Adverse Medication Reactions

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Abstract

Cutaneous adverse drug reactions (ADRs) are among the most frequent adverse reactions in patients receiving drug therapy. They have a broad spectrum of clinical manifestations, are caused by various drugs, and result from different pathophysiological mechanisms. Hence, their diagnosis and management is challenging.

Severe cutaneous ADRs comprise a group of diseases with major morbidity and mortality, reaching 30 % mortality rate in cases of Toxic Epidermal Necrolysis.

This chapter covers the terminology, epidemiology, pathogenesis and classification of cutaneous ADR, describes the severe cutaneous ADRs and the clinical and laboratory approach to the patient with cutaneous ADR and presents the translation of laboratory-based discoveries on the genetic predisposition and pathogenesis of cutaneous ADRs to clinical management guidelines.

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Terminology

The World Health Organization defined an adverse drug reaction (ADR) in 1972 as "a response to a drug that is noxious and unintended and occurs at doses normally used in man" [1]. Edwards and Aronson [2] proposed a different definition in 2000: "an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product."

The terms 'adverse reaction' and 'adverse effect' are interchangeable, except that an adverse reaction is seen from the point of view of the patient and adverse effect is seen from the point of view of the drug. However, both terms must be distinguished from 'adverse event'. An adverse event is an adverse outcome that occurs while a patient is taking a drug, but is not or not necessarily attributable to it [2].

Differentiating between serious ADR and severe ADR is imperative. Serious ADR is a legal term applied to any untoward medical occurrence that at any dose results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect [3]. Conversely, the term 'severe' is a clinical term used to describe the intensity (severity) of a medical event, as in the grading 'mild', 'moderate', and 'severe'; thus, a severe skin reaction need not be serious [2].

Epidemiology

ADRs are associated with significant morbidity and mortality and have considerable economic implications. Clinical manifestations of an ADR are variable and may include cutaneous and or systemic features [4].

When analyzing the type of ADRs most encountered, two major groups emerge; **common-mild reactions** and **rare-severe reactions**. Common-severe reactions are not approved for clinical usage and rare-mild reactions are usually not noticed or reported. Cutaneous ADRs are among the most frequent adverse reactions in patients receiving drug therapy [5]. They accounted for 65 % of all reported ADRs in a 4-year retrospective study in Taiwan [6].

The prevalence and incidence of cutaneous ADRs vary greatly among different populations [7–11]. In the USA, a 7-year prospective study found that the prevalence of cutaneous ADRs was 2.2 % in hospitalized patients [7]; and an 11-year retrospective study found the annual incidence of cutaneous ADRs to be 2.26 per 1,000 persons [11]. In Denmark, in a 1-year cross-sectional study the prevalence of cutaneous ADRs was 0.33 % in in-patients and 0.14 % in out-patients [8]. In southern China, in an 8-year retrospective study, the prevalence of cutaneous ADRs was 0.14 % in hospitalized patients [9]. In India, in a 12-month prospective study, the primary incidence of cutaneous ADRs was 2.05 per 1,000 persons [10].

The need to survey ADRs in clinical practice is universally recognized. Various methods may be employed: spontaneous surveillance, prescription-event monitoring (PEM), linkage analysis, case-control surveillance and cohort studies [5]. In 1963, the 16th World Health Assembly reaffirmed the need for early detection and rapid dissemination of information on adverse reactions due to medications. This affirmation led to the creation of the World Health Organization (WHO) Programme for International Drug Monitoring, under whose auspices systems have been created in member states for the collection and evaluation of individual case safety reports (ICSRs) [12]. In 1978 the WHO set up its international drug monitoring programme in Sweden at the Uppsala Monitoring Centre (UMC) http://www.who-umc.org. The US Food and Drug Administration (FDA) provides several options for reporting adverse events. One such option is MedWatch, the FDA Safety Information and Adverse Event Reporting Program http://www.fda.gov/safety/MedWatch/default.htm, founded in 1993 as a system for both consumers and healthcare professionals to report adverse events. MedWatch is intended to detect safety hazard signals for medical products; in the event a signal is detected, the FDA can issue medical product safety alerts or order product recalls, withdrawals, or labelling changes to protect the public health [13].

A number of international research groups are investigating severe cutaneous ADRs (SCARs): the RegiSCAR network, an international registry of SCAR established in 2003, the Japanese Research Committee, J-SCAR, the Asian SCAR consisting of Japan and Taiwan SCAR groups (J-SCAR and T-SCAR) established in 2010, and the Southeast Asia network, SEA-SCAR, with ten member countries: Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Thailand, Singapore, and Vietnam. The International Serious Adverse Event Consortium (iSAEC), a non-profit organization formed in 2007, is a pharmaceutical industry- and FDA-led international consortium that focuses on identifying and validating DNA variants useful in predicting the risk of rare drug-induced serious adverse events [14].

Pathogenesis

Immunologic Versus Non-immunologic Mechanisms

Immunological Mechanisms

Mechanisms of adverse drug reactions (ADRs) can be classified into immunologic and non-immunologic etiologies. There are two common types of immune-mediated drug reactions: immediate-type hypersensitivity (Type I hypersensitivity) and delayed-type hypersensitivity (Type IV hypersensitivity).

1. Immediate-type drug hypersensitivity: Immediate-type drug hypersensitivity reactions usually occur minutes to hours after drug exposure, with clinical manifestations including pruritus, urticaria, angioedema, and bronchospasm to anaphylaxis. The reaction is mediated mainly by drug-specific IgE, the most common causative agents being penicillins, cephalosporins and neuromuscular blocking agents. IgE-mediated reactions to drugs are usually thought to be an immune response to a hapten/carrier complex. In the primary drug sensitization, drug-specific IgE is formed when plasma cells transformed from activated B cells interact with T cells. In an allergic reaction, drug allergens bind to mast cells with high-affinity Fc receptor, to which drug-specific IgE is bound, causing

mast cells to release mediators, such as histamine, leukotrienes, prostaglandins and cytokines [15].

2. Delayed-type drug hypersensitivity: Delayed-type drug hypersensitivity reactions usually take several days to weeks following drug exposure, with variable clinical presentations that may include Maculopapular Eruption (MPE), Fixed Drug Eruption (FDE), Acute Generalized Exanthematous Pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). T cell receptor (TCR), CD4+ and CD8+ T cells are involved in different delayed-type drug hypersensitivity reactions [16].

Drug Recognition by T Cells in Delayed-Type Drug Hypersensitivity

Drugs are low molecular weight and usually considered not able to bind to TCRs to activate adaptive immunity. In the case of drug allergy, drug interactions with TCRs may involve a drug-peptide complex presented by human leucocyte antigen (HLA) molecules of antigen-presenting cells (APCs). This process is known as the hapten concept; an example is β-lactams that covalently bind to lysine residues [17].

Drugs can also interact directly with TCRs without binding to the peptide/HLA of the APC in what is known as the P-i concept (pharmacological interaction of drugs with immune receptors) [18]. For example, carbamazepine is not able to bind covalently to peptides or proteins, but can associate with low affinity to TCRs and provoke T cell activation [19].

Immunohistologic Characteristics and Functions of Drug-Specific T Cells in Delayed-Type Drug Hypersensitivity

The immunohistologic characteristics of delayed type drug hypersensitivity are summarized in Table 25.1. The skin of MPE is infiltrated by numerous mononuclear cells (CD4 and CD8 T cells, monocyte/macrophages) and some eosinophils. Typically, interface dermatitis is seen with a predominance of CD4+ T cells. These cells are located mainly in the perivascular dermis, and both CD4+ and CD8+ T cells are located at the dermoepidermal junction [20].

Skin manifestations of DRESS may vary from MPE-like to exfoliative dermatitis and are characterized by a heavy infiltration of CD4+ and CD8+ T cells, monocyte/macrophages and eosinophils [21]. MPE and DRESS share many pathological features, but DRESS exhibits more severe dyskeratosis (keratinocyte death in epidermis) and a greater extent of systemic involvement and eosinophilia [26].

Immunohistology of skin lesions in AGEP reveals intraepidermal pustules with infiltration of neutrophils surrounded by IL-8 producing T cells [22].

Despite very diverse clinical presentations, constant features of delayed-type drug hypersensitivity are the presence of high numbers of drug-specific CD8+ cytotoxic T cells and low numbers of innate NK lymphocytes [20, 27, 28].

CD8+ T cells of cutaneous ADRs have classic cytotoxic functions: lysis of autologous lymphocytes or keratinocytes in an MHC class I–restricted and drug-dependent manner [28].

Cytotoxic Immune Cells in SJS/TEN

Drug-induced SJS and TEN are severe cutaneous ADRs in which cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells are activated, and subsequently carry out the cellular immune reactions directed at keratinocytes in a major histocompatibility class (MHC) I-restricted manner. Upon activation of these immunocytes, various cytotoxic signals, including granulysin, perforin/granzyme B, Fas/Fas ligand, and cytokines/chemokines, are relayed to the skin lesions to mediate the disseminated keratinocyte death [23–25]. It is noteworthy that the number of granulysin-positive cells in fixed drug eruptions was found to be similar to that observed in SJS/TEN [27].

Non-Immune-Mediated Hypersensitivity

Non-immune-mediated hypersensitivity is commonly referred to as pseudoallergic reactions because they do not involve a specific immune mechanism – neither IgE-mediated (Type I) nor delayed (Type IV) hypersensitivity. Clinical manifestations, which range from milder erythematous to urticarial reactions to severe lethal anaphylaxis, may be indistinguishable from immune system-mediated hypersensitivity reactions. Common non-immune-mediated hypersensitivity can be caused by contrast media, vancomycin, non-steroidal anti-inflammatory drugs (NSAIDs), opiates, plasma expanders, and drugs used in general anesthesia [29].

NSAIDs-induced pseudoallergic reactions have been attributed to cyclooxygenase-1 inhibition and overproduction of leukotrienes, and may require higher drug doses than are needed for true IgE-mediated reactions [30]. Mast cell

Table 25.1 Summary of immunohistologic characteristics of delayed-type drug hypersensitivity [16, 20–25]

Phenotypes	Major immune cells	Major cytokines or cytotoxic mediators
MPE	CD4+>CD8+ T cells	IFN-γ, TNF-α, IL-4, IL-5, perforin/granzyme B
DRESS	CD4+>CD8+ T cells, eosinophils	IFN-γ, TNF-α, IL-4, IL-5, TARC/CCL17
SJS/TEN	CD8+ T cells, NK cells	IFN-γ, TNF-α, Fas-FasL, perforin/granzyme B, granulysin
AGEP	Neutrophils	IL-8

MPE maculopapular drug eruption, *DRESS* drug reaction with eosinophilia and systemic symptoms; *SJS/TEN* Stevens-Johnson syndrome/toxic epidermal necrolysis, *AGEP* acute generalized exanthematous pustulosis

degranulation is involved in some of these pseudoallergic reactions.

The Role of Cytokines or Inflammatory Mediators

Drug-specific T cells mediate skin inflammation in variable clinical presentations of delayed-type drug hypersensitivity through the release and induction of different cytokines and chemokines (Table 25.1) [31]. The heterogeneous cytokines include Th1 cytokines (interferon-γ) and Th2 cytokines (IL-4, IL-5) [22]. Increased expression of IL-5, which is a key cytokine for activation of eosinophils, is commonly seen in delayed-type drug hypersensitivity [32]. The activation of eosinophils can be further enhanced by the chemokines eotaxin and RANTES [33]. Thymus and activation-regulated chemokine (TARC/CCL17) has been reported to be a DRESS specific cytokine [34]. In addition to Th1 and Th2 cytokines, a recent study demonstrated the involvement of IL-17A-producing Th17 in DRESS and SJS/TEN [35]. Elevated expression of the neutrophil-attracting IL-8 has been known to be the key cytokine involved in AGEP.

