

Nonallergic Drug Hypersensitivity Reactions

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Key Words

Nonallergic hypersensitivity · Pseudoallergy · Nonsteroidal anti-inflammatory drugs · Local anesthetic · Chemotherapy · Opiates · Anaphylaxis · Urticaria · Angioedema · Drug allergy

Abstract

Background: Nonallergic drug hypersensitivities, also referred to as pseudoallergic or anaphylactoid reactions, have clinical manifestations that are often indistinguishable from allergic reactions. **Methods:** We performed a PubMed search using the terms 'drug allergy, drug hypersensitivity, pseudoallergies, anaphylaxis and nonallergic drug reactions' and reviewed 511 publications dated between 1970 and 2012. A total of 160 papers that were relevant to the most common nonallergic drug hypersensitivity reactions were selected for discussion. **Results:** Nonallergic drug hypersensitivities do not involve either IgE-mediated (type 1) or delayed (type 4) hypersensitivity. Nonallergic hypersensitivities are commonly referred to as pseudoallergic or idiosyncratic reactions. The common nonallergic drug hypersensitivities are secondary to chemotherapeutic drugs, radiocontrast agents, vancomycin, nonsteroidal anti-inflammatory agents, local anesthetic reactions and opiates. Protocols for skin testing of radiocontrast, nonsteroidal anti-inflammatory agents, local anesthetics and chemotherapeutic agents have been developed, though most have not been validated or standardized.

Other diagnostic tests include in vitro-specific IgE tests, and the current 'gold' standard is usually an oral challenge or bronchoprovocation test. In the case of aspirin, even though it is not believed to be IgE-mediated, a 'desensitization' protocol has been developed and utilized successfully, although the mechanism of this desensitization is unclear. **Conclusions:** Diagnostic methods exist to distinguish allergic from nonallergic drug hypersensitivity reactions. The best option in nonallergic drug hypersensitivity is avoidance. If that is not possible, premedication protocols have been developed, although the success of premedication varies amongst drugs and patients.

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Introduction

Adverse drug reactions can affect up to 25% of outpatients and 10–20% of hospitalized patients [1–3]. However, true allergies to drugs constitute only a small portion of adverse drug reactions. Adverse drug reactions can be separated into type A, B, C, D and E reactions [4]. Type A reactions are predictable reactions that occur based on a known pharmacologic property of a drug, an example being the sedative effects of a first generation antihistamine like diphenhydramine. Type B reactions are unpredictable reactions that are not based on the pharmacologic property of the drug, but may instead be

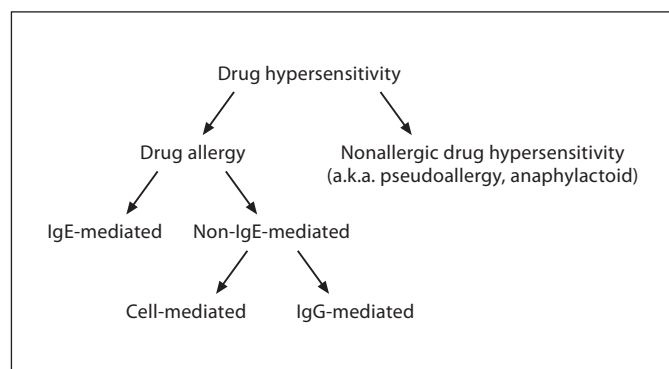


Fig. 1. Classification of drug hypersensitivity [5].

solely or partially dependent on the patient. Type C reactions are related to the cumulative dose of a medication and are dependent on both time and dosage [4]. Type D reactions are time dependent and manifest in a delayed fashion after the initiation of the drug [4]. Type E reactions refer to withdrawal symptoms after discontinuation of the drug [4]. Type B reactions can be further divided into intolerances, idiosyncratic drug reactions and immunologic drug reactions. Immunologic drug reactions are reactions that have a drug-specific immune response and may include IgE-mediated or cell-mediated drug allergy. Idiosyncratic reactions do not involve IgE- or cell-mediated immunologic mechanisms, and the mechanism is usually unclear [5]. Idiosyncratic drug reactions are also referred to as pseudoallergic reactions.

A consensus statement from the World Allergy Organization clarified the classification of idiosyncratic reaction and immunologic drug reactions. They defined hypersensitivity as objectively reproducible symptoms or signs initiated by exposure to a defined stimulus at a dose tolerated by normal persons [6, 7]. Thus, both idiosyncratic reactions (i.e. pseudoallergy) and immunologic drug reactions can be classified as drug hypersensitivity. If a drug hypersensitivity reaction has a specific immunologic mechanism it is known as a drug allergy. Furthermore, drug allergies can be classified as having an IgE-mediated mechanism or a non-IgE mechanism (fig. 1). Non-IgE mediated drug allergies can be further classified as cell-mediated or IgG-mediated (fig. 1). Drug allergy can be classified into four different groups based on the Gell Coombs classification (table 1). Nonallergic drug hypersensitivity reactions have also been termed pseudoallergic or idiosyncratic reactions. Table 2 provides a comparison of allergic and nonallergic drug hypersensitivity reactions.

Table 1. Gell and Coombs classification of drug allergy

Gell and Coombs	Mechanism	Example
Type I	IgE-mediated	Anaphylaxis Urticaria
Type II	complement-mediated (IgG or IgM)	Hemolytic anemia Thrombocytopenia
Type III	immune complex (IgG or IgM)	Serum sickness
Type IV	delayed hypersensitivity	Contact dermatitis Morbilliform eruptions Stevens-Johnson syndrome

Table 2. Differences between allergic and nonallergic drug hypersensitivity

	Allergic drug hypersensitivity	Nonallergic drug hypersensitivity
Mechanism	IgE- or cell-mediated	Nonimmunologic
Prior exposure	Required to drug or cross reacting drug	Not required
Diagnosis	History Skin test Graded drug challenge In vitro diagnostic tests	History Graded drug challenge
Cross reactivity	Drug with similar structure	Drugs with similar function (NSAIDs and narcotics)

Similarly to drug allergic reactions, nonallergic drug hypersensitivity reactions can present with urticaria, angioedema, or bronchospasm. The same effector cells involved in drug allergy such as basophils and mast cells are also involved in nonallergic drug hypersensitivity. These effector cells are activated by nonimmune mechanisms, and resulting clinical effects are induced by the ionicity of radiocontrast agents or direct stimulation of mast cells by vancomycin. Nonallergic drug hypersensitivity reactions can also present similarly to anaphylaxis. Anaphylaxis is defined as an acute hypersensitivity reaction that involves two or more organ systems, with or without urticaria, or by hypotension with or without other system involvement [8]. The diagnosis is supported when there is a temporal relationship between a known

Table 3. Differences between desensitization and challenge

	Drug challenge	Desensitization
Indication	Unlikely to be an allergic reaction	Allergic reaction established or likely
Situation	To determine if a drug is truly tolerable	To change a drug from being nontolerable to tolerable
Number of steps	Fewer	Higher
Interval of dosing	May be 10-fold or greater	Usually doubled
Time interval between doses	Depends on side effect being monitored	If IgE mediated, usually 30 min
Goals	To determine conditions in which drug may be tolerable	To induce temporary tolerance to medication
Immunological effect	No change	Change of host immune status from hypersensitive to tolerant

Table 4. Common chemotherapy infusion reactions

Cardiovascular	Hypotension, hypertension, tachycardia, bradycardia, palpitations, chest pain
Central nervous system	Dizziness, syncope
Dermatologic	Macular rash, urticaria, pruritus, angioedema, flushing
Endocrine	Fever, rigors, diaphoresis
Musculoskeletal	Myalgia, fatigue
Respiratory	Dyspnea, cough, bronchospasm, stridor, tachypnea, rhinitis, sneezing, hypoxemia

trigger and the event. When the mechanism does not involve an immunologic cause it has been referred to as anaphylactoid. Though still used in some circles, this is an outdated terminology, and the World Allergy Organization has proposed that reactions without an immunologic mechanism be referred as nonallergic anaphylaxis, and that the term anaphylactoid no longer be used [7].

For the purposes of our discussion, the term nonallergic drug hypersensitivity will be used in place of pseudo-allergy, and nonallergic anaphylaxis will be used in place of anaphylactoid. In addition, ‘desensitization’ protocols are presented for a variety of agents, but strictly speaking, if there is no sensitization, meaning the development of an immunologic sensitivity that is sustained over time as a result of the development of immunologic memory, then the term ‘desensitization’ is not entirely accurate,

and many of these protocols may in fact be administration regimens tested under different conditions to determine whether or not they can be tolerated without adverse side effects (i.e. a drug challenge; table 3).

Chemotherapeutic Agents

Chemotherapeutic agents have been implicated in local and systemic reactions (table 4). Some of these reactions, such as those resulting from platinum-based compounds, are thought to be classic IgE-mediated drug allergy. However, the mechanisms of drug hypersensitivity from other agents are unknown and are believed to be ‘nonallergic’ in nature.

Taxanes

Taxanes are chemotherapeutic agents that include paclitaxel and docetaxel. These agents have been approved for treatment for breast, ovarian, and non-small-cell lung cancer. Paclitaxel is an alkaloid derived from *Taxus brevifolia* and docetaxel is a semisynthetic compound produced from *Taxus baccata*. Common reactions include facial flushing (80%), chest discomfort (67%), back pain (51%), tachycardia (45%), erythematous rash (36%), hypotension (25%), pruritus/urticaria (20%) and facial swelling (18%) [9]. Many of the reactions to taxanes can occur upon the first administration which suggests a nonallergic drug mechanism [10]. The reactions can occur during or after the infusion of the taxane. The reactions may occur within minutes to several days of starting the infu-

sion [10]. The mechanism of the reactions to taxanes may be related to the vehicle used to prepare the agent. Paclitaxel is prepared with Cremophor-EL which is a compound made with amphiphilic lipid molecules and has been shown to cause activation of complement, potentially leading to production of anaphylatoxins [11].

Taxane adverse drug reactions are unpredictable. Since IgE is not involved, skin testing has not been a reliable predictor for hypersensitivity reactions, though an IgE-mediated event related to taxane administration has been reported [12]. The treatment of a taxane drug reaction involves premedication regimens and/or 'desensitization'. The use of premedication regimens with steroids and antihistamines has been shown to decrease the frequency of taxane adverse reactions from 30% [13] to 2–4% [14]. One premedication regimen for paclitaxel involves intravenous administration of 20 mg of dexamethasone 12 and 6 h before infusion, intravenous administration of 50 mg of diphenhydramine 30 min before infusion, and intravenous administration of 300 mg of cimetidine or 50 mg of ranitidine 30 min before infusion [15]. Several studies have shown that giving only one course of dexamethasone 30 min before infusion may be as effective as two courses [16, 17]. Yet, a study comparing single-dose intravenous dexamethasone with two doses of oral dexamethasone premedication showed a higher rate of hypersensitivity reactions with the single dose regimen (17.3 vs. 7.5%, respectively) [18]. 'Desensitization' protocols for taxanes have been described, the most recent of which was published by Castells et al. [19], outlining a 12-step protocol that took 5.8 h and was successful in desensitizing to paclitaxel for all patients who underwent the protocol.

L-Asparaginase

L-asparaginase is an enzyme derived from either *Escherichia Coli* (Elspar), *Erwinia chrysanthemi* (Kidrolase, Erwinase) or *E. Coli* asparaginase that is attached to polyethylene glycol (Oncaspar). It is used in the treatment of acute lymphoblastic leukemia and has been associated with frequent hypersensitivity reactions. The route of administration determines the rate of frequency of reaction to the drug. Studies using L-asparaginase have documented hypersensitivity reactions occurring in 6–43% of cases [20]. When L-asparaginase is given as a single agent the reaction rate occurs more frequently (25–43%) than when it is given in combination with other chemotherapeutics (less than 10%) [21]. However, hypersensitivity reactions

with L-asparaginase are much lower with subcutaneous or intramuscular administration than with intravenous administration [22]. Therefore, the drug is no longer given intravenously.

