

Practical Management of Patients with a History of Immediate Hypersensitivity to Common non-Beta-Lactam Drugs

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Abstract Immediate hypersensitivity reactions to medications are among the most feared adverse drug reactions, because of their close association with anaphylaxis. This review discusses a practical management approach for patients with a history of an immediate hypersensitivity to a non-beta-lactam medication, where reexposure to the implicated, or similar, medication is clinically necessary. Mechanisms associated with severe immediate hypersensitivity reactions include IgE-mediated mast cell activation, complement-mediated mast cell activation, and direct mast cell activation. Immediate hypersensitivity reactions may also be mediated by vasodilators, other pharmacologic mechanisms, or be secondary to underlying patient-specific biochemical abnormalities such as endocrine tumors or chronic spontaneous urticaria. The key features in the reaction history and the biochemistry of the implicated medication are discussed. Most individuals with a history of immediate hypersensitivity to a medication, who require reuse of that drug, can be safely retreated with a

therapeutic course of the implicated drug after a full-dose challenge, graded challenge, or desensitization, with or without premedication and/or any preliminary diagnostic testing, depending on the specific situation.

Keywords Adverse drug reaction · Allergy · Challenge · Complement · Desensitization · Graded challenge · Immediate hypersensitivity · IgE · Intolerance · Mast cell · Nanoparticle · Skin test

Abbreviations

ACE	Angiotensin converting enzyme
AERD	Aspirin exacerbated respiratory disease
BSA	Bovine serum albumin
GBCA	Gadolinium-based contrast agent
IV	Intravenous
MCAS	Mast cell activation syndrome
NMBA	Neuromuscular blocking agent
NERD	Non-steroidal anti-inflammatory drug exacerbated respiratory disease
NSAID	Non-steroidal anti-inflammatory drug
PPV	Positive predictive value

Introduction

Only a minority of medication *allergies* noted in medical records are associated with immediate hypersensitivity reactions. Because the word *allergy* is associated with all adverse reactions noted in medical records, anaphylaxis is often the feared result of reexposure. This can result in the use of alternative therapy that is less effective or more dangerous than properly managed reexposure. Immediate onset adverse drug reactions or immediate hypersensitivities are a significant

This article will restrict the word “allergy” to mean a confirmed clinically significant IgE-mediated immediate hypersensitivity. When “*allergy*” is used, it will refer to what is noted in a medical record pertaining to an adverse reaction or intolerance associated with the previous use of a specific medication or medication class that has not been confirmed to be IgE-mediated. The term “immediate hypersensitivity” will be restricted to reactions that start within 6 h of exposure to the implicated drug (1).

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problem with a wide range of medication use. These reactions can range from hives to anaphylaxis and, by definition, start within minutes to up to 6 h after exposure [1]. This review will concentrate on the management of the common, non-beta-lactam drug-associated, immediate hypersensitivity reactions seen in clinical practice.

Based on recent data obtained from the electronic medical records of the over 2.3 million individuals cared for by the Kaiser Permanente Health Care program in Southern California, representing about a 1 % sample of the US population who use healthcare, about 20 % report at least one drug *allergy* [2]. The five most common drug class *allergies* reported are to penicillins, sulfonamide antibiotics, opiates, non-steroidal anti-inflammatory drugs (NSAIDs), and angiotensin converting enzyme (ACE) inhibitors. There have been several recent reviews on the diagnosis and management of penicillin and other beta-lactam-associated adverse drug reactions published in Current Allergy and Asthma Reports, and these classes of antibiotics will not be covered in this review [3, 4]. Sulfonamide antibiotics and ACE inhibitors are rarely associated with immediate hypersensitivity. Most sulfonamide antibiotic-associated rashes, often T-cell mediated, take days to manifest. ACE inhibitor-associated cough or angioedema typically occurs after prolonged exposures; desensitization is not possible, and reexposure, particularly after angioedema, is contraindicated. ACE inhibitor-associated angioedema is thought to be a bradykinin-mediated reaction. Opiates and NSAIDs are often associated with immediate hypersensitivity reactions because of their direct effects on mast cell receptors. The other medication classes associated with *allergy* population prevalence rates on the order of 1 in 200 or greater include macrolide antibiotics, tetracyclines, quinolones, proteins, non-ACE inhibitor anti-hypertension medications, lipid regulators, and radio-contrast. Local anesthetics have *allergy* population prevalence rates of only about 1 in 500. Clindamycin, metronidazole, nitrofurantoin, antiepileptics, antidepressants, corticosteroids, stimulants, and neuromuscular blocking agents (NMBAs) all have relatively low rates of immediate hypersensitivity reactions and low *allergy* population prevalence. Vital dyes and platinum containing cancer chemotherapeutic agents have relatively high rates of immediate hypersensitivity reactions per exposure, but very low *allergy* population prevalence.

