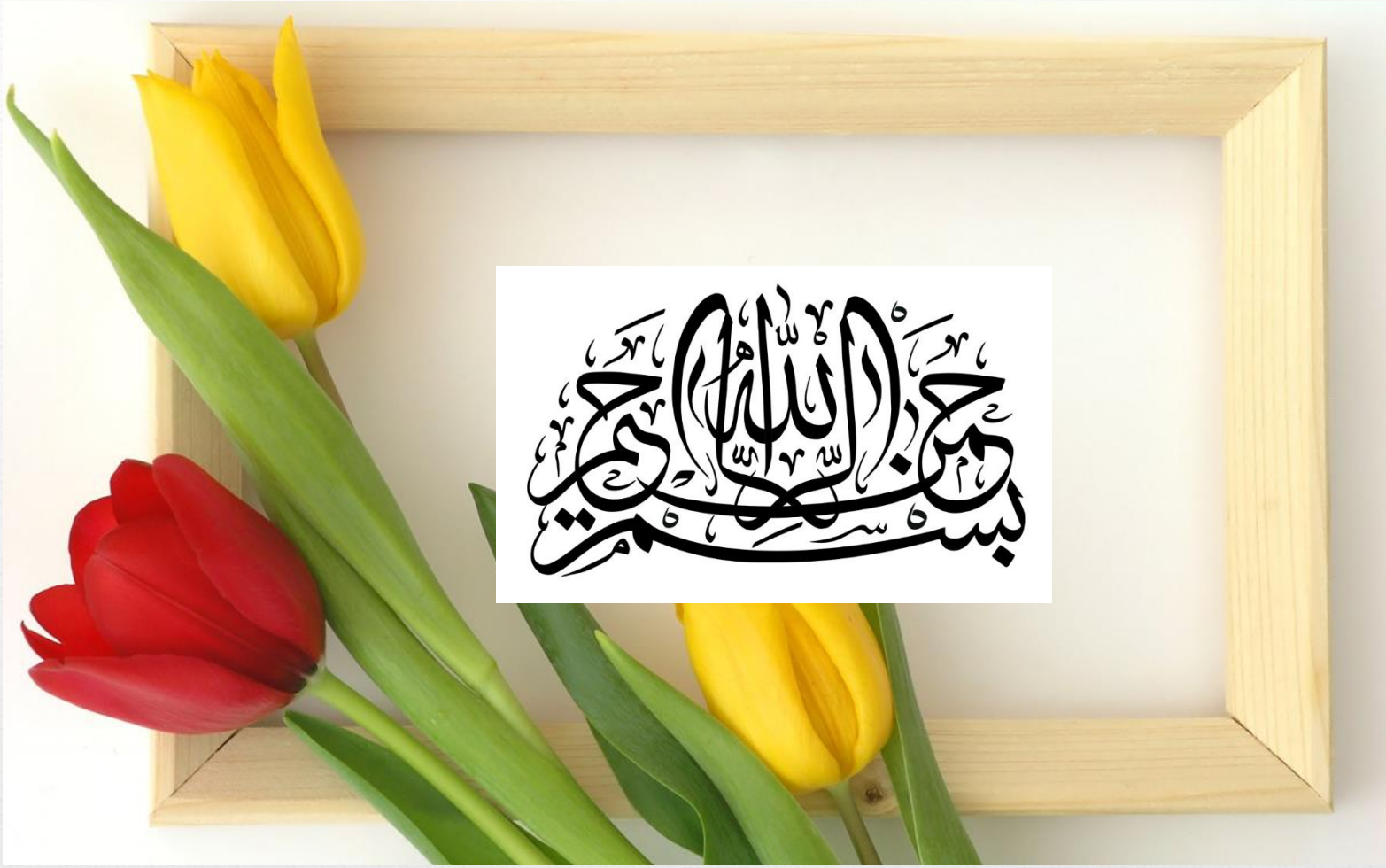
