

Anaphylaxis to Drugs, Biological Agents, and Vaccines



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KEYWORDS

- Anaphylaxis • Aspirin-exacerbated respiratory disease
- Contrast-induced anaphylaxis • Drug-induced anaphylaxis
- NSAID-Induced anaphylaxis • Vaccine-induced anaphylaxis

KEY POINTS

- -Drug allergy is a common cause of anaphylaxis in adults, most often from antibiotic or analgesic use.
- There are few antibiotics with well-validated skin testing concentrations; however, evaluation by a board-certified allergist/immunologist in cases of antibiotic anaphylaxis is paramount to consider skin testing and graded dose challenge.
- Aspirin and NSAIDs may cause serious adverse reactions, including anaphylaxis; desensitization can be accomplished successfully for patients with aspirin-exacerbated respiratory disease and nonsteroidal anti-inflammatory drug-induced urticaria/angioedema, but not for patients with nonsteroidal anti-inflammatory drug exacerbated cutaneous disease.
- As the use of biological agents is becoming more common, immediate and nonimmediate hypersensitivity reactions are being observed; elucidating the mechanism for these reactions can direct the next steps in diagnosis and management.
- Risk of anaphylaxis after vaccines is rare; when it occurs, typically this is due to an additive rather than the active antigen component.

INTRODUCTION

Anaphylaxis is a life-threatening systemic reaction, defined by a range of clinical characteristics. Definitions for the diagnosis of anaphylaxis generally include acute onset and involvement of multiple organ systems.¹ The reported prevalence of anaphylaxis is 1.6% to 5.1%,^{1,2} which is increasing, and is likely an underestimate.³ Older age and comorbidities (eg, cardiac and lung disease) are associated with greater risk for severe anaphylaxis.⁴ The most common inciting agents for anaphylaxis are foods,

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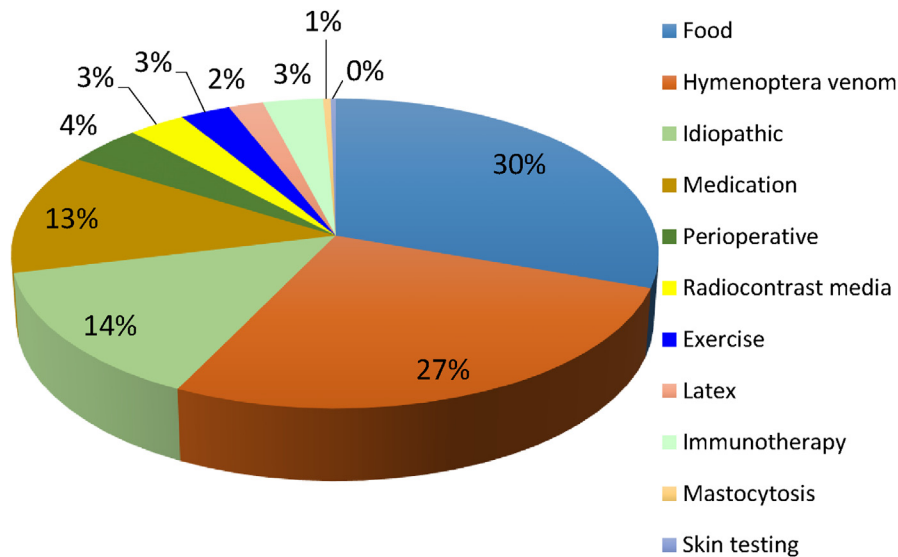


Fig. 1. Causative agents for anaphylaxis. This pie figure displays relative proportions of causes for anaphylaxis in the Department of Allergy and Clinical Immunology at Cleveland Clinic for 730 cases from July 2002 to October 2013. Food allergy was the most common etiology of anaphylaxis, followed by hymenoptera venom, idiopathic anaphylaxis, and medications; 3.6% of cases had more than a single cause for anaphylaxis.

hymenoptera venom, and medications (Fig. 1).⁵ The frequency of these triggers varies by age: for adults medications and hymenoptera venom are more commonly observed, for children, foods, and hymenoptera venom.²

DRUGS

Drugs account for a large proportion of anaphylaxis cases in adults, ranging from 22% to 42%, depending on geographic location. In the United States, 1% of the population experiences at least one episode of drug-induced anaphylaxis (DIA).⁶ In an electronic medical record (EMR) review of over 2.7 million patients, 14% of individuals in the United States reported a drug-induced hypersensitivity reaction (HSR), 8% were consistent with anaphylaxis.⁶

The incidence of DIA increases with age. In a Latin American registry, DIA comprised 43.5% of cases in those over 40 years old, 33% of cases in 18 to 40 years old, and 20% of cases in those under 20 years old.⁷ These findings have been replicated in other countries.^{8,9} Apart from age, female sex is associated with higher rates of DIA and more severe reactions.^{9,10} Although older individuals may acquire this risk due to greater medication exposures, chromosomal genetics, or hormonal factors could account for the female predilection for DIA.

DIA is associated with increased reaction severity; for this reason, in evaluating potential etiologies it is paramount to maintain a high index of suspicion for DIA. Among emergency department visits for anaphylaxis, DIA has been associated with more frequent hospitalizations.⁹ DIA is more likely to result in fatality, accounting for over half of anaphylaxis fatalities in the United States and Australia.^{11,12} Antibiotics,

radioiodinated urographic contrast media (RUCM), and other diagnostic agents have been implicated most commonly in fatal anaphylactic events.¹¹

The most common causative agents for DIA are antibiotics and analgesics, dependent on geographic location. In the United States, antibiotics account for 66% of DIA cases.¹³ Data from the United Kingdom and China report similar rates. Studies from Portugal and Latin America found nonsteroidal anti-inflammatory drugs (NSAIDs) comprised the majority (73%) of DIA cases.⁷ The causes of these variations are unknown, but likely are related to drug prescription patterns and genetic predisposition for HSRs.

