# Application of precision medicine to the treatment of anaphylaxis

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**Purpose of review**
Recognize the presentation of anaphylaxis for prompt management and treatment and to provide tools for the diagnosis of the underlying cause(s) and set up a long-term treatment to prevent recurrence of anaphylaxis.

**Recent findings**
The recent description of phenotypes provides new insight and understanding into the mechanisms and causes of anaphylaxis through a better understanding of endotypes and biomarkers for broad clinical use.

**Summary**
Anaphylaxis is the most severe hypersensitivity reaction and can lead to death. Epinephrine is the first-line treatment of anaphylaxis and it is life-saving. Patients with first-line therapy-induced anaphylaxis are candidates for desensitization to increase their quality of life and life expectancy. Desensitization is a breakthrough novel treatment for patients with anaphylaxis in need of first-line therapy, including chemotherapy, mAbs, aspirin and others. Ultrarush with venom immunotherapy should be considered in patients who present with life-threatening anaphylaxis after *Hymenoptera* sting with evidence of IgE-mediated mechanisms. Food desensitization is currently being expanded to provide increased safety to adults and children with food-induced anaphylaxis.

**Keywords**
acute treatment, anaphylaxis, desensitization, hypersensitivity reactions, long-term treatment

## INTRODUCTION

Anaphylaxis is the most serious manifestation of an allergic reaction and due to misdiagnosis, anaphylaxis is undertreated leading to fatalities. Epinephrine is the first-line life-saving therapy. The aim of this review is to raise awareness to help patients and clinicians identify, treat and prevent anaphylaxis.

A new clinical approach based on precision medicine through phenotypes, endotypes and biomarkers provides clinicians with new tools to understand the mechanisms involved in hypersensitivity reactions (HSR) [1▪–3▪]. Phenotypes are based on symptoms and timing of the clinical presentation and are classified into Type-1 reactions, cytokine release reactions (CRR), mixed reactions and complement reactions. Endotypes, underlying these phenotypes, are based on biological and molecular mediators supported by biomarkers. These endotypes include IgE and non-IgE, cytokine, mast cell, bradykinin and complement-mediated mechanisms. Desensitization is a treatment modality which can decrease and prevent anaphylaxis.

## CLINICAL VIGNETTE: WELCOME, THERE IS HOPE

A 32-year-old woman was referred by her general practitioner (GP) to our allergy outpatient clinic with a 1 year history of episodic hives and angioedema on her forearms, legs, torso and face. On one occasion cutaneous manifestations were accompanied by itchy eyes, wheezing and chest tightness. These symptoms resolved within 24–48 h after

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## KEY POINTS

- Phenotypes, endotypes and biomarkers provide a better understanding of the pathways of anaphylaxis.
- Epinephrine is the first-line life-saving treatment for anaphylaxis.
- Patients with first-line therapy-induced anaphylaxis are candidates for rapid drug desensitization to increasing their quality of life and life expectancy.

onset and appeared immediately before or at the onset of her monthly menstrual cycle. She was then symptom free for 3–4 weeks without recurrence. She had been previously diagnosed with chronic idiopathic urticaria by her GP and controlled her symptoms with Benadryl (Johnson and Johnson, New Brunswick, New Jersey, USA) (Difenhidramyne) 100 mg and Zantac (Ranitine) 150 mg. She had been on uninterrupted oral contraceptive pills for the past 15 years and was attempting to conceive via IVF. She was worried about the suspected diagnosis of progestogen hypersensitivity could affect her possibility of pregnancy. How can we help our patient? Does the risk of anaphylaxis in women with progestogen hypersensitivity prevent successful pregnancies? Is there a safe and effective way to manage and prevent anaphylaxis in this case?

## DEFINITION AND DIAGNOSIS; PATHWAYS OF ANAPHYLAXIS; PHENOTYPES, ENDOTYPES AND BIOMARKERS

In 1901, the term anaphylaxis was coined from ana = absence, phylaxis = protection in Greek. A universal definition has not been established for anaphylaxis; however, it is universally accepted that anaphylaxis is rapid in onset and may cause death. Ambiguity around the definition of anaphylaxis may lead to the underrecognition, underdiagnosis and undertreatment.

