Drug Hypersensitivity Reactions

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KEYWORDS

• Drug hypersensitivity • Drug allergy • Adverse drug reaction
• Hypersensitivity reactions • Anaphylaxis • Severe cutaneous adverse reactions

KEY POINTS

- Drug hypersensitivity reactions result from various immune system-mediated responses to exposure to a drug.
- The Gell and Coombs classification divides immunologic drug hypersensitivity reactions into 4 major categories based on immunologic mechanism.
- Dermatologic manifestations are the most common clinical finding of a drug allergy.
- Type IV hypersensitivity reactions include severe cutaneous adverse reactions (SCARs) such as drug reaction with eosinophilia and systemic symptom (DRESS) syndrome, Stevens–Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP).
- Epinephrine is the first-line treatment of anaphylaxis. Antihistamines may be given to alleviate cutaneous manifestations but, they do not treat the underlying process of anaphylaxis.

INTRODUCTION

Drug hypersensitivity reactions (DHRs) are a diverse group of reactions mediated by the immune system after exposure to a drug. The mechanisms underlying the development of a hypersensitivity reaction are complex and not always fully characterized. Anaphylaxis is a DHR that requires immediate recognition and treatment. Other types of reactions are slow to develop and do not always require rapid treatment. Emergency physicians should have a good understanding of these various types of DHRs and how to approach the patient regarding evaluation and treatment.

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EPIDEMIOLOGY

The true burden of disease due to allergic reactions is difficult to determine because epidemiologic data are limited in quality due to variations in terminology used, different methodological approaches for determining the prevalence of disease, and different outcomes used to determine the presence of an allergy. Overall, adverse drug reactions (ADRs) have been estimated to affect up to approximately 15% of hospitalized patients.[1] In a 2013 study using random digit dialing to survey members of the general public, the prevalence of anaphylaxis using the most stringent criteria was at least 1.6%, whereas the prevalence was 7.7% using the least stringent criteria. Respondents in the survey attributed episodes of anaphylaxis to drugs in 35% of cases.[2] From 2001 to 2012, there was an increase in the percentage of emergency department (ED) visits due to allergic drug reactions—from 0.49% to 0.94%.[3] In New York City between 2004 and 2008, anaphylaxis accounted for 0.18% of pediatric ED visits.[4] Overall, medications are the leading cause of anaphylaxis that results in death.[5] In children, however, exposure to food causes the greatest number of anaphylaxis fatalities.[6] In contrast to anaphylaxis in general, whereby there has been a rise in hospital admissions without a rise in fatalities, for drug-induced anaphylaxis, one study of an Australian database found a threefold increase in deaths due to anaphylaxis but only a 1.5x increase in the number of hospital admissions between 1997 and 2005. In this study, over half of all the fatalities due to anaphylaxis were likely caused by drug allergies.[7] The risk of anaphylaxis to drugs increases with age.[8] The United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is a web-based system used to compile adverse event reports to assist with postmarketing surveillance of drugs to identify potential safety concerns. Analysis of FAERS data demonstrated that the rate of anaphylaxis due to monoclonal antibodies (mAbs) is rising faster than any other class of drug. In 1999, mAbs accounted for 2% of all reported cases of anaphylaxis, but this had risen to 17.37% in 2019.[9]

RISK FACTORS

Most ADRs are an extension of the usual pharmacologic effect of the drug. Factors that increase the risk of ADRs include the type of drug, the dose of the drug, specific pharmacokinetic properties of the drug, and other factors that play a role in the metabolism and action of the drug. A study by Gurwitz and colleagues in 2003 found that ADRs were common in the elderly population and that as many as one-fourth were preventable.[10] The elderly experience age-related changes in drug metabolism but also are subject to polypharmacy and inappropriate prescribing.[11] At the other end of the age spectrum, Clavenna and Bonati found that the incidence of ADRs in pediatric patients was 10.9% for in-hospital patients and 1.0% for outpatients.