Antibiotics

Although nearly one-third of patients report allergy to antibiotics, this is still a relatively rare occurrence. Although up to 15% of individuals self-report beta-lactam allergy,¹⁴ fewer individuals have documented cases of anaphylaxis. A review of 1.7 million patients found penicillin anaphylaxis in 45.9 per 10,000 patients, followed by sulfonamides (15.1 per 10,000 patients), cephalosporins (6.1 per 10,000 patients), and macrolides (3.8 per 10,000 patients).¹³ Fatal anaphylactic events are rare: one fatal anaphylactic event from oral amoxicillin was found over 35 years, with 100 million treatment courses in the United Kingdom.¹⁵

The prevalence of antibiotic-induced anaphylaxis is low; nevertheless, the life-threatening nature of this reaction necessitates careful evaluation when drug allergy is listed in the medical record. It is imperative to determine which patients with self-reported allergy are at risk for anaphylaxis and should avoid future exposure to a given medication. Alternatively, it is important to identify which patients can safely reintroduce antibiotics listed as “allergic”, as needless avoidance is also associated with untoward outcomes.¹⁶ Thoughtful consideration of drug allergy history, risk factors, and availability of validated testing all play a role in determining appropriate antibiotic allergy evaluation.

DIA can occur through immunologic or nonimmunologic means. Nonimmunologic reactions involve direct stimulation of mast cells or basophils. This occurs more commonly with analgesic medications, but is also reported with RUCM and antibiotics (eg, vancomycin). Comprehensive clinical history, skin testing, and/or serologic testing can aid in identifying IgE-mediated sensitivity.

Anaphylaxis is a clinical diagnosis. When clinical suspicion is warranted, based on symptoms that occur soon after antibiotic exposure, skin testing is often the next step. Drug skin testing involves percutaneous (“prick”) and intradermal skin tests at nonirritating concentrations.^{17,18} This is a safe procedure, even in individuals with a history of severe anaphylaxis. Validity of these skin tests varies considerably by drug. For example, skin testing for penicillin is well-established, and carries a high negative predictive value of 98%.^{19,20} Most other antibiotic skin testing is based on limited data of nonirritating concentrations.

Serum-specific IgE testing to beta-lactams is available, but not recommended due to poor sensitivity. A negative result necessitates skin testing, thus most providers proceed directly to skin testing. Basophil activation testing measures mediator release after in vitro basophil stimulation. This testing is not frequently used, as it has low sensitivity and limited availability.²¹

If skin testing and/or serologic evaluation is negative, observed direct provocation challenge is recommended. This can be conducted as a single dose or a graded-dose challenge, depending on drug reaction history and patient risk factors. Much of the data regarding the safety of oral challenge derives from beta-lactams. After negative penicillin skin testing with major and minor determinants, only 2% to 3% of

individuals exhibit clinical reaction—generally mild and limited to the skin—on challenge.^{20,22}

If skin testing is positive, continued avoidance with the use of an equally efficacious alternative is recommended. When no equally effective substitute can be used, drug desensitization can be performed. This procedure induces drug tolerance using gradually increasing doses of the medication. Drug desensitization does not “cure” the IgE-mediated sensitivity, but rather induces a temporary state of tolerance to allow for treatment.²³ Anaphylaxis during this procedure is infrequent, but still can occur.

Nonsteroidal Anti-inflammatory Drugs

Aspirin (ASA) and NSAIDs have been implicated in a wide variety of adverse reactions, including cutaneous reactions in patients with NSAID exacerbated cutaneous disease (NECD) and NSAID-induced urticaria angioedema (NIUA), and respiratory reactions in patients with aspirin-exacerbated respiratory disease (AERD)—each occurring via cyclooxygenase (COX)-1 inhibition.^{24–26} Although patients and health care providers may label such reactions as an “allergy”, it is important to establish the understanding that such reactions are more related to biochemistry than to IgE-mediated pathogenesis. Aspirin and NSAIDs also account for other drug-induced adverse reactions—including anaphylaxis^{27,28}; in contrast to the above sensitivity syndromes, patients with single NSAID-induced urticaria, angioedema, or anaphylaxis (SNIUAA) do not cross-react with structurally unrelated NSAIDs. The characteristics of these aspirin sensitivity syndromes are displayed in [Table 1](#).

AERD

The initial report of ASA intolerance appeared more than a century ago, only 3 years after aspirin was synthesized.²⁹ Fatal reactions from aspirin were described in the 1930s.^{30,31} However, it was not until 1968 that Samter and Beers described a clinical “triad” of nasal polyposis, bronchial asthma, and “life-threatening reactions to acetyl-salicylic acid” as a clinical syndrome.³²

Table 1 Aspirin sensitivity syndromes			
Aspirin Sensitivity Syndrome	Underlying Condition	Cross-Reaction with Structurally Unrelated COX-1 Inhibitors	Induction of Tolerance Achievable
AERD	Chronic Rhinosinusitis with Nasal Polyposis and Asthma*	Yes	Yes
NECD	Chronic Urticaria	Yes	No
NIUA	N/A	Yes	Yes
SNIUAA	N/A	No	Possibly

Abbreviations: AERD: aspirin-exacerbated respiratory disease; NECD: Nonsteroidal anti-inflammatory drug exacerbated cutaneous disease; NIUA: Nonsteroidal anti-inflammatory drug-induced urticaria/angioedema; SNIUAA: Single nonsteroidal anti-inflammatory drug-induced urticaria, angioedema, and/or anaphylaxis.

