European Handbook of Dermatological Treatments

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Editors

Fourth Edition

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Preface

It is with great pleasure that we introduce the fourth edition of the *European Handbook of Dermatological Treatments*. The book was first published in 2000 by editors Andreas Katsambas and Torello M. Lotti, and over the years has strived to meet the need for state-of-the-art treatments for patients with skin diseases in clinical practice.

The updated fourth edition aims to provide a comprehensive textbook on treatments for skin diseases compiled by European specialists. Up-to-date treatments are discussed, including recent developments on biologic agents for atopic dermatitis and psoriasis, targeted therapies and immunotherapy for melanoma, as well as current guideline recommendations. Every chapter has been reviewed and updated with all the recent developments in treatment. The book has kept its attractive overall format, divided into three main parts: (1) skin diseases, (2) methods of treatment, (3) drugs, and each chapter describes the etiopathogenesis, the clinical characteristics, the diagnosis and differential diagnosis, while detailing the available treatments. Indications, dosing regimens, and treatment algorithms are accompanied by colored illustrations, informative tables, and synoptic key points.

We want at this point to thank the authors. Through the editing process, we have made friends internationally, even though we have only met some through email correspondence. As we review and edit each chapter we recognize the talent, devotion, and expertise each author brings to his or her work.

In the era of overwhelming information, we hope this book may serve as a reader-friendly reference in the field of Dermatology-Venereology.

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Part III Drugs

Drug Hypersensitivity Reactions

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Andrea Szegedi, Éva Remenyik and Emese Gellén

Key Points

- In the therapy of drug hypersensitivity reactions at the time of the acute symptoms, the main tasks are to state the correct diagnosis, classify the reaction, score the severity, withdraw the suspected drug, treat the symptoms, and prepare the drug history documentation properly, which can help the allergological examinations in the future.
- After the resolution of the symptoms, the physician's next duties are the identification of the eliciting drug and the treatment of sequelae if needed.
- Different pathomechanisms are involved in drug hypersensitivity reactions.
- Since morphology and distribution of the rash do not help in determining the responsible drug, allergological investigations should be performed on the basis of the patient's history.
- Allergological tests are best prepared between 3 weeks to 6 months after the incident.
- A detailed history is one of the most important assessments when a patient presents with drug hypersensitivity reaction.

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General Principles, Classification, Pathomechanisms

Adverse drug reactions (ADR) are still widely divided into two main groups, type A and type B reactions, and are observed in 10–20% of hospitalized patients. Type A reactions represent nearly 80–85% of ADRs, are caused by predictable pharmacological actions of the drug (drug-induced toxicity, side effects, drug interactions), and may occur in every individual. But type B reactions develop on the basis of individual predisposition (idiosyncratic reactions due to enzyme deficiency and hypersensitivity reactions) and account for 15–20% of adverse effects (Pichler 2019). Hypersensitivity reactions include allergic-immune reactions, pharmacological interaction with immune receptors (p-i concept), and pseudoallergy. In case of allergic-immune reactions, T and B cell responses are elicited via hapten (drug binds covalently to proteins and a new antigen is formed), or prohapten (drug metabolite binds covalently to proteins) mechanisms, resulting in IgE-mediated urticaria, anaphylaxis, T-cell mediated maculopapular

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exanthem, or IgG-cell mediated haemolytic anaemia, and immune-complex disease (Pichler 2019; Francheschini et al. 2019). In p-i concept, the drug binds directly to immune receptor proteins (HLA or TCR) via noncovalent bonds and elicit T-cell-mediated reactions, therefore in vitro and in vivo skin tests can be positive. Allergic-immune reactions and p-i concept are the immune-mediated drug hypersensitivity reactions, which comprise a heterogeneous group of diseases and are classified according to Gell and Coombs (antibody-mediated drug hypersensitivity reactions: type I—IgE, type II and III—IgG and type IV—T cell-mediated). After better understanding of T cell functions and discovery of subgroups, the late type IV reaction has been further subdivided in the revised form of Gell and Coombs classification (type IVa—T helper 1, type IVb—T helper 2, type IVc—T cytotoxic-mediated and type IVd) (Pichler 2019; Francheschini et al. 2019). Pseudoallergic reactions are non-immune-mediated hypersensitivity reactions, when drugs directly bind to receptors and enzymes of effector cells, without the involvement of IgE or T cell reactions. These reactions are dose-dependent, no sensitization is required, and usually imitate IgE-mediated reactions with wheal and oedema formation, but sometimes anaphylaxis can also develop. They tend to arise less rapidly than true IgE-mediated allergies and require higher doses of drugs. MAS-receptor (MRGPRX2)-mediated mast cell degranulation, arachidonic acid pathway activation [non-steroid anti-inflammatory drugs (NSAID)-induced urticaria/angioedema, NSAID-exacerbated cutaneous diseases, NSAID-exacerbated respiratory disease], bradykinin pathway alteration [angiotensin-converting enzyme (ACE) inhibitors induced angioedema], and complement activation can be detected in the background. Besides NSAIDs and ACE-inhibitors, opioids, plasma expanders, and radiocontrast media are the most common causes of pseudoallergic reactions (Pichler 2019; Francheschini et al. 2019; Zhang et al. 2018). Some drugs can elicit drug hypersensitivity reactions via hapten and p-i (e.g. beta-lactam antibiotics, sulphanilamides) or p-i and pseudoallergic (e.g. vancomyin), or hapten and pseudoallergic (e.g. muscle relaxants) or hapten and p-i and pseudoallergic mechanisms (e.g. metamizole, chinolones, radiocontrast media) (Pichler 2019; Francheschini et al. 2019; Bellón 2019).

The therapy of drug hypersensitivity reactions comprises two fundamental steps. At the time of the acute symptoms, the main tasks are to state the correct diagnosis, classify the reaction, score the severity, withdraw the suspected drug, treat the symptoms, and prepare the documentation properly, which can help the allergological examinations in the future. The second step is the identification of the eliciting drug and the treatment of sequelae if needed. Since morphology and distribution of the rash do not help to determine the responsible drug, according to data of the history, allergological investigations should be done between 3 weeks and 6 months after the incident in order to find the causative agent**.** The recommended test type depends on whether the diagnosis of the rash was an immediate or delayed type reaction (Pichler 2019; Francheschini et al. 2019; Bellón 2019; Brockow et al. 2019; Pichler 2007). (See Table 22.1).

This chapter will deal with the most common and severe forms of drug hypersensitivity reactions like urticaria, angioedema and anaphylaxis, maculopapular drug eruption (MDE), acute generalized exanthematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), Stevens-Johnson syndrome (SJS), and toxic epidermal necrolysis (TEN).

