Drug Allergy and Adverse Drug Reactions

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Abstract

Adverse reactions to drugs are common and may result in increased healthcare utilization and cost. It is important to distinguish between medication side effects and hypersensitivity, as recommendations regarding medication use and diagnostic testing depend on this classification. Hypersensitivity is driven by immune reactions to medications and can be categorized according to the Gell and Coombs classification, as discussed in this chapter. Hypersensitivity to antibiotics account for a

majority of allergic drug reactions. However, reactions can occur to almost any drug, and allergy to anesthetics, chemotherapeutic agents, NSAIDs, biologics, and radiocontrast are important considerations. This chapter will review the mechanisms and clinical features that underlie allergy to each of these classes of medications. Furthermore, approaches to diagnosis and management of drug hypersensitivity will be discussed. The chapter will also review severe drug reactions, such as Stevens-Johnson Syndrome, toxic epidermal necrolysis, acute generalized exanthematous pustulosis, and drug rash with eosinophils and systemic symptoms, as these are life threatening reactions that require immediate recognition.

Keywords
Drug allergy · Hypersensitivity · Desensitization · Mechanism

21.1 Introduction

Adverse drug reactions (ADRs) occur when a medication produces any noxious, unintended, or undesirable effects. These ADRs can be classified into two types: predictable (Type A) and unpredictable (Type B). Type A drug reactions are dose-dependent "side effects" related to the pharmacology of the drug, and account for at least 80% of ADRs. For example, an adverse reaction of urinary retention to ipratropium would be classified as "Type A," given its mechanism of action as an anti-cholinergic drug.

In contrast, Type B reactions are unpredictable and typically unrelated to the pharmacology of the drug. Type B reactions can be further subdivided into drug intolerance, idiosyncratic or pseudoallergic reactions, and drug hypersensitivity. Drug intolerances occur when an individual experiences a known adverse reaction at subtherapeutic drug dosage in the absence of abnormalities in metabolism, excretion, and bioavailability of the drug. An example is development of tinnitus with aspirin. Idiosyncratic reactions are often driven by pharmacogenomic effects, where genetic factors related to drug metabolism, drug–receptor interactions, or other effects in pathways regulated by a drug, result in ADRs. An example (as discussed later in the chapter) is aspirin exacerbated respiratory disease, as class effect of NSAIDs that lead to overactivity of the leukotriene pathway that leads to bronchospasm and airway inflammation. Along these lines, pseudoallergies occur when mast cells and basophils (or other immune cells) are directly activated by a drug mechanism that is not due to a specific antigen–receptor interaction (like specific interaction between the drug and IgE, IgG, or T-cell receptor).

True hypersensitivity reactions are immunologically-mediated reactions that are specific to a drug. Initially described in 1963, the Gell and Coombs classification of hypersensitivity reactions has become the most widely used approach for categorizing immune-mediated drug reactions (Coombs and Gell 1963). This system subdivides drug allergies into four different types: immediate hypersensitivity (Type I), cytotoxic (Type II), immune-complex reactions (type III), and delayed hypersensitivity (Type IV). Although some immunologic drug reactions may have unknown or mixed mechanisms, majority of drug allergies still fall in one of four types of Gell and Coombs classification. True hypersensitivity to drugs is an uncommon mechanism of ADR, though commonly implicated.

21.2 Importance of History and Diagnostic Testing for Drug Hypersensitivity

Because patients with drug allergies only represent a small amount of ADRs, a comprehensive history should be obtained to determine if the patient's presentation fits with an immunologic drug reaction. An accurate and exhaustive account of a patient's clinical presentation can help guide further diagnostic testing and management. These include decisions about whether or not the drug-in-question can be re-administered safely. In the case of Type A reactions, the causative drug can usually be used again in lower doses, or a different drug in the same family can be used.

When taking a history, the physician should focus on the previous and current medication use as well as the timeline of events from the initial drug introduction to the onset of symptoms. Details of such indications for taking the drug, dose, duration, and nature of symptoms should be established. Any previous exposure to the suspected offending drug or any other drug in the same structural class must be determined. Other concurrent medications must be verified as some of these drugs may be confounders, or even be the inciting trigger for the drug reaction. Specific information about the pharmacology and immunogenicity of the patient's medications can help determine which drug is the culprit.

The onset of symptoms relative to course of treatment with the suspected offending drug can ascertain if the patient's current clinical presentation is compatible with an allergic drug reaction. A thorough review of systems will help characterize the involved organ systems. Further, any underlying condition that can mimic or predispose a patient to allergic drug reactions should be determined. This information is crucial when diagnosing an allergic drug reaction. For instance, true hypersensitivity to a drug requires a previous sensitizing course, so a reaction that occurs with the very first dose should question whether it is a true allergy.

