QATAR UNIVERSITY

COLLEGE OF HEALTH SCIENCE

NATIONAL STUDY OF ANAPHYLAXIS IN A LARGE TERITIARY CARE HOSPITAL IN QATAR: A RETROSPECTIVE STUDY

BY

TAGHREED ABUNADA

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COMMITTEE PAGE

The members of the Committee approve the Thesis of Taghreed H. A. Abunada defended on 20/05/2018.

Dr. Hatem Z. Ibrahim
Thesis/Dissertation Supervisor

Dr. Mariam Alnesf
Committee Member

Dr. Hesham Abdelsattar
Committee Member

Dr. Nasser Rizk
Committee Member

Dr. Hassan Mobayed
External Examiner

Approved:

Asma Al-Thani, Dean, College of Health Science

ABSTRACT

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Title: NATIONAL STUDY OF ANAPHYLAXIS IN A LARGE TERTIARY CARE HOSPITAL IN QATAR: A RETROSPECTIVE STUDY-

Supervisor ofThesis: Dr. Hatem Z. Ibrahim.

Background: Anaphylaxis is a serious systemic allergic disease that often manifests with a broad array of symptoms and leads to death if not immediately treated by the administration of epinephrine auto-injector (EAI). **Aims and objectives:** To assess EAI dispense as an indicator to estimate anaphylaxis in Qatar, to determine the common causes of anaphylaxis in Qatar, to dissect the clinical profile of patients, and to determine the comorbidity factors in patients with anaphylaxis in Qatar. **Methods:** A retrospective study conducted using 1,068 electronic medical records (EMR) of anaphylaxis patients through the period of 2012 to 2016. The majority of the patients were collected from dispensed EAIs of outpatients (622) and the remainder (446) were from ICD-10 codes. To assess the feasibility of using the dispensed EAIs as possible measure for anaphylaxis, we calculated the sensitivity and specificity of this test on our patients' cohort (1,068). The demographics data, triggers, co-morbidity factors, symptoms, and clinical manifestations were categorized and thoroughly analyzed. Statistical analysis was performed with version 24 SPSS statistic software package. **Results:** The sensitivity of dispensed EAIs to detect anaphylaxis was 87.0% with positive predictive value (PPV) of 80%. There were 574 patients (53.5%) diagnosed with anaphylaxis, male to female ratio was 1.2, and 300 patients (77.9%) were

less than ten years. Food was the leading trigger of anaphylaxis (n=316, 55.0%) followed by insect stings (n=161, 28.0%) and drugs (n=103, 17.9%). Asthma (n=208, 36.2%), atopic dermatitis (n= 195, 33.9%) and allergic rhinitis (n=81, 14.1%) were the common comorbidity factors that significantly associated with anaphylaxis. Symptoms included 87.9% cutaneous, 69.1% respiratory, 47.5% gastrointestinal, 15.8% cardiac, and 8.8% neurological. Patients treated without the use of EAIs (n=143, 77.7%) were exposed to more serious adverse events including two deaths and one shock. **Conclusion:** This study will serve as a clinical guide for clinicians at allergic and pediatrics clinics and might be used as a baseline to assess the future trend of anaphylaxis in Qatar.

DEDICATION

To my lovely mum who taught me how to face challenges and risks with confidence and to my three lovely kids: Ezdin, Alanood and Zaina who I am proud to be their mother.

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This study conducted in collaboration between College of Health Science at Qatar University and the Department of Immunology and Allergy at Hamad Medical Corporation.

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LIST OF ABBREVIATIONS

EAI	Epinephrine Auto-injector
WAO	World Allergy Organization
AAAAI	American Academy of Allergy, Asthma and Immunology
ACAAI	American College of Allergy, Asthma, and Immunology
EAACI	European Academy of Allergy and Clinical Immunology
WHO	World Health Organization
NA	Not applicable
NR	Not reported
M:F ratio	Male to female ratio
IV	Intravenous
ICD10-AM	International Classification of Diseases, Tenth Revision, Australian Modification
DM	Diabetes mellitus
ED	Emergency department
LOS	Length of stay
A/I	Allergy and immunology
NSAID	Non-steroidal anti-inflammatory drugs
URTI	Upper respiratory tract infection
HTN	Hypertension
G_6PD	Glucose-6-phospahte dehydrogenase
EMR	Electronic medical records
PPV	Positive predictive value
NPV	Negative predictive value
LTB4	Leukotriene B4
LTC	Leukotriene C
LTD	Leukotriene D
PAF	Platelets activating factor

CHAPTER 1: INTRODUCTION

1.1 Introduction

Anaphylaxis is a severe systemic allergic reaction associated with different triggers, clinical presentations, co-morbidity factors and clinical outcomes. Allergens such as food, drugs, and venom insects trigger the onset of anaphylaxis, and can rapidly progress in unpredictable manner to life-threating complications or even death within minutes if not recognized and treated immediately. Anaphylactic reactions usually occur when the patients are in the community away from clinical settings. Therefore, early self-administration of epinephrine in the form of EAI is essential to save the patient life and avoid the culprit lifelong complications of anaphylaxis.

Characterization of anaphylaxis is crucial in term of its triggers, clinical presentation, risk factors, and clinical outcome of patients especially with the limited number of published case reports and studies in Qatar. For instance, two cases of food-dependent exercise-induced anaphylaxis have been reported and managed successfully (1). Another study reported delayed clavulanic acid-induced anaphylaxis in a patient during bariatric surgery (2). In a prospective cohort study conducted between 2007 and 2010 on 38 children to assess cow's milk allergy, 29 children (76.3%) presented with anaphylactic episodes (3). Two recent abstracts also highlighted the incidence of anaphylaxis among children and adults in Qatar (4, 5). EAIs are dispensed in the form of Epipen by Hamad General Hospital to all over other hospitals and health centers in

Qatar. Therefore, we believe that EAI dispense is a useful indicator to estimate the frequency of anaphylaxis and characterize it in Qatar which might act as a clinical guide for allergic clinics in Qatar.

1.2 Hypothesis

The primary hypothesis is that epinephrine auto-injector (EAI) dispense is a measuring tool to characterize anaphylaxis in Qatar. The secondary hypothesis is that patients treated with epinephrine auto-injectors will have no serious adverse events.

1.3 Aim

This study aimed to investigate EAI dispense as a clinical indicator to estimate anaphylaxis in Qatar.

1.4 Objectives

1. To estimate anaphylaxis in Qatar in the period of 2012 – 2016.
2. To determine the most common triggers of anaphylaxis in Qatar according to gender, age, and nationality
3. To characterize the most common clinical symptoms and co-morbidity factors associated with anaphylaxis in Qatar.
4. To define the outcome of anaphylaxis among patients who treated with and without EAIs.

CHAPTER 2: LITERATURE REVIEW

2.1 Definition of Anaphylaxis

The term "anaphylaxis" was introduced in 1901 to describe a phenomenon of increased sensitivity resulted in the death of an experimental animal (dog) after re-administration of the venom of anemone species *(6).* Because the result of the experiment was opposite to the scientists' intention to immunize the dog, the phenomenon was called "anaphylaxis" ("ana" means "against" or "opposite", and "phylaxis" means "protection" in Greek) (6, 7). Whether the same phenomenon occurred in human beings or not was in doubt until 1945; when increased use of medications resulted in recognition of anaphylaxis in human beings as well (6). Despite such recognition, there was no consensus over the definition of anaphylaxis and its treatment among physicians, which imposed National Institute of Health (NIH), and Food Allergy and Asthma Network (FAAN) to recruit an international panel of physicians from North America, Europe, and Australia who established consistent, clinically relevant criteria to diagnose anaphylaxis (2005 – 2006)(6). Following this international consensus, many independent guidelines of anaphylaxis management were published during the period from 2010 to 2014 by four allergy/immunology organizations : World Allergy Organization (WAO), American Academy of Allergy, Asthma and Immunology (AAAAI), the American College of Allergy, Asthma, and Immunology (ACAAI) and the European Academy of Allergy and Clinical Immunology (EAACI) (8). Accordingly, anaphylaxis is currently defined as "*a serious, generalized or systemic, allergic or hypersensitivity reaction that can be life-threatening or fatal*" (6, 8-10).

2.2 Diagnosis Criteria of Anaphylaxis

Diagnosis of anaphylaxis is likely when any one of the following criteria is fulfilled:

Criterion 1. Acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue or both accompanied with either respiratory compromise or reduced blood pressure or associated symptoms of end-organ dysfunction (11-13).

Criterion 2. Involvement of two or more systems that occur rapidly following the exposure to a ***likely*** allergen. Systems that might be involved include skin-mucosal tissues, respiratory compromise, reduced blood pressure and associated symptoms, or persistent gastrointestinal symptoms. A likely allergen is a substance that (i) the patient exposed to it before the development of symptoms; (ii) deemed as the cause of anaphylaxis by attending physician and did not induce a previous known reaction (11-13).

Criterion 3. Reduced blood pressure after exposure to a ***known*** allergen. This definition considers blood pressure as "reduced", in general, if it is lower by 30% than the patient's baseline (11-13). The definition also specifies reduced blood pressure based on patient's age as the following: (i) For adults and adolescents (11-17 years): Systolic blood pressure is less than 90 mmHg, (ii) For children (1-11 years): Systolic blood pressure is less than (70 mmHg + [2*age]), (iii) For infants (1 month – 1 Year): Less than 70 mmHg.

Despite that these criteria are likely to capture more than 95% of anaphylactic cases, patients may present with unusual symptoms which make the diagnosis of anaphylaxis difficult for clinicians (14). In Qatar, expert physicians in the field of immunology and allergy at HMC developed two anaphylaxis clinical protocols: one for pediatrics (CPRO

10550, Year: 2016) and another one for adults (CPRO 10538, Year: 2014). These two clinical protocols are in accordance with the international guidelines and are available online for HMC clinicians.

2.3 Pathophysiology of Anaphylaxis

Anaphylaxis is divided in to "allergic anaphylaxis" mediated by an immunological mechanism and "non-allergic anaphylaxis" mediated by a non-immunological mechanism (15). Idiopathic anaphylaxis is a third category suggested by Simons et al. (2006) because considerable number of anaphylactic cases are not easily to be included in any one of the previous two categories.

Introducing the allergen directly to the blood stream initiates anaphylaxis in sensitized individuals. In the classical pathway of IgE-mediated anaphylaxis, the major anaphylaxis patho-mechanism, the allergen-specific IgE antibody is bounded to the membrane of mast cells and basophils through its high affinity receptor (mainly FcεRI). Binding of the allergen to the allergen-specific IgE antibody results in cross-linking of its receptor FcεRI, its aggregation and activation of the mast cells and basophils. This leads to degranulation and release of potent mediators, which act directly on different tissues, recruit other inflammatory cells and amplify the allergic symptoms (9, 10, 16). Histamine, tryptase, leukotrienes, and platelets activating factors are the most potent mediators of IgE-mediated anaphylaxis (16).

On the other hand, alternative pathways of anaphylaxis are less common in human subjects compared to the classical pathway (17). These pathways include IgG and complement mediated anaphylaxis. In IgG-mediated anaphylaxis, the reaction is mediated by IgG/allergen complex that crosslink Fc gamma receptors (FcγRs) on macrophages, basophils and neutrophils. The IgG/allergen complex has higher affinity than monomeric IgG antibody to FcγRs and can therefore displace it to activate these receptors (16-18). Herein, the platelet-activating factor, produced from neutrophils, is the predominant released mediator not the histamine (16). Augmentation of such hypersensitivity responses is associated with the release of C3a complement (16). Some cases of anaphylaxis after the administration of monoclonal antibodies (mAbs) without detectable anti-drug IgE support the presence of IgG mediated mechanism in human subjects (19) . In complement-induced anaphylaxis, complement-derived peptides C3a, C5a and C5b9 mediate anaphylaxis in the absence of immune complex by direct binding to their specific receptors on mast cells, basophils, and other myeloid cells (16, 17). The re-exposure response for allergen in such direct complement-induced anaphylaxis is milder than the first time exposure (16). In support to complement mediated anaphylaxis mechanism, studies showed immediate wheal-and-flare reactions after the injection of low doses of C3s, C4a or C5a in the skin of healthy volunteers (19). Moreover, the concentration of these complements in blood correlate with the severity of anaphylaxis in human subjects (19).

Non-immunologic anaphylaxis involves mast cell mediator release due to cold temperature exposure, exercise or from medications such as opioids or vancomycin (20). This type of anaphylaxis is under-reported in the literature and the exact mechanism is unknown.

2.4 Potential Mediators of Anaphylaxis

The pathophysiological activities and clinical manifestation of anaphylaxis depends on the effect of mediators released from mast cells and other immune cells at the time of anaphylaxis and their subsequent binding to specific tissue receptors on the target organ(s) affected (21). Such mediators of anaphylaxis are as listed below:

Tryptase. Tryptase is stored in the granules of mast cell and basophiles and released from them upon their activation and degranulation. It peaks in the blood of human subjects within 60 to 90 minutes after the anaphylactic symptoms onset. This increase of tryptase level is temporary and resolve within 24 -48 hours (21). Therefore, tryptase is the most widely used biomarker to confirm anaphylaxis retrospectively (19, 22). Tryptase plays a role in airway homeostasis, vascular relaxation and contraction, gastrointestinal smooth muscle activity, intestinal transport, and coagulation (23). It activates matrix met-alloproteinases and initiates connective tissue matrix remolding or disintegration (24).

Histamine. The main source of histamine is mast cells and basophiles (19). There are four known histamine receptors: H1, H2, H3 and H4 (19). Histamine release and its subsequent binding to H1 receptors leads to coronary vasoconstriction and bronchial constriction while its binding to H2 receptors induces systemic vasodilation, gastric acid secretion, and cardiac contractility (10, 25). Both H1 and H3 receptors modulate nasal congestion, cutaneous itching and the characteristic wheal-and flare reaction of anaphylaxis (10, 25) . Histamine levels rise 5 to 10 minutes after the onset of anaphylaxis and returns to normal within 60 minutes (19).

Platelet activating factor (PAF). Platelets activating factor (PAF) is a potent phospholipid-derived mediator (19, 26). Cells that produce and respond to PAF include platelets, mast cells, neutrophils and macrophage (19). PAF induces platelets aggregation and activation. It results in increased vascular permeability, circulatory collapse, and decreased cardiac output. Recent studies showed that Platelets activating factor correlates inversely to the severity of anaphylaxis reaction (26).