Most fatal anaphylaxis in the USA is thought to be associated with medication use [5]. Other significant causes include venom and food allergy. Medication-associated fatal anaphylaxis has been historically noted to be more common in African Americans and the elderly. Antibiotics and hyperosmolar intravenous (IV) contrast have been historically most commonly implicated in fatal anaphylaxis. Anesthesia and the perioperative period have been associated with about 20 % of fatal anaphylaxis cases in the USA, and iatrogenic causes have been associated with a majority of the fatal anaphylaxis cases in the United Kingdom [6].

Avoidance is still the mainstay of management of individuals with a history of immediate hypersensitivity to a specific medication, but rechallenge or desensitization should be considered when the potential benefits of reuse of the medication outweigh potential risks. There are a very limited number of clinically useful tests to help gauge the risk of full-dose rechallenge versus graded rechallenge versus desensitization for non-beta-lactam medications. The goal of this review is to provide an approach to patient management which minimizes the risks associated with both avoidance and reexposure.

Mechanisms

There are four general pathophysiologic categories one should be concerned about when evaluating individuals with a history of an immediate hypersensitivity reaction attributed to a medication. Certain drugs can be associated with more than one mechanism.

IgE-Mediated Activation of Mast Cells

In order for antigen-specific IgE to be produced, the medication must be either a protein or be able to haptenate a serum protein. An immediate hypersensitivity reaction mediated by antigen-specific IgE requires at least one exposure prior to the index reaction for the IgE to be produced and bind to mast cells. This may occur through a cross-reaction with another related chemical entity or a non-medical exposure. IgE-mediated reactions typically occur within minutes of an IV exposure or within minutes to up to an hour after an oral exposure to a small molecule that is able to haptenate serum proteins and react with preformed antigen-specific IgE. There can be a delay of up to several hours with IgE-mediated reactions associated with an oral exposure to an alpha-gal containing protein because of a lag in getting a sufficient quantity of the relatively large protein molecule through the gastrointestinal tract and into the intravascular space where it can bind to antigen-specific IgE on mast cells and induce anaphylaxis. Exercise can potentiate IgE-mediated reactions. A serum tryptase obtained during an acute event or within several hours of event onset has a ≥ 80 % positive predictive value (PPV) for identifying IgE-mediated anaphylaxis with a percent change over baseline tryptase of >141 % or an absolute tryptase of >15.7 mg/dl [7]. The mean histamine or tryptase levels in individuals undergoing cardiovascular collapse or shock from non-allergic cause or with resuscitation are not elevated [8].

Complement-Mediated Activation of Mast Cells

Certain medications, including most therapeutic proteins and high molecular weight dextran, can induce antigen-specific IgG, form immune complexes, and activate the complement system. This can then trigger mast cell mediator release and

potentially result in anaphylaxis. Liposome- and polymer-based nanomedicines can also directly activate the complement system and release C3a and C5a [9]. Direct complement activation appears to be the mechanism responsible for some intravenous iron-associated and cremophor-associated immediate hypersensitivity reactions.