The risk of having an allergic reaction to a drug is greatest when there is a history of allergic relation to the same or closely related compounds. Drug-specific factors influence the likelihood of developing an allergy. Large molecular weight compounds such as proteins and polysaccharides have increased rates of allergic reactions. The route of administration of a drug may influence the likelihood of developing an allergic reaction although the data supporting these statements is weak. Some polymorphisms of human leukocyte antigen (HLA) region carry a higher risk of certain forms of allergic reaction.[12]

The risk of anaphylaxis increases with age, presence of comorbid conditions, and the use of angiotensin-converting enzyme (ACE) inhibitors.[13,14] A retrospective analysis of a European registry of anaphylaxis cases found that age was the greatest risk factor for having severe cardiovascular complications from anaphylaxis (adjusted

odds ratio 6.08).[15] Asthma and other respiratory conditions have been associated with greater severity of anaphylactic reactions.[14,16,17]

CLASSIFICATION & MECHANISMS

Multiple systems have been developed to characterize and classify different reactions to drugs. These reactions may occur as the result of a multitude of different pathways with an immunologic basis being just one. In 1955, Brown wrote that the use of the term drug allergy was used "as a sort of wastepaper basket into which are cast many unexplained phenomena."[18] The FDA defines an adverse event as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."[19] In the report published in 1972, International Drug Monitoring: The Role of National Centers, the World Health Organization (WHO) defined an ADR as "one that is noxious, is unintended, and occurs at doses normally used in man."[20]

The Rawlins–Thompson classification of ADRs was proposed in 1977.[21] The system broke ADRs into Type A, which are dose-dependent and predictable and Type B, which are not dose-dependent or predictable. Type A reactions make up 85% to 90% of all ADRs and have been referred to as "augmented" as these reactions are an extension of the normal pharmacologic properties of the drug. Prolongation of the QRS complex in tricyclic antidepressant overdose is an example of a Type A reaction. Type B reactions comprise 10% to 15% of ADRs and have been referred to as "bizarre" because they are not a normal, expected property of the drug. Anaphylaxis resulting from exposure to penicillin is an example of a Type B reaction. Subsequently, additional categories have been added by some to further characterize different types of ADRs. These include: Type C (dose-related and time-related), Type D (time-related), Type E (withdrawal), and Type F (unexpected failure of efficacy).[22]

A DHR is a response to a drug that results in symptoms or signs due to exposure to a drug at a dose normally tolerated by nonhypersensitive people and is induced by immunologic or inflammatory pathways. The term DHR is preferred in cases of suspected drug allergy because clinically it is difficult to distinguish between a true drug allergy and nonallergic DHR. In its International Consensus on Drug Allergy, the World Allergy Organization classified DHRs based on the timing of onset of symptoms after exposure. Immediate DHRs such as urticaria, anaphylaxis, and bronchospasm, typically occur within 1 to 6 hours of exposure although usually within 1 hour. Nonimmediate or delayed DHRs occur after 1 hour of exposure and frequently many days later.[23]

Gell and Coombs Classification of Hypersensitivity Reactions

The Gell and Coombs classification divides immunologic DHRs into 4 major pathophysiologic categories based on the immunologic mechanism (**Table 1**). In this classification which was first proposed in 1963, each reaction has a distinct and mutually exclusive mechanism. In the following years, advances in the understanding of various immunologic effectors and pathways have exploded and it is now known that there may be overlap across different Gell and Coombs reaction types.[24]

Type I, or immediate-type hypersensitivity reactions occur when exposure to a previously encountered antigen causes crosslinking of IgE bound to high-affinity receptors (FcεRI) on the surface of sensitized mast cells and basophils leading to release of preformed vasoactive mediators such as histamine, tryptase, and chymase.[25,26] These mediators cause vasodilation and increased capillary permeability. The initial reaction is followed 4 to 8 hours later by a late phase release of cytokines such as

Table 1
Gell and coombs classification of hypersensitivity reactions

Type		Reactant	Mechanism	Clinical Symptoms
I (Immediate)		IgE	Antigen-induced crosslinking of IgE bound to FcεRI receptors on mast cells and basophils leads to release of vasoactive mediators	Anaphylaxis, angioedema, urticaria, bronchospasm, hypotension
II (cytotoxic)		IgG	IgG recognition of cell surface epitopes leads to the assembly of the complement C5–C9 membrane attack complex (MAC) and subsequent lysis of the cell or, antibody-dependent cell-mediated cytotoxicity (ADCC) whereby natural killer (NK) cells recognize IgG attached to target cells bearing these antigens leading to perforin release and NK cell-mediated lysis	Autoimmune hemolytic anemia and Rh incompatibility
III (Immune Complex Disease)		IgG or IgM	IgM or IgG and complement or FcR	Serum sickness, vasculitis
IV (cell-mediated)	IVa	IFN-γ, TNF-α, T_H1 cells	Antigen is presented by cells or there is direct T-cell stimulation	Eczema
	IVb	IL-5, IL-4/IL-13, T_H2 cells	Antigen is presented by cells or there is direct T-cell stimulation	Maculopapular exanthema with eosinophilia, DRESS
	IVc	Perforin and Granzyme B, Cytotoxic T Cells	Cell associated antigen or direct T-cell stimulation	SJS/TEN, pustular exanthema
	IVd	CXCL8, GM-CSF, T Cells	Soluble antigen presented by cells or direct T-cell stimulation	AGEP

