Diagnosis and management of anaphylaxis in precision medicine

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Activity Objectives:

1. To recognize anaphylaxis phenotypes based on clinical symptoms and potential triggers and to understand their underlying pathogenesis.
2. To understand the utility of various biomarkers in diagnosing anaphylaxis.
3. To understand appropriate circumstances when rapid desensitization might be considered.
4. To recognize cardiac complications that can occur in patients with anaphylaxis.

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Anaphylaxis is the most severe and frightening of the allergic reactions, placing patients at high risk and demanding prompt recognition and immediate management by health care providers. Yet because its symptoms imitate those of other diseases, such as asthma and urticaria, current data suggest that its diagnosis is often missed, with underuse of tryptase measurement; its treatment is delayed, with little use of epinephrine; and its underlying cause or causes are poorly investigated. Deaths from anaphylaxis are difficult to investigate because of miscoding. Surprisingly, patients treated with new and powerful chemotherapy agents and humanized mAbs present with nonclassical symptoms of anaphylaxis, and patients may present with unrecognized clonal mast cell disorders with *KIT* mutations may present as Hymenoptera-induced or idiopathic anaphylaxis. The goal of this review is to recognize the presentations of anaphylaxis with the description of its current phenotypes, to provide new insight and understanding of its mechanisms and causes through its endotypes, and to address its biomarkers for broad clinical use. Ultimately, the aim is to empower allergists and heath care providers with new tools that can help alleviate patients' symptoms, preventing and protecting them against anaphylaxis. (J Allergy Clin Immunol 2017;140:321-33.)

Key words: *Anaphylaxis, adverse drug reactions, drug hypersensitivity reactions, hypersensitivity reactions, IgE, mAbs*

Anaphylaxis is a word recognized and feared by most, if not all, health care providers because of its association with potential death from cardiovascular collapse or asphyxiation caused by laryngeal edema. Yet its diagnosis is missed in 80% of patients who are seen in the emergency department (ED), undergoing anesthesia and surgery or being treated with chemotherapy, mAbs, or biological agents. Patients are given codes for asthma, urticaria, angioedema, or hypotension, but occurrence of the

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Abbreviations used
ACE: Angiotensin-converting enzyme
ED: Emergency department
FTEIA: Food-triggered exercised-induced anaphylaxis
THIQ: Tetrahydroisoquinoline

alarming signs and symptoms of anaphylaxis together does not trigger an immediate suspicion for a multiorgan system syndrome and does not result in the prompt use of epinephrine or an evaluation of an acute serum tryptase level. The diagnosis of a toxic reaction is often given mistakenly to chemotherapy-induced anaphylactic events.

Because anaphylaxis mimics common syndromes, such as asthma and urticaria, and because it can present without hypotension, its diagnosis is often missed or delayed. There is a new understanding that atypical symptoms, such as pain, can be seen during chemotherapy-induced anaphylaxis and that clonal disorders, such as monoclonal mast cell activation syndrome, are part of the wide spectrum of anaphylaxis. Anaphylaxis occurs more in women. Anaphylaxis can be one of the most traumatic events in a patient's life, with long-lasting and sometimes incapacitating sequelae. Empowering patients by using the correct label, educating them about the potential triggers and causes, providing them with appropriate acute treatment, and giving them an effective treatment plan have been shown to help increase the quality of life and safety of these patients.

The purpose of this review is to redefine the phenotypes and endotypes of anaphylaxis in light of new evidence-based information regarding its presentation and causes. The goal is to help allergists and health care providers recognize newly appreciated anaphylaxis-associated symptoms, look for biomarkers, and apply best practice management and treatment options to improve quality of life for patients with anaphylaxis.

CLINICAL VIGNETTE: "DOC, NOBODY KNOWS WHAT I HAVE"

This was the opening sentence during the first visit of a 39-year-old man and his wife to the allergy clinic after being seen by no less than 10 specialists. They wanted to start a family but would not because he feared he would die any minute of an unknown cause or trigger.

Twenty years ago, as a landscaper at age 19 years, he passed out in the grass after being stung by several wasps. He was revived and given an epinephrine injectable device. A few months later, he had an unexplained L5 fracture and was given a tentative diagnosis of osteoporosis and started on bisphosphonates. He changed jobs because he presented with episodes of flushing, fatigue, fever, abdominal bloating, pain, and diarrhea unexpectedly. He was told he had irritable bowel syndrome, but the symptoms of diarrhea were so unpredictable that he limited his social life. Five years ago, he was cutting bushes, hit a nest, and was stung by many bees. He became flushed with a sense of impending doom, had syncope and seizures, and required an intravenous epinephrine drip before a pulse returned. Last August, he was working at a liquor company moving beer cases, and during a hot and humid day, he felt very flushed, passed out, and was revived in the ED after several epinephrine injections and liters of fluid and told he was dehydrated.

He never had a rash and was told that his osteoporosis, bone fractures, and gastrointestinal problems were unrelated and that he could die at any time because nobody knew why his blood pressure went so low or the specific triggers for these events. A diagnosis of anaphylaxis was not attached to his official chart, which contained more than 200 pages, and an investigation of the potential cause or causes was never undertaken. A tryptase measurement was done during his last ED visit, and the level was found to be increased.

"Could all this be explained by a mast cell disorder?," he asked after going online and reading several hundred documents on mastocytosis. Why would a mast cell disorder be associated with anaphylaxis?

ANAPHYLAXIS: DEFINITION AND NEW CLASSIFICATION

From the initial definition by Charles Richet and Paul Portier in 1901 as an immune reaction that accomplished the opposite of protection (*ana* = absence, *phylaxis* = protection in Greek)[1,2] to a casual definition given recently by an educated lawyer at a trial of an allergic patient who died after intravenous contrast dye injection as "something that can be treated if properly recognized," anaphylaxis has eluded definition because of the lack of a single organ target and a broad spectrum of presentations.[3] This is exemplified by the new International Classification of Diseases, 10th Edition (ICD-10), coding system, which provides one code for anaphylaxis without qualifiers (T78.2XXA) and more than 100 codes (the last one in alphabetical order being T63.94XD) for anaphylaxis qualifiers.

Despite this plethora of possible diagnoses, the symptoms of anaphylaxis continue to be underrecognized for all age groups, sexes, and races; its diagnosis is often missed; its treatment is often delayed, including the lack of epinephrine use; and the underlying causes are underinvestigated across the globe.[4-6] From its initial description as a clinical entity with acute onset of symptoms involving 2 or more organs or associated with hypotension or upper respiratory compromise by expert panels,[7,8] its definition has evolved to a more mechanistic description based on precision medicine into phenotypes with underlying endotypes supported by diagnostic biomarkers.[9] As seen in Fig 1, *A*, anaphylaxis phenotypes are defined by clinical presentation into type I–like reactions, cytokine storm–like reactions, and mixed reactions. The endotypes underlying these phenotypes include IgE- and non–IgE-mediated mechanisms, cytokine release, mixed reactions, and direct activation of immune cells.

