Faculty of Medicine
Anesthesia & Intensive care department

Anaphylaxis in Intensive care unit

Essay

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Deena Mohsen Abou-zaid

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List of abbreviations

ACEI	Angiotensin converting enzyme inhibitor
BP	Blood pressure
BW	Body weight
C	Complement
CT	Computed tomography
D5W	5% Dextrose water
EDTA	Ethylene diamine tetra-acetic acid
ELISA	Enzyme-linked immunosorbent assay
FcεRI	Fc epsilon RI
G/Kg	Gram per Kilogram
ICU	Intensive care unit
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IL	Interleukin
IM	Intramuscular
IV	Intravenous
LT	Leukotriene

List of abbreviations

Mg/Kg	Milligram per Kilogram
MRI	Magnetic resonance imaging
Ng/Ml	Nanogram per Milli
PAF	Platelet activating factor
PGD2	Prostaglandin D2
PO	Per os
$	Dollars
SC	Subcutaneous
SIRS	Systemic inflammatory immune response
SJS	Stevens-Johnson syndrome
TEN	Toxic epidermal necrolysis
Th2	T helper type2 cells
TNF	Tumor necrosis factor
µg/L	Microgram per Liter
US	United States
VIP	Vasoactive intestinal polypeptide
WAO	World allergy organization
WHO	World health organization

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Introduction

The term "Anaphylaxis" is derived from the Greek "ana" meaning backward and "phylaxis" meaning protection. Anaphylaxis is an acute, potentially fatal, multi-organ system reaction caused by the release of chemical mediators from mast cells and basophils. The classic form involves prior sensitization to an allergen with later re-exposure, producing symptoms via an immunologic mechanism **(Kemp and Lockey, 2002)**.

Anaphylaxis is a medical emergency that requires immediate recognition and intervention. Therefore; prompt recognition and management of the condition are imperative. Patient management and disposition are dependent on the severity of the initial reaction and the treatment response noting that guidelines for the emergency medical treatment of anaphylaxis vary internationally **(Alrasbi and Sheikh, 2007)**.

The more rapidly anaphylaxis develops, the more likely the reaction is to be severe and life-threatening **(Lieberman et al., 2010)**.

Comorbidities and concurrent medications may also affect the severity of anaphylactic reactions and patient response to treatment **(Simon, 2006)**.

Anaphylaxis most commonly affects the cutaneous, respiratory, cardiovascular, and gastrointestinal systems. The skin or mucous membranes are almost always involved. A majority of adult patients have some

combination of urticaria, erythema, pruritus, or angioedema **(Webb and Lieberman, 2006)**.

However, for poorly understood reasons, children may present more commonly with respiratory symptoms followed by cutaneous symptoms **(Braganza et al., 2006)**.

Diagnosis can be difficult, with skin features being absent in up to 20% of people. Anaphylaxis must be considered as a differential diagnosis for any acute onset respiratory distress, bronchospasm, hypotension, or cardiac arrest **(Brown et al., 2004)**.

A simple definition has been applied by the Australasian Society of Clinical Immunology and Allergy (ASCIA) which is: "Anaphylaxis is a rapidly evolving generalized multisystem allergic reaction characterized by one or more symptoms or signs of respiratory and/or cardiovascular involvement, and involvement of other systems such as the skin and/or the gastrointestinal tract" **(ASCIA, 2004)**.

The lack of a universally accepted severity grading system for anaphylaxis and lack of a reliable biomarker to confirm the diagnosis has not only hampered research, but has also resulted in failure to diagnose and treat anaphylaxis in a consistent and timely manner. Furthermore, there is no single test to diagnose anaphylaxis in routine clinical practice. Finally, anaphylaxis is often under-recognized and treated inadequately. Diagnosis and management are challenging since reactions are often immediate and unexpected **(Waserman et al., 2010)**.

Aim of the work

Here, we provide a concise overview about anaphylaxis; possible causes in ICU, summation anaphylaxis, its differential diagnosis and complications.

Furthermore we discuss risk factors for fatal anaphylaxis, anaphylaxis early diagnosis, its management in ICU, and its preventive measures.

Chapter I
Etiology and pathophysiology of anaphylaxis

Anaphylaxis is an acute, potentially lethal, multi-system syndrome resulting from the sudden release of mast cell- and basophil-derived mediators into the circulation **(Sampson et al., 2006)**. It most often results from immunologic reactions to foods, medications and insect stings, although it can also be induced through nonimmunologic mechanisms by any agent capable of producing a sudden, systemic degranulation of mast cells or basophils **(Kemp and Lockey, 2002)**.