There are several cytokines involved in SJS/TEN. Numerous studies have shown tumor necrosis factor alpha (TNF-α) strongly expressed in SJS/TEN lesions and correlated with disease severity [24, 36, 37]. TNF-α is a potent cytokine that induces cell apoptosis, cell activation, differentiation, and inflammatory processes [38, 39]. Interferon gamma (IFN-γ) is a common cytokine involved in delayed-type drug hypersensitivity, including SJS/TEN. IFN-γ was intensely expressed in the superficial dermis and epidermis of SJS/TEN lesions [36, 37]. IFN-γ is also known to promote antigen presentation and thus stimulate the cell-mediated immunity by upregulation of MHC molecules [40–42]. In addition to TNF-α and IFN-γ, several cytokines and chemokine receptors that are responsible for trafficking, proliferation, and activation of T-cells and other immune cells have been found elevated in the skin lesions, blister fluids, blister cells, PBMCs, or plasma of SJS/TEN patients. These cytokines/chemokines include IL-2, IL-5, IL-6, IL-10, IL-12, IL-13, IL-15, IL-18, CCR3, CXCR3, CXCR4, and CCR10 [24, 36, 37, 43–45].

Immune Mediators for Cell-Mediated Cytotoxicity in SJS/TEN

The central hypothesis proposed to explain the severe muco-cutaneous lesions of SJS/TEN is the CD8+ cytotoxic T cell and natural killer (NK) cell-mediated cytotoxic immune reactions. Three major cytotoxic signals from cytotoxic cells are reported to be involved in the extensive skin necrosis of SJS/TEN, including the Fas–FasL interaction, perforin/granzyme B, and granulysin, which can induce keratinocyte apoptosis [23, 28, 46].

Granulysin is not only a cytotoxic protein; it is also a chemoattractant and proinflammatory activator that can promote monocyte expression of CCL20 [47], and is capable of promoting antigen-presenting (dendritic) cells and leukocyte recruitment, and activating specific immune responses, such as IL-1b,IL-6, IL-10, TNF-a [48].

Genetic Predisposition

Genetic Factors in Delayed-Type Drug Hypersensitivity

Reports on the familial occurrence of severe drug hypersensitivity and cases occurring in identical twins suggest genetic links [49–52]. The HLA genes show strong association with drug hypersensitivity. Examples of strong associations of HLA alleles with specific drug-induced hypersensitivity reactions include abacavir, nevirapine, carbamazepine, and allopurinol (Table 25.2).

The view that HLA alleles are the main genetic determinants of SJS/TEN was first proposed by Roujeau et al. [61], who reported the weak associations of HLA-A29, B12, and

Table 25.2 Recently reported HLA associations with drug hypersensitivity reactions

Drug	HLA association	Hypersensitivity reactions	Reference
Carbamazepine	B*1502	SJS/TEN	Chung et al. [53]
Allopurinol	B*5801	SJS/TEN/DRESS	Hung et al. [54]
Abacavir	B*5701	MPE/DRESS	Mallal et al. [55]
Flucloxacillin	B*5701	Hepatotoxicity	Daly et al. [56]
Lumiracoxib	DRB1*1501, DQB1*0602, DRB5*0101, DQA1*0102	Hepatotoxicity	Singer et al. [57]
Dapsone	B*1301	MPE/DRESS	Zhang et al. [58]
Nevirapine	DRB1*0101	MPE/DRESS	Martin et al. [59]
Methazolamide	B*5901	SJS/TEN	Kim et al. [60]

MPE maculopapular drug eruption, *DRESS* drug reaction with eosinophilia and systemic symptoms, *SJS/TEN* Stevens-Johnson syndrome/toxic epidermal necrolysis

DR7 in sulfonamide-related TEN, and HLA-A2, B12 in oxicam-related TEN in Europeans [61]. Following the immunological hypothesis, the most striking evidence of genetic susceptibility to SJS/TEN was provided by the findings that HLA-B*15:02 is strongly associated with carbamazepine-induced SJS/TEN [53], HLA-B*58:01 with allopurinol-induced SJS/TEN or DRESS [54], and HLA-B*5701 with abacavir hypersensitivity [62].

The HLA association to specific drug-induced hypersensitivity can be ethnic and phenotype-specific. The strength of HLA associations with specific drug-induced hypersensitivity in different populations has been found related to the prevalence of the susceptibility allele in the ethnic population. The association of HLA-B*15:02 with carbamazepine-induced SJS/TEN was replicated in other Asian countries, including Thailand, Hong Kong, Malaysia, China, Vietnam, Cambodia, Reunion, Philippines and Indian ethnicities, which carry high HLA-B*15:02 allele frequency, but not in Europeans, which carry low HLA-B*15:02 allele frequency (<1 %) [63]. In contrast, the strong association of HLA-B*58:01 with allopurinol-induced SJS/TEN is more universal, being found in Han Chinese in China, Thai populations, Korean, Japanese, and European populations; HLA-B*58:01 is the allele common to all these populations [64]. The phenotype-specific characteristics are exemplified by carbamazepine hypersensitivity. While HLA-B*15:02 is strongly associated with carbamazepine-induced SJS/TEN, it is not associated with carbamazepine-induced DRESS; in an international study, HLA-A*31:01 was strongly associated with carbamazepine-induced DRESS, but not with carbamazepine-induced SJS/TEN [65].

Phenytoin – an aromatic antiepileptic drug structurally related to carbamazepine – also frequently causes SJS/TEN and DRESS [66, 67]. HLA-B*15:02 has been associated with phenytoin-related SJS/TEN in Asians, although the association is much weaker than that found for carbamazepine-related SJS/TEN [68]. A recent genome-wide association study by Chung WH et al. turned up cytochrome (CYP) 2Cvariants, including CYP2C9*3, that showed a strong association with phenytoin-related SCAR. The significant association between CYP2C9*3 and phenytoin-related severe cutaneous ARDs was replicated in different Asian populations [69].

Genetic Factors in Immediate-Type Drug Hypersensitivity

Similar to delayed-type drug hypersensitivity, genetic predisposing factors have been reported in immediate-type drug hypersensitivity. β-lactam allergy was reported associated with gene variants of IL13, IL4, and IL4RA [70–73]. Several genetic predisposing factors, including gene polymorphisms in cysteinyl leukotriene receptor type 1 (CysLTR1) and leukotriene C4 synthase (LTC4S) [74] and high-affinity IgE receptor (FcepsilonR1) [75], were associated with aspirin.

Classification

Cutaneous ADRs may be classified in terms of their presumed mechanism, severity of the reaction, histological findings, and cutaneous morphological manifestations.

Mechanism of ADRs

The modern pharmacological classification of ADRs differentiates two basic types of reactions; type A, predictable reactions, and type B, unpredictable or idiosyncratic reactions. Type A reactions ('augmented') are dose-dependent, common and predictable based on the pharmacology of the drug; about 80 % of all ADRs are type A. Type B reactions ('bizarre') do not occur at any dose in most patients, but may be dose dependent in susceptible individuals. They are uncommon, affecting a small number of patients based on an individual predisposition that depends on both genetic and environmental factors [76, 77].

The pathogenesis of Type A reaction was described in the sixteenth century by Paracelsus, the Swiss German Renaissance physician who founded the discipline of toxicology: "All things are poison, and nothing is without poison; only the dose permits something not to be poisonous" [78]. The pathogenesis of Type B reaction was designated in the first century BC didactic poem, De rerum natura (On the Nature of Things), by the Roman poet and philosopher Lucretius: "One man's meat is another man's poison" [79].

Type B reactions can be categorized into different subtypes according to Gell and Coombs' classification system [80]. The effector phase of the allergic reaction is classified into four types: Type I mediated by drug-specific IgE antibodies, Types II and III mediated by drug specific IgG or IgM or IgA antibodies, and Type IV induced by drug-specifc T lymphocytes [81]. This classification system may be helpful in daily clinical practice as a guide to diagnostic and therapeutic decisions.

In addition to the basic classification of Type A and B reactions, further types of reactions were subsequently added; Type C- dose and time-related, 'Chronic'; Type D- time-related. 'Delayed'; Type E- withdrawal effects, 'End of use'; and Type F- unexpected failure of therapy, 'Failure' [2].

Severity of Cutaneous ADRs: Skin only (Simple) Versus Skin and Systemic Involvement (Complex)

The diagnosis of a cutaneous ADR must be followed by differentiation between a simple reaction involving only the skin and a complex reaction that includes systemic involvement of organs in addition to the skin [82]. Systemic

involvement should be explored even in a mild cutaneous eruption due to a drug since the severity of skin manifestation does not necessarily mirror the severity of the systemic involvement. Systemic involvement is evaluated by assessing the patient's symptoms, including fever, facial edema, malaise, chills, dyspnea, cough, palpitations, nausea, vomiting, diarrhea, sore throat and arthralgia. Further investigation is based on the patient's symptoms. Basic laboratory screen, conducted in cases of suspected systemic involvement, includes a full blood count, liver and renal function tests, and urine analysis [83].

Histological Classification of Cutaneous ADRs

Skin biopsy is an invaluable diagnostic modality in the assessment of drug eruptions. Histologically, drug eruptions can elicit a variety of inflammatory disease patterns in the skin and panniculus, and overlapping reaction patterns. Ackerman et al.'s basic patterns of inflammatory skin diseases [84] (Table 25.3) are a helpful guide. The most common pattern of drug eruptions is the perivascular type, while psoriasiform and granulomatous patterns are rarely reported [85]. Drug eruptions may also mimic specific skin diseases

such as lupus, lichen planus or lymphoma [85]. A single drug may cause a wide range of reaction patterns and no reaction pattern is specific for a particular drug [88]. While the histological changes are not distinctive in many cases of drug eruption, a few important histopathological clues may aid in the diagnosis: (1) Overlapping histological patterns in one specimen (e.g., lichenoid and spongiotic). (2) Presence of eosinophils (although not mandatory); although eosinophils are an important tell-tale sign of a drug-induced reaction, they may also be conspicuous in skin rashes devoid of a drug association and sparse or absent in some drug exanthems. (3) Apoptotic keratinocytes. (4) Mismatch between clinical and histomorphological features [85, 86, 88].

In a study assessing the histological pattern of 104 cases of diagnosed drug eruption during a 5-year period in one institution [89], the majority of the cases (94%) were morbilliform-type rashes. The most common histological pattern was superficial perivascular and interstitial with interface changes. Eosinophils were present in only 50% of cases, and approximately half (53%) of the cases exhibited epidermal-dermal interface changes [89].

In view of the large diversity of cutaneous drug reactions, it is helpful to approach them as clinicopathologic entities and to base the diagnosis on a combination of clinical, histo-

Table 25.3 Pattern analysis of the main types of cutaneous ADRs according to Ackerman et al.'s classification of inflammatory skin diseases [84–87]

Perivascular	Superficial perivascular	Mixed infiltrate	Spongiotic	Psoriasiform	Interface pattern

	Purpuric drug eruption	Urticarial drug eruption	Pityriasis rosea–like eruption
			Photosensitive drug eruptions:
			  Phototoxic reaction
			  Photoallergic reaction
				Psoriasiform drug eruption	Vacuolar:
					  EM
					  SJS
					  TEN
					  FDE
					  Morbilliform drug eruption
					  Lupus erythematosus-like eruption
					  Chemotherapy-induced interface dermatitis
					Lichenoid drug eruption

Nodular and diffuse	*Lymphomatous*	*Neutrophilic*	*Granulomatous drug eruptions*		
	Pseudolymphomatous drug reaction	Drug-induced Sweet syndrome	Interstitial granulomatous drug reaction (IGDR) Drug-induced accelerated rheumatoid nodulosis Drug-induced granuloma annulare Drug-induced sarcoidosis		
Vesiculobullous	Drug-induced linear IgA bullous dermatosis	Drug-induced pemphigus	Drug-induced bullous pemphigoid	Drug-induced pseudoporphyria cutanea tarda	
Pustular	AGEP				
Vasculitis	Drug-induced vasculitic reaction				
Folliculitis and perifolliculitis	Acneiform drug eruptions	Drug-induced eosinophilic pustular folliculitis (Ofuji's disease)			
Fibrosing dermatitis	Sclerodermoid drug reaction				
Panniculitis	Drug-induced panniculitis				

EM erythema multiforme, *SJS* Stevens-Johnson syndrome, *TEN* toxic epidermal necrolysis, *FDE* fixed drug eruption, *AGEP* acute generalized exanthematous pustulosis

logical and disease course data [89]. Heightened awareness of the possible mimicry of other skin diseases and of the suspicious histopathological clues pointing to drug etiology are key elements to the appropriate histological diagnosis of drug reactions in the skin [85, 88, 89].