* In a small proportion of AERD cases, chronic rhinosinusitis with nasal polyps is present without asthma.²⁴

In patients with AERD, respiratory reaction with potentially serious bronchospasm occurs after exposure to ASA or an ASA-like drug; even a subtherapeutic dosage of ASA or NSAID can lead to potentially life-threatening bronchospasm. ASA and NSAIDs, including ibuprofen, naproxen, indomethacin, and so forth, share the action of COX-1 inhibition and are 100% cross-reactive in AERD patients. Cross-reaction may also occur with higher doses of nonacetylated salicylates³³ or acetaminophen,³⁴ which are poor inhibitors of COX-1 and COX-2. Selective inhibitors of COX-2 (eg, celecoxib) do not cross-react.³⁵

AERD affects an estimated 7% of adult asthmatics, and twice as many with severe asthma.³⁶ AERD generally develops in the 3rd or 4th decade of life.³⁷ Once AERD develops, it is present lifelong.

The pathogenesis of respiratory reaction provoked by ASA or NSAID in patients with AERD is related to COX-1 inhibition.^{24,37} COX-1 blockade leads to loss of inhibition of the enzyme PGE₂, leading in turn to the activation of inflammatory cells—mast cells, basophils, eosinophils, and platelets, and excessive production of histamine, PGD₂, tryptase, and sulfidopeptide leukotrienes (LTC₄, LTD₄, LTE₄). Upper and/or lower respiratory reaction occurs in 30 to 180 minutes. These inflammatory cells and mediators also contribute to ongoing airway obstruction and inflammation that persists in AERD despite avoidance of ASA and other COX-1 inhibiting drugs.²⁴ Although AERD includes several phenotypes,³⁸ this condition can appropriately be designated as an endotype in terms of being a mechanistically distinct asthma subgroup.

ASA-provoked reaction can be attenuated by administration of antileukotriene drugs; however, the protection is incomplete, and the response is heterogeneous.³⁹ Antileukotriene drugs shift the dose-response curve to the right, and transfer ASA-provoked reaction to the upper airway. More recently, omalizumab has also been associated with attenuation of ASA-provoked respiratory reaction.⁴⁰

Management of AERD includes avoidance of ASA/NSAIDs, medications as appropriate based on best evidence for chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma, and performance of sinus surgery in properly selected patients.²⁴

The term “desensitization” has traditionally been used to describe a procedure that entails modification of IgE-mediated (allergic/anaphylactic) potential to a substance—frequently an antibiotic such as penicillin, via its repetitive administration in a graded-dose fashion. Widal managed a patient in 1922,⁴¹ with gradually increasing doses of ASA, such that instead of reacting when a previously-established provoking dose was administered, ASA re-exposure was tolerated without adverse reaction. Zeiss and Lockey⁴² observed the same phenomenon of tolerance induction, and ultimately this procedure was used to allow individuals with AERD who required ASA (eg, for the treatment of cardiovascular conditions) to take ASA safely.

The ASA desensitization procedure, in which a state of “tolerance” can be induced and maintained, entails the administration of incremental oral doses of aspirin until a dosage of 325 mg can be taken without respiratory reaction.²⁴ Several protocols for ASA desensitization have been published,⁴³ some including intranasal ketorolac challenge.⁴⁴ ASA tolerance can be perpetuated indefinitely if ASA is taken on a daily basis.

Improvement with ASA desensitization treatment has included improved upper and lower airway symptoms, reduced medication reliance, and less morbidity as reflected in fewer annual episodes of infection and fewer sinus surgery procedures over time.⁴⁵ ASA desensitization can be considered for patients with AERD who are not well controlled, including those with frequent corticosteroid reliance and/or refractory rhinosinusitis who require repeated sinus surgeries.²⁴

Dupilumab, omalizumab, and mepolizumab are efficacious for the treatment of patients with AERD,^{46,47} and have been approved by the FDA for refractory asthma and

CRSwNP, respectively. Each has been associated with improved outcome measures of upper and lower airways and quality of life. No head-to-head studies comparing the relative efficacy or safety of these biologic agents have been published to date, nor has there been a study comparing a biological agent vis-à-vis ASA desensitization for treatment outcomes of AERD.

There are 5 randomized controlled trials,^{48–52} as shown in **Table 2**, in which the efficacy of ASA desensitization treatment was assessed. All demonstrated benefit, however, several do not provide high-quality evidence in support of ASA desensitization treatment as a therapeutic intervention. Of note is the study by Swierczynska-Krepa, and colleagues—which included subjects who were ASA-tolerant. In contrast to the benefit observed in AERD subjects, those without AERD exhibited no benefit with ASA compared with placebo, underscoring the importance of not encouraging patients who are ASA tolerant to proceed with the daily administration of ASA with the expectation this may have a salutary effect.

NONSTEROIDAL ANTI-INFLAMMATORY DRUG EXACERBATED CUTANEOUS DISEASE

Approximately 20% to 30% of patients with chronic urticaria have NECD—which entails the acute exacerbation of urticaria/angioedema with exposure to ASA/NSAID.⁵³ This can be viewed as a cutaneous form of ASA sensitivity in which all agents that inhibit COX-1, via release of cysteinyl leukotrienes,⁵⁴ provoke the exacerbation of the underlying disease. Similar to AERD, COX-2 inhibitors are tolerated in patients with NECD without untoward reaction. Attempts to induce tolerance via desensitization protocols have been unsuccessful, and in general, these patients should be encouraged to avoid ASA and NSAIDs. When ASA is clearly indicated without an equally effective alternative, such as for cardioprotection,⁵³ direct challenge should be carried out as the provoking dose for the reaction is frequently less than 81 mg.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS-INDUCED URTICARIA ANGIOEDEMA

In patients with NIUA, ASA/NSAIDs provoke urticaria or angioedema in the absence of underlying chronic urticaria. The mechanism also entails COX-1 inhibition. These patients will also cross-react with structurally unrelated NSAIDs. If favorable from an individualized risk/benefit standpoint, when aspirin is required for primary or secondary cardioprotection, NIUA patients are candidates for ASA challenge. In contrast to NECD, when a reaction occurs the induction of tolerance in properly selected cases can be achieved.⁵³