Reactions typically occur within one to several hours of administration of the drug, and manifest as pruritus, urticaria, skin rash, bronchospasm and hypotension [23]. However, anaphylactic reactions can occur in less than 10% of cases [24]. The mechanism of hypersensitivity reactions to L-asparaginase has been proposed to be an IgE-mediated mechanism based on findings of IgE anti-asparaginase antibodies [25]. However, others have suggested a complement-mediated mechanism with IgM and IgG antibody complexes [26].

Skin testing with L-asparaginase has been previously described; however, the protocol is not standardized and has been associated with false-positive and false-negative reactions [27]. The recommendation to skin prick test using 0.1 ml of a 20 IU/ml dilution of the drug before the first dose or whenever an interval of 1 week or greater has elapsed between doses [27]. If the skin test is positive then the drug should not be given or desensitization to the drug should be performed.

Several options exist to treat hypersensitivity reaction to L-asparaginase. One option is to switch to a different L-asparaginase drug preparation. Patients who react to the *E. Coli*-derived L-asparaginase can be switched to the *Erwinina*-derived enzyme with low rates of recurrent reaction [28]. In addition, the patient can be switched to the polyethylene glycol formulation, which when given intramuscularly is associated with lower hypersensitivity reaction rates [27]. The reaction rates to polyethylene glycol formulation are much lower compared to the other formulations and it is now being used as a first line preparation for L-asparaginase. If the patient cannot tolerate any of the L-asparaginase formulations, 'desensitization' must be performed if the patient is to continue receiving the chemotherapy.

Epipodophylotoxins

The epipodophylotoxins are antimitotic agents and include teniposide and etoposide. Teniposide is used to treat neurologic and hematologic malignancies while etoposide is used to treat testicular cancer and small-cell lung cancer. Both these agents are given intravenously but etoposide can also be given orally. Hypersensitivity reactions to these drugs include dyspnea, hypotension and bronchospasm and are usually mild in nature [29].

The reaction rate for teniposide and etoposide ranges from 6 to 41% for hypersensitivity reactions and 0.7 to 14% for anaphylactic reactions [30, 31]. Reactions can occur on the first infusion or during subsequent infusions [27]. Moreover, they can occur minutes to hours after initiating the infusion [32].

The exact mechanism for the hypersensitivity reactions is unknown. Similar to taxanes, the solvent in which the epipodophylotoxins are dissolved may play a role in the mechanism of hypersensitivity reactions. Intravenous teniposide is dissolved in Cremophor and intravenous etoposide is dissolved in polysorbate (Tween) 80. It is thought the solvent plays a role because oral etoposide has not been associated with hypersensitivity reactions [23]. In addition, etoposide phosphate, a water soluble prodrug without polysorbate 80, has been shown in several cases not to induce reactions in patients with reactions to etoposide dissolved in polysorbate 80 [32, 33]. This has been a controversial issue. Nolte et al. [34] showed that basophils from sensitized patients degranulated upon exposure to teniposide but not to Cremophor. This suggests that the dissolvent indeed may not play a role in hypersensitivity reactions and that the compounds themselves are the cause of the reactions.

A slow infusion rate and premedication with antihistamine has been shown to prevent reactions upon challenge with the epipodophylotoxins. This protocol was demonstrated to be successful in 78% of cases [35]. Moreover, several published cases have shown that patients with reactions to etoposide can be safely treated with etoposide phosphate [32, 33]. In a case report reported by Collier et al. [33], 6 patients with hypersensitivity reactions to etoposide tolerated etoposide phosphate infusion. Only 1 out of the 6 patients required premedication prior to etoposide phosphate.

Radiocontrast Agents

Radiocontrast agents can be separated by virtue of their physical characteristics of osmolality, ionization in solution and chemical structure [36]. Based on these characteristics, these agents can be separated into four different groups: ionic monomers, nonionic monomers, ionic dimers, and nonionic dimers [36]. Hypersensitivity reactions to contrast media can be divided into immediate (occurring within 1 h of contrast administration) and delayed reactions (occurring over 1 h after contrast administration) [37].

Common clinical manifestations of immediate reactions include pruritus, urticaria, angioedema, abdominal pain, bronchospasm, laryngeal edema and hypotension [22]. Nonimmediate reactions commonly involve pruritus and exanthems (macular or maculopapular eruption) that are mild and self-limiting [38]. However, severe life-threatening reactions have been reported, including Stevens-Johnson syndrome, toxic epidermal necrolysis or 'anaphylactic' shock. The prevalence of these severe adverse reactions ranges from 0.03 to 0.16% [39].

The prevalence of immediate type reactions is 3.8–12.7% in patients with high-osmolar, ionic contrast media versus 0.7–3.1% in patients receiving low-osmolar non-ionic contrast media [22, 40–42]. In addition, the prevalence rate of severe immediate reactions is between 0.1 and 0.4% for ionic contrast media and between 0.02 and 0.04% for nonionic contrast media [22, 40–42]. Even though the rate of reactions for nonionic compounds is less than the rate for ionic compounds, the death rate is the same between the two agents with an occurrence of 1 in 100,000 examinations [43]. For nonimmediate reactions the range of prevalence rates has been wide (between 0.5 and 23%), in part because of the difficulty in determining if a reaction that occurs hours or days after contrast media can be attributed to the radiocontrast [37]. While these reaction rates are low, when one considers that there are 60 million doses of iodinated contrast used worldwide each year, it can still be a significant problem.

Several important risk factors have been determined for the development of an immediate reaction to contrast media. These include a previous history of an immediate reaction to a contrast agent, a history of asthma and history of atopic diseases (allergic rhinitis, atopic dermatitis or food allergies) [22]. Certain medications such as beta-blockers or nonsteroidal anti-inflammatory drugs may increase the risk, but no consensus has been reached on this [44]. Seafood allergy is not a risk factor for contrast hypersensitivity reaction even though a recent survey indicated that this is a common misperception [45]. This misconception was created from an association between contrast agents containing iodine and the high iodine content in seafood. However, tropomyosin is the main allergen found in shellfish [46], and is structurally different from iodine in the contrast agent. Moreover, most reactions to contrast media are non-IgE mediated and unlikely to be a result of cross sensitization between the iodine in shellfish and contrast media [45]. While there has been an association between patients with seafood allergy and contrast reaction [47], the likely explanation can be attributed to the fact that seafood allergy is a common

cause of food allergy and atopic patients have a higher risk for contrast reaction.

The mechanisms behind the immediate reactions to contrast media are not entirely clear. Several mechanisms may be involved. The osmolality of the contrast media may be a trigger for direct histamine release from mast cells. Alternatively, certain characteristics of the chemical structure of the contrast agents may also stimulate direct histamine release [48, 49]. It is also possible that complement activation [50, 51] may play a role. This also does not answer the question as to why osmolality and chemical structure does not lead to reactions in all individuals receiving radiocontrast media [52]. Case reports have suggested a role for an IgE-mediated mechanism [53, 54]. This may be the mechanism in a small number of cases but cannot explain all of the cases. Nonimmediate hypersensitivity reactions with the involvement of T cells may present another mechanism of action [48, 49, 55]. The evidence for this comes from skin biopsies performed in patients with delayed reactions to contrast media which showed infiltration of CD4+ and CD8+ lymphocytes [49]. Further evidence of a T cell-mediated process comes from patch testing and delayed intradermal testing [55]. Several studies have shown that patients with delayed hypersensitivity reactions had positive reactions to both delayed intradermal testing and patch testing to the contrast media [37, 52, 56]. Lastly, positive lymphocytes activation tests to contrast agents have been demonstrated, although the number of patients in the study was very small [49].

For immediate contrast reactions, if there are clinical manifestations of anaphylaxis then a serum tryptase should be checked within 3 h of the reaction. Serum tryptase is a marker of mast cell activation and a serum tryptase will be elevated in any IgE-mediated drug allergy if checked within 3 h of the reaction. If radiocontrast hypersensitivity reactions do not involve an IgE-mediated mechanism, then it would follow that skin testing is of limited value. However, there are several recent studies which suggest that skin testing with contrast media may be able to identify patients with immediate or delayed contrast hypersensitivity reactions [57–59]. In a European multicenter study, 122 patients with a history of immediate reactions to contrast were tested with skin prick (1:1 dilution of contrast agent) and intradermal skin tests (1:10 dilution of contrast agent) within 2–6 months of their reaction [57]. Either skin prick or intradermal skin tests eliciting a positive reaction occurred in 50% of patients with immediate hypersensitivity reactions to contrast media. In 28 cases, the offending contrast agent

Table 5. Classification of radiocontrast agents

Ionic	Nonionic (low osmolality)	Nonionic (isoosmolal)
Diatrizoate	Iohexol	Iodixanol
Iothalamate	Iopamidol	
Ioxaglate	Ioversol Iopromide Ioxilan	

was known, and of these, skin test to the agent was positive in 86% of cases, indicating the presence of an IgE-mediated event. This was further supported by the observation that 96% of controls had negative reactions to the skin tests.

Another recent study evaluated 26 patients with immediate hypersensitivity reactions to contrast agents. Intradermal skin tests were performed at several dilutions to the contrast agent implicated by the patient's history [58]. Positive intradermal skin tests were found in 19 patients (74%) and 7 patients reacted to the agent at an undiluted strength. The patients were tested to ten different contrast media agents. There was little cross-reactivity to other contrast agents with only 7% of patients testing positive to another commercial cross-reacting contrast agent. However, false positive and false negatives could have occurred in these studies. A study evaluated 29 patients who had a history of contrast media reaction over the last 9 years. The patients were skin tested and rechallenged with contrast agent. The results showed a negative predictive value of 96.6% and none of the reactions in skin test-negative patients was severe [60].

Prevention of reactions to radiocontrast media involves the use of a different contrast agent or use of a premedication protocol. If a patient reacts to the contrast agent then another agent must be used [37]. Ionic high osmolar agents are associated with higher reaction rates compared with nonionic low osmolar agents [40–42]. Therefore if the patient developed a reaction to an ionic high-osmolar agent then they should be switched to a nonionic lower osmolar agent [61]. In addition, patients who develop reactions to nonionic lower osmolar agents should be switched to a nonionic isomolar agent [61]. A list and categorization of radiocontrast agents is shown in table 5. Based on the American College of Radiology guidelines, it is recommended that patients with a history of contrast reactions receive premedication prophylaxis

Table 6. A pretreatment protocol for radiocontrast media-related allergy [62–64]

Radiocontrast media pretreatment protocol

Prednisone 50 mg given 13, 7 and 1 h before procedure
Diphenhydramine 50 mg IV given 1 h before procedure

[61]. There is published evidence showing a reduction in reaction rates with the use of a premedication protocol from 17 to 60% down to 9% [62–64]. A premedication protocol is shown in table 6 [62–64]. These studies have shown a decrease in immediate hypersensitivity reactions to contrast agents. To date there is no evidence documenting prevention of delayed hypersensitivity reactions to contrast agents using pharmacologic prevention.

The efficacy of a pretreatment protocol is not universal and there have been case reports of patients who developed repeated reactions despite use of a pretreatment protocol [65, 66]. In addition, in a review of the literature on premedication protocols [67], it was found that the usefulness of a premedication regimen is doubtful as a large number of patients had to be treated in order to prevent one reaction. However, if the patient does have a reaction even after premedication, the reaction will usually be of the same severity as the original reaction. A study performed by Davenport et al. [68] reviewed repeated reactions to low osmolality contrast. 81% of repeated reactions were of a severity that was similar to the original reaction and only 8% had a reaction that was more severe than the original reaction. From these observations, it appears to be relatively unlikely that a reaction to contrast media will become more severe with subsequent reactions.

