23.16 Cutaneous reactions to drugs 5752 Sarah Wals

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ESSENTIALS Adverse reactions to medications are common and important cause of iatrogenic illness. Severe cutaneous adverse drug reactions in- clude toxic epidermal necrolysis, Stevens–Johnson syndrome, drug reaction with eosinophilia and systemic symptoms, and acute gen- eralized exanthematous pustulosis, which together constitute 2% of all adverse drug reactions and may be life-threatening. Less severe drug-induced skin reactions such as exanthems, urticaria, lichenoid drug rashes, and fixed drug eruptions are more common, sometimes termed benign cutaneous adverse reactions, and generally resolve without sequelae. Drugs may also cause adverse events due to alteration of the normal function of the skin or its appendages. This may take the form of photosensitivity, abnormal pigmentation, or disrupted growth of hair or nails. The field of adverse drug reactions is changing constantly with the advent of new targeted therapies, particularly in the domain of on- cology. Reaction patterns in the skin resulting from these new agents include pustular eruptions, palmoplantar erythrodysaesthesia, and eruptive keratoacanthomas. Ascribing culpability to a particular drug when an adverse reac- tion has occurred requires careful assessment of the drug history, including latency, notoriety, and the reaction pattern in the skin. The most important first step in the management of any adverse drug re- action is cessation of the culprit drug or drugs. In vivo or in vitro tests are of limited use because, for most drugs, the antigenic molecule, hapten, or metabolite is not known or available. Introduction Adverse reactions to medications are common and are an important cause of iatrogenic illness. While only 2% of all drug-induced skin reactions are severe, they may all cause considerable morbidity for the patient affected, and can have medicolegal and health economic consequences. In addition, cutaneous adverse reactions to a medi- cation may influence the

patient’s future adherence to prescribed therapy. Assessment of the patient with a suspected cutaneous adverse drug reaction is important both in the acute phase of illness—so that the offending drug can be stopped—and for the long-term well- being of the patient, so that the drug implicated and all related agents can be avoided in future. Careful documentation of the conclusions of such assessment, and any testing performed, is paramount to avoiding inadvertent re-exposure. Assessment of drug causality is rendered difficult by the following principles which underpin adverse reactions to medications: • Almost any drug can cause any rash • Unrelated drugs might cause similar eruptions • The same drug might cause different patterns of eruption in dif- ferent patients • Some drug reactions can resemble specific skin diseases such as eczema, acne, or lichen planus making it difficult to distin- guish between idiopathic skin disease and a drug-induced phenomenon Drug-induced skin disease can be classified as follows: a. Drugs causing alteration of normal skin function b. Drugs causing exacerbation of an existing dermatosis c. Benign drug-induced skin disease: exanthems, urticaria/ angioedema, lichenoid reactions, fixed drug eruption, pruritus. These are sometimes referred to as benign cutaneous adverse reactions (BCAR) d. Severe drug-induced skin disease: acute generalized exanthema- tous pustulosis (AGEP); drug reaction with eosinophilia and systemic symptoms (DRESS); Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN); and generalized bullous fixed drug eruption (GBFDE). These are sometimes referred to as se- vere cutaneous adverse reactions (SCAR) Clinical approach to drug causality The identification and withdrawal of the culprit drug is key to the management of all adverse drug reactions. Clinical assess- ment of drug causality relies on a comprehensive drug history 23.16 Cutaneous reactions to drugs Sarah Walsh, Daniel Creamer, and Haur Yueh Lee

 and recognition of the morphology and type of adverse reaction. Causality reasoning relies on two broad principles: a. Latency of the particular reaction pattern b. Epidemiological risk of certain drug/drugs groups in causing a particular reaction. This is sometimes referred to as the notoriety of the drug (e.g. allopurinol is a high notoriety drug for Stevens– Johnson Syndrome). Latency Recognition of the different morphology and types of adverse reac- tions is essential as these reactions have varying latencies between the administration of the drug and the onset of the reaction (Table 23.16.1). For example, urticaria and angioedema are immediate re- actions which occur typically within 1–6 hours of drug exposure whereas exanthematous eruptions, Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN) and drug hypersensitivity reactions are delayed reactions with latencies of 1 week, 5–28 days, and 2–8 weeks, respectively. Drugs that are taken within the latency period are considered potential culprits for inciting the reaction. Epidemiological risk The risk of inciting a particular drug reaction differs between drugs with some being high-risk for a specific reaction. These drugs are summarized in Table 23.16.1. Information regarding such epi- demiological risk is largely derived from pharmacovigilance reports, disease registries, and published literature. For example, most SJS/ TEN can be attributed to a few high-risk drugs, such as allopurinol, carbamazepine, phenytoin, co-trimoxazole, oxicam nonsteroidal anti-inflammatory drugs (NSAIDs), nevirapine. With the help of a drug exposure time-line, a list of possible culprit drugs can be compiled (Fig. 23.16.1). In a patient who de- velops toxic epidermal necrolysis, the latency period from drug initiation to onset of symptoms is typically 5–28 days. A complete drug exposure history is taken from the patient and annotated. Allopurinol and paracetamol best fits the temporal sequence. Between the two, allopurinol is the more likely causative drug due to its high epidemiological risk. The rest of medications are un- likely; aspirin and enalapril are long-term