Furthermore, the types of symptoms that constitute the reaction are crucial to establish a mechanism, and physical findings during an acute reaction can be vital. Hypersensitivity reactions often present with exanthema. Urticaria and angioedema, particularly when they develop rapidly (minutes to an hour after administration of drug), are usually associated with Type I hypersensitivity reactions and can be associated with involvement of other organs (bronchospasm, gastrointestinal symptoms, hypotension). In contrast, Type IV reactions can be macular or maculopapular and usually take more than 1 week to develop. Rashes associated with bullous lesions or mucosal involvement can help to identify severe reactions like Stevens-Johnson syndrome or toxic epidermal necrolysis, where immediate discontinuation of a drug may be lifesaving. Other presenting symptoms of immunologic drug reactions including fever, arthralgia, lymphadenopathy, hepatosplenomegaly, and pleural irritation can be helpful to categorize the reaction and determine severity.

Laboratory evaluation during an acute reaction can also be crucial to establish a mechanism. Elevated liver enzymes or serum creatnine can point to severe, systemic drug reactions. When blood eosinophilia is present (particularly at levels >1000 cells/μl) in this setting, one should consider a diagnosis of drug rash with eosinophilia and systemic symptoms (DRESS) (Mckenna and Leiferman 2004). Urine eosinophils can be useful to diagnose intersititial nephritis. Furthermore, skin biopsy can be helpful to diagnose drug reactions and differentiate from other diseases. The number and types of inflammatory cell infiltrate, immunostaining, and gross histological findings can assist with establishing a diagnosis.

21.3 Mechanisms of Drug Hypersensitivity

21.3.1 Type I Drug Reactions

Type I, or immediate hypersensitivity reactions, is driven by IgE directed against a drug. As the case with all IgE-mediated reactions, an initial sensitization phase is essential to the pathophysiology. This usually occurs during the prior treatment course with the suspected offending drug. Although this phase is asymptomatic, the stage is set for an allergic reaction. Most small molecule drugs (chemicals) are too small to be immunogenic. However, some drugs can bind covalently to proteins in the blood, like albumin. The drug (acting as a hapten) and the protein (carrier) together form a "neo-antigen," which appears foreign to the immune system (Fig. 1) (Parker et al. 1962). In some cases, the metabolite of a drug acts as a hapten (sulfonamide antibiotics). The hapten–carrier complex can be taken up by antigen-presenting cells (APCs), where the complex is proteolytically degraded, and the covalently-linked drug-peptide complex is presented via MHC-II complexes. The APCs migrate to lymph nodes, where they encounter

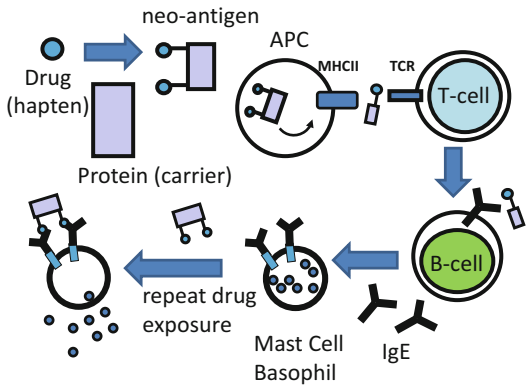

Fig. 1 Mechanism of type I drug hypersensitivity. The small molecule drug (hapten) covalently binds to a circulating protein (carrier). The complex appears foreign to the immune system (neo-antigen), is taken up by antigen presenting cells, proteolytically processed, and presented via MHCII to CD4+ T-cells. T-cells differentiate toward a Th2 phenotype, which promote class switching in B-cells towards IgE. The IgE binds to the surface of mast cells and basophils. On the next exposure to drug, the hapten–carrier complex binds to IgE and triggers degranulation

T-cells whose T-cell receptor (TCR) recognizes the drug-peptide complex, and drive differentiation of these cells down a Th2 lineage. These Th2-differentiated T-cells can promote IgE isotype switching in B-cells that produce antibodies that recognize the drug-peptide complex. These IgEs bind to mast cells and basophils, and will lead to activation of these cells on subsequent encounter of the drug. This process likely takes weeks, which explains why patients are asymptomatic during a course of therapy (like antibiotic treatment, with lasts typically for 7–14 days). Re-exposure to the drug results in activation of mast cells and basophils thereby producing the classic symptoms of allergic reactions that can include urticaria, angioedema, bronchospasm, nausea, vomiting, and hypotension. These symptoms typically have an onset of minutes to hours after re-exposure, and occur with the first dose. Furthermore, activation of mast cells and basophils require that two IgE molecules crosslink, so the hapten–carrier complex also needs to be "multivalent," or able to bind multiple molecules of IgE. Large molecular weight drugs, such as recombinant proteins or general anesthetics, can be large enough to bind to antibodies, and be multivalent. As such, these "complete" or "direct" allergens do not need to bind to a carrier. Humanized monoclonal antibodies, insulin, and vaccines are examples of direct immunogens.

