

Clinical evaluation and management of drug hypersensitivity

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Adverse drug reactions are a major health problem encountered frequently in the inpatient and outpatient setting. The clinical evaluation of a drug hypersensitivity reaction can be a formidable task for several reasons. Often, the evaluation is undertaken after the hypersensitivity reaction has taken place, making the history and physical signs and symptoms difficult to assess. Laboratory evaluations to aid in the diagnosis, which are limited, are often not performed at the time of the suspected drug reaction. Use of multiple medications can also make assessment difficult. Even when the history is clear, there is much confusion about what constitutes a drug reaction and how to classify it. Misperceptions on the part of the patient and physician can contribute to erroneous “drug allergies” listed in the patient’s chart. Using universally accepted definitions of various drug reactions and classifying the drug reaction correctly are important first steps in evaluating a drug reaction.

Reactions to drugs can be divided into two main categories: (1) predictable drug reactions and (2) unpredictable drug reactions. The predictable drug reactions account for approximately 80% and include reactions owing to the pharmacologic actions of the drug. These reactions are typically dose dependent and include reactions owing to overdosage, side effects, secondary effects (indirect effects such as *Clostridium difficile* colitis with antibiotic use), and drug-drug interactions. Knowledge of the basic pharmacology of the drugs in question is required in evaluating these reactions. Often, a patient will claim an allergy to a drug based on side effects, secondary effects, and drug-drug interactions; therefore, a detailed history of the reaction is paramount.

Unpredictable reactions to drugs are typically dose independent and not related to the pharmacologic action of the drug. Examples include drug intolerance, idiosyncratic reactions, and immune-mediated reactions. Drug intolerance is defined as an undesired effect produced by the drug at therapeutic or

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subtherapeutic dosages, whereas idiosyncratic reactions are uncharacteristic reactions that are not explainable in terms of the known pharmacologic actions of the drug [1]. The immune-mediated reactions can be further characterized using the Gell and Coombs classification. Hypersensitivity reactions are classified into one of four categories based on the immune mechanism: type 1, immediate hypersensitivity; type 2, cytotoxic; type 3, immune complex; and type 4, cell mediated. Unfortunately, many immune-mediated reactions to drugs do not fall neatly into these categories, and, in a large number of immune-mediated drug reactions, the actual immune mechanism is unknown. Although any drug has the potential for eliciting an immune response, the drugs most commonly associated with immune reactions are antimicrobial agents, anticonvulsants, chemotherapeutic agents, heparin, insulin, and protamine.

This review delineates the general principles used in the clinical evaluation and management of drug hypersensitivity, followed by a discussion of the most common syndromes based on the type of reaction: Gell and Coombs types 1 to 4, morbilliform, erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis (TEN), anaphylactoid, and hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms (HSS/DRESS).

Clinical evaluation and management of suspected drug hypersensitivity

Despite the difficulties inherent in evaluating drug allergy, appropriate clinical data should be obtained to evaluate a drug reaction. Key points that should be addressed include the following:

- Complete drug administration history
- Complete prior drug reaction history
- Temporal relationship between administration of the drug and the drug reaction
- List of all medications with starting points, stopping points, and dose changes
- Identifying any other causes for the signs and symptoms
- Determining whether the medications used have been associated with similar drug reactions

History

The history is the primary tool in trying to discern a drug reaction. Obtaining a complete drug history can be tedious, especially in a patient on multiple medications, but there simply is no substitution for the history, including a complete medication list from the time of the drug reaction. A complete list is obtainable for hospitalized patients and can be confirmed with the hospital pharmacy. For outpatients, it can be more difficult to have a complete list, and it is especially important to inquire about over-the-counter medications, health supplements, or any other type of ingested, because the patient will often not