medications, omeprazole was stopped seven weeks prior to onset of disease, the latency period of frusemide is too short to cause Stevens–Johnson syn- drome/ toxic epidermal necrolysis and amoxicillin was started after the onset of symptoms. Diagnostic testing Skin testing and in vitro testing are available for the evaluation of hypersensitivity reactions; however, these tests have an overall low sensitivity and are not routinely available in most centres. Choice of tests is dependent on the suspected immune mechanism underlying the drug reaction. Skin testing (i.e. prick, intradermal, and patch testing) is usually performed four weeks to six months after the resolution of the reaction. Prick and intradermal tests are useful for immediate hypersensitivities such as urticaria, angioedema, and ana- phylaxis. Protocols have been standardized for some drug classes such as β-lactams, neuromuscular blocking agents, and iodinated contrast. However, for most drugs, test reagents, and concentrations have not been sufficiently validated. Patch tests and intradermal testing with delayed readings on the other hand may be useful for the evaluation of delayed hypersensitivity reactions such as drug exanthems, acute generalized exanthematous pustulosis, drug reac- tion with eosinophilia and systemic symptoms, and Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis. Validated concentrations of the drug are applied on the patient's back in special test chambers and are left in place for 48 hours. Readings of these tests are per- formed at three and five days after the application of test chambers. In vitro tests such as basophil degranulation tests, lymphocyte proliferation, cytokine secretion, and cytotoxicity assays are avail- able mainly in research centres with a interest in drug allergies. Positive basophil degranulation tests indicate the presence of spe- cific IgE on the surface of basophils and are useful in the evaluation of immediate hypersensitivity reactions. Lymphocyte proliferation, cytokine secretion, and cytotoxicity assays are typically used for the evaluation of delayed reactions. Their use remains limited to the do- main of research at the present time. Despite being the gold standard to confirm or exclude a drug al- lergy, provocation testing should not be taken lightly. A risk-benefit analysis needs to be undertaken. It should never be performed in patients with severe cutaneous adverse reactions, high-risk patients with severe comorbidities such as severe asthma, cardiac disease, or in patients who are unlikely to need the drug in the future. Drugs causing alteration to normal skin function Pigmentary change Alteration of the skin's normal colour might be seen in response to medication. This can occur in either a localized or a generalized pat- tern, though the former is more commonly recognized. Common causes of drug-induced skin pigmentation include melasma, the mid-brown discolouration seen on the upper lip and peripheral part of the face, particularly in female patients taking the oral contracep- tive pill. Amiodarone and minocycline characteristically produce a grey facial pigmentation in susceptible individuals. Several mechanisms are proposed for the process of drug-induced skin pigmentation, though none are definitively accepted. The drug, or a metabolite thereof, may be deposited in the dermis or epidermis, causing dyspigmentation. This process may require, or be enhanced by, environmental ultraviolet light, causing it to predominate in sunlight-exposed sites. This has been suggested to contribute to the pathogenesis of amiodarone dyspigmentation. Alternatively, it has been proposed that melanin production might be enhanced, with or without an increase in the number of melanocytes. This is likely to be the mechanism for increased pigmentation in melasma. Photosensitivity Drug-induced photosensitivity can be classified as phototoxic or photoallergic (Box 23.16.1). Phototoxic reactions resemble severe sunburn, and occur 5–15 hours following exposure to the drug, and subside quickly on withdrawal. Phototoxic reactions demon- strate a dose-response relationship both to the drug and to sunlight. Photoallergic reactions are more insidious and difficult to diagnose. This reaction pattern occurs after exposure to normal levels of ultra-violet (UV) light and are not dose-dependent. Withdrawal of the drug may not result in immediate