Morphological Classification of Cutaneous ADRs

A widely accepted approach to diagnosing the type of drug eruption is a simplified method based on the morphology of the primary lesions. The four main categories are maculopapular, urticarial, pustular and blistering [82]. The diagnosis of the drug eruption can be challenging since the same cutaneous morphology can be manifested in a simple reaction involving only the skin and in a complex reaction including systemic involvement in addition to the skin. Therefore, there are two major steps in diagnosing drug eruptions: determine the morphology and assess systemic involvement [90].

Maculopapular Eruptions – MPE (Synonyms: Morbilliform, Exanthematous)
Terminology The term 'maculopapular' is descriptive. Morbilliform means measles-like, the rash of measles consisting of macules and papules that tends to confluence. The etymon of 'exanthema' is the Greek 'exanthema', which means 'a breaking out'. Thus exanthema merely means 'rash', and 'exanthematous rash' literally means 'rash-like rash'. Therefore, the terminology is redundant [89].

Skin Signs Polymorphous pink-to-red macules and or papules usually in a symmetric distribution that may coalesce to form plaques (Fig. 25.1) [91]. The eruption begins on the trunk and upper extremities and progressively becomes confluent. In addition, purpuric lesions may appear on the ankles and feet [90]. The drug eruption can also manifest in a scarlatiniform pattern of pinpoint-sized pink-red papules coalescing and giving the skin the texture of sandpaper [92].

Maculopapular Eruptions – MPE – Simple (Skin Only)
Frequency The most common drug-induced eruptions, occurring in 1–5 % of first-time users of most drugs [91].

Lag Period 7–14 days [90].

Symptoms Pruritus and low-grade fever are common [91].

Common Sites of Involvement The eruption usually begins on the trunk and becomes generalized. Palms and soles are often involved; mucous membranes are usually spared [90].

Histology Nonspecific changes consisting of mostly superficial but also deep perivascular and interstitial infiltrate of lymphocytes. Eosinophils and epidermal-dermal interface changes appear in approximately half the cases [89].

Differential Diagnosis viral exanthems, scarlet fever, toxic shock syndrome, acute graft versus host disease (GVHD), Kawasaki disease, juvenile idiopathic arthritis [90].

Treatment Identifying and discontinuing the causative drug are the most important steps in management. Symptomatic treatment with antipruritic agents and potent topical glucocorticoids may be helpful [91]. A decision can be made to continue the drug and offer symptomatic treatment if the drug is of paramount importance, but the risk: benefit ratio of this option has to be carefully weighed, and the evolution of the eruption must be meticulously monitored [90].

Prognosis The eruption often fades within 7–14 days of discontinuation of the offending drug and scaling and desquamation may follow. Re-challenge may lead to reappearance of the reaction within a few days [90].

Offending Drugs The most common classes of drugs implicated are penicillins, sulfonamides, cephalosporins, and antiepileptics [90].

Maculopapular eruptions – MPE – Complex (skin + systemic involvement): DRESS – See Severe Cutaneous Adverse Drug Reactions.

Urticarial Eruption
Terminology The term 'urticaria', first introduced by William Cullen in the eighteenth century, is derived from urtica urens (common European stinging nettle). One of the earliest descriptions of urticaria comes from China, and is more than
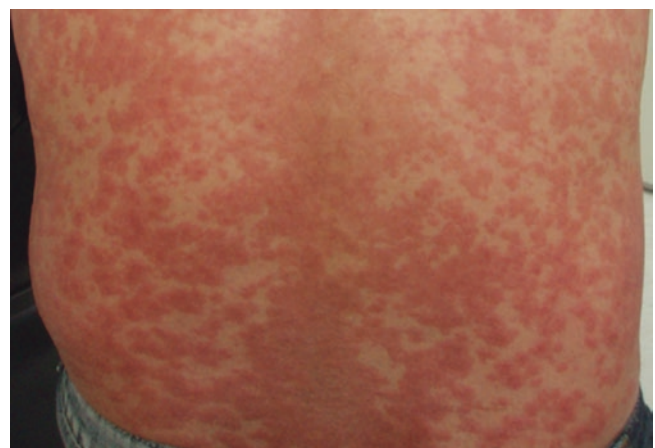

Fig. 25.1 Erythematous macules and papules coalescent into ill-defined plaques on the trunk – maculopapular morphology of cutaneous ADR

2,000 years old. In the Huangdi Neijing, written around 200 BC, urticaria is referred to as Feng Yin Zheng ('wind type concealed rash'). In ancient Latin medical literature, urticaria was called 'uredo' (urere means 'to burn'), and in the old Persian medical texts, 'essera' (meaning 'elevation') [93].

Skin Signs Urticaria is induced by superficial dermal swelling due to plasma leakage and vasodilation triggered by activation of mast cells. The skin manifestations of this process include erythematous and edematous papules and plaques (wheals) of various sizes that may coalesce to form large plaques [94]. Wheals may be characterized by pink or pale center and assume a figurate or polycyclic configuration. Linear lesions can be seen with dermatographism [92, 94].

Urticarial Eruption – Simple (Skin Only)

Frequency Drug-induced urticarial eruptions are the second most common type of cutaneous drug eruption and account for approximately 5 % of all cutaneous drug eruptions [85].

Lag Period Urticaria occurs within minutes to days of drug administration [94].

Symptoms A major clinical feature is pruritus, the lack of which should put the diagnosis in doubt. The lesions can also be painful if they occur on the soles, over joints, or in areas where the skin is tightly adhered to subcutaneous tissue [94]. A single lesion lasts less than 24 h and upon resolution leaves normal skin. However, new lesions may continue to arise for various periods of time. Acute urticaria is defined when a bout of hives lasts less than 6 weeks; when it lasts longer, it is defined as chronic urticaria [95].

Urticaria may be associated with angioedema [93]. Angioedema is defined as a deep, dermal, subcutaneous and/or mucous swelling that may involve the intestinal lining and the upper respiratory tract. Symptoms include slight heat, burning, pain and sensation of pressure or tightness. However, pruritus is minimal or absent. Swelling of gastrointestinal tract mucosa can induce abdominal pain, vomiting and diarrhea. Edema of the respiratory tract may induce various symptoms including life-threatening asphyxia. Drug-induced angioedema is associated with urticaria in approximately 50 % of cases. Some drugs may induce angioedema without urticaria [96].

Common Sites of Involvement Lesions of urticaria can appear anywhere on the skin, including the palms, soles and scalp, but not on mucosal surfaces [94]. Angioedema most commonly occurs in the head, neck and hands, but can occur anywhere and frequently involves mucosal tissue. Swelling may be more prominent in areas of looser skin, such as the scrotum, labia, lips, and eyelids [94].

Histology Urticarial drug reactions are characterised by dermal edema and a superficial and deep perivascular and interstitial dermatitis. The mixed inflammatory infiltrate comprises lymphocytes, histiocytes, mast cells, eosinophils and neutrophils. The presence of neutrophils and deep vascular plexus involvement may be a clue to the drug-induced nature of the urticaria [86].

Differential Diagnosis The wheals with central red halo of urticaria may resemble the target lesions of erythema multiforme. Four clinical signs of urticaria can help distinguish it from erythema multiforme: (1) The central zone consists of normal skin, whereas in erythema multiforme, skin is dusty, bullous or crusted. (2) Each lesion is transient, lasting less than 24 h, whereas erythema multiforme lesions are 'fixed' for a few days. (3) New lesions appear daily and in erythema multiforme all lesions appear within the first 72 h. (4) There may be associated swelling of face, hands and feet and in erythema multiforme there is no edema [97]. Differential diagnosis of urticaria includes also bullous pemphigoid, urticarial vasculitis and serum sickness-like reaction (SSLR). Drug-induced urticaria needs to be differentiated from cases of urticaria induced by other etiologies, such as food, environmental allergens, insects, systemic illness, physical stimuli, genetic and idiopathic [94].

Urticaria and angioedema are the most common symptoms of anaphylaxis (88 % of cases), and are one of the clinical criteria of the National Institute of Allergy and Infectious Disease (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) for the diagnosis of anaphylaxis [98]. Therefore, all cases of sudden acute urticaria and angioedema should be evaluated for indications of the anaphylactic type of reaction: presence of respiratory compromise, decreased blood pressure, and end-organ dysfunction (collapse, syncope, incontinence) [98].

Treatment The most important step in the management of drug induced urticaria with or without angioedema is withdrawal of the causative agent. In most cases of acute urticaria, when the trigger is removed the rash quickly resolves. H1-receptor blockers are the mainstay of treatment for patients with only cutaneous symptoms. Systemic glucocorticoids are indicated in all cases with upper airway edema and should be considered in cases with extensive cutaneous involvement. Epinephrine is reserved for angioedema with upper airway involvement [94]. The presence or absence of any airway involvement should be specifically investigated.

Prognosis Both urticaria and angioedema fade without visible sequelae. Following resolution, there should be no residual pigmentary changes unless excoriated [94].

Offending Drugs Many drugs can induce acute urticaria, and do so by both immunologic and non-immunolgic mechanisms. The major drugs responsible for immunologically based urticaria are antibiotics, especially penicillins

and cephalosporins [90]. The major drugs triggering mast cell release (non-immunolgic mechanisms) are aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), opioids and radiocontrast media [90]. Viral infections or connective tissue diseases may induce or augment urticarial drug reactions [86].

Urticarial Eruption – Complex (Skin + Systemic Involvement)

• **Anaphylaxis**

The National Institute of Allergy and Infectious Diseases (NIAID) and the Food Allergy and Anaphylaxis Network (FAAN) defined anaphylaxis as a systemic reaction resulting from the sudden release of multiple mediators from mast cells and basophils, often life threatening, and usually unexpected. The World Allergy Organization (WAO) has divided anaphylaxis into immunologic (further divided into immunoglobulin E [IgE]-mediated and non-IgE-mediated), non-immunologic, and idiopathic causes. Drugs are the second most common cause of anaphylaxis after food, which constitutes 20 % of triggers [98]. Common medications associated with anaphylaxis include penicillins, NSAIDs, and biologic response modifiers [99]. The NIAID/FAAN definition of anaphylaxis has been translated into clinical diagnostic criteria that include an acute onset of illness (minutes to hours) and involvement of the dermatologic, respiratory, cardiovascular, or gastrointestinal systems [98]. Epinephrine is the only first-line treatment for anaphylaxis and is the sole effective treatment for an acute reaction. Delays in administration have been associated with fatalities. Supportive treatment with oxygen, fluids and additional drugs are also necessary according to the cardiopulmonary resuscitation (CPR) anaphylaxis algorithm [98].

• **Serum sickness-like reaction (SSLR) – See Severe Cutaneous Adverse Drug Reactions**.

Pustular Eruptions

Terminology   The term pustule originates in classical Latin in which pustule means a blister [100].

Skin Signs   Pustular drug eruptions are characterized by monomorphic eruption consisting of erythematous papules (mostly follicular) and pustules at the same location lacking comedones.

Pustular Eruptions – Simple (Skin Only)

Acneiform Drug Eruptions (Acne Medicamentosa)
The term acneiform is applied to eruptions that resemble acne vulgaris.

Frequency   Varies, depending on the drug. The highest incidence involves epidermal growth factor receptor inhibitors (EGFRIs), affecting 60–100 % of patients [101].

Lag Period   The eruption begins after a variable delay; corticosteroids may induce an acneiform eruption from shortly after their introduction (2–4 weeks) to several months [101]. Acneiform eruptions induced by EGFRIs usually appear after 1–2 weeks of treatment but can also occur after only a few days [102].

Symptoms   Pruritus, tenderness and pain may occur. In cases of chemotherapy-related side effects, their appearance and severity are part of the criteria used for the classification of the ADR [103].

Common Sites of Involvement   Lesions may be located in and beyond the seborrheic areas, such as the arms, trunk, lower back and genitalia [104].

Histology   Drug-induced acneiform eruptions show histopathologic features similar to acne vulgaris. Early lesions most commonly have a corneocytic plug within a widened infundibulum, accompanied by infundibular spongiosis, perifollicular edema, with sparse perivascular and peri-infundibular infiltrates of neutrophils and lymphocytes. Larger older lesions show similar findings but the infiltrate is denser, with more neutrophils around the involved follicles, and infundibular rupture [85, 88]. In a review of the histological findings of acneiform eruptions induced by EGFRIs [105], all ten cases showed a superficial, predominantly neutrophilic suppurative folliculitis with ectatic infundibula and a rupture of the epithelial lining.