Vancomycin

Vancomycin can cause two types of adverse drug reactions: red man syndrome and anaphylaxis [69]. Red man syndrome is a drug hypersensitivity reaction to vancomycin that can occur in 5 to 14% of adults [70]. It typically occurs when vancomycin is administered parenterally, but there have been case reports of red man syndrome occurring when vancomycin is administered orally [71–73]. The syndrome usually involves symptoms of pruritus, flushing and an erythematous rash that involves the upper body and neck [74]. Hypotension, chest pain and muscle cramping have also been reported with

this syndrome [75, 76]. The symptoms usually occur within several minutes after infusing vancomycin, but delayed reactions can occur at the end of a 90–120 min infusion [70].

Red man syndrome is a nonallergic drug hypersensitivity reaction and is thought to involve direct stimulation of mast cells by vancomycin without involvement of IgE. In rats vancomycin has been shown to directly degranulate mast cells [77, 78]. Several studies have shown an increase in serum histamine levels associated with red man syndrome [79, 80]. The reaction is related to the rate in which vancomycin is infused. Usually infusions of less than 1 h are associated with reactions and slower infusions have been shown to be less likely to induce a similar adverse reaction. In a randomized double blind trial involving 10 adult males, vancomycin was administered either as a 2- or 1-hour infusion [81]. With the 1-hour infusion, 8 out of 10 patients developed red man syndrome reactions. Only 3 out of 10 patients developed red man syndrome with the 2-hour infusion. Therefore, it is recommended that patients receive vancomycin infusion over at least 1 h to prevent red man syndrome [82].

The concomitant use of certain medications that cause nonspecific histamine release from mast cells may precipitate red man syndrome in patients receiving vancomycin infusion. These include opioids, radiocontrast agents and muscle relaxants [83]. Avoiding concomitant narcotics in patients receiving infusion of vancomycin has been shown to prevent the recurrence of red man syndrome [83].

Premedication with diphenhydramine has been shown to prevent red man syndrome. Wallace et al. [84] administered 1 g of vancomycin over 1 h to 17 patients pretreated with placebo and 16 patients pretreated with 50 mg of intravenous diphenhydramine 1 h before the infusion. In the placebo-treated group, 47% of patients developed red man syndrome, while in the diphenhydramine group none of the patients developed the reaction. Therefore, pretreatment with diphenhydramine prior to vancomycin can be a recommended approach in preventing red man syndrome.

If clinical features of red man syndrome appear, then the vancomycin infusion must be stopped immediately and treatment with diphenhydramine should be instituted. If the patient is hypotensive, intravenous fluids should be administered. The red man syndrome reaction must be distinguished from anaphylaxis. Symptoms of dyspnea, wheezing, stridor or hives would suggest anaphylaxis and intramuscular epinephrine should be administered promptly [85].

Table 7. Classes of NSAIDs

COX-1 and COX-2 inhibitors	Inhibitors of COX-2 at low doses but COX-1 inhibitors at higher doses	Selective COX-2 inhibitors	Weak COX-1 or COX-2 inhibitors
Ibuprofen	Nimesulide	Celecoxib	Salsalate
Naproxen	Meloxicam	Rofecoxib	Acetaminophen
Naproxen sodium		Valdecoxib	
Indomethacin		Etoricoxib	
Diclofenac		Parecoxib	
Sulindac		Lumiracoxib	
Piroxicam			
Ketoprofen			
Ketorolac			
Nabumetone			
Fenoprofen			
Oxaprozin			
Flurbiprofen			
Meclofenate			
Tolmetin			
Mefenamic acid			
Diflunisal			
Etodolac			

Nonsteroidal Anti-Inflammatory Drug Hypersensitivity Reactions

Nonsteroidal anti-inflammatory drugs (NSAIDs) are some of the most common over the counter drugs used. NSAIDs inhibit cyclooxygenases (COX) which are involved in the conversion of arachidonic acid into prostaglandins and thromboxanes. Two types of COX can be found in the body. COX-1 is constitutively expressed in all cells in the body, but COX-2 is inducible by cytokine stimulation, and is expressed only in inflammatory cells. NSAIDs such as aspirin will block both COX-1 and COX-2 whereas selective COX-2 inhibitors such as celecoxib blocks only COX-2. This is why COX-2 inhibitors are not associated with the gastric side effects as seen with the COX-1 inhibitors. A list of the different NSAIDs and the forms of COX that they inhibit is shown in table 7.

Hypersensitivity reactions to NSAIDs were first described by Widal et al. [86] in their paper on the association of asthma, aspirin sensitivity and nasal polyps and this has been referred to as Samter's triad. Since then, multiple types of reactions to NSAIDs have been described. These NSAID reactions can be categorized into nonallergic or allergic reactions. They include NSAID-induced rhinitis/asthma (also known as Aspirin Exacerbated Respiratory Disease), NSAID-exacerbated urticar-

ia/angioedema in patients with underlying chronic idiopathic urticaria, multiple drug-induced urticaria/angioedema without underlying disease and single drug-induced anaphylaxis [87]. Table 8 illustrates the characteristics of the common NSAID reactions.

Aspirin-Exacerbated Respiratory Disease

Aspirin-exacerbated respiratory disease (AERD) is characterized by nasal polyposis, asthma, chronic rhinosinusitis and sensitivity to aspirin [88]. The term signifies that the disease progresses whether or not aspirin is ingested but aspirin can exacerbate the clinical manifestations [88]. The disease is an acquired disorder with onset of symptoms between the 2nd and 5th decades of life, with an average age of onset of 34 years seen in one study [89]. It progresses over the years and usually initially manifests as nasal congestion, with patients commonly reporting having an upper respiratory infection that never resolves [90]. Subsequently, they will develop chronic rhinosinusitis with nasal polyposis [90]. The asthma component may have been present since childhood, or may appear within several years after onset of chronic rhinosinusitis with polyposis [91]. The sinusitis is severe and patients may have repeated polypectomies if the AERD is left untreated [92–94]. After ingestion of aspirin or other NSAIDs, nasal congestion, rhinorrhea, periorbital edema, conjunctival injection, shortness of breath and wheezing may develop within 30–120 min [88]. The provoking dose of aspirin or NSAID can vary significantly from 10 up to 600 mg [92].

Jenkins et al. [95] performed a meta-analysis in 2004 and extracted data from 21 papers (15 in adults and 6 in children) that provided information on the prevalence of AERD. The study population in most of these studies included asthmatics followed as outpatients. The overall prevalence was much higher when oral provocation was done than when history alone was used to determine aspirin sensitivity. The prevalence among asthmatics was much higher in adults than in children (21 vs. 5% by oral provocation testing and 2.7 vs. 2% by history). In another study, AERD was estimated to be present in 4.3–11% of adult asthmatics [96], but in 34% of asthmatics who also have nasal polyposis and chronic rhinosinusitis [90]. In a study of 300 patients in the USA, the female to male ratio was found to be 3:2 [89]. There is no predilection for AERD based on race, ethnicity or family history [89]. The asthma in AERD is usually more severe, requires higher doses of inhaled corticosteroids and is more frequently

Table 8. Different categories of NSAID hypersensitivity reactions

NSAID reaction	Clinical manifestations	NSAID intolerant	Pathologic mechanism	Treatment
Aspirin-exacerbated respiratory disease	Rhinosinusitis Nasal polyposis Asthma	All COX-1 inhibitors	COX-1 inhibition	Avoid COX-1 inhibitors ASA 'desensitization'
NSAID-exacerbated urticaria/angioedema	Chronic urticaria with exacerbation of urticaria or angioedema with ingestion of NSAID	All COX-1 inhibitors	COX-1 inhibition	Avoid COX-1 inhibitors Recommend COX-2 inhibitors if oral challenge negative
Multiple NSAID-induced urticaria/angioedema	Urticaria/angioedema induced by NSAIDs with no underlying chronic skin disorder	All COX-1 inhibitors	COX-1 inhibition	Avoid COX-1 inhibitors Recommend COX-2 inhibitors if oral challenge negative
Single NSAID-induced reaction	Urticaria/angioedema/anaphylaxis induced by single NSAID	Specific COX-1 inhibitor reacted to	IgE-mediated	Avoid specific COX-1 reacted to

associated with near fatal asthma when compared with non-AERD asthmatics [97–99].

All NSAIDs that are COX-1 inhibitors (including aspirin) will cause exacerbations in patients with AERD. A list of NSAIDs and their classification are shown in table 6. Paracetamol and salsalate are weak COX-1 inhibitors and can be tolerated in patients with AERD up to a certain dose. With regard to paracetamol, most patients with AERD can tolerate up to 650 mg with no reaction, but 28% develop mild asthmatic reactions when ingesting 1,000 mg [90]. Salsalate can be tolerated up to a dose of 2,000 mg per day, but doses above this may cause mild respiratory reactions in 10% of AERD patients [98]. NSAIDs that are COX-2 inhibitors at lower doses, but which have partial COX-1 inhibition at higher doses include meloxicam and nimesulide. These agents can usually be given safely to patients with AERD, but rarely have been associated with mild reactions. COX-2 inhibitors can be safely given to AERD patients based on several trials in which patients with AERD were challenged with COX-2 inhibitors [100–103]. However, there have been case reports of AERD patients reacting to COX-2 inhibitors [104, 105]. The mechanism of COX-2-related AERD is unknown and it may be prudent in patients with known AERD to perform an oral provocation test with the COX-2 under close observation before recommending its use [106]. Currently, celecoxib is the only COX-2 inhibitor available in the USA.

The pathogenesis of AERD stems from the effect of COX-1 inhibitors on the eicosanoid lipid mediator pathway. This pathway is involved in the production of leukotrienes and prostaglandins from arachidonic acid.

Phospholipids found in the cell membrane are converted to arachidonic acid through several steps involving hydrolysis of fatty acids. From there arachidonic acid can be shunted down either the cyclooxygenase pathway to produce prostaglandins or down the cysteinyl leukotriene pathway to produce the leukotrienes. The cyclooxygenase pathway is catalyzed by the enzymes COX-1 and COX-2. Both COX-1 and COX-2 are involved in the conversion of arachidonic acid to the prostaglandins PGD₂, PGF₂, PGI₂ and PGE₂. Of the prostaglandins, PGE₂ has been the most extensively studied in the pathogenesis of AERD. The effects of PGE₂ depend on which receptor it binds to. Within the lung, binding of PGE₂ to the EP2 receptor causes smooth muscle relaxation and inhibits methacholine-induced bronchoconstriction [107]. Moreover, PGE₂ is involved in decreasing activated mast cell release of cysteinyl leukotrienes (which causes bronchoconstriction and recruitment of inflammatory cells) [108]. Pretreating AERD patients with inhaled PGE₂ will prevent aspirin-induced bronchoconstriction [109]. Thus, PGE₂ plays a pivotal role in reducing inflammation in the lung and the associated bronchoconstrictive effects.

In AERD patients, peripheral blood cells at baseline produce less PGE₂ compared to healthy controls [110]. In addition, there is decreased expression of the EP2 receptor in inflammatory cells in the nasal mucosa of AERD patients with chronic rhinosinusitis [111]. Moreover, epithelial cells from nasal polyps that are removed from AERD patients produce less PGE₂ at baseline compared with non-AERD asthmatic controls [112]. Thus, at baseline AERD patients already produce decreased levels of

Table 9. Protocol for oral aspirin challenge for diagnosis of AERD [121, 122]

Time	Day 1	Day 2	Day 3
8 a.m.	Placebo	20.25 mg	162.5 mg
11 a.m.	Placebo	40.5 mg	325 mg
2 p.m.	Placebo	81 mg	

Measure FEV₁ 7 days before oral aspirin challenge. FEV₁ should be greater than 70% predicted and greater than 1.5 liters. Measure FEV₁ every hour for 3 h. There must be less than 10% variability.