Leukotrienes and prostaglandin. Leukotrienes are lipid mediators that are synthesized in the leukocytes from arachidonic acid (AA) via the actions of 5-lipoxygenase (5-LO). They are divided into two classes: LTB4 and cysteinyl leukotrienes. LTB4 is a potent chemoattractant for leukocytes and plays an important role in activating phagocytic cells, differentiated T-cells and dendritic cells. On the other hand, cysteinyl leukotrienes such as LTCs, LTDs, and LTE_4 were known previously as "slow-reacting substance of anaphylaxis" Their pathophysiological role in anaphylaxis result in mast cell activation and vascular permeability. Moreover, studies show that cysteinyl leukotrienes have potent bronchoconstriction effect in asthma patients (27).

2.5 Signs and Symptoms of Anaphylaxis

Clinical manifestation of the patient is the gold standard to diagnose anaphylaxis. The symptoms are heterogonous in nature and variable. Anaphylaxis can begin with relatively minor symptoms and progress in unpredictable manner to a life-threatening reactions (14). Organs that are affected by anaphylaxis include skin (90%), respiratory (70%), gastrointestinal (30 -45%), cardiovascular (35%) and central nervous system (10 -15%) (9, 28).

The signs and symptoms of anaphylaxis include the below symptoms (12, 28, 29):

1. Skins symptoms such as rash, itching, erythema, urticaria, swelling of the face, lips and periorbital area.
2. Respiratory symptoms such as nasal congestion, rhinorrhea, throat itching, laryngeal edema, stridor, choking, wheezing, cough and dyspnea.

3. Gastrointestinal symptoms such as vomiting, abdominal cramping, nausea and diarrhea.
4. Cardiovascular symptoms such as tachycardia, hypotension and hypotonia.
5. Central nervous symptoms such as anxiety, mental confusion and seizures.

Despite of the presence of the diagnostic criteria and guidelines for clinicians, anaphylaxis is often under-recognized especially if cutaneous symptoms are absent (20% of the cases) (30). Moreover, atypical symptoms of anaphylaxis start to emerge and they include fever and chills without apparent involvement of IgE mediated mechanisms (21). Severity of anaphylaxis varies from episode to episode even with identical stimulus in the same patients (14). Cox et al. (2017) suggested a new modified grading system for systemic allergic reaction that might enhance recognition of mild systemic allergic reactions apart from anaphylaxis and allow better classification of anaphylaxis in clinical trials and surveillance studies (31). In general, anaphylaxis has three patterns based on disease manifestation (28).

1. Uniphasic anaphylaxis: It accounts for 70% -90% of anaphylactic cases. The symptoms peak within 30 -60 minutes from exposure for the allergen trigger. It is not recurrent once it is resolved.
2. Biphasic anaphylaxis: It accounts for 1% - 23% of anaphylactic cases. Usually the symptoms peak within hours. The symptoms re-occur within eight hours without re-exposure to the allergen trigger.

3. Protracted anaphylaxis: It is rare and symptoms might become persistent for days and weeks.

Failure to give optimal dose of epinephrine initially may be associated with increased risk of biphasic anaphylaxis (14).

2.6 Triggers of Anaphylaxis

Triggers of anaphylaxis are variable in the community (9). The intrinsic characteristics of the trigger, its dose and the patients' associated co-morbidity factors determine the severity of the anaphylactic reaction (16). In general, any agent that is capable of producing a sudden degranulation of mast cells or basophils can induce or trigger anaphylaxis(14). Among biological triggers, food especially peanut, tree nut, shellfish, cow's milk and egg are common in children while drugs and insect stings are more common in adults (9). Some reports show evidence of anaphylaxis due to whole seminal fluids in females (32, 33). Moreover, progesterone surge is currently considered as a trigger of anaphylaxis in females presenting with catamenial anaphylaxis before and during their menstrual cycles (21). Some studies indicate anaphylaxis due to vaccines and intravenous immunoglobulin (34-36). Physical triggers of anaphylaxis include cold and exercise. In some patients, exercise alone can't initiate anaphylaxis rather than combination of exercise and food ingestion (9). In other cases, the trigger remains idiopathic.

2.7 Risk Factors and Comorbidity Associated with Anaphylaxis

Some co-morbidity factors worsen the outcome of the anaphylactic reaction for the patient if synchronized with the anaphylaxis onset. Examples include asthma, atopic dermatitis, allergic rhinitis, frequent infections, other respiratory tract disorders, cardiovascular diseases and mastocytosis (9, 37).

Asthma. Asthma is a chronic lung disease that results from inflammation and narrowing of airway tubes leading to shortness of breath, frequent wheezing, chest tightness and coughing. According to the World Health Organization (WHO), approximately 235 million people worldwide have asthma. The disease is most common in children (http://www.who.int/respiratory/asthma/en/). Several studies highlight asthma as a risk factor that can worsen the outcome of anaphylactic reaction and induce death in adolescents and young adults (12, 28). Analysis of United Kingdom national anaphylaxis data over 20-year period (1992-2012) stated that 78% of 124 fatal cases of anaphylaxis were in patients with a physician's diagnosis of asthma (38).

Atopy. Atopy is the genetic tendency to develop allergic disease (15, 39). Considering atopy as a risk factor for anaphylaxis depends on the type of antigen involved, route of administration and sensitization (15, 39) . Atopic individuals especially in response to inhalant and food triggers are at increased risk of having anaphylaxis (15, 20). Such predisposition to anaphylaxis is not justifiable by the increase levels of IgE alone since many atopic individuals with elevated IgE to food, inhalant and insect venom fail to develop anaphylaxis on exposure and during immunotherapy (15). Therefore, it is believed that additional factors account for anaphylaxis in atopic individuals (15).

Mastocytosis. About 30% of patients having mastocytosis due to the somatic mutation KIT (D816V) can show unprovoked anaphylaxis (21). This mutation is responsible for constitutive KIT receptor activation on mast cells even in the absence of its corresponding ligand (Stem cell factor) leading to intensive release of mast cell mediators (40).

2.8 Incidence of Anaphylaxis

The incidence of anaphylaxis is difficult to characterize due to the transient acute nature of the disease (39). However, data from hospital admission rates indicates that anaphylaxis is common and had increased in the UK, USA, Canada and Australia over the last 10 -20 years (41). Most studies depend on self-report, medical coding systems, epinephrine dispense rate, or hospital admission rate to gather data that characterize anaphylaxis (41). Below is a list of some retrieved studies of reported incidence of anaphylaxis in the world.

Table 1

Reported Anaphylaxis Cases in Different Countries

Abbreviations: NA= not applicable, NR= not reported

Country	Study Type	Study period	M:F ratio	Age (Y)	Screened Patients	Anaphylaxis cases	Reference
USA	Retrospective cohort	2007 -2012	1.50	0.5 - 18	7303	5947	(42)
	Retrospective	2009 - 2010	0.58	0 - 65	122	77	(43)
	Retrospective	2008 -2010	1.46	0 - 21	313	43	(44)
	Prospective	-	1.65	3.4 - 13.5	186	53	(45)
	Case Report		NA	71	1	1	(46)
	Retrospective	2004 - 2008	0.84	0.33 - 18	213	192	(47)
	Retrospective	2005 - 2006	0.74	0 - 85	3024	2751	(48)
	Retrospective	2001 - 2006	1.63	5.9 - 7.4	1255	685	(49)
	Retrospective	1999 -2007	1.37	5 - 10.5	436	79	(50)
	Retrospective	1990 - 2000	0.79	0.8 - 78.2	211	211	(51)
	Retrospective	Jan-July, 2012	0.52	37.9 - 69.7	11761	92	(52)
	Retrospective cross sectional	2009 - 2013	1.34	2.6 - 12.0	10351	10442	(53)
	Case Report	-	NA	50	1	1	(54)
	Retrospective	2009 - 2013	1.28	5.9	10442	5203	(55)
	Retrospective	1999 - 2010	1.19	20 - 73	2,458	2,458	(56)
	Case report	1994	NA	67	1	1	(57)
UK	Retrospective	2013 - 2016	0.63	18 - 83	31	31	(58)
	Retrospective cohort study	10 Years	0.92	30.3 - 60.9	761	340	(59)
	Retrospective	2005 – 2009	0.55	0 -85	537,605 admissions	1350	(60)
	Case report	2011	NA	25	1	1	(61)
	Retrospective	2005 -2012	0.33	35 -65	NR	161	(62)
UK/ Ireland	Retrospective	2008 - 2009	NR	0 - 16	15	7	(63)
Qatar	Case report	2009 & 2011	1	14 – 15	2	2	(1)
	Prospective cohort study	2007- 2010	1.92	0.2 – 10.5	35	9	(64)
	Clinical pilot study	2007- 2010	1.92	0 - 14	38	10	(3)

Continue Table 1

Reported Anaphylaxis Cases in Different Countries

Abbreviations: NA= not applicable, NR= not reported

Country	Study Type	Study period	M:F ratio	Age (Y)	Screened Patients	Anaphylaxis cases	Reference
UAE	Cross sectional	2006	0.94	6.1 – 8.3	397	143	(65)
	Cross sectional	NR	0.24	18 – 76	177	94	(66)
	Case report	2010	NA	6	1	1	(67)
KSA	Case report	2016	NA	6	1	1	(68)
	Case report	2017	NA	19	1	1	(69)
KSA	Retrospective	2010 – 2011	0.93	Child ≤ 18 Adult > 18	238	238	(70)
	Retrospective	1 year	1.26	18 - 70	43	1	(71)
	Case report	2014	NA	12	1	1	(72)
	Case report	2013	NA	62	1	1	(73)
	Case report	2010	NA	4	1	1	(74)
	Case report	2010	NA	5	1	1	(75)
	Case report	2006	NA	32	1	1	(76)
	Case report	1997	NA	36	1	1	(77)
	Case report	1995	NA	34	1	1	(78)
Kuwait	Survey	2017	0.29	0 - 19	865	20	(79)
Lebanon	Case report	1997	NA	18	1	1	(80)
	Cross sectional	1 year	NA	NR	1842	23	(81)
	Retrospective study	2009	NA	NR	245	39	(82)
	Survey questionnaire	2014	0.54	Child ≤ 14 Adult > 14	506	55	(83)
Algeria	Case report	2005	NA	4	1	1	(84)
Turkey	Retrospective	2008 -2011		Adults	24,443 admissions	516	(85)
Portugal	Case report	2008	NA	18	1	1	(86)
	Survey questionnaire	2007 – 2010	0.5	2 - 89	313	313	(87)
Spain	Observational study	2013 – 2015	1.01	12 – 47	277	55	(88)
Thailand	Observational cohort study	2004 – 2008	1.12	0.1 - 70	208	208	(89)

2.8 Treatment of Anaphylaxis

Anaphylaxis can rapidly progress in unpredictable manner to lead to life-threating complications or even death if not immediately recognized. Delaying the treatment until the development of multi-organ symptoms is risky if not lethal (14). Successful management depends on removal of potential trigger (if possible) and placing the patient in a recumbent position (if tolerated). ABCDE approach is used as soon as anaphylaxis is recognized to assess the patient's airway, breathing, circulation, disability and skin reactions (11). Administration of IV fluids with isotonic crystalloid fluid is essential as soon as possible for volume resuscitation.

2.8.1 Immediate First Line Intervention Measures

First-line intervention to treat anaphylaxis is the administration of epinephrine (adrenaline) (14). Epinephrine (adrenaline) is a cathecolamine that is naturally released from the neurons and the medulla of adrenal gland in response to exertion or stress. It has a molecular weight of $C_9H_{13}NO_3$ with relative molecular mass of 183.2 (90, 91).

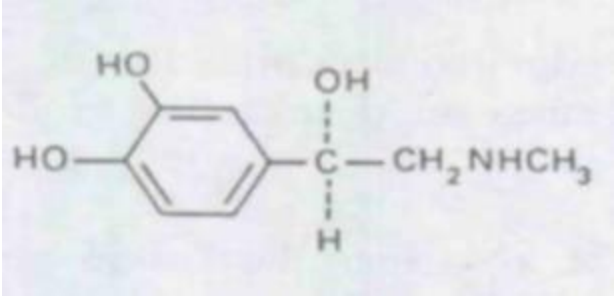

Figure 1. Epinephrine (adrenaline) graphic formula. (90)

Epinephrine (adrenaline) discovery as a drug and its subsequent applications in medicine was the fruitful effort of many scientists in the latter half of the 19th century. George Oliver, a general practioner in Harrogate, North Yorkshire discovered that adrenal extract rise the blood pressure (92). In 1895, he proved with the assistance of Professor Edward Schafer, a physiologist at University College London, that this adrenal extract constricted blood vessels and enhanced ventricle constriction by an active component from adrenal medulla not the cortex (92). However, crude extract induced some allergic reactions. Therefore, trials to identify and purify this vasoactive component were intensified. Otto von Furth in Strasbourg isolated a substance and called it suprarenin while John Jacobs Abel, of Johns Hopkins University isolated a slightly different substance and called it epinephrine (92). Despite the fact that these substances were vasoactive, none of them proved to be adrenaline. In 1900, a pure crystalline substance from the adrenal medulla that is 2000 times stronger was isolated and purified by the Japanese chemist, Jokichi Takamine in cooperation with Parke, Davis and Co Laboratories (92). Takamine's pure crystalline

had the trademark of adrenaline in 1901. Without regulatory authorities at that time, adrenaline found its way in many medical applications mainly to stop bleeding. Physicians' demonstration that it improved allergic diseases such as allergic rhinitis hives and asthma resulted in extensive studies about its therapeutic action (92).

Epinephrine exerts its therapeutic action via its effect on α- and β- adrenergic receptors. Its effect on α_1-adrenergic agonist receptors induces vasoconstriction, increases peripheral vascular resistance, and decrease mucosal edema (10, 14). It increases inotropy and chronotropy via β_1-adrenergic agonist receptors while it induces bronchodialation and decreases inflammatory mediators released from mast cells and basophils via β_2-adrenergic agonist receptors (10, 14, 25, 93).