Adapted from: Pichler WJ, Adam J, Daubner B, Gentinetta T, Keller M, Yerly D. Drug Hypersensitivity Reactions: Pathomechanism and Clinical Symptoms. Med Clin N Am. 2010;94(4):645 to 664.[34]

IL-1, IL-4, IL-5, granulocyte monocyte colony-stimulating factor (GM-CSF), and tumor necrosis factor (TNF)-α. Type I hypersensitivity reactions lead to the development of urticaria, angioedema, bronchospasm, and hypotension.[27]

Type II hypersensitivity reactions are delayed cytotoxic reactions in which host cells are destroyed through complement-mediated reactions, antibody-dependent cell-mediated cytotoxicity, or antibody-mediated cellular dysfunction. Host cells coated with antigen bind to IgG, or less commonly, IgM antibodies. This can lead to the activation of the classic complement pathway leading to the assembly of the membrane attack complex (C5–C9) and subsequent lysis of the host cell. Natural killer cells and macrophages can also be activated by binding antibodies to FcγRIIb receptors expressed on their surface. Examples of Type II hypersensitivity reactions include autoimmune hemolytic anemia, Rh-incompatibility, and Goodpasture syndrome (anti-glomerular basement membrane disease).[28]

In Type III hypersensitivity reactions, IgG or IgM form immune complexes with antigens and activate the complement system. This leads to inflammation and tissue injury by activated neutrophils. The clinical manifestations of this process result from the site whereby the immune complexes deposit rather than the specific antigen or antibody and usually take at least a week to appear.[29] Serum sickness and Arthus reactions are examples of Type III hypersensitivity reactions.[30,31]

Type IV hypersensitivity reactions are distinct from Types I through III in that Type IV reactions are not mediated by antibodies but instead involve the activation and expansion of T cells. This process is not immediate and sometimes takes days to weeks to develop. Since the original classification by Gell and Coombs, Type IV reactions have been further characterized into 4 subclasses based on the cytokines produced and the cells involved.[32] There is a strong link to T cell-mediated hypersensitivity reactions and specific HLA risk alleles.[33] Stevens–Johnson syndrome/toxic epidermal necrolysis (SJS/TEN), acute generalized exanthema pustulosis (AGEP), and drug reaction with eosinophilia and systemic symptoms (DRESS) are examples of Type IV hypersensitivity reactions.

DHRs have also been classified based on the mode of action of the drug with immune/inflammatory cells. In this system, there are 3 types of reactions-allergic/immune, pseudoallergic, and pharmacologic stimulation of immune receptors (p-i concept). Large molecular weight drugs can be recognized directly by immune cells and antibodies. However, most drugs act as haptens in that they are too small (<1000 Da) to elicit an immune response and must bind covalently to a protein to form an antigen.[26] In the pseudoallergic class, drugs cause the release of mediators from mast cells, basophils, and other effector cells without the involvement of immunoglobulins or T cells. In the p-i concept, some drugs may bind noncovalently to nonactive sites of HLA molecules or T cell receptors to cause activation. The drugs are thus not acting as antigens.[35]

CLINICAL MANIFESTATIONS

Patients experiencing an allergic reaction to a drug may have a wide variety of clinical presentations based on the immunologic mechanism underlying the drug allergy. Within the same mechanism, there may be substantial differences in presentation and organ systems involved from patient to patient. Dermatologic manifestations are the most commonly seen presentation in allergic reactions to drugs.[36,37]