Differential Diagnosis   The main differential diagnosis is acne. The following clinical characteristics of acneiform drug eruptions may aid in differentiating between the two entities: (1) Clinical presentation: monomorphic pattern, lack of comedones and cysts and localization on areas beyond the seborrheic area. (2) Patient characteristics: age of onset before or after the teens, and absence of past history of acne. (3) Resistance to conventional acne therapy. (4) Time relationship: onset after recent drug introduction, improvement after drug withdrawal, and recurrence after drug reintroduction [101]. The differential diagnosis also includes folliculitis, rosacea, perioral dermatitis, demodicosis, acne cosmetic, acne mechanica, chloracne, acne necrotica and acneiform presentation of cutaneous lymphomas [104].

Treatment   The main treatment is withdrawal of the offending drug and the application of topical treatments as needed (benzoyl peroxide topical antibiotics and topical retinoids) [90]. The management of acneiform eruptions associated

with chemotherapy differs from all other types of acneiform drug euptions, as acneiform eruption is an expected outcome and discontinuation of the medication is not an option in a patient who is responding to therapy [102, 103, 106, 107]. In fact, continuation of EGFRI therapy in these patients may be especially favourable in view of studies that have shown an increased survival with increasing severity of rash [102]. The cutaneous reaction serves as an important clinical tool for determining tumor response and survival [102]. The National Cancer Institute developed a scale for defining the degree of rash and laid down management guidelines for each stage [103]. Other management protocols were suggested by Bachet et al. [107], who recommended that unless contraindicated, a tetracycline should be routinely prescribed for the prevention of acneiform eruption in patients treated with an EGFRI for more than 6 weeks. Chiang et al. [106] reported successful treatment with isotretinoin for high grade and refractory cases.

Prognosis In most patients with acneiform drug eruption, the rash resolves upon discontinuation of the offending drug and the use of topical treatment. In EGFRI-induced acneiform eruption, prophylactic administration of a tetracycline was associated with significantly lower incidence of grade 2–3 folliculitis and improved quality of life of patients [107].

Offending Drugs The drugs responsible for acneiform eruptions include [101]:

- Hormones: corticosteroids and corticotropin – adrenocorticotropic hormone (ACTH), androgens and anabolic steroids, hormonal contraceptives; other hormones – thyroid-stimulating hormone, danazol.
- Neuropsychotherapeutic drugs: tricyclic antidepressants, lithium, antiepileptic drugs, aripiprazole, selective serotonin reuptake inhibitors.
- Vitamins: B1, B6, B12, D2.
- Cytostatic drugs: dactinomycin – actinomycin D, azathioprine, thiourea, thiouracil.
- Immunomodulating molecules:cyclosporine, sirolimus.
- Antituberculosis drugs: isoniazid, rifampin, ethionamide.
- Halogens: iodine, bromine, chlorine.
- Targeted therapies: EGFRIs (cetuximab, panitumumab), multitargeted tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib,sorafenib, sunitinib, imatinib), vascular endothelial growth factor inhibitor (bevacizumab), proteasome inhibitor (bortezomib), tumor necrosis factor-a inhibitors (lenalidomide,infliximab), histone deacetylase inhibitor (vorinostat).
- Miscellaneous: dantrolene, quinidine, antiretroviral therapy antibiotics.

Drug-Induced Eosinophilic Pustular Folliculitis (Ofuji's Disease)

Few cases of drug-induced eosinophilic pustular folliculitis have been reported [88, 108–111]. Drugs reported include chemotherapy (cyclophosphamide, methotrexate, and 5-fluorouracil) [108], minocycline [109], carbamazepine [110], and allopurinol with timedium bromide [111]. Clinical presentation includes pruritic follicular papules and pustules on the face, scalp, trunk and arms [88]. Histological findings include spongiosis of the follicular epithelium, and an intra- and perifollicular lymphohistiocytic infiltrate with numerous eosinophils that form microabscesses within the follicular epithelium [88]. Topical steroids are the first line of treatment [108].

Pustular eruptions – Complex (skin + systemic involvement)

Acute generalized exanthematous pustulosis (AGEP) – See Severe Cutaneous Adverse Drug Reactions.

Bullous Eruptions

Bullous Eruptions – Simple (Skin Only)

Pseudoporphyria
Terminology The term pseudoporphyria was coined in 1975 by Korting to describe patients with chronic renal failure and a bullous disease resembling porphyria cutanea tarda (PCT) [112].

Frequency The incidence of pseudoporphyria is unknown. However, in a 6-month prospective study, 12 % (9/74) of children taking naproxen for juvenile idiopathic arthritis developed pseudoporphyria [113].

Lag Period The skin lesions appear following drug intake combined with exposure to light. Various time durations were reported, weeks to months [114–116].

Skin Manifestations The clinical features of pseudoporphyria may be identical to those of PCT; both exhibit vesicles, bullae, milia, and scarring on sun-exposed skin. In contrast to PCT, however, hypertrichosis, hyperpigmentation, sclerodermoid changes, and dystrophic calcification are rarely reported in pseudoporphyria [117]. Often, fragility and bruising may be the only clinical signs [116]. In children, facial scarring resembling erythropoietic protoporphyria (EPP) may be found [117].

Symptoms Skin fragility and photosensitivity [116].

Common Sites of Involvement The lesions appear on sun-exposed skin, particularly the hands and feet, but also on the face and extensor surfaces of legs [116].

Histology the histological features are identical to those seen in PCT. The blisters are subepidermal and the floor of the blister is typically lined by well-preserved dermal papillae (festooning). There is usually no significant inflammatory component although a light perivascular lymphocytic infiltrate may occasionally be seen in the superficial dermis. Thickening of the superficial vessels (highlighted by a PAS stain) and dermal sclerosis with elastosis may be apparent. In both pseudoporphyria and PCT, direct immunofluorescence reveals granular deposits of IgG and C3 at the basement membrane zone and in the perivascular region [115].

Differential Diagnosis While pseudoporphyria and PCT share clinical and histologic features, they can be differentiated by several features. Most important, by definition, biochemical porphyrin abnormalities are absent in pseudoporphyria. Epidemiologically, pseudoporphyria affects mainly women while is a male predilection in PCT. Clinically, hypertrichosis, hyperpigmentation, sclerodermoid changes, and dystrophic calcification are frequently evident in PCT and conspicuously absent in pseudoporphyria [117]. The differential diagnosis also includes other types of cutaneous porphyria that manifest with blistering, epidermolysis bullosa acquisita, polymorphous light eruption, and other photosensitive dermatosis [117].

Treatment Treatment entails discontinuation of suspected agents and sun protection, especially against UVA wavelengths, for several months following withdrawal of the drug [114].

Prognosis Blisters may continue to appear for weeks-months after discontinuation of the offending drug [117].

Offending Drugs The most common group of drugs causing pseudoporphyria are NSAIDS [117]. Other groups are antibiotics, diuretics and retinoids. Additional culprits are hemodialysis, renal failure, tanning beds and excessive sun exposure [117].

Fixed Drug Eruption (FDE)

Terminology Fixed drug eruption (FDE) was first reported by Boums in 1889 [118], and the term was coined by Brocq in 1894 [119].

Frequency The incidence is not known, but is suspected to vary greatly by geographic region [120].

Lag Period After initial use of the offending agent, a variable refractory period of weeks, months or years may pass before the lesions first appear on the skin of a sensitized individual [121]. Repeated exposure to the agent typically results in acute lesions within 30 min to 8 h. A refractory phase may occur following an acute flare in which exposure to the offending drug will not exacerbate the lesion for weeks to months [121].

Skin and Oral Membrane Manifestations In its classical form, FDE typically presents round or oval, sharply demarcated, red to livid, slightly elevated plaques ranging from several millimeters to over 10 cm in diameter. Vesicles or even blisters can develop [122]. Usually only a single lesion appears. Sometimes, multiple lesions are present and even lead to generalized FDE characterized by multiple, sharply defined, deep red macules distributed bilaterally and often symmetrically. Generalized bullous FDE is characterized by flaccid blisters arising on these macules. Mucosal lesions are usually bullous and may appear with or without involvement of other areas of the skin [122].

Symptoms Patients often complain of burning and itching in the lesions. General symptoms such as fever, nausea, dysuria, abdominal cramps and diarrhea are rare [122]. Pruritus and burning may be the only manifestations of reactivation in a postinflammatory hyperpigmentation lesion [121].

Common Sites of Involvement The eruption can occur anywhere on the body, but the lips, palms, soles, genitalia (especially male genitalia), groin and occasionally oral mucosa are favored sites [121]. The diagnostic hallmark of FDE is the reappearance of the lesions precisely over the previously affected sites. Studies investigating the predilection areas indicate that some specific kind of drugs cause FDE predominantly at specific sites: examples are tetracycline and location on the male genital area, and naproxen and FDE on the lips [122]. In rare cases, FDE manifests in old trauma sites such as BCG vaccination, burn scar, venipuncture site or insect bite. With each recurrence, additional sites may be affected. The presence of numerous lesions is referred to as generalized FDE [122].

Histology Histologically, the acute phase is characterized by marked basal cell hydropic degeneration, with lymphocyte tagging along the dermoepidermal junction and individual keratinocyte necrosis. Marked pigmentary incontinence is typical, and may be the sole histological finding in late lesions [121].

Differential Diagnosis Skin lesions can imitate various dermatoses, including lichen planus, erythema multiforme, erythema annulare centrifugum, and pityriasis rosea. In generalized FDE, residual pigmentation in healed lesions may be reminiscent of erythema dyschromicum perstans. Involvement of oral and genital mucosa raises the possibility of herpes simplex, pemphigus vulgaris, aphthous stomatitis, Behçet syndrome, and erosive lichen planus [122]. Generalized bullous FDE may resemble SJS/TEN. The following typical

clinical features of generalized bullous FDE may aid in differentiating between conditions: (1) Blistering usually affects only a small percentage of body surface area, and between the large blisters there are sizable areas of intact skin. (2) Erosive mucosal involvement is rare, and when it does occur is rather mild. (3) Patients usually do not feel sick or have fever, and generally are in much better overall health than those with SJS/TEN. (4) Most patients report a history of a similar, often local reaction [123].

Treatment For mild lesions, topical corticosteroids usually suffice. In severe involvement, especially generalized bullous FDE, systemic corticosteroids may be indicated. Strict avoidance of the causative drug and cross-reacting substances is essential for prophylaxis. Successful desensitization was reported [122].

Prognosis The prognosis of localized FDE is good and the lesions fade within a few days to leave a post-inflammatory brown pigmentation [122]. Generalized bullous FDE does not have this benign nature and the mortality rate was 22 % in a recent case control study of 58 patients [120].

Offending Drugs The most common groups of drugs implicated are antibiotics, analgesics, antiphlogistics and hypnotics [122]. There is usually only one causative drug (monosensitivity), but sometimes several drugs can induce FDE in the same patient (multisensitivity). It has also been claimed that recurrences of FDE can be induced in nonspecific fashion by mast cell degranulators such as food, acetylsalicylic acid, bacterial toxins, or physical stimuli [122].

Bullous Eruptions – Complex (Skin + Systemic Involvement)

- **Drug-induced/triggered autoimmune blistering dermatosis (pemphigus, bullous pemphigoid (BP)) and linear IgA bullous dermatosis (LABD)**

Terminology Pemphigus Two Italian dermatologists, Caccialanza and Bellone, were the first to imply activation of pemphigus by a drug (penicillin) in 1951 [124]. However, Degos's publication in 1969 of penicillamine-induced pemphigus in a patient with Wilson's disease is considered the first report of drug-induced pemphigus [125].

BP	Bean et al. reported the first case of drug-induced BP in 1970 [126].
LABD	Baden et al. reported the first case of drug-induced LABD in 1988 [127].

