

Approach to the Patient with Drug Allergy

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KEYWORDS

- Drug allergy • Pseudoallergy • Immediate hypersensitivity
- Nonimmediate type hypersensitivity • Diagnosis • Therapy

Adverse drug reactions are frequent and occur in 10% to 20% of hospitalized patients and approximately 7% of the general population.¹ Whenever a patient treated with a drug develops an exacerbation or a new medical problem, an adverse drug reaction must be included in the differential diagnosis. The clinician should investigate whether one of the involved drugs is known to cause such a reaction and determine the temporal link between the onset of the reaction and drug administration. Adverse drug reactions have been classified by Rawlins and Thompson² in four types: (1) type A reactions that are common (approximately 80%) owing to the pharmacologic or toxic property of the causative drug and thus predictable that may occur in any individual; (2) type B reactions that are uncommon (approximately 10% to 15%), not predictable, and occur only in susceptible individuals; (3) type C reactions that are associated with long-term therapy (eg, benzodiazepine dependence); and (4) type D reactions that are carcinogenic and teratogenic effects.

Drug allergies are type B reactions that are mediated by the specific immune system (IgE- or T cell-mediated or, rarely, immune complex-mediated reactions). Other type B reactions without involvement of the specific immune system (5% to 10%) are classified as nonimmune-mediated (or nonallergic) hypersensitivity reactions.^{3,4}

MAKING THE DIAGNOSIS

Two questions are essential for the diagnosis of a drug allergy: (1) Is it a drug allergy? (2) Which drug has caused the disease? The most frequent manifestations of drug allergies are a skin rash, maculopapular exanthema, and anaphylactic reactions. Biologic agents may more often cause serum sickness and vasculitis; however, different conditions may mimic immune-mediated type B reactions and vice versa (**Table 1**). Sometimes blood eosinophilia may be helpful for the differential diagnosis. No single standardized diagnostic test is able to confirm a drug allergy; therefore, immune-mediated drug hypersensitivity reactions and their causative drugs must be

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Table 1 Signs of drug allergy/intolerance		
	Symptoms	Examples
Guiding signs of frequent reactions	Urticaria, angioedema Skin rash (macular exanthema) Maculopapular exanthma (MPE) Eosinophilia	Urtikaria after acetylsalicylic acid After vancomycin infusion After 10 day amoxicillin treatment During MPE, DRESS
Guiding signs of rare reactions	Sharply localised pruritic erythematous reaction Symmetrical erythema in the flexural or intertriginous folds Disseminated, 1- to 3-mm sterile pustules in the skin Cytopenia	Fixed drug eruption Symmetrical drug related intertriginous and flexural exanthema (SDRIFE) Acute exanthematous pustulosis (AGEP) Thrombocytopenia after biologicals
Atypical signs mimicking other diseases	(Perioperative) cardiac arrest Fever, malaise Lymphadenopathy Multiorgan failure Single organ involvement like nephritis, hepatitis or other Arthralgia Palpable purpuric papule of the legs	After muscle relaxants During Drug rash with eosinophilia and systemic symptoms (DRESS) DRESS (minocyclin) DRESS (allopurinol) Interstitial nephritis after floxapen Serum sickness Vasculitis after NSAID

recognized by the constellation of exposure, timing, and clinical features including the pattern of organ manifestation. For the assessment during a drug-induced type B reaction, a comprehensive investigation is important (including documentation of fever or lymphadenopathy, an examination of the skin including mucous membranes, and an assessment for blood eosinophilia or signs of liver involvement such as elevated transaminases and icterus). Initial questions on clinical assessment include the following:

- Which active drug substances and xenobiotics are involved (including phytodrugs)?
- What is the temporal relationship between the exposure of each drug and the onset of the reaction?
- What is the nature of the reaction? Does it correspond to known adverse reactions to (one of) the involved drugs?
- Were any other drugs administered concurrently that could have caused the reaction?
- Are there any underlying conditions of the patient that could explain the reaction (eg, infections, food)?
- If the reaction occurred in the past, did the reaction resolve after cessation of the drug (and, if so, how long did the recovery take)?
- What is the genetic background of the patient? Recent findings show a strong genetic association between HLA alleles and the susceptibility to drug-specific immune-mediated hypersensitivity. HLAB*5701 is associated with abacavir hypersensitivity, HLA-B*5801 with allopurinol-induced severe cutaneous adverse reactions including drug-related eosinophilia with systemic symptoms