The manifestations of Type I (immediate) hypersensitivity reactions are a direct result of the actions of the vasoactive mediators that are released from mast cells and basophils. Common dermatologic manifestations include urticaria and

angioedema associated with flushing and pruritus. The classic description of this swelling associated with vasodilation-induced erythema is the wheal-and-flare response.[38] The respiratory system may be involved resulting in wheezing due to bronchoconstriction and stridor due to edema of the upper airway including the vocal cords. Death due to asphyxiation may occur in severe cases.[39] Gastrointestinal involvement may present with crampy abdominal pain, nausea, and vomiting, as well as diarrhea although these may also be attributable to a non–immune-mediated ADR. Vasoplegia and third-spacing of fluids may result in hypotension and loss of consciousness. Anaphylaxis is the most severe presentation of an IgE-mediated allergic reaction. The clinical presentation of Type I hypersensitivity reactions usually occurs within minutes to hours of the exposure.

The clinical presentation of Type II (cytotoxic) hypersensitivity reactions is usually the result of anemia, thrombocytopenia, or neutropenia, as these are the most common cell types involved. Symptoms most commonly occur within days of exposure. When red blood cells are targeted, drug-induced immune hemolytic anemia (DIIHA) occurs. The drugs most frequently associated with the development of DIIHA are antimicrobials (mostly penicillin and cephalosporins), anti-inflammatories, and antineoplastic agents.[40] Patients will present with typical signs and symptoms of anemia including fatigue, pallor, jaundice, darkened urine due to bilirubinuria, tachycardia, tachypnea, and hypotension. Destruction of platelets via this mechanism leads to drug-induced immune thrombocytopenia (DIITP). This is a secondary form of immune thrombocytopenia (ITP). In this condition, low platelet counts lead to easy bruising and bleeding. In one review of 309 cases, the median time between exposure to the offending drug and development of DIITP was 21 days and the median minimum platelet count was 11,000/μL.[41] Drug-induced immune neutropenia (DIIN) occurs when exposure to a drug results in the development of antibodies that cross-react with glycoproteins on neutrophil cell walls leading to their destruction and placing the patient at risk for infection.[42]

In Type III (immune complex) hypersensitivity reactions, there is an abnormal formation of antigen–antibody complexes that are deposited in tissues and result in the activation of the complement system. Diseases that are the result of Type III hypersensitivity reactions include poststreptococcal glomerulonephritis, serum sickness, hypersensitivity pneumonitis (also called extrinsic allergic alveolitis), and systemic lupus erythematosus (SLE). The clinical presentation depends on the disease. SLE is a prototypical Type III hypersensitivity reaction whereby antibodies develop to components of the cellular nucleus—antinuclear antibodies (ANA). The type of ANA that develops often has a strong association with the patient's clinical presentation. For example, anti-Smith antibodies are frequently associated with kidney disease.[43] Drug-induced lupus (DIL) occurs when exposure to a drug leads to the development of autoantibodies and loss of self-tolerance. The use of procainamide and hydralazine is associated with a high risk of the development of DIL. DIL may not develop until after years of use of the associated drug. Patients with DIL most commonly present with fatigue, low-grade fever, and other systemic symptoms. Generally, DIL tends to present with more mild symptoms than SLE. Development of major organ system involvement is less frequent in DIL than in SLE.[44]

Type IV hypersensitivity reactions occur as a result of T cell response to an antigen leading to an inflammatory response. These reactions are further subdivided (IVa through IVd) based on the type of T cells involved. The clinical presentation is based on the distinct condition that develops. The skin is a depository for a large number of T cells so dermatologic involvement is common in Type IV hypersensitivity reactions. Contact dermatitis is a very common Type IV hypersensitivity reaction. During the

sensitization (afferent) stage, a hapten contacts the skin and leads to the formation of hapten-specific T cells. During the elicitation (efferent) phase, re-exposure to the same hapten causes the release of mediators that are responsible for the clinical presentation including the development of an erythematous, pruritic rash with swelling. Severe cutaneous adverse reactions (SCARs) are a group of dermatologic diseases that result from a Type IV hypersensitivity process.