resolution of photosensitivity, but may linger on for months or years following discontinuation of the culprit drug. The morphology of a photoallergic rash is usually

section 23 Disorders of the skin 5754 Table 23.16.1 Summary of clinical features, latency and common inciting drugs of cutaneous adverse reactions SJS/TEN DRESS AGEP GFBDE Fixed drug eruption Drug Exanthem Urticaria/ angioedema Clinical features Purpuric macules, atypical targets, blisters, erosions, and sheet-like detachment Maculopapular exanthema, exfoliative dermatitis, pustules, facial oedema Multiple pinpoint pustules on background of erythema Multiple large dusky plaques, bulla, skin detachment with normal intervening skin Round/oval erythematous / dusky plaques, occasionally bullous Macules and papules, confluent erythema Wheals and flare, perioribital and lip oedema Differential diagnosis GBFDE, SSSS GVHD, acute cutaneous lupus, autoimmune blistering diseases, post-infectious EM Viral infections Drug exanthem Lymphoma Hypereosinophilic syndromes Pustular psoriasis SSSS SJS/TEN in GBFDE Post-infectious EM Viral exanthem Chronic spontaneous urticarial, physical urticaria Latency period 5–28 days 2–8 weeks 1–12 days Few hours to 3 days Few hours to 3 days 5–14 days Within 1–6 hours High-risk drugs Allopurinol, phenytoin, carbamazepine, lamotrigine, phenobarbital, infective sulphonamides, oxicam NSAIDS, nevirapine Allopurinol, anti- infective sulphonamides, phenytoin, carbamazepine, minocycline, vancomycin Penicillin, quinolones, pristinamycin, sulphonamides, antimalarials, terbinafine, diltiazem Co-trimoxazole NSAIDs β-lactams Allopurinol Co-trimoxazole, tetracyclines, NSAIDS, doxycycline, paracetamol β-lactams NSAIDs Sulphonamides Fluoroquinolones β-lactams Neuromuscular blocking agents Local anaesthesia AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; EM, erythema multiforme; GBFDE, generalized bullous fixed drug eruption; GVHD, graft-versus-host disease; NSAIDs, nonsteroidal anti-inflammtory drugs; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis; SSSS, staphylococcal scalded skin syndrome.

23.16 Cutaneous reactions to drugs 5755 eczematous, but lichenoid, bullous, urticarial, and purpuric variants are described. Nail disorders The growth and appearance of finger and toenails can be altered by drugs. Specifically, chemotherapeutic drugs may interfere with normal nail growth, resulting in changes to the pigmentation or the texture of the nail. Leuconychia (white nails) may be caused by cyclo- phosphamide, doxorubicin, or vincristine. Onycholysis describes sep- aration of the nail plate from the nail bed; any cytotoxic agents may cause this by toxicity to the nail matrix. Photo-onycholysis is a specific form of the disorder described with minocycline, whereby UVA ex- posure is required in combination with the drug to cause onycholysis. Hair disorders Drugs might interfere with any of the phase of the hair cycle, produ- cing hair loss (Box 23.16.2). A simple illustration of the hair cycle is included in Fig. 23.16.2. The latency of onset of hair loss following introduction of the medication will depend on the part of the hair cycle with which the drug interferes. Cytotoxic drugs interfere with anagen, or the growth phase of the hair cycle, thus hair loss is dra- matic and occurs within one to two weeks of drug exposure. Drugs which interfere with the telogen or resting phase of the hair cycle produce a more insidious form of hair loss which occurs gradually over months following drug initiation. Onset of reaction Latency period Toxic epidermal necrolysis – 8 wks Aspirin Enalapril Omeprazole Allopurinol Paracetamol Furosemide Amoxicillin Drug exposures – 6 wks – 4 wks – 2 wks 2 wks Fig. 23.16.1 Drug time-line analysis. Box 23.16.1 Drugs causing photosensitive eruptions Phototoxic reactions Amiodarone NSAIDs Chlorpromazine Tetracyclines Photoallergic reactions NSAIDs Sulphonamides Sulphonylurea Thiazide diuretics Statins Box 23.16.2 Drug-induced hair disorders Alopecia Acitretin and

isotretinoin (retinoids) Anticoagulants B blockers Cytotoxic drugs Gold salts Interferon Lithium Statins Tacrolimus Hirsutism/hypertrichosis Anabolic steroids Corticosteroids (topical and systemic) Ciclosporin Danazol Minoxidil Oral contraceptive pill Penicillamine Phenytoin Tamoxifen Verapamil