Direct Activation of Mast Cells

Some medications directly activate mast cells, through a variety of mast cell receptors and metabolic pathways, and can induce immediate hypersensitivity reactions. Opiates, which directly bind a mast cell surface receptor, and NSAIDs, which inhibit the function of cyclooxygenase-1, are the medications most commonly implicated. A novel mast cell-specific receptor that may be directly activated by drugs has been recently identified in mice [10]. It is the mouse version of the human G protein-coupled receptor MRGPRX2. Nicotinic receptor agonist non-steroidal NMBA and quinolone antibiotics can bind this receptor and cause mast cell mediator release. This human G protein-coupled receptor may help explain the higher frequency of positive NMBA skin test results in individuals who are also quinolone skin test positive [11]. Heat, alcohol, and exercise can also potentiate direct mast cell activation. Direct non-specific mast cell activation is also more common in mast cell activation syndrome (MCAS). MCASs are associated with significantly higher rates of anaphylaxis in the setting of envenomation or anesthesia [12•]. Primary MCAS is associated with a c-KIT (proto-oncogene c-Kit, tyrosine-protein kinase Kit, or CD117) mutation, and clonal mast cells are detected. Primary MCAS is associated with an elevated baseline tryptase. Secondary MCAS is associated with an underlying inflammatory disease and often IgE-mediated allergy. Idiopathic MCAS has no known associations.

Other Pharmacologic Effects

Other medication-specific reactions resulting in apparent immediate hypersensitivity are also possible. Examples include the “red man” syndrome noted with vancomycin, amphotericin B, rifampicin, and teicoplanin infusions. Alcohol, nitrates, niacin, calcium channel blockers, prostaglandin E5 inhibitors, monosodium glutamate, sulfites, and alprostadil are all examples of small molecules that can act as either direct vasodilators or induce flushing, which may be interpreted as an immediate hypersensitivity reaction. The use of an ACE inhibitor may potentiate immediate hypersensitivity reactions caused by other medications. The specific physiology of the affected individual, such as having a lower level of alcohol-dehydrogenase activity, can predispose certain individuals to reactions. Individuals with carcinoid syndrome may have flushing with the use of selective serotonin reuptake

inhibitors, and individuals with pheochromocytoma may have reactions with beta-blocker exposure.

Determining the Risk of Reexposure

The history is the most important component of the work-up and management of an individual with an immediate hypersensitivity to a drug that requires that specific medication for future use. It is important to determine the timing from the index exposure to the start of the clinical symptoms that define the condition. If there is an IgE-mediated mechanism or direct mast cell activation potentially responsible for an immediate hypersensitivity reaction, then the immediate hypersensitivity reaction should occur with an initial therapeutic exposure, or a subsequent exposure, at least five serum half-lives after a previous exposure. It is not possible for a serous IgE-mediated reaction, anaphylaxis, or direct mast cell activation to occur if the mast cells are constantly exposed to the inciting medication with no more than a 50 % change in exposure concentration over a 15-min period. If there is a direct vasodilation or irritant effect from the medication, then the reaction typically will occur within minutes to perhaps an hour or two of exposure. It is also always possible that the reaction observed is completely unrelated to the medication implicated, and the adverse reaction has an alternative explanation.