Table 22.1 Pathogenesis, first onset of symptoms, elicitors, and diagnostic steps in drug hypersensitivity reactions

Clinical manifestation	Potential pathogenesis	Onset of skin reaction	Most common drugs	Diagnostic tests
Urticaria, angioedema	IgE-mediated, pseudoallergy, rarely immune complex	Within 1 h	Beta-lactams antibiotics, sulphonamides, quinolones, NSAIDs, radiocontrast media, general anaesthetics, opiates	Prick test, intradermal skin tests, specific IgE, basophil tests, LTT, provocation
Anaphylaxis	IgE-mediated, pseudoallergy, rarely immune complex activation (C3a, C5a)	Within 1 h	Beta-lactams antibiotics, sulphonamides, quinolones, NSAIDs, radiocontrast media, general anaesthetics, opiates	Prick test, specific IgE, basophil tests, serum tryptase measurement, LTT
MDE	T-cell mediated (IVc)	4–14 days	Beta-lactams, sulfamethoxazole, quinolones, anticonvulsants, NSAIDs, allopurinol	Patch test, LTT, (Prick test, intradermal skin test)
AGEP	T-cell mediated (IVd)	1–12 days	Aminopenicillins, cephalosporins, macrolides, celecoxib, diltiazem, hydroxychloroquine or chloroquine, sulphonamides, and terbinafine	Patch test, LTT, (intradermal skin test)
DRESS	T-cell mediated (IVb) Viral reactivation?	Up to 12 weeks	Anticonvulsants (phenytoin, carbamazepine, phenobarbital, lamotrigine), minocycline, allopurinol, thalidomide, dapsone, sulphonamides, abacavir, nevirapine	Patch test, LTT
SJS and TEN	T-cell mediated (IVc) and other non-drug specific amplification mechanisms	4–30 days	Anticonvulsants (carbamazepine, phenytoin, phenobarbital, lamotrigine), allopurinol, sulphonamides, oxicam NSAIDs, nevirapine	Patch test, LTT (low sensitivity)

Detailed Description of Different Clinical Manifestations

Urticaria, Angioedema, Anaphylaxis

Definition, Epidemiology, Pathophysiology

Urticaria, angioedema, and anaphylaxis are the most common immediate type drug hypersensitivity reactions and urticaria is the second most common cutaneous manifestation of drug allergy after MDE. In urticarial, disseminated wheals (oedema in the upper part of the dermis) are limited to the skin and can be accompanied by angioedema (tense, non-pitting oedema of the deeper skin layers, and mucosa) (Kanani et al. 2018). Anaphylaxis has been defined as a severe, life-threatening generalized or systemic hypersensitivity reaction that occurs immediately after drug intake and affects more than one organ, whether or not accompanied by hypotension (anaphylactic shock) (Montañez et al. 2017). Urticaria can be caused by immune-mediated hypersensitivity reactions (type I, IgE-mediated reaction or less frequently type III, immune complex-mediated reaction), or by non-immune-mediated, so called pseudoallergic mechanisms (Kanani et al. 2018). Angioedema can be hereditary [e.g. hereditary C1 inhibitor deficiency (C1-INH HAE I, -II), FXII gene mutation (FXII-HAE)] or acquired. Acquired angioedema can further be classified as histaminergic (IgE-dependent or independent), ACE-inhibitor induced, and acquired C1-inhibitor deficiency induced. In the pathogenesis of anaphylaxis, immunological reactions involving IgE or rarely immune complexes and also non-immunological mechanisms are detected (called as nonallergic anaphylaxis or anaphylactoid reaction) (Bova et al. 2018). Many different drugs can cause urticaria or anaphylaxis, most commonly beta-lactam and non-beta-lactam antibiotics, e.g. sulphonamides, quinolones, NSAIDs, radiocontrast media, general anaesthetics, opiates, and latex (Kanani et al. 2018; Montañez et al. 2017).

Clinical Features

In drug-induced acute urticaria, symptoms appear usually within 1 h after drug intake. Rapidly emerging, migrating, and extensively itching wheals occur on large body parts (See Fig. 22.1). The lesions typically disappear in hours in one location without leaving any remnant signs (Kanani et al. 2018). Pruritus, urticaria, and angioedema may also present as initial or partial symptoms of full-blown anaphylaxis. In anaphylactic patients, flushing, itching, and pruritus of the palms and soles, together with generalized urticaria and angioedema, are followed by respiratory symptoms (in up to 70% of patients) and by gastrointestinal symptoms (in up to 40% of patients). Asphyxia due to laryngeal oedema is probably the main cause of lethal anaphylaxis. Laryngeal swelling may be suspected in case of difficulty of speaking or swallowing and if the voice becomes hoarse. Hypotension, manifest as dizziness, tachycardia, shock, and cardiorespiratory arrest, occurs in only 10–30% of cases. Typically, anaphylactic symptoms start within minutes (seldom later than 20 min) after exposure to the causative drug. In the diagnosis, the physician should consider the wide spectrum of symptoms and the continuum of signs and symptoms (Pichler 2007; Montañez et al. 2017).

Differential Diagnosis

The diagnosis of acute urticaria and anaphylaxis is based largely on history and physical findings at the time of the event. Usually skin biopsy is not needed, only if urticaria vasculitis has to be distinguished. Laboratory tests available to support the diagnosis of anaphylaxis have proved to be somewhat disappointing in the clinical practice (Pichler 2007; Kanani et al. 2018; Montañez et al. 2017). Transiently elevated plasma histamine level of >10 nM correlates with severity and persistence of cardiopulmonary manifestations or gastrointestinal manifestations, but as histamine needs to be measured within 1 h of the onset of anaphylaxis, this test is seldom used.

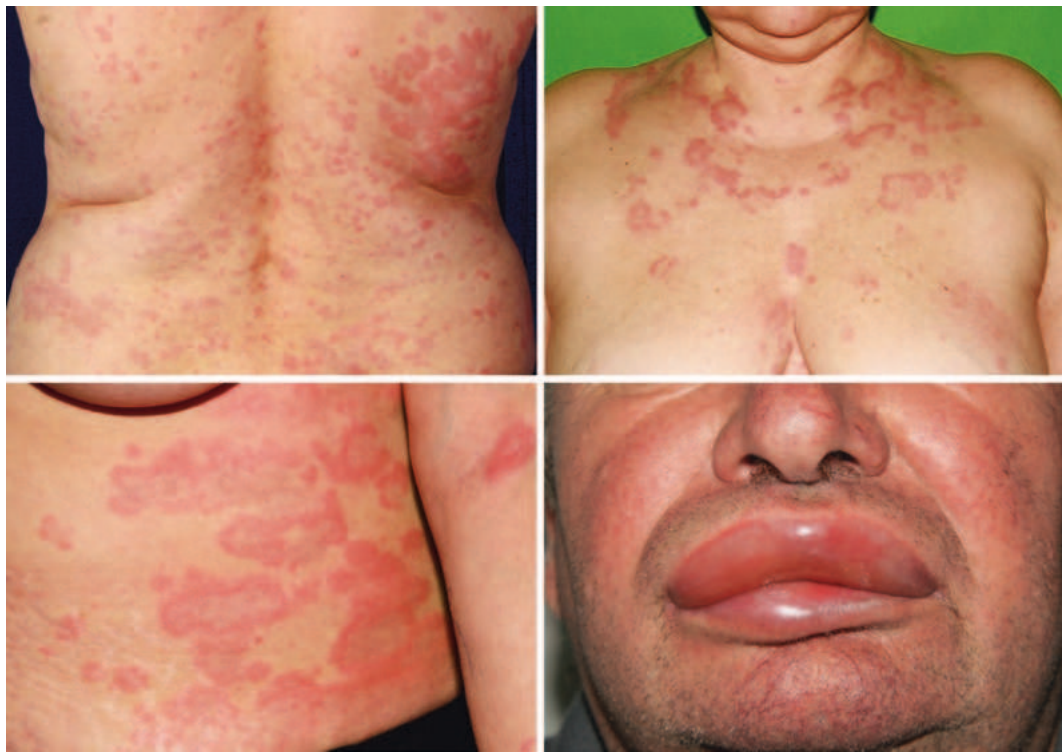

Fig. 22.1 Clinical signs of urticaria and angioedema

Measuring serum tryptase level within 12 h is more widely used, although this method also has its limitations (Montañez et al. 2017).