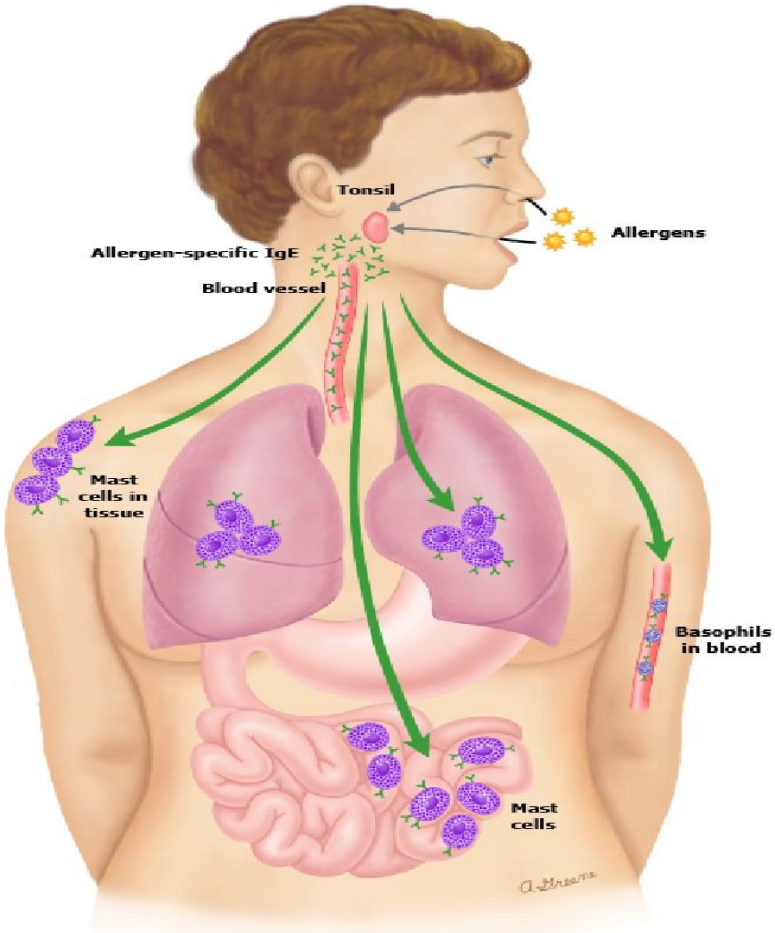
Etiology and pathophysiology:

The term anaphylaxis has traditionally been reserved for IgE-dependent events, and the term "anaphylactoid reaction" has been used to describe IgE-independent events, although the two reactions are often clinically indistinguishable. The World Allergy Organization (WAO), an international umbrella organization representing a large number of regional and national professional societies dedicated to allergy and clinical immunology, has proposed discarding this nomenclature. The WAO categorizes anaphylaxis as either immunologic or nonimmunologic where immunologic anaphylaxis includes IgE-mediated reactions, IgG-mediated reactions, immune complex/complement mediated reactions, and other proposed mechanisms **(Johansson et al., 2004)**.

1- Immunologic anaphylaxis:

IgE-mediated: The classical mechanism associated with human allergic disease is initiated by an antigen (allergen) interacting with allergen-specific IgE bound to the receptor Fc-epsilon-RI (FcεRI) on mast cells and/or basophils. The events leading to allergen-specific IgE production in an atopic individual are complex. In brief B cells are driven to differentiate into IgE-producing cells via the activity of the type 2 subset of CD4-bearing helper T cells (Th2 cells). This process largely takes place in the peripheral lymphoid tissues. The cytokines interleukin-4 (IL-4) and its receptors (IL-4Rα/γc and IL-4Rα/IL-13Rα1) and IL-13 and its receptor (IL-4Rα/IL-13Rα1) contribute to IgE responses in humans. Once produced, allergen-specific IgE diffuses through the tissues and vasculature, and constitutively occupies high-affinity IgE receptors (FcεRI) on mast cells and basophils (Figure 1.1). When allergen diffuses into the proximity of a mast cell or basophil, it interacts with any surface bound IgE that is specific for that allergen. Certain allergens are able to interact with IgE molecules on two or more receptors of the cell surface to cause cross-linking, which in turn causes the receptors to become aggregated and initiate intracellular signaling. Allergens that are capable of cross-linking are either multivalent allergens (which have multiple identical sites for antibody binding), or univalent allergens that have multiple different epitopes to which IgE molecules can bind. If signaling is sufficiently robust, the mast cell (or basophil) becomes activated and degranulates, releasing preformed mediators, enzymes, and cytokines (such as

Figure 1.1 Allergen-specific IgE production and dissemination **(Schwartz, 2004)**.



Allergens (in this figure, aeroallergens) enter the tonsils, within which they are taken up and degraded by antigen presenting cells (APC). APCs then interact with T helper cells type 2 (TH2) cells and B cells in the lymph nodes, leading to allergen-specific IgE production. The IgE enters the blood stream, and then diffuses through tissues (especially the skin and mucosal tissues of the respiratory and gastrointestinal tracts). The IgE binds to high affinity Fc receptors (Fc-epsilon-RI) on the surface of the tissue mast cells and circulating basophils. When these IgE-coated cells encounter that specific aeroallergen subsequently, they become activated, leading to the release of inflammatory mediators, which result in the signs and symptoms of IgE-mediated allergic reactions.

