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The Final thesis

Management of Anaphylaxis in Emergency Department

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1 Abstract

Anaphylaxis is frequent problem at the emergency department. There are currently very heterogenic practices and guidelines about anaphylaxis starting already from the different definitions. This thesis dives deeper into pathophysiology of anaphylaxis and then to the evidence behind the different guidelines and practices and tries to establish that which practices are on solid base and which not. This thesis was done as narrative literature review using mostly recent studies published in reputable journals. During the search of literature, it was found that there were very variable criteria used for diagnosing and managing anaphylaxis and currently there is no consensus which criteria are best, reflecting the heterogeneous practices and management in different parts of world. It seems that anaphylaxis is severely underdiagnosed and often as well misdiagnosed. In the thesis it was established that there is evidence that for some reason physicians are reluctant to administer adrenaline and thus some parts of the world are moving to less strict indications for administrating adrenaline. The usage of corticosteroids and antihistamine instead of adrenaline to anaphylaxis have remained extremely high, especially in USA. However, there is increasingly more new evidence that corticosteroids and antihistamine administration to anaphylaxis will cause mismanagement, misdiagnosis and even potentially can be harmful. Some countries have drawn their conclusions like UK, Australia and New Zealand and are not recommending antihistamines or corticosteroids at all anymore.

Keywords

Management, Anaphylaxis, Emergency department, Pathophysiology, Diagnosis, Adrenaline, Corticosteroids, Antihistamines

2 Introduction

WHO ICD 11 defines anaphylaxis as “Anaphylaxis is a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes (1). Anaphylaxis is caused usually by either food, venom, or a medication. According to a one study, the mean time of onset of anaphylaxis to cardiac arrest was 30min for food, 15 minutes for venom and 5 minutes for medication (2). In theory almost anything could cause anaphylaxis. Although, most often foods causing anaphylaxis are peanuts, fish, shellfish, celery, kiwi, eggs, and milk. The most common medications causing are antibiotics, especially penicillin and sulphonamides (3). Other common causative drugs are opioids and Acetylsalicylic acid, biological medications, and vaccines (3). Also, some medications can either complicate the treatment or influence the treatment. For example, beta blockers can weaken the effect of adrenaline and ACE inhibitors can complicate the anaphylaxis (3). The symptoms can vary but the World allergy organization anaphylaxis guidance 2020 defines that anaphylaxis is highly likely when a person has acute onset of an illness with involment of skin, mucosal tissue, or both (1). Meaning either hives, pruritus, flushing or swollen lips-tongue-uvula and symptoms of airway/breathing compromise or poor circulation caused symptoms for example syncope or incontinence or severe gastrointestinal symptoms. According to the world allergy organization, one should also suspect that anaphylaxis is highly likely even without typical skin involment after acute onset of hypotension or bronchospasm or laryngeal after exposure to a known or highly probable allergen for that patient (1). Recognizing anaphylaxis at the emergency department is a crucial job which unfortunately many of us fail to do. The golden standard treatment for anaphylaxis is adrenaline. In this literature review I will take a closer look of the pathophysiology, diagnosis, and management of the anaphylaxis in the emergency department.

3 Pathophysiology

The clear pathophysiology of anaphylaxis is still unknown. The article about pathophysiology of anaphylaxis in the Allergy and Clinical immunology suggests that there are IgE and FcεRI triggered pathway mediated by mast cells and basophils as effectors, but mouse models suggests that there is IgE independent pathway with IgG and FcγR as triggers and platelet activating factor and Cysteinul leukotriene receptors as potential mediators (4). According to the article there is strong evidence that histamine contributes to some of the symptoms but there are still studies that suggest that CysLTs can also contribute especially to bronchoconstriction and enhanced vascular permeability (4).