(DRESS), Stevens-Johnson syndrome induced (SJS), and toxic epidermal necrolysis (TEN), and HLA-B*1502 with carbamazepine-induced SJS and TEN but not with maculopapular exanthema. Carbamazepine induced SJS/TEN associated with B*1502 is seen in Southeast Asians but not in Caucasians.⁵

Sometimes the answers to these questions allow the classification of drug hypersensitivity into immediate and nonimmediate types of reactions (**Table 2**). This differentiation may narrow the differential diagnosis and be helpful for further management.

Various signs and symptoms of drug allergy listed in **Table 3** are described as potential early danger signals.⁶ Even though the predictive value of these signs has not been investigated prospectively, it is prudent to take heed of them.

Immediate-type Hypersensitivity Reactions

Clinical aspects

Immediate-type hypersensitivity reactions manifest typically as urticaria (**Fig. 1**) with or without angioedema and anaphylaxis. Anaphylaxis is a severe allergic reaction involving multiple organs. The clinical presentation may be variable, and its definition is still a matter of debate.⁷ The reaction may start with skin manifestations. Typical initial symptoms are a palmar or plantar itch with or without urticaria and angioedema. Additionally, there may be nausea, abdominal pain, vomiting, and diarrhea. There may be rhinoconjunctivitis, obstructive respiratory symptoms, cardiovascular events, altered mental state, and fainting.⁷ Severe respiratory and cardiovascular manifestation such as arterial hypotension and cardiovascular collapse may be the primary manifestations, particularly in perioperative reactions.⁸ Reactions typically follow a uniphasic course; however, 20% are biphasic in nature.⁹

Immediate-type hypersensitivity reactions may comprise type I allergies or poorly understood mechanisms such as so-called “pseudoallergic reactions” (nonimmune-mediated hypersensitivities).

IgE-mediated allergies (type I) usually occur within less than 1 hour after drug administration.¹⁰ Sometimes, especially after oral drug intake, mild reactions may even appear after a few hours. It has been a dogma that allergic reactions to drugs are only those observed on re-exposure or longer lasting exposure (at least 3 days); however, more recent data show that a previous contact to the causative drug is

Table 2
Classifying drug hypersensitivity: immediate versus nonimmediate reaction

Parameter	Immediate Reaction	Nonimmediate Reaction
Time between exposure and onset of the reaction	≤ 1 h (in special conditions such as intolerance to acetylsalicylic acid ≤ 3 h)	≥ 6 h (in the case of strong T-cell sensitization earlier)
Time of recovery	Few hours	Several days to weeks
Clinical nature of the reaction	Urticaria, angioedema, anaphylaxis	Maculopapular exanthema and other skin manifestations including late appearing urticarial rash and angioedema, disorder of blood cells, systemic reactions such as drug rash with eosinophilia, and systemic symptoms (DRESS)

Table 3 Signs of severity	
Type of Reaction	Signs of Severity
Immediate onset reactions	Involvement of extradermal organs, such as rhinconjunctivitis, obstructive respiratory symptoms, nausea, vomiting Sudden onset of generalized pruritus Itching of the perioral area, the inguina, palms, or soles Sudden flush if accompanied by conjunctivitis or rhinitis
Delayed onset reactions	Fever, malaise Prolonged clinical symptoms after discontinuation of the causative drug Lymphadenopathy Burning or painful skin Bullous lesions, epidermal detachment (Nikolsky's sign) Mucosal involvement Facial edema or diffuse erythematous swelling Confluent lesions of extended body surfaces Eosinophilia $>1.5 \times 10^9/L$ Liver involvement

not an obligatory prerequisite for immune-mediated drug hypersensitivity.^{11–13} This paradox might be best explained by cross-reactivity between the involved drug and other xenobiotics to which the affected subject was previously exposed (see the article by Florwaag and Johansson elsewhere in this issue).