Cellular targets for IgE-mediated reactions include mast cells, basophils, and other immune cells and symptoms related to the actions of mediators on the target organs.[10] The common triggers for these reactions include foods, drugs, Hymenoptera venoms, and environmental allergens. Among common allergens are foods, such as peanut, milk, eggs, and nuts; antibiotics, such as β-lactams; chemotherapy agents, such as platins and taxanes; chimeric, humanized, and human mAbs; general anesthetics; and immunotherapy allergens. Flushing, pruritus, hives, angioedema, shortness of breath, wheezing, nausea, vomiting, diarrhea, hypotension, oxygen desaturation, and cardiovascular collapse are classical clinical manifestations caused by the release of inflammatory mediators from mast cells and basophils (Fig 1, *B*). More recently, in addition to these

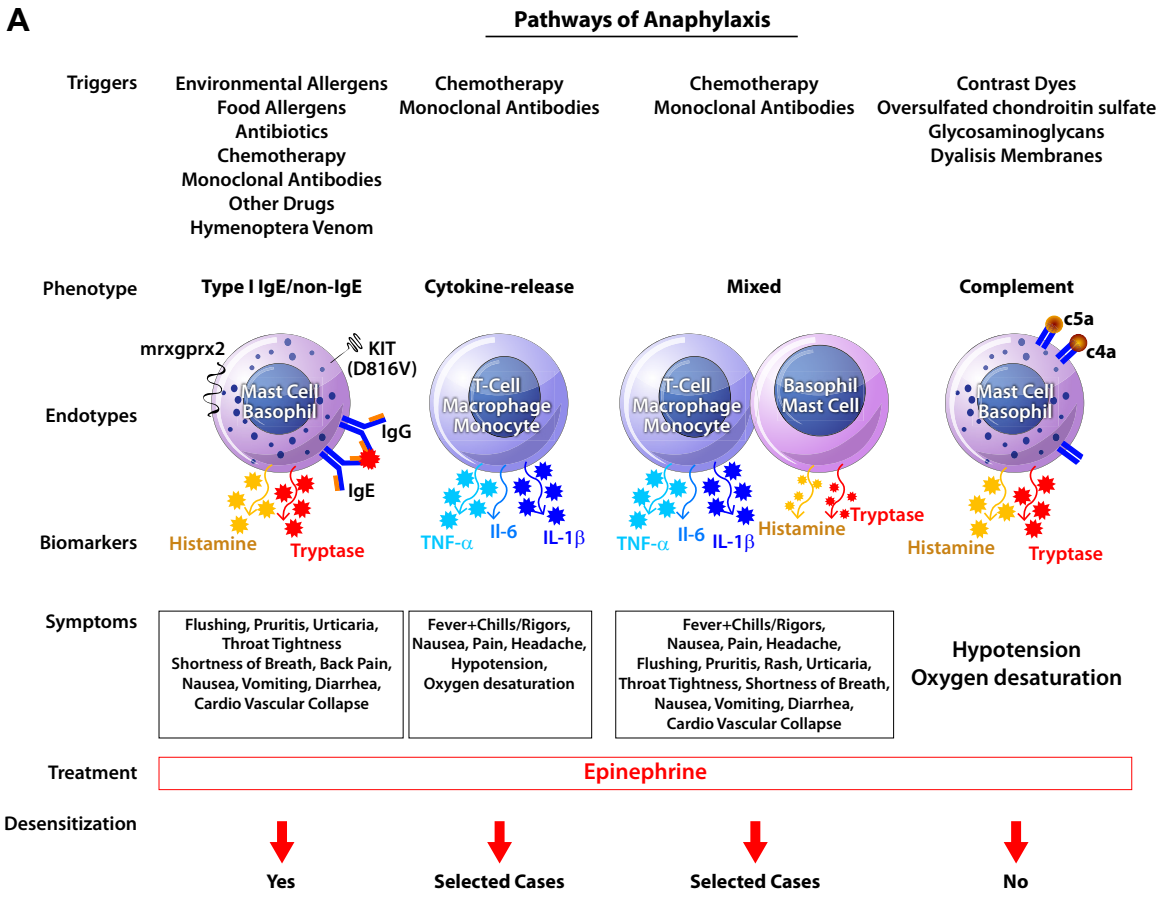

FIG 1. A, Pathways of anaphylaxis. Phenotypes of anaphylaxis include type I reactions, cytokine storm–like reactions, and mixed reactions. Endotypes of anaphylaxis include IgE- and non–IgE-mediated reactions, direct mast cell and basophil activation, cytokine release, and mixed reactions. Biomarkers include tryptase, histamine, and other mast cell/basophil mediators, as well as cytokines, such as TNF-α, IL-1β, and IL-6. Desensitization is indicated in type I reactions and selected cases of cytokine storm and mixed reactions but not in direct mast cell/basophil release. **B,** Mediators of anaphylaxis. Mediators are typically released from mast cells and basophils at the time of anaphylaxis, bind to specific tissue receptors, and induce clinical symptoms depending on the target organ or organs affected.[108-110] *MCAS*, Mast cell activation syndrome; *PAF*, platelet-activating factor.

symptoms, atypical symptoms have emerged, such as chills and fever, during reactions to chemotherapy agents, such as oxaliplatin, and pain during taxane and mAb reactions. These symptoms can also occur during reactions to chemotherapy and mAbs in which no evidence for IgE can be demonstrated. The new G-coupled receptor MRGPRX2, which is expressed on mast cells and other cells, has been shown to be activated by quinolone antibiotics, such as ciprofloxacin and levofloxacin; general anesthetics, such as atracuronium and rocuronium; icatibant; and other drugs with Tetrahydroisoquinoline (THIQ) motifs.[11] Its participation in human hypersensitivity reactions and anaphylaxis is being investigated and does not involve IgE.

In animal models anaphylaxis can proceed through mechanisms that involve multiple myeloid cells, including mast cells, basophils, neutrophils, and macrophages, and through distinct IgE and IgG pathways.[12] Whether IgG can participate in human anaphylaxis and whether inhibitory Fc receptors have a role in limiting its extent are subject to debate. A recent human-to-mouse low-affinity FcγR locus swap with expression of human low-affinity FcγR presented cognate passive and active anaphylaxis, indicating that the activatory low-affinity human IgG receptors FcγRIIIb and FcγRIIB dominate over inhibitory receptors, such as FcγRIIb. The differential expression of inhibitory FcγRIIB on myeloid cells and the differential binding and contribution of IgG subclasses to anaphylaxis indicated a high degree of complexity, which is difficult to explore in human subjetcs.[13,14] Chimeric IgG mAbs, such as rituximab, can induce the release of tryptase and histamine in the context of hypotension and cytokine storm–like symptoms, indicating the potential role for IgG in patients with anaphylaxis.