The medical literature should be reviewed on the ability of an implicated medication to produce antigen-specific IgE, if any standardized skin test protocol or in vitro test has been developed to determine the presence of antigen-specific IgE or if the medication is known to directly activate complement or mast cells. The level of potential risk with future exposures that a medication associated with an immediate hypersensitivity reaction has can generally be divided into low-risk and high-risk based on a combination of the index reaction and the biochemical and immunologic properties of the medication. A low-risk history would be those with only hives, other rashes, GI upset, headache, flushing, or one other benign symptom in isolation. A high-risk history would be any with anaphylaxis, shortness of breath, or multiple organ symptoms involved. Low-risk medications would include those that are generally unable to efficiently haptenate serum proteins and/or produce antigen-specific IgE, are too small to be antigens by themselves, do not activate complement, and/or are not able to bind to or activate mast cells directly or indirectly. Specific examples of low-risk medications include macrolide antibiotics, local anesthetics, and non-ionic radiocontrast. High-risk medications would include large molecules that are able to directly function as immunogens, molecules able to haptenate serum proteins effectively and produce antigen-specific IgE or antigen-specific IgG with immune complex and complement activation, compounds able to directly activate complement, and/or are direct mast cell activators. Specific examples of high-risk medications include some

nanomedications, many therapeutic proteins, chlorhexidine, intravenous iron, isosulfan blue dye, methylparabens, cremophor, opiates, NSAIDs, quinolone antibiotics, NMBAs, and platinum containing anticancer medications.

Any exposures to the implicated medications prior to the index reaction should be determined. Any exposures, with or without symptoms, after the index reaction should be determined. Cofactors associated with the potential hypersensitivity event that may increase or decrease the risk of a subsequent reaction should be determined. These include the condition the drug was used to treat, if chronic urticaria was present, if potential mastocytosis was present, or if alcohol use or exercise was associated. If an underlying humoral immunodeficiency is present, with an inability to make serum IgE, then IgE-mediated allergy is not a possible mechanism for an acute hypersensitivity reaction.

Management

Select an alternative medication, whenever possible, if there is a confirmed history of an immediate hypersensitivity reaction. If, after careful consideration, reuse of the implicated medication is mandated because of a life-threatening condition or the potential risks of reexposure are less than the potential benefits of reuse, then proceed as directed below. Table 1 provides a general overview of the decision process on whether to give a full-dose challenge, graded challenge, or proceed with desensitization. Routine corticosteroid premedication has not been shown to prevent immediate hypersensitivity or anaphylaxis in individuals receiving non-ionic radiocontrast, snake antivenom therapy, or allergy immunotherapy and is generally ineffective in preventing recurrent immediate hypersensitivity

[13]. Antihistamines may blunt the clinical symptoms associated with IgE-mediated, complement-mediated, or direct mast cell activation, but one needs to be aware that anaphylaxis requiring epinephrine therapy may still occur.

Full-Dose Rechallenge

Full-dose rechallenge should only be used where there is a very low risk of serious immediate hypersensitivity. It is essential to observe for a long enough period to identify a potential serious reaction. For most medications, this will only be 1 h. For NSAIDs, 2 h may be necessary. Patients need to be informed of several things: the possibility of an immediate hypersensitivity reaction occurring up to 6 h after exposure, a plan to treat symptoms, and that delayed reactions occurring up to several days after any drug exposure are possible.

Graded Rechallenge

A graded challenge is generally used where there is a significant degree of uncertainty as to the mechanism of reaction or the severity of potential repeat reactions, but anaphylaxis is a very unlikely event. Graded challenges should be performed in an environment ready to treat anaphylaxis. The key feature to a graded rechallenge is the use of a 10-fold dosing increment and observation for a long enough time for the most serious suspected reactions to manifest. This is typically 1/2 to 1 h after each dose for most medications, and up to 2 h for NSAIDs. A usual starting dose is 1/10th of a therapeutic dose, followed by a full dose. If a higher risk is suspected, then the starting dose can be moved down to 1/100th of a therapeutic dose, followed by a 1/10th, and then a full dose.

Table 1 Suggested reexposure method to an implicated medication in patients with a history of an immediate hypersensitivity reaction

Risk factors	Direct full-dose challenge (oral if possible)	Graded challenge ^a (1/10th and then a full dose with 1 hour of observation after each dose)	Desensitization ^b (12-step, oral if possible, or IV using the 3-bag technique)
Low probability medication Hives or other benign index reaction	X		
Low probability medication Possible anaphylaxis		X	
High probability medication Hives or other benign index reaction No evidence for antigen-specific IgE		X	
High probability medication Possible anaphylaxis Evidence for antigen-specific IgE			X

^a A 3-dose graded challenge starting with 1/100th of a dose, and one hour of observation, could be used if there is heightened concern about the risk of starting with only 1/10th of the final therapeutic dose.