Pseudoallergic reactions tend to arise within 1 to 3 hours after drug administration. Often they require a higher dose than true IgE-mediated allergies. In susceptible persons, many active drug substances can elicit such reactions. Typical inducers are listed in **Table 4**.

Laboratory evaluations during the reaction

No optimal and readily available laboratory test can confirm the clinical diagnosis of an anaphylactic episode. Measurements of total tryptase in serum 60 to 240 minutes after the onset of symptoms may be helpful. A rise can be quantified as soon as 30 minutes after the onset of symptoms. The half-life of tryptase is about 120 minutes. To enable a comparison with baseline levels, a new sample should be collected more than 2 days after the reaction.¹⁴ A transient increase of serum tryptase indicates an involvement of mast cells; however, the sensitivity of serum tryptase is low, and it does not allow differentiating between immunologic and nonimmunologic mast cell activation.



Fig. 1. Drug-induced urticaria.

Table 4
Immediate reactions and typically involved drugs

Type of Reaction	Involved Drugs
IgE-mediated reaction	Beta-lactam antibiotics, quinolones, sulfonamide antibiotics, macrolides, pyrazolones, latex Neuromuscular blocking agents ^a Contrast medium ^a
Pseudoallergic reactions	Acetylsalicylic acid and other non-steroidal antirheumatics (NSAID) Plasma volume expander (colloids) Neuromuscular blocking agents ^a Contrast medium ^a

^a Drugs that can induce IgE-mediated or pseudoallergic reactions.

Nonimmediate-type Hypersensitivity Reactions

Clinical aspects

Nonimmediate reactions occur more than 1 hour after drug administration; however, there is a certain overlap in the time of manifestations. Some IgE-mediated reactions occur after 1 hour, and some nonimmediate reactions may start prior to 1 hour. Non-immediate drug allergies are most frequently T cell mediated, whereas IgG-mediated responses are rare. Nonimmediate drug allergies may be clinically manifested as a broad spectrum of diseases. Frequently involved drugs are listed in **Table 5**.

Maculopapular or morbilliform exanthema The most frequent type B reactions are maculopapular and morbilliform exanthemas, which are manifested as erythematous macules and infiltrated papules, particularly affecting the trunk and proximal extremities (**Fig. 2**). Typically, a more or less pronounced desquamation occurs after clearing of the lesions. Maculopapular exanthemas are observed in about 2% of hospitalized patients.¹⁵ They usually appear more than 2 to 9 days after the drug has been started. A large body of experimental and clinical data indicates that these rashes correspond frequently to T cell-mediated (type IV) hypersensitivities.

Fixed drug eruption The most characteristic finding of a fixed drug eruption is the recurrence of similar lesions at the same sites, typically healing with residual hyperpigmentation. Rarely there are nonpigmenting forms. The validity of skin tests for identification of the causative drug is not known.¹⁶ They may be positive only if performed in the affected area.

Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE) Rarely, drug eruptions may present with a characteristic distribution pattern consisting of a sharply limited symmetrical erythema in the gluteal area and the flexural or intertriginous folds without any systemic symptoms and signs. This particular reaction was originally described as a special form of systemic contact-type dermatitis that occurs after ingestion or systemic absorption of a contact allergen in individuals previously sensitized by topical exposure to the same allergen in the same areas. Similar eruptions have been reported after systemic exposure to beta-lactam antibiotics and other drugs. Latency periods vary between a few hours and a few days after exposure.¹⁷

Acute generalized exanthematous pustulosis (AGEP) AGEP is a rare disease with disseminated, 1- to 3-mm sterile pustules in the skin that appear rather rapidly after 3 to 5 days of treatment. Patients have fever and massive leukocytosis in the blood,

