Reactions generally begin with a rash on the face or in armpits

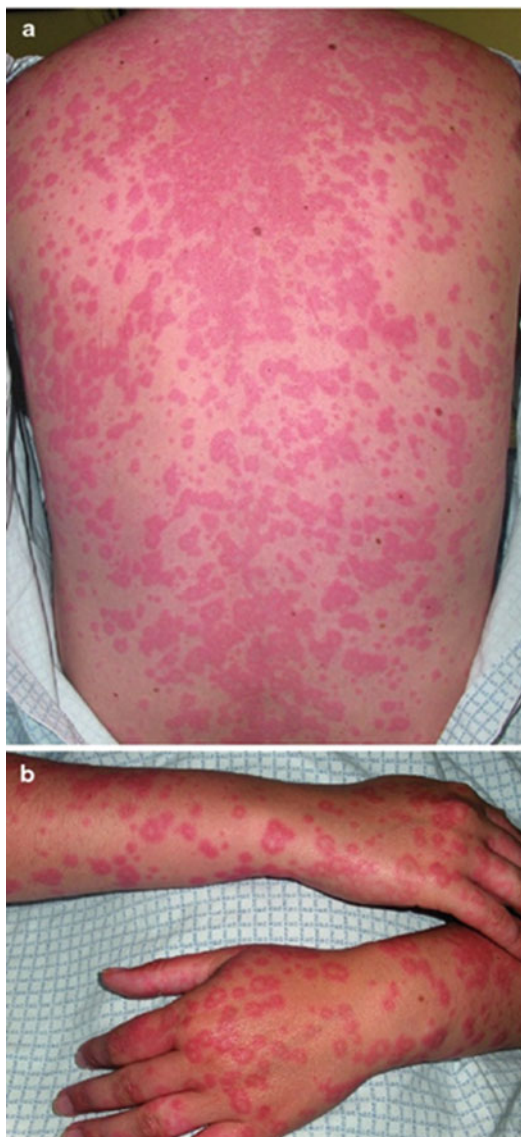


Fig. 2.7 Generalized maculopapular exanthema following the introduction of amoxicillin therapy showing lesions on the trunk (a) and targeted lesions on the hands and forearms (b). The patient had positive patch tests to amoxicillin and ampicillin and negative tests to benzylpenicillin, dicloxacillin, and a number of cephalosporins. From Gonçalo M, in: Johansen JD, Frosch PJ, Lepoittevin J-P, editors. *Contact Dermatitis*. 5th ed. Berlin: Springer-Verlag; 2011. With kind permission from Springer Science+Business Media

and groin a few days after administration of the offending drug before becoming widespread. Time of onset after drug administration can be



Fig. 2.8 A case of acute generalized erythematous pustulosis (AGEP) to hydroxychloroquine sulfate (photograph courtesy of Dr. Adrian Mar)

remarkably short—even as little as 24 h in some cases. The rash lasts about 2 weeks, and the reaction regresses with skin desquamation as it resolves 5–10 days after drug withdrawal, often with rapid spontaneous healing. AGEP is characterized by symmetrical widespread edematous erythema with small non-follicular sterile pustules (Fig. 2.8) due to neutrophil accumulation predominating in body folds. Recruitment of neutrophils occurs in the late phase of development of lesions. Histopathology shows spongiosis, sub-corneal pustules, leukocytoclastic vasculitis, discrete vacuolar keratinocyte degeneration, and dermal and intradermal infiltration of lymphocytes. AGEP is also characterized by the great predominance (over 80 % of cases) of antibiotics (including amoxicillin, ampicillin, tetracycline, spiramycin, pristinamycin, and metronidazole) as causative agents. Other implicated drugs include hydroxychloroquine, cotrimoxazole, diltiazem, terbinafine, and carbamazepine.

2.2.4.5 Drug Reaction (Rash) with Eosinophilia and Systemic Symptoms

Drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS), also referred to as hypersensitivity syndrome or drug-induced hypersensitivity syndrome, is a severe life-threatening adverse drug reaction with an incidence reported to be between 1 in 1,000 and 1 in 10,000 depending