^b Fewer steps could be used if there was higher systemic exposure to the implicated medication during skin testing.

Desensitization

Desensitization may be considered when antigen-specific IgE or complement activation has been identified or the index reaction is confirmed as anaphylaxis. Desensitizations should only be performed by medical teams skilled in the management of allergic diseases and who are ready and able to treat severe anaphylaxis. When possible, oral desensitization should be done prior to a parenteral medication exposure. Table 2 provides an outline of a generic oral desensitization protocol starting with 1/2000th of a final therapeutic dose of 100 mg. It is generally more convenient to use dilutions of a solution of the medication, whenever possible, to obtain the low doses needed for the beginning of an oral desensitization. Castells and coworkers have published extensively on their clinical successes using a standardized 3-bag, 12-step IV desensitization protocol on individuals with both documented IgE-mediated and non-IgE-mediated immediate hypersensitivity reactions [14•]. Table 3 gives a generic version of their protocol for a medication requiring a 1000-mg parenteral therapeutic dose. The starting dose for an oral desensitization or the dose given during the first 15 min of an intravenous desensitization should be no more than 2 to 4 times higher than the systemic exposure a person would experience with a positive skin test result to that material. The common feature of both an oral desensitization and a 3-bag, 12-step IV desensitization is the use of a very low starting dose, 1/50,000th to 1/2000th of the final dose, and then doubling the dose every 15 min. If the threshold dose for inducing severe immediate hypersensitivity is known, starting at about ½ of that threshold dose, and then doubling the exposure every 15 min until a therapeutic dose is administered can be done. This may

Table 2 Generic 12-step oral desensitization protocol based on a 100-mg final therapeutic dose

Step	Dose (mg)	Time (min)
1	0.05	0
2	0.1	15
3	0.2	30
4	0.4	45
5	0.8	60
6	1.6	75
7	3.125	90
8	6.25	105
9	12.5	120
10	25	135
11	50	150
12	100	165

Total time = 180 min (3 h). OK to multiply the doses given by whatever factor is necessary for the final dose needed (for example if 250 mg is the final therapeutic dose, multiply all doses by the factor 2.5).

significantly shorten the time needed to achieve the desensitization. The slow change in the concentration of the medication does not allow mast cell activation to occur. The time interval between dose escalations may be extended to 30 to 60 min when complement activation appears to be the mechanism, if needed. If reactions occur, they are treated, the reacting dose is repeated, and the desensitization may proceed. Continued exposure to the medication is essential to maintain acute tolerance. If dosing is interrupted for more than five serum half-lives, then repeat desensitization is essential. Repeat desensitization is also essential prior to any future therapeutic exposure.

Specific Medications Associated With Immediate Hypersensitivity Reactions

Neuromuscular Blocking Agents

Pholcodine in over-the-counter (OTC) cough medications available in some parts of Europe may predispose people to NMBA-associated anaphylaxis [15]. Substituted ammonium ions are common to both NMBAs and pholcodine. Anaphylaxis to NMBA can occur without any previous known exposure to an NMBA. When pholcodine was withdrawn from the market in Norway in 2007, the incidence of NMBA-associated anaphylaxis fell by about one half by 2009. Pholcodine has not been used in the USA. NMBA-associated anaphylaxis accounts for typically less than 10 % of anesthesia-related reactions in the USA versus approximately 60 % of anesthesia-related reactions in France. Direct mast cell activation appears to be an important factor and the production of NMBA-specific IgE also appears possible. Atracurium and cisatracurium have the lowest rates of NMBA-associated immediate hypersensitivity [16].