Treatment

Acute Stage

In the majority of moderate drug-induced urticaria cases, stopping the causative agent and treatment with a non-sedative histamine H1 antagonist is sufficient. Locally, corticosteroid containing creams or lotions can be applied to decrease pruritus. In case of widespread lesions with oedema formation, oral corticosteroids provide symptomatic relief and attenuate the reaction (Kanani et al. 2018). Patients with anaphylaxis should be lied down with their legs elevated and epinephrine should be administered at the first sign of respiratory failure or cardiovascular collapse. The intramuscular route for epinephrine administration is recommended when compared to subcutaneous mode (Muraro et al. 2014; Simons et al. 2015). The dose is usually 0.5 mL of a 1:1000 dilution in adults and this dose can be repeated in every 5–15 min until symptoms improve. Intravenous epinephrine (1:1000 dilution) should be given in case of inadequate response to 2–3 intramuscular adrenaline doses by trained staff because of the higher risk of cardiac arrhythmias, hypertension, and myocardial infarction. The most common side effects of epinephrine are anxiety, tremor, palpitation, and increased blood pressure. Beta-blockers may increase the severity of an anaphylactic reaction and antagonize the response to epinephrine; accordingly, the anaphylaxis of patients on beta-blockers can be severe and treatment-resistant. Corticosteroids are often used to decrease the risk of recurrent or protracted anaphylaxis, but it is still not entirely clear how steroids work. At least 3 L of normal saline (20 mL/kg rapidly under pressure) should be given and bolus should be repeated if hypotension persists. Patients should be warned of the possibility of an early relapse and kept under observation for 8 to 24 h, particularly if the patient has asthma, a history of biphasic response, or may continue to absorb the drug. Oxygen should also be applied in respiratory or circulatory failure. In case of severe laryngeal oedema, in order to maintain the airway, endotracheal intubation or tracheostomy should be carried out (Montañez et al. 2017; Muraro et al. 2014; Simons et al. 2015).

Chronic Stage

The main purpose is the identification of the eliciting drug. Since both urticaria and anaphylaxis can be the result of immune-mediated and also of non-immune-mediated reactions, this often causes difficulties in the allergological investigations, which are recommended between 3 weeks and 6 months after the incident, when complete clearing of clinical signs and normalization of laboratory values occurred. In the case of acute urticaria, prick test which is less sensitive but safer should be the first skin test, and if it is negative, intradermal skin test can be carried out. The negative result is not a guarantee that the drug is tolerated, because of the weak sensitivity of these tests (Pichler 2007; Kanani et al. 2018; Montañez et al. 2017). Whenever possible, one should carry out in vitro tests, like drug-specific IgE measurements, basophil activation test (BAT), basophil sulphidoleukotriene or histamine release assays, or the lymphoblast transformation test (LTT) (Mayorga et al. 2019). The markers of basophil activation are CD63 and CD203c, which are expressed on the surface of the cell membrane and can be measured by flow cytometry. BAT is recommended mainly in case of selective NSAID (mainly pyrazolone) and beta-lactams induced immediate hypersensitivity reactions (IHR) as a complement of skin testing, and in neuromuscular blocking agents (NMBA) induced IHRs, even for the identification of cross-reactive NMBAs. Newer approaches are IFN-γ producing cells determination by Enzyme-linked immunospot assay (ELISpot) and its modified version, using pre-activated T cells. If the above-mentioned in vitro tests are negative, provocation is needed or with other words a graded challenge test is done (Mayorga et al. 2019). In case of anaphylaxis, prick test and in vitro tests (e.g. BAT) can be performed, but intradermal test or provocation are usually not advised. Serum tryptase levels increase greatly after anaphylactic shock and

anaphylaxis, but are negative in anaphylactoid non-IgE-mediated reactions. The concentration of tryptase peaks 1–2 h after the onset of the reaction and remains elevated with a half-life of 1.5–2-5 h, so the samples for tryptase test should be collected within 6 h of initiation of anaphylaxis. According to the international consensus, in case of perioperative anaphylaxis in the acute phase, the mast cell tryptase level should be >1.2× baseline tryptase+2 mg/L and it is recommended to be measured 30–180 min after the onset of symptoms. In case of high tryptase level, the measurement should be repeated few weeks later to exclude mast cell disorders (Montañez et al. 2017). In pseudoallergic reactions, skin tests and in vitro tests are also negative, since adaptive immune reactions are not involved to our present knowledge (Zhang et al. 2018). Drug provocation test (DPT) is considered to be the gold standard for the confirmation or exclusion of drug hypersensitivity, but only recommended in case of negative skin tests and if the clinical history is not conclusive. Provocation tests can be informative but often negative suggesting that additional cofactors might be needed to develop clinical symptoms. DPT is also applied to find a safe alternative drug instead of the culprit drug (Pichler 2007; Kanani et al. 2018; Montañez et al. 2017; Mayorga et al. 2019). Desensitization should be offered only when benefits outweigh the risks. Rapid desensitization protocols are available with antibiotics (penicillin), chemotherapeutic agents, and monoclonal antibodies, but with NSAIDs (e.g. aspirin) as well (Mayorga et al. 2019; Chastain et al. 2019). Patients may be advised to wear a Medical Alert bracelet and instructed on the use of a self-administration epinephrine device in the event of further episodes.

Maculopapular Drug Eruption (MDE)

Definition, Epidemiology, Pathophysiology

The so-called exanthematous reactions, the MDEs, are the most common drug hypersensitivity eruptions affecting the skin and present 31–95% of all drug-induced cutaneous reactions. Antimicrobials (beta-lactams, sulfamethoxazole, quinolons), anticonvulsants, NSAIDs, and allopurinol are the most frequently involved drugs, but it is important to know that any drug can play an initiating effect. There are a lot of cofactors in the development of MDEs, like viral infections, connective tissue diseases, older age, and genetic factors. MDEs belong to the Type B hypersensitivity reactions, so they are unpredictable and occur in individuals with personal susceptibility. Drug-specific, $CD4^+$ cytotoxic T cells are the dominant effector cells, and MDEs are considered to be a Gell and Coombs type IVc, cell-mediated delayed type hypersensitivity reactions (Pichler 2019; Bellón 2019; Brockow et al. 2019).

Clinical Features

The clinical picture characteristic of MDEs consists of hyperaemic or pink coloured papules and macules, which sometimes become confluent (See Fig. 22.2). The rush usually starts on the trunk and upper extremities and affects other body parts, like lower extremities, gradually. The palms, feet, and mucous membranes are free and this can be an important differential diagnostic feature. Moderate to severe pruritus can occur. Low-grade fever and eosinophilia can sometimes accompany it as well. In the uncomplicated forms, the skin lesions usually begin to evolve 4–14 days after the patient start to take the causative drug and disappear 1–2 weeks after discontinuation. MPE often heals with desquamation. On the other hand, in some cases the primary maculopapules can represent the beginning of more severe drug reactions, like SJS/TEN or DRESS, so all patients should be monitored for markers of severe reactions (See Table 22.2). In late type reactions, including MDE, certain laboratory tests (complete blood count, liver function test, CRP, serum creatinin) are recommended to assess severity (Brockow et al. 2019).