The most widely-studied drug allergy is penicillin allergy. Penicillin is widely used and most of the population receives at least one course of penicillin by adulthood. The pathogenesis of penicillin allergy is drive by the classic hapten–carrier model. The beta-lactam ring of penicillin is a chemical group that makes them highly likely to covalently bind to circulating proteins (usually albumin). In normal physiologic conditions, penicillin readily forms various intermediates that can act as haptens (Parker et al. 1962). The most common is the penicilloyl moiety, also known as the major allergenic determinant of penicillin and is responsible ~60–85% of penicillin reactions. Penicillin can also isomerize to other intermediates such as penicilloate and penilloate that can also act as haptens. These minor determinant account for 10–20% of penicillin allergies.

Penicillin allergy is the most frequently reported drug allergy in the United States (Macy 2011). There are several known risk factors for developing penicillin allergies. Increased frequency of exposure to penicillin and parenteral route of administration have been hypothesized to contribute to the risk of developing a penicillin allergy (Contributors 2010). Having a personal history of atopic conditions such as allergic rhinitis or eczema and having a history of sensitivity to other drugs such as sulfonamides are also risk factors. Interestingly, children and elderly have lower rates of penicillin allergies and this may be attributed to an immature immune system in the former and a senescent immune system in the latter (Idsoe et al. 1968).

Although penicillin is the most commonly documented drug allergy, at least 90% of patients labeled with penicillin allergy are not truly allergic (Gadde et al. 1993; Blaxall et al. 2000). The true incidence of true penicillin allergy is about 1–3% (Contributors 2010). Patients labeled with penicillin allergies are often prescribed more expensive and broader spectrum antibiotics. Ultimately, this leads to higher health care costs and

has been associated with increased antibiotic resistance (Macy and Contreras 2014). In order to prevent needless avoidance of penicillin, and to identify the small number of patients who are truly allergic, it is crucial to perform allergy testing to this antibiotic.

21.3.1.1 Skin Testing to Diagnose Drug Allergy

Skin testing can be a crucial component of evaluation of Type I hypersensitivity drug reactions caused by penicillin and other drugs such as recombinant proteins, succinylcholine, and quaternary amines. For most of these drugs, skin prick testing with a full strength concentration followed by intradermal testing to 1:100 and 1:10 dilutions represents a typical protocol. However, the utility of skin testing to other small molecule drugs have poor skin test sensitivity. As skin testing to native drugs does not mimic the hapten–carrier as such, the sensitivity is usually low. In general, a negative test cannot rule out allergy but a positive test may represent a true allergy. However, this needs to be interpreted in the right context, as some drugs are irritating to the skin and cannot be tested in high concentrations. If skin testing will be performed to a drug without published irritating concentrations, it is best to perform multiple serial dilutions for prick and intradermal testing, and perform the test on a negative control subject in parallel. Another important limitation is that skin testing to drugs whose metabolites are the haptens (indirect haptens) is not useful. For instance, sulfonamide antibiotics are metabolized by the liver to a form that readily acts as a hapten, but is not present in the native drug that would be used for testing.

Penicillin testing is the most useful form of drug testing, as it is possible to use reagents that mimic the hapten–carrier complex. The major determinant can be mimicked using a poly-lysine polypeptide covalently-linked to penicillin in vitro. Furthermore, minor determinants can be produced chemically in vitro. When performed using major and minor allergic determinants, penicillin skin testing has a 99% negative predictive value (Gonzalo et al. 2007; Sogn et al. 1992). Thus, a negative result indicates no increased risk of type I hypersensitivity compared to the general population. However, the positive predictive value of penicillin skin testing has not been well studied (due to the inherent risk of challenging patients with positive skin tests), but some studies suggest it may be as low as 50% (Chandra et al. 1980; Sogn et al. 1992). Usually, patients with a positive test should avoid the medication and receive drug desensitization if penicillin is indicated. Major determinant of penicillin for skin testing is commercially available in the US, but not minor determinants. Most often, penicillin G can be substituted for the minor determinants with a slight drop in sensitivity to ~97% (Macy 2014). As a result, it is necessary to perform a challenge to penicillin in this setting to ensure that there was not a false negative skin test.

For drugs where skin testing is not available or not able to provide high sensitivity, a challenge can be considered. Usually this is performed by giving a small amount of a medication (10% dose) followed by a full dose. While this is the gold standard to determine true allergic status to a medication, it has to be weighed against risk. If a patient requires a specific medication on their allergy list, the decision whether to perform an oral challenge or drug sensitization depends on the history and clinical presentation of the suspected allergy and the clinician's index of suspicion for a true drug allergy. Oral challenge is typically performed in low risk situations where the degree of suspicion is low, while desensitization is done in moderate to high risk situations where there is a convincing history that fits with a recent allergic reaction.