Route of administration and proper dose is significant to achieve the optimal therapeutic effect and to avoid the occurrence of biphasic anaphylaxis (14). Administration of epinephrine intramuscularly in the anterolateral thigh provides complete rapid absorption and is preferred over subcutaneous or intravenous routes (9, 10, 14). Currently, EAIs are available as pre filled epinephrine auto-injecting devices such as Epipen® (Dey, LP, Napa, CA, USA), Anapen® (Lincoln Medical, Salisbury, Wiltshire, UK), Twinject® (Shionogi & Co., Ltd., Osaka, Japan) and Adrenaclick® (Shionogi Pharma, Inc., Atlanta,GA, USA) (94, 95). Two fixed doses of EAIs are available: 0.15 mg for children who weigh 10 -25 Kg and 0.3 mg for children who weigh more than 25 Kg and adults (14, 30). Pharmacokinetic studies show that 8 minutes are required for epinephrine to reach a maximum concentration in plasma (2.136 pg/mL) after the intramuscular injection (96). Such finding

correlates with the pharmacodynamics evidence of increase blood pressure and heart rate within 10 minutes of epinephrine injection (96). Repeating the epinephrine dose is possible every 5 - 15 minutes and depends on the severity of the anaphylactic reaction (14).

Epinephrine has a narrow therapeutic window (14). Adverse effects of epinephrine at recommended doses as well as over dosage do not absolutely contraindicate epinephrine administration in case of anaphylaxis (14, 25, 97, 98). Usual adverse effects include agitation, anxiety, headache, dizziness, pallor, or palpitation. Rarely myocardial ischemia, infraction or intracranial hemorrhage may occur (14). Special care should be maintained when epinephrine is given for individuals who have increased number of β-adrenergic receptors in their vasculature system such as individuals with untreated hyperthyroidism because expected strong effect of epinephrine on the heart (14). However, the benefits of using epinephrine far outweigh the risks in an anaphylactic reaction and prompt administration of it can be life-saving (39). Ideally, patients at risk of developing anaphylaxis should receive epinephrine auto-injectors and referred to allergist or immunologist for further investigation (14).

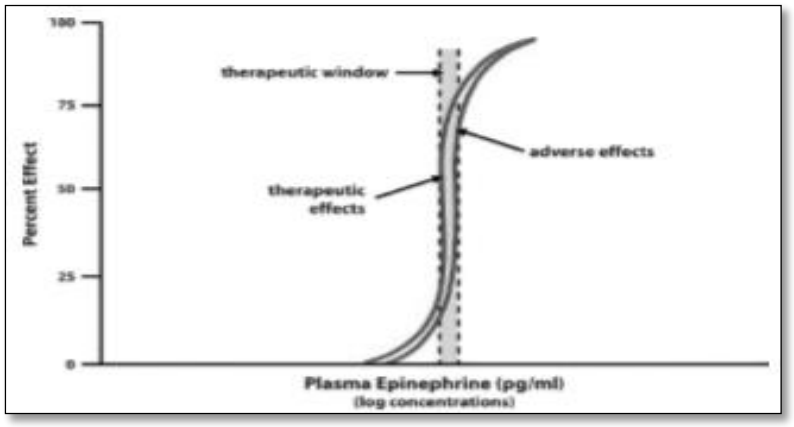

Figure 2. Therapeutic window of epinephrine. (14)

2.8.2 Second Line Intervention Measures

The second line intervention includes H1-antihistamines, H2-antihestaminss corticosteroids, and beta-2 agonists (39). H_1 antihistamines (e.g. diphenhydramine, fexofenadine, hydroxyzine, cetirizine) decrease skin symptoms such as itching, erythema, and urticaria but they do not treat airway obstruction or hypotension in similar manner to epinephrine (97). In combination to H1-antihistamines, H_2 antihistamines (e.g. ranitidine) are effective at reducing hives and tachycardia but have no significant effect on itching symptoms (25). β_2 agonist bronchodilator induces and improve the symptoms of respiratory distress by relaxation of bronchial smooth muscles (99) . Corticosteroids are in use to prevent biphasic anaphylaxis (25). Corticosteroids switch off transcription of activated genes that encode pro-inflammatory proteins and decrease late phase allergic response (11).

These drugs are inferior to epinephrine and should never replace epinephrine since they are not life-saving and could not alone resolve the serious consequences of anaphylaxis (25). However, despite the fact that antihistamines have slow absorption and require 1 – 3 hours for maximum plasma concentration after oral administration, data shows their frequent use rather than epinephrine to treat anaphylaxis (25).

CHAPTER 3: METHOD

3.1 Data Collection

This study was approved by the Medical Research Center, Hamad Medical Corporation in Qatar (HMC_IRB; 17122/17) for enrolment of 1,000 medical records (Appendix A: Approval of Research protocol # 17122/17).

The EAI dispense records were collected from 2012 to 2016 from Hamad Medical Corporation. A total of 1,068 medical records were collected, 622 from the EAIs dispense list of HMC, and 446 from the medical coding system: the International Classification of Diseases, Tenth Revision, Australian Modification (ICD10AM) codes. The following codes were used to retrieve the data from the HMC medical registry: T78.0 Anaphylactic shock due to adverse food reaction; T78.1 Other adverse food reactions, not elsewhere classified; T78.2 Anaphylactic shock, unspecified; T80.5 Anaphylactic shock due to serum; T88.6 Anaphylactic shock due to adverse effect of correct drug or medicament properly administered. Duplicates were removed after combing the two lists. The records were reviewed using Cerner Power-Chart system (Citrix XenApp, Cerner Millennium, USA). All patients' data was collected anonymously to protect patients' rights.

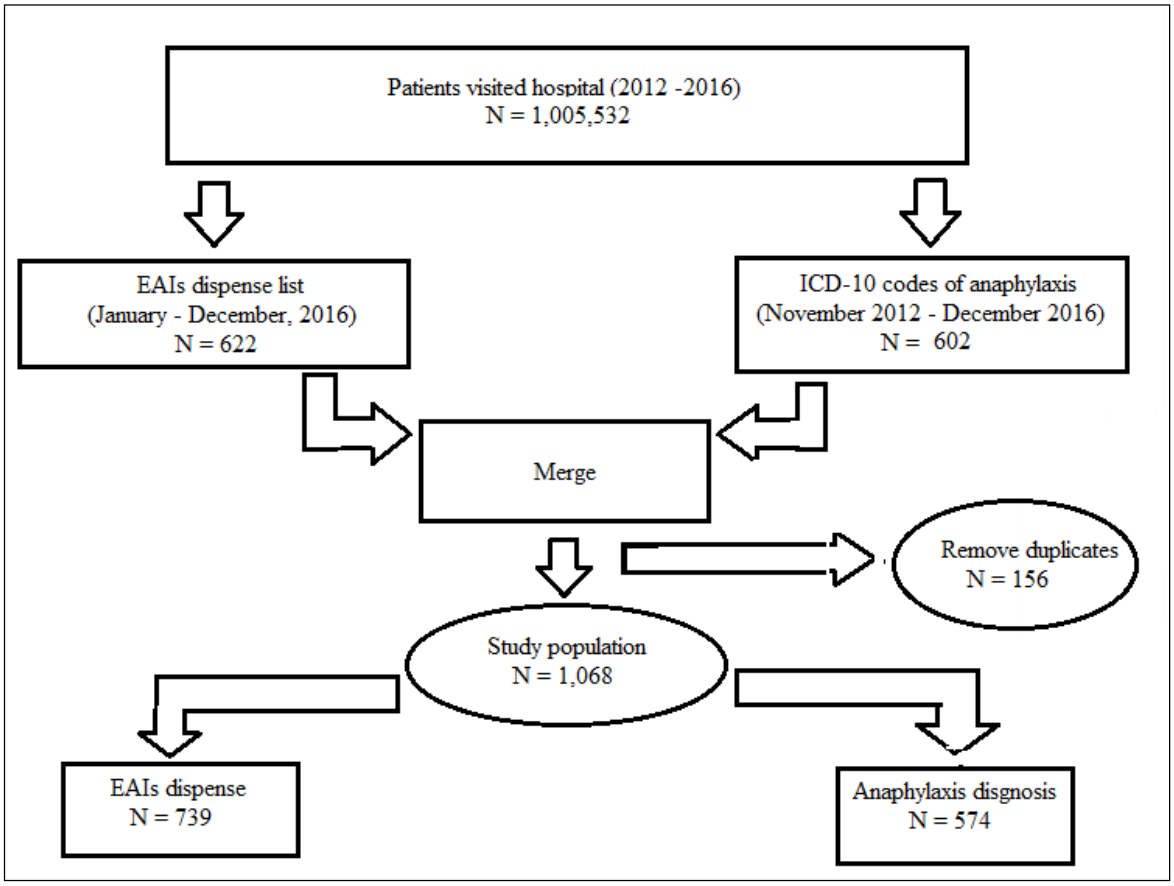

Figure 3. Flow chart of screened electronic medical records

3.2 Study Definitions

Anaphylaxis was defined based on physician diagnosis and in accordance to the clinical criteria of anaphylaxis guidelines. Our inclusion criteria for Anaphylactic patients were either one of the following: (1) acute onset of illness (minutes to several hours) with involvement of the skin, mucosal tissue or both, and at least respiratory compromise or reduced blood pressure; (2) involvement of two or more systems out of four (skin-submucosal tissue, respiratory, cardiovascular and gastrointestinal) in reactions that occur rapidly (minutes to several hours) after exposure to a likely allergen; or (3) reduced blood pressure after exposure to a known allergen (minutes to several hours). Allergy was identified as (1) patients who either have diseases other than anaphylaxis such as asthma, atopic dermatitis, urticaria, angioedema or allergic rhinitis; or (2) known triggers of allergic reaction and symptoms without fulfilling the clinical criteria of anaphylaxis.

3.3 Clinical Data of the Study Population

Electronic medical records were reviewed to collect patients' demographics such as age, gender, nationality, and family history; characteristics of anaphylaxis events such as frequency of anaphylactic events, and symptoms where symptoms begin; characteristics of EAIs dispense such as frequency of dispense, times EAIs used by patients or others and indications of EAIs dispense; clinical presentation of anaphylaxis such as symptom related to skin, respiratory, gastrointestinal, cardiovascular and central nervous systems; anaphylaxis triggers such as food, drugs, venom insects, idiopathic or others; medical history; associated comorbidity factors thought to worsen the anaphylactic reaction; outcome of the

anaphylactic reaction when treated with or without EAIs, hospital admission, its duration (if any), associated complication and death occasions.

Collected data was recorded in an approved data collection sheet (Appendix B: Data collection sheet). A standardized search method was used to extract the data from Cerner Power-Chart system as indicated below (Figure 4).

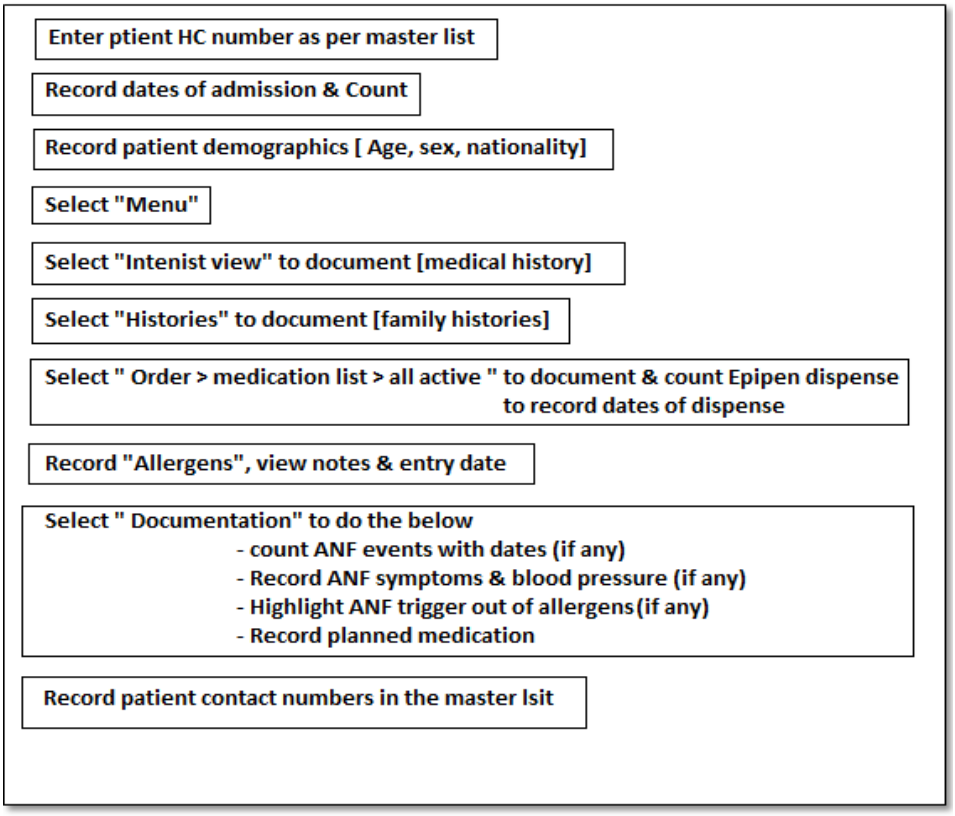

Figure 4. The standardized search method in Cerner power-chart system

Confused/complicated cases were referred for allergy/immunology specialist in Hamad Medical Corporation. Collected data was abstracted into a spreadsheet using Microsoft Excel 2010 for analysis.

3.4 Statistical Analysis

Multi-variant statistical analysis using Statistical Package for Social Science (SPSS), Windows version 24 (SPSS Inc, Chicago, USA) was performed. Categorical variables using frequency distributions, one and two-way tabulations, and percentages were summarized. Social demographics of the study population across groups, most common triggers, co-morbidity factors, symptoms and outcome were compared with a chi-square test. In 2 X 2 tables, the Fisher's exact test (one- or two-tailed) replaced the chi-square in case of small sample size and where the expected frequency is less than 5 in any of the cells. The level where P-value < 0.05 was considered as significant.

CHAPTER 4: RESULTS

4.1 Social Demographics of the Study Population

Patients' data (1,068) was collected from the electronic medical records of Hamad Medical Corporation from November 2012 to December 2016, of which 574 (53.5%) patients were diagnosed with anaphylaxis and 132 (12.3%) patients were with allergy (Table -1). Difference between patients with and without anaphylaxis was significant (*P*-value = 0.009) in term of age and nationality, but insignificant in term of gender, family history and consanguinity. The incidence of anaphylaxis among children (<10 years) and adults (20 – 55 years) was the highest in Qatar followed by adolescents (10 – 19 years) and elderly (> 55 years) patients. In Qatar, anaphylaxis was more common within male than female with a ratio of 1.2. Among anaphylaxis cases, there was one patient with no listed nationality, 251 (43.7%) patients were Qatari, 162 (28.2%) patients were non-Qatari Arabs, and 118 (20.5%) patients were Asian. There was limited number of patients registered with family history of atopy, diabetes mellitus, hypertension and anaphylaxis. The social demographics of the study population in term of anaphylaxis were summarized below (Table 2).