The description of phenotypes, endotypes and biomarkers has improved the understanding of HSR and anaphylaxis [1▪–3▪]. As we can see in Fig. 1, a majority of Type I reactions [4,5] are mediated by IgE, which requires previous exposure to the culprit agent. Other non-IgE-mediated Type I pathways in animal models have been described and involve IgG and stimulating platelet activating factor (PAF) [6–8]. The endotype for Type I reactions are mediated by mast cell and basophils which release tryptase, histamine, leukotrienes, prostaglandins and PAF causing flushing, pruritus, urticaria, throat tightness, shortness of breath, back pain, nausea, vomiting, diarrhea and cardiovascular collapse [9]. The common triggers for these reactions include foods, drugs, environmental allergens, immunocomplex and *Hymenoptera* venom. CRR endotype is mediated by T cells, monocytes and macrophages. These reactions can occur at first lifetime exposure but have also been described after several exposures and are typical with mAbs. The major mediators are TNF-α, IL-6 and IL-1β which are responsible for fever, chills, rigors, nausea, pain, headache, oxygen desaturation and hypotension. Mixed reactions (Type 1 and CRR) have been reported after chemotherapy and mAb therapy; however, the mechanism is difficult to differentiate. Complement/bradykinine-like reactions can induce flushing, hives, hipoxia, vasodilation and hypotension due to the direct activation of mast cells generating anaphylotoxins such as C3a and C5a, as well as the activation of the intrinsic coagulation pathway [10,11]. This mechanism has been seen in contrast dye, dialysis membranes, oversulfated chondroitin sulfates and drugs infusions suspended in certain lipid vehicles, such as Cremophor EL (BASF Corporation, Florham Park, New Jersey, USA), polysorbate 80 and polyethylene glycol infusion [5]. Mast-cell activation syndrome endophenotype can be triggered by stress, drugs, foods, alcohol, surgery, vaccines, *Hymenoptera* venom and exercise due to an inappropriate release of mediators commonly caused by the KIT D816V mutation [12▪▪,13,14].

Measurement of biomarkers during or shortly after anaphylaxis, such as tryptase or IL-6 [15,16], can help elucidate mechanisms behind the reaction. Tryptase levels can be detected a few minutes after the onset of the reaction and return to normal levels within 24–48 h. Increases above 11.4 ng/nl are indicative of acute mast-cell/basophil activation. An increase in tryptase levels at least 2 ng/ml + 1.2 × baseline value is also considered clinically meaningful. Familial tryptasemia is a disease recently described in which several members of a family, without mastocytosis, present elevated baseline tryptase levels due a greater number α-tryptase genes [14]. Levels of other inflammatory mediators such as TNF-α, IL-6 and IL-1β may identify a CRR but have not yet been validated [17].

Skin testing is a useful tool to identify the involvement of IgE-mediated mechanisms. The specificity of skin testing has been defined in Type I-mediated reactions; however, skin testing has not been validated in CRR reactions.

## ACUTE AND LONG-TERM TREATMENT OF ANAPHYLAXIS: 'WALKING IN A PATIENT'S SHOES'

Acute treatment must focus on prompt recognition of symptoms and prompt use of life-saving epinephrine. Long-term treatment is based on identification