Drug desensitization carries a risk of inducing an allergic reaction and requires a high amount of nursing care. The procedure must therefore be performed in a setting where the patient can be closely monitored such as the ICU. Prior to starting the desensitization, it is necessary to document that there are no other viable options as in the case of neurosyphilis. Epinephrine and oxygen must be available at bedside. The patient is initially administered a low dose, typically 1:10,000 dilution of the therapeutic dose. The dose is then increased two- to threefold every

Table 1 Sample drug desensitization table

Drug	Bag[a]	Dose #	Rounded dose (mg)	Rate (mL/h)	Infusion time (min)	Concentration (mg/mL)
Cefazolin	1	1	0.25	10	15	0.1
Cefazolin	1	2	0.5	20	15	0.1
Cefazolin	1	3	1	40	15	0.1
Cefazolin	1	4	2.5	100	15	0.1
Cefazolin	2	5	5	20	15	1
Cefazolin	2	6	10	40	15	1
Cefazolin	2	7	20	80	15	1
Cefazolin	2	8	25	100	15	1
Cefazolin	3	9	50	20	15	10
Cefazolin	3	10	200	40	30	10
Cefazolin	4	11	500	100	30	10
Cefazolin	5	12	750	100	30	15
Cefazolin	6	13	1000	100	30	20

[a]Bag concentrations: Bag 1, 5 mg/50 mL (0.1 mg/mL); Bag 2, 100 mg/100 mL (1 mg/mL); Bag 3, 500 mg/50 mL (10 mg/mL); Bag 4, 500 mg/50 mL (10 mg/mL); Bag 5, 750 mg/50 mg (15 mg/mL); Bag 6, 1000 mg/50 mL (20 mg/mL)

30 min. The cumulative dose must be kept track of especially when renal dosing. Desensitization can be maintained with once per day drug dosing. A sample protocol is shown in Table 1.

Penicillin is a member of the beta-lactam antibiotic class which includes cephalosporins, monabactams, and carbapenems. All these antibiotics contain a beta-lactam ring which is a four-member cyclic amide with three carbon atoms and one nitrogen atom. Because of their structural similarities, it was previously thought that there is a high rate of cross-reactivity among these antibiotic classes.

Studies have shown that the highest rate of cross-reactivity occurs between penicillin and first-generation cephalosporins, with a cross-reactivity rate of about 10% (Depestel et al. 2008). More recent studies have suggested that the actual cross reactivity rate may be even lower, but there is a lack of well-designed, prospective studies to address this question. Later generations of cephalosporins exhibit less cross-reactivity, which may be due to dissimilarity of the side chains between the two classes (Khan and Solensky 2010). If a penicillin-allergic patient requires a cephalosporin, a graded oral challenge with a cephalosporin containing a different side chain can be performed. Additionally, patients can also be skin tested to determine the presence of a cephalosporin allergy. Cephalosporin desensitization is also an option when indicated.

Carbapenem is another important beta-lactam antibiotic that was previously thought to have significant cross-reactivity with penicillin. In 2007, Romano et al. looked at 104 adult patients with skin testing-positive penicillin hypersensitivity (Romano et al. 2007). Of the 104 individuals, only 1 patient (0.9%) was skin test-positive for meropenem hypersensitivity. The remaining 103 were orally challenged to meropenem and were confirmed negative for meropenem allergy. A similar study involving 108 pediatric patients also reported similar findings of less than 1% cross-reactivity between penicillin and meropenem (Atanasković-Marković et al. 2008). Thus, while cross-reactivity between penicillin and carbapenem also exist, they occur at a much lower rate than previously expected.

Monobactams are beta-lactams that can be safely used in penicillin-allergic patients. The lack of a second ring structure makes monobactams unique, and may underlie the lack of cross-reactivity with penicillin.

It is also important to note that beta lactamase inhibitors (clavulante, sulbactam, tazobactam) are also beta lactams. The cross-reactivity to penicillin is low. However, allergy can occur to these agents specifically. As a result, patients that react to a penicillin–beta lactamase inhibitor combination need to be skin tested to both drugs (if available) and need to receive challenge to both.

21.3.2 Type II Hypersensitivity

Type II hypersensitivities are cytotoxic reactions mediated by IgM or IgG antibodies, and can be directed to a hapten–carrier complex. In type II reactions, the drug binds covalently to a cell surface protein on cells, which produces a neo-antigen. Typically, generation of IgG, or less commonly IgM, is responsible for hypersensitivity. The antibody then binds to the antigen on a cell surface, activates complement, and is cleared by macrophages.

The timing of the reaction may vary anywhere from 1 week to months after drug initiation. If a drug is stopped and reinitiated, symptoms can start within hours, due to presence of antibodies in circulation.