Table 2

Social Demographics of the Study Population, N = 1068

Abbreviations: DM = Diabetes Mellitus

Characteristics	Total (n)	Percent (%)	Frequency, n (%) [a]		P-value
			Anaphylaxis (N=574)	Allergy (N=132)	
Age (Years)					
< 10	603	56.3	300 (77.9)	85 (22.1)	0.009 [b]
10 - 19	210	19.7	109 (83.2)	22 (16.8)	
20 - 55	209	19.6	137 (86.7)	21 (13.3)	
> 55	46	4.3	28 (87.5)	4 (12.5)	
Gender					
Male	612	57.3	315 (79.1)	83 (20.9)	0.095
Female	456	42.7	259 (84.1)	49 (15.9)	
Nationality (N=1067)					
Qatari	438	41.0	251 (79.9)	63 (20.1)	0.009
Non-Qatari, Arab	303	28.4	162 (86.6)	25 (13.4)	
Asian	228	21.4	118 (83.1)	24 (16.9)	
Others	98	9.2	42 (67.7)	20 (32.3)	
Family History (N = 123)					
Atopy [c]	70	56.9	58 (87.9)	8 (12.1)	0.989
DM and/or hypertension	29	23.6	22 (88.0)	3 (12.0)	
Other diseases	18	14.6	13 (86.7)	2 (13.3)	
Anaphylaxis	6	4.9	5 (83.3)	1 (16.7)	
Consanguinity (N=33)	30	90.9	25 (92.6)	2(7.4)	1.000*

[a] row percentage

[b] Chi-Square for trend (linear by linear association)

[c] Atopy includes asthma, atopic dermatitis, allergic rhinitis, and urticaria

[*] P-value is for Fischer test (exact significant 2-sided)

4.2 Characterization of Anaphylaxis in the Study Population

Medical records showed that patients had anaphylaxis multiple times in Qatar. Among recorded anaphylactic events, 48.3 % patients had anaphylaxis one time; 30.3 % patients had it 2-3 times, while 2.7 % had more than three recorded anaphylactic events (Table 3) . Symptoms of anaphylaxis for about 507 (92%) patients began in the community. Community setting is a location other than a medical care facility such as home, school, street, party and restaurant. However, about 44 (7.9%) patients' symptoms started inside hospitals, clinics and emergency department (Table 3).

Table 3

Characterization of Anaphylaxis in the Study Population, N = 706

Abbreviations: ED= emergency department

Characteristics	**Frequency (n)**	**Percent (%)**
Anaphylaxis	574	81.3
Frequency of anaphylaxis event		
None	132	18.7
1 time	341	48.3
2 - 3 times	214	30.3
> 3 times	19	2.7
Location where symptoms began (N=551)		
Community	507	92.0
Inside hospital/clinic/ED	44	7.9

The patients' outcome due to anaphylaxis was variable. About 360 (62.7%) of anaphylactic cases were admitted to the emergency department, of which 262 cases (24.5%) length of stay was less than 24-hours. Approximately half of the anaphylactic cases referred to the allergy and immunology clinics. Only 71 (12.4%) of anaphylactic cases required close regular monitoring as inpatient. Comparing severe adverse events across patients groups showed that anaphylactic patients who were more frequently associated with respiratory arrest (5, 0.9%), profound hypotension (3, 0.5%), and cardiac arrest (2, 0.3%). (Table 4).

Table 4

Characteristics of Anaphylaxis Outcome in the Study Population, N =1068

Abbreviations: ED = emergency department, LOS = length of stay, A/I = allergy and immunology

		Anaphylaxis		
Patients' outcome	**All subjects**	**Yes**	**No**	
	N=1068	**N=574**	**N=132**	
	n (%)	**n (%)**	**n (%)**	**P-value**
ED admission	576 (53.9)	360 (62.7)	9 (6.8)	**< 0.001**
ED LOS , N=372				
< 24 hours	262 (24.5)	253 (44.1)	9 (6.8)	0.070 trend
24 -72 hours	71 (6.6)	71 (12.4)	0 (0.0)	
> 72 hours	39 (3.7)	39 (6.8)	0 (0.0)	
Referral to A/I clinic	630 (59.0)	293 (51.0)	66 (50.0)	**<0.001**
Admission as inpatient	568 (53.2)	71 (12.4)	1 (0.8)	0.157f
Serious Adverse Event	22 (2.1)	22 (3.8)	0 (0.0)	0.264
Respiratory arrest	5 (0.5)	5 (0.9)	0 (0.0)	*
Profound hypotension	3 (0.3)	3 (0.5)	0 (0.0)	*
Cardiac arrest	2 (0.2)	2 (0.3)	0 (0.0)	*
Death	2 (0.2)	2 (0.3)	0 (0.0)	*
Endotracheal intubation	10 (0.9)	10 (1.7)	0 (0.0)	*
Pulmonary edema	9 (0.8)	9 (1.6)	0 (0.0)	*
Persistence of cutaneous manifestations	3 (0.3)	3 (0.5)	0 (0.0)	*
Infection	2 (0.2)	2 (0.3)	0 (0.0)	*
Sub conjunctival hemorrhage	1 (0.1)	1 (0.2)	0 (0.0)	*
Shock	1 (0.1)	1 (0.2)	0 (0.0)	*
Angioedema	3 (0.3)	3 (0.5)	0 (0.0)	*

* P-value not calculated due to small sample size

4.3 Characterization of EAI Dispense in the Study Population

Out of the 1,068 medical records, 739 (69%) patients had documented EAI dispense with anaphylaxis being the primary indication of EAIs dispense for 477 (64.5%) patients. Valid indications of EAIs dispense include asthma/allergy (16.5%), known fatal/near fatal food allergy (5.8%), and urticaria possible to prelude to anaphylaxis (2.97%). Other indications such as allergy, mucopolysacharidosis type IV, C1 esterase inhibitor deficiency counted for 3.5%. All patients received one or multiple EAIs dispense; however, only 89 (12%) patients had documented EAIs use (Table 5).

Table 5

Characterization of EAIs Dispense in the Study Population

Characteristics	Frequency (n)	Percent (%)
EAI dispensed	739	92.6
Indication of EAI dispensed*		
Anaphylaxis (N=712)	477	67.0
Other indications (N=213)		
Asthma & allergy	122	16.5
Known fatal / near fatal food allergy	43	5.8
Urticaria possible to prelude anaphylaxis	22	2.9
Others	26	3.5
Frequency of EAI dispense , (N=996)		
None	257	25.8
1 time	355	35.6
2 - 3 times	277	27.8
> 3 times	107	10.7
EAI compliance*, (N= 464)	89	19.2
EAI administered in community*, (N = 30)		
Parents	20	66.7
Self	7	23.3
Others	3	10.0

*As listed in the electronic medical record of Cerner power chart system

4.4 Anaphylaxis versus EAIs Dispense

After reviewing the entire electronic medical records of 1,068 patients, data showed that 499 (71.1%) of patients who had anaphylaxis received EAIs, while 74 (10.5%) did not, 118 (16.8%) of patients who received EAIs had no anaphylaxis (Table 6). There were ten patients (1.4%) with neither anaphylaxis nor EAI.

Table 6

Epinephrine EAIs Dispense Against Anaphylaxis, N= 702

Anaphylaxis	**EAI Dispense, n (%)**	
	Yes	No
Yes	499 (71.1)	74 (10.5)
No	118 (16.8)	10 (1.4)

In order to understand whether the EAIs dispense can be used as a measuring tool for anaphylaxis, we estimated the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) for the 1,068 patients. The sensitivity of the EAIs dispense as indicator for anaphylaxis was 87% with PPV of 80%; however, the specificity was 8% with NPV of 11.9% (Figure 5).

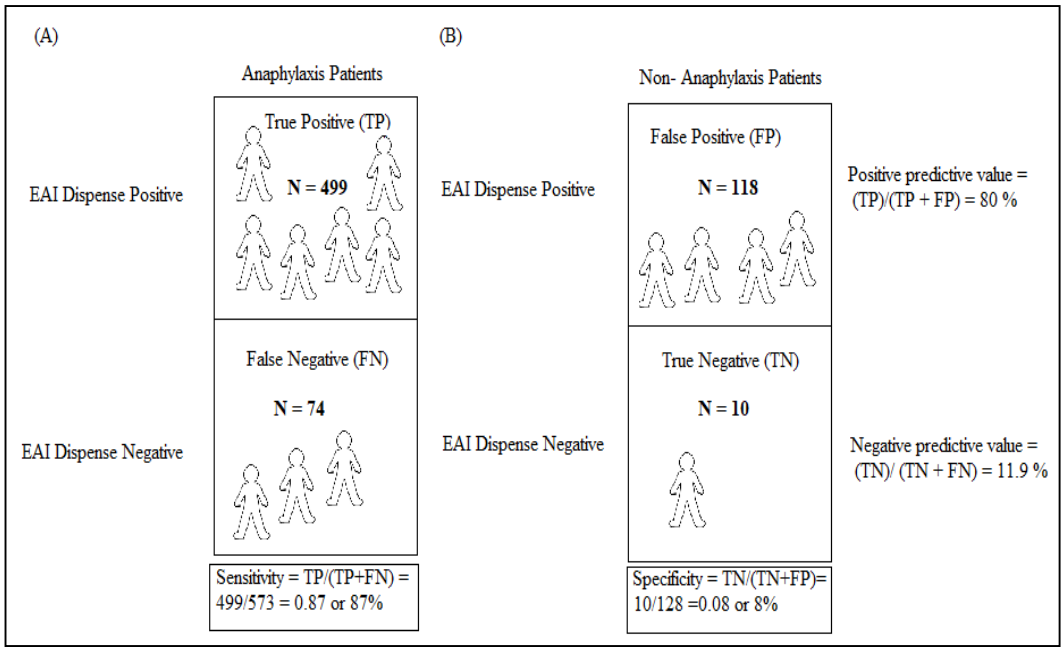

Figure 5. The sensitivity (A) and specificity (B) of EAIs dispense for anaphylaxis.

4.5 Common Triggers of Anaphylaxis in Qatar

Most common of triggers of anaphylaxis in Qatar included food (316, 55.0%), venom insects (161, 28.0%) and drugs (103, 17.9 %). However, idiopathic triggers accounted for 44 (7.6%) of the cases (Table 7 -9).

4.5.1 Food Triggers of Anaphylaxis in Qatar

Among the most common trigger of anaphylaxis in Qatar, food was significantly associated with 316 (55.0%) of the cases. Dry fruits triggers such as nuts, cashew, pistachio and tree nuts were responsible for 173 (30.1%) of the cases. Other food triggers include egg (15.5%), seafood (12.5%), peanuts (12.3%), cow's milk (10.6%), sesame seeds (8.7%), and wheat (6.1%) (Table 7).

Table 7

Most Common Food Triggers of Anaphylaxis in Qatar, N = 1068

Triggers	**All subjects N = 1068 n (%)**	**Anaphylaxis N= 574 n (%)**	**Allergy N= 132 n(%)**	**P-value**
Food (All)	403	316 (55.0)	87 (65.9)	< 0.001
Nuts [a]	232	173 (30.1)	59 (44.6)	< 0.001
Egg	113	89 (15.5)	24 (18.1)	0.171
Seafood	93	72 (12.5)	21 (15.9)	0.111
Peanut	92	71 (12.3)	21 (15.9)	0.100
Cow's milk	77	61 (10.6)	16 (12.1)	0.326
Sesame seeds	65	50 (8.7)	15 (11.3)	0.158
Wheat	38	35 (6.1)	3 (2.2)	0.130
Others	150	126 (21.9)	24 (18.1)	0.933

[a] trigger includes nuts, cashew, pistachio, and tree nuts.

4.5.2 Drug Triggers of Anaphylaxis in Qatar

About 103 (17.9%) of anaphylactic cases in Qatar were induced by drugs with 49 (8.5%) of them rose due to antibiotics such as augmentin (2.7%), penicillin (1.9%), ceftriaxone (1.0%) and amoxicillin (0.8%). Other antibiotics such as clarithromycin, cefixime, clindamycin, vancomycin, and streptomycin were responsible for 3.3% of anaphylactic cases. Within non-steroidal anti-inflammatory drugs (NSAID), anaphylaxis was triggered by ibuprofen (4%), followed by paracetamol (1.3%), diclofenac (1.2), aspirin (0.5%). Other NSAID such as celebrex and voltaren counted for 0.6% of the anaphylactic cases. Drug triggers other than antibiotics and NSAID included intravenous immunoglobulin (4, 0.6%) and vaccines (3, 0.5%). Having more than one drug as a trigger of anaphylaxis was noted. However, drug triggers contributed insignificantly (*P*-value = 0.978) for anaphylaxis in Qatar (Table 8).

Table 8

Most Common Drug triggers of Anaphylaxis in Qatar, N = 1068

Abbreviations: NSAID = Non-steroidal anti-inflammatory drugs

Triggers	**All subjects N = 1068 n (%)**	**Anaphylaxis N = 574 n (%)**	**Allergy N= 132 n (%)**	**P-value**
Drugs (All)	123 (11.5)	103 (17.9)	20 (16.2)	0.978
Antibiotics	58 (5.4)	49 (8.5)	9 (6.8)	0.883
Augmentin	19 (1.7)	16 (2.7)	3 (2.2)	1.000 *
Penicillin	14 (1.3)	11 (1.9)	3 (2.2)	0.484 *
Ceftriaxone	6 (0.5)	6 (1.0)	0 (0.0)	0.596 *
Amoxicillin	6 (0.5)	5 (0.8)	1 (0.7)	1.000 *
Other antibiotics	22 (2.0)	19 (3.3)	3 (2.2)	1.000 *
NSAID	36 (3.3)	30 (5.2)	6 (4.5)	0.938
Ibuprofen	28 (2.6)	23 (4.0)	5 (3.7)	0.794 *
Paracetamol	8 (0.7)	8 (1.3)	0 (0.0)	0.366 *
Diclofenac	8 (0.7)	7 (1.2)	1 (0.7)	1.000 *
Aspirin	3 (0.3)	3 (0.5)	0 (0.0)	1.000 *
Other NSAID	4 (0.3)	4 (0.6)	0 (0.0)	1.000 *
Others	41(3.8)	35 (6.1)	6 (4.5)	0.779

* P-value is for Fischer test (exact sig. 2-sided)

4.5.3 Venom Insect Triggers of Anaphylaxis in Qatar

Venom insects' triggers were associated with 161 (28.0%) of anaphylactic cases with 135 (23.5%) of the cases due to black ants. Other venom insects' triggers such as bee (0.5%) and wasp (0.1%) were less common in Qatar. However, unspecified venom insects counted for 24 (4.1%) of the cases (Table 9).