section 23 Disorders of the skin 5756 Excessive growth of hair may be a troublesome adverse effect of a medication. Hirsutism is the term used to describe excess hair growth in a male-pattern distribution, such as the development of facial hair in women. Hypertrichosis is the growth of hair in quantities greater than would be normal for an individual of that age, sex, and ethnicity. Phenytoin and ciclosporin may cause hirsutism in certain individuals. The therapeutic potential of minoxidil to produce hypertrichosis was noted in early trials of this drug as an agent to lower blood pressure; this has subsequently been exploited with the development of topical solutions of minoxidil which are used to treat baldness. Drugs exacerbating existing skin complaints Certain medications can exacerbate or precipitate idiopathic skin complaints. These are summarized in Box 23.16.3. Withdrawal of the medication may in part resolve the problem, but often supple- mentary treatment is required. Benign drug-induced skin disease (BCAR) Simple drug exathems Exanthems are the most common type of drug reaction in the skin, and typically have a latency of seven days or fewer following first exposure to the culprit medication. The morphology of the rash may vary, consisting of macular or maculo-papular erythema. A morbilliform (measles-like) eruption is also recognized. The distribution is usually generalized, with the exact proportion of the body surface area (BSA) involved varying from case to case. The mucous membranes are spared. Any drug can provoke an exanthem, but, in practice, common causes include antibiotics (penicillins, sulphonamides, cephalosporins, carbopenams), anti- convulsants (phenytoin, carbamazepine), and quinine-containing medications. Identification of the culprit medications using these interrogative techniques is imperative to preventing inadvertent re-exposure to the drug. The adverse reaction should be clearly conveyed to the pa- tient, documented in the patient notes, and communicated to the primary care physician. The reaction should also be reported to the appropriate pharmacovigilance agency in that country, for example, the Medicines and Healthcare products Regulatory Authority (MHRA) in the United Kingdom. Most simple drug exanthems respond to application of a potent topical steroid such as mometasone fuorate ointment once a day for five to seven days, with antihistamines being taken orally. Urticaria and angioedema These two conditions may be considered to be idiopathic, but can exist in a drug-induced form. Urticaria is characterized by the ap- pearance of transient, pruritic, erythematous weals in the skin; angioedema described sudden, dramatic soft tissue swelling, most noticeable in the head and neck area. Urticaria/angioedema may be a cutaneous manifestation of anaphylaxis to a drug, and thus prompt medical attention is required. Common drugs which cause urticarial eruptions, or which exacerbate pre-existing idiopathic chronic urti- caria are listed in Box 23.16.4. Treatment consists of identification and withdrawal of the culprit medication, and administration of combination antihistamine therapy. Lichenoid drug eruption (LDE) These eruptions are so named as their clinical appearance resembles that of lichen planus, with its purplish flat-topped Anagen Catagen Telogen Growth phase Transitional phase Resting phase Hair Growth Cycle Fig. 23.16.2 The hair growth cycle. Box 23.16.3 Drugs exacerbating existing skin conditions Acne Androgens (in women) Corticosteroids (oral and topical) Ciclosporin EGFR receptor antagonists (e.g. cetuximab) Lithium Oral contraceptive pills (particularly progesterone only) Phenytoin Eczema Calcium channel blockers Statins Diuretics Alcohol Retinoids—acitretin, isotretinoin Calcium channel blockers—nifedipine, amlodipine Psoriasis ACE inhibitors Alcohol Antimalarials (chloroquine, mepacrine) B blockers Corticosteroids Lithium Rosacea Corticosteroid (oral or topical) Alcohol Box

23.16.4 Drugs causing urticaria/angioedema Antibiotics—particularly penicillin given by parenteral route Drugs acting on the angiotensin pathways—ACE inhibitors and angio- tensin receptor blockers (ARBs) Nonsteroidal anti-inflammatory drugs (NSAIDs)—aspirin, diclofenac, naproxen Opiate anagesics—codeine, morphine Antimalarials—quinine, chloroquine, hydroxychloroquine, mepacrine Rifampicin Sulphur-containing drugs