Cytolysis reactions can be serious and life threatening. Hemolytic anemias have occurred after treatment with quinidine, penicillin, and alpha methyldopa (Joint Task Force on Practice et al. 2010). A positive direct and indirect Coombs test may point to a drug specific IgG, complement, or Rh determinant autoantibody. Thrombocytopenia can occur secondary to a wide variety of medications, including heparin, vancomycin, and beta lactams. Drug–immune serum complexes mediate platelet membrane damage, which are then absorbed onto platelet membranes (Joint Task Force on Practice et al. 2010). As the case with most hypersensitivity reactions, management consists of withdrawal of the offending drug and future avoidance. Supportive care may be needed in the setting of severe anemia or thrombocytopenia.

21.3.3 Type III Hypersensitivity

Type III reactions are immune complex mediated, consisting of circulating antibody–antigen complexes. A drug carrier such as penicillin, procainamide, or a heterologous protein (e.g., animal thymoglobulin) acts as a soluble antigen and binds to IgG. Antigen–antibody equivalence leads to immune complex formation, which can deposit in tissue including blood vessels, joints, and kidney. The immune complexes activate complement or bind to Fc receptors on leukocyte cells. The resulting immune reactions can produce symptoms of vasculitis and organ-specific damage. Symptoms of serum sickness, including fever, rash, urticaria, lymphadenopathy, and arthralgias usually occur 1–3 weeks after drug exposure (Joint Task Force on Practice et al. 2010). Blood testing may show low complement levels (due to consumption) and skin biopsy can show immune complex deposition, though the sensitivity may be low. Management consists of withdrawal of the offending drug and symptomatic treatment with NSAIDs and antihistamines. Corticosteroids have not been well studied, but can be considered. In general, prognosis is excellent, but symptoms may last for weeks. It is generally recommended that patients continue to avoid the culprit drug, through it is not clear whether it can safely be used again years later.

21.3.4 Type IV Hypersensitivity

Type IV hypersensitivity, also known as delayed cell-mediated reactions are CD4+ or CD8+ T cell-mediated reactions. There are four subtypes, that are driven by the effects of T-cells on the following effector cells: monocytes (type IVa), eosinophils (type IVb), CD4/CD8 T cells (type IVc), or neutrophils (type IVd). There are two predominant mechanisms of T-cell activation. First, drugs can act as haptens, which then covalently link proteins, where are then taken up by APCs and presented to a T-cell, whose T-cell receptor (TCR) specifically recognizes the drug–peptide–MHC complex and lead to T cell activation (Fig. 2). Recently, a new concept of "p-i," or pharmacologic interaction with immune receptors has been proposed as a second model. In this concept, a drug does not act as hapten, but rather binds noncovalently to a MHC–peptide complex on the APC (without going through the typical antigen presentation pathway), facilitating interaction with a T cell receptor and leading T-cell activation (Pichler 2003; Schmid et al. 2006).

Reactions occur on a spectrum of severity, and from mild to severe. A macular drug reaction to antibiotics such as amoxicillin and sulfonomides is

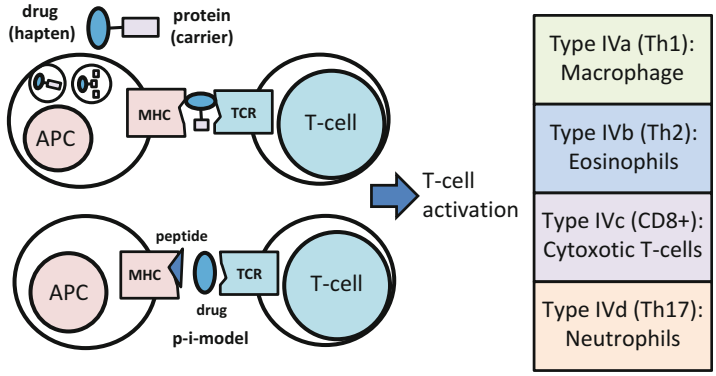

Fig. 2 Two mechanisms of T-cell activation in type IV hypersensitivity reactions. In the top model, a hapten–protein carrier is taken up by an APC undergoes proteolytic processing and is presented via MHC to a T-cell, whose T-cell receptor (TCR) recognizes the drug–peptide complex. In the bottom, "p-i" model, the drug binds noncovalantly to MHC–peptide complex, facilitating interaction with a T cell receptor (without proceeding through the antigen presentation pathway). T-cells can produced hypersensitivity via four main pathways (Type IVa–d), characterized by different effector cells and different clinical characteristics

one of the most common and mild in nature. These tend to be type IVa reactions and the drug can safely be used again. In type IVa reactions, T_H1 cells produce IFNγ and TNFα, which help to mediate macrophage activation. Patch testing may be used to verify contact dermatitis from topical medications.