SINGLE NON-STEROIDAL ANTI-INFLAMMATORY DRUG INDUCED URTICARIA, ANGIOEDEMA, AND/OR ANAPHYLAXIS (SNIUAA)

Although any NSAID can theoretically cause anaphylaxis, this has been most commonly recognized with certain NSAIDs, such as phenylbutazone.⁵⁵ Anaphylaxis has also been observed more frequently than expected with tolmetin.⁵⁶ Zomepirac,⁵⁷ a structurally analogous pyrrole acetic acid differing in structure by only one methyl and one chlorine atom, was voluntarily withdrawn by its manufacturer from the US market, based on more than 1000 suspected “allergic” reactions, including 5 deaths.⁵⁸

Typically, anaphylaxis is provoked by a single NSAID or 2 NSAIDs that are structurally similar.²⁶ Patients with DIA to one NSAID generally tolerate structurally unrelated NSAIDs, including ASA, without untoward reaction; unlike AERD and NECD, all

Table 2

Randomized controlled trials examining the role of aspirin desensitization in aspirin-exacerbated respiratory disease

	Study Design	Subjects Enrolled	Subjects Completing Participation	Results	Comments
Stevenson et al, ⁴⁸ 1984	RDBPC Cross-over	38	25	Improved symptoms and reduced medication reliance for rhinosinusitis, 50/50 for asthma. Trend for greater improvement with higher ASA dose	Subjects were treated with 325 mg daily, 325 mg QID, 650 mg QID.
Fruth et al, ⁴⁹ 2013	RDBPCPG	70	31	Improved rhinosinusitis symptoms and QOL, trends for lower polyp score and polyp relapse.	Subjects enrolled after sinus surgery. ASA desensitization treatment dose 100 mg/d.
Swierczynska-Krepa et al, ⁵² 2014	RDBPCPG	20	15	Improved symptoms, SNOT-20, ACQ, PNIF, ICS reliance	ASA-tolerant asthmatics also randomized to treatment or placebo – no benefit with ASA
Esmaelizadeh et al, ⁵⁰ 2015	RDBPCPG	39	31	Improved symptom scores, FEV1, QOL.	Antihistamines, beta-agonists, corticosteroids suspended 48 h before intranasal ketorolac/oral ASA challenge
Mortazavi et al, ⁵¹ 2017	RDBPCPG	41	38	Improved symptom and medication scores, FEV1, QOL.	Antihistamines, beta-agonists, corticosteroids suspended 48 h before intranasal ketorolac/oral ASA challenge

Abbreviations: ACQ, asthma control questionnaire; ASA, aspirin; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; PNIF, peak nasal inspiratory flow; QOL, quality of life; RDBPC, randomized, double-blind, placebo-controlled; RDBPCPG, randomized, double-blind, placebo-controlled, parallel-group.

NSAIDs need not be avoided. Positive skin tests have been reported in cases of anaphylaxis to pyrazolones²⁹; however, in most cases, it is prudent to recommend avoidance of the culprit drug and structurally similar NSAIDs, and perform oral challenge under observation to ASA or a structurally dissimilar NSAID. Some reactions may occur via IgE-mediated pathogenesis; however, DIA with initial exposure to the NSAID implies non-IgE-mediated anaphylaxis also accounts for a proportion of these cases.³⁰ Desensitization is generally not recommended for patients with NSAID-provoked anaphylaxis, as a structurally unrelated NSAID that is, equally efficacious can be tolerated. Should anaphylaxis occur related to ASA, assuming this is IgE-mediated and that ASA is required without an equally effective substitute—for example, for secondary cardioprotection, a desensitization procedure may be entertained. However, IgE-mediated anaphylaxis to aspirin is very rare, if it exists at all.

BLENDING REACTIONS

It should also be noted there are patients who exhibit a “blend” of cutaneous and respiratory reaction, with/without gastrointestinal symptoms, to ASA/NSAIDs,⁵⁹ and do not neatly fit into one of the categories displayed in [Table 1](#). This subgroup has not been as well characterized, but seems to reflect a combination of AERD and NIUA, which otherwise present as distinct phenotypes.

Radioiodinated Urographic Contrast Media

Anaphylaxis to RUCM is relatively rare, reported in 0.02% to 0.04% of patients.⁶⁰ Fatal anaphylaxis is reported in 1 to 3 per 100,000 RUCM administrations. Most reactions begin within 5 minutes of RUCM exposure. These reactions were thought to be primarily nonimmunologic, reflecting mast cell/basophil degranulation leading to anaphylaxis. However, recent data also implicate IgE-mediated sensitization accounting for RUCM HSRs.

These media previously were high-osmolar relative to plasma, consisting of a single benzene ring that ionized in solution. This was associated with a relatively high rate of adverse reactions (including non-IgE-mediated HSRs), with one study identifying a prevalence of 12.66%. In the late 1980s, low-osmolar contrast media were introduced. These monomers dissolved in water, but did not dissociate, thus their “low osmolar” designation. Rates of adverse reactions were much lower. Iso-osmolar agents that do not dissolve in solution have also been developed. These also have a lower rate of adverse reactions. Iso-osmolar agents have been associated with a higher rate of HSRs than low-osmolar agents.⁶¹

Standard of care for the management of prior reactors who require administration of RUCM involved pretreatment with antihistamines and corticosteroids. Administering these medications at specific time intervals to prior reactors before RUCM re-exposure significantly reduced the rate of HSRs. Because high-osmolality contrast material is rarely used, pretreatment has become more controversial. A 2020 systematic review found no reduction of risk for HSRs in patients receiving glucocorticoid and/or antihistamine pretreatment, with a calculated risk ratio of 1.07 (95% CI 0.67–1.71).¹ Davenport and colleagues found that premedication with a 13-h prednisone regimen was associated with increased length of hospital stay, longer time to obtain imaging, and increased risk of hospital-acquired infections.⁶² Based on this evidence, the 2020 anaphylaxis practice parameter issued a conditional recommendation against the use of prophylactic glucocorticoid and/or antihistamine pretreatment for prior reactors who require RUCM.¹