report these as medications. Once the list is complete, the timing of the use of the medications in relationship to the reaction is important, as is a history of how long the patient has been on each of the medications. Often, the drug reaction is caused by the last medication added to the overall regimen. In complex situations, a flow diagram with a date/time chart of all medications can help show the relationship between the medications and the reaction. A reaction can be immediate or delayed depending on the mechanism. For example, a type 1, IgE-mediated reaction is immediate as opposed to a serum sickness-like reaction that can occur 3 weeks after drug administration. A history of prior drug reactions, no matter how remote or seemingly unrelated, can be helpful, because different medications in the same class can be associated with the same drug reaction. Because the patient may have only limited knowledge of the specific past reaction, a thorough review of the medical record can yield more information. A detailed history of the actual reaction is important to help ensure that a systemic reaction (as opposed to skin only) is not overlooked. Knowledge of the classes of drugs most likely to be associated with the type of reaction can help narrow down the list. Host risk factors can also be helpful. In general, women tend to have a higher incidence of adverse cutaneous reactions to medications and reactions to radiocontrast material [2,3]. Atopic patients, that is, those with allergic rhinitis, allergic asthma, or atopic dermatitis, tend to have a higher rate of reactions to radiocontrast material and proteins but not to low molecular weight agents [4,5]. A history of atopy increases the risk of a more severe anaphylactic reaction to a drug. Patients with autoimmune disorders seem to have an increased prevalence of drug reactions. It is not clear whether this observation is related to an underlying pathophysiologic mechanism or represents an increased use of medications.

Physical examination

A complete physical examination is helpful in categorizing the drug reaction, because multiple organ systems have the potential for involvement. The skin is the most common organ system involved, and a detailed description of the skin findings aids in diagnosis. The most common skin finding is a maculopapular or morbilliform eruption. This eruption can be difficult to differentiate from a viral exanthem. The maculopapular eruption consists of red/pink macules and papules that are distributed in a symmetric pattern throughout the body, often sparing the face. This eruption tends to be mildly pruritic. The pathogenesis is unknown but most likely T-cell mediated, not IgE mediated, in contrast to urticaria. Urticaria is manifested by pruritic red wheals that vary in size from small papules to large plaques. These wheals can be associated with angioedema and swelling of the deep dermal and subcutaneous tissues. Mechanisms of drug-induced urticaria include IgE-mediated anaphylactic reactions, serum sickness, and direct histamine release. Erythema multiforme minor is a distinctive exanthem characterized by a “target” lesion that consists of a central clearing and erythematous outer ring. This lesion can progress to erythema multiforme major with the develop-

ment of blisters and mucous membrane involvement; therefore, a mouth and throat examination is required in these patients. Further along this spectrum is TEN, in which epidermal cell death results in sloughing of the skin and the appearance of “scalded” skin.

Other skin manifestations of drug reaction include fixed drug eruptions. Fixed drug eruptions consist of single or multiple round sharply demarcated plaques that appear soon after drug exposure and recur in exactly the same site with subsequent drug exposure. Pruritus and burning are often associated with this type of drug reaction. Purpura or petechiae are seen in cutaneous vasculitis. These lesions are usually most concentrated on the lower legs but may be generalized. If found, further evaluation of the kidneys and joints is in order.

In addition to a detailed skin examination, a complete physical examination can reveal more clues. Vital signs should be monitored. Tachycardia, tachypnea, and hypotension can be seen with an anaphylactic reaction. Fever, alone or in combination with other signs and symptoms, can be seen with a drug reaction. Other critical components of the physical examination include an assessment of the lymph nodes, lungs, liver, spleen, and joints. These areas should be examined in every patient when evaluated during a reaction.

Clinical assessment

The history and the physical examination are the most important diagnostic procedures when evaluating drug allergy. The most commonly used tests include specific drug testing and laboratory tests to help characterize the drug reaction. Immediate-type skin tests are the most rapid and reliable method for detecting drug-specific IgE antibodies. The use of skin testing is limited to large molecular weight proteins and the major and minor determinants of penicillin. The radioallergosorbent test (RAST) is available for detection of the major determinant of penicillin. Other measures of a type 1 response include *in vitro* measurement of leukotriene synthesis, basophil activation, and basophil histamine release. These tests are not readily available, and their sensitivity and specificity are not well delineated. Testing is limited for Gell and Coombs types 2 and 3 reactions. For drug-induced hemolysis, a positive Coombs’ test can be a useful screening procedure followed by drug-specific antibodies if available. In delayed hypersensitivity type 4 reactions, patch testing and delayed intradermal drug testing have been used. The lymphocyte transformation test measures *in vitro* T-cell proliferative responses to drugs. This test is being studied in morbilliform reactions and is not widely available.