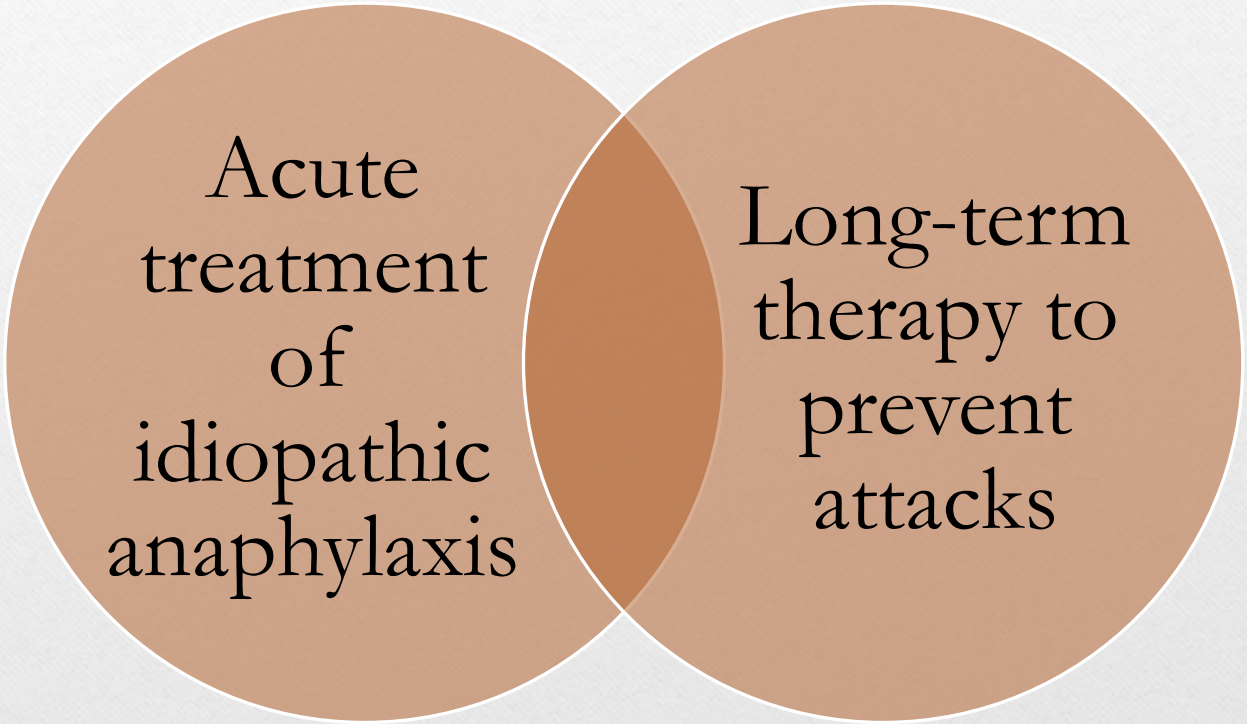