Skin testing is not routine; however, this may be considered in the evaluation of selected patients with RUCM anaphylaxis. Skin testing may be performed with undiluted RUCM, and if negative completing intradermal testing with a 1:10 dilution.^{60,63} If positive, testing to other RUCMs may also be performed. Cross-reactivity between different RUCMs has been defined sufficiently to guide the use of alternative agents.⁶⁴

Gadolinium-based Contrast Media

Gadolinium is a heavy metal with paramagnetic properties that provides contrast for intravascular or intraluminal use in MRI studies. Gadolinium-based contrast media (GBCM) can be categorized based on net charge (ionic or nonionic) and structure (linear or macrocyclic),^{65,66} as shown in [Table 3](#).

Adverse reactions to GBCM occur at a lower rate than to RUCM. The rate of anaphylaxis ranges from 0.004% to 0.7%; severe reactions occur rarely, in a range of 0.001%–0.01%.⁶⁷ Fatal anaphylaxis has been reported.⁶⁸

Similar to RUCM reactions, pathogenesis frequently entails activation of mast cells and basophils due to the hyperosmolar nature of GBCM, with elevation in serum tryptase.⁶⁵ Some cases of anaphylaxis occur on first exposure to GBCM, consistent with a non-IgE-mediated mechanism. However, wheal/flare reaction on skin testing has also been reported⁶⁹; positive Prausnitz–Kustner reaction has been observed.⁷⁰

As is the case for RUCM, elevated risk for anaphylaxis exists in prior reactors with re-exposure to GBCM and has been reported in association with female gender, patients with “drug allergy”, “food allergy”, or patients with a history of “allergies and asthma”.⁷¹ It is unclear whether patients who have had non-IgE-mediated anaphylaxis from RUCM are directly at elevated risk from receiving GBCM, as there may be an indirect hazard associated with shared risk factors; however, the overwhelming most of the prior reactors to RUCM tolerate GBCM without adverse reaction.

Skin testing with a panel of GBCM has been recommended to confirm IgE-mediated potential to the GBCM associated with anaphylaxis and to identify a skin test negative alternative GBCM that can be used.⁶⁵ When GBCM administration is required despite wheal/flare reactions to all GBCM, desensitization can be performed so that GBCM re-exposure can be tolerated without remarkable untoward reaction.⁷²

Management of anaphylaxis to GBCM is similar to anaphylaxis from other causes, with the additional recommendation that patients be immediately removed from the imaging room so that none of the resuscitative equipment becomes a magnetic threat.⁶⁷

BIOLOGICAL AGENTS

Monoclonal antibodies (mAb) are used as targeted therapy in many medical conditions—including allergic/immunologic disorders, chronic inflammatory conditions, and malignancy. As mAb are used more commonly, more frequent HSRs, both immediate and nonimmediate, have been observed.⁷³ As detailed in [Table 4](#), there are 3 categories of immediate reactions associated with mAb; clinical symptoms vary accordingly.⁷³ Elucidating the likely mechanism of reaction can direct next steps in evaluation and management.⁷³

Omalizumab

Omalizumab is a humanized mAb administered subcutaneously for treatment of moderate to severe allergic asthma, chronic idiopathic urticaria, and nasal polyps.⁶³ Its mechanism of action entails the formation of small immune complexes with free IgE antibodies.⁷⁴ Anaphylaxis to omalizumab is rare and has been reported in 0.09% to

Table 3 Gadolinium-based contrast agents			
Brand Name	Generic Name	Molecular Structure and Net Charge	Comments
Magnevist	Gadopentetate dimeglumine	Linear, ionic	Oldest agent in use
MultiHance	Gadobenate dimeglumine	Linear, ionic	
Omniscan	Gadodiamide	Linear, nonionic	
Dotarem, Clariscan	Gadoterate meglumine	Macrocytic, ionic	
ProHance	Gadoteridol	Macrocytic, nonionic	Lowest osmolality and viscosity
Gadavist	Gadobutrol	Macrocytic, nonionic	Highest viscosity
Eovist	Gadoxetate disodium	Linear, ionic	Used for hepatic imaging

0.2% of patients.^{75,76} A majority occur within 1 hour of administration. Delayed reactions have also been reported. Two hours observation after the first 3 doses of omalizumab, when anaphylaxis is more likely,⁷⁶ has been recommended, followed by 30 minutes with subsequent doses.⁷⁵ More recently, at-home administration was approved by the FDA for properly selected patients.⁷⁷ A recent case-control study found a prior history of anaphylaxis was associated with greater risk of anaphylaxis to omalizumab (odds ratio (OR): 8.1; 95% confidence interval (CI): 2.7–24.3)⁷⁸ The mechanism of anaphylaxis to omalizumab is unclear. In the same study, no serum IgE or IgG toward omalizumab was detected in 21 patients with anaphylaxis.⁷⁸ Skin testing protocols have been described, using skin prick testing with full strength omalizumab and intradermal testing with a 1:10,000 dilution. In patients with HSR to omalizumab, it is not recommended to rechallenge. Successful desensitization has been reported.⁷⁹

Anti-IL-5/IL-5 Receptor Biologics

Mepolizumab

Mepolizumab, approved for the treatment of persistent asthma, CRSwNP, and eosinophilic granulomatosis polyangiitis is a humanized mAb that exerts its effect by binding to IL-5. The FDA package insert reports no anaphylaxis.^{80,81} In several studies of subjects with severe eosinophilic asthma treated with mepolizumab, there were no