Laboratory tests used to help characterize a reaction include assays of tryptase, complement levels, and immune complex. Tryptase is a mast cell mediator released approximately 1 to 2 hours after an anaphylactic reaction. An elevated level is helpful in implicating a mast cell-mediated process. Complement levels are typically decreased in a serum sickness reaction but not in a serum sickness-like reaction. Immune complex assays can be helpful in determining a serum sickness reaction.

Therapeutic plan

Once a drug reaction has been characterized, specific treatment can be instituted as outlined in the following sections for the specific type of reaction. In addition to immediate management, future use of the medication or similar medications needs to be addressed. For Gell and Coombs type 1 reactions, future use of the drug is generally contraindicated. If a clinical situation arises in which the drug must be used, a desensitization procedure can be performed. This procedure converts the patient from a sensitive state to a normal state by cautious incremental increases in drug dosage according to a protocol. The desensitization produces a nonresponsive state as long as the therapy is uninterrupted. Desensitization is only recommended for type 1 reactions. It is not recommended for reactions such as Gell and Coombs types 2 to 4, erythema multiforme, Stevens-Johnson syndrome, TEN, and HSS/DRESS. In these aforementioned reactions, future use of the drug is contraindicated. In addition to avoiding the offending drug, one must make the patient and other physicians aware of the avoidance of medicines in the same class, especially the avoidance of all aromated anti-convulsants in patients with HSS/DRESS.

A myriad of drug sensitivities affect all organ systems. Using the guidelines outlined previously, the remainder of this article focuses on the most commonly seen immune-mediated drug reactions, with an emphasis on their clinical evaluation and management. These reactions include the Gell and Coombs types 1 to 4 immune reactions, morbilliform reactions, erythema multiforme, Stevens-Johnson syndrome, TEN, anaphylactoid reactions, and HSS/DRESS syndrome (Table 1).

Clinical manifestations and management of drug hypersensitivity

Immediate-type hypersensitivity reactions (type 1)

Nearly every drug has the potential of inducing an IgE-mediated hypersensitivity reaction. The primary effector cell is the mast cell. The mast cell releases a number of mediators, including histamine, the leukotrienes C4, D4, and E4, eosinophil chemotactic factors, neutrophil chemotactic factors, the mast cell marker tryptase, and platelet-activating factor. These factors have many systemic effects, including smooth muscle spasm, bronchospasm, increased capillary leakage, and mucosal edema and inflammation. The clinical manifestations can involve any organ system but are mainly seen in the cutaneous, respiratory, gastrointestinal, and cardiovascular systems. Classic signs and symptoms include, but are not limited to, urticaria and angioedema, dyspnea, wheezing, upper airway edema, dizziness, hypotension and shock, nausea, vomiting, crampy abdominal pain, and flushing [6]. Any one or a combination of these signs and symptoms may occur. The reaction may occur within minutes of drug administration or, less commonly, hours after administration. Several factors seem to

Table 1

Identification and future management of the most common drug reactions

Reaction type	Clinical characteristics	Laboratory testing	Future use of medication
Gell and Coombs Type 1	Urticaria, angioedema, wheezing, hypotension, nausea, vomiting, abdominal pain, diarrhea	Skin testing, radioallergosorbent testing	Desensitization
Gell and Coombs Type 2	Hemolytic anemia, granulocytopenia, thrombocytopenia	Complete blood count	Contraindicated
Gell and Coombs Type 3	Fever, urticaria, arthralgias, lymphadenopathy 2–21 days after therapy initiated	Complement levels	Contraindicated
Gell and Coombs Type 4	Skin erythema, skin blistering	Patch testing	Likely contraindicated
Morbilloform	Maculopapular rash becoming confluent	Possibly patch testing, intradermal skin testing (delayed reaction)	Use with caution
Erythema multiforme	Distinctive target lesions	None	Contraindicated
Stevens-Johnson/TEN	Target lesions, mucous membrane involvement, skin desquamation	None	Contraindicated
Anaphylactoid	Urticaria, wheezing, angioedema, hypotension	None	Pretreatment with prednisone and Benadryl for radiocontrast sensitivity
HSS/DRESS	Exfoliative dermatitis, fever, lymphadenopathy	Complete blood count, liver enzymes, creatinine, urinalysis	Contraindicated