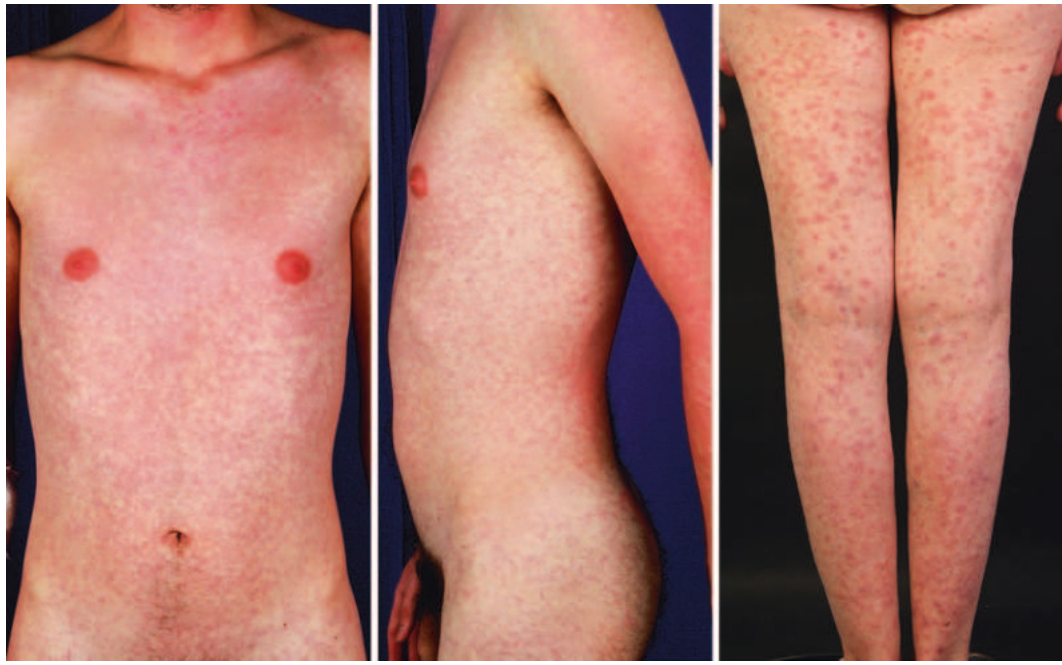

Fig. 22.2 Skin rash of MDE (maculopapular drug eruption)

Table 22.2 Markers of severe reactions in patients with MDE[a]

1. Skin pain or burning
2. Widespread eruptions (i.e. confluent erythema)
3. Affecting more than 60% of the body surface area
4. Dusky red or purpuric macules
5. Atypical target lesions
6. Blisters or epidermal detachment
7. Positive Nikolsky sign
8. Involvement of mucous membranes
9. Facial oedema
10. Lymphadenopathy
11. Arthralgia
12. High fever (>40 °C)
13. Laboratory results: eosinophilia, atypical lymphocytes, and abnormal liver-function tests

[a]Maculopapular drug eruption

Differential Diagnosis

In the differential diagnosis of MDE, dermatologist should consider acute viral infections, collagen vascular diseases, acute graft-versus-host disease, and secondary syphilis (See Table 22.3). Usually skin biopsy is not needed, anamnestic data, clinical picture, and some laboratory tests are enough to state the diagnosis (Brockow et al. 2019).

Treatment

Acute Stage

The suspected drug should be withdrawn as the first step of treatment. Sometimes it is not easy to identify the causative drug. In these cases, all drugs that are not essential and were started in the last few weeks should be stopped. In mild-moderate cases, topical corticosteroid creams and systemic antihistamines can be used, in severe cases systemic corticosteroids can be initiated, and then gradually decreased when the symptoms disappear.

Chronic Stage

After the patient became symptom free, the next step is to identify the causative drug, if there are several suspected medications in the history. The patch test and the LTT can be performed after recovery and after stopping antihistamines and corticosteroids; however, Prick test and intradermal test (IDT) are potentially useful as well, according to a recent international consensus document. However, the European Academy of Allergy and Clinical Immunology (EAACI) and European Society of Contact Dermatitis (ESCD)

Table 22.3 Differential diagnosis of MDE[a]

	Clinical picture/histology	Laboratory alterations
1. MDE	Polymorphous clinical picture, frequent confluence, elderly age group	Eosinophilia in peripheral blood
2. Acute viral infections (paramyxovirus, togavirus, Epstein-Barr virus, enterovirus, CMV, parvovirus)	Younger age groups, concomitant general symptoms, dermal hemorrhage	Serological test for infections is positive, laboratory signs of infections (CRP, leukocytosis)
3. Collagen vascular diseases	General symptoms differ, epidermal atrophy, focal parakeratosis, thickening of the basement membrane zone on histology	Immunological alterations, (autoantibodies, complement serology)
4. Acute graft-versus-graft reactions	Specific anamnesis, epidermal atrophy, parakeratosis, necrotic keratinocytes on histology	
5. Secondary syphilis	Palmoplantar lesions, plasma cell rich mononuclear infiltration in histology	Specific serology

[a]Maculopapular drug eruption

guidelines about how to perform delayed IDT are not uniform (Phillips et al. 2019). Patch tests are recommended to carry out within 6 months after the MDE, and they are not well standardized so false positive and false negative results can occur. LTT validation is also not well organized in different laboratories. Provocation tests after MDEs are questionable since they need longer time period and hold the risk of inducing a more severe reaction, although after negative skin test results and after mild exanthems it is considered to be performed (Brockow et al. 2019; Mayorga et al. 2019; Phillips et al. 2019). Desensitization may be considered in those cases where the drug is mandatory without available alternative and has been described with allopurinol, vemurafenib, dabrafenib, antituberculotic drugs, and in HIV patients with MDEs to sulphonamides (Dursun and Sahin 2014; Bar-Sela et al. 2015; Thong et al. 2014).

Acute Generalized Exanthematous Pustulosis (AGEP)

Definition, Epidemiology, Pathophysiology

AGEP is a T cell-mediated, late type, IVd hypersensitivity drug-induced skin reaction with a rapid and dramatic appearance, but with a benign course. It is a rare disease with an estimated incidence equal to severe bullous skin diseases. The main causative medications are aminopenicillins, cephalosporins, macrolides, celecoxib, diltiazem, and anti-malarial drugs such as hydroxychloroquine or chloroquine, but there are reports on the role of sulphonamides and terbinafine. Usually the onset of the skin reaction occurs 1–12 days after the initiation of the suspected medication (1–2 days in case of antibiotics, up to 12 days for other drugs) (Francheschini et al. 2019; Brockow et al. 2019; Sidoroff et al. 2001; Cho and Chu 2017). In the pathogenesis, drug specific T lymphocytes are supposed to migrate into the epidermis, where keratinocytes and T cells secrete IL-8, which attracts neutrophils and neutrophil recruitment will result in the formation of subcorneal pustules. Studies have also suggested the role of Th17 lymphocytes and IL-36 in the pathogenesis of AGEP (Bellón 2019).