Cytokine storm–like reactions are caused by release of proinflammatory mediators, such as TNF-α, IL-1B, and IL-6, and the target cells include monocytes, macrophages, mast cells, and other immune cells with FcγR. Triggers for these reactions include chimeric, humanized, and human mAbs and chemotherapy, including oxaliplatin. Reactions are characterized by chills, fever, generalized malaise followed by hypotension, desaturation, and cardiovascular collapse. Premedication with anti-inflammatory COX-1 inhibitors and corticosteroids can decrease the intensity of these symptoms but does not protect from severe reactions.

Mixed reactions with features of type I– and cytokine storm–like reactions can be seen with chemotherapy and mAbs in which pruritus, hives, and swelling are associated with chills, fever, hypotension, and desaturation.

Direct activation of mast cells and other immune cells can occur with vancomycin[15] or through complement activation by highly charged chondroitin sulfate glycosaminoglycans[16] and contrast media,[17] with generation of the anaphylatoxins C3a and C5a, which can bind to complement receptors.[18] The resulting release of histamine, leukotrienes, and prostaglandins can induce flushing, hives, hypoxia, vasodilation, and hypotension.

ANAPHYLAXIS DIAGNOSIS THROUGH BIOMARKERS

Tryptase and other inflammatory mediators

Within a few minutes after the initial symptoms of anaphylaxis, including hypotension, mature tryptase released from mast cells and basophils can be detected in serum. This increase is transient and typically resolves in 24 to 48 hours. Commercial immunoassays allow for detection of total (baseline release, reflecting mast cell and basophil burden) and mature (released only at the time of activation) tryptase but do not discriminate between the two. Increases to greater than the normal range of 11.4 ng/mL are indicative of acute mast cell/basophil activation.[19] At least 4 tryptase genes (alpha, beta, gamma and delta) have been identified,[20] and 27% of white patients can have an absence of α-tryptase genes,[21] but the expression of tryptase haplotypes does not seem to influence tryptase expression or levels. Patients with low baseline tryptase levels can have increases during anaphylaxis that do not reach the normal range, and levels of 2 ng/mL plus 1.2 times baseline[22] are considered significantly increased. Tryptase specificity is high but its sensitivity is low because it is released from different mast cell subsets and basophils, depending on the trigger. Tryptase levels are lower in mucosal mast cells than in cutaneous and perivascular mast cells, and anaphylactic reactions to intravenous drugs can elicit greater and more persistent increases than oral triggers, such as foods. A recent syndrome of familial tryptasemia has been described in which several members of a family present with increased tryptase levels because of more than 2 α-tryptase genes in the absence of mastocytosis.[23]

Other mast cell proteases, such as chymase and carboxypeptidase, have been detected during anaphylaxis, but no commercial assays are available. Other mast cell and basophil mediators can be released during anaphylaxis, such as histamine and its metabolite methylhistamine, prostaglandin D_2 and its metabolite 9-α-11-β prostaglandin F_2, and leukotrienes E_4 and C_4, and can be measured in 24-hour urine collection. Although specific for anaphylaxis, the sensitivity might be low because of the difficulties in timing 24-hour urine collections to symptom onset. One study indicated an inverse correlation between serum platelet-activating factor and acetylhydrolase levels and the severity of anaphylaxis, with low enzymatic levels associated with high platelet-activating factor levels, severe hypotension, and fatal and near-fatal anaphylaxis.

Levels of other serum inflammatory mediators, such as TNF-α, IL-6, and IL-1β, can be increased in patients with cytokine storm–like reactions and anaphylaxis, but their sensitivity or specificity has not been demonstrated. Their measurement provides insight into the phenotype of reactions and can help guide recommendations for desensitization and premedications.

Skin testing

Skin testing can be done within 2 to 4 weeks after anaphylaxis, and results provide evidence of IgE and mast cell involvement. Skin tests are highly specific for type I reactions to foods, drugs (eg, platins), β-lactams, general anesthetics, and Hymenoptera venoms. Because current extracts for skin testing might not contain all allergenic components, after a negative skin test result, the gold standard to demonstrate the lack of food and drug allergy is a challenge. Skin testing is safe for patients with a history of anaphylaxis and mastocytosis provided comorbidities, such as asthma, are controlled and medications, such as β-blockers and angiotensin-converting enzyme (ACE) inhibitors, are discontinued before testing. Patients with cytokine storm–like reactions and complement activation are likely to have negative skin test results, indicating the lack of IgE participation, but patients with mixed reactions can have positive skin test results.[24]

The specificity and sensitivity of mAb skin testing have not been defined because allergenic components are not known for most mAbs and non–IgE-mediated mechanisms can be active. For chimeric mAbs, such as rituximab and infliximab, mouse epitopes are thought to be involved in the allergic response, and skin test results are positive in 60% to 70% of patients with type I and mixed reactions for rituximab, but only 50% of patients with infliximab-induced type I reactions have positive skin test results.[25] The negative predictive value for most mAbs is not known. Of 23 patients desensitized to trastuzumab, infliximab, or rituximab, 13 had positive skin test results, but all had symptoms compatible with type I or mixed reactions.[25] For humanized and human mAbs, glycosylation patterns during manufacturing can differ from natural human IgG glycosylation, generating allergenic epitopes, as seen in patients with positive skin test results to trastuzumab.[26]

For evaluation of penicillin allergy, skin testing requires major and minor determinants because patients with anaphylaxis are likely to be sensitized to minor determinants, which are not currently commercially available.[27] For patients with a distant history of penicillin allergy and symptoms inconsistent with type I reactions, a direct oral challenge with penicillin might be indicated.[28-30] Anaphylactic reactions to other β-lactams are seen in patients reactive to side-chain epitopes of aminopenicillins and cephalosporins, who might be able to tolerate penicillin.[31] Efforts are currently underway to generate suitable skin test reagents and establish the predictive value of cephalosporin skin tests.[32]

Serology and specific IgE

Specific IgE levels can be measured for food, environmental, Hymenoptera venom, and drug allergens, including antibiotics and chemotherapy.[33,34] Diagnostic performance of serologic demonstration of specific IgE levels might be superior to skin tests for foods and environmental allergens because of their crude nature, lack of potency assessment, and variability among lots and manufacturers of allergenic extracts.[35] Because allergens can be complex, resolving the different components has allowed for recent advances in precision medicine by identifying patient-specific IgE antibodies directed against different components.[36] Component-resolved diagnosis has allowed for the recent identification of food-specific allergens that carry predictive value, such as seen with Ara h 1, 2, and 3 in patients with peanut-induced anaphylaxis in contrast to patients with specific IgE to Ara h 8, 9, and 10, who might have oral allergy syndrome caused by cross-reactivity with tree pollen allergens and might not be at risk for anaphylaxis.[37] The role of component-resolved diagnosis is being defined for most allergenic foods, and peanut and nut components are commercially available for clinical use.[38] The predictive values for each component will require extensive clinical studies across race, sex, and ethnic background.