Type IVb, IVc, and IVd reactions have the potential to be severe. Drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) is a type IVb hypersensitivity reaction. T_H2 cells mediate secretion of IL-4, IL-5, and eotaxin, which recruit eosinophils. It has been proposed that a concomitant viral infection such as HHV6 and EBV leads to T cell activation, although it is also possible that DRESS syndrome itself, leads to viral reactivation (Shiohara et al. 2007). Aromatic anticonvulsants (phenytoin, phenobarbital, carbamazepine), dapsone, sulfonamides, allopurinol are known instigators. It can present days to months after medication initiation, with cutaneous eruptions, fever, lymphadenopathy, and eosinophilia that can then lead to liver failure, kidney failure, and death (Peyrière et al. 2006). The offending agent should be stopped immediately, and systemic steroids (usually with a long, tapering course over weeks to months) are helpful. However, resolution may still take weeks and symptoms can progress after drug discontinuation.

Once thought to be on the spectrum of severe exfoliative dermatitis, erythema multiforme is now recognized to be a distinct entity. It can present with targetoid lesions, is typically self-limited, and usually virally mediated. On biopsy, a mononuclear cell infiltration is seen. The offending agent should be withdrawn, and steroids may be needed.

In contrast, Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are examples of severe Type IVc reactions are T-cell, mediated via effects of CD8+ T-cells. The TCR-drug-specific cytotoxic T-cells induce widespread apoptosis of epithelial cells, which causes confluent purpuric macules on face and trunk, mucosal erosions, fever, and constitutional symptoms. Eventually, there is end organ damage, including eyes, liver, kidneys, and lungs. In SJS, there is detachment of $<10\%$ of the body surface; in TEN, there is detachment of $>30\%$ of the body surface (Bastuji-Garin et al. 1993a). If there is detachment of between 10% and 30% of the body surface, it is an SJS/TEN overlap. Over 100 medications have been implicated, including sulfonamides, cephalosporins, anticonvulsants, and steroids. Mortality may be as high as 50% (Bastuji-Garin et al. 1993b). Given the seriousness of these reactions, patient should be treated in an ICU setting or burn unit with attention to fluid balance, nutrition, eye

care, and pain management. Skin care consists of debridement of necrotic epidermis, artificial membranes on skin, and biologic dressings. Sepsis with *Staphylococcus aureus* and *Pseudomonas* species are frequent. Treatment with IVIG (usually at doses over 2 g/kg) may be helpful (Viard et al. 1998; Bachot et al. 2003). Glucocorticoid use is controversial, but should be avoided late in the course of TEN (Roujeau and Stern 1994; Tripathi et al. 2000).

In type IVd reactions, neutrophils are the primary effector cells, and production of cytokines like CXCL8 and GM-CSF from drug-specific T-cells are important in disease pathogenesis (Schaerli et al. 2004). Antibiotics and calcium channel blockers have been the most common drugs to be implicated in acute generalized exanthematous pustulosis (AGEP), the most common type IVd reaction. Patients develop widespread pustules on an erythematous base on the face or intertriginous areas. Biopsy shows intraepidermal pustules, marked papillary edema, and polymorphus perivascular infiltrates with neutrophils (Speeckaert et al. 2010).

21.4 Hypersensitivity to Nonantibiotic Drugs

21.4.1 Anesthetics

Reactions to local anesthetics are commonly reported, and symptoms like angiodema, flushing, hives, and tachycardia may occur. However, true allergy to local anesthetics may be extremely rare. In our clinic, for example, we have challenged over 250 patients with reported reactions to lidocaine and none have had a positive challenge. Our experience is similar to a recent publication by Kvisselgaard et al., who found no evidence of allergy to local anesthetics in 162 patients that underwent testing (Kvisselgaard et al. 2017). It may be that other agents (like narcotics) may confound the picture, or that swelling as a result of trauma (in dental procedures for example) may lead to an erroneous label of allergy. Protocols for skin testing to lidocaine and other local anesthetics are described (Berkun et al. 2003). In general, skin prick testing to full strength of the local anesthetic followed by intradermal testing to 1:100 and 1:10 dilutions can be performed, and if negative, a small volume can be injected subcutaneously as a challenge dose. In the rare event of a confirmed allergy, a different local anesthetic can be used (and skin testing/challenge can help to confirm safety). There are two major chemical classes of anesthetics that differ based on their hydrophilic amine side chains (amino amide vs. amino ester), and the typical approach would be to use a member of a different family if true allergy is established.

In contrast, hypersensitivity to other anesthetic agents is well described. Traditionally, drugs associated with general anesthesia are known to cause type I reactions. Members of the muscle relaxant families (succinylcholine, rocuronium) are multivalent compounds that can illicit drug allergy (Joint Task Force on Practice et al. 2010). These fit a classic picture of sensitizing course followed by an acute reaction, usually minutes after administration, which can produce cutaneous symptoms (hives, angioedema), bronchospasm, or hypotension. Skin testing can be very useful to confirm the presence of a type I reaction. Other agents that may be given as part of anesthesia, like antibiotics, propofol, benzodiazepines, or even skin cleansers, can cause allergic reactions; so often these may need to be considered for skin testing if a patient has an allergic reaction during surgery. In addition, latex allergy should be part of the differential, as exposure can occur with products such as gloves, catheters, or rubber components in syringes or vial stoppers.