Clinical Features

In the course of AGEP, a widespread erythema suddenly occurs on the face, trunk, and extremities, mainly affecting the flexural surfaces and skin folds. On the top of the erythema, a lot of small non-follicular sterile pustules develop rapidly (See Fig. 22.3). Usually mucous membranes are not involved, but patients have fever and massive neutrophilia. Internal organ involvement is not typical, but transient renal failure or liver involvement can occur in elderly. A diagnostic score for validation of AGEP was introduced and this system distin-

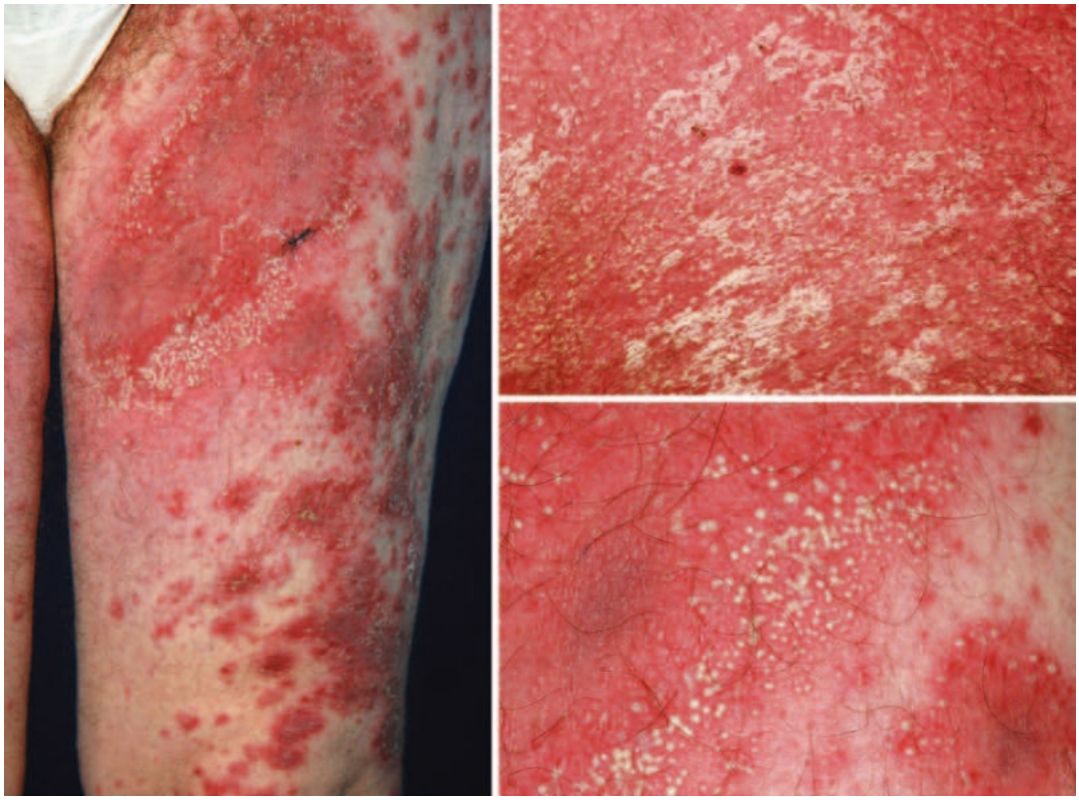

Fig. 22.3 Characteristic picture of AGEP

guishes definite, probable, and possible AGEP diagnosis according to the final score. Spontaneous resolution in less than 15 days and post-pustular desquamation is also characteristic (Brockow et al. 2019; Pichler 2007; Sidoroff et al. 2001).

Differential Diagnosis

A pustular smear and culture should be taken to exclude infectious pustular disorders. A skin biopsy is also needed to differentiate other pustular skin diseases. Spongiform subcorneal and/or intraepidermal pustules and perivascular infiltrate of neutrophils with oedema of the papillary dermis are visible. Bacterial folliculitis, furunculosis, acne, acneiform eruptions, varicella, impetigo, Sweet syndrome, or staphylococcus scalded skin syndrome (SSSS) are easy to differentiate from AGEP. On the other hand, psoriasis pustulosa generalisata and Sneddon-Wilkinson syndrome are rather difficult to distinguish. In the former one history of psoriasis and histological signs of psoriasis can help, in the later one larger pustule with hypopyon formation and slower development are characteristic (Brockow et al. 2019; Pichler 2007; Sidoroff et al. 2001).

Treatment

Acute Stage

Once the trigger was identified and discontinued, the disease has a self-healing resolution and symptomatic therapy is sufficient. In those cases, with severe and widespread inflammation, a short course of systemic corticosteroids can be useful (Pichler 2007; Sidoroff et al. 2001; Cho and Chu 2017).

Chronic Stage

During the latter allergological investigations, patch test is recommended, since it is frequently positive in AGEP. The patch test reaction at 48 h imitates the early phase of the disease with T cell infiltration,

after 96 h pustules can be observed. Moreover, IDT can be potentially useful (Mayorga et al. 2019; Phillips et al. 2019; Sidoroff et al. 2001).

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Definition, Epidemiology, Pathophysiology

The term DRESS has been suggested in place of Hypersensitivity syndrome (HSS) or drug-induced hypersensitivity syndrome (DiHS) which has long been used to describe drug reactions with internal organ involvements. Th2 T cells and cytokines (IL-4, 5, 13) are considered to play important role in the pathogenesis of DRESS (Shiohara and Mizukawa 2019; Cho et al. 2017; Kardaun et al. 2007). However, in a recent study increased number of Tregs were detected in the acute phase, while in the resolution phase the amount of Th17 cells was elevated (Shiohara and Mizukawa 2019). In another previous study, increased number of $CD8^+$ T cells were found as well. Moreover, it is also suggested that virus reactivation may be important in the development of the disease due to the prolonged courses and flare-ups after the withdrawal of the culprit medication. It is not clearly revealed whether reactivation of latent herpes viruses (HHV-6, HHV-7, EBV, and cytomegalovirus) may play a causal role or just can be considered as complications (Bellón 2019; Cho and Chu 2017; Shiohara and Mizukawa 2019; Cho et al. 2017). In Europe, elevated HHV-6 IgG levels are not yet included in the diagnostic criteria of DRESS. Polymorphism in HLA alleles can also predispose to DRESS (e.g. HLA-B*58:01 and allopurinol-induced DRESS; HLA-A*32:01 and vancomycine-induced DRESS; HLA-B*13:01 and dapsone-induced DRESS, HLA-A*31:01 and carbamazepine-induced DRESS in northern Europeans) (Bellón 2019; Mayorga et al. 2019). After the initiation of the suspected drug, symptoms can start up to 12 weeks, the disease often persists for a long time even after stopping the indicated drug and introducing the correct treatment. Most commonly, registered causative drugs in the development of this disease are aromatic anticonvulsants (phenytoin, carbamazepine, phenobarbital, lamotrigine), but there are reports on the triggering effect of minocycline, allopurinol, thalidomide, dapsone, sulphonamides, abacavir, and nevirapine. Neurologists who often indicate anticonvulsants should be aware of DRESS as it might occur in 1:3000 treated patients (Bellón 2019; Brockow et al. 2019; Cho and Chu 2017; Shiohara and Mizukawa 2019; Cho et al. 2017; Kardaun et al. 2007).