Oral food challenges can identify highly sensitive patients not identified by means of either skin tests or specific IgE measurements. A recent study suggests that a single 1.5 mg of peanut protein challenge can be safely administered and can elicit objective reactions in fewer than the predicted 5% of patients with peanut allergy not identified by means of skin tests or specific IgE measurement. This approach will need validation and should be personalized by individual risk assessment.[39]

Hymenoptera venom–specific IgE has high sensitivity and specificity, and components of the venoms are under recent evaluation, with few components commercially available for clinical use. It has become apparent that patients treated with venom extracts with severe anaphylaxis when re-stung in the field might be sensitized to minor determinants, such as Api m 10, which is absent in most current vaccines.[40,41] Patients with specific IgE to Hymenoptera venoms and sensitized to major and minor determinants might not be protected after vaccination, and although increasing the dose of venom has been recommended, evaluation of components might uncover unrecognized allergens.[42] Whether controlled challenge with live Hymenoptera would enhance safety in the field is still controversial.[43]

Specific IgE drugs

Penicillin specific IgE has low sensitivity and is currently reserved for patients with near-fatal anaphylaxis, in whom skin testing can be deemed unsafe.[44] Measurement of specific IgE to other β-lactams, such as cephalosporins, has been used to assess cross-reactivity, but its clinical utility has not been defined.[45] Specific platin IgE has been shown to have sensitivity less than that of skin testing but high specificity.[46] A major advantage of specific IgE for platins is the ability to detect IgE antibodies shortly after the reactions without the need to wait several weeks to determine skin test reactivity, which can impair the cancer response to chemotherapy.[47] Another advantage is the detection of cross-reactivity, which is seen in patients reactive to oxaliplatin with specific IgE for oxaliplatin, carboplatin, and cisplatin.[48]

Basophil activation test

Basophils have been thought to be surrogate mast cells because assessment of human mast cells is limited to obtaining specific tissues biopsy specimens because there are no mature circulating mast cells.[49] Activating basophils *in vitro* with food, environmental, Hymenoptera venom, or drug allergens and measuring surface activation markers or the release of mediators, such as histamine and leukotrienes, are thought to reflect the sensitization and activation of tissue mast cells.[50] The test has not been US Food and Drug Administration approved or standardized, requires activation of blood basophils immediately after extraction, and is not commercially available. Basophil Activation Tests with food allergens have high background noise with increased histamine release at baseline. In contrast, Basophil Activation Tests with drug allergens, such as platins, have provided reliable information regarding sensitization, with higher expression of CD203c, and reaction severity has been correlated with a higher expression of CD63,[51] but the clinical utility will require further studies.

Mastocytosis is a clonal disorder associated with mutation of the membrane tyrosine kinase *KIT*, and 30% of patients with mastocytosis can present with unprovoked anaphylaxis or Hymenoptera venom–induced anaphylaxis,[52,53] such as the young patient presented in the clinical vignette. Because of the lack of cutaneous mastocytosis, maculopapular rash in the form of urticaria pigmentosa, or urticarial pigmentosa,[54] the diagnosis is often missed or delayed. Patients with syncope, hypotension, or cardiovascular collapse with severe anaphylaxis after Hymenoptera sting should be evaluated for the *KIT* mutation D816V, which

is present in more than 95% of patients with systemic mastocytosis, and if results are positive, a bone marrow biopsy is recommended.[55] Tryptase level increase to 20 ng/mL or greater at baseline 4 to 6 weeks after the anaphylactic event is a minor criterion of systemic mastocytosis and an indication for bone marrow biopsy.[56] Patients with idiopathic anaphylaxis and Hymenoptera venom–induced anaphylaxis with normal tryptase levels at baseline need evaluation for the *KIT* D816V mutation in peripheral blood, and if results are positive, a bone marrow biopsy is also recommended.[57]

In addition to *KIT* mutations, other genetic mutations have been shown to affect the occurrence and severity of anaphylaxis. For female patients with ovarian cancer presenting with *BRCA1* and *BRCA2* mutations, carboplatin allergy occurs early and with fewer exposures.[2,58]

ANAPHYLAXIS DIAGNOSIS: TRIGGERS AND PHENOTYPES (FIG 2)

Food-induced anaphylaxis and food-triggered exercise-induced anaphylaxis

Since the initial description by Sampson et al[59] of fatal anaphylaxis, it has been difficult to predict patients at risk, and asthma has been the only predictor associated with death. In a study of 1094 patients with peanut and tree nut allergy done in a United Kingdom allergy clinic, severity of atopic disease was associated with the most severe reactions. More severe pharyngeal edema was associated with severe rhinitis, life-threatening bronchospasm was associated with severe asthma, and altered mental status was associated with severe eczema. This was independent of sex and age, although adults were 9 times more likely to have severe reactions than children, and of 122 patients in whom ACE and aminopeptidase levels were measured, patients with low levels had more severe reactions, underscoring the role of bradykinins in food-induced anaphylaxis and the need to discontinue ACE inhibitors in patients with food allergies.[60] Food-triggered exercised-induced anaphylaxis (FTEIA) has been recognized for more than 30 years, with wheat and omega-5 gliadin as the dominant trigger, but its mechanisms are not fully understood.[40] FTEIA was initially described as a syndrome in which anaphylaxis was induced during or shortly after exercise in patients sensitized to specific foods.[61] Wheat was found to be the most common food implicated, and elimination of wheat before exercise induced remission of the symptoms.[62] In contrast to regular food allergies, patients who present with FTEIA in which wheat is found to be the trigger can consume wheat at rest and do not need to eliminate wheat from their diets.[63] Eliminating wheat ingestion 4 to 6 hours before exercise is recommended to avoid anaphylaxis. Wheat and other food allergens are thought to be metabolized during exercise, generating allergenic epitopes. In the case of wheat, omega-5 from gliadin has been identified as the epitope responsible for FTEIA.[64] Recently, exercise has not been deemed necessary for the modification of food allergens, and other augmentation factors, such as alcohol, menstrual period, or drugs, such as nonsteroidal anti-inflammatory drugs, can be triggers associated with food ingestion.