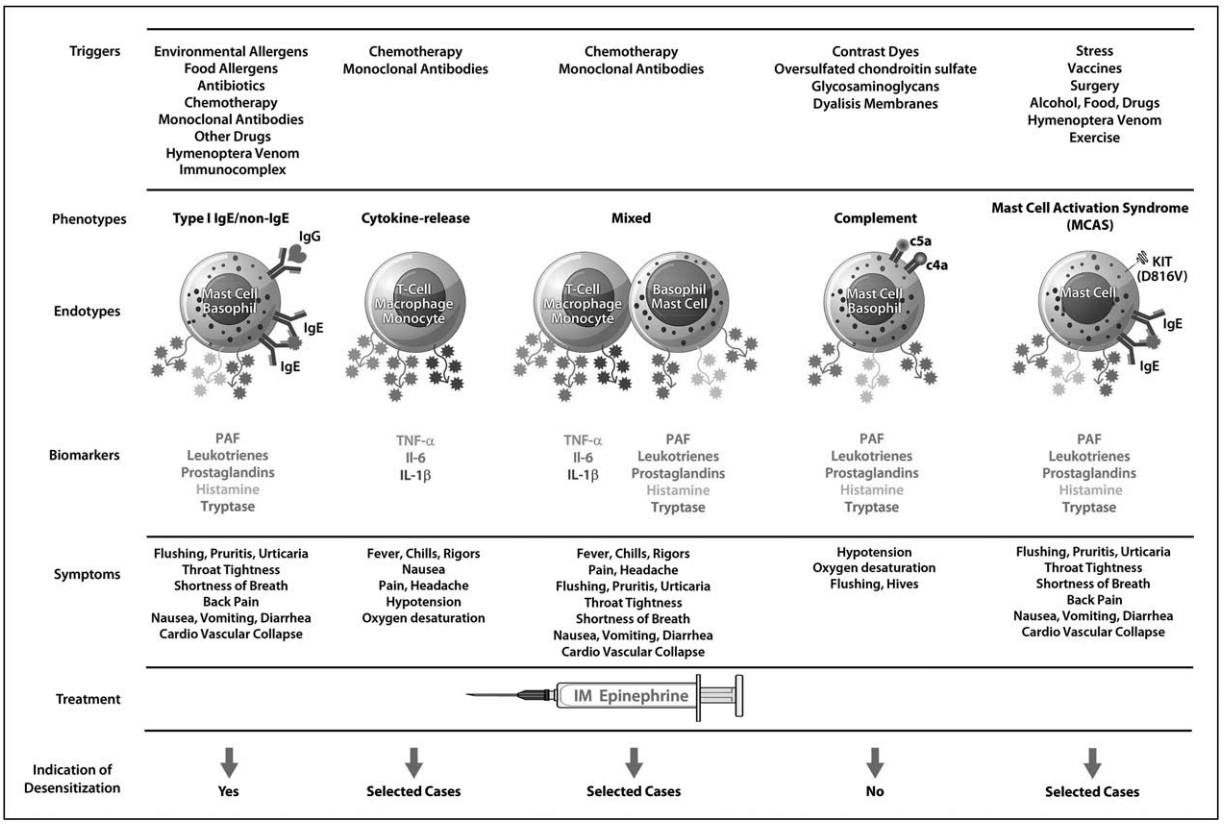


**FIGURE 1.** Pathways of anaphylaxis. Phenotypes of anaphylaxis include Type 1 reactions, cytokine release reactions, mixed reactions, complement-like reactions and mast cells activation syndromes. Phenotypes are defined by endotypes and underlying biomarkers such as prostaglandins, leukotrienes, platelet activating factor, histamine, tryptase, TNF-α, IL-6 and IL-1β. The first line of treatment is epinephrine and desensitization is indicated is selected cases. Reproduced with permission [2▪].

of the cause of agent implicated in anaphylaxis and can be treated via desensitization, immunotherapy, TKI (tyrosine kinase inhibitors) and anti-IgE therapy.

## Acute treatment

The first step to successfully manage the acute treatment of HSR and anaphylaxis is its identification. HSR and anaphylactic reactions are classified into three grades based on their severity (Fig. 2). Grade I or mild reactions are generally characterized by their cutaneous symptoms (80%), or the involvement of only one organ. Grade II or moderate reactions involve two or more organ systems but without vital sign changes. Grade III or severe reactions are characterized by the involvement of two or more organs with vital sign changes or an acute onset of hypotension, laryngeal edema, hypoxia or seizures [1▪].

Epinephrine is the first-line treatment in Grade III reactions and should be considered for Grade II reactions. Delayed administration of epinephrine has been associated with fatalities [18]. Intramuscular epinephrine may be repeated at 5–15-min intervals if there is no response or an inadequate response, or even sooner if clinically indicated [19–26].

Patients at risk for anaphylaxis, who lack cardiovascular disease, are recommended to avoid beta-blockers and ACE (angiotensin converting enzyme) inhibitors due to the increased severity of anaphylaxis, masking of cardiac signs of anaphylaxis and reduced response to epinephrine. However, for those patients with cardiovascular disease, beta-blockers and ACE inhibitors have been shown to decrease mortality and increase life expectancy overall and should not discontinue their use [27,28].

Adverse effects of epinephrine include anxiety, headache, palpitations, ventricular arrhytmias, myocardial infarction and intracranial hemorrhage; however, the most serious symptoms have been associated with intravenous epinephrine. The use of intravenous and prolonged epinephrine could have a detrimental role in patients with allergic angina (Kounis syndrome) and stress miocardiopathy (Takotsubo syndrome) [29–31].