بسم الله الرحمن الرحيم

Managment of Idiopathic anaphylaxis

M.H Bemanian professor of allergy and Clinical immunology, Hazrat rasoul hospital Iran university of medical sciences

30 june 2022

Management of IA



Acute management

- The emergency treatment of idiopathic anaphylaxis is identical to the emergency treatment of anaphylaxis with a known trigger.
- Epinephrine is the drug of choice for acute treatment of anaphylaxis.
- It is the only drug that prevents or reverses **laryngeal edema**, ***severe bronchospasm***, and **cardiovascular** collapse.

Risk factors for IA

- Although risk factors specifically for IA have not been formally statistically assessed, the rate of IA is substantially higher in **women** than in men.
- A history of **atopy** or **intermittent urticaria** or angioedema also appears to increase the risk of IA.
- Mastocytosis is an important risk factor for IA Idiopathic anaphylaxis is therefore classified under **idiopathic mast cell activation** syndromes

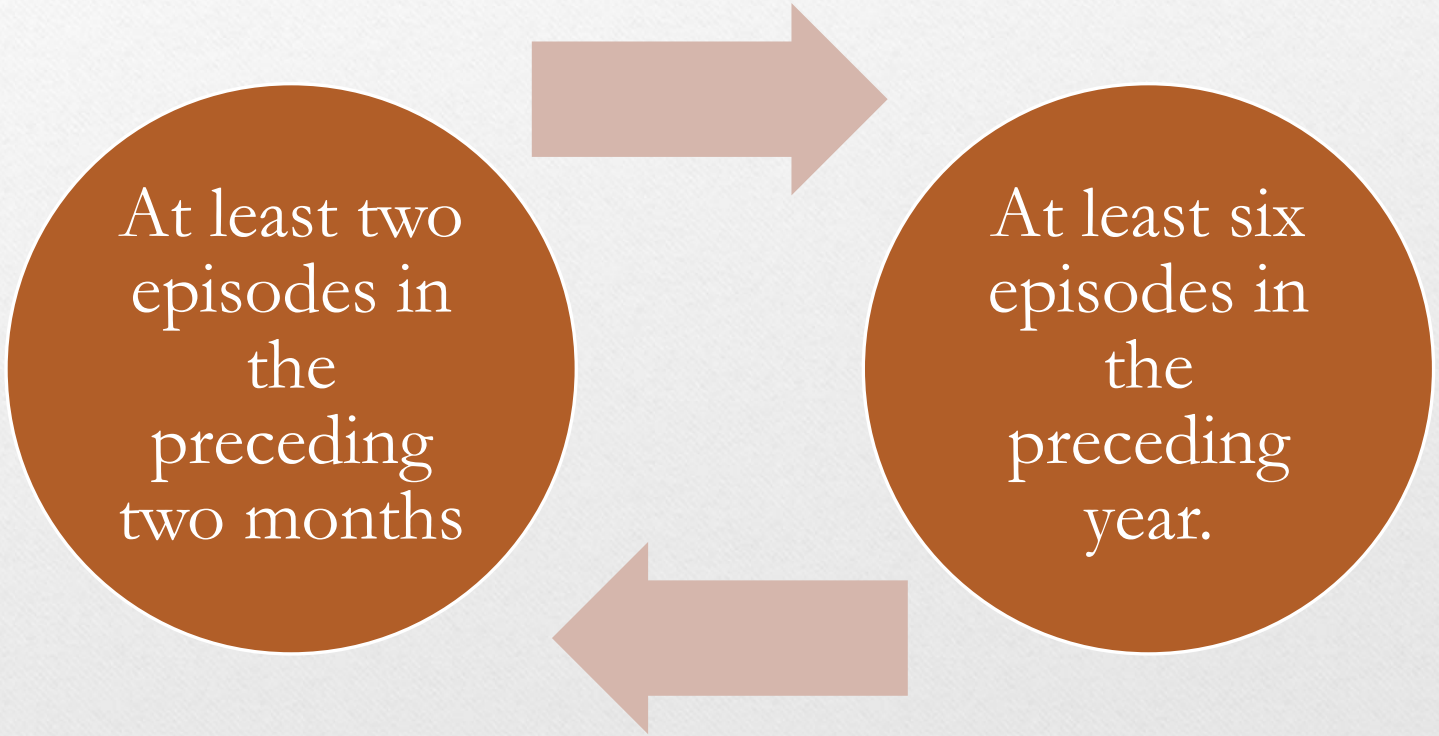
Long-term management

- Episodes of idiopathic anaphylaxis tend to decline in frequency over time.
- Recommendations for the management of patients with idiopathic anaphylaxis are based upon data from observational studies, case reports/series, and clinical experience.

- Long-term management is based upon the frequency of episodes

Manage stress that may be caused by not being able to know what triggers to avoid?

Frequent/infrequent Idiopathic anaphylaxis



Frequent/infrequent Idiopathic anaphylaxis

- Frequent – Patients with frequent idiopathic anaphylaxis are sometimes treated with a combination of prednisone and an H1 antihistamine, usually for a minimum of three months.

- Infrequent – Patients with infrequent idiopathic anaphylaxis are not treated prophylactically.

Management of IA

New medications culprit/triggers

- A thorough medical history including scheduled and as-needed medication use should be obtained.
- Any temporal relationship of symptoms to starting new medications should be noted, and the patient should be considered for switching to an equally effective alternative if one exists.

Management of IA

Medication cause flushing

- If feasible, drugs that can potentially cause flushing may be held or switched to an alternative to assess the response.
- Systemic glucocorticoids often administered in high doses in treatment of anaphylaxis may themselves cause flushing, which may be confused with symptoms of anaphylaxis.