Clinical Features

The diagnosis of DRESS is definite if at least five out of the seven criteria (RegiSCAR) are fulfilled: (1) acute skin rash, (2) reaction suspected drug related, (3) hospitalization, (4) fever (>38 °C), (5) at least one present of laboratory abnormalities (lymphocyte above or below normal; low platelet count; eosinophilia), (6) involvement of at least one internal organ (hepatitis, nephritis, pneumonitis, carditis, colitis, pancreatitis, arthritis), (7) enlarged lymph nodes >2 sites. DRESS is probable if the final score is 4–5 and possible in case of 2–3 points (Kardaun et al. 2013). In the beginning of the disease, the skin lesions mainly have a morbilliform appearance, but can be eczema-like, target-like, and superficial pustules and vesicles can appear as well. Facial oedema is quite common. As the disease progresses, erythroderma develops with deeper infiltration, purpuric lesions and sometimes exfoliative dermatitis occurs. In the later stage, marked desquamation is visible. Fever accompanies the skin rash frequently. Lesions are distributed symmetrically on the trunk and extremities and then can be widespread. The clinical symptoms can temporarily worsen 3–4 days after discontinuation of the culprit drug (Bellón 2019; Brockow et al. 2019; Cho and Chu 2017; Shiohara and Mizukawa 2019; Cho et al. 2017; Kardaun et al. 2007, 2013).

Differential Diagnosis

During the development of DRESS, the initial rash has a maculopapular appearance, so MDE has to be excluded. In MDE, mild liver or kidney involvement can also occur, but prominent creatinine and transaminase elevation and haemato-

logical abnormalities, which are characteristic to DRESS, cannot develop. As the skin lesions of DRESS progress, the infiltration becomes severe and erythroderma evolves. In this phase, lymphoma or pseudolymphoma should be taken into consideration. Acute viral infections (e.g. mononucleosis, parvovirus B19 infection, measles, Coxsackie virus infection) should also be excluded. During the diagnostic steps of DRESS, physicians have to keep in mind that skin changes and also histological findings are rather nonspecific, the time-period of the application of the causative drug is variable, and the laboratory alterations can also develop in other diseases. Differential blood count, liver and kidney function tests, and also serum CK, CK-MB, troponin, and LDH levels should be determined (Brockow et al. 2019; Shiohara and Mizukawa 2019; Cho et al. 2017; Kardaun et al. 2007, 2013).

Treatment

Acute Stage

The first step in the management of DRESS is the immediate cessation of the offending medication. Systemic corticosteroid therapy in a minimum dose of 0.5–1.0 mg/kg/day is very effective both in the management of clinical and laboratory alterations. It is usually advised to decrease the systemic corticosteroid dose very slowly over 3–6 months in order to avoid relapse. However, immune reconstitution inflammatory syndrome has to be taken into consideration, due to the prolonged immunosuppression. Topical corticosteroids applied on the skin lesions can cause symptomatic relief. It is better to avoid empiric antibiotics or anti-inflammatory drugs, since they can exacerbate the symptoms. When DRESS is associated with severe exfoliative dermatitis lesions, the patients should be provided supportive care in an intensive care or burn unit. In some severe cases, other immunosuppressive medications should be considered (IVIG, plasmapheresis, cyclophosphamide, cyclosporine, mycophenolate mofetil, rituximab). Most patients recover completely, but chronic complications and mortality in about 10% can occur, primarily from visceral organ failure ().

Chronic Stage

In order to determine the culprit drug in DRESS, patch test and LTT are used. Results of patch tests vary significantly based on the specific drug and the higher specificity was detected when antiepileptic medications (carbamazepine, phenytoin) were tested. In the case of LTT, positive values are more informative than negative ones (Mayorga et al. 2019; Phillips et al. 2019; Shiohara and Mizukawa 2019; Cho et al. 2017).

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

Definition, Epidemiology, Pathophysiology

SJS and TEN, the later also called as Lyell syndrome, belong to the most severe drug-induced hypersensitivity reactions with a high mortality rate. SJS has a mortality of 9% and TEN of 48% and depends on the extent of the epidermal detachment and age of the patient. SJS and TEN are considered to be end points of a single disease, differing only by their extent of skin detachment. Acute and disseminated epidermal necrolysis on large skin areas and on the full thickness of the epidermis is the hallmark of this disease group together with a relatively mild inflammatory cell infiltration. SJS and TEN are rare diseases affecting approximately 1.5–1.8 cases per million inhabitants per year (Harr and French 2010). SJS and TEN are specific drug hypersensitivity reactions in which cytotoxic $CD8^+$ T lymphocytes play a crucial role in the drug-specific immune response (type IVc), but the relative paucity of these infiltrating T cells suggests that non-drug-specific amplification mechanisms should accompany the immune reaction and cause the massive apoptosis of keratinocytes. On the basis of extensive research, the co-expression of the membrane form of the death ligand (FasL) and its cognate death receptor (Fas) on keratinocytes, perforin and granzyme B cytotoxic proteins secreted by cytotoxic T cells and NK cells, and granulysin (a cationic cytolytic protein secreted by Tc, NK cells, and NKT cells) are key players in the amplification of keratino-

cyte apoptosis. In a recent study, IL-15 was identified as a potential diagnostic and prognostic biomarker in SJS/TEN. IL-15 not only promotes the differentiation of cytotoxic T cells and NK cells, but influence the expression of granulysin by these cells as well. Furthermore, IL-17 and IFN-γ also increase the release of proinflammatory cytokines by keratinocytes. TNF-α is also secreted and has a role in keratinocyte apoptosis, making it a potential therapeutic target (Bellón 2019; Cho and Chu 2017). Most cases occur 2 weeks (range 4–30 days) after the first exposure to the suspected drug. It is well described that certain polymorphism of HLA alleles predispose to SJS/TEN (e.g. HLA-B*15:02 and carbamazepine and HLA-B*58:01 and allopurinol-induced SJS/TEN in Han Chinese patients and also to a lesser extent in other populations; HLA-B*38:01 and lamotrigine-induced SJS/TEN; HLA-A*31:01 and carbamazepine-induced SJS/TEN in northern Europeans) (Bellón 2019; Brockow et al. 2019; Mayorga et al. 2019).