Table 1 Factors of anaphylaxis

IgE	Antigen-specific IgE antibodies are crucial to acute allergic manifestations (5).
IgG	Results in mice showing similar anaphylaxis severity with IgG mediated anaphylaxis (6). Anaphylaxis with undetectable IgE in blood (7).
Mast Cells	There is higher prevalence of episodes of hypotension in patients with mastocytosis (8).
Neutrophils	Neutrophils were sufficient to induce anaphylaxis in mice without mast cells (9).
Platelets	A drop in platelet numbers have been observed during anaphylactic shock (10).
Histamine	The bronchoconstriction caused by histamine is well known biological action of histamine (11). Similar symptoms to anaphylaxis were noted on a study where humans were administered intravenous histamine (12).
Cysteinyl leukotriene	Increased production of cysteinyl leukotrienes during human anaphylaxis were noted (13). Bronchoconstrictor effect in healthy humans (14).
Platelet activating factor	PAF-Acetyl hydrolase inversely correlates with anaphylaxis severity meaning PAF levels increase the more severe the anaphylaxis is (15).

3.1 IgE dependent anaphylaxis

It is well known that IgE antibodies play a significant role in anaphylaxis and allergic diseases. Total serum IgE levels are often significantly higher in patients with allergic diseases but not always (16). IgE binds to the FcεRI receptor which can be found on the surfaces of basophils in the blood and mast cells in the tissues (4). The crosslinking of the FcεRI-bound IgE activates the mast cells and basophils to release histamine and other proteases enhancing the synthesis of inflammatory mediators (4). It was found in the 1960s that IgE was capable to cause skin reactivity from sensitized subjects to the naïve hosts (17). After the discovery of the IgE importance, the IgE antibodies have been seen as the key risk factor for allergy and anaphylaxis (4). Omalizumab which is IgE antibody has been investigated for the treatment/prevention of the anaphylaxis. In the study (18) patients with omalizumab had a reduction in the frequency of anaphylactic events. It is somewhat clear that IgE cannot alone be the only predictor of the susceptibility to anaphylaxis as previously mentioned in the table 1 that some anaphylaxis reactions can occur without measurable IgE levels.

3.2 IgG dependent anaphylaxis

In the mouse studies it was noted that IgG is capable of causing anaphylaxis, but one needs to have much more of antigens. Also it was noted that mixed antibodies (having both IgG and IgE antibodies) would cause more severe reaction in the mice (6).

3.2.1 Mast cells

Mast cells are classically seen as the biggest contributor in the IgE-dependent anaphylaxis (4). Mast cells normally have high numbers of the IgE receptor FcεR and during the immune response the binding of antigen-specific IgE to FcεR starts the cascade which leads to secretion of histamine and CysLTs (4). There are some clinical implications. For example histamine detection could be used to diagnose anaphylaxis but the problem is that histamine has very short half-life and it can be secreted by other cells as well (19). According to the articles tryptase is much more stable, it is more specific to mast cells and increased levels of tryptase have been noted in anaphylaxis. (4,20). Additionally, as previously mentioned in the table 1 that patients with mastocytosis are more likely having higher prevalence of anaphylactic episodes. So, in theory tryptase levels could be used to detect anaphylaxis.

3.2.2 Neutrophils

There is some evidence especially in the mice studies that neutrophils can have a play in the anaphylaxis. Neutrophils can secret PAF in response to stimulation with immune complexes in vitro (9). In the table 1 I mentioned that PAF levels have been found to correlate with anaphylaxis severity. One study showed that myeloperoxidase concentration levels in patients with moderate or severe symptoms were 2.9 fold higher compared to healthy individuals (20). Since myeloperoxidase is mainly produced by neutrophils it means that there is some evidence that neutrophils are involved during anaphylaxis in humas. Moreover in the mice study (6) they noticed that both IgE and IgG mediated anaphylaxis caused increase in the neutrophils which suggests that neutrophils have a role in both of the IgE and IgG dependent anaphylaxis.

3.2.3 Platelets

Platelet activation is associated in human anaphylaxis. As one can see in the table 1, the platelet numbers are reduced in anaphylaxis. It is presumed that the platelet numbers are reduced in response to PAF or other unknown mechanism (4). Also, one study noticed that platelets have IgE receptors that are similar to FcεR2 (21). In the study they also noticed that in allergic asthma and in Hymenoptera venom sensitivity patients IgE-dependent activation of platelets can be triggered by specific allergen which means that there is some kind of connection between the platelets and the IgE dependent anaphylaxis yet to be uncovered.