Table 9

Most Common Venom Insect Triggers of Anaphylaxis in Qatar, N=1068

Triggers	**All subjects N = 1068 n (%)**	**Anaphylaxis N = 574 n (%)**	**Allergy N= 132 n (%)**	**P-value**
Venom insects(All)	184 (17.2)	161 (28.0)	23 (17.4)	0.122
Black ant	153 (14.3)	135 (23.5)	18 (13.6)	0.101
Bee	3 (0.2)	3 (0.5)	0 (0.0)	1.000*
Wasp	1 (0.1)	1 (0.1)	0 (0.0)	1.000*
Unspecified	29 (2.7)	24 (4.1)	5 (3.7)	0.798*

* P-value is for Fischer test (exact significant 2-sided)

4.5.4 Other Triggers of Anaphylaxis in Qatar

Other triggers of anaphylaxis included animals such as cats, horses, and camels, followed by grass contact, cold, latex, contrast media, exercise alone and food dependent exercise-induces cases. About 44 (7.6%) cases were with idiopathic triggers (Table 10).

Table 10

Other Triggers of Anaphylaxis in Qatar, N =1068

Triggers	**All subjects N = 1068 n (%)**	**Anaphylaxis N = 574 n (%)**	**Allergy N= 132 n (%)**
Idiopathic	49 (4.5)	44 (7.6)	5 (3.7)
Animal	27 (2.5)	20 (3.4)	7 (5.3)
Grass contact	10 (0.9)	9 (1.5)	1 (0.75)
Cold	3 (0.2)	3 (0.5)	0 (0.0)
Latex	2 (0.1)	2 (0.3)	0 (0.0)
Contrast media	2 (0.1)	2 (0.3)	0 (0.0)
Exercise alone	1 (0.1)	1 (0.1)	0 (0.0)
Food-dependent exercise-induced	1 (0.1)	1 (0.1)	0 (0.0)

* P-value not calculated due to small sample size

4.6 Common Anaphylaxis Triggers in Relation to Social Demographics

There was a significant difference between the type of anaphylactic trigger and the age of the patients. Among the most common triggers of anaphylaxis across age groups; food triggered anaphylaxis mainly in children less than 10 years (223, 74.6%) of the cases. Drugs and venom insects triggered anaphylaxis more commonly in adults (20 – 55 years) than any other age group with 33.1% and 44.0% respectively (Table 11). Among the most common triggers of anaphylaxis across gender groups, food triggered anaphylaxis in 63.6% of the males while venom insects and drugs induced anaphylaxis in 38.1% and 21.9% of the females respectively. There was no significant association between nationality of pa-

tients and the type of anaphylactic trigger. However, the nationality with the highest percentage of anaphylaxis was Qatari followed by non-Qatari Arabs and Asian. Limited number of anaphylactic cases were idiopathic with no obvious triggers. Within idiopathic anaphylaxis, 27 cases were children less than 10 years. The majority patients with idiopathic anaphylaxis were males (29, 9.3%). However, no significant association observed between idiopathic anaphylaxis across different age, gender, and nationality groups (Table 11).

Table 11

Common Triggers of Anaphylaxis in Relation to Social Demographics

Characteristics	**Anaphylaxis N= 574 n(%)[a]**	**Food Anaphylaxis N=316 n(%)[a]**	**Drug Anaphylaxis N=103 n (%)[a]**	**Venom Insects Anaphylaxis N=161 n(%)[a]**	**Idiopathic N=44 n(%)[a]**
Age (Years)					
< 10 Years	300 (77.9)	223 (74.3)	31 (10.3)	48 (16.1)	27 (9.0)
10 - 19 Y	109 (83.2)	51 (46.8)	15 (13.8)	40 (36.7)	7 (6.4)
20 - 55 Y	137 (86.7)	36 (27.1)	44 (33.1)	59 (44.0)	10 (7.5)
> 55 Y	28 (87.5)	6 (21.4)	13 (46.4)	14 (50.0)	0 (0.0)
P-value		***<0.001***	***<0.001***	***<0.001***	***0.334***
Gender					
Male	315 (79.1)	199 (63.6)	47 (15.0)	63 (20.2)	29 (9.3)
Female	259 (84.1)	117 (45.7)	56 (21.9)	98 (38.1)	15 (5.9)
P-value		***<0.001***	***0.033***	***<0.001***	***0.130***
Nationality					
Qatari	251 (79.9)	137 (55.2)	40 (16.1)	80 (32.3)	15 (6.0)
Non-Qatari, Arab	162 (86.6)	86 (53.4)	32 (19.9)	39 (24.2)	14 (8.7)
Asian	118 (83.1)	62 (52.5)	21 (17.8)	35 (29.7)	15 (12.7)
Others	42 (67.7)	30 (73.2)	10 (23.8)	7 (17.1)	0 (0.0)
P-value		***0.117***	***0.589***	***0.118***	***0.333***

[a] row percentage

The anaphylaxis triggers distribution among different age and gender groups is presented in figure 6.

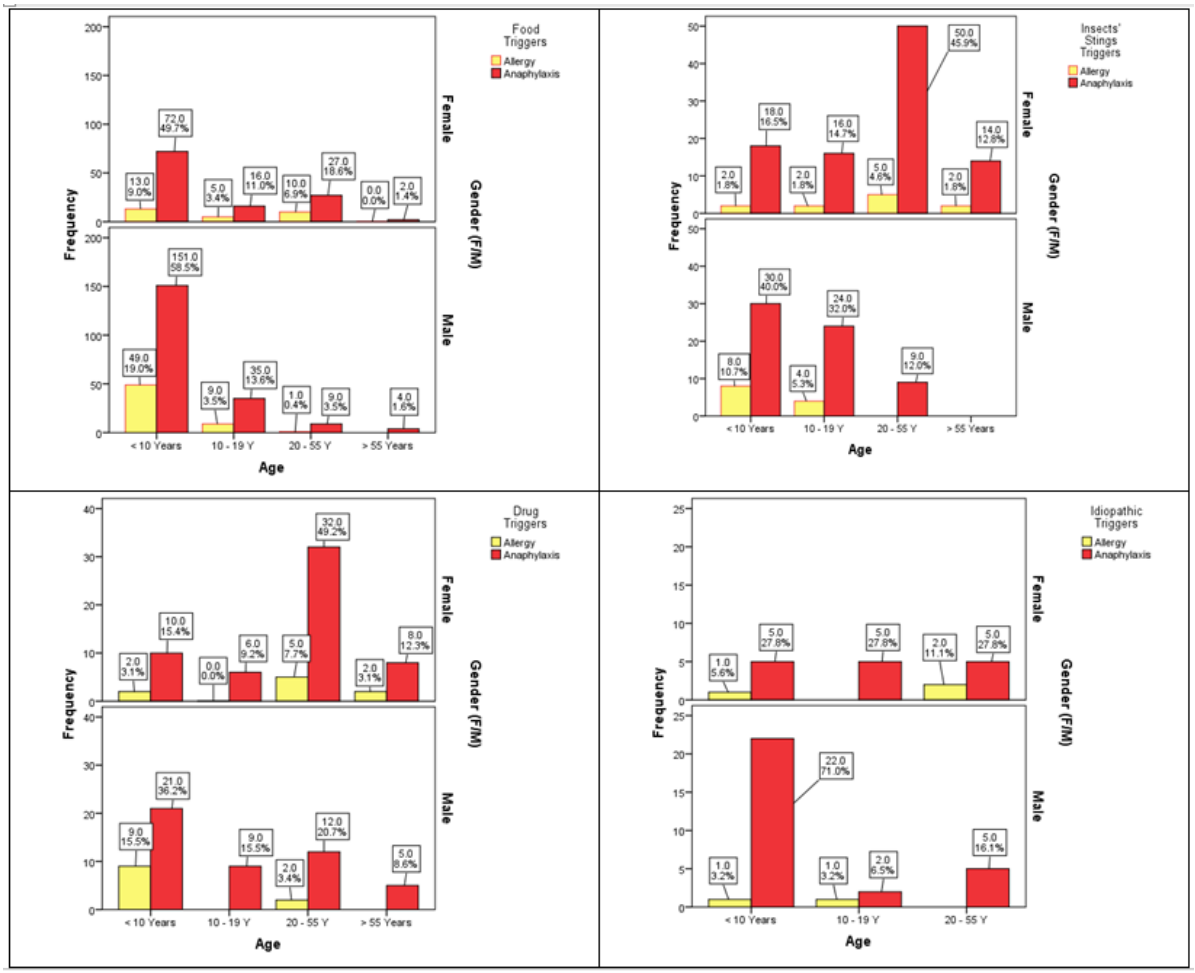

Figure 6. Anaphylaxis triggers distribution among different age and gender groups.

4.6.1 Common Comorbidity Factors Associated with Anaphylaxis in Qatar

The comorbidity factors in the study population, and the frequency of anaphylactic cases within each comorbidity factor was calculated. Although upper respiratory tract infections were the most common comorbidity factor associated with anaphylactic cases in Qatar, the association was insignificant. Asthma (36.2%), atopic dermatitis (33.9%) and allergic rhinitis (14.1%) were the most frequent comorbidity factors significantly associated with anaphylaxis in Qatar (Table 12).

Table 12

Common Comorbidity Associated with Anaphylaxis in Study Population, N = 1068

Abbreviations: URTI= upper respiratory tract infection, DM = diabetes mellitus, HTN = hypertension

Comorbidity factor	**All subjects, N= 1068 n (%)**	**Anaphylaxis N = 574 n (%)**	**Allergy N= 132 n (%)**	***P-value***
URTI	449 (42.1)	240 (41.8)	67 (50.7)	0.064
Asthma	357 (36.4)	208 (36.2)	68 (51.5)	**<0.001**
Atopic Dermatitis	326 (33.2)	195 (33.9)	66 (50)	**<0.001**
Urticaria/Angioedema	254 (25.9)	179 (31.1)	36 (27.2)	0.485
Gastroenteritis	216 (20.2)	111 (19.3)	31 (23.4)	0.288
Allergic Rhinitis	142 (14.5)	81 (14.1)	30 (22.7)	**0.009**
Otitis	165 (15.5)	74 (12.8)	22 (16.6)	0.257
Vitamin D deficiency	109 (10.2)	65 (11.3)	17 (12.8)	0.620
DM	55 (5.2)	41 (7.1)	3 (2.2)	0.370
HTN	58 (5.4)	40 (6.9)	5 (3.7)	0.176
Blood disorders	48 (4.5)	30 (5.2)	2 (1.5)	0.064
Thyroid disease	33 (3.1)	24 (4.1)	3 (2.2)	0.301
Cardiac diseases	34 (3.2)	22 (3.8)	6 (4.5)	0.708
Reproductive disorders	28 (2.6)	18 (3.1)	5 (3.7)	0.437 *
G6PD deficiency	26 (2.4)	16 (2.7)	3 (2.2)	0.511 *
Sinusitis	16 (1.5)	12 (2.1)	2 (1.5)	0.496 *
Cancer	11 (1.0)	7 (1.2)	0 (0.0)	0.233

* P-value is for Fisher test (Exact Sig. 1 sided)

4.6.2 Common Comorbidity Factors in Relation to Triggers

The association between anaphylaxis and its trigger within each comorbidity factor was variable (Table 13). Food trigger of anaphylaxis was significantly associated with patients who had asthma (65.5%), atopic dermatitis (71.8%), urticaria/angioedema (63.1%), otitis (72.6%), vitamin D deficiency (35.4%), diabetes mellitus (22.0%), hypertension (20.0), thyroid disease (25.0%), reproductive disorders (22.2%) and G6PD deficiency (87.5%). On the other hand, drugs induced anaphylaxis significantly for patients with atopic dermatitis (10.8%), gastroenteritis (7.22%), diabetes mellitus (41.5%), hypertension (37.5%), thyroid disorders (50.0%), cardiac diseases (59.1%), and cancer (71.4%). Venom insects triggered anaphylaxis mainly in patients who had atopic dermatitis (17.5%), vitamin D deficiency (50.8%), and reproductive disorders (66.7%).

Notably, Asthma, urticaria/angioedema, otitis, reproductive disorders and G6PD deficiency were significantly associated with food triggers without contribution of the other triggers of anaphylaxis. On the other hand, comorbidity factors such as gastroenteritis, cardiac diseases and cancer were significantly associated only with drug triggers (Table 13).