Causes of Flushing

Type	Causes
Physiologic	Menopause Hot drinks Emotional distress
Drugs	Alcohol (in Asians) Alcohol plus chlorpromazine or disulfuram Diltiazem Amyl nitrate Nicotinic acid Levodopa Bromocriptine
Diseases	Carcinoid syndrome Systemic mastocytosis Basophilic chronic granulocytic leukemia VIPoma Pheochromocytoma Medullary carcinoma of the thyroid Renal cell carcinoma Diencephalic seizures

Management of IA
NSAID

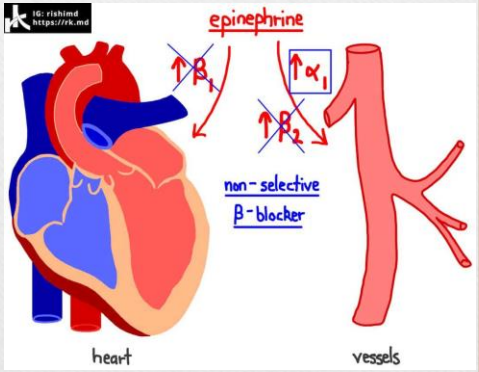
Classification	Kowalski *et al.* [15]	Proposed in this review
Phenotypes	NERD (NSAID-exacerbated respiratory disease)	NERD (NSAID-exacerbated respiratory disease)
	NECD (NSAID-exacerbated cutaneous disease)	NECD (NSAID-exacerbated cutaneous disease)
	NIUA (NSAID-induced urticaria/angioedema)	MNIA (multiple NSAID-induced anaphylaxis type reactions[a])
	SNIUAA (single NSAID-induced urticaria/angioedema or anaphylaxis[b])	SNIA (single NSAID-induced anaphylaxis type reactions)
	SNIDR (single NSAID-induced delayed hypersensitivity reactions)	SNIDR (single NSAID-induced delayed hypersensitivity reactions)

[a]Anaphylaxis type reactions include anaphylaxis, urticaria, angioedema, and blended reactions.
[b]New findings suggest that within SNIUA there would be selective reactors to a single drug or multiple selective reactors [16,17].
Pink: cutaneous acute hypersensitivity reactions.

- Nonsteroidal anti-inflammatory drugs can trigger or potentiate urticaria and angioedema, and, therefore, their use should be limited.

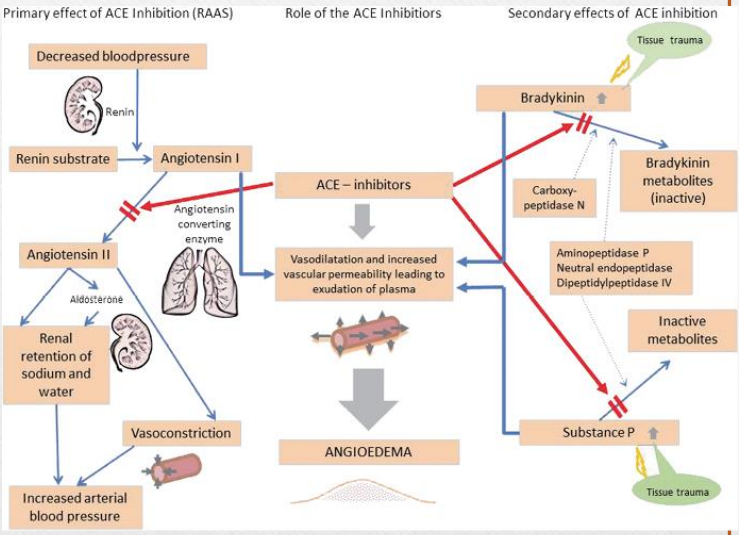
Management of IA
beta blocker

- Controversy exists in the use of beta-blockers in patients with recurrent anaphylaxis because of the concern about potential blockage of epinephrine action if needed to treat an anaphylactic reaction
- However, the data supporting this potential concern are limited, and their use may be necessary in patients with concurrent cardiovascular disease if no suitable alternatives exist.



Management of IA
ACE inhibitors

- In patients with recurrent angioedema who are on angiotensin-converting enzyme inhibitors, (Captopril, Enalapril, Lisinopril)considering an alternative medication such as an angiotensin receptor blockers (Losartan,Valsartan) reasonable.