21.4.2 Radiocontrast

Radiocontrast agents can produce reactions that can range from mild (rash) to severe (anaphylaxis). Some contrast agents, particularly those with high osmolarity, are known to trigger mast cell degranulation via non-IgE pathways. The symptoms of these reactions are indistinguishable from IgE-mediated reactions and can include urticaria, angioedema, bronchospasm, and/or hypotension. Unlike IgE-mediated reactions,

however, these reactions can occur with the first exposure to the contrast. Most of the time, premedication with oral corticosteroids (prednisone 50 mg 13 h, 7 h, and 1 h prior to procedure) and antihistamines (diphenhydramine 50 mg, 1 h prior to procedure) are effective in preventing contrast reactions. Recent publications have indicated that some patients may develop IgE-mediated reactions to contrast, and premedication may not be helpful in this group (Sese et al. 2016; Morales-Cabeza et al. 2017; Trcka et al. 2008). In these cases, choosing a different contrast agent is recommended.

21.4.3 Angiotensin-Converting Enzyme Inhibitors

Angiotensin-converting enzyme (ACE) inhibitors commonly cause cough and angioedema, and these side effects may be mediated by overabundance of bradykinin, a substrate of ACE. The cough occurs anywhere from hours to months after initiation, is dry in nature, and is possibly mediated by bradykinin, substance P, or another mechanism (Nussberger et al. 2002). ACE inhibitor related angioedema can occur hours to years after drug initiation, and accounts for around 1/3 of patients presenting to the emergency department for angioedema (Banerji et al. 2008). Swelling is most often in the head and neck, but laryngeal edema can occur as well. For these patients, they should be switched to an alternate medication, such an angiotensin II receptor blocker.

21.4.4 Biologics

The development and use of immune modulators has dramatically increased in recent years. Reactions can develop as a result of the mechanism of action of these agents, because of hypersensitivity, or because of off-target effects. Some reactions are directly related to high cytokines or from cytokine release, like in capillary leak syndrome, which can be caused by IL-2, GM-CSF, and G-CSF. Patients can develop fever, pulmonary edema, ascites, pleural effusions, pericardial effusions, hypotension, hypoalbuminemia, multiorgan failure, and death. Cytokine dysregulation also lead to immune dysregulation, like autoimmunity.

IVIG is associated with infusion reactions varying from headache, fever, chills, tachycardia, anxiety, nausea, dyspnea, arthralgia/myalgias, and more seriously, hypotension. This reaction is possibly from immunoglobulin aggregates, antigen–antibody complexes, and contaminant vasoactive proteins leading to activation of complement (Ballow 2007).

Biologics can also cause hypersensitivity reactions, through antibody or cell-mediated effects (González-López et al. 2007). Antibodies that contain foreign sequences (like mouse), as the case for the chimeric antibody infliximab, have potential to cause IgE-mediated reactions. Reactions include urticaria/angioedema, hypotension/hypertension, chest pain, fever, and dyspnea (Campi et al. 2007). In some cases of non-IgE reactions, patients can continue with reduced rate or with premedication (Cheifetz et al. 2003). In other cases, it is necessary to switch to a different agent or perform desensitization every time a patient needs the medication. Other mechanisms of hypersensitivity can occur, and patients can have delayed serum sickness like reactions with urticaria/angioedema, fevers, and myalgias. Etanercept, and less commonly adalimumab, can cause these delayed reactions, which usually happen within first 2 months of therapy, and generally does not require discontinuation.

21.4.5 NSAIDs

Reactions to NSAIDs may occur via a variety of mechanisms that ranges from idiosyncratic to hypersensitivity. Aspirin and NSAIDs can cause urticaria, angioedema, anaphylaxis, underlying respiratory disease, and sometimes pneumonitis and meningitis. In the case of IgE-mediated reactions, there is a sensitizing dose of the medication, followed by reaction with the subsequent dose. Symptoms are typical of IgE-mediated reactions, and can produce anaphylaxis. Typically, IgE is specific to a particular NSAID and the patient

can use other NSAIDs without a reaction (Joint Task Force on Practice et al. 2010).

However, the mechanism of reaction can be difficult to elicit based on history. Patients with underlying chronic urticaria/angioedema may experience worsening of symptoms with NSAIDs. NSAIDs may also provoke urticaria/angioedema via idiosyncratic effects, perhaps through its effects on COX-1 inhibition (leading to excess leukotriene production). This may be the mechanism of cutaneous effects in patients with underlying chronic urticaria/angiodema, but can occur in patients without this diagnosis.