4 Diagnosis

There is still no consensus even about the definition of anaphylaxis. The WHO ICD-11 defines anaphylaxis as “a severe, life-threatening systemic hypersensitivity reaction characterized by being rapid in onset with potentially life-threatening airway, breathing, or circulatory problems and is usually, although not always, associated with skin and mucosal changes”. The diagnostic criteria of anaphylaxis are also not globally standardized. The basis of the most used criteria is still from the 2006. In 2020 the World allergy Organization added the “severe gastrointestinal symptoms” to the one of the minor criteria.

Table 2 Diagnostic criteria of adapted from World allergy organization anaphylaxis guidance (1)

Acute onset of an illness (minutes to several hours) with simultaneous involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)	Acute onset of hypotensiona or bronchospasmb or laryngeal involvementc after exposure to a known or highly probable allergend for that patient (minutes to several hours), even in the absence of typical skin involvement.
AND AT LEAST ONE OF THE FOLLOWING	
☐ Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)	
☐ Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)	
☐ Severe gastrointestinal symptoms (eg, severe crampy abdominal pain, repetitive vomiting), especially after exposure to non-food allergens	

Anaphylaxis diagnosing at emergency department can be challenging since for example severe exacerbation of asthma or COPD could mimic anaphylaxis or an inexperienced physician could mistake anaphylaxis for simple allergic reaction. A study was conducted in Turkey where they gathered all the ED patient's data from 2005 to 2010 and then cross searched the files to find all the patient with findings suitable for anaphylaxis diagnostic criteria (22). They ended up with total 816 patients which fulfilled the criteria. Eighty-eight of the patients which fulfilled the criteria of anaphylaxis were not diagnosed with anaphylaxis and only two of them were treated with adrenaline. Meaning in their study around 11% of patients which fulfilled the anaphylaxis criteria were misdiagnosed and not treated accordingly.

If counting rough number of total visits of the Turkey ER in their mentioned timeframe extrapolating the 42000 visits per year totalling to about 252000 visits in their 6-year timeframe. Using estimate of anaphylaxis prevalence 0.3% from a study in 2018 (23). Then in the Turkish emergency department case they should have had around 756 patients with anaphylaxis in that timeframe meaning that their prevalence of anaphylaxis derived from the searched patient files using the diagnostic criteria of World allergy organization roughly matches the epidemiological study. Assuming similar physician education and resources we could assume that at least 1/10 of patients will be misdiagnosed. In one article it is mentioned that with the current diagnostic criteria of world allergy organization, around 1/20 of cases of anaphylaxis will be misdiagnosed but they also state that in some retrospective studies in emergency department up to ¼ of anaphylaxis cases are misdiagnosed (24). By taking that "error" into account in the Turkish study. It means that they likely had missed 10%+5=15% of people with anaphylaxis.

The number one most commonly misdiagnosis in emergency department is fracture but it mainly does not cause very high level of harm. The number 1 serious harm causing misdiagnosis in emergency department is a stroke (25). In a study made in USA, stroke had highest percentage of misdiagnosis of conditions that can cause serious harm if misdiagnosed at emergency department being at least 12.7%. of total stroke cases (26). Anaphylaxis being serious condition and being misdiagnosed 15% of cases is quite worrying number and to make matters worse in some places the percentage of misdiagnosis can be up to 25% (24).

4.1 What could we then do to decrease the amount of misdiagnosis of anaphylaxis?

The most used criteria which was also mentioned in the table 2 already misses 5% of cases of anaphylaxis meaning maybe we need new criteria? Although as earlier discussed in the pathophysiology, anaphylaxis can have in some case haves very atypical presentation which mostly

can account for the 5% of missed diagnosis even if using the criteria correctly. Also, if we change the criteria for too hard to interpret or to use it can also cause some misdiagnosis. If we do not want to change or cannot change the criteria, we could have a different criterion for administering adrenaline since adrenaline is relatively safe medication and by having more loose criteria for administering adrenaline, we could treat some proportion of the ED patients that otherwise would be misdiagnosed. According to a study with 492 patients, the intramuscular injection of epinephrine lead to cardiovascular complications in 3.5% in patients >50 and 0.5% of younger (27). Similar other study was performed where out of 245 patients receiving intramuscular epinephrine only 1 had angina and 2 experienced hypertension (28). These both studies suggest that administering I.M adrenaline is relatively safe especially in the younger population meaning having more loose criteria for administrating adrenaline is probably not inherently bad idea. Furthermore, many studies state that physicians are underusing adrenaline when diagnosing anaphylaxis. In the 2010 study by Russel, Monroe and Losek 44% of paediatric emergency department patients which fitted anaphylaxis criteria did not receive adrenaline (29). Having more loose criteria for administrating adrenaline also would most likely help with the underuse of adrenaline.