Drug Reaction with Eosinophilia and Systemic Symptoms Syndrome

DRESS syndrome, also known as drug-induced hypersensitivity syndrome (DIHS), is a SCAR that has a long latency period before the development of clinical symptoms which include fever, adenopathy, hematologic abnormalities, and multiorgan system involvement. The onset of disease usually occurs within 3 weeks of exposure to the drug but may be delayed by as much as 3 months.[45] Reactions to the medication phenytoin were described soon after its introduction in the 1930s. Over time various terms were used to describe similar reactions including anticonvulsant hypersensitivity syndrome and drug-induced pseudolymphoma. In 1996, Bocquet and colleagues introduced the term drug rash with eosinophilia and systemic symptoms.[46] Due to variations in dermatologic involvement the word "rash" in the name was subsequently replaced with "reaction." Different diagnostic criteria have been proposed to define disease patterns that are likely a continuum of DRESS (**Table 2**). A Japanese consensus group proposed a set of diagnostic criteria in 2006 and later developed a scoring system.[47,48] In 2007, the RegiSCAR group, a multinational effort that collects data on cases of SCAR, proposed a similar set of diagnostic criteria and a scoring system to help classify cases as definite, probable, or not DRESS.[49] DRESS is associated with the reactivation of human herpes virus (HHV), especially HHV-6, HHV-7, Epstein–Barr virus (EBV), varicella-zoster virus (VZV), and cytomegalovirus (CMV).[50] Aromatic anticonvulsant medications such as phenytoin, carbamazepine, and phenobarbital have classically been associated with DRESS. Several other drug classes have now been implicated as causative agents including antidepressants, sulfonamides and sulfones, nonsteroidal anti-inflammatories (NSAIDs), antibiotics, ACE inhibitors, and beta-blockers.[51] The overall mortality of DRESS is approximately 5% to 10%.[52] In cases with cardiac involvement, one retrospective analysis demonstrated the mortality increases to 37.5%.[53]

Stevens–Johnson Syndrome and Toxic Epidermal Necrolysis

SJS and TEN are SCARs with skin necrosis and detachment that represent different points on a continuum of severity based on the percentage involvement of body surface area (BSA). SJS involves less than 10% BSA, whereas TEN involves more than 30%. SJS/TEN overlap describes cases whereby there is between 10% and 30% BSA involved.[54] Previously considered to be on the continuum of the same disease, erythema multiforme is now thought to be a distinct entity. Drugs are the most common triggers for the development of SJS/TEN with aromatic antiepileptics, NSAIDs, and antibacterial sulfonamides frequently implicated. Infections are also implicated in the development of SJS/TEN. Cases associated with *Mycoplasma pneumoniae* often have a less severe presentation.[55]

Patients with SJS/TEN initially present with an influenza-like prodromal phase which may include fever and burning sensation. This prodrome precedes the development of skin findings by 1 to 3 days.[56] The rash of SJS/TEN typically begins as erythematous macules with purpuric centers and ill-defined borders. Lesions are first present on the face and thorax before spreading to other areas. The distribution is symmetric and usually spares the scalp, palms, and soles. Over time, sometimes within hours,

Table 2
Diagnostic criteria for DRESS syndrome, also known as drug-induced hypersensitivity syndrome (DIHS)

Bocquet et al[46]	Japanese Consensus Group[47]	RegiSCAR[48]
Presence of a cutaneous drug eruption	Maculopapular rash developing > 3 wk after starting drug	Acute rash
Systemic involvement: Lymphadenopathy $\geq$2 cm in diameter, hepatitis (transaminase $\geq$2 times upper limit of normal), interstitial nephritis, or interstitial pneumonitis or carditis	Clinical manifestation of reaction continuing >2 wk after discontinuing drug	Hospitalization
Hematologic abnormalities eosinophilia $\geq 1.5 \times 10^9$/L or presence of atypical lymphocytes	Fever (>38°C)	Fever (>38°C)
	Hepatic involvement with ALT > 100 or other organ involvement	Lymphadenopathy at $\geq$ 2 sites
All 3 criteria must be present for diagnosis	At least 1 abnormality of leukocytes • Leukocytosis (>11 $\times 10^9$/L) • Atypical lymphocytosis (>5%) • Eosinophilia (>1.5 $\times 10^9$/L)	Involvement of at least 1 internal organ system
	Lymphadenopathy	Blood count abnormalities • Lymphocytosis or lymphopenia • Eosinophilia • Thrombocytopenia
	HHV-6 reactivation	
		* A scoring system is available for classifying HSS/DRESS cases as definite, probable, possible, or no case
	*Typical DIHS occurs with all 7 criteria. Atypical form is when only the first 5 are present.	