Table 5 Nonimmediate reactions and typically involved drugs	
Type of Reaction	Involved Drugs
Hemolytic anemia	Methyldopa, levodopa, interferon-alpha, cyclosporine, and fludarabine
Leucopenia	Aminopyrine and dipyrone, thyroid inhibitors, co-trimoxazole, sulfasalazine, clomipramine
Thrombopenia	Heparin, quinine, quinidine, therapeutic antibodies (biologics)
Serum sickness syndrome	Beta-lactam antibiotics
Drug-induced lupus	Hydralazine, procainamide, quinidine, minocycline, and anti-TNF-alpha agents
Vasculitis	Sulfonamide antibiotics and diuretics
Maculopapular exanthema (MPE)	Beta-lactam antibiotics, sulfonamide antibiotics, macrolides, diuretics
Fixed drug eruption	Phenytoin, sulfonamide antibiotics, tetracycline, barbiturates
Symmetrical drug-related intertriginous and flexural exanthema (SDRIFE)	Beta-lactam antibiotics, mercury
Acute generalized exanthematous pustulosis (AGEP)	Aminopenicillins, cephalosporins, macrolides, sulfonamide antibiotics, celecoxib, diltiazem, quinolone diltiazem, terbinafine, corticosteroids
Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN)	Nevirapine, allopurinol, phenytoin, carbamazepine, lamotrigine, co-trimoxazole, barbiturate, NSAID (oxicams), sertraline, pantoprazole, tramadol
Drug rash with eosinophilia and systemic symptoms (DRESS)	Carbamazepine, phenytoin, lamotrigine, minocycline, allopurinol, dapsone, sulfasalazine, co-trimoxazole, abacavir

sometimes with eosinophilia. Some pustules merge together and may form bullae. The lethality rate is about 4%, particularly in older people. Epicutaneous patch test reactions can cause a similar pustular reaction locally.^{18,19}

Bullous exanthema Severe bullous exanthema may encompass different disorders. The most severe bullous skin diseases are SJS and TEN. These diseases differ solely in the extent of affected skin (<10% in SJS and >30% in TEN), with SJS/TEN overlap and skin detachment of 10% to 30% of the body surface. They are different from erythema exudativum multiforme, which is mainly caused by viral infections, is often recurrent, and affects younger persons.²⁰ SJS/TEN usually starts within the first 3 weeks of treatment with a macular, purple-red exanthema that can be painful. Within 12 hours, bullae may develop, even after stopping the drug. Mucous membranes (mouth, genitalia) are involved with blister formation. Lethality is dependent on age and the extent of skin detachment. The rate in SJS is approximately 10% and in TEN greater than 30%.²¹ In the authors' experience, SJS/TEN may also evolve in patients despite concomitant high-dose prednisone treatment.



Fig. 2. Maculopapular or morbilliform exanthema.

Drug-hypersensitivity syndrome or drug-related eosinophilia with systemic symptoms Typical for this severe systemic disease are a macular exanthema, an erythematous centrofacial swelling, fever, general malaise, lymph node swelling, and involvement of other organs including hepatitis (50%), nephritis (10%), and more rarely pneumonitis, colitis, and pancreatitis.²² The type of organ involvement depends on the type of drug causing it.²³ Minocycline-induced DRESS is associated with lymphadenopathy, whereas allopurinol-induced DRESS has renal insufficiency. Over 70% of these cases have a marked eosinophilia (often >1 G/L), and activated T cells are often found in the circulation. Symptoms can start up to 12 weeks after the start of treatment, often after increasing the dose, and the condition may persist and recur for many weeks even after cessation of drug treatment. The lethality rate is about 10% and is mainly due to liver failure. A recurrence of symptoms, often in the third week, is typical. It is related to reactivation of herpes viruses, in particular human herpes virus 6, Epstein-Barr virus, or cytomegalovirus.

Japanese researchers have recently proposed diagnostic criteria for the diagnosis of this disease, which often remains unrecognized:²⁴

1. Maculopapular rash developing more than 3 weeks after starting a limited number of drugs
2. Prolonged clinical symptoms after discontinuation of the causative drug
3. Fever ($>38^{\circ}\text{C}$)
4. Liver abnormalities (alanine transaminase >100 U/L) or other organ involvement
5. Leukocyte abnormalities (at least one present):
 - Leukocytosis ($>11 \times 10^9/\text{L}$)
 - Atypical lymphocytosis ($>5\%$)
 - Eosinophilia ($>1.5 \times 10^9/\text{L}$)

6. Lymphadenopathy
7. Human herpes virus 6 reactivation (detected in the second to third week after the start of symptoms)

The diagnosis is confirmed by the presence of all seven criteria (typical drug induced hypersensitivity syndrome [DIHS]) or five¹⁻⁵ of them (atypical DIHS). The symptoms of DRESS/DIHS differ substantially depending on the drug (see the article by Kano and Shiohara elsewhere in this issue).