affect the incidence and severity of anaphylaxis. The route of administration of the drug affects the frequency of occurrence and the severity. Events may occur if the drug is given by any route but are most frequent and severe with the intravenous route. If prior therapy was interrupted, creating gaps in administration, there is an increased risk for a subsequent reaction [7]. Antibiotics are the most important class of drugs causing anaphylactic reactions. Penicillin is the most common cause of anaphylaxis, accounting for approximately 75% of fatal anaphylactic cases in the United States each year [8]. Other commonly used drugs that cause allergic reactions include insulin, enzymes, heterologous antisera, murine monoclonal antibodies, protamine, and heparin.

Clinical evaluation of an acute allergic reaction is typically straightforward, with the signs and symptoms compatible with histamine release involving various organ systems. Serum levels of tryptase, a neutral protease stored in mast cell granules, can help confirm mast cell activation. Tryptase levels peak approximately 90 minutes after an anaphylactic episode has started and remain elevated

up to 4 hours after the reaction [9]. Unless the patient has mastocytosis, an elevated tryptase level supports the occurrence of an anaphylactic event.

There are two main methods for testing possible offending drugs in an IgE-mediated reaction: (1) *in vivo* skin testing for immediate reaction to the suspected agent and (2) *in vitro* testing of drug-specific IgE from the affected patient's blood. In prick testing, a small amount of test solution containing a concentration of the suspected medication is placed on the skin. A sterile needle or standard skin prick test (SPT) lancet is then placed through the test solution into the epidermis and gently lifted upward. The area is evaluated after 15 minutes for a wheal and flare reaction. Intradermal injection of the medication can be used if the prick test is negative. Intradermal testing increases sensitivity. Three case reports in the literature have related death to skin testing by prick or intradermal methods for penicillin allergy [10]. Prick and intradermal skin testing can be performed to test for reaction to β -lactam antibacterial agents, latex, local anesthetics, ciprofloxacin, trimethoprim, cisplatin, neuromuscular blocking agents, thiobarbiturates, and some anticonvulsants. Standardized skin testing for medications has only been established for penicillin. During penicillin degradation, several metabolites are formed. The majority of the degradation is to the "major" determinant, the penicilloyl moiety. Other breakdown products can cause an allergic reaction, the "minor" determinants. The original minor determinant mixture consisted of benzylpenicilloate and benzylpenilloate. Testing for the major and minor determinants should be performed for the assessment of penicillin allergy [11].

In vitro testing of allergen-specific IgE antibodies is most often performed by measuring circulating IgE antibodies by a solid phase radioimmunoassay, a RAST assay. Application of this assay is limited by insufficient knowledge of the relevant drug metabolites in the allergic drug reactions. Assays have been developed to measure IgE antibodies to the major determinant of penicillin but not the minor determinants. Only a limited number of reliable drug RAST tests are commercially available.

Acute management of an anaphylactic drug reaction can be lifesaving. The initial steps in the management of anaphylaxis are the same as for all life-threatening events, that is, the control of airway, breathing, and circulation. A sometimes overlooked step is the need to start oxygen at the outset of the resuscitation. The most critical medication is epinephrine. In children or adults in an office setting, intramuscular or subcutaneous administration can be used. The intramuscular or subcutaneous dose for adults, using 1:1000 epinephrine, is 0.2 to 0.5 mL (0.3–0.5 mg). In children, the dose is 0.01 mg/kg (maximum, 0.5 mL [0.5 mg] per dose). The intramuscular route was found to be the route of choice in an evaluation of the absorption of epinephrine given by subcutaneous or intramuscular injection [12]. If the patient worsens despite repeated doses of intramuscular or subcutaneous epinephrine, intravenous epinephrine could be considered. This dose is initially titrated at 1 μ g/min, which can be increased to 2 to 10 μ g/min as needed.