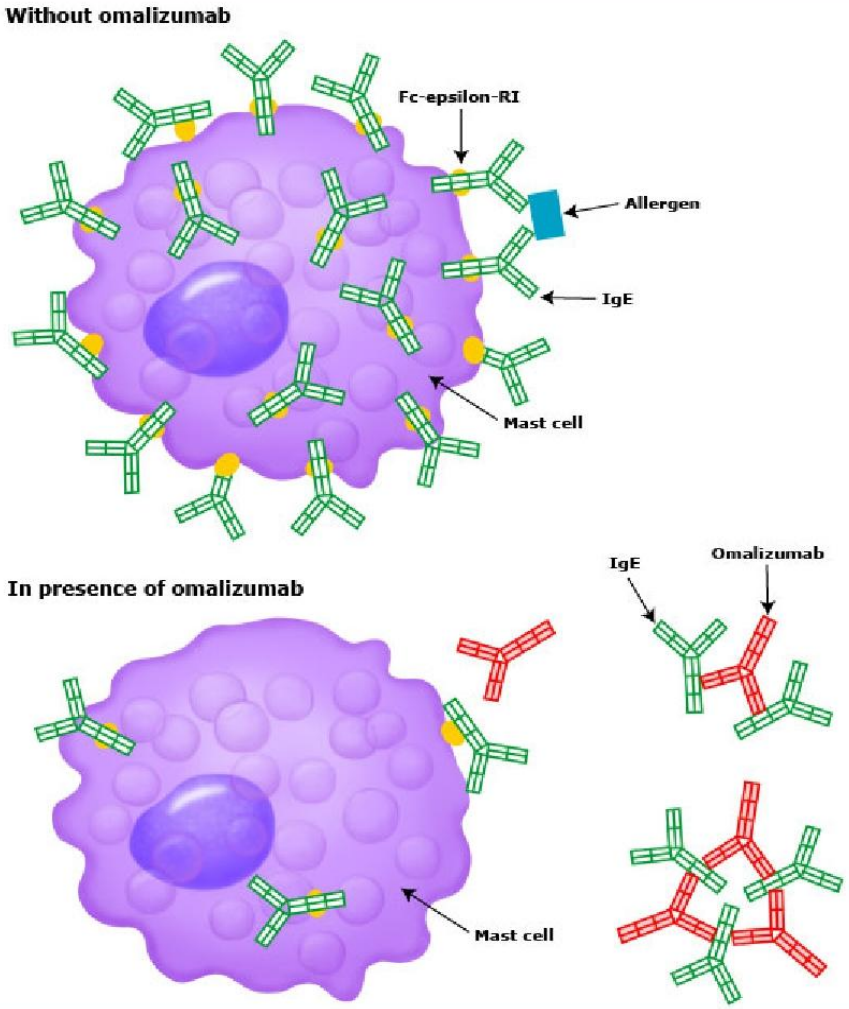
histamine, tryptase, and TNF respectively) and initiating additional mediator, cytokine, and enzyme production. These mediators either act directly on tissues to cause allergic symptoms, or recruit and activate additional inflammatory cells, particularly eosinophils. The recruited cells, in turn, release more mediators and propagate a fulminant "chain-reaction" of allergic inflammation. **(Strait et al., 2006)**.

IgG-mediated: (in animal models) IgG-dependent anaphylaxis has not been demonstrated in humans. However, human IgG receptors are capable of activating macrophages and neutrophils to secrete Platelet activating factor "PAF" **(Jönsson et al., 2012)**, and PAF can activate mast cells in vitro **(Kajiwara et al., 2010)**, so PAF potentially may contribute to human anaphylaxis. Additionally, anaphylaxis has been reported to be more severe in individuals who catabolize PAF slowly **(Vadas et al., 2008)**.

Rare individuals have experienced anaphylaxis after receiving therapeutic preparations of IgG anti-IgE antibodies "Omalizumab" **(Cox et al., 2007), (Limb et al., 2007)**. Omalizumab blocks the binding of IgE to FcεRI receptors and does not bind FcεRI-associated IgE (figure 1.2). These anaphylactic reactions could conceivably be IgG-mediated, with the patient's IgE acting as the antigen and the IgG of the drug acting as the causative antibody **(Dreyfus and Randolph, 2006)**.

IgE-independent anaphylaxis has also been reported in some patients receiving another monoclonal antibody preparation "Infliximab" **(Cheifetz et al., 2003), (Stallmach et al., 2004)**.

Figure 1.2 Omalizumab mechanism of action **(Dreyfus and Randolph, 2006)**.



Omalizumab binds free IgE in the serum, forming trimers and hexamers. The drug binds to IgE at the same site that the high affinity IgE receptor (Fc-epsilon-RI) binds, so IgE bound to drug cannot bind its receptors on mast cells and basophils. Omalizumab does not bind IgE that is already bound to Fc-epsilon-RI, and so should not result in cross-linking of receptors. As a result of the binding of free IgE, the number of IgE receptors on the surface of mast cells and basophils declines over time, which is believed to be a critical component of the clinical effect of the drug. Omalizumab also blocks binding of IgE to the low affinity IgE receptor (Fc-epsilon-RII or CD23, not shown) although the therapeutic relevance of this is not known.