Start intravenous line with heparin lock.

Use a pill cutter and a 81-mg aspirin tablet to obtain aspirin doses. Doses can be increased every 3 h or 90 min if the patient is not exhibiting any reaction.

FEV₁ and clinical assessment should be performed at least every 1–1.5 h or with any symptoms.

Reactions usually occur with one of the early doses (usually 81 mg). When the reaction occurs treat with one of the medications found in table 10. This dose is known as the provoking dose. Lower respiratory tract reaction is defined as a 15% decrease in FEV₁ from baseline.

Wait at least 3 h and for symptoms to completely resolve. Once this has occurred, repeat the provoking dose and if it is tolerated, dose escalation can continue.

PGE₂, and this effect is amplified upon administration of COX-1 inhibitors, leading to a proinflammatory state within the lungs and sinuses.

In the lipoxygenase pathway, arachidonic acid can also be converted to leukotrienes through the enzyme 5-lipoxygenase and leukotriene C4 synthase. The cysteinyl leukotrienes, LTC₄, LTD₄ and LTE₄ are known to cause bronchoconstriction, vasodilation and mucous secretion [113]. At baseline, AERD patients have higher levels of leukotrienes in bronchoalveolar lavage fluid compared with asthmatic controls [114]. In addition, increased levels of LTE₄ have been found in the urine of patients with AERD at baseline and after aspirin challenge [115]. Bronchial biopsies from AERD patients have also been shown to have elevated levels of leukotriene C4 synthase [116]. Leukotrienes bind to the cysteinyl leukotriene receptors cysLT₁ and cysLT₂. Most of the proinflammatory actions in the lung and upper airway are mediated through the cysLT₁ receptor [117]. Sousa et al. [118] showed that among patients with chronic rhinosinusitis with nasal polyposis, those with the full AERD syndrome had more nasal inflammatory leukocytes expressing the cysteinyl leukotriene receptors compared with non-AERD patients (i.e. non-aspi-

Table 10. Treatment of oral aspirin challenge reactions [121, 122]

Reaction	Treatment
Pulmonary	Albuterol inhaler with spacer or nebulizer: inhale 5 breaths every 5 min until comfortable
Laryngeal	Racemic epinephrine nebulized treatment: 5 inhalations
Nasal	Oral antihistamines and/or nasal decongestants
Ocular	Topical antihistamine
Urticaria/angioedema	Intravenous diphenhydramine
Hypotension	Epinephrine intramuscularly. Follow anaphylaxis practice parameter [85]

rin-sensitive patients). Since PGE₂ impairs synthesis of leukotrienes, the reduction in PGE₂ levels induced by COX-1 inhibitors leads to an increase in leukotriene levels. Thus not only do AERD patients have increased levels and production of leukotrienes, they also have higher expression of receptors for these leukotrienes, and this leads to an even greater proinflammatory state in the lungs and sinuses.

The diagnosis of AERD requires an oral aspirin challenge. This is so because in a study performed on 50 asthmatic patients with chronic rhinosinusitis and nasal polyposis with a history of an asthma attack after ingestion of an NSAID, 8 of the patients (16%) did not react upon oral aspirin challenge [119]. The ingestion of the NSAID and its temporal proximity to the asthma attack may have been coincidental, which illustrates the dangers of relying on history alone [90]. Dursun et al. [120] studied 243 patients who underwent oral aspirin challenges and determined that predictors for positive challenges included age younger than 40, a poor sense of smell and 2 or more severe reactions associated with ingestion of NSAIDs. An aspirin challenge will confirm or rule out AERD in patients who have these risk factors. It is important to make the diagnosis because ‘desensitization’ to oral aspirin has been found to be successful in decreasing disease severity [121]. A protocol for oral aspirin challenge is shown in table 9 and treatment for oral aspirin challenge can be found in table 10.

In patients with AERD, it is imperative that their underlying asthma be under good control. They should be managed as any persistent asthmatic, with the use of controller medications such as inhaled corticosteroids, long-

acting bronchodilators, cysteinyl leukotriene receptor antagonists or 5-lipoxygenase inhibitors. Compliance with their medication regimen is an important factor [122].

Prior to an aspirin challenge, good asthma control should be achieved. Spirometry should be checked 1 week prior to oral aspirin challenge and the forced expiratory volume in 1 s (FEV₁) should be greater than 70% and greater than 1.5 liters [122]. Medications that should be discontinued 24 h before challenge include antihistamines (it may mask upper respiratory symptoms during the challenge) and short-acting inhaled beta agonists or anticholinergics (these may lead to a false-positive reaction once the effect has worn off) [121]. If a patient is not on a cysteinyl leukotriene receptor antagonist they should be started on it 1 week prior to oral aspirin challenge [122]. Cysteinyl leukotriene receptor antagonists have been shown to decrease the lower airway response in patients undergoing an oral aspirin challenge, although there is an increase in the upper airway reactions [123, 124]. For the purposes of the challenge, cysteinyl leukotriene receptor antagonists thereby shift the oral aspirin challenge reaction from the lower airways to the upper airways, and increase the safety of the procedure [122]. Cysteinyl leukotriene receptor antagonists are not believed to influence the test. Indeed, negative responses to oral aspirin challenges was similar in patients treated with cysteinyl leukotriene receptor antagonists versus those that were not treated [123].

If a positive response is elicited during oral aspirin challenge, then the procedure will proceed to aspirin 'desensitization'. This is effectively a continuation of the oral aspirin challenge but the goal is to eliminate the clinical response to aspirin. If symptoms occur during 'desensitization', the patient should be treated with appropriate medications (i.e. beta agonists for pulmonary symptoms, oral or intravenous antihistamines for nasal symptoms, topical antihistamines for ocular reactions, racemic epinephrine nebulizer for laryngeal symptoms or injectable epinephrine for anaphylaxis) until the symptoms have stabilized [121]. Once the symptoms have resolved then the eliciting dose should be repeated again and if there is no reaction then the dose should be escalated up to 325 mg. Tables 9 and 10 show an example of an aspirin 'desensitization' protocol. Once this dose has been reached without exacerbation of symptoms, the patient should be maintained on 650 mg twice a day. The dose can be tapered to 325 mg twice a day after the 1st month if symptoms are absent [121]. In patients with AERD, aspirin 'desensitization' and daily aspirin use can improve asthma

symptoms, reduce the formation of nasal polyps and sinus infections, reduce the need for oral corticosteroids and sinus surgeries and improve asthma scores after 1 year of follow-up [125, 126].

NSAID-Exacerbated Urticaria/Angioedema

Patients with chronic idiopathic urticaria can have an exacerbation of their urticaria or angioedema upon ingestion of an NSAID. This can occur in up to 30% of patients with chronic urticaria. Typically symptoms of urticaria or angioedema can present within several minutes up to several hours after ingestion of an NSAID. The urticaria usually resolves after several hours. The underlying mechanism for acute exacerbations of urticaria/angioedema is believed to be similar to the mechanism of AERD, with inhibition of COX-1 enzyme as a key mechanism. Mastalerz et al. [127] demonstrated that patients with chronic urticaria with exacerbation of urticaria or angioedema upon ingestion of aspirin had higher levels of baseline urinary LTE₄ and an increase in levels after ingestion of aspirin, when compared with patients with chronic urticaria who had no exacerbation after ingestion of aspirin. The authors suggested that chronic urticaria with aspirin sensitivity is characterized by the eicosanoid alterations similar to AERD patients [127]. Another study showed that patients with sensitivity to COX-1 inhibitors generally tolerated COX-2 inhibitors with rare adverse effects [128]. On the other hand, a separate study did show a 7% reaction rate to rofecoxib (angioedema) and valdecoxib (urticaria) in patients with aspirin-induced urticaria [129]. Therefore, the authors suggested that oral provocation tests in a controlled setting with COX-2 inhibitors should be performed before prescribing these agents to patients with chronic urticaria and exacerbations with NSAIDs [129].

Performing a thorough history and clinical examination is important but not universally diagnostic. In some instances the history may not be clear or the patient may not remember correctly the association between the ingestion of an NSAID and worsening of their urticaria. The gold standard for diagnosis is an oral provocation test [130]. Table 11 illustrates an oral aspirin challenge protocol used for the diagnosis of NSAID-induced urticaria or angioedema. If the diagnosis is confirmed by oral challenge, then the patient should avoid COX-1 inhibitors. As noted above, COX-2 inhibitors can generally be safely tolerated, though there are rare instances of cross reactivity. As in the case with AERD, it is rec-

Table 11. Oral aspirin challenge for diagnosis of NSAID-induced urticaria/angioedema [96]

Day 1	Day 2	Day 3	Day 4
Placebo	ASA 100 mg	ASA 325 mg	ASA 650 mg
Placebo	ASA 200 mg		

At day 1 and day 2, aspirin is administered every 2 h with skin scores assessed every 2 h.

ommended that the first dose of a COX-2 inhibitor be given in an observed setting to monitor for adverse reactions [129].

Multiple NSAID-Induced Urticaria/Angioedema

This type of reaction occurs in individuals who do not have chronic urticaria or angioedema, except when they ingest a COX-1 inhibitor. The angioedema primarily involves the facial area, and patients present with lip, tongue or periorbital swelling. These patients will react to any COX-1 inhibitors but rarely react to COX-2 inhibitors [131, 132]. Even though these patients do not initially have chronic urticaria, this may develop subsequently. In a study of patients with multiple NSAID-induced urticaria, 45 out of 121 patients (37%) developed chronic urticaria on follow-up 1–10 years later [133]. The diagnosis of this condition is based on history, as there is no validated oral provocation challenge protocol. Management involves avoidance of all COX-1 inhibitors. Up to 80% of patients can tolerate paracetamol [92]. In addition, these patients can tolerate COX-2 inhibitors and these agents may be considered for pain management [131, 132].

Single NSAID-Induced Reactions

These patients develop urticaria, angioedema or anaphylaxis from a single NSAID. The prevalence of these reactions ranges from 0.1 to 3.6% of patients who take NSAIDs [134]. As in the case of multiple NSAID-induced urticaria/angioedema patients, 30% of single NSAID-induced urticaria are likely to develop subsequent chronic urticaria [133]. It has been noted that single NSAID reactors have a higher prevalence of atopy. In a study of 50 patients with NSAID hypersensitivity, 87% had positive

skin prick test to aeroallergens [135]. The authors also found that single NSAID reactors had higher skin test reactivity compared with the multiple NSAID reactors [135].

The most commonly implicated NSAIDs in single-NSAID reactions are diclofenac, naproxen and ibuprofen. There is no cross reaction with other COX-1 or COX-2 inhibitors. Thus, the mechanism of action is unlikely to be via the arachidonic acid pathway. Instead, these patients may be experiencing a true IgE-mediated reaction. This has been difficult to substantiate using skin prick or specific-IgE in vitro tests. However, in a study involving patients with symptoms suggestive of IgE-mediated anaphylaxis to a class of NSAIDs known as pyrazolones (e.g. phenylbutazone, oxyphenbutazone), either positive skin testing or serum specific-IgE measured using a novel ELISA was found in 51 of 53 patients (96%) [136]. However, the skin test results for pyrazolone hypersensitivity did not translate to other classes of NSAIDs. In a case report involving 12 patients with a history of selective hypersensitivity to diclofenac, skin prick and intradermal testing with diclofenac was performed. Ten patients had negative skin testing. Therefore, skin testing cannot be recommended in patients with selective NSAID hypersensitivity reactions.