Drugs Used to Prevent or Lessen Severity

- A number of drugs have been shown to prevent or lessen the severity of IA

Drugs That May Prevent or Lessen the Severity of IA
Prednisone[128]
H1 and H2 receptor antagonists[128]
Albuterol
Ketotifen[129, 130]
Leukotriene receptor antagonists
Omalizumab[131-134]
Rituximab[135]

Corticosteroids
acute/long term management

- No evidence suggests a role for systemic corticosteroids in the treatment of acute anaphylactic reactions; however, they are often administered in acute care settings to prevent delayed or biphasic reactions.
- No randomized, controlled clinical trials validate the efficacy of this practice.
- Chronic long-term use of corticosteroids may be necessary in some patients with recurrent IA.

September 2017 European Annals of Allergy and Clinical Immunology

As anaphylaxis is a medical emergency, there are no randomized controlled clinical trials on its emergency management

30 original research papers were found with 22 human studies and 8 animal or laboratory studies

Corticosteroids appear to reduce the length of hospital stay, but did not reduce revisits to the emergency department.

There was no consensus on whether corticosteroids reduce biphasic anaphylactic reactions.

we conclude that there is no compelling evidence to support or oppose the use of corticosteroid in emergency treatment of anaphylaxis

REVIEW | Eur Ann Allergy Clin Immunol | Vol 49, N 5, 196-207, 2017

C. K. Liyanage[1], P. Galappatthy[1], S.L. Seneviratne[2,3]

Corticosteroids in management of anaphylaxis; a systematic review of evidence

[1]Department of Pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka
[2]Department of Surgery, Faculty of Medicine, University of Colombo, Sri Lanka
[3]Department of Clinical Immunology, Royal Free Hospital, London, UK
Work was carried out at Department of Pharmacology, Faculty of Medicine, University of Colombo, Sri Lanka

Key words
Anaphylaxis; emergency management; corticosteroids; prednisolone; allergy

Corresponding author
Chiranthi Kongala Liyanage
Department of Pharmacology,
Faculty of Medicine
University of Colombo
25, Kinsey road, Colombo 08, Sri Lanka
Phone: +94 11 2697 483, +94 77 2330 362
Fax: +94 11 2697 483
E-mail: chiranthiliyanage@gmail.com

Doi
10.23822/EurAnnACI.1764-1489.15

Abbreviations
ED, Emergency department; IgE, Immunoglobulin E; IL-6, Interleukin 6; IL-33, Interleukin 33; PAF, Platelet activating factor; RCT, Randomized control trial; TNF α, Tumor necrosis factor α.

Summary
As anaphylaxis is a medical emergency, there are no randomized controlled clinical trials on its emergency management. Therefore, current guidelines are mostly based on data from observational studies, animal and laboratory studies. Although epinephrine is the mainstay of recommended treatment, corticosteroids are also frequently used. This review evaluates the evidence on the use of corticosteroids in emergency management of anaphylaxis from published human and animal or laboratories studies. Thirty original research papers were found with 22 human studies and eight animal or laboratory studies. The average rate of corticosteroid use in emergency treatment was 67.99% (range 48% to 100%). Corticosteroids appear to reduce the length of hospital stay, but did not reduce revisits to the emergency department. There was no consensus on whether corticosteroids reduce biphasic anaphylactic reactions. None of the human studies had sufficient data to compare the response to treatment in different treatment groups (i.e. corticosteroids, epinephrine, antihistamines). Animal studies demonstrated that corticosteroids act through multiple mechanisms. These modulate gene expression, with effects becoming evident 4 to 24 hours after administration. A much quicker response has been detected within 5 to 30 minutes, through blockade of signal activation of glucocorticoid receptors independent of their genomic effects. Therefore, we conclude that there is no compelling evidence to support or oppose the use of corticosteroid in emergency treatment of anaphylaxis. However, based on the available data, it appears to be beneficial and there was no evidence of adverse outcomes related to the use of corticosteroids in emergency treatment of anaphylaxis.