Local Anesthetics

True IgE-mediated allergy to local anesthetics is extremely rare [17]. The use of local anesthetic may be associated with anxiety, toxicity from intravascular administration or over-dosage, as well as reactions to materials it is coadministered with such as epinephrine and methylparabens. To date, we have not identified any individuals who were skin test positive to a pure, full-strength local anesthetic in the Kaiser Permanente San Diego County healthplan members we serve. We have identified only 2 (0.8 %) individuals who were skin test positive to methylparabens out of the 252 we evaluated for local anesthetic-associated immediate hypersensitivity between 1985 and 2001 [18]. We identified 1 additional case of methylparaben skin test positivity since our previous publication through early 2015, out of 116 (0.9 %) additional individuals tested for lidocaine allergy, with 3 subjective challenge reactions also noted. One subjective reaction was also

Table 3 Generic 12-step parenteral 3-bag desensitization protocol to deliver 1 g of medication

Step	Rate (ml/h)	Time (min)	Volume (ml)	Dose (mg)	Cumulative dose (mg)
1	2	15	0.5	0.02	0.02
2	5	15	1.25	0.05	0.07
3	10	15	2.5	0.1	0.17
4	20	15	5.0	0.2	0.37
5	5	15	1.25	0.5	0.87
6	10	15	2.5	1.0	1.87
7	20	15	5.0	2.0	3.87
8	40	15	10.0	4.0	7.87
9	10	15	2.5	9.922	17.792
10	20	15	5.0	19.843	37.635
11	40	15	10.0	39.686	77.321
12	80	174.375	232.50	922.681	1000.00

Prepare three 250 ml bags of the medication with the following concentrations: Bag 1 (doses 1, 2, 3, and 4)=0.04 mg/ml; Bag 2 (doses 5, 6, 7, and 8)=0.40 mg/ml; Bag 3 (doses 9, 10, 11, and 12)=3.9685 mg/ml. Total time = 339.37 min (5 h and 39 min). OK to multiply the medication concentrations in bags 1 through 3 by whatever factor is necessary to deliver the needed dose (for example, if the final dose needed is 3500 mg, multiply the medication concentrations in bags 1 through 3 by the factor 3.5). The time may be increased to 30 or even 60 min at each step, if needed, for complement-mediated reactions.

noted out of 34 individuals tested to other local anesthetics. We use a 1-cc subcutaneous placebo saline challenge prior to a 1-cc subcutaneous full-strength local anesthetic challenge after the negative skin testing to provide proof to the patient that they are able to tolerate the local anesthetic [19]. Individuals who are T-cell-mediated contact sensitive (patch test positive) to typically applied local anesthetics typically tolerate the same chemical when injected without any immediate hypersensitivity.

Biologicals (Proteins)

Monoclonal antibodies and protein biologics have been widely reported to be associated with IgE- and IgG-mediated reactions [20]. Excipients, such as polysorbate in omalizumab and cremophor in taxanes, have also been implicated in immediate hypersensitivity reactions [21]. Even humanized or fully human monoclonal antibodies or human enzymes are able to induce antigen-specific IgE or IgG. Skin testing is able to identify anti-specific IgE, and desensitization protocols for immediate hypersensitivity to biologicals are well established [22]. Laboratory tests for antigen-specific IgG and evidence of complement activation during infusion reactions should be obtained.

True IgE-mediated allergy to natural rubber latex protein is becoming rarer since the late 1980s. The current prevalence of clinically significant sensitization is more than an order of magnitude lower than what was observed 20 to 30 years ago [23]. The commercially available blood allergy tests for IgE to latex protein are generally adequate to rule out clinically significant latex allergy in individuals with a poor latex allergy

history [24]. Contact dermatitis, a T-cell-mediated reaction, to chemicals in gloves and other rubber products is still fairly common.