Interstitial nephritis Some drugs, in particular beta-lactam antibiotics, proton-pump inhibitors, sulfonamide antibiotics, disulfiram, non-steroidal anti-inflammatory drugs (NSAIDs), and others can cause an interstitial nephritis.²⁵ Some manifestations are associated with an exanthema, but, often, the symptoms start insidiously. Lower back pain and some malaise may be the only symptoms until renal insufficiency is discovered.

Cytopenia Drug-induced, IgG-mediated immune cytopenia may manifest as hemolytic anemia, an unexpected precipitous fall in peripheral leukocyte count. Drugs that are typically involved in such reactions are listed in **Table 5**.

Serum sickness syndrome Fever, arthralgias, macular and urticarial exanthemata, lymphadenopathy, and sometimes edema are the classical clinical manifestations of serum sickness. In the past, the widespread use of heterologous serum frequently produced the full serum sickness syndrome 1 to 3 weeks after antiserum administration. Currently, nonprotein drugs such as penicillins and cephalosporins are the most common causes of serum sickness, with a latency period of 6 to 8 hours. Drug-induced serum sickness is usually self-limited, with symptoms lasting 1 to 2 weeks before resolving.

Drug-induced lupus Typical clinical symptoms of drug-induced lupus erythematosus (DILE) are sudden onset of fever, malaise, myalgia, arthralgia, and arthritis several weeks after drug initiation. The skin is affected in about 25% of cases. Characteristic is an erythematous eruption, often on light-exposed surfaces. The average age of patients with DILE is nearly twice that of patients with idiopathic systemic lupus erythematosus (SLE). Approximately half the patients with drug-induced SLE are women compared with 90% of patients with idiopathic SLE. Similarly to idiopathic lupus, DILE can be divided into systemic, subacute cutaneous, and chronic cutaneous lupus. The clinical and laboratory manifestations of drug-induced SLE are similar to those of idiopathic SLE, but central nervous system and renal involvement are rare in DILE. Recognition of DILE is important because it usually reverts spontaneously within a few weeks after stopping the drug.²⁶

Vasculitis Drugs may rarely elicit cutaneous or systemic vasculitis (incidence of 10 to 30 cases per 1 million people per year). Typical clinical manifestations are palpable purpuric papules predominantly of the legs; however, sometimes the condition manifests as a clinical syndrome indistinguishable from classical systemic forms of vasculitis such as Wegener's granulomatosis, polyarteritis nodosa, and Churg-Strauss syndrome. Withdrawal of the offending agent alone is often sufficient to induce prompt resolution of clinical manifestations, without the need for systemic therapy.²⁷

Laboratory evaluations during the reaction

Laboratory tests during the acute phase may determine the severity and involvement of internal organs. The finding of an eosinophilia supports the diagnosis of an immune-mediated hypersensitivity reaction, and increased liver enzymes may indicate liver

involvement. For atypical skin lesions, a biopsy with histologic examination may help to recognize or exclude an important differential diagnosis.

In the rare cases with a presumed type II or III reaction, the IgG-mediated mechanism, the direct antiglobulin test (Coombs' test) helps diagnose immune hemolytic anemia, leading to further detailed analyses, often requiring the close collaboration of several disciplines.²⁸ Assessment of complement levels (C3, C4, CH50) and immune complexes (C1q binding or Raji cell assays) can support the diagnosis in cases with serum sickness syndrome, but negative values do not rule it out.

Allergologic Investigations

The clinical symptoms described previously are indicative of a drug reaction but do not in most instances provide sufficient evidence as to which drug has caused it. Allergologic tests with the suspected drugs may provide additional information and allow one to identify the causative agent.