Cases of autoimmune blistering dermatosis resulting from exposure to drugs present clinical, histologic and immunopathologic features identical or very similar to those seen in idiopathic disease, but are induced by systemic ingestion or local use of certain drugs. There appear to be two main types: drug-induced autoimmune blistering dermatosis proper, the acute and self-limiting type with rapid resolution after withdrawal of the offending agent; and drug-triggered autoimmune blistering dermatosis in which the role played by the drug is only secondary to hereditary and immunologic factors. The drug stimulates a predisposition (hidden susceptibility) to develop the disease and is considered the chronic type in which the disease persists despite withdrawal of the offending agent [128, 129].

Frequency Unknown.

Lag Period	Pemphigus	Weeks to months [130, 131]
BP		Days to weeks [132, 133]
LABD		Days to weeks [134, 135]

Symptoms/Common Sites of Involvement/Histology Similar to the idiopathic type of autoimmune blistering dermatosis.

Differential Diagnosis There are no distinctive clinical features that enable differentiation between drug-induced/triggered and idiopathic autoimmune bullous dermatosis. It is obvious that spontaneous remission following withdrawal of the offending drug points to a drug-induced autoimmune blistering dermatosis. However, other clinical findings may also be suggestive of a drug origin in cases of pemphigus and BP: (1) Patients are younger than those with idiopathic disease. (2) Mucous membranes are frequently involved. (3) Combined clinical and immunohistologic features of various immunobullous diseases may exist. (4) Severe general status may appear including high fever. (5) In cases of drug-induced pemphigus, features of pemphigus foliaceus are more common than those of pemphigus vulgaris [130, 133, 136]. Of note, drug-induced LABD patients tend to be older than idopathic type patients [134, 135].

The polymorphic nature of the eruption may mimic other bullous diseases and or drug-induced bullous diseases such as SJS, TEN, and FDE [136].

Treatment Treatment consists of discontinuing the offending agent, and, depending on the severity of the disease, systemic immunosuppressive treatment [129].

Prognosis Drug-induced autoimmune blistering dermatosis remits after the offending drug is withdrawn, while drug-triggered autoimmune blistering dermatosis may persist despite withdrawal of the offending agent and chronic immunosuppressive treatment may be required [129, 130].

Offending Drugs Pemphigus Two major groups of chemical structures were found in the drugs or their metabolites implicated in pemphigus: sulfhydryl radical drugs (thiol drugs or SH drugs) such as penicillamine, and phenol drugs such as aspirin [128, 137, 138].

BP	Many drugs were reported [129, 132, 136], the most frequent being NSAIDS, cardiovascular

agents and penicillin-derived antibiotics [136]. In addition, external use of skin and mucous membrane preparations has been documented to provoke cases of either BP or cicatricial pemphigoid [136].

LABD   Of the various drugs reported, vancomycin is the most common [134, 135, 139].

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) – See Severe Cutaneous Adverse Drug Reactions.

Severe Cutaneous Adverse Drug Reactions

Drug reaction with eosinophilia and systemic symptoms (DRESS), Drug-induced hypersensitivity syndrome (DIHS), Drug-induced delayed multiorgan hypersensitivity syndrome.

Epidemiology

The incidence of DRESS remains to be determined because of variable presentations and lack of universally accepted diagnostic criteria [140]. The estimated risk at first or second prescription of an aromatic antiepileptic drug was 1–4.5 in 10,000 [141]. A slight female predominance was found in the RegiSCAR study (male/female 0.8) [142].

Etiology

The drugs most commonly inducing DRESS are anti-convulsants (mainly aromatic anti-convulsants such as carbamazepine), allopurinol, sulfonamides (the anti-infective sulfamethaxazole-trimethoprim, and the anti-inflammatory sulfasalazine), and antibiotics (such as vancomycin and minocycline) [142]. Numerous other drugs have been reported [140, 143, 144].

The role of human herpesvirus (HHV) reactivation in the development of this adverse drug reaction is well recognized, especially HHV-6 [145]. HHV-6 reactivation is among the diagnostic criteria of the Japanese consensus group for DRESS/drug-induced hypersensitivity syndrome [146]. The reactivation of other herpesviruses, including HHV-7, cytomegalovirus (CMV), Epstein-Barr virus (EBV), and human herpes simplex virus was also reported [147].

DRESS is considered to result from complex interactions between genetic predisposition, exposure to drug and viral reactivation [148].

Lag Period

Delayed onset of 2–8 weeks after drug administration followed by a stepwise development of manifestations. Rechallenge can result in a reaction within hours to days [26]. The lag period differs between drugs; carbamazepine tended to show a longer latency (median 29 days) than allopurinol (median 20 days) in the RegiSCAR study [142].

Clinical Features

DRESS has multi-organ involvement with cutaneous, mucosal, hematological and solid organ manifestations.

Skin   The cutaneous involvement in DRESS is typically extensive and symptomatic (pruritus, burning and pain) [142, 143]. Various dermatological features were reported. Walsh et al. [143] proposed a classification system based on four distinct patterns: (1) urticated papular exanthema, the most common, (2) morbilliform erythema, (3) exfoliative erythroderma, and (4) erythema multiforme-like (EM-like), which was prognostic of more severe hepatic involvement. The extent of skin involvement varies between studies: it exceeded 50 % of the body surface area in most of the patients (79 %) according to the RegiSCAR study [142]; head and neck edema observed in most patients [26, 142]; and pustules reported in various studies, predominantly in a facial distribution of the edema [142, 143].

Mucous Membranes   Mild mucosal involvement was recorded in 56 % of patients with DRESS (66/117 cases) in the RegiSCAR study [142]. Most frequent were oral lesions including lips, oral cavity and throat [142]. The manifestations of oral lesions in DRESS include cheilitis, erosions and dysphagia that may appear before skin lesions, and oropharaynx is considered the first site of herpesvirus reactivation in DRESS [149]. Involvement of eyes and genitalia were also reported in the RegiSCAR study [142].

Systemic Involvement   Multi-organ involvement is common in DRESS and may include a wide variety of systems. High-grade fever (38–40 °C) is a typical early manifestation that may last for several weeks; it often precedes the cutaneous eruption by several days [142]. Lymphadenopathy is common and has two distinct types: a benign pattern of lymphoid hyperplasia and a pseudolymphoma pattern [150]. Hematologic abnormalities are frequent and diverse, the most common being marked leukocytosis, eosinophilia and atypical lymphocytes [142]. However, neutrophilia, monocytosis, thrombocytopenia, anemia, pancytopenia and hemophagocytic syndrome were also reported [140, 142, 143, 151]. Hypereosinophilia and activated neutrophils, if persistent, can contribute to organ damage [142]. The liver is the most frequently affected visceral organ in DRESS; hepatitis with isolated elevation of liver enzymes is common and usually anicteric and without cholangitis. However, severe acute hepatitis with liver failure may result and is the primary cause of mortality in DRESS [150]. Renal involvement is common [150]. Involvement of the following organs was also reported: lungs, muscle, heart, pancreas, colon, thyroid, joints, parotid

gland and brain [150]. The type of organs involved was found to be related to the eliciting drug [152].

Histology

The most common pathological changes found in a study of 32 patients with DRESS were basket-weave hyperkeratosis (94 %), dyskeratosis (97 %), lymphocytic exocytosis (91 %), spongiosis (78 %), papillary edema (66 %), perivascular lymphocytic infiltration (97 %), eosinophilic infiltration (72 %), and interface vacuolization in the dermoepidermal junction (91 %) [26]. The presence of severe dyskeratosis was correlated with a greater extent of systemic involvement [26]. In a different study assessing the histological findings of 27 cases with DRESS [143], the predominant pathological pattern was spongiotic dermatitis with superficial lymphocytic infiltrate (59 %); necrotic keratinocytes were noted in 33 % of cases, and were associated with a worse hepatic involvement [143].

Diagnostic Criteria

The diverse presentations in DRESS have hampered efforts to define diagnostic criteria. Three diagnostic criteria have been proposed: Bacquet et al. [153], the Japanese study group of severe cutaneous adverse reactions to drugs (J-SCAR) [146], and the RegiSCAR network [154].

Treatment

The first step in the management is immediate withdrawal of the culprit drug. The treatment is tailored according to the severity and extent of systemic involvement, and the diagnosis of viral reactivation of herpesviruses (mostly HHV-6) [150, 155, 156]. Management protocol for DRESS based on the consensus of experts was designed by the French Society of Dermatology [156], and includes four visceral involvement severity categories and corresponding treatment: (1) No severe systemic involvement: topical corticosteroids (potent or very potent), emollients, H1-antihistamines. (2) Severe systemic involvement (transaminases >5 times normal, renal involvement, pneumonia, hemophagocytosis, cardiac, etc.): systemic corticosteroids equivalent to 1 mg/kg/day of prednisone and multidisciplinary evaluation. (3) Life-threatening signs (hemophagocytosis with bone marrow failure, encephalitis, severe hepatitis, renal failure, and respiratory failure): systemic steroids with intravenous immunoglobulin (IVIG) at a dose of 2 g/kg over 5 days. The IVIG should not be used without associated steroids. The treatments are to be conducted under multidisciplinary supervision. (4) Severe systemic involvement and confirmation of a major viral reactivation: combining steroids and antivirals (such as ganciclovir) and/or IVIG.

Counselling both the patient and his family members about drug avoidance is necessary. First-degree relatives have a higher risk of developing the same drug reactions [90]. Increased knowledge of HLA susceptibility genes enables screening patients with DRESS for several high risk drugs [148, 157].

Prognosis

Symptoms are usually present for several weeks even after discontinuation of the offending agent and appropriate treatment [155]. Late complications include the appearance of autoimmune diseases such as lupus erythematosus and autoimmune thyroiditis, with laboratory evidence of autoantibodies [144]. Systemic corticosteroids were found beneficial in the prevention of autoimmune disease. However, this effect needs to be counterbalanced against the higher risk of viral reactivation and infection. [144]. In a 1-year follow-up study of 52 affected patients with DRESS in Taiwan, the overall cumulative incidence of long-term sequelae was 11.5 %; four developed autoimmune diseases (Graves disease, type 1 diabetes mellitus and autoimmune hemolytic anemia); and the other two developed renal failure and required lifelong hemodialysis. The author concluded that the sequelae of DRESS can be divided into two major types that appear in different age groups: young patients tend to develop autoimmune diseases; elderly patients are more vulnerable to end-organ failure [158].

Mortality in DRESS has been estimated at 10 %, with most patients dying from liver failure [159]. Pancytopenia, leukocytosis, tachycardia, tachypnea, coagulopathy, gastrointestinal bleeding and systemic inflammatory response syndrome were associated with a poor outcome in DRESS patients [159, 160].

Serum Sickness-Like Reaction (SSLR)

Epidemiology

The incidence of SSLR is unknown. Epidemiology studies in children suggest that the overall frequency induced by cefaclor is 0.024–0.2 % per course of the drug [76]. Most reactions were reported in children under 5 years old, mainly during the second and third courses of therapy [161].

Etiology

Cefaclor is the most common cause of SSLR in children, inducing 84.1 % of cases [162]. Other drugs implicated include other cephalosporins, [163] penicillins, [164] minocycline, [165] insulin, [166] and infliximab [167].

Lag Period

Usually 7–14 days (range 0–20 days) [162, 168].

Clinical Features

Skin The skin is the most frequent finding in SSLR, including erythema that progresses to urticarial lesions (pruritic and migratory), urticarial wheals with dusty to purple centers ('purple urticaria') that morphologically resemble erythema multiforme (EM) [161] and other cutaneous manifestations including morbilliform or scarlatiniform eruptions [82].

Mucous Membranes Mucous membranes are not involved [161].

Systemic Involvement Joint involvement may be prominent, presenting with edema, decreased range of motion, warmth, pain, and difficulty walking. Polyarticular involvement is often observed, with involvement mainly of the wrists, ankles, hips and knees [169]. Some authors suggested that joint involvement may be related in part to increased fluid in the skin around affected joints due to urticarial eruption rather than arthritis [161]. Fever, malaise, myalgia and lymphadenopathy were also reported. Neurologic involvement, gastrointestinal symptoms and renal complications were rarely documented [163]. Notable laboratory abnormalities include elevated erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and leukocytosis [163, 170].

Histology

The histological findings of SSLR appear to be in the spectrum of urticaria with no vasculitis [171]. Histology can be helpful in differentiating SSLR from acute hemorrhagic edema of infancy, which is characterized by vasculitis [171].