More recently, food ingestion associated with other cofactors, such as alcohol or the menstrual period, have been able to induce anaphylaxis, expanding the understanding of FTEIA as a syndrome in which exercise might not be necessary.[65]

Mast cell clonal disorders and anaphylaxis

Mastocytosis and clonal mast cell disorders can present as anaphylaxis with or without known triggers,[66] and the incidence of anaphylaxis is increased in male patients with systemic mastocytosis and increased IgE levels.[53] Patients presenting with recurrent hypotension with cardiovascular collapse in the absence of urticaria or angioedema are at high risk for clonal mast cell disorders,[58,67] and the *KIT* D816V mutation should be investigated along with tryptase levels. Patients with monoclonal mast cell activation syndrome and early stages of systemic mastocytosis can have normal tryptase levels.[68,69]

Recently, a new presentation for systemic mastocytosis in adult male patients without cutaneous manifestations and the lack of urticaria pigmentosa has been described. These patients, as in the case of the clinical vignette, present with acute onset of hypotension and cardiovascular collapse at the time of Hymenoptera stings and typically require intense therapy with several epinephrine injections.[56,70] Systemic symptoms of mast cell mediator release, such as osteoporosis, bone fractures, and gastrointestinal symptoms, such as bloating and diarrhea, can precede the event for many years and are typically unrecognized.

Treatment with venom immunotherapy once the presence of an IgE mechanism can be demonstrated, with and without omalizumab, provides a dramatic increase in patient safety when re-stung.[56,71,72] Although there is no increase in the prevalence of drug allergy in patients with clonal mast cell disorders,[73] reactions to nonsteroidal anti-inflammatory drugs are greater in these patients and can present as anaphylaxis.[74]

Drug allergy and anaphylaxis

Anaphylaxis to drugs has increased in the last 20 years, and more drugs are now implicated in patients with hypersensitivity reactions, including chemotherapy agents, mAbs, replacement factors, and biological agents. The pattern of presentation of reactions has changed, and new symptoms are now recognized, such as pain and chills. Anaphylaxis to antibiotics has been reported in patients sensitized to β-lactams and other medications through IgE mechanisms,[75] and certain populations, such as patients with cystic fibrosis and patients treated with multiple courses of antibiotics, are at high risk.[76,77] Recently, a new receptor, MRGPRX2, has been discovered for which medications with THIQ motifs, such as the general anesthetics atracuronium and rocuronium, and quinolones, such as ciprofloxacin, levofloxacin, and icatibant, can bind and activate mast cells without IgE, but its participation has not been confirmed in human subjects.[78] Patients presenting with anaphylaxis during anesthesia or after quinolone use for whom an IgE mechanism cannot be demonstrated by skin testing may have either increased protein levels or functional MRGPRX2 receptors. Whether mast cell stabilizers, such as ketotifen, could block anaphylactic reactions in patients in need of these medications needs to be investigated.

Because of the increased use of chemotherapies and targeted therapies, including mAbs, drug hypersensitivity reactions and anaphylaxis have increased dramatically worldwide, preventing the use of first-line therapies and affecting patients' survival and quality of life.[79] Some of the more frequently used drugs include carboplatin, cisplatin, and oxaliplatin and taxanes for ovarian, lung, breast, colon, and prostate cancers.[80] mAbs are used in the treatment of neoplastic, autoimmune, and inflammatory

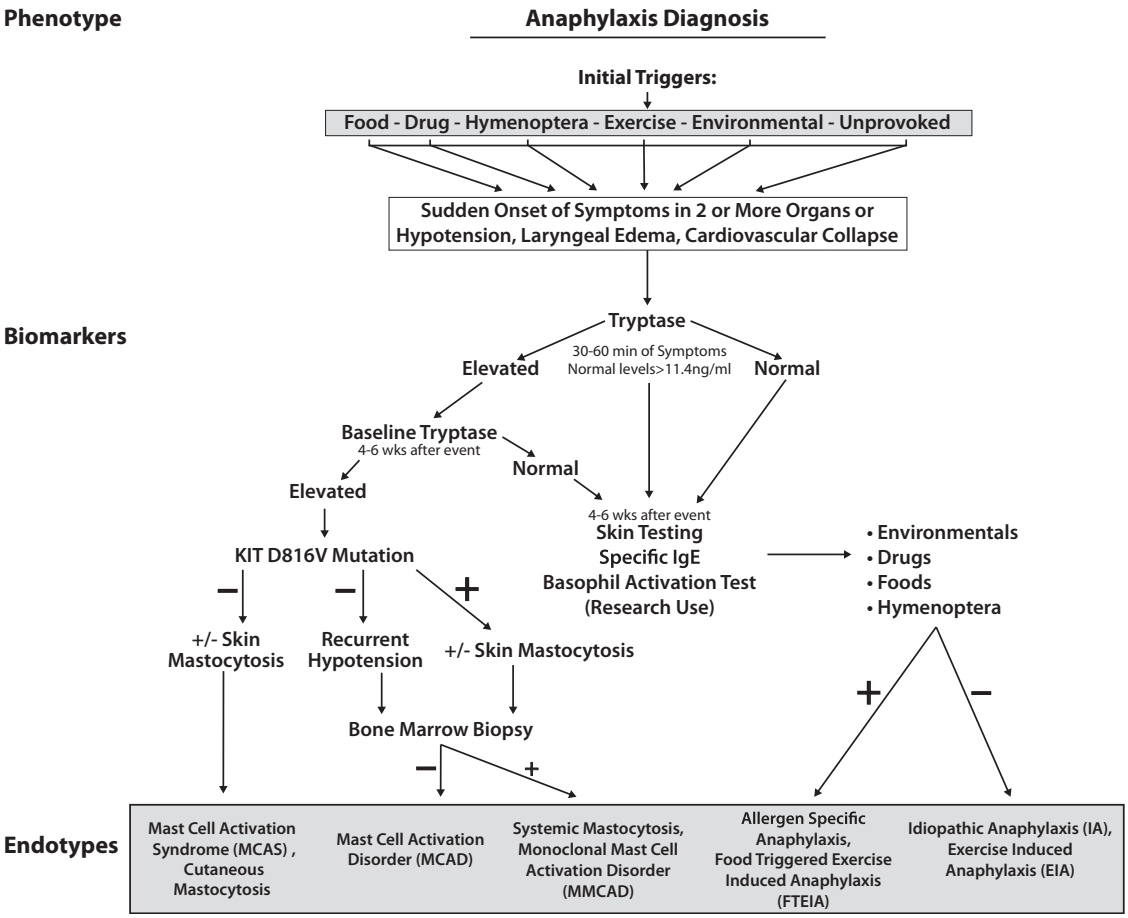

FIG 2. Algorithm for the diagnosis of anaphylaxis. *MCAS*, Mast cell activation syndrome.