Histamine receptor antagonist therapy can be used with epinephrine. In adults, diphenhydramine may be given by the intramuscular or intravenous route at a

dose of 25 to 50 mg. Children can be administered the medication by the oral, intramuscular, or intravenous route at a dose of 1 to 2 mg/kg; ranitidine, an H₂ blocker, can be given in conjunction at a dose of 1 mg/kg. The role of corticosteroids in the initial management of the acute event is unclear; however, because of a possible late phase reaction, steroids may help from a preventive standpoint, although studies are still lacking in this area. Patients with mild anaphylactic symptoms may benefit from 30 to 60 mg of oral prednisone. Corticosteroids are available for intravenous infusion if the clinical situation warrants. Other supportive care includes fluid resuscitation and the use of vasopressors depending on the clinical scenario. Patients should be observed after stabilization for at least 2 hours with mild episodes and probably for 24 hours after severe anaphylaxis.

Patients may undergo drug desensitization if that drug is required for treatment. Various protocols are available for different drugs. These protocols consist of the administration of incremental doses of a drug over a period of hours or days to convert the patient from being drug sensitive to drug tolerant. The patient needs to be observed closely during this procedure. The patient will remain in the desensitized state for as long as he or she receives the drug. After discontinuation of the drug, a repeat desensitization would have to be performed before the drug could be given at maintenance dosage.

Cytotoxic reactions Gell and Coombs (type 2)

Cytotoxic reactions involve IgG, IgM, and IgA antibodies to erythrocytes, leukocytes, and platelets. The immune response may be directed toward the native drug, drug metabolites, or red blood cell antigens. Once the immune response is elicited and complement activated, cells with antigen and those without antigen may be damaged. Immuno-hemolytic anemias have been associated with penicillin, cephalosporins, quinidine, and alpha-methyldopa. Thrombocytopenia has been associated with quinine, quinidine, acetaminophen, sulfonamides, gold, and propylthiouracil. Granulocytopenia has been associated with phenothiazines, thiouracils, sulfonamides, and anticonvulsants. Clinically, other causes of the cytopenias should be assessed. Knowledge of the drugs typically associated with this type of reaction is important. A thorough review of the medication list, including start dates of the medications, is helpful. The only treatment is drug withdrawal.

Immune complex reactions Gell and Coombs (type 3)

Serum sickness is produced by circulating immune complexes. The first detailed descriptions of this type of reaction were made in the early 1900s and observed in patients treated with horse serum containing diphtheria antitoxin. Eight to 12 days following injection, the patients experienced a syndrome consisting of fever, lymphadenopathy, skin eruptions, arthralgias, and proteinuria. Subsequently, the underlying mechanism was found to be triggered by circulating

immune complexes and complement activation. In one of the largest prospective studies on serum sickness, 12 patients with bone marrow failure treated with daily infusions of horse antithymocyte globulin were studied [13]. Serum sickness developed in 11 of the 12 patients. This sickness was manifested by fever (100%), malaise (100%), cutaneous eruptions (100%), arthralgias (55%), gastrointestinal disturbances (45%), and lymphadenopathy (18%). Symptoms occurred 8 to 13 days after the beginning of therapy. The skin manifestations were primarily urticarial and morbilliform skin rashes. Interestingly, a thin band of erythema was noted along the sides of the hands, fingers, feet, and toes at the junction of the palmar or plantar skin with the skin of the dorsolateral surface. Levels of serum C3 and C4 were markedly decreased.

In general, serum sickness begins 2 to 21 (usually 7 to 10) days after the medication is given. The delay in symptoms corresponds with the time needed to form antibody and subsequent immune complexes. Decreased complement levels (C3, C4) and abnormal urinalysis are helpful in making the diagnosis. It is helpful to differentiate true serum sickness and serum sickness-like reactions. Serum sickness-like reactions include fever, rash, and arthralgias occurring 1 to 3 weeks after drug exposure. Lymphadenopathy and eosinophilia may also be present; however, immune complexes, decreased complement levels, and renal lesions are not seen. The medications most commonly associated with this type of reaction are penicillin, cephalosporins, sulfonamides, hydantoin, ρ -aminosalicylic acid, and streptomycin. Cefaclor, in particular, has been associated with a serum sickness-like syndrome. The reaction is thought to result from the hepatic biotransformation of the drug [14]. Management of serum sickness is primarily symptomatic, because the reaction is generally self-limited. NSAIDs and glucocorticoids may be helpful for symptom control.