Diagnostic Criteria

There are no diagnostic criteria. The diagnosis is based on clinical findings [161].

Treatment

Withdrawal of the offending agent and symptomatic treatment with oral antihistamines and topical corticosteroids are usually sufficient. A short course of oral corticosteroids may be required in patients with severe symptoms [82].

Prognosis

The disease course is benign and resolves in a few days. However, a few cases lasting several weeks have been described [170]. No long-term morbidity has been reported [172].

Acute Generalized Exanthematous Pustulosis (AGEP)

Epidemiology

The estimated incidence of AGEP is 1–5 cases per million per year [173]. Female predominance was reported in several studies [174–176].

Etiology

The majority of cases appear to be related to drugs (>90 %), mainly antibacterials [4]. In a large multinational case-control study (the EuroSCAR study), the following agents were highly suspected drugs for AGEP: prestinomycin, ampicillin/amoxicillin, quinolones, (hydroxy)chloroquine, anti-infective sulfonamides, terbinafine and diltiazem [176].

Lag Period

Latent periods fall into two categories, according to the offending drug: median duration of 1 day, associated with antibiotics (including sulphonamides), and median duration of 11 days for all other associated drugs [176]. Longer periods of months were reported in a few AGEP cases with an underlying malignancy [177].

Clinical Features

AGEP is a severe acute pustular cutaneous reaction characterized by a rapid clinical course [174].

Skin The typical morphology of AGEP is an acute edematous erythema with burning and or itching sensation, followed by dozens to hundreds of small (pinhead sized) non-follicular sterile pustules with a predilection for the big folds, or with widespread distribution (Fig. 25.2). Sometimes confluence of pustules may mimic a positive Nikolsky's sign [176, 178]. Additional cutaneous manifestations include marked edema of the face, purpura, blisters and target-like lesions [173, 174, 179], all of which overlap with manifestation of AGEP and TEN [180, 181], and acute localized exanthematous pustulosis (ALEP) [179, 182].

Mucous Membranes Mild, nonerosive mucous membrane involvement of one location (mostly oral) occurs in about 20 % of cases [183].

Systemic Involvement Fever (above 38 °C) and leukocytosis with neutrophilia are almost always apparent. Lymphadenopathy, myalgia, headache, mild eosinophilia, elevated CRP, slight reduction of creatinine clearance, and mild elevation of aminotransferases were also reported [173, 175]. A 10-year retrospective review of 58 patients with AGEP [184] turned up 10 patients (17 %) with at least one systemic involvement in the acute phase, 7 with abnormal hepatic function test, 6 with renal insufficiency, two with acute respiratory distress and one patient with agranulocytosis. Mean peripheral neutrophil counts and mean C-reactive protein levels were elevated significantly in patients with systemic involvement [184].

Histology

Biopsy specimen should be obtained from an early pustular lesion [183]. A histopathological study of 102 AGEP cases [185] found the following histopathological features: (1) All cases demonstrated pustules (sub/intracorneal and or intraepidermal). (2) The main epidermal features were spongiosis (80 %), neutrophil exocytosis (77 %) and necrotic keratinocytes (67 %). (3) The main dermal features were mixed superficial (100 %), interstitial (93 %) and mid/deepdermal infiltrates (95 %) containing neutrophils (100 %) and eosinophils (81 %).

Fig. 25.2 Multiple, pin-head sized, non-follicular pustules on erythematous skin on the trunk in a patient with AGEP

Diagnostic Criteria

The AGEP validation score developed by the Euro- SCAR study group is a standardized scoring system made up of data related to clinical features (morphology and clinical course) and histopathology. Based on this score, AGEP cases can be categorized as no AGEP, possible AGEP, probable AGEP, and definite AGEP [173].

Treatment

Treatment consists of discontinuation of the causative drug and supportive treatment. Although, specific treatment is generally unnecessary, topical and systemic steroids were reported [174, 175]. The treatment of overlapping AGEP and TEN cases is not yet established [180], although successful treatment with infliximab was documented [181].

Prognosis

After elimination of the causative drug, pustules usually spontaneously disappear in a few days with desquamation, and the reaction fully resolves within 15 days [183]. The overall prognosis is good, although high fever or superinfection of skin lesions can sometimes lead to life-threatening situations in patients of old age or poor general condition [173]. The mortality rate is about 5 % [4].

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

Epidemiology

The annual incidence of SJS and TEN is 1.2–6 and 0.4–1.2 per million individuals, respectively [186, 187]. The annual incidence of SJS and/or TEN in HIV patients is estimated at 1–2 per 1000 individuals, approximately 1000-fold higher than that of the general population [188]. The incidence of SJS/TEN increases with age; children less than 15 years of age account for only 10 % of the samples in most studies [189]. Women are two times more likely to be affected by SJS/TEN than men in the adult population, while the male to female ratio is about equal in children [189].

Etiology

Drug exposure is the most common cause of SJS/TEN [190], with more than 200 drugs identified [191]. The groups of medications associated with high risk of inducing SJS/

TEN vary according to the population. In the general population in Europe, high risk drugs for SJS/TEN include allopurinol, carbamazepine, cotrimoxazole and other anti-infective sulfonamides, lamotrigine, nevirapine, oxicam-NSAIDS, phenytoin, phenobarbital and sulfasalazine [192]. In the pediatric population in Europe, they include anti-infective sulfonamides, phenobarbital, carbamazepine and lamotrogone [189]. In Africa, they include antibacterial sulfonamides, nevirapine, tuberculosis drugs, NSAIDs, antiepileptics, aminopenicillin, analgesics and allopurinol [193]. Non-medication triggers, implicated mainly in SJS, include infections, contrast media and vaccinations [194–196]. ALDEN is an Algorithm for the Assessment of Drug Causality in SJS/TEN developed by the RegiSCAR study group and consists of 6 parameters according to which the drug causality is classified as very unlikely, unlikely, possible, probable and very probable [197].

Lag Period

Usually 4–28 days. The median latency was longer (above 30 weeks) for drugs with no associated risk [192].

Clinical Features

SJS and TEN represent different degrees of a severe, acute and life-threatening mucocutaneous reaction. We will refer to this disease spectrum as a single entity, namely SJS/TEN. The classification of SJS/TEN, defined by Bastuji-Garin et al. [198], is based on the extent of epidermal detachment and the findings of characteristic skin lesions (Table 25.4). It should be emphasized that only necrotic skin, which is already detached (e.g., blisters, erosions), or detachable skin (positive Nikolsky sign whereby slight rubbing of the skin results in exfoliation of the outermost layer) should be included in the evaluation of the extent of epidermal detachment [190].

Skin The characteristic skin morphology of SJS/TEN consists of 'flat, atypical target lesions' and 'spots/macules', which are defined as follows. Flat, atypical target lesions are round lesions, with only two zones and/or a poorly defined border, nonpalpable with the exception of potential central blister. 'Spots/macules' are nonpalpable, erythematous or purpuric macules with irregular shape and size, often confluent [198]. Epidermal necrosis, the hallmark process of SJS/TEN, induces flaccid blisters with positive Asboe-Hansen sign (lateral extension of bullae with pressure), erosions, positive Nikolsky sign, and in severe cases extensive skin sloughing [199]. At least 1 % of epidermal detachment is required for the diagnosis of SJS/TEN [83]. In rare instances, extensive epidermal necrosis occurs with only widespread erythema and no evidence of 'flat, atypical target lesions' or 'spots/macules'; these cases were classified as 'TEN without spots' (Table 25.4). A characteristic sign of SJS/TEN is severe pain and tenderness of the skin [83].

Mucous Membranes Mucosal involvement is evident in most of the cases with erythema, erosions and ulceration, due to necrosis of the epithelial lining [199]. SJS/TEN involve more than 2 mucosal sites in 17–71 % of cases [200]. Most common sites are oral (Fig. 25.3), ocular and genital mucous membranes, although any mucous membrane may be involved, such as respiratory, gastrointestinal and urethral [199]. Fuchs syndrome is a unique type of SJS that involves the mucosa without skin lesions and was reported to be associated with mycoplasma pneumoniae, mostly in children and adolescents [201].

Table 25.4 Classification of erythema multiforme major (EMM), Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) according to Bastuji-Garin et al. [198]

	EMM	SJS[a]	SJS-TEN overlap	TEN	
				TEN with spots	TEN without spots/TEN with widespread erythema
Skin detachment (%) detached skin, blisters, erosions and/or detachable skin – positive Nikolsky sign[b]	<10 %	<10 %	10–30 %	>30 %	>10 %
Typical target lesions individual lesions less than 3 cm in diameter with a regular round shape, well defined border, and at least three different zones	+	–	–	–	–

Atypical target lesions Round lesions with two zones and/or a poorly defined border
    Raised – edematous, palpable lesions
    Flat – nonpalpable with the exception of potential central blister
	Raised	Flat	Flat	Flat	–

Spots/macules with or without blisters nonpalpable, erythematous or purpuric macules with irregular shape and size, often confluent	–	+	+	+	–

[a]At least 1 % of epidermal detachment is required for the diagnosis of SJS
[b]Slight rubbing of the skin results in exfoliation of the outermost layer

Fig. 25.3 Erosions with hemorrhagic crust on the lips, tongue and skin in a patient with TEN

Systemic Involvement Systemic findings in SJS/TEN include: (1) Flu-like symptoms (malaise, fever, anorexia) that are usually the initial signs of the disease in the prodromal phase prior to the cutaneous involvement. (2) Epidermal barrier breakdown-related symptoms including hypothermia, dehydration and sepsis. (3) Organ involvement induced by necrosis of epithelial lining, including respiratory distress syndrome, colitis, hepatitis and nephritis [199].

Histology

Characteristic histologic features include extensive keratinocyte destruction via apoptosis with separation of the epidermis from the dermis at the dermoepidermal junction. A paucicellular, dermal mononuclear infiltrate has been commonly described. Lymphocytes cross the dermoepidermal junction with moderate infiltration of the epidermis. EM and SJS often demonstrate less keratinocyte destruction on a background of extensive dermal mononuclear inflammation [202]. In a retrospective analysis of the clinical records and histologic material of 37 patients with TEN, the histologic spectrum ranged from sparse to extensive dermal mononuclear inflammation, the extent of which predicts clinical outcome approximately as well as SCORTEN. Increased inflammation correlated with a worse prognosis; a mean cell count of dermal mononuclear >215 cells per high-power

field predicted a worse prognosis (65 %) vs 24 % mortality in those with <215 cells in patients with 30 % or more total body surface area sloughing [202]. However, in a retrospective study analyzing clinical records and skin biopsy of 108 patients with SJS, SJS/TEN overlap and TEN, dermal infiltrate severity was not associated with day-1 SCORTEN or hospital death, but full-thickness epidermal necrosis was associated with mortality [203].

Diagnostic Criteria

Diagnostic criteria based on integration of the major clinical characteristics of skin and mucous membrane findings, pathology assessment, lag period and systemic signs remain to be defined.

Treatment

The management of SJS/TEN consists of a multidisciplinary approach that includes the following important aspects:

1. **Identification and withdrawal of the culprit drug**: documenting the medication history during the previous 2 months and withdrawal of all suspected and unessential medications [123].
2. **Transfer of the patient to intensive care, burn unit or other specialty unit**: supportive care including thermoregulation, fluid replacement, nutritional support, monitoring for infection, sedation and pain management, and psychological support [204].
3. **Assessment of skin, mucous membranes and systemic involvement and the SCORTEN score**: Type of lesions in the skin, extent of epidermal detachment, and mucous membranes and systemic involvement. All patients should be evaluated by an ophthalmologist promptly following the diagnosis and at regular follow-up intervals to minimize potential long-term ocular sequelae [205]. Possible acute manifestations include the eyelids, conjunctiva and cornea, and result in the classification of ocular involvement as mild, moderate or severe [206]. Bringing other specialists in on the patient's care is decided in accordance with the relevant findings. The SCORTEN system, a severity-of-illness score for Toxic Epidermal Necrolysis, developed to stratify severity of illness and predict mortality in patients with TEN, includes seven independent risk factors: age, malignancy, tachycardia, initial body surface area of epidermal detachment, serum urea, serum glucose, and bicarbonate [207].
4. **Skin treatment**: There are no clinical guidelines for the skin care of patients with SJS/TEN. Debridement of the necrotic epidermis was recommended in past publications

[187, 204]. Recent publications advise avoiding debridement, which may cause hypertrophic scars, and recommend considering the detached epidermis as a natural biological dressing that favors reepithelialization [14, 205, 208]. Various topical treatments reported include bioactive skin substitutes, semi-synthetic and synthetic dressings, and topical antimicrobials [187, 204]. A recent report on the management of SJS/TEN in an experienced French referral center described the following treatment; wound care once a day with minimal manipulation to prevent skin detachment, including a bath containing a solution of chlorhexidine 1/5000 (morphine is given prior to the bath and/or equimolar mix of oxygen and nitrogen monoxide during the bath); if bathing is not possible, the chlorhexidine solution is sprayed 2–3 times daily on the skin, blister fluid is aspirated while maintaining the blister roof, vaseline is systemically applied over all detached skin areas, topical sulfa-containing medications are avoided, and hydrocellular or absorbent nonadhesive dressings are applied at least once daily to cover pressure points [205].