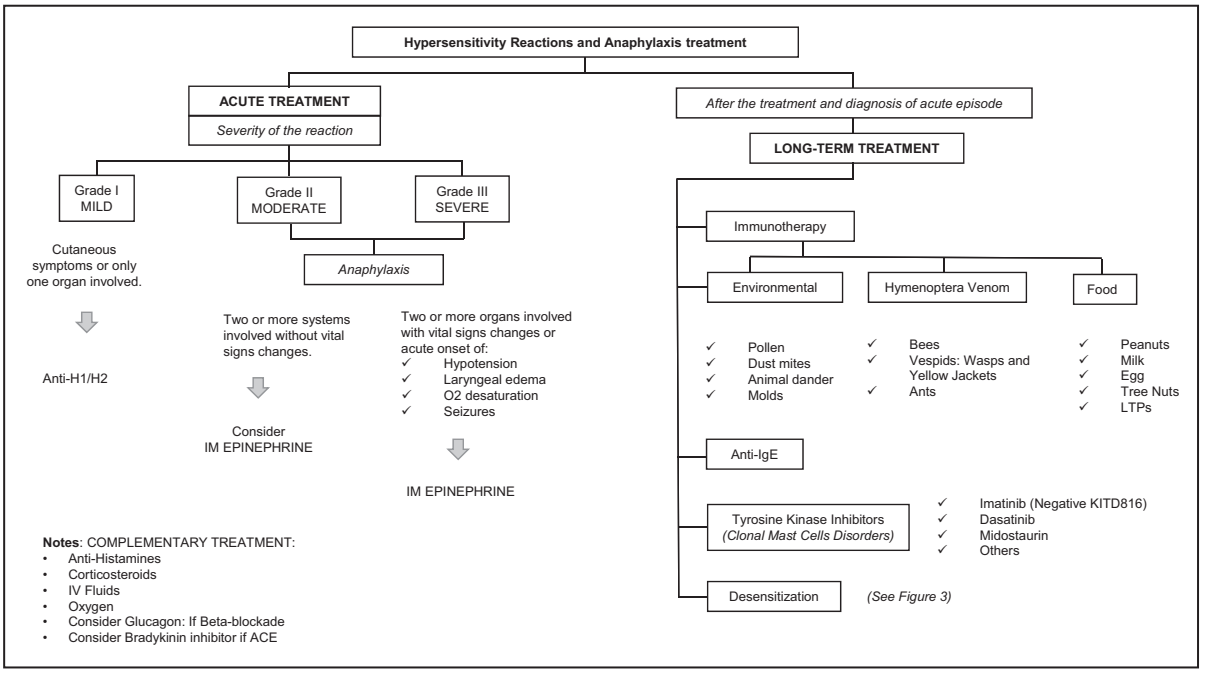


**FIGURE 2.** Hypersensitivity reactions and anaphylaxis treatment. Acute treatment must focus on prompt recognition of symptoms and prompt use of epinephrine of life-saving. Long-term treatment is based on identification of the cause(s) and desensitization, immunotherapy, tyrosine kinase inhibitors and anti-IgE. *Source:* Based on [2▪].

Corticosteroids and antihistamines are not life-saving, they have not been demonstrated to prevent biphasic anaphylaxis and their use should never delay epinephrine administration [20–28].

Psychological sequelae are often undervalued. Anaphylaxis can also affect the quality of life of patients and the people around them leading to alteration in their social interactions [32–34].

## Long-term treatment

Long-term management and treatment for acute episodes include education, early recognition of future episodes, avoidance of specific allergens, optimal management of relevant comorbidities and interventions to reduce or prevent anaphylaxis [35].

Subcutaneous immunotherapy to environmental allergens such as pollen, dust mites, animal dander and molds constitutes an effective treatment for respiratory allergies reducing and preventing symptoms [36]. Immunotherapy has the ability to modify the underlying immunologic mechanisms of allergic rhinitis and asthma with the potential for long-term benefits even after treatment is discontinued. Immunotherapy may also prevent progression of rhinitis to asthma. Sublingual and oral immunotherapy (OIT) are a self-administered alternative to subcutaneous immunotherapy that also provide benefits without the inconvenience of frequent office visits or the discomfort of injections but require an almost daily administration. The most common adverse events are local reactions such as pruritus and erythema [37,38].

Omalizumab, anti-IgE mAb, has been shown to be a successful treatment for reducing the number and severity of anaphylactic reactions and improving the quality of life in patients with IgE-mediated diseases [39].

TKI have been used in patients with systemic mastocytosis [40,41]. Imatinib has demonstrated positive results in patients with negative KIT D816V mutation. Recently, Midostaurin, a KIT inhibitor, has been approved for advanced systemic mastocytosis, neutralizing the release of mast cells and basophil mediators [42,43▪▪]. Indications for desensitization as a long-term treatment for anaphylaxis, including *Hymenoptera* venom, food allergies, drugs and human proteins are discussed in Fig. 3.