Oral provocation challenge should not be performed in patients with severe anaphylactic reactions. However, it may be performed using another NSAID to rule out cross reactivity, and to prevent unnecessary exclusion of medications. ‘Desensitization’ protocols have not been developed for use in single NSAID-induced reactions because of the possibility of using an alternative NSAID.

Local Anesthetics

Local anesthetic (LA) reactions are commonly reported by patients undergoing dental procedures. However, the majority of these reactions are not true allergic reactions but rather psychosomatic, vasovagal or toxic in origin [137]. LAs contain an aromatic ring, an amine group and an intermediate chain linkage. LAs can be divided into two groups based on the intermediate chain linkage: the ester agents and the amide agents [138]. Table 12 shows the categorization of the different LA agents.

Reactions to LAs may be either allergic or nonallergic. Allergic reactions to LAs may be either IgE-mediated (type I) allergic or non-IgE-mediated (type IV) allergic reactions. IgE-mediated reactions present with urticaria, pruritus, angioedema, bronchospasm and hypotension

within seconds to minutes after the administration of an LA. Non-IgE-mediated type IV reactions present with delayed erythema, swelling, vesiculation, eczema and dermatitis at the site of administration. Typically, type IV reactions occur within 72 h after the administration. Allergic reactions to LAs are very rare. This is illustrated in a study by Gall et al. [139] in which 177 patients with a reported history of an adverse reaction to LA were evaluated. All the patients were skin prick tested to the LA, followed by intracutaneous testing and challenge with the suspected LA and its preservative [139]. All patients had negative prick and intracutaneous tests. A total of three reactions occurred with the LA challenge. Two were deemed to be an immediate reaction and the third was a delayed reaction. The authors concluded that allergic reactions to LA are rare events, confirming the findings of other studies [139]. In general the overall incidence of allergic reactions to local anesthetics is estimated to be less than 1% [137].

The majority of reactions to LA are thought to be secondary to nonallergic mechanisms [140]. Anxiety reactions may appear similar to anaphylaxis with palpitations, dyspnea, lightheadedness and tachycardia. However, unlike anaphylaxis, patients will describe peripheral or perioral paresthesias. In addition, the blood pressure will usually be elevated, contrary to that seen in anaphylaxis. Patients may also develop vasovagal reactions with syncope, but unlike those with anaphylaxis, these patients will have bradycardia and pallor as opposed to tachycardia and flushing as seen in anaphylaxis. The presentation of hives or pruritus may be suggestive of an allergic anaphylactic reaction.

Dentists and physicians commonly administer epinephrine with LA in order to cause vasoconstriction of local blood vessels and decrease the rate at which local anesthetics are systemically absorbed. However, a small amount of epinephrine could be systemically absorbed and cause symptoms of palpitations, tachycardia, hypertension and cardiac arrhythmias [141]. A study conducted in 14 men who were injected with lidocaine and epinephrine showed significant increases in plasma epinephrine concentration [142]. In addition, these patients had a slight increase in heart rate but no significant change in mean arterial pressure [142]. Thus epinephrine did not appear to cause a significant hemodynamic response but may affect certain susceptible individuals by inducing symptoms that may be confused with anaphylaxis [140].

Allergists will encounter patients referred from dentists or surgeons for evaluation of an adverse reaction to

Table 12. Categories of local anesthetic agents

Ester agents	Amide agents
Benzocaine	Bupivacaine
Procaine	Lidocaine
Tetracaine	Mepivacaine
Proparacaine	Articaine
Cocaine	Levobupivacaine
Chloroprocaine	Dibucaine
	Etidocaine
	Prilocaine
	Ropivacaine

a LA. A thorough history should be performed, and attention should be paid to the clinical signs and symptoms experienced by the patient, the onset of these symptoms in relation to administration of the LA, the particular LA used, whether or not epinephrine was administered, and objective records from the referring physician to corroborate the history. If the history cannot clearly discriminate between an allergic or nonallergic reaction, further testing should be performed. If the history suggests an immediate reaction, skin prick and intradermal testing along with graded drug challenge is the next step. It has been suggested that if an anaphylactic reaction occurred, then the skin testing should usually be performed with an LA agent from a different class [143]. For example, if an ester LA caused the reaction then testing to the LA from the amide class should be performed and vice versa. However, with the limited availability of ester LA in some countries this may be difficult and it would be reasonable to perform skin testing with a different LA agent in the same class.

If the history does not suggest an anaphylactic reaction, the same agent in question should be used for testing and challenge [139]. In addition, communication with the referring physician or dentist should be made in order to determine which LA reagents they commonly use and stock, as this will affect the choice of which LA reagents to test for tolerability. When none of this information is available, lidocaine can be used for testing as it is frequently used and rarely associated with adverse reactions [143].

If the reaction is delayed, or if the history is consistent with a type IV-mediated reaction, then patch testing to the LA should be performed. Patch testing with the T.R.U.E. test panel includes a test for 'caine mix', a combination of esters and amide LA that consists of benzo-

Table 13. A comparison of different local anesthetic graded drug challenges reported in the literature

Authors	Protocol
Macy et al. [160]	Inject subcutaneously 1 ml of saline Observe for 20 min Inject subcutaneously 1 ml of undiluted LA agent and observe for 20 min
deShazo and Nelson [152]	Inject subcutaneously 0.5 ml of saline if suspect reaction is psychosomatic and then observe for 15 min Inject subcutaneously 0.1 ml of 1:100 dilution of LA Observe for 15 min Inject subcutaneously 0.1 ml 1:10 dilution of LA Observe for 15 min Inject subcutaneously 0.1 ml full-strength LA Observe for 15 min Inject subcutaneously 0.5 or 1 ml of full-strength LA Observe for 1 h Inject subcutaneously 0.5 ml of saline if suspect reaction is psychosomatic and then observe for 20 min Inject subcutaneously 0.1 ml of full-strength LA Observe for 20 min
Schatz and Fung [143]	Inject 0.5 ml subcutaneously of full-strength LA Observe for 20 min Inject 1 ml subcutaneously of full-strength LA Observe for 1 h

Symptoms considered to be a positive reaction include: positive wheal and flare reaction at site of undiluted LA administration, acute onset pruritic rash distant from the site, 15% decrease in FEV₁ of pulmonary function test during the post-test observation period [154].

caine, tetracaine and dibucaine. However, any other LAs can be patch tested for as well.

To evaluate for immediate-type allergic reactions skin prick testing should be done with an undiluted form of the LA along with positive and negative controls (histamine and saline, respectively). Preferably, the LA should not contain epinephrine as it can mask the wheal and flare response leading to false negatives with skin testing [144, 145]. Also, the test reagent should not contain parabens as it has been implicated in allergic-like reactions and can lead to false-positive skin tests [146, 147]. However, parabens are common components in multidose vials and paraben-free LA preparations may be difficult to find [148]. Moreover, the effect of parabens in causing allergic reactions or false-positive skin tests may not be a common confounding cause [149]. Testing with paraben-containing preparations can be used if available [150]. However, any positive skin test

with paraben-containing preparations should be confirmed with paraben-free LA to eliminate the possibility of a false-positive test.

If the skin prick test is negative then one should proceed to intradermal testing with 0.02 ml of a 1:100 dilution of the drug, along with both negative and positive controls [140]. Use of 1:10 dilutions for intradermal testing have also been recommended by clinical guidelines [151]. If the intradermal test is negative, a graded drug challenge with the LA should be performed. Several different graded drug challenge schemes for LA are available in the literature [152]. A common graded drug challenge is the following: successive injections of 0.1 ml of 1:100 dilution, 1:10 dilution and full strength solutions injected subcutaneously or intracutaneously administered in 15-min intervals. If the patient does not react to the final dose, then 0.5–1 ml of the LA is injected subcutaneously.

Because of the unlikelihood of an IgE-mediated reaction, other protocols have proposed a more expedited graded LA challenge. These have also been proven to be safe. A sample of these protocols is shown in table 13. The patient should be observed in a clinical setting by physicians trained in recognizing and treating anaphylaxis. If the history suggests an anxiety- or vasovagal-related reaction, administration of a single blinded placebo injection may be warranted prior to undergoing the graded LA drug challenge. If the patient reacts to the LA then another LA should be selected and repeat skin testing and graded drug challenge performed to confirm a negative reaction. Once a particular LA has been cleared by the above methodologies, then it can be recommended as safe to use for future injections.

Opiates

Opiates such as morphine, meperidine and codeine have been known to cause symptoms of pruritus, urticaria and hypotension. These effects have been shown to be secondary to direct histamine release from mast cells [153]. In a study by Grossman [153], rat mast cells were incubated with morphine, meperidine and pethidine. Morphine and meperidine caused a rapid histamine release but pethidine resulted in a slower histamine release [153]. Histamine release was partially reduced when naloxone (an opioid antagonist) was coadministered with codeine and meperidine [153]. The author concluded that meperidine and codeine had a similar mechanism of action that was different from pethidine [153].

Skin testing with narcotics has been known to cause positive wheal and flare responses. One study demonstrated that 39 out of 56 subjects had positive wheal responses to codeine [154]. Intradermal skin testing with narcotics has also been shown to elicit positive wheal and flare responses [155]. A study was done by Nasser [156] to determine whether opiate-sensitive patients had a different response to opiate skin test compared with non-opiate-sensitive control subjects. There was no difference in the skin prick tests between the two groups and the authors concluded that skin prick testing is not useful in diagnosis of opiate sensitivity [156]. A single case report describes a patient developing IgE-mediated anaphylaxis several minutes after receiving papaveretum, a mixture of several different opioids including morphine, codeine, narcotine and papaverine [157]. The authors were able to detect IgE antibodies to morphine and codeine in the serum of the subject and showed positive intradermal skin test to morphine and papaveretum [157]. In general, opiate-induced reactions are not life threatening. Moreover, if a patient develops reactions to narcotics they can be switched to non-opioid pain relief medications. Pretreatment with antihistamines can be considered to prevent opiate reactions. In a placebo-controlled trial Juneja et al. [158] demonstrated that 50 mg of intramuscular diphenhydramine improved pruritus in patients who had received epidural morphine for cesarean sections. It has been recommended in the USA practice parameters for drug allergy that nonallergic opiate reactions be attenuated with preadministration of antihistamines [159].

Conclusion

There are several drugs that have been implicated as causing nonallergic adverse drug reactions and great strides have been made in elucidating the mechanisms. The identification of clinical situations in which such reactions exist and the management of such reactions have been described for some agents. Distinguishing allergic from nonallergic drug reactions occasionally presents a challenge to the clinician. Taking a thorough history and physical examination is critically important, but additional testing such as skin testing and graded drug challenge will help to rule out or rule in an allergic etiology. 'Desensitization' protocols have been described for many drugs and it is unfortunate that this term has been loosely used even when the mechanism of the hypersensitivity is unknown, and may likely be nonallergic in nature. If the reaction is nonimmunologic then there is in truth no sensitization, and therefore there can be no 'desensitization'. In many of these cases the procedure may actually be a challenge done under different conditions that may or may not include factors such as slowing of the rate of infusion, use of an alternate form of the medication and premedication regimens. Desensitization implies a modulation of immunologic conditions in the host, rather than simply identifying external conditions that allow a drug to be administered safely and without adverse effects.