Fig. 2.9 A patient with drug reaction (or rash) with eosinophilia and systemic symptoms (DRESS), also referred to as hypersensitivity syndrome or drug-induced hypersensitivity syndrome. The patient experienced systemic symptoms, skin reactions with nonspecific maculopapular rash, and exfoliative dermatitis with facial edema (photograph courtesy of Dr. Adrian Mar)

on the drug. DRESS involves systemic symptoms and skin reactions with nonspecific maculopapular rash or a more generalized exfoliative dermatitis and facial edema (Fig. 2.9). Symptoms consist of fever, malaise, arthralgia, enlarged lymph nodes, hepatitis, renal impairment, pneumonitis, and hematological abnormalities with atypical activated lymphocytes and elevated levels of eosinophils that infiltrate the skin and other organs and are thought to cause tissue damage. Visceral involvement differentiates DRESS from other exanthematous serious acute drug reactions. Another distinguishing feature is the extended interval between drug exposure and the onset of symptoms, which is usually about 2–8 weeks. DRESS also tends to regress more slowly and the disease may sometimes reactivate after exposure to an unrelated drug or even without drug exposure. Viruses may have a role in the development of the symptoms of DRESS. This is suggested by reactivation of the Herpesviridae viruses, cytomegalovirus, EBV, and human herpes virus 6 (HHV-6), the latter evidenced by the rise of anti-HHV-6 IgG titers and the presence of HHV-6 DNA 2–3 weeks

after the onset of rash. The main drugs involved in eliciting reactions are the anticonvulsants carbamazepine, lamotrigine and phenytoin, phenobarbitone, dapsone, sulfonamides, allopurinol, minocycline, and mexiletine. In a retrospective analysis of 1,544 DRESS cases reported to the United States Food and Drug Administration between 2004 and 2010, 137 cases (8.9 %) had a fatal outcome; the sex ratio was five females to four males and the most frequently involved age range was the 60–69 group. Those older than 70 had a higher incidence of fatalities. Approximately 60 % of cases developed DRESS within 4 weeks but some late-onset cases developed after 6 months exposure to the drug. The top 20 drugs most frequently implicated in provoking DRESS, in order of highest to lowest frequency, were: carbamazepine, sulfasalazine, allopurinol, vancomycin, amoxicillin, lamotrigine, phenytoin, minocycline, zonisamide, abacavir, ciprofloxacin, piperacillin, rifampicin, ibuprofen, diclofenac, valproate, acetaminophen, phenobarbital, lamivudine, omeprazole. Increased reporting of DRESS is apparent, although this increase is not related to newly marketed drugs but rather the already well-known causes. Only 12 % of the 1,544 cases reported to the FDA were from the USA whereas 527 cases (34 %) were reported from France, 286 (19 %) from Japan, 79 (5 %) from the UK, and 135 cases (9 %) unknown. It is clear that there is underreporting to the extent, as some have claimed, that the reports received by the FDA are only 1–10 % of the real number. Finally, there is some disagreement over the variability of the clinical pattern of cutaneous symptoms and the classification of some patients as having DRESS. Some claim that use of the term DRESS is not consistent; cutaneous and systemic signs vary and eosinophilia is not a constant finding. With this in mind, the designation DIHS/DRESS to include DRESS and drug-induced hypersensitivity syndrome (DIHS) has been suggested.

2.2.4.6 Fixed Drug Eruption

Fixed drug eruption (FDE) is due to drug hypersensitivity in more than 95 % of cases. Patients may complain of burning in the affected area before the appearance of lesions but systemic



Fig. 2.10 A fixed drug eruption showing the characteristic, often-seen circular shape. Lesions often resolve with post-inflammatory pigmentation (photograph courtesy of Dr. Adrian Mar)



Fig. 2.11 An example of a well-circumscribed bullous fixed drug eruption. The reaction was induced by carbamazepine, a drug implicated in some severe drug-induced delayed hypersensitivity responses (photograph courtesy of Dr. Adrian Mar)

symptoms are usually absent. The period required for sensitization ranges from weeks to years and the time between drug administration and eruption can be anything from a day or two to a few weeks. Initially, one or a small number of round or oval pruritic, well circumscribed, erythematous macules appear (Fig. 2.10). These may progress to edematous plaques or bulla (Fig. 2.11) and may regress over a period of 10–15 days. In a few cases, lesions can be so widespread that it is difficult to distinguish FDE from TEN. FDE is so named because the site of

the eruption is fixed, that is, it occurs in exactly the same place when the same drug is again encountered. Upon discontinuation of the drug, lesions resolve leaving hyperpigmentation although pigmentation is often absent when the skin is fair. A FDE can occur anywhere on the skin or on mucous membranes, but the most commonly affected sites are the hands, feet, penis, groin and perianal areas, and the lips. Drugs implicated in causing FDE include allopurinol, cotrimoxazole, antibiotics (tetracycline, doxycycline, amoxicillin, ampicillin, cephalosporins, and clindamycin), NSAIDs (aspirin, ibuprofen, naproxen, and diclofenac), acetaminophen, carbamazepine, dapsone, quinine, phenolphthalein, and benzodiazepines. To confirm diagnosis of FDE, oral challenge with a single dose of the suspected drug at one-tenth the normal therapeutic dose is accepted as safe. Interestingly, desensitization has been successful for allopurinol-induced FDE but allopurinol appears to remain the only drug where desensitization for FDE has worked.