5. **Mucous membranes treatment**: Specialized care is essential to prevent lifelong complications [208]. Although there is no standardized care for ocular management, the following supportive local treatment is advised: tear replacement solutions, removal of pseudomembranes, lysis of symblepharon, debridement of loosened epithelium, topical antibiotics to prevent secondary infection, topical corticosteroid to prevent scar formation, and cycloplegic drops to relieve pain, photophobia and ciliary spasm [206]. Amniotic membrane transplantation was found effective in the acute and chronic stages of SJS/TEN [209, 210]. A 'Triple-TEN' protocol for severe ocular cases was recently reported [211], comprised of the following: (1) Subconjunctival triamcinolone (Kenalog 20 mg) administered into each of the fornices to curb the local inflammatory response without compromising systemic immunity. (2) Placement of amniotic membrane tissue mounted on a polycarbonate skirt (ProKera) over the corneal and limbal regions to facilitate reepithelialization of the ocular surface. (3) insertion of a steeply curved acrylic scleral shell spacer (Technovent, SC21) to vault the lids away from the globe and provide a barrier to symblephara formation. This treatment offers an effective therapeutic option, without the need for microsurgical equipment, microscope, or sutures in the critical care setting.

Oral- The mouth should be rinsed several times a day with an antiseptic or anifungal solution and the lips lubricated with an ointment such as dexpanthenol [123].

Genital- Wet dressings or sitz baths and lubrication with emollient are recommended to avoid adhesions and strictures of genital erosions in females [123, 205].

A specialist is required in case of involvement of other mucous membranes: respiratory, gastrointestinal and/or urethral.

6. **Systemic immunomodulatory treatment**: The optimal therapeutic regimen has yet to be established, but according to recent publications, the following conclusions can be drawn: the use of IVIg does not yield survival benefits in SJS/TEN [212]; cyclosporine decreased the death rate and the progression of detachment (dosage of 3 mg/kg/day for 10 days) [213]; systemic corticosteroids were associated with clinical benefit according to the Euroscar-study [214] and were reported to be the most common treatment for SJS/TEN in a recent survey of 50 drug hypersensitivity experts from 20 countries [14]. One of the suggested protocols is IV dexamethasone 1.5 mg/kg pulse therapy (given for 30–60 min) for 3 consecutive days [215]. Treatment with anti-TNF biologic treatment was reported to be beneficial [216–218]. A prospective, randomized, open-label trial currently underway in Taiwan [14] comparing etanercept versus systemic corticosteroids in patients with SJS/TEN, reported that the average duration to reach maximal skin detachment and complete skin healing was shorter in the etanercept group. In vitro investigations demonstrated that etanercept, steroids or thalidomide significantly decreased granulysin expression of blister cells. Etanercept did not, however, increase the cytotoxic effect to keratinocytes found with thalidomide [14].

7. **Causality assessment and communication with the patient and his/her family, health-care providers and regulatory agencies**: Recent discoveries of specific HLAs that predict genetic susceptibility to SJS/TEN offer a simple, fast, safe and reliable method for establishing clear causality between a drug and a disease [148]. The HLAs are specific to a drug and an ethnic background [148]. Since these tests are available only for certain drugs and a negative test does not exclude the drug as the offending agent, additional clinical and laboratory methods are available for assessing causality. (**See Practical approach to the diagnosis and management of cutaneous ADRS and Clinical and laboratory assays in the diagnosis of cutaneous ADRs**.) For information on communication with the patient and his/her family, health-care providers and regulatory agencies **see Practical approach to the diagnosis and management of cutaneous ADRS**.

Prognosis

The mortality rates of SJS/TEN are variable. That of TEN may approach 30% [191], and that of children with SJS/TEN is approximately 2–7.5% [189]. In a large-scale, population-based, 1-year follow-up study of 460 SJS/TEN patients, the

6-week in-hospital mortality rate was 23%, and the death rate from 6 weeks to 1 year was 14% [219]. The mortality rate at 1 year in this study was 24% for SJS, 43% for SJS and TEN overlap, and 49% for TEN. Several factors were found to affect mortality: age, severity of reaction, recent malignancy, pre-existing severe kidney or liver disorder, and recent infection. The last two factors were recognized for the first time in this study as being independent risk factors for death. All other factors are part of the SCORTEN [207]. The severity of the reaction was a major risk factor for death in the first few weeks, and severe co-morbidities and older age had major impact on mortality after 6 weeks [219]. Early and late physical complications are common among patients who survive SJS/TEN [219], with some 80% experiencing long-term sequelae [220]. Complications may affect multiple organ systems including skin, nails, hair, oral and genital mucosal sufaces, eyes, kidneys, gastrointestinal tract, and respiratory system [221]. Ocular complications, which can lead to blindness, are the major long-term morbidity [206]. A few studies have dealt with the quality of life of patients surviving SJS/TEN [221–223], which was found to be lower in every domain from before hospitalization to follow-up and a low rate of return to previous employment was documented [221]. Patients reported concerns about social interactions, fear of taking medications, and fear of contracting an illness necessitating medication [223]. Insufficient information and support for patients surviving SJS/TEN was also documented [221–223]. Unfortunately, because of the rarity of SJS/TEN, most physicians are not aware of the long-term complications of the diseases [220].

Practical Approach to the Diagnosis and Management of Cutaneous Adverse Drug Reactions

There are several methods to approach a patient with a cutaneous ADR. The following is the authors' protocol:

Clinical Assessment of Drug-Induced Skin Injury: 4Ds by Dr. Shear

Diagnosis of the Adverse Event
A cutaneous eruption in a patient taking a medication should immediately raise the suspicion of a cutaneous ADR. The physician must then determine whether the patient's clinical symptoms are signs of a cutaneous ADR or of another skin disease not related to a drug. The diagnosis of a cutaneous ADR is based on three key clinical elements (Fig. 25.4): (1) **Appearance**- the morphology of the cutaneous eruption according to four main categories of the primary lesion: maculopapular, urticarial, bullous and pustular (see section "Morphological Classification of Cutaneous ADRs"). (2)
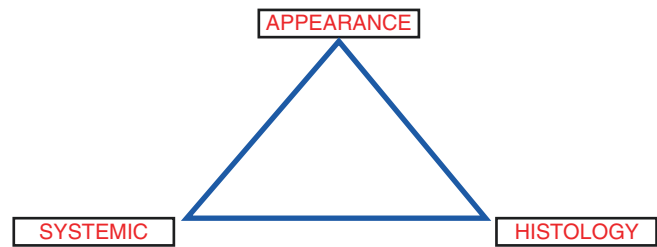

Fig. 25.4 Shear's Diagnostic Triangle of adverse cutaneous drug reactions

Systemic- extra-cutaneous signs (fever, dyspnea, lymphadenopathy, etc.) that distinguish between a simple reaction involving only the skin and a complex reaction that includes systemic involvement in addition to the skin (see section "Severity of Cutaneous ADRs: Skin only (Simple) Versus Skin and Systemic Involvement (Complex)") and (3) **Histology**- histopathology and direct immunofluorescence studies of skin biopsies to confirm the clinical impression and to distinguish between a drug-induced eruption and other skin diseases (see section "Histological Classification of Cutaneous ADRs").

Differential Diagnosis
Establishing a differential diagnosis that takes into account all possible diagnoses is essential. Ranking the approximate likelihood of each condition is encouraged.

Drug Exposure (Timing)
All medications, regardless of route of administration, must be considered, especially new drugs taken in the 8 weeks prior to the skin reaction. Drugs taken intermittently, such as vitamins, sedatives, pain relievers, laxatives and natural products, must also be considered. Assessment of the lag period – the time between initiation of the drug and onset of the cutaneous reaction – is crucial in view of the different lag times for different cutaneous drug reactions. A recommended method for drug exposure analysis is to chart a timeline in order to visualize the chronology and facilitate comprehension of the event. The timeline includes the relevant information (starting day, dosage, and discontinuing day) for each drug and the signs and symptoms throughout the period in question [82].

Determine Probabilities
The most important challenge in assessing drug-induced skin injury is establishing whether there is a causal relationship between the suspected drug and the untoward clinical event. The following methods are helpful: (1) Patient history: the patient should be questioned about previous cutaneous reactions to drugs, and whether rechallenge with the drug improved the eruption [82]. These data should also be part of the above timeline. (2) Analysis of the literature: search for information regarding the frequency with which the type of reaction is related to a particular drug. (pubmed

http://www.ncbi.nlm.nih.gov/pubmed/, Litt's D.E.R.M. Drug Eruptions and Reactions Manual and database http://www.drugeruptiondata.com/). (3) Rate the reaction on Naranjo et al.'s adverse drug reaction probability scale, which classifies the drug reaction according to a probability category as definite, probable, possible or doubtful [224], and or on Edwards et al.'s causality assessment criteria [2]. (4) In vitro and in vivo diagnostic assessments including HLA genetic tests. (see section "Clinical and Laboratory Assays in the Diagnosis of Cutaneous ADRs").

Communication with the Patient and Family, Health-Care Providers and Regulatory Agencies

Patient and Family

Good communication strategies will aid in the interactions with the patient and family following a cutaneous ADR and decrease the likelihood of lawsuits, especially in cases of severe reactions such as SJS/TEN. Physicians are advised to follow these steps: (1) Express empathy and say "sorry" according to the "apology laws" in an honest and respectful fashion and in a way that protects the physician from having an apology used against him in case of legal action. http://www.sorryworks.net/. (2) Provide disclosure in a "disclosure meeting" planned according to the acronym CONES: Context – arrange the setting for a quiet, uninterrupted meeting and decide on the participants; Opening shot – the first sentence in the meeting explains the aim of the conversation; Narrative – lay out the facts; it is advised to avoid using the words "error" and "mistake" since the ADR is a result of multiple factors, particularly when the facts are not completely known; Emotions – provide an empathic environment; Summary (3) Provide the patient with clear information on his cutaneous ADR, the name of the offending drug, potential cross-reacting drugs, and drugs which can be safely taken as an alternative to the offending drug. In addition, advise the patient to wear a medic-alert bracelet. (4) Family counselling is part of the management plan since the predisposition to some cutaneous ADRs may be genetic [191].

Health-Care Providers

Information on the adverse event must be provided to the family physician and entered in the patient's records.

Regulatory Agencies

Report the cutaneous ADR to the manufacturer and regulatory agencies [225]. International reporting systems: MedWatch, the FDA Safety Information and Adverse Event Reporting Program http://www.fda.gov/safety/MedWatch/default.htm, and WHO Uppsala Monitoring Centre (UMC) http://www.who-umc.org.

Clinical and Laboratory Assays in the Diagnosis of Cutaneous ADRs

Pharmacogenomic Aspects of Drug Reactions

The strong associations found between HLA alleles and specific drug-induced hypersensitivity reactions have fostered pharmacogenetic testing to prevent the development of life-threatening drug-induced hypersensitivity reactions, such as SJS/TEN and DRESS. The usefulness of such testing is dependent on a number of factors, including the incidence and severity of the adverse event, the sensitivity and specificity of the predictive markers, and the availability of equally effective, alternative medications for individuals who test positive.