4.1.1 Biphasic reactions

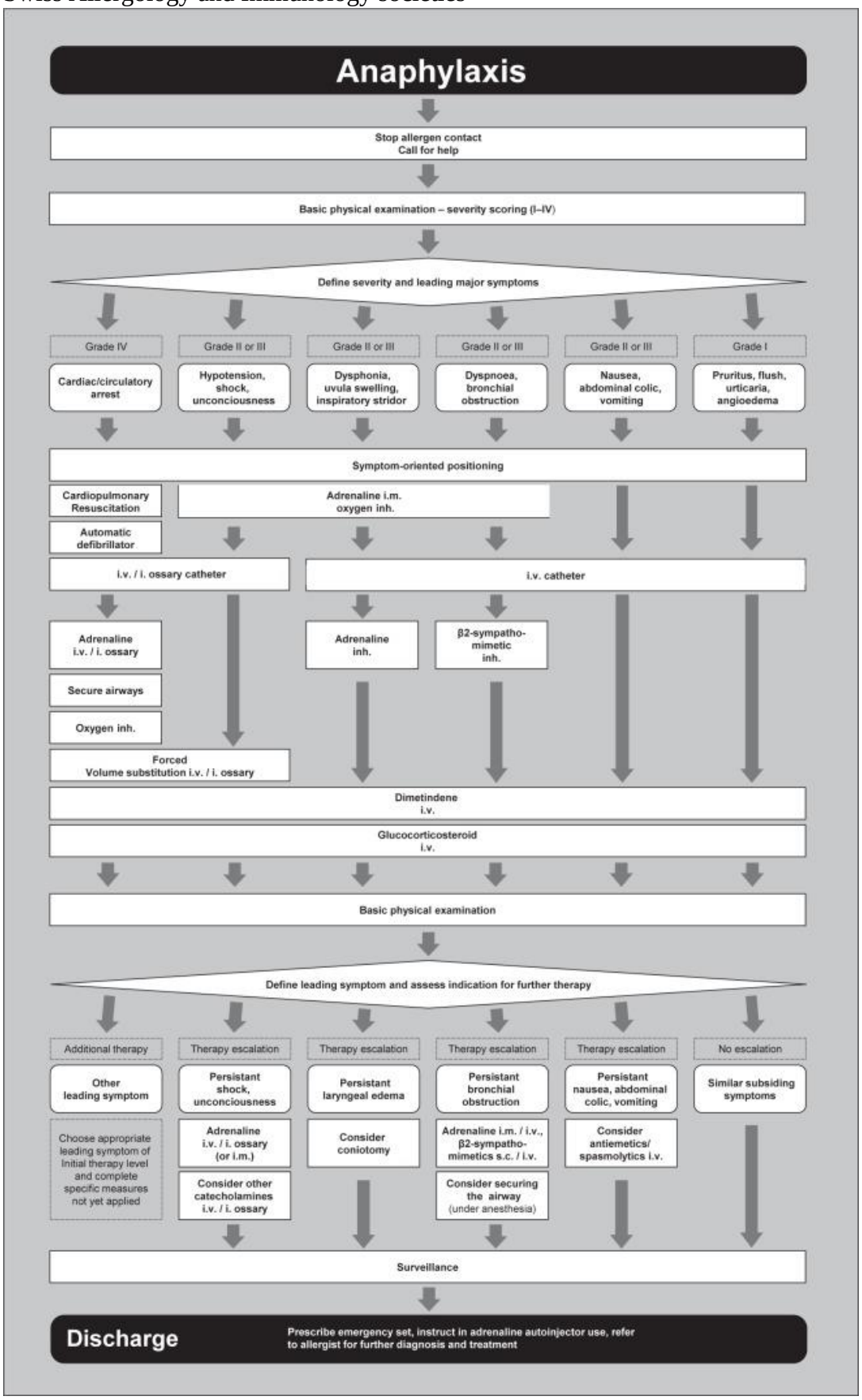
It is well known that sometimes anaphylaxis has biphasic pattern, meaning after relief of the primary reaction the second exacerbation of symptoms will start later. According to an study the incidence of biphasic reaction is highly variably ranging from 1% to 20% (30). They found out that the late reaction can be fatal but most often the late reaction is mild to moderate in severity meaning that in the case if we decide to administer the adrenaline more loosely for the patients that will not fulfil the criteria of anaphylaxis, we could skip the observation period in those cases and prescribe an adrenaline self-injecting device for them.