Table 13

Anaphylaxis in Relation to Triggers and Associated Comorbidity

Abbreviations: URTI= upper respiratory tract infection, DM = diabetes mellitus, HTN = hypertension

Comorbidity	Anaphylaxis N = 574 n (%)	Food trigger N=316			Drug triggers N=103			Venom insect triggers N= 131		
		n	(%)[a]	P-value[$]	n	(%)[a]	P-value[$]	n	(%)[a]	P-value[$]
URTI	240 (41.8)	135	56.2	0.674	34	14.2	0.37	70	29.3	0.671
Asthma	208 (36.2)	136	65.4	**< 0.001**	34	16.3	0.438	46	22.2	0.017
Atopic Dermatitis	195 (33.9)	140	71.8	**< 0.001**	21	10.8	**<0.001**	34	17.5	**< 0.001**
Urticaria/Angioedema	179 (31.1)	113	63.1	0.013	28	15.6	0.323	48	27.0	0.674
Gastroenteritis	111 (19.3)	69	62.2	0.113	8	7.22	**<0.001**	28	25.2	0.416
Allergic Rhinitis	81 (14.1)	46	57.5	0.694	16	20	0.613	26	32.5	0.349
Otitis	74 (12.8)	53	72.6	**0.002**	10	13.5	0.272	17	23.3	0.304
Vitamin D deficiency	65 (11.3)	23	35.4	**<0.001**	11	16.9	0.793	33	50.8	**< 0.001**
DM	41 (7.1)	9	22.0	**< 0.001**	17	41.5	**< 0.001**	15	36.6	0.224
HTN	40 (6.9)	8	20.0	**< 0.001**	15	37.5	**0.001**	17	42.5	0.039
Blood disorders	30 (5.2)	12	41.4	0.117	5	16.7	0.834	12	41.4	0.110
Thyroid disease	24 (4.1)	6	25.0	**0.002**	12	50.0	**< 0.001**[*]	9	37.5	0.309
Cardiac diseases	22 (3.8)	10	45.5	0.336	13	59.1	**< 0.001**[*]	3	13.6	0.118
Reproductive disorders	18 (3.1)	4	22.2	**0.004**	3	16.7	1.000[*]	12	66.7	**< 0.001**
G6PD deficiency	16 (2.7)	14	87.5	0.009	1	6.3	0.327[*]	2	12.5	0.258[*]
Sinusitis	12 (2.1)	3	25.0	0.032	1	80.3	0.704[*]	7	58.3	0.045[*]
Cancer	7 (1.2)	2	28.6	0.146	5	71.4	**0.003**[*]	1	14.3	0.697[*]

[a] row percentage out of anaphylactic cases who had the comorbidity factor
[$] p-value is for anaphylactic patients within the comorbidity factor with and without the listed triggers
[*] p-value of fisher exact test (Exact sign. 2 sided)

4.7 Common Symptoms of Anaphylaxis in Qatar

The common symptoms in relation to anaphylaxis summarized (Table 14). The anaphylactic patients showed symptoms related to skin (505, 87.9%), respiratory (397, 69.1%), gastrointestinal (273, 47.5%), cardiovascular (91, 15.8%), and nervous (51, 8.8%) systems. Anaphylactic patients with skin related symptoms looked for medical attention due to rash (70%), itching (38.6%), urticaria (34.6%), erythema (27.3%), angioedema (27.3%), local edema (20.9%), periorbital swelling (12.1%), fever (5.9%) and conjunctivitis (5.2%). Local edema (*P*-value=0.019) and erythema (*P*-value=0.058) were statistically significant in anaphylactic patients. The major respiratory related symptom that was significantly associated with anaphylaxis was dyspnea (44.1%, *P*-value=0.011). In our study cohort, respiratory symptoms such as hoarseness, upper airway obstruction, tachypnea, and stridor manifested only in patients with anaphylaxis. In term of gastrointestinal symptoms, vomiting was significantly associated with anaphylaxis (31.8%, *P*-value=0.042). Tongue swelling with/without itching, swallowing difficulty, nausea, abdominal pain and diarrhea noted only in patients with anaphylaxis. Among patients with anaphylaxis, tachycardia, syncope, loss of conscious, cyanosis, bradycardia, and crepitation were the major cardiac related symptoms. The most common nervous system related symptom was dizziness (5.9%) (Table 14). Fever, which is a constitutional symptom, was common among 34 patients with anaphylaxis (5.9%).

Table 14

Common Symptoms of Anaphylaxis in the Study Population, N =1068

Symptoms	All subjects, N= 1068, n (%)	Anaphylaxis N = 574, n (%)	Allergy N = 132, n (%)	P-value
Skin-mucosal tissue	564 (52.8)	505 (87.9)	15 (11.3)	0.098 *
Rash	434 (40.6)	402 (70.0)	11 (8.3)	0.269
Itching	241 (22.5)	222 (38.6)	7 (5.3)	0.835
Urticaria	217 (20.3)	199 (34.6)	8 (6.1)	0.524
Erythema	173 (16.1)	157 (27.3)	9 (6.8)	**0.058**
Angioedema $	169 (15.8)	157 (27.3)	5 (3.7)	0.893
Lips swelling, +/- itching	78 (7.3)	75 (13.1)	3 (2.2)	0.729 *
Tongue swelling, +/- itching	25 (2.3)	21 (3.6)	0 (0.0)	1.000 *
Local edema $	137 (12.8)	120 (20.9)	9 (6.8)	**0.019** *
Periorbital swelling	78 (7.3)	70 (12.1)	3 (2.2)	0.719 *
Conjunctivitis	33 (3.1)	30 (5.2)	3 (2.2)	0.085
Respiratory	419 (39.2)	397 (69.1)	6 (4.5)	**<0.001** *
Dyspnea	268 (25.1)	253 (44.1)	3 (2.2)	**0.011**
Cough	138 (12.9)	132 (22.9)	3 (2.2)	0.582
Wheezing/Bronchospasm	99 (9.2)	95 (16.5)	1 (0.7)	0.337 *
Gasping	69 (6.4)	68 (11.8)	0 (0.0)	0.149
Congested oropharynx/nose	52 (4.8)	48 (8.3)	1 (0.7)	1.000 *
Rhinitis	38 (3.5)	35 (6.1)	3 (2.2)	0.119 *
Hoarseness	23 (2.1)	23 (4.0)	0 (0.0)	1.000 *
Upper airway obstruction	17 (1.5)	17 (2.9)	0 (0.0)	1.000 *
Tachypnea	17 (1.5)	16 (2.7)	0 (0.0)	1.000 *
Stridor	12 (1.1)	12 (2.1)	0 (0.0)	1.000 *
Chest pain/tightness	11 (1.0)	9 (1.5)	1 (0.7)	0.254 *
Gastrointestinal	284 (26.5)	273 (47.5)	5 (3.7)	**0.054**
Vomiting	186 (17.4)	183 (31.8)	2 (1.5)	**0.042**
Abdominal pain	53 (4.9)	53 (9.2)	0 (0.0)	0.401 *
Diarrhea	20 (1.8)	20 (3.4)	0 (0.0)	1.000 *
Nausea	11 (1.0)	11 (1.9)	0 (0.0)	1.000 *
Swallowing difficulty	6 (0.5)	6 (1.0)	0 (0.0)	1.000 *
Cardiac	94 (8.8)	91 (15.8)	1 (0.7)	0.333*
Hypotension	123 (11.5)	119 (20.7)	2 (1.5)	0.339
Tachycardia	35 (3.2)	32 (5.5)	1 (0.7)	1.000 *
Syncope/loss of conscious	22 (2.0)	22 (3.8)	0 (0.0)	1.000 *
Cyanosis	16 (1.4)	16 (2.7)	0 (0.0)	1.000 *
Bradycardia	5 (0.4)	5 (0.8)	0 (0.0)	1.000 *
Crepitation	4 (0.3)	4 (0.6)	0 (0.0)	1.000 *
Nervous system	56 (5.2)	51 (8.8)	2 (1.5)	0.686
Dizziness	39 (3.6)	34 (5.9)	2 (1.5)	0.328

$ Local edema and angioedema are as reported by physicians in the patients' electronic medical records.

4.7.1 Common Anaphylaxis Symptoms of the Patients' Cohort in Relation to the Triggers

Symptoms of anaphylaxis were variable. For anaphylaxis triggered by food, the symptoms were related to gastrointestinal (71.1%, *P* value < 0.001), cardiac (28.6%, *P* value < 0.001), and nervous (37.3%, *P* value=0.005) systems, which was statistically significant (Table 15). However, the anaphylaxis triggered by drugs was significant in association with skin (16.4%, *P* value=0.003) and cardiac (34.1%, *P* value < 0.001) manifestations. Venom insect triggers were significantly associated with symptoms related to gastrointestinal (15.8%, *P* value <0.001) and nervous systems (45.1%, *P* value = 0.003) (Table 15).

Table 15

Anaphylaxis Symptoms in Relation to Triggers and Organ Systems, N = 574

Symptoms	**Anaphylaxis N= 574**	**Food triggers N = 316**		**Drug triggers N = 103**		**Venom insect triggers N =131**	
	n (%)	**n (%)[a]**	**P-value[$]**	**n(%)[a]**	**P-value[$]**	**n(%)[a]**	**P-value[$]**
Skin	505 (87.9)	281(55.6)	0.947	83 (16.4)	**0.002**	144 (28.6)	0.006
Respiratory	397 (69.1)	214(53.9)	0.163	70 (17.6)	0.952	119 (30.1)	0.014
Gastrointestinal	273 (47.5)	194 (71.1)	**< 0.001**	40 (14.7)	0.061	43 (15.8)	**< 0.001**
Cardiac	91 (15.8)	26 (28.6)	**< 0.001**	31 (34.1)	**< 0.001**	27 (29.7)	0.567
Nervous	51 (8.8)	19 (37.3)	**0.005**	14 (27.5)	0.055	23 (45.1)	**0.003**

[a] row percentage out of anaphylactic cases who manifested the concerned symptoms
[$] p-value is for anaphylactic patients within the concerned symptoms with and without the triggers

4.7.2 Common Anaphylaxis Symptoms in Relation to Dispensed EAIs

EAI dispensed in Qatar to treat anaphylactic symptoms that were related to skin(445, 89.1%), respiratory (349, 69.9%), gastrointestinal (235, 47.1%), cardiac (63, 12.6%), and nervous (41, 8.2%) systems. No EAIs dispensed for 74 anaphylactic cases, of which skin, respiratory, gastrointestinal, cardiac, and nervous-related symptoms were present as 79.7%, 64.8%, 51.3%, 37.8%, and 13.5%, respectively. Based on status of anaphylaxis and EAI, the study population was divided into four groups: (i) anaphylactic patients with dispensed EAI, (ii) anaphylactic patients without dispensed EAI, (iii) patients without anaphylaxis and had dispensed EAI, (iv) patients without anaphylaxis nor dispensed EAI. The latest group had only ten patients with no symptoms (not shown in Table 16). Significant difference observed for the symptoms of the other three groups, especially in term of respiratory- and cardiovascular- (*P* value < 0.001) and skin- (*P* value 0.008) related symptoms (Table 16).

Table 16

Anaphylaxis Symptoms in Relation to Dispensed EAIs, N = 555

Symptoms	**EAI (+) Anaphylaxis (+) N = 499 n (%)**	**EAI (+) Anaphylaxis (-) N = 118 n (%)**	**EAI (-) Anaphylaxis (+) N = 74 n (%)**	**P-value**
Skin	445 (89.1)	15 (12.7)	59 (79.7)	**<0.001**
Respiratory	349 (69.9)	6 (5.1)	48 (64.8)	**< 0.001**
Gastrointestinal	235 (47.1)	5 (4.2)	38 (51.3)	0.175
Cardiac	63 (12.6)	1 (0.8)	28 (37.8)	**<0.001**
Nervous	41 (8.2)	2 (1.6)	10 (13.5)	0.545

There were ten patients with no symptoms within EAI (-) and (-) anaphylaxis group (not shown)

4.8 Patients' Outcome in Relation to EAIs Compliance

Patients with anaphylaxis treated using three approaches: 294 patients (51.2%) treated by EAIs in combination to other drugs, 143 patients (24.9%) treated with other drugs without EAIs while 97 patients (16.8%) treated exclusively with EAIs. Out of 574 patients diagnosed with anaphylaxis, only 22 patients (3.8%) had serious adverse events. Patients treated with drugs other than EAIs at the time of the anaphylactic episode had more serious adverse events (n=10, 7.0%). Incidents of two deaths and one shock occurred in patients where no EAI used (Table 17).

Table 17

Patients' Outcome of Anaphylaxis in Relation to EAIs

Patients outcome	Anaphylaxis	Anaphylaxis cases Treated by			
	Yes	Epinephrine (+) other drugs (-)	Epinephrine (-) other drugs (+)	Epinephrine (+) other drugs (+)	
	N =574	N =97	N =143	N = 294	
	n (%)	n (%)	n (%)	n (%)	P-value
Serious Adverse Event	22 (3.8)	2 (2.1)	10 (7.0)	8 (2.7)	0.053
Respiratory arrest	5 (0.9)	1 (1.0)	2 (1.4)	2 (0.7)	*
Profound hypotension	3 (0.5)	1 (1.0)	1 (0.7)	1 (0.3)	*
Cardiac arrest	2 (0.3)	0 (0.0)	1 (0.7)	1 (0.3)	*
Death	2 (0.3)	0 (0.0)	2 (1.4)	0 (0.0)	*
Endotracheal intubation	10 (1.7)	1 (1.0)	4 (2.8)	4 (1.4)	*
Pulmonary edema	9 (1.6)	0 (0.0)	5 (3.5)	3 (1.0)	*
Infection	2 (0.3)	0 (0.0)	0 (0.0)	2 (0.7)	*
Shock	1 (0.2)	0 (0.0)	1 (0.7)	0 (0.0)	*

* P-value not calculated due to small sample size

Admission of patients with anaphylaxis to the health care facilities was statistically significant among the three treated groups. The majority of patients were admitted to ED (n =360) and discharged within the same day (n=253). Patients treated with both EAIs and other drugs had more admission than the other two groups. Interestingly, the lowest inpatient and ICU admission was for patients treated with EAIs alone (Table 18).

Table 18

Admission of Patients with Anaphylaxis in Relation to EAIs

Abbreviations: ED = emergency department, LOS = length of stay, A/I = allergy and immunology

Patients outcome	Anaphylaxis Yes N =574 n	Anaphylaxis cases Treated by Epinephrine (+) other drugs (-) N =97 n (%)[a]	Epinephrine (-) other drugs (+) N =143 n (%)[a]	Epinephrine (+) other drugs (+) N = 294 n (%)[a]	P-value
ED admission	360	51 (14.2)	82 (22.8)	221 (61.4)	< **0.001**
ED LOS, n =372					
< 24 hours	253	46 (18.2)	51 (20.2)	153 (60.5)	< **0.001**
24 -72 hours	71	5 (7.0)	18 (25.4)	47 (66.2)	
> 72 hours	39	1 (2.6)	14 (35.9)	22 (56.4)	
Referral to A/I clinic	293	70 (23.9)	70 (23.9)	134 (45.7)	< **0.001**
Inpatients admission	71	2 (2.8)	10 (14.1)	58 (81.7)	< **0.001**
ICU admission	11	0 (0.0)	5 (45.4)	5(45.4)	*
Discharged against advice	6	1 (16.7)	2 (33.3)	3 (50.0)	*

[a] row percentage

* P-value not calculated due to small sample size

CHAPTER 5: DISCUSSION

In this study, we examined EAIs dispense as a possible indicator for the frequency of anaphylaxis in Qatar; therefore, we pulled out the ICD-10 codes of anaphylaxis and EAIs dispense records from HMC Cerner system and we obtained 1,068 electronic medical records during the period 2012-2016. We reviewed each EMR for EAIs dispense and physician diagnosis of anaphylaxis and classified anaphylaxis triggers according to age, gender, nationality, and co-morbidity factors. In addition, we compared the clinical outcomes of patients treated with and without EAIs. We identified 739 patients with EAIs dispense, of whom 574 patients were diagnosed with anaphylaxis (Tables 2, 4). The sensitivity of detecting the cases of anaphylaxis by EAIs was 87.0% with PPV of 80.0%. However, the specificity (8.0%) was low (Figure 5). The female/male ratios were higher with predominance among the children (Figure 6). The main triggers were Food, insect stings, and drugs (Table 7 - 8). The associated atopic diseases among our patients' cohort were mainly asthma, atopic dermatitis, and allergic rhinitis (Table 12). Unfortunately, EAIs records were not available for 74 patients (Table 6). Additionally, 143 patients treated using alternative drugs in discordance to the international and local guidelines of anaphylaxis management (Table 17), consistent with the serious adverse events among patients that were treated without EAIs. This study is expected to serve as a guide for clinicians and health care professionals in Qatar in allergy clinics.