Abbreviations: SJS, Stevens–Johnson syndrome; TEN, toxic epidermal necrolysis.

vesicles and bullae form, and then the skin begins to slough off. The blisters will demonstrate Nikolsky sign whereby the application of lateral pressure results in sloughing. The Asboe-Hansen sign may also be present whereby lateral pressure on the edge of a blister will cause the blister to spread into previously uninvolved skin.[57] Greater than 90% of cases of SJS/TEN will have mucosal involvement with erythema and erosions of the buccal, genital, and ocular tissue. The eyes may

demonstrate conjunctival erythema, periorbital edema, discharge, crusting, and development of a pseudomembrane.[58]

The severity-of-illness score for toxic epidermal necrolysis (SCORTEN) was developed to assess the severity and predict prognosis. Using logistic regression techniques, 7 independent variables were identified and assigned a value of either 1 or 0 based on the presence or absence of the variable. These variables included age $\geq$40, associated cancer, heart rate $\geq$120 beats per minute, serum blood urea nitrogen greater than 28 mg/dL, BSA $\geq$10%, serum bicarbonate less than 20 mEq/L, and serum glucose greater than 250 mg/dL. With increasing scores, the mortality rate increases. A score of 5 or more is associated with a greater than 90% mortality.[59] Recently, another scoring system was derived from an international dataset, the ABCD-10 Score, named for age, bicarbonate, cancer, dialysis, and 10% BSA.[60] Recent comparisons of the 2 scores have demonstrated better performance of SCORTEN than ABCD-10.[61,62]

Acute Generalized Exanthematous Pustulosis

Acute generalized exanthematous pustulosis (AGEP) is a SCAR that is almost exclusively caused by exposure to a drug with a very short latency period, frequently less than 2 days.[63] It presents with numerous nonfollicular pustules on an erythematous base. The multinational EuroSCAR group found that the medications most often implicated in the development of AGEP were pristinamycin, ampicillin and amoxicillin, quinolones, chloroquine and hydroxychloroquine, anti-infective sulfonamides, terbinafine, and diltiazem.[64] The rash tends to first appear in the axillary, submammary, and inguinal intertriginous regions. Mucosal involvement is limited and only seen in about one-fourth of patients.[62] Evidence of systemic inflammation includes the development of fever, leukocytosis with elevated neutrophils, and elevated C-reactive protein. The lesions of AGEP typically spontaneously regress after 2 weeks with the development of collarette desquamation in previously affected areas. The mortality rate of AGEP is about 5% and death usually occurs in patients with significant comorbidities.[65]

EVALUATION

In the ED, the initial evaluation of a patient with a possible DHR focuses on the clinical stability of the patient by assessing the airway, breathing, and circulation. Once the patient is stable, clinical evaluation of a patient with a possible DHR focuses on the drug and on the patient. Information to gather include the name of the medication, the timing from drug exposure to the development of symptoms, a history of similar reactions especially in the absence of the suspected drug, and the signs and symptoms of the reaction. Clearly delineating the timing of all symptoms and the timing of drug exposure can help to avoid protopathic bias. In this form of bias, a symptom occurs for which the patient takes a drug which is followed by the full development of the disease. The disease is erroneously thought to be caused by the drug even though the exposure actually occurred after the onset of disease.[66]

Type I hypersensitivity reactions are acute in onset after exposure to the offending agent. Evaluation of patients in the ED is often conducted without the aid of laboratory or radiographic testing. Clinical evaluation is what is used to differentiate a simple allergic reaction from life-threatening anaphylaxis. The National Institutes of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network (NIAID/FAAN) criteria are used to determine the presence of anaphylaxis based on the presence of any one of the 3 clinical scenarios. The first criterion requires the presence of mucocutaneous findings coupled with either respiratory or cardiovascular involvement. In the

second criterion, there is the involvement of any 2 of the following 4 organ systems after exposure to a *likely* allergen—mucocutaneous, respiratory, cardiovascular, and gastrointestinal. For the final criterion, hypotension develops after exposure to a *known* allergen for the patient.[67]

Evaluating a patient with a Type II hypersensitivity reaction requires laboratory evaluation with a complete blood count. Considering DIIHA, DIITP, and DIIN as a diagnosis requires a high degree of suspicion and is made by the demonstration of reduced red blood cells, platelets, or neutrophils in the setting of drug administration. Similarly, when patients present with a Type III hypersensitivity reaction, the signs and symptoms are nonspecific and require a high degree of suspicion. The diagnosis is usually made during an admission whereby other possible etiologies can be ruled out.