5 Management of anaphylaxis

Management of anaphylaxis consists of a few important aspects. Since anaphylaxis can cause immediate problems that needs to be addressed in either cardiovascular, pulmonary, or gastrointestinal system, The key aspects to manage anaphylaxis are adrenaline, oxygen, airway management and cardiac output management. In the table 3 that is from guidelines from German speaking countries they suggest following management strategy that was updated 2021.

The invasive airway management strategies in anaphylaxis and usage of other catecholamines were left out of this thesis since in case we would need to intubate the patient and or use other catecholamines the suitable place for that patient would be intensive care unit. Cardiopulmonary resuscitation can be needed in the case of anaphylaxis at the emergency department but there are no special guidelines or studies for anaphylaxis cardiopulmonary resuscitation, so it is not discussed in this thesis.

Table 3 Anaphylaxis management strategy from joint collaboration with German, Austrian and Swiss Allergology and Immunology societies



5.1 General management

First, like in almost all emergencies the first thing to do is to stop the exposure to the harming agent if possible. Stopping the exposure is kind of easy when it is caused by iv medication but in the case of food caused anaphylaxis one cannot do much to stop the exposure. Previously it was recommended that in the case of venom or insect bites to apply tourniquet to extremities, but it is not recommended anymore since its effect is seen questionable and it will take some time and distract from more important actions (31). Since the management of anaphylaxis can lead even to cardiopulmonary resuscitation the next best step is to call for help. If one is in the hospital the best practice would be to alert the resuscitation team/on call anaesthesiologist team, depending on the hospital policy.

The next step is quite self-explanatory. Basic physical examination of the patient is needed to assess the severity of situation for example using the ABCDE approach to assess the situation quickly.

5.2 Adrenaline

The next step in the guidelines from the German speaking countries is little bit controversial. They recommend grading the anaphylaxis and then decide the suitable treatment. Generally, I would agree but the problem here lies in Grade 1 and Grade two-thirds with nausea as the main symptom. For example, here the severity group 1 would not fulfil the criteria of anaphylaxis by World allergy organisation since it is missing one of the additional criteria. Also, in the treatment of the grade 1 severity they only recommend antihistamines + glucocorticoids.

Recent study was investigating whether to use adrenaline when there are no symptoms and their conclusion was that there is no evidence supporting the preventive use and the preventive use could lead to problems of patients not going to emergency department or emergency medical service responses downgrading in priority (32). However, For example there is only low certainty evidence that adrenaline should be administered early or before symptoms (33). To avoid confusion and misdiagnosis of anaphylaxis I think that the German guidelines should not include the grade 1 severity or that the grade 1 severity should be administered adrenaline. Since like it was earlier discussed that misdiagnosis of anaphylaxis is a huge problem and the mainstay of treatment of

anaphylaxis is adrenaline thus a non-adrenaline option of treatment of anaphylaxis should not exist in the guideline. Furthermore delayed administration of adrenaline is associated with increased mortality (34)

Also, if thinking the German guideline from a practical perspective. Following logically the guideline, if one sees a patient having skin allergic reaction without other symptoms, they should alert medical emergency team, start intravenous access, and constantly monitor the patient, but not give adrenaline. The only way to ensure the rapid administration of adrenaline when needed in that case is to admit the patient to ICU which is very costly. Adrenaline is very safe especially in younger population (27). To avoid delayed administration of adrenaline and to causing confusion to physicians whether to give or not to give, the guideline should include adrenaline administration when anaphylaxis is diagnosed.