Bovine serum albumin (BSA) in tissue culture material has been associated with IgE-mediated allergy during bone marrow transplantation [25]. Extensively washing the cells to remove the BSA can allow safe administration of the lifesaving cells. The role of IgG or IgE anti-IgA in causing immediate hypersensitivity reactions with immunoglobulin infusions is still controversial [26]. Typically slowing the immunoglobulin infusion rate, pretreatment with antihistamines and NSAIDs, and/or choosing an alternative preparation will allow repeat treatment in individuals with humoral immunodeficiency. Immunologically mediated immediate hypersensitivity is very common with enzyme replacement therapy. It can be both IgE- and IgG-mediated.

Chlorhexidine

There are rare case reports of chlorhexidine, particularly in the surgical setting, of being associated with immediate hypersensitivity reactions. Chlorhexidine can haptenate serum proteins. It is possible to skin test using chlorhexidine at 0.005 to 0.5 % [27]. Thermo Scientific also has a commercially available anti-chlorhexidine ImmunoCAP test, though there is limited data on its PPV.

Heparin

Skin testing protocols to evaluate potential IgE-mediated heparin immediate hypersensitivity have been published. Skin test

positivity to unfractionated heparin has been documented with tolerance to dalteparin, enoxaparin, tinzaparin, and fraxiparin [28].

Non-steroidal anti-inflammatory drugs

It is important to identify by history any individuals with potential aspirin exacerbated respiratory disease (AERD) or non-steroidal anti-inflammatory drug exacerbated respiratory disease (NERD) from individuals with only urticaria and/or angioedema associated with or exacerbated by exposure to NSAIDs [29]. Protocols for aspirin desensitization in the setting of NERD are well-established and should only be attempted by medical teams skilled in the management of Allergic diseases and who are ready and able to treat severe anaphylaxis [30]. The mean provocative dose of aspirin in individuals with NERD is about 86 mg [31]. Table 4 outlines a typical aspirin rechallenge protocol for an individual with a history of urticaria and/or angioedema associated with NSAID use, but no history compatible with AERD or NERD. Desensitization protocols for individuals with a history of urticaria or angioedema who react during the rechallenge protocol have been published [32].

Contrast Material

Ionic radiocontrast historically has been associated with most of the immediate hypersensitivity attributed to radiocontrast use. The use of low osmolar or iso-osmolar radiocontrast has dramatically reduced the frequency and severity of immediate hypersensitivity reactions. Kolbe and coworkers reviewed 299,413 low-ionic radiocontrast exposures and noted only 245 (0.08 %) with immediate hypersensitivity reactions, all hives [33]. No anaphylaxis was noted. There were 50 subjects with 133 total repeat exposures and about 20 % of the time urticaria occurred again. Premedication was associated with a higher reaction rate. Skin testing has not been shown to be useful based on very low rates of positive test results to implicated agents [34]. Selection of an alternative non- or low-ionic contrast, when possible, seems warranted as opposed to any attempt at a graded challenge or desensitization.

Linear ionic gadolinium-based contrast agents (GBCA) were noted by Aran and coworkers to cause immediate hypersensitivity reactions in 204 (0.1 %) of 1,944,000 exposures

Table 4 Three-dose oral aspirin challenge protocol for individuals with a history of NSAID-associated urticaria or angioedema without any evidence for AERD or NERD

Step	Aspirin dose	Observation time
1	40 mg	1 h
2	80 mg	1 h
3	324 mg	2 h

[35]. There were 33 (0.017 %) reactions which met criteria for anaphylaxis and 5 (0.0026 %) were severe, all occurring within 60 min of exposure. There were 8 individuals with a history of previous reactions, 5 were premedicated, and all still had reactions. Jung and coworkers reviewed 141,623 GBCA exposures at a single hospital and also noted females were more likely to have immediate hypersensitivity reactions than males [36]. They noted recurrent reactions in about 30 % of those individuals with a previous reaction history. A slightly higher rate of reactions was noted in individuals receiving multiple exposures, and premedication again did not help prevent reactions. The use of an alternative GBCA appears to be a reasonable approach at this time as opposed to any attempt at a graded challenge or desensitization.