5.1 Dispensed EAIs as an Indicator Tool to Estimate Anaphylaxis

Our data showed that over a period of four years from 2012 to 2016, 739 patients had EAIs dispense, 574 patients were with anaphylaxis; of which, 499 patients had EAIs dispense while 74 patients had no EAIs dispense at the time of their discharge (Table 3, 4, 5). The sensitivity of using the EAIs dispense was 87.0% with PPV of 80% (Figure 5). Such high sensitivity of EAIs dispense to detect anaphylaxis might be due to HMC anaphylaxis guidelines which demand that EAIs should be provided for patients who were exposed to an anaphylactic episode at the time of their discharge as a long-term care plan. The specificity of EAIs dispense was low (8.0%) with NPV of 11.0% (Figure 5). Many reasons could explain this finding. First, a considerable cohort of patients were diagnosed with merely allergic condition (n=132, 12.3%); of which 118 patients had EAIs, ten patients had no EAIs and four had incomplete charts (Table 6). Secondly, patients who were non-anaphylactic, most likely received EAIs as a prophylactic measure. These patients might be thought to be at high risk of developing anaphylaxis due to their strong history of other atopic disorders such as asthma (n=68, 51.5%), atopic dermatitis (n=66, 50.0%), urticaria (n=36, 27.2%), and allergic rhinitis (n=30, 22.7) (Table 12). Such similar strong history of atopy observed in patients with anaphylaxis (Table 12) and this similarity might create difficulties in the ability of physicians to distinguish between anaphylaxis and non-anaphylaxis conditions, and would influence the physicians' decision to prescribe EAIs for non- anaphylactic cases. Third, the indication of EAIs dispense for these non-anaphylactic cases was valid which highlighted that EAIs dispense is a potential medication for some non-anaphylactic cases (Table 5). Therefore, EAIs dispense was unable to correctly classify non-anaphylactic cases and showed low specificity.

Combining research methods in our study to detect anaphylaxis was crucial to estimate anaphylaxis frequency since none of the methods estimated anaphylaxis correctly on individual basis. For instance, using EAIs dispense in combination with the ICD-10 codes of anaphylaxis enabled us to capture 74 patients with anaphylaxis, which we could not capture using EAIs dispense method alone (Table 6). Additionally, using EAIs dispense as the sole indicator to estimate anaphylaxis would result in overestimation due to its low specificity and require critical review of patients' medical records. These two observations are important observations for clinical research in this field. Previous studies used EAIs dispense as a surrogate approach to study anaphylaxis (100-106). In an epidemiological study, Simons *et al*. (2002), found that 0.95% of the population had epinephrine dispensing in Manitoba province, Canada over a period of five years (1995 -2000) and accordingly estimated anaphylaxis rate as 954 per 100,000 persons (101). A different study from Israel showed that the total rate of EAI dispensing increased by 76% from 1997 to 2004 (102). However, this study, unfortunately, was not inclusive to estimate anaphylaxis rate and it discussed only food allergy and asthma (102). Motosue *et al.* (2017), reported that EAIs dispense rate among pediatrics had a similar percentage of food-induced anaphylaxis in the United States over a period of nine years (2005 – 2014) and both increased by approximately 16.0% (106). Another retrospective study over six years period (1999 – 2004) estimated a low prevalence of anaphylaxis among Singapore population and characterized anaphylaxis based on EAIs dispense records (105). However, none of these studies calculated sensitivity, specificity, positive and negative predictive values of EAI dispense as we did (Figure 5). To our knowledge, this is the first study that calculates the sensitivity and PPV

in these settings; therefore, our findings indicate that using EAIs dispense to estimate the frequency of anaphylaxis in a large cohort of patient is a potential sensitive method to indicate the number of patients with anaphylaxis, but need to be used in combination with other methods not to miss or overestimate anaphylactic cases. These findings have important application in clinical practice and research.

5.2 Anaphylaxis Triggers in Relation to Patients' Demographics in Qatar

The distribution of anaphylaxis among different age and gender groups is variable in Qatar (Figure 6). Our data showed a predominance of anaphylaxis among pediatrics (n =300, 77.9%) (Table 2); which is reasonable since, at a single time point, anaphylaxis initially diagnosed at childhood and relevant triggers avoidance recommended as preventive measures of a long-term action plan and risk reduction. However, such avoidance measures are neither easily nor strictly followed by children of this age group (68, 84, 107). In this study, we found that anaphylaxis was common among male children (n = 224, 39.0%) and female adults (n=114, 19.8%) (Figure 6); a finding that is consistent with other Qatari studies in which the incidence of anaphylaxis was common among pediatric males (69.0%) and adult females (78.0%) (4, 5). This variation probably attributed to the sample size difference in each study (4, 5). Several studies around the world showed similar distribution of anaphylaxis among different age and gender groups. A population-based epidemiological study of emergency department visits in Florida reported that the highest anaphylaxis incidence rate was among the youngest males (8.2/100,000 visits) and the adult females (10.9/100,000 visits) (48). Similar to that, findings of Rochester epidemiology project from 1990 through 2000 showed that age-specific incidence rate of anaphylaxis was the highest

for ages 0 -19 years (51). In contrast, anaphylaxis among UK critical care units between 2005 and 2009 reported higher admissions among adults than children (60). However, such variation might be related to the higher number of participated female adults (65%) in this study (60).

In our patients' cohort, we observed that the association between anaphylaxis and the national origin was statistically significant (P= 0.009), Qataris (43.7%), non-Qatari Arab (28.2%) and Asian (20.5%). Such considerable variation can be due to the difference of the genetic makeup of Qatar population as the structure of Qatar community is a melting pot of hundreds of nationalities of migrant workers that have different genetic predisposition to Allergy and anaphylaxis, consistent with the ethnic variations of anaphylaxis. In general, anaphylaxis was common (42, 48, 49, 51, 53), more associated with repeated use of epinephrine (108) and more fatal (56) among Caucasians compared to Black, Latino/Hispanic and Asian ethnicities. In contrast, Mahdavinia et al. (2017) reported that Caucasians had a lower rate of food allergy associated anaphylaxis than African American and Hispanic children and demonstrated ethnicity differences of food allergen profiles, coexistent atopic condition and clinical outcome (109). Additionally, Buka et al. (2015) reported that Caucasians had less incidence, and less likely to present with severe anaphylactic symptoms than South Asian British children living in Birmingham (110). Unfortunately, such ethnicity correlation lack in Arabic studies and there is no ethnicity nor anaphylaxis registry in Qatar. Therefore, our data might provide the baseline for assessing future trends.

5.3 The Profile of Anaphylaxis Triggers in Qatar

Our results showed that food was the major trigger of anaphylaxis in Qatar and affected mainly children less than ten years (Figure 6A). The main allergen triggers of food-induced anaphylaxis were nuts and eggs (Table 7), a finding that was consistent with a Saudi study reported in 2015 (70). Peanuts, a significant trigger of food-related anaphylaxis in the United States (42, 53, 55), ranked in the fourth position after seafood in Qatar (Table 7). In a prospective cohort study conducted in Qatar from 2007 to 2010, cow's milk proteins anaphylaxis found in ten children out of 38 subjects and camel milk suggested as being a safer alternate choice (3, 64). With a larger study population, anaphylaxis induced by cow's milk accounted for 61 cases (10.6%) from 2012 to 2016 (Table 7). In comparison, cow's milk protein anaphylaxis resulted in 6-9 % of children hospital admission in the USA (42, 47, 49). It induced 10% of anaphylactic reactions in the UK (111) where eight children fatalities occurred during the period from 1992 - 2012 (38). Our data showed that sesame seed accounted for 8.7% of anaphylaxis cases in Qatar (Table 7). However, as a global allergen, sesame seed is affecting approximately 0.1% of North American population and is the third common food allergen in Israel (112). In Lebanon, a cross-sectional study showed that allergic reactions triggered by sesame seed were of severe grade and manifested mainly in the form of anaphylaxis (81). This study suggested that the sesame seed is the "Middle Eastern" peanut (81).

Anaphylaxis and allergic reactions attributable to Hymenoptera stings in our study demonstrated predominance in female adults (n = 50, 45.9%) and male children (n = 30, 40.0%) (Figure 6B). Interestingly, 135 patients (23.5%) developed anaphylaxis by the sting of black ants (Table 9); which are widespread ants in tropical Africa and the Middle

East and is a native insect in Arabian desert countries including Qatar (113, 114). Allergic reactions due to black ant stings range from pain with local itching at the sting site to severe anaphylactic shock. AlAnazi et al. (2009) showed a diversity of manifestation and human response to black ant stings in four cases encountered in Al Riyadh, the capital city of Saudi Arabia, and three patients were adult females (115). In contrast to our findings, lower prevalence of black ant induced anaphylaxis reported in Saudi Arabia (3.2%) (70), and Singapore (12.9%) (116). The unreported incidence of black Samsum ant induced anaphylaxis recognized in Iran where most stings resulted in mild allergic reactions (117). However, in United Arab Emirate, four deaths were recorded after the sting of this ant (118). Several studies attribute diversity of symptoms to the antigenicity variation of black ants' toxin composition according to geographical regions (117, 119). Anaphylaxis in Najran, a city in southwestern Saudi Arabia, was triggered by a different species of black ant, Solenopsis Richteri, in non-Saudi expatriates (1997 -1999) (120). A Turkey retrospective review defined prevalence of Hymenoptera stings anaphylaxis among adult patients, however, the causative triggers were mainly honey bees and different wasp species (85). In contrary to Qatar, the later Turkish study showed a predominance of Hymenoptera induced anaphylaxis among male adults (57.1%) (85). In light of the absence of studies published about black ant abundance, distribution, and its toxin antigenicity in Qatar, our results flag it as a public health hazard in Qatar owing to its strong association with anaphylaxis. Additionally, black ant immunotherapy is not available in Qatar. Thus, we would recommend integrating entomology, bioecology and medicine points of view in future studies.

5.4 Co-morbidity Factors of Anaphylaxis in Qatar

Our findings indicate that Asthma ($p<0.001$), atopic dermatitis ($p<0.001$), and allergic rhinitis ($p=0.009$), were the main comorbidity factors that were significantly associated with anaphylaxis in Qatar (Table 12). Anaphylaxis was common in 208 patients with asthma (36.2%), 195 patients with atopic dermatitis (33.9%), and 81 patients with allergic rhinitis (14.1%) (Table 12). These observations might be explained by a recent concept called "atopic march", which suggested that atopic disorders are related to each other and coexist in sequential manner throughout the patient life (121, 122). Several studies reported similar association of atopic disorders among patients with anaphylaxis and visualized such association as a risk factor that might worsen the prognosis of the anaphylactic episodes, boost their severity grade, and their recurrence probability (4, 5, 47, 49, 51, 89, 116, 123, 124). Figure 7 provides summary of these previous studies. Among patients with anaphylaxis, asthma was the most common atopic disorder in Qatar and USA and the second most common atopic disorder among patients in Turkey, Singapore, Thailand and Latin America (Figure 7). However, allergic rhinitis was the most frequent atopic disorder among patients with anaphylaxis in Turkey, Singapore, Thailand and Latin America (figure 7) Although we have reported the co-existing of allergic rhinitis with anaphylaxis in our patients' cohort, none of the two presented Qatari studies reported its co-existing (Figure 7). On the other hand, atopic dermatitis was the second most frequent atopic disorder among patients with anaphylaxis in Qatar and USA and the least frequent disorder reported by the other studies in Turkey, Thailand and Latin America (Figure 7). Knowing this association of atopic disorder among patients with anaphylaxis is important for clinicians to ensure timely therapeutic plan and proper management of the patients.

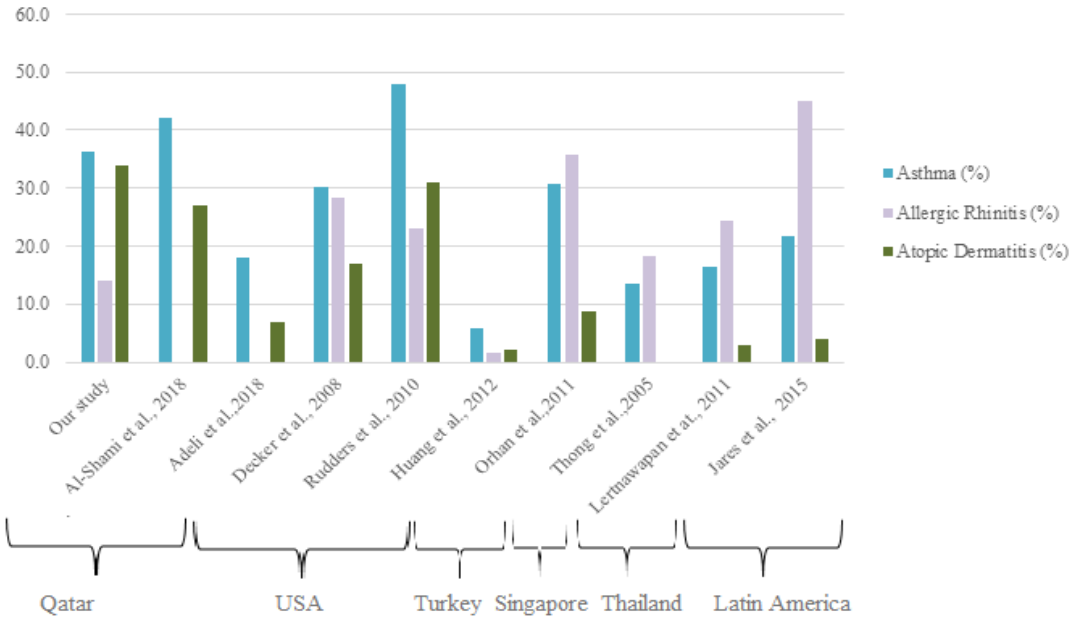

Figure 7. Summary of Atopic disorders among patients with anaphylaxis in the studies (4, 5, 45, 47, 49, 87, 114, 121, 122)

We reported family history of atopy and anaphylaxis in 63 patients (Table 3). Having positive family history of atopy among patients with anaphylaxis suggest presence of common genetic, epigenetic, and environmental factors (7, 122, 125). These factors might interact with each other in a yet unclear manner to influence the patients' predisposition toward development of more severe allergic reactions (anaphylaxis).