23.16 Cutaneous reactions to drugs 5757 polygonal papules. However a lichenoid drug eruption may have an atypical distribution, and will usually be resistant to topical therapies which alleviate idiopathic lichen planus. Lichenoid drug eruptions may be caused by several different agents (Box 23.16.5). Following withdrawal of the culprit medication, resolution of lichenoid drug eruption may take some time, oc- casionally even months, differing from simple exanthems in this respect. Pronounced post-inflammatory hyperpigmenta- tion might also be seen following resolution of lichenoid drug eruption. Fixed drug eruption (FDE) Fixed drug eruption describes a specific reaction pattern in the skin, the pathogenesis of which is poorly understood. It consists of one or multiple inflammatory, erythematous macules, sometimes with a blistering centre, appearing at diverse sites on the body. The typical sites are the torso, the hands, feet, face, or genital skin. The pecu- liarity of fixed drug eruption is that on re-exposure to the culprit medication, the eruption recurs at exactly the same sites as the pre- vious exposure. While fixed drug eruption is largely self-limiting, re- covery can be accelerated by the application of topical steroid to the affected area. Post-inflammatory hyperpigmentation may remain. Although any drug may cause a fixed drug eruption, more common culprits are listed in Box 23.16.6. Severe cutaneous adverse drug reactions Adverse cutaneous drug reactions differ in clinical features and prognosis with the most severe, life-threatening reactions col- lectively termed as severe cutaneous adverse reactions (SCARs) (Fig. 23.16.3). These reactions include Stevens–Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), drug reaction with eosino- philia and systemic symptoms (DRESS), and acute generalized ex- anthematous pustulosis, and are summarized in Table 23.16.1. These reactions are life-threatening and the mortality rate of such reactions ranges from 5% in DRESS to more than 40% in TEN. Previously thought to be idiosyncratic and unpredictable, recent advances have shown a pharmacogenetic association with certain drug-induced SCARs (Table 23.16.2). Stevens–Johnson syndrome/Toxic epidermal necrolysis Stevens–Johnson syndrome and toxic epidermal necrolysis are rare conditions; the incidence of toxic epidermal necrolysis is estimated to be one to two cases per million per year. Both conditions repre- sent a disease spectrum, and are classified according to the extent of body surface area detachment with epidermal detachment of less than 10% body surface area being classified as SJS, cases with greater than 30% as toxic epidermal necrolysis and those between 10 to 30% as SJS-TEN overlap. The terms erythema multiforme (EM) and SJS have been historically linked and thought to be part of the disease process but it is now known that EM can be distinguished from SJS/ TEN based on clinical pattern (EM presents with typical targets which are well-defined papules with 3 different zones of erythema distributed peripherally, as opposed to atypical targets in SJS/TEN which are flat erythematous/purpuric macules with blisters distrib- uted centrally) and aetiology (EM is typically post-infectious versus drugs in SJS/TEN). The process is immune-mediated and involves interactions be- tween drug-specific T cells, drugs, and HLA molecules with the sub- sequent release of cytotoxic mediators, such as granulysin. This leads to the pathologic hallmark of widespread keratinocyte apoptosis The clinical presentation of SJS/TEN is acute and may be preceded by constitutional symptoms of fever, malaise, upper respiratory tract symptoms, followed by the onset of a painful rash characterized by purpuric macules, target-like lesions, vesicles, bullae, and sheet-like detachment. Mucosal surfaces

including the conjunctiva, oral and anogenital regions are affected in more than 90% of cases. Following the active phase of detachment which typically lasts 1 week from the onset of symptoms, the detachment stops with subsequent re- epithelialization of the skin. Consequent to this ‘acute skin failure’, there is a loss of the barrier, thermoregulatory and homeostatic function of the skin resulting in excess fluid loss, hypothermia, sepsis, and prerenal failure. In severe cases, multiorgan failure and death can occur. Mortality ranges from 10% in SJS to more than 40% in TEN.
A prognostic scoring SCORTEN consisting of seven clinical and biochemical markers are useful to predict outcome (Table 23.16.3/Table 23.16.4). Supportive care remains the mainstay of treatment and pa- tients should be managed in specialized referral centres. The cul- prit drug should be immediately discontinued. Although various immunomodulatory treatments such as corticosteroids, intravenous immunoglobulins, and ciclosporin have been proposed, none has been validated in controlled studies. Long-term sequelae affecting the skin and eyes such as dyspigmentation, corneal scarring, and blindness can profoundly impact the quality of life in survivors. Drug reaction with eosinophilia and systemic
symptoms (DRESS) Drug reaction with eosinophilia and systemic symptoms (DRESS), also known as drug-induced hypersensitivity syndrome (DIHS), is characterized by cutaneous eruption that is associated with internal organ involvement, prolonged latency from drug initiation, chron- icity, and relapsing nature. Box 23.16.5 Causes of lichenoid drug eruptions Antimalarials—quinine, chloroquine, hydroxychloroquine, mepacrine Aspirin ACE inhibitors and angiotensin receptor blockers Calcium channel blockers Gold Lithium Methyldopa NSAIDs Penicillamine Thiazide diuretics Sulphoylureas Box 23.16.6 Causes of fixed drug eruptions Antibiotics—penicillin, metronidazole, sulphonamides, tetracyclines Aspirin Dapsone NSAIDs Oral contraceptive pills Phenytoin