The SCARs that develop as a result of a Type IV hypersensitivity reaction carry a high risk of mortality and thus rapid evaluation is paramount to ensure that the patient receives proper treatment. Usually, patients that present with DRESS, SJS/TEN, or AGEP have such profound skin findings that suspicion is easily raised for these diagnoses. The patient may present early whereby the full clinical picture has not yet evolved making the diagnosis that much harder to make. Early involvement of a dermatologist to facilitate histopathologic analysis is recommended. Laboratory studies are used to assess the severity of illness and to help guide supportive care.

TREATMENT

The first step in the treatment of any DHR is discontinuing the offending agent. Further treatment is dictated by the acuity and severity of the reaction. All patients should be assessed for clinical stability by first evaluating the ABCs—patency of the airway, ensuring breathing is adequate, and assessing for the effectiveness of cardiac output.

For cases of anaphylaxis, epinephrine is the first-line medication.[68] For patients not in cardiac arrest, epinephrine should be administered intramuscularly in the anterolateral thigh—at the location of the vastus lateralis muscle, a large, highly vascularized muscle. Administration in the thigh leads to better absorption than either subcutaneous injection or intramuscular injection into the deltoid muscle.[69] The concentration of epinephrine used for intramuscular injection is 1:1000 (1 mg/mL). The dose is 0.01 mg/kg to a maximum of 0.5 mg for adults and 0.3 mg for children. This can be repeated every 5 to 15 minutes as needed for persistent symptoms of anaphylaxis.[70] Epinephrine can be given as a continuous infusion using a 1:10,000 (0.1 mg/mL) concentration for patients that fail to respond to intramuscular doses. In cases of severe anaphylaxis, patients can lose up to one-third of their intravascular volume through plasma extravasation into surrounding tissue leading to cardiovascular collapse.[71] Patients should have adequate intravenous access established with 2 large-bore IV catheters. In the anticipation of intravascular volume loss, crystalloids should be administered. Supplemental oxygen should be administered to all patients in respiratory distress, those requiring multiple doses of epinephrine, and patients with chronic cardiac or respiratory diseases.[72] Antihistamines may be given for the treatment of pruritus and cutaneous signs in anaphylaxis. It is important to realize the limits of antihistamine treatment, specifically that it lacks the bronchodilatory, inotropic, vasoconstrictive, and mast cell stabilization properties of epinephrine. Glucocorticoid steroids are also frequently given in cases of anaphylaxis. These have a slow onset of action and there is no compelling evidence that their use reduces the occurrence of biphasic reactions.[73] Some guidelines now recommend against the routine use of steroids for the treatment of anaphylaxis.[74]

Patients with drug-induced Type II hypersensitivity reactions will need treatment tailored to the abnormalities that are specific to the reaction. In severe cases of DIIHA, transfusion of packed red blood cells may be required. In cases of DIITP, there is limited evidence for the use of immunosuppressive therapy; however, because DIITP may not be distinguished from ITP, intravenous immune globulin (IVIG) may be administered. Transfusion with platelets should be given in cases of severe thrombocytopenia.[75] Patients with DIIN who develop infections should be treated aggressively with broad-spectrum antibiotics and possibly antifungal agents. Administration of recombinant granulocyte colony-stimulating factor (G-CSF) may shorten the time to recovery of normal neutrophil counts. Transfusion of granulocyte concentrates are generally reserved for cases of severe, life-threatening infection.[76]

The treatment of drug-induced Type III hypersensitivity reactions is generally more long-term management options. Acute presentations due to infections or organ damage (eg, acute kidney injury) may occur. The treatment will need to be directed to the presenting problem.