Often, idiosyncratic effects of NSAIDs are associated with respiratory symptom. Aspirin exacerbated respiratory disease (AERD) is a condition where patients with chronic respiratory diseases (asthma, rhinitis, sinusitis, nasal polyposis) develop respiratory reactions in response to aspirin or NSAIDs. In fact, it is expected that these symptoms are 100% cross-reactive to non-selective COX inhibitor (due to inhibition of COX-1 effects). It affects up to 20% of adult asthmatics, usually starts around 30 years old, and affects women more than men (Stevenson and Szczeklik 2006). After taking aspirin/NSAIDs, patient can develop rhinoconjunctivitis and bronchospasms, which can be severe enough to require mechanical ventilation. AERD usually presents as rhinitis, and then progresses to hyperplastic sinusitis, nasal polyposis, and possibly asthma. Gastrointestinal symptoms and urticaria are possible extrapulmonary manifestations. The development of this condition involves increased cysteinyl leukotriene production, increased inflammatory cells expression of cysteinyl leukotriene 1 receptors, and increased airway responsiveness to the leukotrienes. Aspirin/NSAIDs inhibit COX-1, leading to decreased prostaglandin E2 levels, thus increasing arachidonic acid metabolism through 5-lipoxygenase pathway, leading to increased cysteinyl leukotriene production. Since the effect is mediated through COX-1, AERD is not usually associated with COX-2 inhibitors or acetaminophen (though high doses >1000 mg has been reported to trigger respiratory symptoms in some patients). Diagnosis can be confirmed with a controlled oral challenge with aspirin. Desensitization to aspirin is an effective method to reduce polyp formation, reduce need for future sinus surgeries, improve asthma control, and allow patients to take NSAIDs (for pain control or use aspirin for cardiovascular reasons) (Stevenson 2009; Macy et al. 2007).

21.4.6 Chemotherapeutic Agents

Hypersensitivity reactions are associated with most chemotherapeutic agents. Taxanes (paclitaxel, docetaxel) can cause non-IgE-related immediate anaphylactoid reactions, often with first administration. Pretreatment with steroids and antihistamines helps to prevent anaphylaxis in most cases (Eisenhauer et al. 1994). Platinum compounds (cisplatin, carboplatin, oxaliplatin) can cause hypersensitivity reactions after several treatments, and are thought to be IgE-mediated. Cetuximab is a monoclonal antibody used in colorectal cancer, and can cause IgE-mediated anaphylaxis (Chung et al. 2008). Drug desensitization procedures have been successful (Castells et al. 2008).

21.4.7 Drug Reactions in HIV

Anti-retrovirals have been associated with reactions ranging from mild rashes to SJS/TEN. Abacavir is a nucleoside reverse transcriptase inhibitor associated with a hypersensitivity reaction of fever, rash, fatigue, respiratory symptoms, and GI symptoms in 4% of treated patients (Hetherington et al. 2001). Recent studies showed an association between the HLA-B*5701 gene and hypersensitivity, and subsequent screening reduced reaction rates significantly (Young et al. 2008). Observations show that patients with HIV have an increased chance of drug-induced reactions (Davis and Shearer 2008).

In HIV positive patients, the incidence of a generalized maculopapular eruptions, fever, and pruritis a few weeks after initiation of trimethoprim/sulfamethoxazole is significantly increased (Dibbern and Montanaro 2008). Induction of drug tolerance can be performed in these patients to use trimethoprim/sulfamethoxazole in

the future. Sulfonamide antibiotics (sulfadiazine, sulfamethoxazole) are a common cause of drug induced allergic reactions (Dibbern and Montanaro 2008). They are the most common cause of SJS/TEN (Roujeau et al. 1995). Delayed reactions to sulfonamides are mediated through the N4 aromatic amine and N1 substitute ring, but since nonantibiotic sulfonamides lack these structural components, they do not cross react with sulfonamide antibiotics (Strom et al. 2003).

21.5 Conclusion

Drug hypersensitivity reactions occur via different immunological mechanisms and have different clinical presentations. It is important to perform thorough history and physical exams, as these are crucial to characterizing the mechanism of drug allergy. It is particularly important to identify severe drug allergy syndromes (e.g., SJS, TEN, DRESS, AGEP), as these can be life threatening. Skin testing can be useful for Type I hypersensitivity reactions, but there is a great need for development of diagnostic tests for other hypersensitivity reactions. Although much of the drug allergy literature has focused on antibiotic allergy, hypersensitivity/pseudoallergic reactions to anesthetics, chemotherapeutic agents, NSAIDs, biologics, and IV contrast are important considerations. Evaluation and management of these drug reactions varies by the nature and mechanism of reaction to these medications.

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