Cell-mediated reactions Gell and Coombs (type 4)

Allergic contact dermatitis represents the most common medication-induced, delayed-type hypersensitivity. The clinical manifestations of allergic contact dermatitis depend on the severity of the eruption, which is determined by the sensitivity of the patient, the dose of exposure, and the potency of the exposed dose. The clinical skin lesions range from a mild erythema to edematous erythematous papules that become vesicular and weep. Pruritus is a hallmark of the disease and varies in intensity depending on the sensitivity. The dermatitis is initially limited to the skin area that has come in contact with the topical medication, although, over time, it may spread to other areas.

Knowing the start date of the topical medication can be helpful. Typically, it takes 7 to 20 days for the initial sensitization to take place. With subsequent exposures, reactions may occur within 8 to 120 hours depending on the patient's sensitivity and amount of exposure. Over 3000 different compounds have been implicated as causes of allergic contact dermatitis. The most common medications implicated are topical formulations of penicillin, local anesthetics, antihistamines, and neomycin. In addition to the drug itself, preservatives and excipients

can elicit a contact dermatitis. Potent topical sensitizers include parabens, formaldehyde, ethylenediamine, lanolin, and thimerosal [15]. The diagnosis can be confirmed via patch testing, open or closed. During an open patch test, the suspected allergen is applied to the skin and left uncovered. Application is repeated twice daily for 2 days and then read. With closed patch testing, the material is applied to the skin and covered with an adhesive. The adhesive is removed in 48 hours for initial interpretation. Further readings are performed at 72 and 96 hours.

Initial management consists of avoidance of the allergic agent and chemically related or cross-reacting materials. For the treatment of mild-to-moderate erythema, topical steroid ointments or creams (class III to V) applied two to four times a day will suppress erythema and itching. For blisters and intense erythema, cold wet compresses should be used for 15 to 30 minutes several times a day for 1 to 3 days until blistering and severe itching is controlled. Topical steroids do not penetrate well through blisters, and systemic steroids should be used for severe widespread inflammation. Other symptomatic relief measures include short, cool tub baths and oral antihistamine medications.

Morbilliform reactions

Morbilliform or maculopapular eruptions are the most commonly encountered immunologic reactions to medications. This type of reaction can be seen with a wide range of drugs, including penicillins, sulfonamides, phenytoins, and NSAIDs, among others. The actual pathogenesis of these reactions is unclear, and they do not always recur with rechallenge. Based on the delay between exposure to the drug and the morbilliform reaction, a T cell-mediated process is likely. Penicillin- and sulfonamide-specific T-cell clones have been isolated from patients with morbilliform reactions from these drugs [16,17]. Clinically, the skin lesions are typically symmetric and consist of macules and papules that become confluent. The face, palms, and soles are typically spared. The rash resembles a viral exanthem. Typically, no true urticarial lesions are present. When the patient is examined at the time of the reaction, it is usually clear whether the reaction is a morbilliform or an urticarial reaction; however, if the reaction is remote, by history, it is difficult to differentiate a morbilliform reaction from an urticarial one. This differentiation is important, because an urticarial reaction could be IgE mediated and the specific drug contraindicated, unless a desensitization procedure is performed, whereas a morbilliform reaction is not necessarily a strong contraindication to future use of the drug.