Introduction

Anaphylaxis is a "serious, generalized or systemic acute immunologic reaction" that is "rapid in onset and that would be fatal or life threatening" (1-3). Based on available data from international studies, the life-time prevalence of anaphylaxis has been estimated at 0.05 to 2% (4), with an estimated incidence ranging from 10 to 20/100,000 population per year (5-7). The incidence of anaphylaxis is also reportedly increasing worldwide, particularly food-induced anaphylaxis (8,9).

Anaphylaxis is brought about by direct or indirect activation of mast cells. Anaphylaxis classically involves the skin (80%), respiratory (70%), gastrointestinal (30-45%), cardiovascular (10-45%) and central nervous (10-15%) systems (2,6,10-12). Symptoms generally appear suddenly, progress over minutes to hours and increase in severity. Although only one organ system may be initially involved, symptoms will typically progress to eventually involve at least two organ systems (13,14). The diagnosis of anaphylaxis relies heavily on clinical judgment due to

Corticosteroids
long term management

- Typical regimens for adults start from 40 to 60 mg prednisone daily and taper the dose by 5 to 10 mg every 2 weeks.
- In these patients, the lowest dose of steroid capable of preventing anaphylaxis should be used.
- Steroid-sparing alternatives, including omalizumab, should be considered in those with recurrent episodes when steroids are tapered.

H1 or H2 Receptor Antagonists

- Patients with recurrent frequent IA require daily management with H1 receptor antagonists.
- Nonsedating antihistamines may be used up to 4 times per day, similar to the treatment guidelines for chronic urticaria.
- Supplemental use of shorter-acting antihistamines such as diphenhydramine or hydroxyzine still may be required.

H1 or H2 Receptor Antagonists

- Twice-daily use of H2 receptor antagonists can be useful adjunctive medication to H1 receptor antagonists, especially in patients on glucocorticoids (to prevent gastrointestinal complications), or because of their complementary effects on histamine blockade in skin and blood vessels.

Sympathomimetic Drugs
(eg, Albuterol)

- Inhaled bronchodilators should be available to treat acute IA episodes presenting with bronchoconstriction.
- Little evidence supports use of oral albuterol in maintenance therapy of IA.

Ketotifen

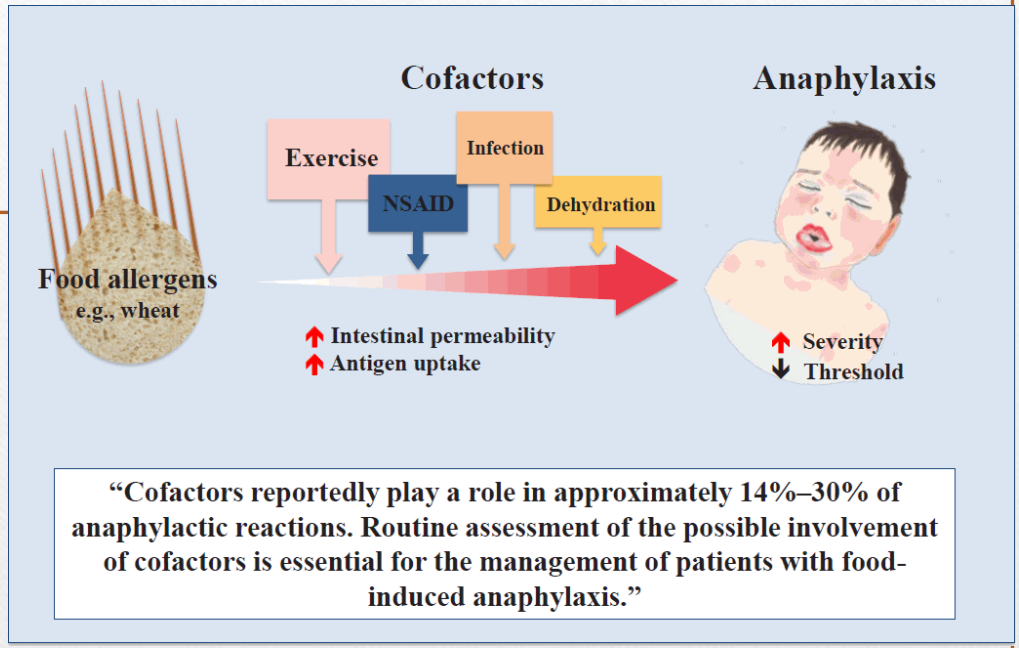
- Little evidence has been published using ketotifen in IA, but its mast cell estabilizing properties have been demonstrated in mastocytosis.
- Ketotifen for IA may be more effective when used in combination with H1 or H2 receptor antagonists.
- Doxepin is an alternative mast cell stabilizer but is not recommended for most patients because of its sedating effects and other potential side effects.