HLA-B*1502 Test for Prevention of Carbamazepine-Induced SJS/TEN

Although the incidence of SJS/TEN is relatively low, it is life-threatening and many patients who survive have long-term sequelae, such as ocular complications. HLA-B*1502 is a useful and strong predictive marker with high sensitivity and specificity for carbamazepine-induced SJS/TEN in Asian populations. This genetic association is strong enough that it prompted the USFDA and many countries to relabel the genetic information for carbamazepine, and to recommend screening for HLA-B*1502 before prescribing the drug for subjects of Asian descent. The HLA-B*1502 test for carbamazepine-induced SJS/TEN has very high sensitivity (near 100 %) and specificity (97 %). With the 0.25 % prevalence rate of carbamazepine-induced SJS/TEN among Chinese, the HLA-B*1502 test has a 7.7 % positive predictive value and 100 % negative predictive value for detecting [226]. In view of the serious consequences of SJS/TEN and the availability of alternative drugs, withholding carbamazepine from screened patients who test positive for HLA-B*1502 and switching to alternative anti-epileptic drugs is reasonable and feasible in the high risk populations, including Chinese and South-East Asians.

HLA-B*5701 Test for Prevention of Abacavir Hypersensitivity

Abacavir is used in the treatment of HIV infection, and has been associated with drug hypersensitivity syndrome in 8 % of patients [227]. HLA-B*5701 is a strong and useful predictive marker with high sensitivity and specificity for abacavir hypersensitivity in Caucasians, prompting the USFDA and many other countries to recommend screening for it before prescribing the drug. The HLA-B*5701 test for immunologically-mediated abacavir hypersensitivity has very high sensitivity (100 %) and specificity (97.4 %) as well as positive predictive value (55 %) and negative predictive value (100 %) [55].

Other Potential Genetic Tests in Drug Hypersensitivity

HLA-B*5801 is a potentially useful predictive marker for allopurinol-induced SJS/TEN or DRESS, with 3 % positive predictive value and almost 100 % negative predictive value for detecting allopurinol-induced SJS/TEN or DRESS in Chinese (Table 25.2). This association was significant in Caucasian and other Asian populations as well. The recent American College of Rheumatology guidelines for the management of gout recommend HLA-B*5801 screening for populations with high frequency of the allele [228].

Other recently discovered HLA alleles related to drug hypersensitivity of potential usefullness in clinic practice are HLA-B*1301 for dapsone hypersensitivity [58], HLA-A*3101 for carbamazepine-related DRESS [65], and CYP2C9*3 for phenytoin hypersensitivity [69].

In Vitro Assessment

Lymphocyte Transformation Test (LTT) and Lymphocyte Activation Assays

The lymphocyte transformation test (LTT) is a widely used in vitro assay for the diagnosis and identification of offending drugs with T cell-mediated drug hypersensitivity [229]. LTT is based on the activation and proliferation of T cells from PBMC obtained from drug-sensitized patients after stimulation, and incubation with the culprit drug in vitro [230]. Following in vitro stimulation by specific drugs, drug-specific T cells are activated and release several cytokines that promote proliferation of T cells. This in vitro proliferation of specific drug-activated T cells can be detected by the incorporation of 3H-thymidine during DNA synthesis after 6 days of culture. The results of LTT are expressed as the stimulation index (SI): the relationship between the 3H-thymidine uptake in cells (counts per minute (c.p.m.)) with and without the drug antigen [229]. The general sensitivity of the LTT is 50–80 %, varying with different drugs and different phenotypes of delayed-type hypersensitivity reactions; thus, a negative result does not exclude the possibility of drug hypersensitivity. Extensive studies on LTT for beta-lactam drugs report even higher sensitivity [230–234]. The specificity of the LTT is 85–100 % in different studies [231–233, 235].

LTT for the diagnosis of drug hypersensitivity has limitations. Because it is measured by radioisotopes, the sensitivity can be very low and negative results are commonly observed for specific drugs (e.g., allopurinol, lamotrigine) and specific phenotypes (e.g., SJS/TEN) [236, 237]. Several non-radioactive methods have been developed for measuring lymphocyte proliferation or activation in in vitro tests for diagnosis of delayed-type drug hypersensitivity, including the use of carboxyfluorescein succinimidyl ester (CFSE) cell staining dye [238, 239], and measuring cytokines or cytotoxic proteins expression, such as INF-γ, IL-2, IL-4, IL-5, IL-13, granzyme-B, and macrophage migration inhibitory factor [240–244].

Basophil Activation Test (BAT)

Flow cytometry-assisted basophil activation test (BAT), which measures specific cell makers such as CD69 or CD203c to quantify basophil activation after antigen-specific stimulation, has been widely used in the diagnosis of immediate-type drug hypersensitivity [245]. BAT directly measures basophil responses instead of IgE sensitization. It has been applied to the diagnosis of different drugs implicated in immediate-type hypersensitivity, including beta-lactam antibiotics, neuromuscular blocking agents, aspirin, NSAIDs and radiocontrast media [246–248]. The sensitivity of BAT varies in different types of drugs: that for beta-lactam antibiotics ranged from 28.6 to 55 % [249, 250]; that for NSAIDs ranged from 30 to 70 % [251, 252].

Computational Analysis for HLA Alleles

Recent data have shown that the unique interaction between drug, T-cell receptor and HLA molecule is a key factor in the development of immune-mediated adverse reactions to drugs. The discovery of strong association of specific HLA alleles with specific drug-induced hypersensitivity (e.g., HLA-B*1502 to carbamazepine-SJS/TEN, HLA-B*5801 to allopurinol-SJS/TEN/DRESS, and HLA-B*5701 to abacavir hypersensitivity), and studies of the functional role of HLA-B* allele (e.g., HLA-B*1502) directly interacting with a specific drug (e.g., carbamazepine) and unique T-cell receptor support the hypotheses of the 'pharmacological interaction with immune receptors' (p-i) [18, 19, 253].

In recent years, bioinformatics and computer modeling have been applied to elucidate how drug molecules interact with specific HLA in drug hypersensitivity. HLA alleles have been associated with liver injury induced by different drugs (such as flucloxacillin). Using silico strategies to examine HLA haplotype relationships, and bioinformatics tools, Alfirevic et al. [254] demonstrated a connection between the different HLA alleles associated with drug-induced liver injury caused by therapeutically and structurally different drugs, suggesting a mechanism of peptide binding of one of the associated HLA alleles [254]. Computer modeling of the molecular interaction between HLA-B*1502 and carbamazepine predicted a favorable drug-binding position in the B pocket of the HLA-B*1502 protein, where the side chain of Arg62 could form a hydrogen bond with the ketone group of 5-carboxamide of carbamazepine (Fig. 25.5) [253].
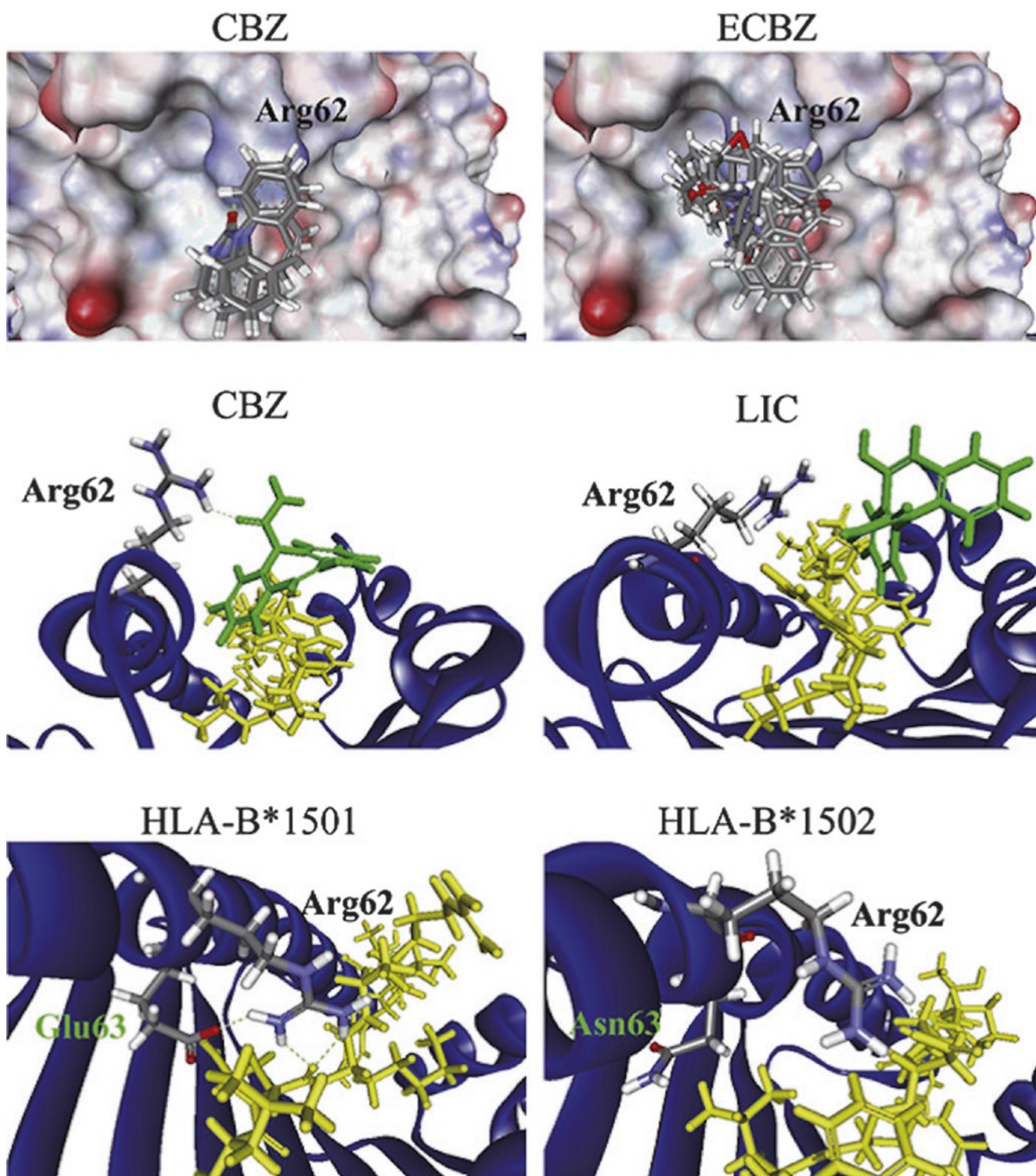
Fig. 25.5 Computer modeling of the molecular interaction between HLA-B*1502 and carbamazepine and its derivatives (Figure from Wei et al. [253])

Conclusion

Cutaneous ADRs have a wide spectrum of clinical manifestations that may be caused by multiple drugs and different mechanisms. In this decade, our understanding of the pathogenesis of cutaneous ADRs had progressed greatly. Understanding how a drug can possibly cause reactions in the skin has led to an understanding of the cellular immunology, cytokines and immunogenetics. These key insights can help mitigate the risk of reactions by testing for genetic factors, and to understand the treatment of drug reactions by better understanding the pathways involved. The future will depend on better genetic screening and directed approved therapies.

Review Questions

1. What is the major immune cell in acute generalized exanthematous pustulosis (AGEP)?
   A. CD4 T cells
   B. CD8 T cells
   C. Eosinophils
   D. Neutrophils
   E. NK cells

2. In which of the following delayed-type hypersensitivity reactions is interleukin (IL) 8 known to be involved?
   A. acute generalized exanthematous pustulosis (AGEP)
   B. drug reaction with eosinophilia and systemic symptoms (DRESS)
   C. maculopapular drug eruption (MPE)
   D. Stevens-Johnson syndrome (SJS)
   E. Toxic epidermal necrolysis (TEN)

3. The HLA gene B5701 and hypersensitivity reactions MPE/DRESS are associated with use of which of the following drugs?
   A. Abacavir
   B. Allopurinol
   C. carbamazepine
   D. Dapsone
   E. Nevirapine

4. What is the most common group of drugs causing pseudoporphyria?
   A. Antibiotics
   B. Diuretics
   C. NSAIDS
   D. Protease inhibitors
   E. Reverse transcriptase inhibitors

5. Which drug is most closely associated with fixed drug eruptions on the male genitalia?
   A. Allopurinol
   B. Carbamazepine
   C. Minocycline
   D. Tetracycline
   E. Vancomycin

Answers

1. D
2. A
3. A
4. C
5. D

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