diseases, and their clinical applications are becoming broader. mAb targets include CD20, HER-2, epidermal growth factor receptor, IL-6 receptor, TNF-α, CD30, vascular endothelial growth factor A, programmed cell death protein 1/programmed death ligand L, IL-4, IL-5, IL-13, and IgE among others.[15] Although chimeric mAbs, such as rituximab and infliximab, are reported to present the highest incidence of reactions, humanized and human mAbs are engineered with different glycosylation patterns, which can result in allergenic determinants. Even with fully human mAbs, such as adalimumab and ofatumumab, anaphylaxis has been reported.[14,81] Anaphylaxis at first exposure has been observed with cetuximab in patients with preformed carbohydrate galactose-a-1,3-galactose IgE antibodies[82] because of tick exposure *(Amblyomma americanum)*. Galactose-a-1,3-galactose is expressed on nonprimate mammalian proteins and present on the cetuximab heavy chain.[83] The clinical presentation of drug hypersensitivity reactions to chemotherapy and mAbs ranges from mild cutaneous reactions to anaphylaxis, and at least 3 different phenotypes have been observed (Fig 1, *A*).

Type I reactions with classical symptoms of flushing, pruritus, urticaria, shortness of breath, nausea, vomiting, diarrhea, hypotension, oxygen desaturation, and cardiovascular collapse can be seen with platins, are due to an IgE-mediated mechanism, and typically require repeated exposures.[84] Taxanes can induce similar reactions with atypical symptoms, such as back pain, through IgE- and non–IgE-mediated mechanisms, and Cremophor and Polysorbate 80 used as diluents are thought to be implicated in non–IgE-mediated reactions, which can occur at first or second exposure reactions.[19] One study of 164 patients treated for taxane hypersensitivity in which 145 patients had skin testing indicated that 103 (71%) had positive results.[85]

Cytokine storm–like reactions can occur with mAbs and might be due to off-target effects with binding to the Fc receptors on T cells, monocytes, and macrophages and associated with chills, fever, and hypotension.[86] An anti-CD28 mAb (TGN1412) induced multiorgan failure as a result of severe cytokine storm during a phase 1 trial in 6 volunteers,[26] underscoring the critical importance of protecting patients against the potential side effects of mAbs.[87,88] These reactions can occur at first exposure but have also been seen after several exposures.[89,90] Mixed reactions occur when these symptoms are associated with pruritus and hives, mast cells/basophils are involved, and skin test results are positive, demonstrating an IgE mechanism in addition to the release of IL-6.[20,48]

Latex allergy

Latex in gloves, condoms, and surgical materials has been shown to induce anaphylaxis[91] and its allergens have presented cross-reactivity with fruit allergens.[92] The diagnosis of latex allergy relies on specific IgE measurement, which has poor sensitivity, and materials for skin testing have not been standardized.[93] With the

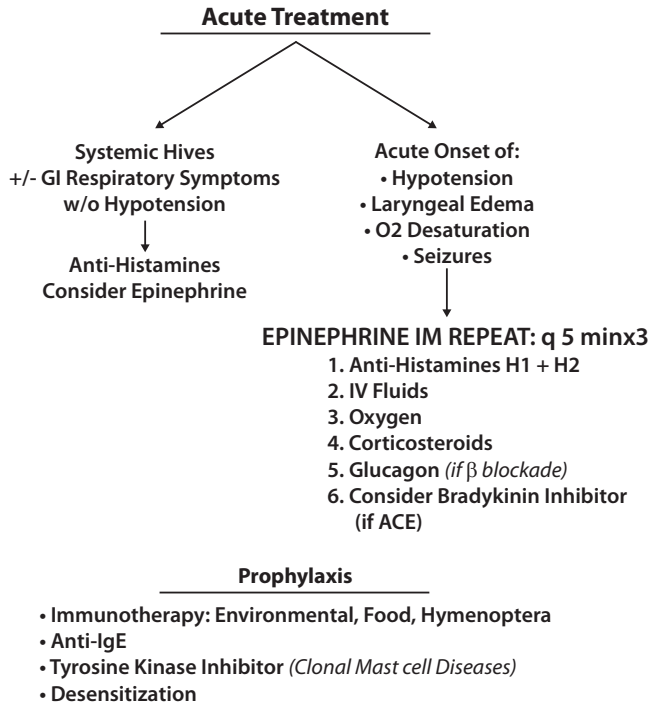

FIG 3. Treatment of anaphylaxis. Consider desensitization for re-exposure to first-line drugs, such as antibiotics, chemotherapy agents, mAbs, and others. *GI*, Gastrointestinal; *IV*, intravenous.

advent of latex-free facilities and the use of nonlatex gloves, the incidence of anaphylaxis has dramatically decreased.[94]

Progestogen hypersensitivity

Female patients presenting with anaphylaxis before and during the menstrual period have been given a diagnosis of catamenial anaphylaxis, and recently, a broader presentation of cyclical symptoms during the progesterone surge has been described. Patients can present with dermatitis simulating fixed drug eruptions, which can lead to permanent scarring and disfiguration. Endogenous and exogenous sources of progesterone can be the allergenic triggers, and desensitization to progesterone has reversed infertility.[95]

Anaphylaxis and the heart: Takotsubo and Kounis syndromes

Kounis syndrome, an acute coronary syndrome with chest pain manifested as unstable angina and associated with increased troponin levels, can occur during anaphylaxis and is thought to be caused by inflammatory mediators of mast cells and other immune cells. Coronary artery disease is typically absent, and symptoms reverse without sequelae within a few hours of initial anaphylactic symptoms. Rarely, coronary damage can occur in severe episodes. Use of intravenous and prolonged epinephrine can have a detrimental role in patients with allergic angina. More severe is the presentation of apical ballooning syndrome or Takotsubo syndrome, which is defined as stress miocardiopathy during anaphylaxis associated with intravenous epinephrine administration in middle-aged women. This can lead to fatal cardiac arrhythmias with cardiac failure.