Table 4 Mechanisms of immediate HSRs to monoclonal antibodies		
Mechanism	Clinical Features	Skin Test
IgE mediated	• May occur on first exposure but onset usually after at least one exposure • Elevated tryptase	Positive
IgG mediated	• Onset usually after several exposures	Negative
Cytokine release syndrome	• Fever and chills • Onset usually on first exposure	Negative

Adapted from Picard M, Galvão VR. Current Knowledge and Management of Hypersensitivity Reactions to Monoclonal Antibodies. J Allergy Clin Immunol Pract. 2017 May-Jun;5(3):600 to 609.

reports of anaphylaxis.^{80,82,83} DREAM, a multicenter study done between 2009 and 2011, reported HSRs in $\leq 1\%$ of patients who received mepolizumab, than 2% who received placebo. There were no reports of anaphylaxis.^{80,84}

Reslizumab

Reslizumab is an IL-5 antagonist mAb used in the treatment of persistent asthma. An RCT reported 2 subjects of 477 randomized to reslizumab had anaphylaxis.⁸⁵ A study looking at long-term safety data reported no cases of anaphylaxis.⁸⁶ The FDA prescribing information reports anaphylaxis in 3 patients treated with reslizumab.^{80,85}

Benralizumab

Benralizumab is a humanized mAb that binds to the α -subunit of the IL-5 receptor used for the treatment of severe eosinophilic and allergic asthma.⁸⁷ The FDA label describes a 3% incidence of HSRs (anaphylaxis, urticaria, rash, and angioedema) in subjects randomized to benralizumab.⁸⁷ A meta-analysis of 8 RCTs did not show an increased risk of HSR with benralizumab than placebo.^{80,88}

Dupilumab

Dupilumab, a humanized mAb, binds to the α unit of the IL-4 receptor and modulates signaling of IL-4 and IL-13. It is approved for the treatment of atopic dermatitis, refractory asthma, and CRSwNP.⁸⁹ one meta-analysis that analyzed 8 RCTs comparing dupilumab to placebo found dupilumab had a higher incidence of injection-site reactions, conjunctivitis, and headache, but no cases of anaphylaxis.^{80,90} In the 2019 EMA report, anaphylactic reaction or angioedema was reported in 3 patients, and anaphylactic shock was reported in one patient.^{80,91} The FDA drug report for dupilumab describes no information about anaphylaxis.^{80,89}

Lanadelumab

Lanadelumab is a humanized mAb used for the treatment of hereditary angioedema, which inhibits plasma kallikrein.⁹² In a 2018 study with 84 subjects, one treated with lanadelumab developed oral tingling and pruritus without need for treatment.⁹³ There have been no reports of anaphylaxis.⁸⁰

Anti-CD20 biologics

Rituximab is a chimeric mAb against CD20, used in the treatment of B-cell malignancies and certain autoimmune conditions.^{73,94} Immediate reactions have been associated with rituximab in 25% to 50% of patients on first exposure, with fewer reported reactions in patients with inflammatory conditions than malignancies.^{73,94} Most reactions were likely consistent with cytokine release syndrome; IgE-mediated reactions were also reported. Though TNF- α and IL-6 levels were shown to correlate with the severity of reaction, these reactions may present solely with cutaneous and respiratory symptoms without classic cytokine syndrome symptoms such as fevers, chills, or rigors.^{95,96} Some patients will go on to tolerate further exposures, often with premedication; others will initially tolerate rituximab, then develop immediate HSRs on subsequent exposures.^{73,97} The latter group should be considered to have IgE-mediated reactions unless proven otherwise.⁷³ Skin testing protocols have been reported.⁹⁷ In patients thought to have IgE-mediated reaction, desensitization can be considered.⁹⁸ In patients whose reactions are thought to be consistent with cytokine release syndrome, premedication with acetaminophen, antihistamines, corticosteroids, and alteration of infusion rates have been recommended.^{73,94,96} Ofatumumab and obinutuzumab are human and humanized mAbs, respectively, which also target CD20 in the treatment of B cell malignancies. These have not been as well studied as rituximab. Both have been reported to cause immediate

HSRs in more than 50% on first exposure. This has been thought to be caused by cytokine release and may occur even with pretreatment.^{99,100} Skin testing has not been described. Severe and fatal reactions to ofatumumab have occurred.¹⁰¹

Cetuximab

Cetuximab is a chimeric mAB that binds and targets the epidermal growth factor receptor (EGFR) for the treatment of head and neck, lung, skin, and colorectal cancers.⁷³ An interesting phenomenon was discovered related to HSRs to cetuximab: the prevalence of immediate HSRs to cetuximab was less than 3%, except in the southeastern United States, whereby the prevalence was 22%.^{73,102} Interestingly, Chung and colleagues found that 17/25 (68%) of patients with a severe immediate HSR to cetuximab on first exposure had pre-existing IgE antibodies directed against an oligosaccharide, galactose-alpha-1,3 galactose (alpha-gal), present on the mAB. Alpha-gal antibodies were then associated with delayed-onset IgE-mediated reactions to mammalian meats.¹⁰³ With further investigation, the Lone Star tick was identified as the main etiology for sensitization to alpha-gal in the United States.¹⁰⁴ Skin testing protocols and a serum-specific anti-cetuximab IgE test are available for the evaluation of patients who have had immediate HSR to cetuximab; however, preemptive skin testing or blood studies before administration are not currently recommended. In patients with positive skin testing or a detectable anti-cetuximab IgE greater than 0.35, desensitization can be attempted.^{73,105–107} Panitumumab, a fully human mAB which also targets EGFR and does not contain alpha-gal, may be used as an alternative.^{108,109}