Non-Beta-Lactam Antibiotics

Immediate hypersensitivity is commonly associated with non-beta-lactam antibiotic use but is rarely IgE-mediated. Viral infections are often associated with rashes, including urticaria, and a macrolide antibiotic, given inappropriately, may be then associated with the rash. Macrolide antibiotics, specifically erythromycin, are also directly irritating when they accidentally get into the extravascular space. Macrolides are unable to haptenate other serum proteins, and they are too small to be direct stimulators of IgE. A graded rechallenge, 1/10th of the oral therapeutic dose followed an hour later by a full oral dose, with the same or an alternative macrolide is a reasonable approach. Quinolone antibiotics can directly activate mast cells, and thus skin testing is not useful. There appears to be significant cross-reactivity for immediate hypersensitivity between quinolones. A graded challenge of 1/100th, 1/10th, and then a full dose with an hour of observation between doses is a reasonable approach, as long as anaphylaxis was not the index event. Desensitization has been reported with quinolones. Tetracyclines, metronidazole, nitrofurantoin, and clindamycin are all unlikely to induce antigen-specific IgE. Again, a graded challenge using 1/10th and then a full dose with an hour of observation between doses is a reasonable approach, as long as anaphylaxis was not the index event.

Platins

Carboplatin hypersensitivity typically occurs after multiple exposures [37]. Skin testing protocols and desensitization protocols have evolved over the last decade. Milder cases can use shorter desensitization protocols, and more serious cases can be managed using the standard 3-bag, 12-step protocols.

Dyes

Vital dyes, which are able to bind serum proteins [38], such as isosulfan blue, have one of the highest rates of immediate

hypersensitivity per exposure (0.73 %) of commonly used materials, though a minority of these reactions meet criteria for anaphylaxis [39]. These reactions occur despite antihistamine premedication and are not correlated to any allergy history. Skin testing can be used to document hypersensitivity but is only useful after an index event. These types of dyes are widely used in food and in textile manufacturing, and, apparently, allergic sensitization can occur without a previous medical exposure. Desensitization is theoretically possible, but not clinically practical. The level of cross-reactivity to similar blue dyes is probably high. The alternative for lymph node mapping is using only a radioactive tracer.

Opiates

Opiates directly activate mast cells. Skin testing with opiates is not clinically useful [40]. Codeine was used in the past as a positive control for skin testing. Modified opiates, such as fentanyl, have been developed that are poorer at direct mast cell activation. Pretreatment with antihistamines allow most individuals to tolerate at least one of the opiates and achieve adequate pain control. A grade challenge using 1/10th and then a full dose can be performed if felt necessary.

Conclusions

It is possible to manage the majority of individuals with a history of immediate hypersensitivity to a medication by continued avoidance or selection of alternative therapy. When the medication must be used to treat a life-threatening condition, or when the reaction history is benign and the potential benefits of reexposure are great, an appropriate use of testing followed by a full-dose rechallenge, graded challenge, or desensitization can be safely accomplished in most clinical scenarios.

Compliance with Ethical Standards

Conflict of Interest The author is a partner of the Southern California Permanente Medical Group (SCPMG). SCPMG provided the majority of the funding for the work reviewed here in which the author participated. Eric Macy is a previous chair of the Adverse Reactions to Drugs and Biologics Committee of the American Academy of Allergy Asthma and Immunology (AAAAI). He has received research grants from the United States Food and Drug Administration (FDA) and ALK Abello, Inc. to study adverse drug reactions. He is a member of clinical trial safety and monitoring committees for BioMarin Pharmaceutical, Inc., Tufts University, and Ultragenyx, and has done consulting for KaloBios. The commentary presented here is the opinion of the author and does not reflect the policy of the AAAAI.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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