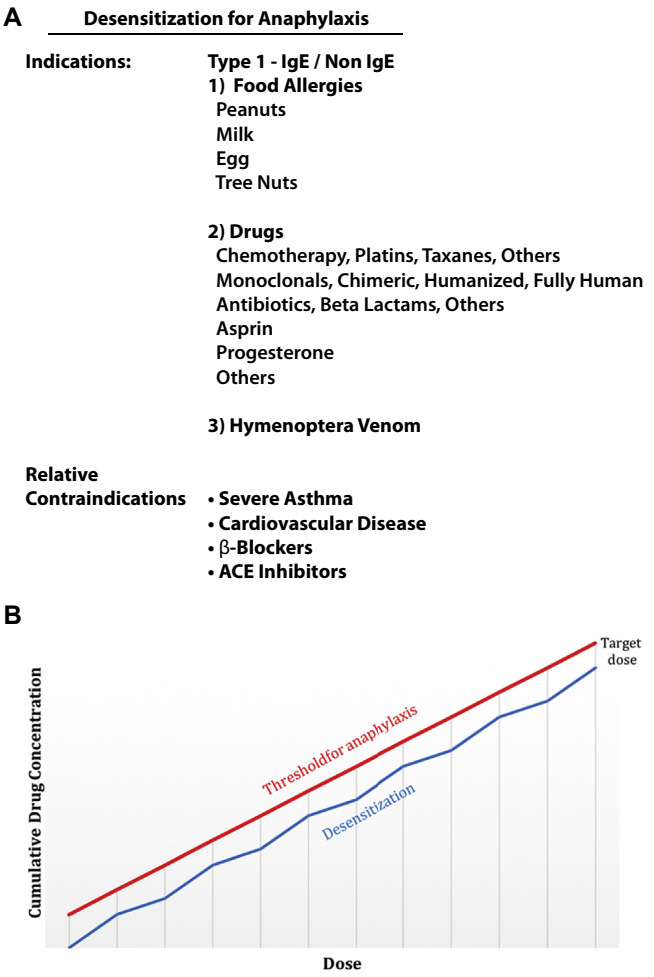

FIG 4. A, Desensitization for the treatment of drug-induced anaphylaxis: indications. **B,** Clinical safety threshold induced by desensitization. The *red line* indicates the threshold for anaphylaxis, and the *blue line* indicates the threshold provided by desensitization, which is less than the anaphylaxis threshold, protecting the patients.

Idiopathic anaphylaxis and nonclonal mast cell activation syndromes

Idiopathic anaphylaxis presents as a vexing problem to the practicing physician and compromises the patient's safety.[96] It is more frequent in female subjects, raising the possibility of a hormonal role, because mast cells and basophils have estrogen and progesterone receptors.[97] Its management with steroids has been challenged because of severe side effects, and recent data suggest that a proportion of these female patients can present with nonclonal mast cell activation syndromes.[98,99]

PATIENT PERCEPTION AND QUALITY OF LIFE

The effect of anaphylaxis on the quality of life of patients experiencing 1 or more episodes of food-, medication-, Hymenoptera venom–, or exercise-induced anaphylaxis is a critical aspect of the patient's management. It affects not only the patient but also her/his family, school, and workplace, as well as traveling and other social interactions.[100] Patients can experience the acute effect with immediate anxiety symptoms, but long-term effects, such as constant fear, can dominate their lives and can restrict social and professional interactions in adults

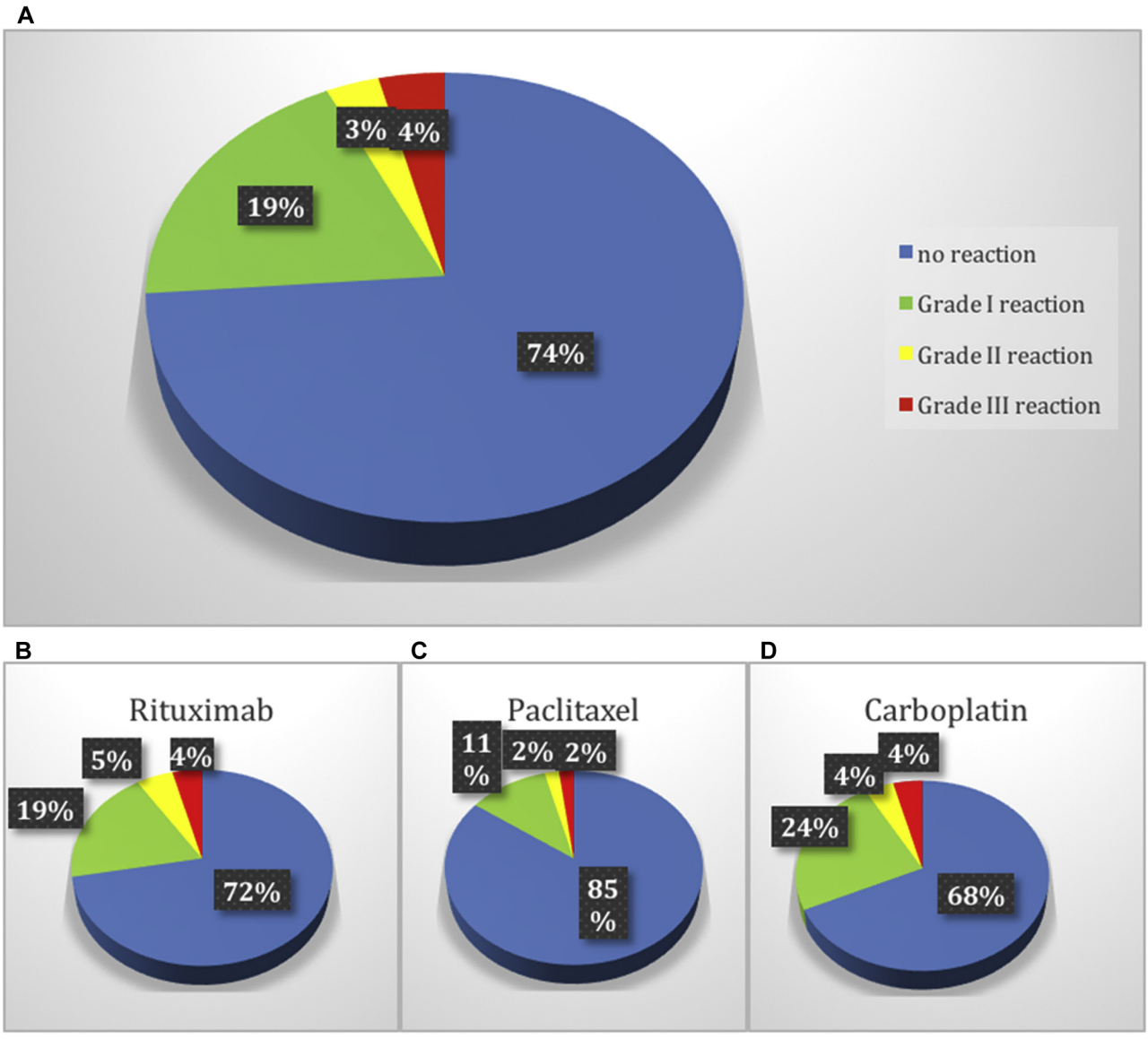

FIG 5. Safety of desensitization. Overall number and severity of breakthrough reactions occurring during 2177 desensitizations to chemotherapy and mAbs. Hypersensitivity reactions are graded as mild/grade I (cutaneous symptoms or with only 1 organ system), moderate/grade II (≥2 systems involved without vital sign changes), and severe/grade III when more than 2 systems are affected with vital sign changes. **A,** Overall reactions in 2177 desensitizations with 74% presenting no reactions. **B,** Reactions during rituximab desensitizations. **C,** Reactions during paclitaxel desensitizations. **D,** Reactions during carboplatin desensitizations. Used with permission from Sloane et al.[24]