 The cutaneous eruption is polymorphous and may present with an maculopapular exanthematous reaction, target-like lesions, pur- pura, pustules, or generalized exfoliative dermatitis. This is often accompanied by prominent facial oedema, eosinophilia, atyp- ical lymphocytosis, and lymphadenopathy. Organ involvement predominantly affects the liver and kidneys, but other systemic com- plications such as arthralgia, myositis, pneumonitis, myocarditis, and pericarditis are known to occur. Unlike other cutaneous adverse reactions, the clinical course in DRESS may be prolonged, lasting Fig. 23.16.3 (a) SJS/TEN overlap with sheet-like detachment with spots and atypical targets. (b) Confluent erythema in a DRESS patient requiring ICU care. (c) GBFDE: Scattered dusky plaques and bulla. (d) AGEP: Multiple pinpoint pustules on erythematous base. AGEP, acute generalized exanthematous pustulosis; DRESS, drug reaction with eosinophilia and systemic symptoms; GBFDE, generalized bullous fixed drug eruption; ICU, intensive care unit; SJS, Stephen–Johnson syndrome; TEN, toxic epidermal necrolysis. Table 23.16.2 Pharmacogenetics of human leukocyte antigen associated severe cutaneous adverse reactions Drug HLA allele Hypersensitivity reaction Ethnicity Abacavir B*57:01 DRESS Caucasian Allopurinol B*58:01 SJS/TEN Han Chinese, Caucasians Carbamazepine B*15:02 A* 31:01 A*31:01 SJS/TEN SJS/TEN DRESS Han Chinese, Indian, Thai, Malay Caucasian Caucasian, Han Chinese Dapsone B*13:01 DRESS Chinese DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis. Table 23.16.3 SCORTEN prognostic scoring system for toxic epidermal necrolysis Independent prognostic factors Weight Age >40 years 1 Cancer/haematological malignancy 1 Body surface area involved at day 1 >10% 1 Serum bicarbonate level <20 mmol/litre 1 Serum glucose level >14 mmol/litre 1 Serum urea level >10 mmol/litre 1 Heart rate >120 beats/min 1 These values were derived from

multivariate analysis of 23 variables in 165 patients with toxic epidermal necrolysis (TEN). Each positive criterion is given a score of 1; the correlation between SCORTEN and mortality is shown in Table 23.16.4. Adapted from N. Fouchard et al. (2000). SCORTEN: A Severity-of-Illness Score for Toxic Epidermal Necrolysis. Journal of Investigatory Dermatology, 115, 149–53. Copyright 2000, with permission from The Society for Investigative Dermatology.