Doxepin

- It is an alternative mast cell stabilizer but is not recommended for most patients because of its sedating effects and other potential side effects.

Leukotriene Receptor Antagonists

FDEIA



Little evidence and no controlled studies support the use of leukotriene receptor antagonists to prevent IA

anecdotal evidence suggests that montelukast can control urticaria, and when combined with antihistamines, prevent food-dependent exercise induced anaphylaxis

Omalizumab

- Several case reports support the benefit of omalizumab for the prevention of IA, as well as the prevention of anaphylaxis associated with Hymenoptera allergy immunotherapy mastocytosis, and MCAS.
- Omalizumab also has been shown in randomized double-blind placebo-controlled and open-label trials to be efficacious in decreasing anaphylaxis associated with oral immunotherapy to food allergens.

Rituximab

- Based on the observation of elevated B-cells in patients with IA
- Ritixumab was given as an exploratory treatment to a woman with frequent refractory IA
- Ritixumab was successful in inducing remission in this patient.
- In our opinion, ritixumab should be considered only after failure of more benign treatments.

Tyrosine Kinase Inhibitors

- Tyrosine kinase inhibitors clearly have been shown to lessen severity and prevent the manifestations caused by mast cell mediator release.
- However, their major role is as a cytoreductive agent to prevent none mast cell induced symptoms, and there are potential side effects from their use.
- In addition, their use, in most instances, should be co-managed with a hematologist/oncologist.

Tyrosine Kinase Inhibitors

- Tyrosine kinase inhibitors (midostaurin and imatinib) in the treatment of mastocytosis have been reported in 1 individual case and in an open-label phase 2 trial.
- No clinical trials of tyrosine kinase inhibitors have been conducted for the potential prevention of anaphylaxis.

Difficult Patients: What to Do When They Do Not Respond

- Patients who do not respond to targeted therapy based on the diagnosis usually have a disease entity that has not been identified or have additional confounding issues that are not responsive to current therapy.
- There are steps that may be helpful to pin down a diagnosis.

Revisit the history and physical examination for information that the patient forgot to report

- a. Patient logs for more precise documentation of timing and severity
- b. Late-night reactions such as those associated with alpha-gal
- c. Potentiating factors such as alcohol, exercise, menses, illness
- d. Psychological issues such as anxiety or depression
- e. Overlooked skin lesions (urticaria pigmentosa can be mistaken for freckles); timing of development is important
- f. Direct observation of symptoms when possible, with supporting vitals
- g. Prescription to obtain serum tryptase level for reactions that require an ER visit and obtaining a baseline tryptase after the event

Pediatric Considerations

- For prevention of IA symptoms in children, nonsedating H1 and H2 receptor antagonists are recommended and have better efficacy for symptom control.
- Systemic dosing of corticosteroids is not recommended for mild or moderate symptoms (undesirable side effects).

Pediatric Considerations

- Retrospective study in patients with chronic urticaria, **ketotifen** may have a suppressive effect on symptoms.
- Alternatively, **doxepin** may be helpful for older children.
- **Leukotriene receptor antagonists** are more effective in children with **asthma** who exhibit respiratory symptoms with their IA episodes, but there is little efficacy for flushing.
- **Oral cromolyn** sodium is most effective in children with **GI manifestations** of their symptoms because it is not typically absorbed into the bloodstream with a positive benefit on flushing.

Pediatric Considerations

- A **local cream of cromolyn** sodium compounded by a pharmacist is helpful for children with **cutaneous symptoms** such as pruritus and blistering.
- Efficacy of **omalizumab** for the prevention of IA episodes in children has been published in case reports.
- **Dosing for omalizumab** should be based on the packet insert, or for patients with low IgE values, using the dosing schedule recommended for chronic idiopathic urticaria.
- **Cytoreductive therapy** is in general not recommended in the pediatric population.

از توجه شما سپاسگزارم