Clinical Features

Typically, unspecific initial symptoms characterize TEN and SJS, like throat pain, fever, malaise, and stinging eyes. Skin and mucous membrane lesions occur in a few days. Cutaneous manifestations are located first on the face and presternal region of the trunk and soon rapid progression and involvement of large body parts develop as characteristic features. The palms and soles are often affected. Erythematous macules, patches, atypical target lesions, flaccid blisters, and erosions are visible, and the spots have a grey to violet colour. The Nikolsky sign is positive since tangential mechanical pressure on erythematous zones induces epidermal detachment (detachable skin). These regions together with already detached regions (blisters, erosions) should be included in the evaluation of the extent of skin involvement. According to the degree of epidermal detachment, we can distinguish SJS (<10%) (See Fig. 22.4a), SJS/TEN overlap (10–30%) (See Fig. 22.4b), and TEN (>30%) (See

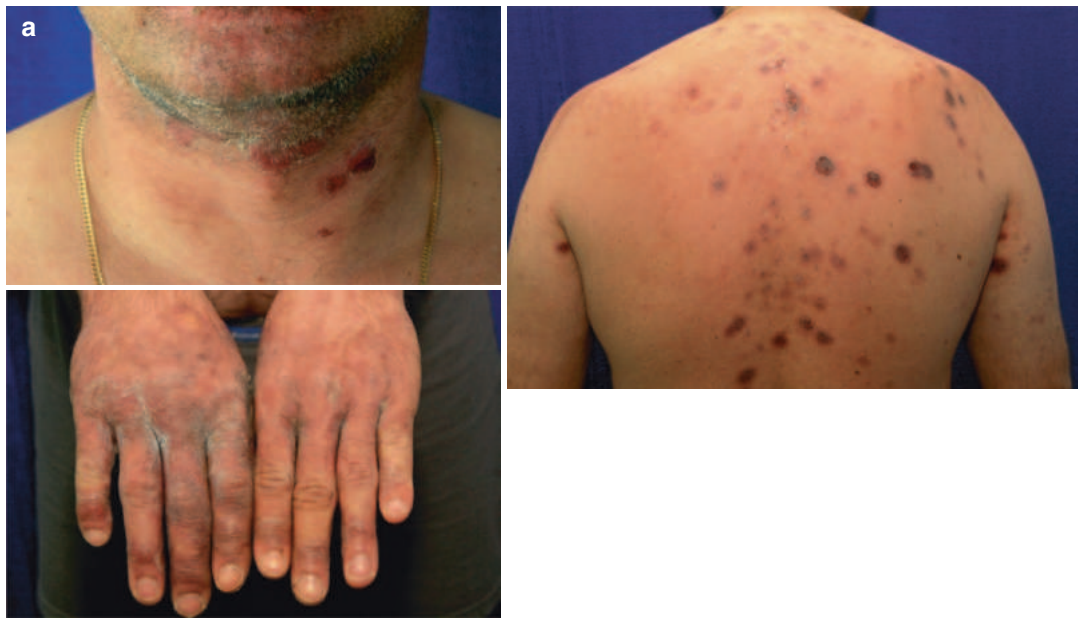

Fig. 22.4 (**a**–**c**) Clinical manifestations of SJS (<10%), SJS-TEN overlap (10–30%), and TEN (>30%)

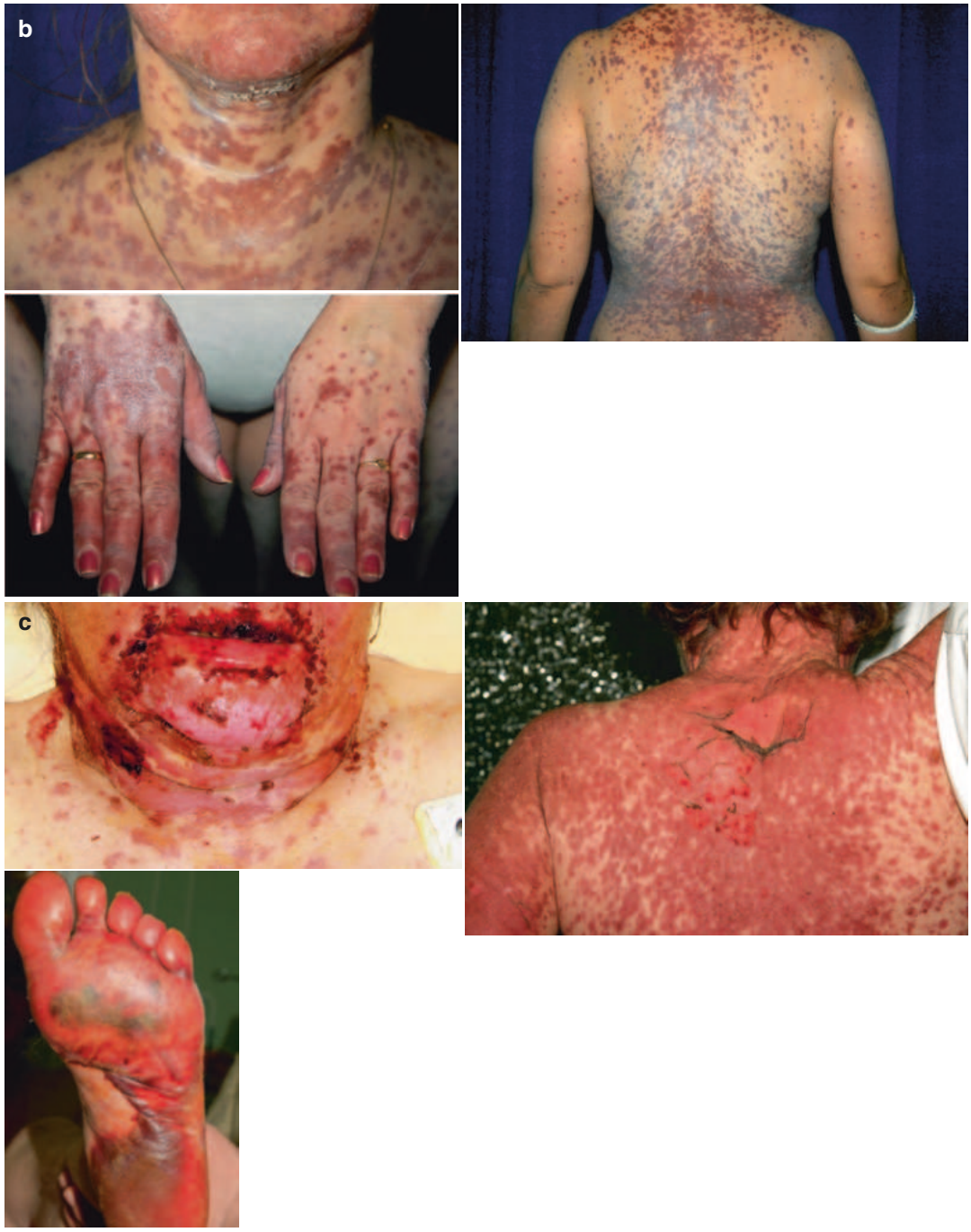

Fig. 22.4 (continued)

Fig. 22.4c). Mucous membranes are involved in 95% of patients, most commonly the buccal, genital, and ocular mucosa and in some cases the respiratory and gastrointestinal tracts are also affected. Early oral lesions may resemble aphthae, but pain, rapid progression, skin lesions, and fever are important signs of a severe systemic disease. The lesions progress for 1 week as a mean, and then re-epithelization starts, sometimes the bullae formation is still progressing on lower parts of the body. The most common acute complications are hypovolemia, sepsis, shock, and multiple organ failure, but destruction of epithelium of the trachea and bronchial tree or other epithelial surfaces can also occur. The most frequent and severe sequelae are the ocular complications. On the skin hyper- or hypopigmentation will remain, but can fade with years if the patient pays attention to sun protection. Nail dystrophies are also common and may result in persistent nail abnormalities (Bellón 2019; Brockow et al. 2019; Cho and Chu 2017; Harr and French 2010).