TNF- α inhibitors

Multiple TNF- α inhibitors are used in the treatment of autoimmune conditions—including but not limited to: rheumatoid arthritis, psoriasis, inflammatory bowel disease, and ankylosing spondyloarthritis. Infliximab is a chimeric mAB that is, administered intravenously, while others such as certolizumab (humanized), adalimumab (fully human), golimumab (fully human), and etanercept (fusion protein) are administered subcutaneously.^{110–113} IgE-mediated reactions have been implicated as the cause of injection site as well as systemic reactions with TNF- α inhibitors. About 10% of patients treated with infliximab develop immediate HSRs with symptoms ranging from flushing, pruritus, dyspnea, dizziness/hypotension as well as headache, fevers, and chills. Although these reactions can occur with first exposure, they are more commonly present after multiple exposures.⁶³ Systemic reactions have rarely been reported with subcutaneous TNF- α inhibitors.⁶³ Skin testing protocols have been published for the evaluation of immediate reactions to infliximab. If skin testing is positive, or patients have severe or recurrent HSRs, desensitization can be attempted.⁶³ Anti-infliximab antibodies can also be measured. Anti-infliximab antibodies do not cross-react with anti-adalimumab antibodies, but patients who develop anti-infliximab antibodies may be more prone to developing anti-adalimumab antibodies.¹¹⁴ Switching to adalimumab remains an option for patients who develop an immediate reaction to infliximab.¹¹⁵ One case series evaluating 12 patients who developed injection site and systemic reactions to adalimumab and etanercept showed that all had a positive skin test to the culprit mAB, implying an IgE-mediated cause of reaction.¹¹⁶ For patients in whom an IgE-mediated reaction is suspected, desensitization can be performed. Immediate HSRs related to other commonly prescribed biologics are summarized in [Table 5](#).^{73,98,117–121}

Table 5
Summary of biologics and reported hypersensitivity reactions

Biologic	Type of Biologic	Conditions Treated	Reaction type Reported	Skin Testing Reported?	Successful Desensitization Reported?
Trastuzumab	Humanized mAb targeting HER2	Breast cancer	Immediate hypersensitivity: reactions consistent with cytokine release syndrome and/or IgE mediated ⁷⁴	Yes ¹¹⁸	Yes ¹¹⁸
Pertuzumab	Humanized mAb targeting HER2	Breast cancer	Immediate hypersensitivity	Yes ¹¹⁹	Yes ¹¹⁹
Tocilizumab	Humanized mAb targeting IL-6	RA and polyarticular juvenile arthritis	Immediate hypersensitivity	Yes ¹²⁰	Yes ¹²¹
Bevacizumab	Humanized mAb targeting VEGF	Multiple cancers	Immediate hypersensitivity	Yes ^{74,98}	Yes ^{74,98}
Brentuximab	Chimeric mAb	CD30+ lymphoma	Immediate hypersensitivity	No ^{74,122}	Yes ^{74,122}

Abbreviations: HER2, human epidermal growth factor receptor 2; IL-6, interleukin 6; mAb, monoclonal antibody; RA, rheumatoid arthritis; VEGF, vascular endothelial growth factor.

Vaccine	Relevant Additives to Consider
MMR	• Gelatin^{127,128} • Alpha-gal¹²⁷ • Previous concern, no longer clinically relevant: egg¹²⁷
MMRV	• Gelatin^{127,128} • Alpha-gal¹²⁷
Varicella	• Gelatin^{127,128} • Alpha-gal¹²⁷
Zoster	• Gelatin^{127,128} • Alpha-gal¹²⁷ • Polysorbate 80^{a,132}
Influenza	• Polysorbate 20^{a,132} • Polysorbate 80^{a,132} • Previous concern, no longer clinically relevant: egg¹²⁷
Intranasal live attenuated influenza vaccine	• Potential concern: alpha-gal¹²⁷
DTaP, Tdap	• Polysorbate 80^{a,132} • Potential concern: cow's milk¹²⁷
Yellow Fever	• Gelatin^{127,128} • Potential concerns: egg, chicken¹²⁷
Rabies	• Potential concerns: egg¹²⁷
Hepatitis A	• Polysorbate 20^{a,132}
Hepatitis B	• Polysorbate 80^{a,132} • Potential concern: yeast¹²⁷
Hepatitis A&B	• Polysorbate 20^{a,132}
Oral polio vaccine	• Potential concern: cow's milk¹²⁷
Pneumococcal 13-valent	• Polysorbate 80^{a,132}
HPV	• Polysorbate 80^{a,132}
Japanese encephalitis	• Polysorbate 80^{a,132}
Rotavirus	• Polysorbate 80^{a,132}
Meningococcal group	• Polysorbate 80^{a,132}
Combination vaccines:	• Polysorbate 80^{a,132}
• DTaP + IPV • DTaP + HepB + IPV • DTaP + IPV • DTap + IPV + HepB + Hib	
SARS-CoV-2 (AstraZeneca, Johnson&Johnson)	• Polysorbate 80^{a,132}
SARS-CoV2(Moderna, Pfizer)	• PEG2000^{a,132}

Abbreviations: DTaP, diphtheria tetanus acellular pertussis; HepB, hepatitis B; Hib, haemophilus influenzae B; HPV, human papillomavirus; IPV, inactivated polio vaccine; MMR, measles, mumps, rubella; MMRV, measles, mumps, rubella, varicella; Tdap, tetanus, diphtheria, acellular pertussis.

^a dose dependent on vaccine manufacturer.