Morbilliform reactions typically occur 4 to 10 days after beginning therapy, but can occur up to 2 weeks after therapy has ceased. The rash typically lasts 1 to 2 weeks and can be associated with pruritus and low-grade fever. It is recommended that the offending drug be stopped at the time of the reaction to help prevent the skin manifestations from progressing to a generalized erythroderma or exfoliative dermatitis. Skin prick testing will be negative in these patients, distinguishing this reaction from an IgE-mediated hypersensitivity. Recently,

studies have been performed to measure the sensitivity and specificity of patch testing and delayed reading (>48 hours) of intradermal skin tests in patients with a history of morbilliform reaction in response to penicillins [18]. Overall, patch testing has a good positive predictive value for delayed cutaneous reactions to drugs. Nevertheless, a negative result is difficult to interpret. Generally, the use of a drug giving a positive result on a patch test or delayed intradermal skin test should be avoided when possible. Antihistamines are typically of no benefit owing to the lack of mast cell involvement. If intradermal skin testing and patch testing are not available, a graded challenge could be performed if the drug is required; however, if there were features consistent with Stevens-Johnson syndrome or TEN, the drug would be contraindicated.

Erythema multiforme

Erythema multiforme is a hypersensitivity reaction associated with infectious agents and medications. Fifty percent of all cases of erythema multiforme are thought to be drug induced [19]. The mechanism is not completely defined, but is thought to be a lymphocyte cell-mediated mechanism. The development of cutaneous lesions in erythema multiforme usually begins symmetrically from the distal extremities, progressing proximally. Initial involvement is typically seen on the palms, soles, and dorsal aspects of the hands and feet. The distinctive iris or target lesions have dusky centers and pink-to-red peripheries. The size and morphology can be variable; however, a single morphology is usually present in an individual patient. The skin manifestations typically occur 1 to 2 weeks after exposure to the drug [20]. Multiple drugs have been associated with erythema multiforme. The most common ones include sulfonamides, penicillins, NSAIDs, hydantoins, phenothiazines, and barbiturates. Re-challenge with the medication usually results in a return of the erythema multiforme. The time course for erythema multiforme is typically 4 weeks if there is no progression to erythema major/Stevens-Johnson syndrome/TEN.

Management of erythema multiforme includes stopping the offending medication and ruling out infectious causes such as herpes simplex virus infections or *Mycoplasma pneumoniae*. It is difficult to predict when and if erythema multiforme will progress to erythema major/Stevens-Johnson syndrome. The patient should be watched closely for progression of the lesions. The use of systemic corticosteroids is controversial. There is no clear evidence that such use will prevent the progression of lesions, and the drugs may immunosuppress the patient.

Erythema multiforme major/Stevens-Johnson syndrome/toxic epidermal necrolysis

Erythema multiforme major, Stevens-Johnson syndrome, and TEN are thought to be similar disorders of varying severity of erythema multiforme. Erythema multiforme major is characterized by target and bullous lesions involving the extremities and mucous membranes. Stevens-Johnson syndrome features conflu-

ent purpuric macules on the face and trunk and severe mucosal erosions, usually at more than one mucosal site. This appearance is accompanied by severe constitutional symptoms and high fever. TEN is also associated with bullous lesions, mucosal involvement, and skin detachment. TEN and Stevens-Johnson syndrome are distinguished by the amount of skin detachment, which is less than 10% in Stevens-Johnson syndrome and more than 30% in TEN. Epidermal detachment between 10% and 30% is considered an overlap of Stevens-Johnson syndrome and TEN [21].

Approximately 50% of cases of Stevens-Johnson syndrome and 80% of cases of TEN are drug induced. More than 100 drugs have been associated with Stevens-Johnson syndrome and TEN. The medications with the highest relative risk are sulfonamides, β -lactam antibiotics, imidazole agents, and NSAIDs. Drugs in the moderate risk category include quinolones, aromatic anticonvulsants, and allopurinol [21]. The treatment of Stevens-Johnson syndrome remains controversial. In some cases, the use of corticosteroids has been associated with delayed recovery [22], whereas in other studies, they have been found to be of benefit [23]. Otherwise, management is geared toward symptom relief. Antihistamines can be used for pruritus, and cutaneous blisters can be treated with cool wet Burow's solution compresses. Papules and plaques can be treated with topical steroids, but topical steroids should not be applied to eroded areas. Ocular involvement should be monitored by an ophthalmologist.