Differential Diagnosis

The diagnosis relies on clinical symptoms and on histological analysis. Characteristic clinical signs are erythematous, grey to livid macules on the skin, rapid progression with bulla formation, Nikolsky sign positivity (although it is not specific for TEN/SJS), simultaneous mucosal involvement, pain, anxiety, and fever. These severe signs should alert the physician and rapid diagnostic confirmation is needed with the help of skin biopsy. Histological evaluation of cryosections or formalin fixed sections demonstrates widespread necrotic epidermis involving all layers. In the differentiation of SJS/TEN from autoimmune bullous diseases, direct immune fluorescent staining is carried out, and neither immunoglobulin nor complement deposition is detected. The main diseases that should be ruled out are linear IgA dermatosis, paraneoplastic pemphigus, pemphigus vulgaris, bullous pemphigoid, AGEP, disseminated fixed bullous drug eruption, and SSSS (Bellón 2019; Brockow et al. 2019; Harr and French 2010).

Treatment

Acute Stage

In the acute stage, severity and prognosis of the disease should be evaluated, the suspected drug(s) should be withdrawn, and supportive care and specific therapy should be initiated.

Evaluation of Severity

The validated SCORTEN disease severity scoring system is generally used to determine the severity and progression of the disease and to define the further management. It consists in attributing 1 point to each of the following: age >40, detachment larger than 10% of body surface area, recent malignancy, tachycardia, serum urea>10 mmol/L, serum glucose>14 mmol/L, and bicarbonate>20 mmol/L. Patients with a SCORTEN score of 3 or above should be managed in an intensive care unit because of the high mortality rate. The risk of dying is about 3% at a score of 0–1, but nearly 60% when it reaches 4 (Cho and Chu 2017).

Withdrawal of Culprit Drug(s)

To suspend the offending drug is a crucial step, since it has been shown that the earlier the pathogenic medication is withdrawn, the better the prognosis. Two data can help to identify the culprit drug, the chronology of drug use and the registered potential of the drug to cause TEN/SJS. The overwhelming majority of cases occur in patients with normal metabolic pathways, after taking a normal dosage of medication for the first time and the development of TEN/SJS is between 1 and 4 weeks (mean 2 weeks), in case of agents with a long half-life even up to 6 weeks (allopurinol and some antiepileptics). Medications with high risk of inducing TEN/SJS are the followings: allopurinol, sulphonamide-antibiotics, antiepileptics (carbamazepine, phenytoin, phenobarbital, lamotrigine), oxicam NSAIDs, and nevirapine. Some authors underline the role of aminopenicillins, cephalosporines, and quinolones as well (Brockow et al. 2019; Harr and French 2010).

Supportive Care

Since TEN/SJS is potentially a life-threatening disease with extensive skin and mucous membrane lesions accompanied by serious acute complications, management of patients is advised to be undertaken in specialized intensive care units or in burn units and the best is to place the patient on air fluidized bed or on Metalline sheet. The basic element of symptomatic therapy is the fluid and electrolyte supplementation. Patients with TEN/SJS usually require less fluid replacement than burn patients, about two-thirds to three-quarters as much. For the purpose of volume substitution, electrolyte solutions rather than colloidal infusion are preferred in the moderately severe cases; in severe hypotension the colloidal and electrolyte solutions should be used simultaneously. Purely prophylactic antibiotic usage can increase the risk of another hypersensitivity reaction and is not advised, but in case of definite infection or sepsis, targeted antibiotics must be initiated. To treat the wounds, it is usually advised to leave the necrotic epidermis in place, without skin debridement, to promote re-epithelization. Antiseptic solutions and non-adhesive wound dressings are used, but sulphonamide-based medications should be avoided. Antiseptic solutions and creams or dexpanthenol-based ointments are recommended for oral mucosa or lip lesions and also to treat genital erosions. Aggressive nutritional support should be initiated promptly to minimize protein loss and it is important to pay attention on warming of the environmental temperature. Mechanical ventilation is necessary in case of hypoxemia and correction of any organ failure if needed (Cho and Chu 2017; Harr and French 2010; Schneck et al. 2008; Zimmermann et al. 2017).

Specific Drug Therapy

Systemic Corticosteroids

There has been a lot of doubt on the use of systemic steroids considering the risks and benefits, but a retrospective monocentre study found that a short course pulse of high dose corticosteroids (dexamethasone) can exert good effect. One year later, another large retrospective multicenter study also found positive effect on the outcome of the severe skin reaction if corticosteroids were given briefly at the beginning of the reaction in moderate-high doses (100–500 mg). In this study, compared to supportive treatment alone, the death rate was importantly, but not significantly, reduced in those who received corticosteroids too. Pulse therapy with high dose of methylprednisolone (500–1000 mg/day for 3 days) led to the survival of all the patients enrolled in two different studies (Cho and Chu 2017; Kardaun and Jonkman 2007; Bachot et al. 2003).

High-Dose Intravenous Immunoglobulins (IVIG)

The main mode of action that is supposed in the background of IVIG usage in TEN/SJS is the presence of antibodies with anti-Fas potential that can block Fas-mediated keratinocyte necrosis. Numerous case reports, non-controlled clinical trials, and meta-analysis studied the effect of IVIG in TEN/SJS and the results are contradictory. Nearly all studies confirmed the excellent tolerability and low toxic potential of IVIG when used with precaution in patients with potential risk factors, but the efficiency is not clearly proven yet, so definite conclusion cannot be drawn (Cho and Chu 2017; Bachot et al. 2003). In spite of this, many practicing physicians, based on clinical and laboratory evidences and also on the favourable effects of IVIG on infections and on fluid balance, prefer its use.

Cyclosporin A

There are case-control, case series, and meta-analysis studies with cyclosporin A. All of these found decreased mortality rate in SJS/TEN after administration of cyclosporin A. The optimal dose is not clarified yet, but mainly 3 mg/kg/day was the initial dose divided twice daily and tapered gradually over 1 month (Cho and Chu 2017; Ng et al. 2018).

Thalidomide

In a double blind, randomized, placebo-controlled study thalidomide, an effective TNF-α blocker, was shown to have harmful effects when used in the therapy of TEN. In the thalidomide-treated group, higher mortality was observed and therefore this drug must be avoided for this indication (Harr and French 2010).

TNF-α Antagonists

Mainly case reports have been published in the literature about the effect of TNF blockers, but randomized controlled trials are also available now. These showed the benefit of etanercept in patient survival (Cho and Chu 2017; Schneider and Cohen 2017; Wang et al. 2018).

Plasmapheresis

Current data are not enough to support the use of plasmapheresis in the therapy of TEN/SJS, due to the small number of treated patients and the variable treatment regimes. However, Japanese doctors recommend it in refractory cases of high-dose of corticosteroids (Cho and Chu 2017).

Cyclophosphamide

Larger studies are needed to gain clear-cut data on the efficiency and also on the potential side effects of this agent in TEN/SJS (Harr and French 2010).

Chronic Stage

In this stage treatment of sequelae and allergological testing is recommended. The treatment of sequelae is an interdisciplinary task, and since ocular complications can become serious, referral to an ophthalmologist is important. In a lot of cases, several medications are candidates to be the causative drug and after recovery allergological testing is needed to identify the most likely candidate. Patch testing is an option, but because of the low sensitivity, only positive test is relevant, while negative result cannot rule out a sensitization. The sensitivity of LTT test is also very low in SJS/TEN. Intradermal testing and provocation are not recommended because of the risk of another hypersensitivity reaction (Mayorga et al. 2019; Phillips et al. 2019).

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