Allergologic investigations in immediate-type hypersensitivity reactions

Skin tests are easy to perform and may provide some help in the identification of the causative drug. Most authors recommend performing these tests 1 to 6 months after the acute event, because effector cells may be exhausted and specific IgE antibodies may be temporarily depleted immediately after the reaction. Because the sensitivity of the tests might decrease over time, they should be performed in the first year after the reaction.²⁹

In cases with severe or anaphylactic reactions, it is advisable to first perform skin tests with the presumably causative drugs only by prick. If responses are negative and the involved drug is available as a parenteral formulation, intradermal tests may than be carried out as described elsewhere;²⁹⁻³¹ however, negative skin tests do not have sufficient sensitivity to exclude an immune-mediated hypersensitivity in the case of a suggestive history.

In penicillin allergies, standardized preparations with penicilloylpolylysine and minor determinant mixture may be used. Although early American reports found a high sensitivity and specificity of skin tests using such standardized preparations, newer reports by Spanish researchers have detected a sensitivity of only 70%.³² Currently, these preparations are not commercially available in the United States.

Penicillin allergy may also be evaluated by *in vitro* tests for specific IgEs; however, these tests have a low sensitivity. Additionally, assays for a few drugs such as suxamethonium, rocuronium, morphine, sulfamethoxazole, and chlorhexidine, are offered, some with potentially higher sensitivity.

A further *in vitro* test to identify the relevant drug may be the basophil activation test. This test is based on flow cytometric quantification of drug-induced CD63 expression or CD203c up-regulation or measurement of sulfo-leukotriene release by ELISA. The sensitivity in IgE-mediated reactions appears to be superior to CAP-based IgE determinations³³ and comparable with skin tests (see the article by Hausmann and colleagues elsewhere in this issue).

In pseudoallergic reactions, skin tests and determination of specific antibodies for identification of the causative drug are negative, because, by definition, such reactions are not based on specific immune reactions to the drug. A role of basophil activation testing in the diagnosis of pseudoallergic reactions could not be established, although some authors postulate some reactivity in NSAID-induced reactions.³⁴

In selected cases with presumed pseudoallergic reactions, a diagnostic oral provocation test may be performed. More frequently, tests are carried out with alternative drugs to establish a safe substitution.

Allergologic investigations in nonimmediate-type hypersensitivity reactions

Skin tests (intradermal testing with readings at 24 hours and 48 hours and patch testing) with the suspected drugs may help to identify the causative agent; however, positive and negative predictive values of these tests are not known for most drugs. Skin tests are best performed after the complete clearing of clinical manifestations 1 to 6 months after the acute event. Patch tests are performed with the commercialized form of the involved drug diluted in petrolatum or water and intradermal tests with sterile sequential dilutions. The methods are described in more detail in guidelines for performing skin tests with drugs, which have been proposed by the Working Party of the European Society of Contact Dermatitis.³⁵

The lymphocyte transformation test is an *in vitro* test. It is complex and requires skilled personnel; therefore, its availability is limited to specialized centers. Usually it is performed 1 to 6 months after the acute event; however, data from Japan suggest that in bullous skin diseases tests are more frequently positive in the first weeks of disease.³⁶

Provocation tests in nonimmediate-type hypersensitivity reactions are not well standardized; neither the dose nor the time of treatment is established. No data on sensitivity or specificity are available. These tests cannot be recommended as a routine procedure for the identification of the culprit drug.

TREATMENT OF DRUG ALLERGY

Immediate-type Hypersensitivity Reactions

The causative or presumably causative drugs should immediately be withdrawn. In mild reactions with urticaria only, antihistamines are the primary recommended treatment; however, antihistamines cannot antagonize activated histamine that has already been released from mast cells.³⁷ In severe reactions with danger signals (see [Table 3](#)), angioedema, respiratory symptoms, or circulatory signs corresponding to an anaphylaxis, epinephrine (10 µg/kg) should be administered promptly via the intramuscular route in the anterolateral thigh. Glucocorticoids when given in pharmacologic quantities have an anti-inflammatory effect and may reduce the risk of late relapse;³⁸ however, the onset of action of glucocorticoids is late (>45 minutes) because it depends on new gene products.

Nonimmediate-type Hypersensitivity Reactions

During systemic T cell-mediated drug allergies, patients are more susceptible to react unspecifically to different xenobiotics. Withdrawal of the causative, potentially causative, or not urgently needed drug is prudent; however, there are some exceptions to this rule. In late occurring maculopapular exanthema in the absence of cutaneous danger signals (immediate-type hypersensitivity reactions), urgently required treatment may be continued. Such “treating through” requires monitoring for systemic involvement (fever, eosinophilia, lymphadenopathy, hepatitis) or involvement of mucosal surfaces.