In our patients' cohort, there was a statistically significant association between co-morbidity factors and categories of anaphylaxis triggers (Table 13). For instance, statistically significant association of atopic dermatitis observed with all the classes of anaphylaxis triggers ($P<0.001$) (Table 13). This finding might be because the loss of skin barrier integrity in atopic dermatitis facilitates easy penetration of food as well as environmental allergens and subsequent enhancement of allergy (121, 126). In our study, asthma showed statistically significant association with food triggers ($P <0.001$) and 65.4% of patients with asthma had food induced anaphylaxis (Table 13). For a long time, scientists thought that asthma triggered exclusively by environmental inhalant allergens. However, the association of asthma with food allergy alters this current concept to suggest that food allergens might play a role in the pathogenesis of asthma by a not yet fully understood mechanism (121). A recent Qatari study linked the prevalence of asthma among Qatar children (19.8%) to the increased construction and poor air quality in the last decades which highlights a role of environmental inhalant allergens (127). Another Qatari cross-sectional study showed that food allergy and positive family history were a significant predictor of asthma in Qatar (128). Several studies emphasized that the severe form of food allergy, anaphylaxis, was common among children with asthma (44, 49, 65, 123) and the hazard of anaphylaxis shock was as high as 5.2 fold in patients with asthma (129). Interestingly, finding such association between asthma and food triggers of anaphylaxis in our study might serve as a base for further researches to figure out the role of gut microbiota in the pathogenesis of asthma, a field of growing interest in the scientific world. Moreover, our study is the first one in Qatar that correlates these atopic disorders with the different categories of anaphylaxis triggers.

5.5 Patients' Clinical Outcomes in Relation to EAIs therapy

Clinical findings of patients' symptoms.

Patients' clinical outcomes were emphasized by assessing the clinical manifestation of anaphylaxis. We found that symptoms included cutaneous (n=505, 87.9%), followed by respiratory (n=397, 69.1%), gastrointestinal (n-273, 47.5%), cardiac (n=91, 15.8%) and neurological (n=51, 8.8%) (Table 14). This order of anaphylactic symptoms' distribution was similar in term of cutaneous and respiratory symptoms in several studies around the world, however, there was slight variability in term of gastrointestinal, cardiac and neurological symptoms (Figure 8) (5, 49, 59, 85, 123).

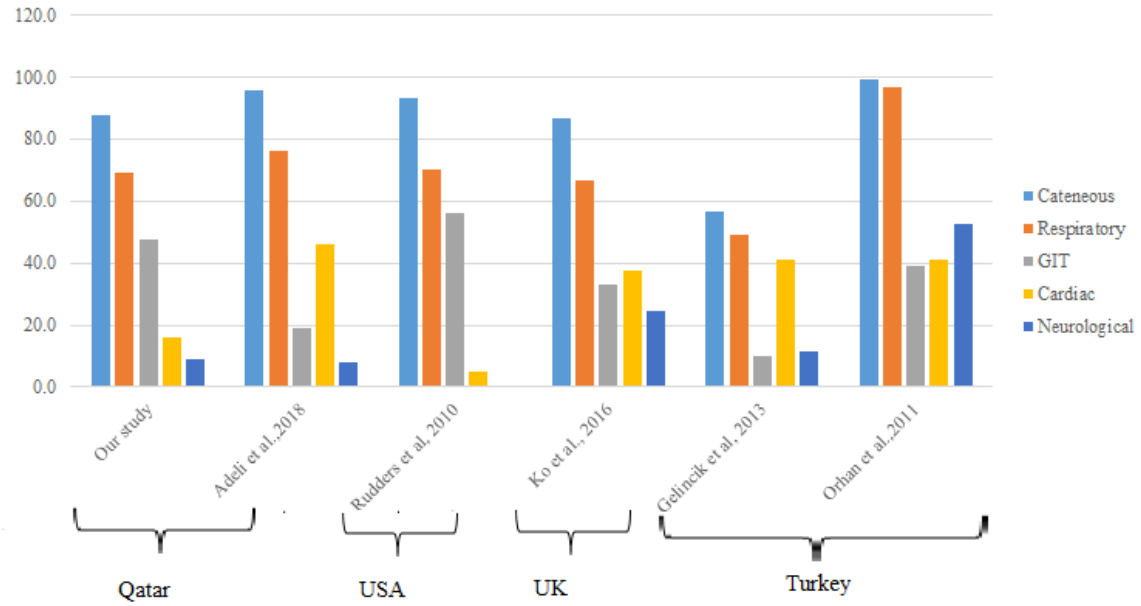

Figure 8. Summary of symptoms among patients with anaphylaxis in the studies (5, 49, 59, 85, 123)

Local edema (P=0.019), erythema (P=0.058), dyspnea (P=0.011), and vomiting (P=0.042) were significantly different among patients with anaphylaxis and allergy in Qatar (Table 14). Similar to our study, two retrospective studies found that dyspnea and vomiting were significantly different among patients with anaphylaxis and allergy in USA (47, 49). In our patients' cohort, some symptoms manifested in patients with anaphylaxis rather than allergy. These symptoms include hoarseness, upper airway obstruction, tachypnea, stridor, gasping, abdominal pain, tongue swelling/itching, diarrhea, nausea, swallowing difficulty, tachycardia, syncope, and cyanosis (Table 14). However, we found that these symptoms were not limited for patients with anaphylaxis since several studies reported them among allergic patients (47, 49).

The involvement of organ systems during anaphylaxis episodes was significantly different based on the type of triggers (Table 15). Gastrointestinal, cardiac and nervous symptoms were significantly associated with food triggers of anaphylaxis while only gastrointestinal and nervous symptoms showed statistically significant association with insects' stings (Table 15). Skin and cardiac symptoms showed statistically significant association with drug triggers of anaphylaxis (Table 15). These findings might serve as a clinical guide for clinicians to predict the type of trigger of anaphylaxis based on the patients' symptoms. Such immediate recognition and sub-sequent identification of the anaphylactic trigger are the most critical aspects to ensure patient safety, and it would assist physicians to set up management plans for anaphylaxis triggers avoidance in future.

Clinical outcomes of patients.

Another part of the assessment of patient's clinical outcome is the evaluation of the benefits, and harms of therapeutic options and comparing them. In our study, patients were treated with three different therapeutic approaches either with epinephrine (n=97, 16.8 %), alternative drugs to epinephrine (n=143, 24.9%), or both (n=294, 51.2%) (Table 17). Interestingly, treating 143 patients (24.9%) without epinephrine use reflected a critical gap in the management of patients with anaphylaxis and raised concern on the physicians' compliance to the international guidelines and HMC policies to manage those patients (Table 17). Using alternative medications such as antihistamines in replacement of epinephrine is risky since antihistamines have slow absorption and require 1-3 hours for maximum plasma concentration after oral administration (25); while intramuscular injection of epinephrine

requires eight minutes only to reverse anaphylactic symptoms and relieve the patients' distress (25, 96). Moreover, antihistamines do not reverse upper air-way obstruction and hypotension (29). Accordingly, this group of patients had more clinically significant consequences such as serious adverse events (n =10, 7.0%), pulmonary edema (n=5, 3.5%), endotracheal intubation (n=4, 2.8%), respiratory arrest (n=2, 1.4%), and cardiac arrest (n=1, 0.7%) compared to patients treated with epinephrine alone (n=97, %) (Table 17). The incident of two deaths and one shock occurred among patients treated without epinephrine (Table 17). A recent study showed a dependence of ED clinicians on antihistamine drugs as first-line treatment of anaphylaxis for adults in Qatar (4, 5). Therefore, our finding raised real concern about the clinical practice of anaphylaxis management in Qatar.

Similar to Qatar, the frequent use of alternative drugs rather than epinephrine to treat anaphylaxis is common in other parts of the world. For instance, A multi-center retrospective case study of Turkish children during the period from 1999 to 2009 showed that out of 158 anaphylactic episodes, 148 (93.7%) received antihistamines while 51 (23.3%) received epinephrine (123). A retrospective study of EAIs re-fill adherence in primary care centers in Manitoba, Canada between 2012 and 2014 showed that odds of EAIs re-fill prescription were inversely related to non-EAI medications re-fill (130). Our finding might highlight improper practice of physicians since the evidence base of using epinephrine to treat anaphylaxis is level B recommendation and is stronger than using antihistamine (level C recommendation) (25, 29). All international guidelines from World Allergy Organization (WAO), American Academy of Allergy, Asthma and Immunology (AAAAI), and Euro-

pean Academy of Allergy and Clinical Immunology (EAACI) recommended antihistamines as adjunctive therapy to treat anaphylaxis and indicated that its action is inferior to epinephrine (8). However, our finding might be a matter of under-recognition when anaphylaxis encountered for the first time in these patients and followed by proper management once recognized by physicians and this is supported by having EAI dispensed for 499 patients with anaphylaxis (87.0%) (Figure.5).This finding reflects the need to educate and train physicians regarding the recognition and treatment of anaphylaxis.

5.6 Compliance toward Dispensed EAIs for Anaphylaxis Therapy

Having dispensed EAIs as first aid measure to manage accidental exposure to anaphylaxis triggers is important and critical for long-term management plan of anaphylaxis. In our study, we found that EAIs dispensed for 499 patients (75.7%) with anaphylaxis, which is good clinical practice (Table 6). However, 72 patients (10.5%) had no dispensed EAIs (Table 6). This finding is crucial, and requires attention from clinicians in Qatar since it indicates that these 72 patients (10.5%) left unprotected. Moreover, in our patients' cohort, 92.5% of anaphylactic events occurred in community setting, and 233 patients (33.0 %) had recurrent anaphylactic episodes, which indicates that the probability to have anaphylaxis in community setting is high. (Table 3). Interestingly, only 19.2% of patients made actual use of the EAIs (Table 5). Such low compliance of EAIs reported in different regions of the world. A UK prospective questionnaire study stated that out of 245 patients with anaphylaxis, only 41 patients (17%) used EAIs (131). The rest 204 patients (83.0%) did not use it although they suffered from potentially life-threatening symptoms of anaphylaxis (131). This was due to various reasons: 54.4% thought it was unnecessary, 7.8%

waited for ambulance arrival, 5.4% had no EAI device at the anaphylaxis episode time, 2.5% were too scared to use it, 2.5% were not trained or had an expired one (131). Similar low compliance to EAIs reported among Victorian governmental schools in Australia where the annual usage rate of EAIs activated per 1000 school students at risk of anaphylaxis ranged from 6 to 8 per year (132). Such low compliance might reflect either the failure to use these devices when needed or the successful strict risk minimization plans within the school settings (132). In our study, we were not able to figure out whether the EAIs are underutilized or it is a matter of under-reporting of EAIs usage by the physicians. Further studies are urgently needed to assure justifiable reasons for such low compliance in Qatar and to determine the cost-effectiveness of EAIs dispense against its usage in the community to protect patients' lives.

CHAPTER 6: CONCLUSION

In this study, we reviewed 1068 electronic medical records to assess EAIs as a clinical indicator of anaphylaxis; shedding light on anaphylaxis triggers, co-morbidity factors, symptoms and patients' clinical outcomes in Qatar for a period of four years (2012 -2016). We quantified 574 patients with anaphylaxis and found that EAIs dispense is a highly sensitive method to estimate anaphylaxis, but its relatively low specificity means that it will be falsely positive for some patients who actually had no anaphylaxis. Therefore, as a clinical indicator, it should be used with care to avoid overestimation of anaphylaxis.

Nuts and black ants were the most common trigger of anaphylaxis in Qatar. Atopic disorders such as asthma, atopic dermatitis and allergic rhinitis were the common comorbidity factors. Our study showed that 143 patients with anaphylaxis were treated with drugs other than epinephrine as first line of intervention, which highlighted a critical gap of anaphylaxis management in Qatar. The current study can be used as a clinical guide for allergy clinics and serves as a baseline to assess future trends of anaphylaxis in Qatar.

6.1 Strengths and limitation

A key strength of this study is that Hamad General Hospital, a member of Hamad Medical Corporation, is the only medical facility that dispenses epinephrine auto-injector in Qatar. Therefore, using dispensed epinephrine auto-injector records of "*outpatients"* in combination with medical coding system (ICD-10AM) of anaphylaxis of "*inpatients"* reflected the frequency of anaphylaxis overall Qatar.

We sought to obtain EAI dispense from pharmacy department for the same period of ICD-10 codes of anaphylaxis for inpatients (2012 – 2016). However, it was not possible to pull out patient identification numbers from HGH outpatient pharmacy for the same period because limitations of the software itself. In addition, Cerner software was not alive for HGH pharmacists before 2016. Therefore, dispensed EAIs records from HGH outpatient pharmacy was available for one year only (January – December 2016). However, using "*Cerner power chart*" to review the EMRs of the one year pulled list included data of EAIs dispense of previous years since EAIs are "refill drugs" and the eldest EAIs dispense in the EMRs of this subset dated in 2007.

Limitations of this study owing to its retrospective nature and the possibility of misreporting and underreporting of cases. Therefore, our reported results should be carefully interpreted "***within the boundary of available data***" in the electronic medical records of Cerner system.

6.2 Recommendation for Future Studies

We believe that changing the direction of anaphylaxis studies from the health care setting to the community setting will provide better care of anaphylaxis cases for two reasons. First, the majority of anaphylaxis episodes occur in the community. Second, compliance to international guidelines is not optimum in clinical setting; therefore, the sensitivity of any selected research tools to identify patients with anaphylaxis will be affected.

We suggest establishing a national registry system of atopic disorders, especially asthma and anaphylaxis in parallel with ethnicity and geographical areas to monitor the trend of these diseases in Qatar, and to carry out genetic and molecular studies to understand and differentiate the genetic makeup of our population in relation to other ethnic groups. Such understanding may enhance the implantation of personalized medicine in future and improve the quality of life of those patients. Having children less than ten years being the majority affected patients by these disorders worth such effort.

An exciting area of research would be studying the antigenicity of black ant toxins in Qatar, identifying the black ant species that induce anaphylaxis correctly and developing customized immunotherapies to the patients in Qatar. Such research would require integration of knowledge from different disciplines of research, including, chemistry, entomology, bio-ecology, pharmacology and medicine.

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