New insights are being investigated to predict early IgE sensitization and provide increased protection and prevention of anaphylaxis. A recent study introduced nanoparticles as a versatile platform for studying allergic sensitization to peanut nanoallergens. This new technique provides information regarding specific allergenic epitopes with the purpose of improving diagnosis, enabling targeted designs for future therapeutics and allowing for personalized treatment options for patients [44,45].

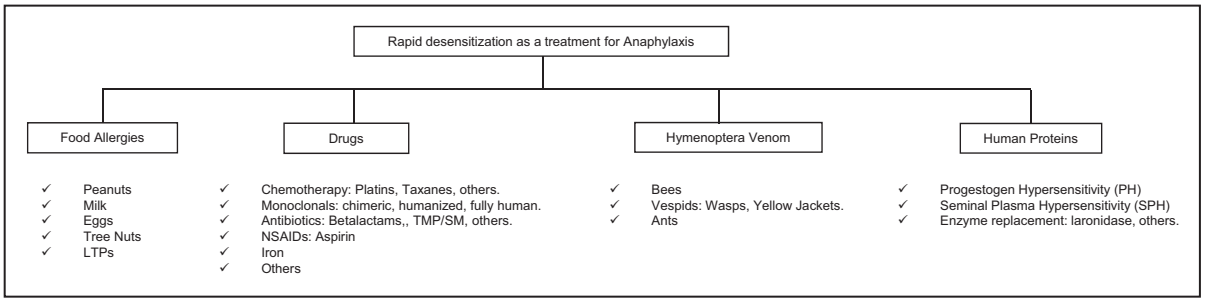


**FIGURE 3.** Rapid desensitization as a treatment for anaphylaxis. Desensitization as a treatment of anaphylaxis for foods, drugs, *Hymenoptera* venom and human proteins. *Source:* Based on [2▪].

## NEW APPROACH TO THE TREATMENT OF ANAPHYLAXIS: DESENSITIZATION

Specific interventions and measures to reduce and prevent the risk of anaphylaxis, such as desensitization, are critical for long-term treatment in the allergic patient (Fig. 3).

Drug desensitization is a safe and effective treatment modality in patients with anaphylaxis to chemotherapeutic agents, mAbs [46▪,47,48,49▪,50,51], antibiotics [52] and other drugs, such as aspirin [53] and iron [54,55]. The goal of desensitization is to maintain patients on their first-line therapy to improve their disease management. Desensitization works by initiating inhibitory mechanisms at low antigen doses, which later dominate over the activation pathways and prevent anaphylaxis [2▪,56,57]. In a 2016 analysis of 2177 rapid drug desensitization (RDD) procedures to chemotherapy and mAbs, 370 patients with cancer, vasculitis and hematological and connective tissue diseases were desensitized and only 402 reactions were recorded. Of the 2177 desensitizations, 93% had no or mild reactions, whereas 7% had moderate-to-severe reactions, which did not preclude the completion of treatment. No deaths were reported. All patients safely received their target dose regardless of their original reaction [49▪]. Efficacy and costs were also analyzed, and it was concluded that patients undergoing desensitized had fewer hospital encounters and lower overall costs than nondesensitized patients. Critically, carboplatin-desensitized patients had a nonstatistically significant lifespan advantage over nonallergic controls, indicating that the efficacy of carboplatin was not reduced in allergic patients and that RDD protocols are as effective as regular infusions [49▪].

Seminal plasma hypersensitivity is also described to cause anaphylaxis in women, typically at the beginning, during or shortly after sexual intercourse. Desensitization to human seminal fluid has been published as a successful treatment [58,59].

Venom desensitization, also called ultrarush venom immunotherapy, should be considered in patients who present life-threatening anaphylaxis after *Hymenoptera* sting with evidence of IgE-mediated mechanism [60]. *Hymenoptera* anaphylaxis might be the presentation of a mast-cell disorder. Venom immunotherapy in patients with mastocytosis has been demonstrated to reduce the risk of anaphylaxis after resting. In those patients, venom immunotherapy is recommended indefinitely due to the chronic nature of mastocytosis and fatalities have been reported after discontinuation of venom immunotherapy and resting. Omalizumab decreases the severity of reactions in patients under venom immunotherapy and should be considered for patients with severe reactions or underlying mastocytosis [61].