The other big problem with German guideline is that they do not recommend adrenaline in the case of anaphylaxis with gastrointestinal symptoms as leading symptoms. For example, ASCIA and World allergy organization do recommend adrenaline in case of gastrointestinal symptoms are the leading symptoms especially if those are caused by drug or insect bite or venom (1,35). Red meat allergy can cause anaphylaxis with predominant abdominal symptoms (36). By following the German guidelines some of those patients would not be administered adrenaline and could die.

5.2.1 Route of adrenaline

Adrenaline can be either administered intramuscularly or parenterally intramuscular being more safe (28,37). The dose recommended for the intramuscular is 0.01mg/kg to a maximum dose of 0.5mg which must be repeated if symptoms wont resolve (38,39). There is yet no comparison study between the effectiveness of intravenous adrenaline and intramuscular adrenaline but for example professor Brown claims at the Emergency medicine Journal that intravenous is more safe than studies state and that it is more effective (40). It is of course true that intravenous route leads to faster release of adrenaline to the bloodstream and could be beneficial in the right setting, but more studies are needed about the matter that if the additional benefits outweigh the increased risks.

5.3 Other measures.

5.3.1 Oxygen and Fluids

Giving oxygen is kind of self-explanatory when we have cardiopulmonary symptoms oxygen is useful. World Allergy Organization recommends 100% oxygen with high flow through facemask (1). Since Anaphylaxis can cause hypovolemia due to vasodilation and increased vascular permeability, intravenous fluid resuscitation is also useful. The German and World Allergy

Organization guidelines recommend 20ml/kg fluid resuscitation. The amount and rate of fluid administration is of course depending on the clinical situation. Vincent and De Backer recommend that in the case of shock one should have an object for example increase in systemic arterial pressure (41). The German guideline recommends 0.5-1 litres up to 3 litres depending on response of NaCl 0.9% or balanced electrolytes in a very short time. (31)

5.3.2 Short-acting-beta-2 agonists

The German and World allergy organization recommend usage of inhaled short-acting beta-2 agonists when there are symptoms of bronchoconstriction and if giving those will not interfere giving adrenaline (1,31). However, A British systematic review states that there is really no evidence of the usage of beta-2 agonist even though those are widely used in clinical practice. The evidence is mostly extrapolated from the usage of those in acute asthma (33).

5.3.3 Corticosteroids

The German guidelines recommend corticosteroids to everyone but The World Allergy Organization will not recommend or state that corticosteroids should not be given (1,31). The UK guidelines will not recommend the usage of corticosteroids anymore (33). However there is Increasing evidence that corticosteroids should not be used in anaphylaxis secondary treatment and those will not prevent the biphasic reaction (42–45). One study even demonstrated harmful effect of corticosteroid in conjunction with adrenaline in case of snake venom (46). Also, focusing on using the corticosteroids could distract from more important management. It seems that corticosteroids should not be given at least in the acute setting.

5.3.4 Antihistamines

H1-antihistamines are widely used as secondary treatment. for anaphylaxis. World allergy organization guideline does not take stance about the antihistamine usage but for example the German guideline as seen from figure 2 recommends usage of first generation intravenous H1-antihistamine for every patient with anaphylaxis and the UK guideline does not recommend using antihistamine in the acute setting at all (1,31,33). Antihistamines may relieve the skin symptoms of anaphylaxis but even that is debated that in case of anaphylaxis it could be that antihistamines will not relieve the symptoms. (39). There is also evidence that administering antihistamines can delay the administration of adrenaline (35,39,47). Furthermore, it seems that even if most guidelines put emphasis on administrating adrenaline to the patients that have anaphylaxis, in reality at least in the USA most patients receive antihistamine and corticosteroids instead of adrenaline (48,49). Administrating first generation antihistamines intravenously like the German guidelines recommend can even lead to hypotension or mimic the symptoms of anaphylaxis (35,39). Antihistamines do not

reduce the occurrence of biphasic reactions (47). Moreover, In a large multinational study administration of antihistamine was associated with increased occurrence of biphasic reactions (50). It seems that the "old practice dies hard" giving corticosteroids and antihistamine as first line or conjunction is still a common practice. However, from the new data it seems that administrating corticosteroids and antihistamine can be harmful either delaying the proper management and or can even increase the biphasic reactions or cause harmful effects. The UK and Australia/New Zealand have drawn their conclusions and will not recommend usage of corticosteroids and antihistamine anymore especially in the acute setting (33,35).