References

- Gandhi TK, Weingart SN, Borus J, Seger AC, Peterson J, Burdick E, Seger DL, Shu K, Federico F, Leape LL, Bates DW: Adverse drug events in ambulatory care. *N Engl J Med* 2003;348:1556–1564.
- Gomes ER, Demoly P: Epidemiology of hypersensitivity drug reactions. *Curr Opin Allergy Clin Immunol* 2005;5:309–316.
- Lazarou J, Pomeranz BH, Corey PN: Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA* 1998;279:1200–1205.
- Edwards IR, Aronson JK: Adverse drug reactions: definitions, diagnosis, and management. *Lancet* 2000;356:1255–1259.
- Utrecht J: Idiosyncratic drug reactions: current understanding. *Annu Rev Pharmacol Toxicol* 2007;47:513–539.
- Johansson SG, Bieber T, Dahl R, Friedmann PS, Lanier BQ, Lockey RF, Motala C, Ortega Martell JA, Platts-Mills TA, Ring J, Thien F, Van Cauwenberge P, Williams HC: Revised nomenclature for allergy for global use: report of the nomenclature review committee of the world allergy organization, October 2003. *J Allergy Clin Immunol* 2004;113:832–836.
- Johansson SG, Hourihane JO, Bousquet J, Brujinzeel-Koomen C, Dreborg S, Haahtela T, Kowalski ML, Mygind N, Ring J, van Cauwenberge P, van Hage-Hamsten M, Wüthrich B: A revised nomenclature for allergy: an EAACI position statement from the EAACI nomenclature task force. *Allergy* 2001;56:813–824.
- Ring J, Behrendt H, de Weck A: History and classification of anaphylaxis. *Chem Immunol Allergy* 2010;95:1–11.
- Syrgiou E, Dannos I, Kotteas E, Makrilia N, Tourkantonis I, Dilana K, Gkiozos I, Saif MW, Syrgios KN: Hypersensitivity reactions to docetaxel: retrospective evaluation and development of a desensitization protocol. *Int Arch Allergy Immunol* 2011;156:320–324.
- Weiss RB, Donehower RC, Wiernik PH, Ohnuma T, Gralla RJ, Trump DL, Baker JR Jr, Van Echo DA, Von Hoff DD, Leyland-Jones B: Hypersensitivity reactions from taxol. *J Clin Oncol* 1990;8:1263–1268.
- Szebeni J, Alving CR, Savay S, Barenholz Y, Prieve A, Danino D, Talmon Y: Formation of complement-activating particles in aqueous solutions of taxol: possible role in hypersensitivity reactions. *Int Immunopharmacol* 2001;1:721–735.

- 12 Prieto Garcia A, Pineda de la Losa F: Immunoglobulin E-mediated severe anaphylaxis to paclitaxel. *J Invest Allergol Clin Immunol* 2010;20:170–171.
- 13 Rowinsky EK, Donehower RC: Paclitaxel (taxol). *N Engl J Med* 1995;332:1004–1014.
- 14 Bristol-Myers Squibb (company): Taxolh (Paclitaxel) Injection (package insert).
- 15 Bookman MA, Kloth DD, Kover PE, Smolinski S, Ozols RF: Intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. *Semin Oncol* 1997;24:S19–S19–15.
- 16 Bookman MA, Kloth DD, Kover PE, Smolinski S, Ozols RF: Short-course intravenous prophylaxis for paclitaxel-related hypersensitivity reactions. *Ann Oncol* 1997;8:611–614.
- 17 Markman M, Kennedy A, Webster K, Peterson G, Kulp B, Belinson J: An effective and more convenient drug regimen for prophylaxis against paclitaxel-associated hypersensitivity reactions. *J Cancer Res Clin Oncol* 1999;125:427–429.
- 18 Kwon JS, Elit L, Finn M, Hirte H, Mazurka J, Moens F, Trim K: A comparison of two prophylactic regimens for hypersensitivity reactions to paclitaxel. *Gynecol Oncol* 2002;84:420–425.
- 19 Castells MC, Tennant NM, Sloane DE, Hsu FI, Barrett NA, Hong DI, Laidlaw TM, Lege-re HJ, Nallamshetty SN, Palis RI, Rao JJ, Berlin ST, Campos SM, Matulonis UA: Hypersensitivity reactions to chemotherapy: outcomes and safety of rapid desensitization in 413 cases. *J Allergy Clin Immunol* 2008;122:574–580.
- 20 Stone HD Jr, DiPiro C, Davis PC, Meyer CF, Wray BB: Hypersensitivity reactions to *Escherichia coli*-derived polyethylene glycolated-asparaginase associated with subsequent immediate skin test reactivity to *E. coli*-derived granulocyte colony-stimulating factor. *J Allergy Clin Immunol* 1998;101:429–431.
- 21 Weiss RB, Bruno S: Hypersensitivity reactions to cancer chemotherapeutic agents. *Ann Intern Med* 1981;94:66–72.
- 22 Katayama H, Yamaguchi K, Kozuka T, Takashima T, Seez P, Matsuura K: Adverse reactions to ionic and nonionic contrast media. A report from the Japanese committee on the safety of contrast media. *Radiology* 1990;175:621–628.
- 23 Weiss RB: Hypersensitivity reactions. *Semin Oncol* 1992;19:458–477.
- 24 Evans WE, Tsiatis A, Rivera G, Murphy SB, Dahl GV, Denison M, Crom WR, Barker LF, Mauer AM: Anaphylactoid reactions to *Escherichia coli* and *Erwinia asparaginase* in children with leukemia and lymphoma. *Cancer* 1982;49:1378–1383.
- 25 Khan A, Hill JM: Atopic hypersensitivity to L-asparaginase. Resistance to immunosuppression. *Int Arch Allergy Appl Immunol* 1971;40:463–469.
- 26 Fabry U, Korholz D, Jurgens H, Gobel U, Wahn V: Anaphylaxis to L-asparaginase during treatment for acute lymphoblastic leukemia in children – evidence of a complement-mediated mechanism. *Pediatr Res* 1985;19:400–408.
- 27 Shepherd GM: Hypersensitivity reactions to chemotherapeutic drugs. *Clin Rev Allergy Immunol* 2003;24:253–262.
- 28 Larson RA, Fretzin MH, Dodge RK, Schiffer CA: Hypersensitivity reactions to l-asparaginase do not impact on the remission duration of adults with acute lymphoblastic leukemia. *Leukemia* 1998;12:660–665.
- 29 Pagani M: The complex clinical picture of presumably allergic side effects to cytostatic drugs: symptoms, pathomechanism, reexposure, and desensitization. *Med Clin North Am* 2010;94:835–852.
- 30 Kellie SJ, Crist WM, Pui CH, Crone ME, Fairclough DL, Rodman JH, Rivera GK: Hypersensitivity reactions to epipodophylotoxins in children with acute lymphoblastic leukemia. *Cancer* 1991;67:1070–1075.
- 31 O'Dwyer PJ, King SA, Fortner CL, Leyland-Jones B: Hypersensitivity reactions to teniposide (VM-26): an analysis. *J Clin Oncol* 1986;4:1262–1269.
- 32 Siderov J, Prasad P, De Boer R, Desai J: Safe administration of etoposide phosphate after hypersensitivity reaction to intravenous etoposide. *Br J Cancer* 2002;86:12–13.
- 33 Collier K, Schink C, Young AM, How K, Seckl M, Savage P: Successful treatment with etoposide phosphate in patients with previous etoposide hypersensitivity. *J Oncol Pharm Pract* 2008;14:51–55.
- 34 Nolte H, Carstensen H, Hertz H: Vm-26 (teniposide)-induced hypersensitivity and degranulation of basophils in children. *Am J Pediatr Hematol Oncol* 1988;10:308–312.
- 35 Hudson MM, Weinstein HJ, Donaldson SS, Greenwald C, Kun L, Tarbell NJ, Humphrey WA, Rupp C, Marina NM, Wilimas J, et al: Acute hypersensitivity reactions to etoposide in a VEPA regimen for Hodgkin's disease. *J Clin Oncol* 1993;11:1080–1084.
- 36 Trcka J, Schmidt C, Seitz CS, Brocker EB, Gross GE, Trautmann A: Anaphylaxis to iodinated contrast material: nonallergic hypersensitivity or IgE-mediated allergy? *AJR Am J Roentgenol* 2008;190:666–670.
- 37 Brockow K, Christiansen C, Kanny G, Clement O, Barbaud A, Bircher A, Dewachter P, Gueant JL, Rodriguez Gueant RM, Mouton-Faivre C, Ring J, Romano A, Sainte-Laudy J, Demoly P, Pichler WJ: Management of hypersensitivity reactions to iodinated contrast media. *Allergy* 2005;60:150–158.
- 38 Brockow K: Immediate and delayed reactions to radiocontrast media: is there an allergic mechanism? *Immunol Allergy Clin North Am* 2009;29:453–468.
- 39 Zafirir Y, Szyper-Kravitz M, Agmon-Levin N: Delayed allergic reaction after coronary angiography. *Am J Med Sci* 2011;342:86–88.
- 40 Lieberman PL, Seigle RL: Reactions to radiocontrast material: anaphylactoid events in radiology. *Clin Rev Allergy Immunol* 1999;17:469–496.
- 41 Palmer FJ: The RACR survey of intravenous contrast media reactions: final report. *Australas Radiol* 1988;32:426–428.
- 42 Wolf GL, Arenson RL, Cross AP: A prospective trial of ionic vs nonionic contrast agents in routine clinical practice: comparison of adverse effects. *AJR Am J Roentgenol* 1989;152:939–944.
- 43 Caro JJ, Trindade E, McGregor M: The risks of death and of severe nonfatal reactions with high- vs low-osmolality contrast media: a meta-analysis. *AJR Am J Roentgenol* 1991;156:825–832.
- 44 Morcos SK, Thomsen HS, Webb JA: Prevention of generalized reactions to contrast media: a consensus report and guidelines. *Eur Radiol* 2001;11:1720–1728.
- 45 Beaty AD, Lieberman PL, Slavin RG: Seafood allergy and radiocontrast media: are physicians propagating a myth? *Am J Med* 2008;121:158 e151–e154.
- 46 Lopata AL, O'Hehir RE, Lehrer SB: Shellfish allergy. *Clin Exp Allergy* 2010;40:850–858.
- 47 Shehadi WH: Adverse reactions to intravascularly administered contrast media: a comprehensive study based on a prospective survey. *Am J Roentgenol Radium Ther Nucl Med* 1975;124:145–152.
- 48 Christiansen C, Pichler WJ, Skotland T: Delayed allergy-like reactions to x-ray contrast media: mechanistic considerations. *Eur Radiol* 2000;10:1965–1975.
- 49 Kanny G, Pichler W, Morisset M, Franck P, Marie B, Kohler C, Renaudin JM, Beaudouin E, Laudy JS, Moneret-Vautrin DA: T cell-mediated reactions to iodinated contrast media: evaluation by skin and lymphocyte activation tests. *J Allergy Clin Immunol* 2005;115:179–185.
- 50 Lang JH, Lasser EC, Kolb WP: Activation of serum complement by contrast media. *Invest Radiol* 1976;11:303–308.
- 51 Szebeni J: Hypersensitivity reactions to radiocontrast media: the role of complement activation. *Curr Allergy Asthma Rep* 2004;4:25–30.
- 52 Bellin MF, Stacul F, Webb JA, Thomsen HS, Morcos SK, Almen T, Aspelin P, Clement O, Heinz-Peer G, Reimer P, van der Molen A: Late adverse reactions to intravascular iodine based contrast media: an update. *Eur Radiol* 2011;21:2305–2310.
- 53 Kanny G, Maria Y, Mentre B, Moneret-Vautrin DA: Case report: recurrent anaphylactic shock to radiographic contrast media – evidence supporting an exceptional IgE-mediated reaction. *Allergy Immunol (Paris)* 1993;25:425–430.