VACCINES

The risk of anaphylaxis after any vaccine is rare: 1.31 per million vaccine doses.¹²² To induce an immune response, vaccines must contain an active component (the

antigen) and additional components or additives. Rather than the antigen of the vaccine, immediate HSR is caused by additives such as gelatin, latex, yeast, and egg protein (Table 6).^{123,124} More recently, alpha-gal, polysorbate 80 and polyethylene glycol (PEG) have been implicated as causes of vaccine-associated anaphylaxis.^{123–125} An IgE-mediated reaction to a vaccination typically occurs promptly after vaccination. Classic symptoms include urticaria, angioedema, flushing, pruritus, wheezing, dyspnea, and hypotension.⁶³ Patients who develop IgE-mediated symptoms after vaccination should undergo skin testing to both the vaccine (using an identical dose and manufacturer) as well as potential culprit components that are contained in the vaccine (gelatin, egg, and so forth).^{63,126}

Skin testing protocols for vaccine anaphylaxis include skin prick testing with 1:1 concentration, and if negative, proceeding to intradermal testing using a 1:100 dilution. Skin testing to components (eg, egg, latex) should be done in the standard manner.¹²⁷ Patients who test positive to the vaccine should be considered allergic; however, in selected cases, patients with positive skin tests have received the vaccine without immediate reaction.^{63,127} Patients with a known allergy to a component may warrant further evaluation via skin testing. For example, a patient with a known history of gelatin allergy should be tested before receiving the varicella-zoster, MMR, or rabies vaccine.⁶³

If a patient tests positive for a culprit component, the patient may still potentially receive the vaccine in a graded fashion. Kelso and colleagues published a 5 step protocol¹²⁷ which is adapted later in discussion in Table 7.

Egg allergy was a concern for patients receiving the influenza vaccine. However, the amount of ovalbumin protein in egg-based vaccines is below the threshold for reaction. The most recent practice parameter, published in 2017, indicated that egg-allergic patients who receive any influenza vaccine, even those that are egg-based, are at no greater risk for a systemic allergic reaction than patients without egg allergy.¹²⁸

The COVID-19 pandemic has led to the rapid development of 3 new vaccines granted emergency-use authorization by the FDA: Pfizer-BioNTech, Moderna, and Janssen. The Pfizer and Moderna vaccines use mRNA packaged in lipid nanoparticles; the Janssen vaccine uses a modified adenovirus as a vector. Recent data describe an anaphylaxis rate of 5.0 cases per million for the Pfizer-BioNTech, and 2.8 cases per million for the Moderna vaccine.¹²⁴ Severe allergic reactions (including anaphylaxis), thrombosis with thrombocytopenia, Guillain–Barré syndrome, and capillary leak syndrome have been reported following administration of the Janssen COVID-19 Vaccine during mass vaccination outside of clinical trials.¹²⁹ Etiologies for anaphylaxis to these vaccines are not fully understood. Potential causes include

Table 7 Protocol for graded dose vaccine administration	
(1)	0.05 mL 1:10 Dilution
(2)	0.05 mL full-strength
(3)	0.1 mL full-strength
(4)	0.15 mL full-strength
(5)	0.2 mL full-strength

For a vaccine with a normal dose volume of 0.5 mL, these doses may be administered at 15-min intervals as tolerated under direct medical supervision. Observation should span at least 30 min after the last dose.

Table 8
Polyethylene glycol testing protocol

	PEG 3350	Control	Polysorbate 20	Polysorbate 80			
	Methyl- prednisolone Acetate (Depo- Medrol)	Methyl- prednisolone Sodium Succinate (Solu-medrol)	Hepatitis a Vaccine or Twinrix	Triamcinolone Acetonide	Refresh –Sterile eye drops	Prevnar 13	
	Miralax						
Step 1 Epicutaneous	1:100 (1.7 mg/ml)	40 mg/mL	40 mg/mL	1:1	40 mg/mL	1:1	1:10
Step 2 Epicutaneous	1:10 (17 mg/mL)						
Step 3 Epicutaneous	1:1 (170 mg/mL)						
Step 4 Intradermal		0.4 mg/mL	0.4 mg/mL	1:100	0.4 mg/mL	1:10	1:100
Step 5 Intradermal		4 mg/mL	4 mg/mL	1:10	4 mg/mL		
Step 6 Intradermal					40 mg/mL		

Adapted from Banerji A, Wickner PG, Saff R, Stone CA Jr, Robinson LB, Long AA, Wolfson AR, Williams P, Khan DA, Phillips E, Blumenthal KG. mRNA Vaccines to Prevent COVID-19 Disease and Reported Allergic Reactions: Current Evidence and Suggested Approach. J Allergy Clin Immunol Pract. 2021 Apr;9(4):1423 to 1437.

an IgE-mediated response to PEG, an ingredient in both mRNA vaccines, complement activation mediated by RNA exposure, contact system activation by nucleic acid, and direct mast cell activation.^{124,130} PEG and related macrogols are found as an ingredient in colonoscopy preparations, bowel adjuncts, PEGylated agents and as an excipient in multiple oral and injectable medications. PEG has been previously implicated in anaphylactic reactions.¹³¹ PEG has been reported to cross-react with other macrogols, including polysorbate, which has also been identified as a rare cause of allergic reactions to vaccines.¹³² The Janssen vaccine contains polysorbate-80 as an excipient. **Table 8** displays a skin testing protocol for the evaluation of IgE-mediated allergy to PEG and polysorbate. At this time, it is recommended that patients who develop anaphylaxis to a COVID-19 vaccine see a board-certified allergist for further evaluation.

CLINICS CARE POINTS

- Skin testing is well validated for patients with reported penicillin allergy. Individuals with this label should routinely be screened by a board-certified allergist/immunologist for consideration of skin testing and/or oral challenge.
- When deemed favorable from an individualized risk/benefit standpoint, patients with a history of aspirin or NSAID intolerance can in most cases successfully accomplish a challenge or desensitization procedure and be able to take ASA or NSAID as indicated.
- Patients with concern for an IgE mediated reaction to certain biologics or vaccines should seek care with a board-certified allergist, as skin testing and/or desensitization protocols may be available.

DISCLOSURES

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