5.3.5 Observation period

It is well known established fact that sometimes biphasic reactions occur. However, in the older literature the rate of biphasic reactions has varied substantially. Two recent individual studies state that the rate of biphasic reactions is around 4.6-4.7%(50,51). The problem is that the onset timing of the biphasic reaction varies quite a bit. For example, in the previously mentioned study the median time of symptom onset was 11h and it ranged between 0.2-72 hours (51). Keeping that in mind by following patients for 4h as instructed in ASCIA guidelines we would miss more than half of the biphasic reactions. One study studied the cost effectiveness of 1,6 and 24hours observation period cost effectiveness and they concluded that short observation is cost effective if the patient is at low risk of biphasic anaphylaxis, or there is low observations costs or low fatality risk (52). The resuscitation council UK now suggests that 2hr observation can be enough if there was good response to adrenaline, patient has unused adrenaline autoinjector at home and knows how to use it and the patient has adequate supervision at home (33). The suggest minimum of 6hr observation if the patient needed 2 doses of adrenaline or has history of previous biphasic reactions and 12hr minimum of observation if there was a severe reaction or patient has severe asthma or the patient has other external causes that would increase the risk of fatality in case of biphasic reaction. (33)

6 Conclusions

Anaphylaxis is a complex syndrome. There are a lot of things that we haven yet understood. However, there are a lot of hints and evidence that anaphylaxis is not only caused simply by IgE and mast cells. Understanding more of the anaphylaxis pathophysiology would be beneficial. Neutrophils and myeloperoxidase, Platelets and platelet activating factor and leukocyte produced cysteinyl leukotrienes could in future give us a diagnostic blood test for anaphylaxis or a new kind of treatment especially in those who experience anaphylaxis often.

There are very variable criteria used for diagnosing anaphylaxis. Currently there is no consensus which criteria are best. There should be some emphasis on future guidelines of creating a comprehensive and easy to understand guidelines for anaphylaxis diagnosis since it seems that anaphylaxis is severely underdiagnosed and often as well misdiagnosed.

The golden standard of treatment of anaphylaxis is adrenaline. It seems that for some reason physicians are reluctant to administer adrenaline even when it has been proven that especially intramuscular adrenaline to younger population is very safe and for now it is the only suitable treatment. It seems that some parts of the world are moving to less strict indications for giving adrenaline. To quote the ASCIA guidelines “if in doubt give adrenaline.” Some places have switched to using intravenous adrenaline instead of intramuscular. There is some argued evidence that intravenous adrenaline can lead to more side effects. However, logically it seems that intravenous adrenaline would be more effective but there are currently no comparison studies made about the matter.

Administrating the inhaled short-acting beta-2 agonists to bronchoconstriction have not yet been found harmful but there are extremely limited number of studies about the matter and the evidence has been extrapolated from asthma studies, so its effectiveness remains questionable.

The usage of corticosteroids and antihistamine to anaphylaxis instead of adrenaline has remained extremely high, especially in USA. Currently some guidelines like the one made by collaboration of German speaking countries does recommend usage of corticosteroids and antihistamine as second line. However, there is increasingly more new evidence that corticosteroids and antihistamine administration to anaphylaxis will cause mismanagement, misdiagnosis and even potentially can be harmful. There is also some evidence that antihistamines will not even relieve the symptoms, can cause increase in biphasic reactions, and can cause even harmful effects like hypotension or drowsiness. The effect of corticosteroids is very questionable and can negate some effect of

adrenaline in suitable setting. Some countries have drawn their conclusions like UK, Australia and New Zealand and are not recommending antihistamines or corticosteroids at all anymore.

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