- 54 Wakkers-Garritsen BG, Houwerzij J, Nater JP, Wakkers PJ: IgE-mediated adverse reactivity to a radiographic contrast medium. *Ann Allergy* 1976;36:122–126.
- 55 Romano A, Viola M, Gaeta F, Rumi G, Maggioletti M: Patch testing in non-immediate drug eruptions. *Allergy Asthma Clin Immunol* 2008;4:66–74.
- 56 Christiansen C: Late-onset allergy-like reactions to x-ray contrast media. *Curr Opin Allergy Clin Immunol* 2002;2:333–339.
- 57 Brockow K, Romano A, Aberer W, Bircher AJ, Barbaud A, Bonadonna P, Faria E, Kanny G, Lerch M, Pichler WJ, Ring J, Rodrigues Cernadas J, Tomaz E, Demoly P, Christiansen C: Skin testing in patients with hypersensitivity reactions to iodinated contrast media – a European multicenter study. *Allergy* 2009;64:234–241.
- 58 Dewachter P, Laroche D, Mouton-Faivre C, Bloch-Morot E, Cercueil JP, Metge L, Carotte MF, Vergnaud MC, Clement O: Immediate reactions following iodinated contrast media injection: a study of 38 cases. *Eur J Radiol* 2011;77:495–501.
- 59 Goksel O, Aydin O, Atasoy C, Akyar S, Demirel YS, Misirliligil Z, Baybek S: Hypersensitivity reactions to contrast media: prevalence, risk factors and the role of skin tests in diagnosis – a cross-sectional survey. *Int Arch Allergy Immunol* 2011;155:297–305.
- 60 Caimmi S, Benyahia B, Suau D, Bousquet-Rouanet L, Caimmi D, Bousquet PJ, Demoly P: Clinical value of negative skin tests to iodinated contrast media. *Clin Exp Allergy* 2010;40:805–810.
- 61 American College of Radiology: Patient selection and preparation strategies: Manual on contrast media. Reston, ACR, 2011.
- 62 Greenberger PA, Patterson R: The prevention of immediate generalized reactions to radiocontrast media in high-risk patients. *J Allergy Clin Immunol* 1991;87:867–872.
- 63 Greenberger PA, Patterson R, Radin RC: Two pretreatment regimens for high-risk patients receiving radiographic contrast media. *J Allergy Clin Immunol* 1984;74:540–543.
- 64 Marshall GD Jr, Lieberman PL: Comparison of three pretreatment protocols to prevent anaphylactoid reactions to radiocontrast media. *Ann Allergy* 1991;67:70–74.
- 65 Williams AN, Kelso JM: Radiocontrast-induced anaphylaxis despite pretreatment and use of iso-osmolar contrast. *Ann Allergy Asthma Immunol* 2007;99:467–468.
- 66 Worthley DL, Gillis D, Kette F, Smith W: Radiocontrast anaphylaxis with failure of premedication. *Intern Med J* 2005;35:58–60.
- 67 Dillman JR, Ellis JH, Cohan RH, Strouse PJ, Jan SC: Allergic-like breakthrough reactions to gadolinium contrast agents after corticosteroid and antihistamine premedication. *AJR Am J Roentgenol* 2008;190:187–190.
- 68 Davenport MS, Cohan RH, Caoili EM, Ellis JH: Repeat contrast medium reactions in premedicated patients: frequency and severity. *Radiology* 2009;233:372–379.
- 69 Wazny LD, Daghigh B: Desensitization protocols for vancomycin hypersensitivity. *Ann Pharmacother* 2001;35:1458–1464.
- 70 Hepner DL, Castells MC: Anaphylaxis during the perioperative period. *Anesth Analg* 2003;97:1381–1395.
- 71 Bailey P, Gray H: An elderly woman with ‘red man syndrome’ in association with oral vancomycin therapy: a case report. *Cases J* 2008;1:111.
- 72 McCullough JM, Dielman DG, Peery D: Oral vancomycin-induced rash: case report and review of the literature. *DICP* 1991;25:1326–1328.
- 73 Nallasivan M, Maher F, Murthy K: Rare case of ‘red man’ syndrome in a female patient treated with oral vancomycin for clostridium difficile diarrhoea. *BMJ Case Rep* 2009, DOI:10.1136/bcr.03.2009.1705.
- 74 Sivagnanam S, Deleu D: Red man syndrome. *Crit Care* 2003;7:119–120.
- 75 Hicks RW, Hernandez J: Perioperative pharmacology: a focus on vancomycin. *AORN J* 2011;93:593–599.
- 76 Southorn PA, Plevak DJ, Wright AJ, Wilson WR: Adverse effects of vancomycin administered in the perioperative period. *Mayo Clin Proc* 1986;61:721–724.
- 77 Horinouchi Y, Abe K, Kubo K, Oka M: Mechanisms of vancomycin-induced histamine release from rat peritoneal mast cells. *Agents Actions* 1993;40:28–36.
- 78 Williams PD, Laska DA, Shetler TJ, McGrath JP, White SL, Hoover DM: Vancomycin-induced release of histamine from rat peritoneal mast cells and a rat basophil cell line (RBL-1). *Agents Actions* 1991;32:217–223.
- 79 Levy JH, Kettlekamp N, Goertz P, Hermens J, Hirshman CA: Histamine release by vancomycin: a mechanism for hypotension in man. *Anesthesiology* 1987;67:122–125.
- 80 Sahai J, Healy DP, Shelton MJ, Miller JS, Ruberg SJ, Polk R: Comparison of vancomycin and teicoplanin-induced histamine release and ‘red man syndrome’. *Antimicrob Agents Chemother* 1990;34:765–769.
- 81 Healy DP, Sahai JV, Fuller SH, Polk RE: Vancomycin-induced histamine release and ‘red man syndrome’: comparison of 1- and 2-hour infusions. *Antimicrob Agents Chemother* 1990;34:550–554.
- 82 Wilhelm MP, Estes L: Symposium on antimicrobial agents – part xii: vancomycin. *Mayo Clin Proc* 1999;74:928–935.
- 83 Levy JH, Marty AT: Vancomycin and adverse drug reactions. *Crit Care Med* 1993;21:1107–1108.
- 84 Wallace MR, Mascola JR, Oldfield EC 3rd: Red man syndrome: incidence, etiology, and prophylaxis. *J Infect Dis* 1991;164:1180–1185.
- 85 Lieberman P, Nicklas RA, Oppenheimer J, Kemp SF, Lang DM, Bernstein DI, Bernstein JA, Burks AW, Feldweg AM, Fink JN, Greenberger PA, Golden DB, James JM, Kemp SF, Ledford DK, Lieberman P, Sheffer AL, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, Lang D, Nicklas RA, Oppenheimer J, Portnoy JM, Randolph C, Schuller DE, Spector SL, Tilles S, Wallace D: The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol* 2010;126:477–480.
- 86 Widal M, Abrami P, Lermeyerz J: Anaphylaxie et idiosyncrasie. *Presse Med* 1922;30:189–192.
- 87 Stevenson DD, Sanchez-Borges M, Szczeklik A: Classification of allergic and pseudoallergic reactions to drugs that inhibit cyclooxygenase enzymes. *Ann Allergy Asthma Immunol* 2001;87:177–180.
- 88 Fahrenholz JM: Natural history and clinical features of aspirin-exacerbated respiratory disease. *Clin Rev Allergy Immunol* 2003;24:113–124.
- 89 Berges-Gimeno MP, Simon RA, Stevenson DD: The natural history and clinical characteristics of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2002;89:474–478.
- 90 Stevenson DD, Szczeklik A: Clinical and pathologic perspectives on aspirin sensitivity and asthma. *J Allergy Clin Immunol* 2006;118:773–778.
- 91 Szczeklik A, Nizankowska E, Duplaga M: Natural history of aspirin-induced asthma. AIAE investigators. European network on aspirin-induced asthma. *Eur Respir J* 2000;16:432–436.
- 92 Kowalski ML, Makowska JS, Blanca M, Baybek S, Bochenek G, Bousquet J, Bousquet P, Celik G, Demoly P, Gomes ER, Nizankowska-Mogilnicka E, Romano A, Sanchez-Borges M, Sanz M, Torres MJ, De Weck A, Szczeklik A, Brockow K: Hypersensitivity to nonsteroidal anti-inflammatory drugs (NSAIDs) – classification, diagnosis and management: review of the EAACI/ENDA(®) and GA2LEN/HANNA*. *Allergy* 2011;66:818–829.
- 93 Stevenson DD, Hankammer MA, Mathison DA, Christiansen SC, Simon RA: Aspirin desensitization treatment of aspirin-sensitive patients with rhinosinusitis-asthma: long-term outcomes. *J Allergy Clin Immunol* 1996;98:751–758.
- 94 Young J, Frenkiel S, Tewfik MA, Mouadeb DA: Long-term outcome analysis of endoscopic sinus surgery for chronic sinusitis. *Am J Rhinol* 2007;21:743–747.
- 95 Jenkins C, Costello J, Hodge L: Systematic review of prevalence of aspirin induced asthma and its implications for clinical practice. *BMJ* 2004;328:434.
- 96 Sanchez-Borges M: NSAID hypersensitivity (respiratory, cutaneous, and generalized anaphylactic symptoms). *Med Clin North Am* 2010;94:853–864.