In contrast, most authorities recommend that corticosteroids not be used in the management of TEN [24]. Because of the similar pathophysiology to burn injury, treatment is best conducted in a multidisciplinary burn center. Intensive treatment includes temporary skin substitutes, fluid and electrolyte monitoring, internal alimentation, infection control, and pain management. In small studies, cyclophosphamide, cyclosporine, plasma exchange, and plasmapheresis have produced an improvement in symptoms [25]. More recently, intravenous immunoglobulin has been shown to lead to marked clinical improvement in TEN by inhibiting Fas-mediated keratinocyte cell death by blocking the Fas receptor [26,27].

Anaphylactoid drug reactions

Anaphylactoid drug reactions are caused by the direct release of mediators from mast cells and basophils. Clinically, the signs and symptoms resemble anaphylaxis, but there is no IgE-mediated mechanism. These types of reactions can be seen with a large number of medications and excipients, most commonly with opiates, aspirin, and radiocontrast material. Reactions may include any combination of the following: pruritus, urticaria, angioedema, bronchospasm, hypotension, syncope, nausea, emesis, and flushing. Because this reaction is not IgE mediated, skin testing is not of value. Management of these patients is essentially the same as for anaphylaxis. In the situation of a patient with a previous reaction to radiocontrast, low molecular weight or nonionic contrast should be used with a pretreatment protocol consisting of prednisone, 50 mg

orally, or hydrocortisone, 200 mg intravenously, 13, 7, and 1 hour before the radioccontrast procedure, plus diphenhydramine, 50 mg orally or intravenously, 1 hour before the procedure. Ephedrine, 25 mg orally, may be added 1 hour before the procedure (as long as there are no contraindications). This protocol reduces the risk of a reaction to 3% to 10% [28].

Hypersensitivity syndrome/drug rash with eosinophilia and systemic symptoms

The DRESS syndrome, previously termed HSS, is a distinct drug reaction characterized by a morbilliform skin rash that may develop into an exfoliative dermatitis, fever, lymph node enlargement, and differing degrees of internal organ involvement. Eosinophilia and atypical lymphocytosis are common hematologic findings. Internal organ involvement can include the bone marrow, liver, kidney, central nervous system, intestinal tract, and lungs. Symptoms usually start within 8 weeks after the initiation of therapy. The aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine) and sulfonamides are the most common causes of DRESS syndrome. Other drugs have also been associated with DRESS syndrome, including lamotrigine, allopurinol, NSAIDs, captopril, calcium channel blockers, mexiletine, fluoxetine, dapsone, metronidazole, minocycline, and antiretroviral drugs [29]. The differential diagnosis includes Stevens-Johnson syndrome, TEN, hypereosinophilic syndrome, and Still's disease. Laboratory tests that are helpful in diagnosis include a complete blood count with differential, liver function tests, a creatinine level, and urinalysis. Skin biopsy is typically not specific. Findings include a lymphocytic infiltrate of the papillary dermis, which may contain eosinophils. The immune mechanism is not fully understood. Drug detoxification most likely has a role, because slow acetylation is associated with an increased risk of DRESS.

The treatment of DRESS is similar to that of other severe drug reactions and consists initially of rapid removal of the offending drug. Supportive treatment includes volume replacement, nutritional support, antibiotics, and extensive skin care. The role of corticosteroids remains controversial. Corticosteroids have been associated with an improvement in clinical symptoms and eosinophilia in case reports, with relapses occurring after tapering or withdrawal of the corticosteroids [30]. Although several investigators suggest their use when internal organ involvement exists [29], without randomized controlled trials to support their benefit, the use of corticosteroids is not automatically recommended. Part of the reason for this caution is the clinically similar presentation of TEN, for which steroids have shown no benefit or increased morbidity or mortality.

Summary

Approximately one-fifth of adverse drug reactions are caused by an immune response by a variety of mechanisms, including antibody-mediated, cellular-mediated, mixed immunologic reactions, and anaphylactoid reactions. Knowl-

edge of the signs and symptoms of these various types of reactions and of the types of medications commonly associated with the reactions in conjunction with a detailed medication history and complete physical examination is helpful in implicating the drug causing the reaction. Discontinuation of the drug is the primary treatment for all reactions. Acute management can be undertaken and future management outlined to prevent similar reactions.

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