23.16 Cutaneous reactions to drugs 5759 weeks to months despite culprit drug withdrawal. Reactivation of viruses of the herpes family such as human herpes virus 6 (HHV6), cytomegalovirus (CMV), and Epstein-Barr virus (EBV) have been recognized and may denote a more chronic and severe clinical course. The mortality of DRESS is about 5–10%. Long-term auto- immune sequelae such as autoimmune thyroid disease, vitiligo, and alopecia areata have been reported in survivors. Treatment consists of drug withdrawal and supportive therapy. To date, no controlled studies on treatment of drug reaction with eosinophilia and systemic symptoms exist. Both potent topical and systemic corticosteroids have been used in its treatment with the latter being widely used in patients with systemic involvement. There is a theoretical risk of worsening of existing viral reactivation with systemic corticosteroids and judicious tapering of corticoster- oids should be done to prevent a flare-up of disease. Acute generalized exanthematous pustulosis (AGEP) The clinical hallmark of acute generalized exanthematous pustulosis (AGEP) is the presence of numerous pinpoint pustules overlying background of erythema or erythematous lesions. These lesions may initially arise in the intertriginous areas before becoming general- ized. This is frequently accompanied with facial oedema, pruritus, fever, and peripheral neutrophilia. Organ involvement occurs in about 20% of cases, typically involving the liver and kidney. The reac- tion is self-limiting with a good prognosis, with mortality occurring in less than 5% of cases. Resolution is characterized by post-pustular desquamation and occurs typically within two weeks of the onset of reaction. Supportive treatment is the mainstay of treatment since it is self-limiting. Although widely used, topical and systemic cortico- steroids have not been shown in controlled studies to modify the clinical course of the disease. Generalized bullous fixed drug eruptions (GBFDE) Generalized bullous fixed drug eruptions are rare, extensive vari- ants of fixed drug eruptions. Unlike typical fixed drug eruption, the lesions consist of large erythematous/purpuric patches with bulla and erosions and involve a larger proportion of the body surface area. Due to the extensive nature and the presence of skin detach- ment, it is often misdiagnosed as SJS/TEN. In distinction from SJS/ TEN, constitutional symptoms are less common and there are dif- ferences in clinical morphology such as absence of atypical targets, purpuric spots, minimal mucosal involvement as well as the pres- ence of normal intervening skin between lesions. A history of pre- vious recurrent episodes is common and the extent of disease may be progressive with each subsequent attack. Traditionally thought to confer a better prognosis than SJS/TEN, a recent study has shown that the prognosis is similar to SJS/TEN of the same body surface area detachment, with an average mortality of 20%. Nonetheless, it is important to distinguish GBFDE from SJS/TEN as the implicated drugs in GBFDE have a shorter latency of hours to 3 days compared to the typical 5–28 days in SJS/TEN. In cases with extensive skin involvement, GBFDE should be managed similarly to SJS/TEN in specialized units with care focused on supportive treatment and im- mediate withdrawal of culprit drug. Cutaneous adverse reactions induced
by targeted anticancer therapies Conventional chemotherapy typically acts on disrupting the specific phases of the cell cycle in actively dividing malignant cells. Their side effects are well-recognized and typically occur in tissues with rapid turnover of cells such as hair follicles and mucosal surfaces, leading to alopecia and mucositis. Other reactions vary depending on the type of

chemotherapy. Pigmentary changes can occur with bulsulphan and 5-fluorouracil. Nail dystrophies, including ridging and onycholysis, can occur in patients receiving taxanes. Extravasation injuries may occur due to leakage of intravenously ad- ministered chemotherapy, such as anthracyclines, vinca alkaloids, paclitaxel, and cisplatin, leading to erythema and necrosis in severe cases. Hand-foot syndrome or palmoplantar erythrodysaesthesia, which is characterized by erythema, oedema, blistering and scaling of the palms and soles, can occur with treatment of cytarabine and 5-fluorouracil. The rest of this section focuses on targeted therapies which are novel anticancer drugs directed against the molecular abnormalities involved in the pathogenesis of neoplastic transformation and me- tastases. Newer agents are constantly being approved and, to date, approved targeted therapies include epidermal growth factor re- ceptor (EGFR) inhibitors, KIT and BCR-Abl inhibitors, multikinase inhibitors, RAF inhibitors, and more recently, immunomodulatory agents that antagonize CTLA4 as well as PD1. Skin toxicities are not uncommon as many of such target molecules are also highly ex- pressed in the skin. EGFR inhibitors (e.g. gefitinib, erlotinib, cetuximab, panitimumab) Papulopustular reactions are the most common adverse reactions affecting up to 90% of patients in trials and arise early in the course of treatment. They develop mainly on the seborrhoeic areas of the head and trunk and are characterized by follicular pustules and pap- ules, resembling acne vulgaris and rosacea. Xerosis or skin dryness is common, often resulting in fissuring of fingers and toes. Nail fold paronychia are described in 10–20% of patients. Hair changes in- clude both scarring and nonscarring alopecia as well as trichomegaly of the eyelashes which can result in corneal erosions and ulcerations. KIT, BCR-Abl, and PDGF inhibitors (e.g. imatinib, nilotinib, dasatinib) Imatinib is the prototypical drug in this class and is used in the treatment of chronic myeloid leukaemia and stromal tumours. Facial oedema is one of the most observed adverse reaction and Table 23.16.4 Mortality rates depending on SCORTEN severity score SCORTEN Mortality rate Odds ratio 0–1 3.2 1 2 12.1 4.1 3 35.3 14.6 4 58.3 42

> 5 90 270 Adapted from N. Fouchard et al. (2000). SCORTEN: A Severity-of-Illness Score for Toxic Epidermal Necrolysis. Journal of Investigatory Dermatology, 115, 149–53. Copyright 2000, with permission from The Society for Investigative Dermatology.