- 97 Mascia K, Haselkorn T, Deniz YM, Miller DP, Bleecker ER, Borish L: Aspirin sensitivity and severity of asthma: evidence for irreversible airway obstruction in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2005;116:970–975.
- 98 Stevenson DD, Hougham AJ, Schrank PJ, Goldlust MB, Wilson RR: Salsalate cross-sensitivity in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 1990;86:749–758.
- 99 Yoshimine F, Hasegawa T, Suzuki E, Terada M, Koya T, Kondoh A, Arakawa M, Yoshizawa H, Gejyo F: Contribution of aspirin-intolerant asthma to near fatal asthma based on a questionnaire survey in Niigata prefecture, Japan. *Respirology* 2005;10:477–484.
- 100 Gyllfors P, Bochenek G, Overholt J, Drupka D, Kumlin M, Sheller J, Nizankowska E, Isakson PC, Mejza F, Lefkowitz JB, Dahlen SE, Szczeklik A, Murray JJ, Dahlen B: Biochemical and clinical evidence that aspirin-intolerant asthmatic subjects tolerate the cyclooxygenase 2-selective analgetic drug celecoxib. *J Allergy Clin Immunol* 2003;111:1116–1121.
- 101 Stevenson DD, Simon RA: Lack of cross-reactivity between rofecoxib and aspirin in aspirin-sensitive patients with asthma. *J Allergy Clin Immunol* 2001;108:47–51.
- 102 Szczeklik A, Nizankowska E, Bochenek G, Nagraba K, Mejza F, Swierczynska M: Safety of a specific COX-2 inhibitor in aspirin-induced asthma. *Clin Exp Allergy* 2001;31:219–225.
- 103 Woessner KM, Simon RA, Stevenson DD: The safety of celecoxib in patients with aspirin-sensitive asthma. *Arthritis Rheum* 2002;46:2201–2206.
- 104 Schellenberg RR, Isserow SH: Anaphylactoid reaction to a cyclooxygenase-2 inhibitor in a patient who had a reaction to a cyclooxygenase-1 inhibitor. *N Engl J Med* 2001;345:1856.
- 105 Weberschock TB, Muller SM, Boehncke S, Boehncke WH: Tolerance to coxibs in patients with intolerance to non-steroidal anti-inflammatory drugs (NSAIDs): a systematic structured review of the literature. *Arch Dermatol Res* 2007;299:169–175.
- 106 Stevenson DD: Aspirin sensitivity and desensitization for asthma and sinusitis. *Curr Allergy Asthma Rep* 2009;9:155–163.
- 107 Sheller JR, Mitchell D, Meyrick B, Oates J, Breyer R: EP(2) receptor mediates bronchodilation by PGE(2) in mice. *J Appl Physiol* 2000;88:2214–2218.
- 108 Celik G, Bavbek S, Misirligil Z, Melli M: Release of cysteinyl leukotrienes with aspirin stimulation and the effect of prostaglandin E(2) on this release from peripheral blood leucocytes in aspirin-induced asthmatic patients. *Clin Exp Allergy* 2001;31:1615–1622.
- 109 Sestini P, Armetti L, Gambaro G, Pieroni MG, Refini RM, Sala A, Vaghi A, Folco GC, Bianco S, Robuschi M: Inhaled PGE2 prevents aspirin-induced bronchoconstriction and urinary LTE4 excretion in aspirin-sensitive asthma. *Am J Respir Crit Care Med* 1996;153:572–575.
- 110 Schafer D, Schmid M, Gode UC, Baenkler HW: Dynamics of eicosanoids in peripheral blood cells during bronchial provocation in aspirin-intolerant asthmatics. *Eur Respir J* 1999;13:638–646.
- 111 Ying S, Meng Q, Scadding G, Parikh A, Corrigan CJ, Lee TH: Aspirin-sensitive rhinosinusitis is associated with reduced E-prostanoid 2 receptor expression on nasal mucosal inflammatory cells. *J Allergy Clin Immunol* 2006;117:312–318.
- 112 Kowalski ML, Pawliczak R, Wozniak J, Siuda K, Poniatowska M, Iwaszkiewicz J, Kornatowski T, Kaliner MA: Differential metabolism of arachidonic acid in nasal polyp epithelial cells cultured from aspirin-sensitive and aspirin-tolerant patients. *Am J Respir Crit Care Med* 2000;161:391–398.
- 113 Kong JS, Teuber SS, Gershwin ME: Aspirin and nonsteroidal anti-inflammatory drug hypersensitivity. *Clin Rev Allergy Immunol* 2007;32:97–110.
- 114 Sladek K, Dworski R, Soja J, Sheller JR, Nizankowska E, Oates JA, Szczeklik A: Eicosanoids in bronchoalveolar lavage fluid of aspirin-intolerant patients with asthma after aspirin challenge. *Am J Respir Crit Care Med* 1994;149:940–946.
- 115 Smith CM, Hawksworth RJ, Thien FC, Christie PE, Lee TH: Urinary leukotriene E4 in bronchial asthma. *Eur Respir J* 1992;5:693–699.
- 116 Cowburn AS, Sladek K, Soja J, Adamek L, Nizankowska E, Szczeklik A, Lam BK, Penrose JF, Austen FK, Holgate ST, Sampson AP: Overexpression of leukotriene C4 synthase in bronchial biopsies from patients with aspirin-intolerant asthma. *J Clin Invest* 1998;101:834–846.
- 117 Drazen JM, Israel E, O'Byrne PM: Treatment of asthma with drugs modifying the leukotriene pathway. *N Engl J Med* 1999;340:197–206.
- 118 Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH: Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. *N Engl J Med* 2002;347:1493–1499.
- 119 Pleskow WW, Stevenson DD, Mathison DA, Simon RA, Schatz M, Zeiger RS: Aspirin-sensitive rhinosinusitis/asthma: spectrum of adverse reactions to aspirin. *J Allergy Clin Immunol* 1983;71:574–579.
- 120 Dursun AB, Woessner KA, Simon RA, Karasoy D, Stevenson DD: Predicting outcomes of oral aspirin challenges in patients with asthma, nasal polyps, and chronic sinusitis. *Ann Allergy Asthma Immunol* 2008;100:420–425.
- 121 Stevenson DD, Simon RA: Selection of patients for aspirin desensitization treatment. *J Allergy Clin Immunol* 2006;118:801–804.
- 122 White A, Laidlaw T, Woessner K: Aspirin and NSAID reactions; in Castells M (ed): *Diagnosis, Pathophysiology, and Management in Anaphylaxis and Hypersensitivity Reactions*. New York, Humana Press, 2011, vol 1, pp 107–127.
- 123 Berges-Gimeno MP, Simon RA, Stevenson DD: The effect of leukotriene-modifier drugs on aspirin-induced asthma and rhinitis reactions. *Clin Exp Allergy* 2002;32:1491–1496.
- 124 White AA, Stevenson DD, Simon RA: The blocking effect of essential controller medications during aspirin challenges in patients with aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol* 2005;95:330–335.
- 125 Berges-Gimeno MP, Simon RA, Stevenson DD: Long-term treatment with aspirin desensitization in asthmatic patients with aspirin-exacerbated respiratory disease. *J Allergy Clin Immunol* 2003;111:180–186.
- 126 Lee RU, Stevenson DD: Aspirin-exacerbated respiratory disease: evaluation and management. *Allergy Asthma Immunol Res* 2011;3:3–10.
- 127 Mastalerz L, Setkowicz M, Sanak M, Szczeklik A: Hypersensitivity to aspirin: common eicosanoid alterations in urticaria and asthma. *J Allergy Clin Immunol* 2004;113:771–775.
- 128 Zembowicz A, Mastalerz L, Setkowicz M, Radziszewski W, Szczeklik A: Safety of cyclooxygenase 2 inhibitors and increased leukotriene synthesis in chronic idiopathic urticaria with sensitivity to nonsteroidal anti-inflammatory drugs. *Arch Dermatol* 2003;139:1577–1582.
- 129 Sanchez Borges M, Capriles-Hulett A, Caballero-Fonseca F, Perez CR: Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol* 2001;87:201–204.
- 130 Nizankowska-Mogilnicka E, Bochenek G, Mastalerz L, Swierczynska M, Picado C, Scadding G, Kowalski ML, Setkowicz M, Ring J, Brockow K, Bachert C, Wohrl S, Dahlen B, Szczeklik A: EAACI/GA2LEN guideline: aspirin provocation tests for diagnosis of aspirin hypersensitivity. *Allergy* 2007;62:1111–1118.
- 131 Asero R: Risk factors for acetaminophen and nimesulide intolerance in patients with NSAID-induced skin disorders. *Ann Allergy Asthma Immunol* 1999;82:554–558.
- 132 Asero R: Multiple sensitivity to NSAID. *Allergy* 2000;55:893–894.
- 133 Asero R: Intolerance to nonsteroidal anti-inflammatory drugs might precede by years the onset of chronic urticaria. *J Allergy Clin Immunol* 2003;111:1095–1098.

- 134 Berkes EA: Anaphylactic and anaphylactoid reactions to aspirin and other NSAIDs. *Clin Rev Allergy Immunol* 2003;24:137–148.
- 135 Sanchez-Borges M, Capriles-Hulett A: Atopy is a risk factor for non-steroidal anti-inflammatory drug sensitivity. *Ann Allergy Asthma Immunol* 2000;84:101–106.
- 136 Himly M, Jahn-Schmid B, Pittertschatscher K, Bohle B, Grubmayr K, Ferreira F, Ebner H, Ebner C: IgE-mediated immediate-type hypersensitivity to the pyrazolone drug propyphenazone. *J Allergy Clin Immunol* 2003;111:882–888.
- 137 Finucane BT: Allergies to local anesthetics – the real truth. *Can J Anaesth* 2003;50:869–874.
- 138 Boren E, Teuber SS, Naguwa SM, Gershwin ME: A critical review of local anesthetic sensitivity. *Clin Rev Allergy Immunol* 2007;32:119–128.
- 139 Gall H, Kaufmann R, Kalveram CM: Adverse reactions to local anesthetics: analysis of 197 cases. *J Allergy Clin Immunol* 1996;97:933–937.
- 140 Phillips JF, Yates AB, Deshazo RD: Approach to patients with suspected hypersensitivity to local anesthetics. *Am J Med Sci* 2007;334:190–196.
- 141 Tetzlaff JE: The pharmacology of local anesthetics. *Anesthesiol Clin North Am* 2000;18:217–233.
- 142 Chernow B, Balestrieri F, Ferguson CD, Terezhalmay GT, Fletcher JR, Lake CR: Local dental anesthesia with epinephrine: minimal effects on the sympathetic nervous system or on hemodynamic variables. *Arch Intern Med* 1983;143:2141–2143.
- 143 Schatz M, Fung DL: Anaphylactic and anaphylactoid reactions due to anesthetic agents. *Clin Rev Allergy* 1986;4:215–227.
- 144 Ravindranathan N: Allergic reaction to lignocaine: a case report. *Br Dent J* 1975;138:101–102.
- 145 Warren JB, Pixley FJ, Dollery CT: Importance of beta 2-adrenoceptor stimulation in the suppression of intradermal antigen challenge by adrenaline. *Br J Clin Pharmacol* 1989;27:173–177.
- 146 Eggleston ST, Lush LW: Understanding allergic reactions to local anesthetics. *Ann Pharmacother* 1996;30:851–857.
- 147 Nagel JE, Fuscaldito JT, Fireman P: Paraben allergy. *JAMA* 1977;237:1594–1595.
- 148 Malamed SF: Allergy and toxic reactions to local anesthetics. *Dent Today* 2003;22:114–116, 118–121.
- 149 Troise C, Voltolini S, Minale P, Modena P, Negrini AC: Management of patients at risk for adverse reactions to local anesthetics: analysis of 386 cases. *J Investig Allergol Clin Immunol* 1998;8:172–175.
- 150 Glinert RJ, Zachary CB: Local anesthetic allergy. Its recognition and avoidance. *J Dermatol Surg Oncol* 1991;17:491–496.
- 151 Mertes PM, Malinovsky JM, Jouffroy L, Aberer W, Terreehorst I, Brockow K, Demoly P: Reducing the risk of anaphylaxis during anesthesia: 2011 updated guidelines for clinical practice. *J Investig Allergol Clin Immunol* 2011;21:442–453.
- 152 deShazo RD, Nelson HS: An approach to the patient with a history of local anesthetic hypersensitivity: experience with 90 patients. *J Allergy Clin Immunol* 1979;63:387–394.
- 153 Grosman N: Histamine release from isolated rat mast cells: effect of morphine and related drugs and their interaction with compound 48/80. *Agents Actions* 1981;11:196–203.
- 154 Lin RY, Erlich ER, Don PC: Skin prick test responses to codeine, histamine, and ragweed utilizing the multitest device. *Ann Allergy* 1990;65:222–226.
- 155 Casale TB, Bowman S, Kaliner M: Induction of human cutaneous mast cell degranulation by opiates and endogenous opioid peptides: evidence for opiate and nonopiate receptor participation. *J Allergy Clin Immunol* 1984;73:775–781.
- 156 Nasser SM, Ewan PW: Opiate-sensitivity: clinical characteristics and the role of skin prick testing. *Clin Exp Allergy* 2001;31:1014–1020.
- 157 Harle DG, Baldo BA, Coroneos NJ, Fisher MM: Anaphylaxis following administration of papaveretum: case report – implication of IgE antibodies that react with morphine and codeine, and identification of an allergenic determinant. *Anesthesiology* 1989;71:489–494.
- 158 Juneja MM, Ackerman WE 3rd, Bellinger K: Epidural morphine pruritus reduction with hydroxyzine in parturients. *J Ky Med Assoc* 1991;89:319–321.
- 159 Joint Task Force on Practice Parameters, American Academy of Allergy, Asthma and Immunology, American College of Allergy, Asthma and Immunology, Joint Council of Allergy, Asthma and Immunology: Drug allergy: an updated practice parameter. *Ann Allergy Asthma Immunol* 2010;105:259–273.
- 160 Macy E, Schatz M, Zeiger RS: Immediate hypersensitivity to methylparaben causing false positive results of local anesthetic skin testing or provocative dose testing. *Permanente J* 2002;6:17–21.