Mild nonimmediate drug reactions are self-limited diseases, and treatment is symptomatic. In clinical praxis, corticosteroids (topical, sometimes systemic), antihistamines, or both are used to block or reduce prolonged or late phase reactions; however, there are no randomized trials for their use.

The management of SJS/TEN should best be undertaken in intensive care units with experience in the treatment of burns and involves warming of the environment, correction of electrolyte disturbances, administration of a high caloric enteral intake, and prevention of sepsis. The efficacy of drug treatment used in some case reports is

difficult to evaluate; cyclosporine, cyclophosphamide, pentoxifylline, and thalidomide have all been tried.³⁹ Some recent data support corticosteroid use.⁴⁰ Intravenous immunoglobulins are widely used but their effectiveness is still debated.⁴¹ Specific nursing care and adequate topical management reduce associated morbidity and allow a more rapid re-epithelialization of skin lesions. After healing, follow-up is needed for ophthalmologic and mucous membrane sequelae. Sun blocks are recommended. Avoidance of the responsible drug and chemically related compounds is essential not only for the patient but also for first-degree relatives.³⁹

For DRESS, corticoids are used. Occasionally, liver transplantation is necessary.

Recommendation of Alternative Drugs

If a patient requires continued treatment, cross-reactivity among drugs should be taken into consideration. In choosing alternative compounds, skin testing may be helpful; however, the sensitivity of these tests remains limited. In patients who especially require one specific drug, a graded challenge with the alternative drug may be performed.

Beta-lactams

IgE-mediated allergy When a patient with immediate penicillin allergy requires an alternative β -lactam drug, consideration can be given to prescribing a cephalosporin of the second or higher generation. A review of several studies of cephalosporin administration to patients with a history of penicillin allergy found cephalosporin reactions in 4.4% of patients with positive skin tests for penicillin.⁴² The incidence of cross-hypersensitivity reactions between penicillins and carbapenems is about 10%;⁴³ therefore, carbapenems may be used in penicillin-allergic patients.

T cell-mediated allergy In vitro data indicate that cross-reactivity of T cells between penicillins and cephalosporins is rare.⁴⁴ This finding is in agreement with clinical experience; however, clinical data on this topic in the literature are scarce.

Sulfonamides

A common clinical problem is the putative cross-reactivity among sulfonamides. Recent data have demonstrated that both IgE-mediated and T cell-mediated cross-reactivity between sulfonamide antibiotics and nonantibiotics are unlikely.^{45,46} In patients allergic to sulfonamide antibiotics, other sulfonamide-derived drugs (eg, diuretics, sulfonyleureas, celecoxib, and sumatriptan) have not been excluded; however, cross-reactions do occur with the anti-inflammatory compound sulfasalazine, which is metabolized to sulfapyridine. There is no relationship between sulfonamide allergy and intolerance to sulfite preservatives in food.

Radiocontrast media

There are both immediate-type and nonimmediate-type hypersensitivity reactions to radiocontrast media. In the specific immune-mediated reactions, iodide ions do not seem to be the causative moiety. Cross-reactivities occur predominantly in nonimmediate T cell-mediated reactions. Detailed intradermal skin testing might help identify non-cross-reactive contrast media.⁴⁷

Desensitization

Desensitization may be a treatment option for drug-allergic patients for whom no alternative drug exists. Starting at a suballergenic dose with gradual increase may allow the application of full therapeutic doses with minimal risk for anaphylaxis.⁴⁸ The desensitized state is not permanent and is sustained only with a daily maintenance

dose of the drug. Classically, the procedure is applied in IgE-mediated reactions, but its use has been extended to other drug reactions.⁴⁹ Drugs for which desensitization may be successful include allopurinol, co-trimoxazole, β -lactam antibiotics, and cisplatin. Patients with intolerance to acetylsalicylic acid can also be desensitized, with occasional beneficial effect in asthma and polyposis symptoms.⁵⁰ The mechanism of drug desensitization is not well understood (see the article by Castells elsewhere in this issue).

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