2.2.4.7 Erythema Multiforme

Erythema multiforme is a self-limiting cutaneous hypersensitivity reaction to infection (mostly) or drugs occurring mainly in adults 20–40 years of age although it can occur in patients at any age. Prodromal symptoms are either lacking or mild (itch, burning) and the condition usually resolves spontaneously in 3–5 weeks without sequelae. Although considered to be closely related to SJS and TEN, and with the designation erythema multiforme major sometimes interchanged with the former, erythema multiforme is now accepted as a distinct condition. Major reasons for this are its lesser severity, minimal involvement with mucous membranes, and the extent of epidermal detachment which is usually less than 10 %. Lesions appear as circumscribed pink-red macules before progressing to papules which may enlarge into plaques, the centers of which become darker or even purpuric (Fig. 2.12). Crusting or blistering may occur. Several days after onset, lesions of various morphology are visible, hence the name “multiforme.” Palms (Fig. 2.13) and soles may be affected and if the mucosa is



Fig. 2.12 Erythema multiforme with circumscribed macular and papular lesions progressing to plaques with dark and purpuric centers (photograph courtesy of Dr. Adrian Mar)



Fig. 2.13 Erythema multiforme involving the hands (photograph courtesy of Dr. Adrian Mar)

involved, it is usually limited to the oral cavity. Patients may experience multiple outbreaks in a year. More than half the cases of erythema multiforme are due to *Herpes simplex* (HSV), and recurrent cases may be secondary to reactivation of HSV-1 and HSV-2. Acyclovir, famciclovir, or valacyclovir have been used to treat recurrent outbreaks. *Mycoplasma pneumoniae* and fungal infection are also commonly involved with reactions. Drugs most commonly associated with erythema multiforme are anticonvulsants, barbiturates, ciprofloxacin, NSAIDs, penicillins, phenothiazines, sulfonamides, and tetracyclines. Some drugs released in more recent years are now being implicated, for example, the monoclo-



Fig. 2.14 Toxic epidermal necrolysis in an adult patient covering more than 30 % of the total body surface area. From Struck MF et al. Severe cutaneous adverse reac-

tions: emergency approach to non-burn epidermolytic syndromes. *Intensive Care Medicine* 2010;36:22. With kind permission from Springer Science+Business Media

nal antibody adalimumab, bupropion, candesartan cilexetil, and metformin and reactions to some vaccines against bacteria (diphtheria–tetanus) and viruses (hepatitis B, hepatitis C, cytomegalovirus, and HIV) are seen.

2.2.4.8 Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN are potentially fatal, severe, rare, adverse cutaneous drug reactions involving both the skin and mucous membranes. Beginning with relatively unremarkable signs like fever, malaise, and perhaps eye discomfort, macular lesions become symmetrically distributed on the trunk, face, palms, and soles. Lesions develop a central bulla and coalesce into large sheets of necrotic tissue covering at least 30 % of the body in the case of TEN (Fig. 2.14). For SJS, skin denudation/detachment is generally less than 10 % of body surface area, and this extent of skin involvement is the main distinguishing feature between the two diseases. Skin erythema and erosions progress to the extremities with more than 90 % of patients experiencing ocular, buc-



Fig. 2.15 Lips and facial involvement in a child with developing drug-induced Stevens–Johnson syndrome (photograph courtesy of Dr. Adrian Mar)

cal, and genital mucosa involvement. Figure 2.15 shows lip and facial involvement in a child with developing drug-induced SJS. Respiratory and gastrointestinal tracts can also be affected. Ocular effects can include acute conjunctivitis with discharge, eyelid edema, erythema, and corneal erosion or ulceration. The collective clinical features sometimes do not fit neatly into

either a clear SJS or TEN diagnosis and may be classified as overlapping SJS or TEN. In the SJS–TEN overlap group, primary lesions tend to be dusky red or purpuric macules or flat atypical targets widely distributed as isolated lesions but with quite marked confluence on the face and upper trunk. As with TEN, but not necessarily with SJS, systemic symptoms are always present. Skin detachment occurs on 10–30 % of the body surface area.

In the second phase of development of the diseases, large areas of epidermis become detached. Sequelae and late effects are common in SJS and particularly TEN. These can include changes in skin pigmentation, nail dystrophies, and ocular problems. Long-term sequelae in surviving TEN patients can include eye afflictions like entropion and symblepharon, on-going mucous membrane erosion, and cutaneous scarring. Dry mouth and dry eyes resembling Sjögren syndrome may be a long-term complication.