Food-triggered exercised-induced anaphylaxis was initially described as a syndrome induced during or shortly after exercise in patients sensitized to specific foods. Recently, food ingestion associated with other cofactors such as alcohol, menses, NSAIDs, has also been shown to trigger anaphylaxis [62–67].

A study showed how long-term treatment with egg OIT enhances sustained unresponsiveness that persists after cessation of therapy. Of 40 OIT-treated patients, 20 (50.0%) demonstrated sustained unresponsiveness by year 4 [68].

Another study has evaluated the clinical and immunological effects of Pru p 3 sublingual immunotherapy (SLIT) on peach and peanut allergy in patients with systemic reactions. The peach nonspecific lipid transfer protein, Pru p 3, is the primary sensitizer in fruits and is responsible for severe reactions in the Mediterranean population. Peach allergy is frequently associated with other allergies such as peanut. After 1 year, Pru p 3 SLIT induced both desensitization and immunological changes not only for peach but also for other food allergens relevant in the induction of severe reactions such as peanut [69].

## CLINICAL VIGNETTE: SUCCESSFUL MANAGEMENT

Progestogen hypersensitivity presents with heterogeneous symptoms, which can range from urticaria to dyspnea, cough, and can lead to anaphylaxis. Symptoms are triggered by endogenous progesterone or exogenous progestogen exposure. Endogenous progesterone triggers are defined as symptoms associated with menses or pregnancy without additional hormone supplementation. Exogenous progestogen triggers are defined as symptoms proximal to exposure to any progesterone source not naturally occurring, such as IVF. Desensitization to progestogens has provided a successful avenue for patients with progestogen hypersensitivity to manage symptoms and tolerate fertility treatments [70▪]. A recent clinical communication describes a case of rapid and sustained regression of cyclic episodes of anaphylaxis due to progestogen hypersensitivity induced successfully by Omalizumab [71].

Skin testing with progesterone was performed on our patient to confirm progesterone hypersensitivity. Skin intradermal test was positive with $3 \times 6$ mm wheal at 1 : 100 dilution. Intramuscular progesterone desensitization was performed 5 days before of the embryo transfer (determined by the fertility team) (Table 1).

Premedication was administered 30 min before the start of the desensitization and included: cetirizine 10 mg, famotidine 20 mg, montelukast 10 mg and two puffs of albuterol. The patient tolerated the desensitization without any HSR or symptoms with a final cumulative dose of 25 mg. She continued with 50 mg of progesterone daily. Five days later, the embryo was transferred and the patient had a successful pregnancy.

**Table 1.** Desensitization protocol for progestogen hypersensitivity through intramuscular administration

| Step | IM progesterone injection dose (mg) | Time (min) | Cumulative progesterone (mg) |
|---|---|---|---|
| 1 | 0.5 | 30 | 0.5 |
| 2 | 1 | 30 | 1.5 |
| 3 | 2 | 30 | 3.5 |
| 4 | 4 | 30 | 7.5 |
| 5 | 8 | 30 | 15.5 |
| 6 | 9.5 | 30 | 25 |

Brigham and Women's Hospital, Boston, Massachusetts, USA. Day 1: target dose 25 mg trough desensitization. Day 2: 50 mg (25 + 25 mg) continued for 10 weeks as indicated by fertility specialist. Day 6: embryo transfer. Day 13: positive pregnancy test. IM, intramuscular.

## CONCLUSION

Anaphylaxis is the most severe HSR and can lead to death. Classification based on phenotypes, endotypes and biomarkers allows for a better understanding of anaphylaxis presentation, mechanisms and mediators. Epinephrine is the first-line life-saving treatment for anaphylaxis and should not be delayed. Patients with first-line therapy-induced anaphylaxis are candidates for RDD increasing their quality of life and life expectancy. Postanaphylaxis assessment is mandatory for patients to learn to identify triggers, early symptoms and the indications and timing of epinephrine autoinjector use. It is important to recognize the psychological impact that anaphylaxis can trigger with long-lasting sequelae. Desensitization is a breakthrough novel treatment for patients with anaphylaxis in need of first-line therapy, including chemotherapy, mAbs, aspirin and others. Ultrarush with venom immunotherapy should be considered in patients who present with life-threatening anaphylaxis after *Hymenoptera* sting with evidence of IgE-mediated mechanism. Food desensitization is currently being expanded to provide increased safety for adults and children with food-induced anaphylaxis.

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### Conflicts of interest

*There are no conflicts of interest.*

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- ▪▪ of outstanding interest

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