 can be mistaken for angioedema. Maculopapular and generalized exfoliative dermatitis may also occur. Pigmentary changes con- sisting of both hyper and hypopigmentation can occur in up to 40% of patients. Rare cases of SJS/TEN have been reported with imatinib. Multikinase inhibitors (e.g. sorafenib, sunitinib) Sorafenib is FDA approved for the treatment of renal cell and hepatocellular carcinoma and targets RAF, VEGF, FLT-3, C-KIT, and RET tyrosine kinases. The targets of sunitinib are VEGFR, PDGFR as well as c-KIT, RET, and FLT 3 receptor tyrosine kinase. The most common side effect is the hand-foot syndrome, which affects up to 70% of patients. This is characterized by skin thickening localized to pressure areas. Other reactions include facial erythema and nail splinter haemorrhages. RAF inhibitors (e.g. vemurafenib, dabrafenib) The most clinically significant adverse reaction is the development of keratoacanthomas and squamous cell carcinoma. This adverse reaction is abrogated with the concurrent use of MEK inhibitors. Other reactions observed in trials include keratosis pilaris-like reac- tions, cysts, photosensitivity, and pruritus. MEK inhibitors The adverse reactions associated with MEK inhibitors (e.g. trametinib) are similar to those of EGFR inhibitors and include papulopustular rash, dry skin with fingertip fissuring as well as paronychia. Anti-CTLA 4 Antibodies

CTLA-4 (Cytotoxic T-lymphocyte-associated protein 4) is a sur- face molecule found on various lymphocyte subtypes and it acts as a brake on immune activation. The use of CTLA-4 antibodies (e.g. ipilimumab, tremelimumab) results in a proliferation of T lympho- cytes with antitumour response and has been approved for the treatment of metastatic melanoma. However, this can lead to imbal- ances in immunologic tolerance and can lead to collateral damage in normal tissues, resulting in inflammatory or autoimmune side effects. Dermatologic adverse reactions associated with anti- CTLA4 molecules include diffuse maculopapular eruptions, usually developing one to two weeks after initiation of treatment, pruritus, and vitiligo. Anti PD-1 Anti PD-1 (Programmed cell death-1) is another immune- checkpoint inhibitor. Dermatological adverse reactions include maculopapular eruptions (the most common) as well as other reac- tions such as bullous disorders like bullous pemphigoid. FURTHER READING Barbaud A, et al. (2001). Guidelines for performing skin tests with drugs in the investigation of cutaneous adverse drug reactions. Contact Dermatitis, 45, 321–8. Bastuji-Garin S, et al. (1993). Clinical classification of cases of toxic epideraml necrolysis: Stevens-Johnson syndrome and erythema multiforme. Arch Dermatol, 129, 92–6. Chung WH, et al. (2004). Medical genetics: a marker for Stevens- Johnson syndrome. Nature, 428, 426. Kardaun SH, et al. (2013). Drug reaction with eosinophilia and sys- temic symptoms (DRESS): an original multisystem adverse drug re- action. Results from the prospective RegiSCAR study. Br J Dermatol, 169, 1071–80. Lipowicz S, et al. (2013). Prognosis of generalized bullous fixed drug eruption: comparison with Stevens-Johnson syndrome and toxic epidermal necrolysis. Br J Dermatol, 168, 726–32. Macdonald J, et al. (2015). Cutaneous adverse effects of targeted therapies. Part I: inhibitors of the cellular membrane. J Am Acad Dermatol, 72, 203–18. Macdonald J, et al. (2015). Cutaneous adverse effects of targeted ther- apies. Part II: inhibitors of intracellular molecular signalling path- ways. J Am Acad Dermatol, 72, 221–36. Mockenhaupt M, et al. (2008). Stevens-Johnson syndrome and toxic epidermal necrolysis: assessment of medication risk with emphasis on recently marketed drugs. The EuroSCAR study. J Invest Dermatol, 128, 35–44. Roujeau JC, Stern R (1994). Severe adverse cutaneous reactions to drugs. N Engl J Med, 331, 1272–85. Sassolas B, et al. (2010). ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson syndrome and toxic epidermal necrolysis: comparison with case-control analysis. Clin Pharmacol Ther, 88, 60–8. Sekula P, et al. (2013). Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol, 133, 1197–204. Sidoroff A, et al. (2001). Acute generalized exanthematous pustulosis (AGEP)—a clinical reaction pattern. J Cutan Pathol, 28, 113–9.

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