Although SJS and TEN are rare with incidences of usually less than two per million per year (e.g., 1.89 Western Germany, 1.9 USA), some infectious diseases can have a marked effect in the incidence. This is seen with HIV where the annual incidence is approximately 1,000 times higher than in the general population. Infections *M. pneumoniae* and *H. simplex* are known to cause SJS and TEN without drug involvement. A strong association shown between HLA-B*15:02, SJS, and carbamazepine in Han Chinese and confirmed in a Thai population is a clear demonstration of a relationship between ethnicity and drug hypersensitivity. This finding has stimulated interest in the investigation of genetic factors in drug hypersensitivity (see Sect. 3.4); one recent demonstration being the large collaborative European RegiSCAR project which showed that HLA-B*15:02 is not a genetic marker for carbamazepine, sulfamethoxazole, lamotrigine, or NSAIDs of NSAID oxicam-type-induced SJS/TEN in Europe. The drugs most commonly responsible for SJS/TEN have been divided by Roujeau into those that provoke the disease after only a short period of administration and those that do so after being taken for longer periods. In the short period group

are trimethoprim–sulfamethoxazole, other sulfonamides, aminopenicillins, cephalosporins, quinolones, and chlormezanone. In the long period group: carbamazepine, phenytoin, phenobarbitone, and valproic acid, NSAIDs of the oxicam type, allopurinol, and corticosteroids. Allopurinol is the drug most commonly implicated in causing SJS/TEN in Europe and Israel. Some newer drugs identified as being of increased comparative risk include nevirapine, lamotrigine, and sertraline. Because of the fear of provoking a second episode or aggravating an existing case of SJS/TEN, skin testing in all its forms and provocation tests are not to be considered although there are at least two reports of intradermal testing that did not trigger another episode. Patch testing and the lymphocyte transformation test (Sect. 4.7.1) have been used but proved to be of low sensitivity. Clinical features and histology therefore remain the mainstay of diagnosing SJS/TEN.

Summary

- In the Gell and Coombs classification of allergic reactions, four types of hypersensitivities designated types I, II, III, and IV are distinguished.
- Type I, also called immediate or anaphylactic hypersensitivity, occurs within about 30 min but reactions can be dramatic and appear within seconds or minutes as in anaphylaxis.
- Type I reactions are IgE antibody-mediated. Receptor-bound drug-reactive IgE on the surface of mast cells is cross-linked by complementary drug determinants causing cell degranulation and the release of inflammatory mediators.
- Drugs well known to cause type I reactions include penicillins, cephalosporins, neuromuscular blocking drugs, some NSAIDs, monoclonal antibodies, quinolones, and proton pump inhibitors.
- The term “anaphylactic” is used to describe an immune-mediated immediate systemic reaction involving the release of potent mediators from mast cells and basophils that produce

a range of possible symptoms including erythema, urticaria, angioedema, bronchospasm, gastrointestinal symptoms, and cardiovascular collapse. The term “anaphylactoid” is used for reactions that show clinically similar signs and symptoms but where no immune-mediated mechanism can be demonstrated.

- It is important to have a suitable clinical grading system for anaphylaxis.
- Urticaria is the second most common cutaneous reaction induced by drugs, often in association with angioedema and anaphylaxis. Many drugs are implicated including β -lactams, NSAIDs, sulfonamides, vancomycin, and contrast media. ACE inhibitors are responsible for approximately one in six patients admitted to hospital with angioedema.
- Type II hypersensitivity is also known as antibody-dependent cytotoxic hypersensitivity. Drugs can attach to cell membranes producing drug-induced hemolytic anemia, thrombocytopenia, and granulocytopenia. Drugs implicated: hemolytic anemia—penicillins, quinidine, methyldopa; thrombocytopenia—quinine, quinidine, propyl thiouracil, vancomycin, sulfonamides; granulocytopenia—pyrazolones, thiouracil, anticonvulsants, and sulfonamides.
- Type III hypersensitivity is mediated by soluble immune complexes mostly involving IgG antibodies. Drug-induced serum sickness-like reaction is the prototype example of type III drug hypersensitivity. Hypersensitivity vasculitis is another example of a type III hypersensitivity response induced by drugs.
- Type IV hypersensitivity reactions are mediated by antigen-specific effector T cells. Reactions generally occur 48–72 h after antigen exposure and are therefore referred to as delayed reactions.
- Important delayed cutaneous reactions include maculopapular exanthema; allergic contact dermatitis; psoriasis; acute generalized exanthematous pustulosis; drug reaction with eosinophilia and systemic symptoms; fixed drug eruption; erythema multiforme; Stevens–Johnson syndrome; and toxic epidermal necrolysis.

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