Patients with a Type IV hypersensitivity reaction will be managed based on the severity of the presentation. For minor reactions such as contact dermatitis, the only treatment required may be the removal of the offending agent. More severe presentations such as a SCAR like SJS or TEN will need aggressive resuscitation and often transfer to a specialty center that cares for burn patients as many of the principles of therapy are similar to that patient population.[77] Other than the initial resuscitation, most treatment decisions will be made by the specialist. There is no clear consensus on the use of debridement or treatment with either steroids or IVIG.[78]

DISPOSITION

The disposition of patients who present to the ED for a DHR depends on the severity of the reaction and the response to treatment. For mild cases such as contact dermatitis, patients can be discharged once they have been evaluated and a treatment plan has been developed and explained to the patient. For cases of anaphylaxis, patients can be discharged home if they have a rapid response to treatment and complete resolution of symptoms. There should be some period of observation in the ED after an episode of anaphylaxis; however, the duration of this observation is based on limited evidence. The Resuscitation Council UK updated guidelines for anaphylaxis released in 2021 suggests a 2 hour observation for patients who responded to epinephrine treatment within 5 to 10 minutes, had complete resolution of symptoms, and who have adequate outpatient resources including an epinephrine autoinjector. A longer observation period of 6 hours is recommended if more than one dose of epinephrine is administered or if there is a history of a previous biphasic reaction. More severe cases require longer periods of observation.[73] The Joint Task Force on Practice Parameters comprised of members from the American Academy of Allergy, Asthma & Immunology and the American College of Allergy, Asthma and Immunology state that it may be reasonable to discharge low-risk patients after a 1 hour period of asymptomatic observation.[69] All patients with anaphylaxis should receive education about the avoidance of triggers, indications for return to the ED, and the use of epinephrine auto-injectors. Patients should be discharged with a prescription for an appropriate epinephrine auto-injector and a referral to an allergist.[69]

For other types of DHRs, the disposition will be determined by the presenting signs and symptoms, the clinical status of the patient, and the treatment needs of the patient. As mentioned previously, patients with SJS or TEN should be considered for transfer to a burn center for specialized treatment. A delay of greater than 7 days in

the transfer of care of patients with TEN to a burn center has been associated with increased mortality.[79]

DELABELING OF DRUG ALLERGIES

Many patients are given a label of having a drug allergy despite not actually having an episode of a DHR. This can lead to substandard care due to the withholding of optimal treatments. Many of these reactions are patient reported and do not meet the clinical criteria for an allergic reaction.[80] Since 2013, there has been an increased focus on the problems of misattributed drug allergies with a push to "de-label" these patients.[81] This issue is commonly encountered with patients who are identified as being allergic to penicillin. In the US, approximately 8% of the population or 25 million individuals carry the label of being allergic to penicillin. In one study of 500 patients who were identified as being allergic to penicillin, only 4 patients (0.8%, 95% confidence interval (CI): 0.32% to 2.03%) had a positive reaction on gold standard testing.[82] A penicillin and cephalosporin testing pathway was implemented at a large academic hospital in Boston whereby patients identified as having an allergy to these antibiotics could undergo test dosing in the ED. Of the 310 test doses given, hypersensitivity reactions occurred in only 10 patients (3.2%; 95% CI: 1.6%–5.9%). In 5 of those cases, the pathway was not followed correctly. This led to a change in allergy labeling for 146 (47%) of the patients.[83] Programs to perform confirmatory testing for patients labeled as having a penicillin allergy may have substantial cost-benefit through improved utilization of resources and selection of treatment options.[84] There should also be an effort to ensure greater accuracy of allergy labeling in the first place.

SUMMARY

The immune system, the body's defense against foreign substances which may be harmful, can respond to the administration of drugs leading to the development of a wide variety of DHRs. These are a form of unpredictable events that have been classified as Type B ADRs. Clinical presentations are heterogeneous, and the exact diagnosis is often beyond the scope of the ED. Care of patients who present to the ED focuses on stabilization, providing supportive care, and, in cases of anaphylaxis, administering epinephrine, the first-line treatment.

CLINICS CARE POINTS

- Patients with new clinical symptoms after the administration of a drug must be carefully evaluated for timing, associated symptoms, and type of drug to help determine if the patient is having a DHR.
- When the possibility of a DHR is being considered, all possible causes of the reaction should be discontinued.
- Initially focus on the tenets of good resuscitation, such as airway, breathing, and circulation as anaphylaxis is a potentially fatal reaction.
- Cutaneous signs and symptoms are the most common manifestation of an allergic reaction to a drug, but one should carefully assess for the involvement of the respiratory and gastrointestinal systems as well as signs of poor circulation resulting in hypotension or loss of consciousness.
- Patients presenting with severe rashes should be queried about the use of drugs, even if the drug was not started recently. These rashes could be a manifestation of SCARs, which has a

high mortality rate.

DISCLOSURE

The authors have nothing to disclose.

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