and children.[101,102] Lack of trust in health care and health care providers can result in undertreatment because patients fear recurrent episodes with all prescribed drugs, foods, or Hymenoptera stings.[103] Adolescents can present with high-risk behavior.[104] Education of patients, health care providers, and ED personnel can have a positive effect.[105,106]

TREATMENT AND MANAGEMENT OF ANAPHYLAXIS: ROLE OF DESENSITIZATION

The acute treatment of anaphylaxis is described in Fig 3 with epinephrine being central to the management when 2 or more organs are effected or there is laryngeal involvement or hypotension. Delaying epinephrine is associated to increased mortality. A recent article in the *New York Times*[107] describes anaphylactic reactions in children with Pompe disease receiving replacement therapy for which no alternative exits. To be able to re-introduce the replacement therapy in patients presenting with anaphylaxis the authors propose a complex modulation of the immune system by removing B cells and replacing IgG in addition to using chronic antibiotics. While the authors ignore the potential use of desensitization, desensitizations have been used for the last 15 years in thousands of cases, with enhanced safety and great efficacy in patients with anaphylaxis to chemotherapy agents, mAbs, and antibiotics without any deaths. Powerful inhibitory mechanisms are initiated at low antigen doses, which can dominate the activatory pathways and prevent anaphylaxis (Fig 4).[108-110] Drug desensitization should be considered standard of care when patients need first line therapy.

In one study there were 77 desensitizations to paclitaxel and docetaxel in 17 patients, 72 of which were without reactions. During the desensitization protocol, 4 patients had symptoms, such as palmar erythema, pruritis, mild abdominal pain, chest burning sensation, and mild flushing. Recent data have provided evidence of successful desensitizations to an increased number of mAbs, including rituximab, ofatumumab, obinutuzumab, trastuzumab, cetuximab, tocilizumab, infliximab, etanercept, adalimumab, golimumab, certolizumab, brentuximab, bevacizumab, and omalizumab. The largest desensitization study worldwide reported that 370 highly allergic patients received 2177 successful desensitizations to 15 drugs. Most importantly, carboplatin-desensitized patients had a nonstatistically significant lifespan advantage over nonallergic control subjects, indicating that the efficacy of carboplatin was not reduced in allergic patients and that rapid drug desensitization protocols are as effective as regular infusions.[50] Based on the results of the 2177 desensitizations, 93% had no or mild reactions, whereas 7% had moderate-to-severe reactions that did not preclude the completion of the treatment, and there were no deaths (Fig 5).[50] Desensitization to antibiotics has been successfully done in targeted populations, such as patients with cystic fibrosis,[69] with a similar protocol as for chemotherapy drugs. Desensitization to aspirin for aspirin-exacerbated respiratory disease has provided increased sense of smell, prevented the regrowth of polyps, and helped stabilize asthma symptoms.[111,112] Rapid drug desensitization is a groundbreaking procedure for the management of immediate drug hypersensitivity reactions. It protects patients against anaphylaxis, maintaining patients on first-line therapy and thus representing an important advance in treatment and prognosis.

CONCLUSIONS AND FUTURE RESEARCH NEEDS

As for the clinical vignette patient, the diagnosis of anaphylaxis should be raised immediately upon the acute onset of symptoms in 2 organs or acute hypotension or laryngeal compromise in patients with and without recent food or drug ingestion or Hymenoptera sting, and epinephrine should be used unless contraindicated. Pain and chills in the setting of chemotherapy infusion should be considered part of the new phenotypic expression of anaphylaxis. Unrestricted used of epinephrine can lead to Takotsubo syndrome, and severe anaphylaxis can lead to Kounis syndrome. Serum tryptase levels increase approximately 30 minutes after the onset of an anaphylactic reaction, peak 1 to 2 hours after the onset of the reaction, and remain increased for up to at least 6 to 8 hours, providing a mechanistic understanding of anaphylaxis. In patients with food-triggered anaphylaxis, tryptase level increases are inconsistent, questioning a mast cell component. In contrast, tryptase measurement can help the diagnosis of anaphylaxis in chemotherapy-treated patients, anesthetized and draped patients, patients with Hymenoptera stings, and patients with idiopathic anaphylaxis. More than 30% of patients with idiopathic or unprovoked anaphylaxis might have an underlying clonal mast cell disorder. Patients with drug-induced anaphylaxis might be candidates for desensitization if in need of first-line therapies.

Little is known of the role of sex and race in anaphylaxis and the different allergenic components and triggers for most foods and drugs. To further understand the pathogenesis of anaphylaxis, population studies are needed to unravel candidate genes and the role of the microbiome. Precision medicine requires further understanding of the biomarkers and specific triggers for each patient. Patients with low ACE and aminopeptidase levels are a targeted population, and we should limit the use of ACE inhibitors in patients with anaphylaxis.

Allergists are strategically positioned to provide the diagnosis and management tools for all patients with anaphylaxis and to educate all specialists and health care providers in its symptoms, presentation, and acute management, increasing the quality of life and safety of patients with anaphylaxis.

What do we know?

- **Anaphylaxis is the most severe of the allergic reactions and can be deadly.**
- **Acute management and treatment depends on early recognition and prompt use of epinephrine.**
- **Triggers include foods, Hymenoptera venoms, drugs, and exercise and can be idiopathic.**
- **Diagnosis relies on skin testing, specific IgE measurement, and food and drug challenges.**

What is still unknown?

- **New symptoms of hypersensitivity caused by chemotherapy drugs, mAbs, and biological agents have not been recognized as anaphylaxis phenotypes.**
- **Anaphylaxis endotypes beyond IgE and mast cells need to be investigated.**
- **Mast cell activation disorders can present as anaphylaxis, including Hymenoptera venom–induced anaphylaxis, but the role of *KIT* mutations is unknown.**
- **Biomarkers beyond tryptase need to be defined.**
- **Treatment modalities, including tyrosine kinase inhibitors, need to be explored.**

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