Chapter 1
General introduction and outline of the thesis

Jacqueline Saleh-Langenberg
INTRODUCTION

Hey, would you like to have some?” your friend asks as she offers you a mouthwatering homemade brownie. You are tempted by the delicious dessert, but then you see the crushed nuts on top. Darn! You are allergic to nuts. Mmm, maybe just one little tiny bite? ……Nope!

Imagine what life would be like if you had to constantly check out the ingredients in your foods to make sure your life was not in danger after eating even a tiny bit. For children and adolescents with food allergies, that is their way of life.

FOOD ALLERGY: DEFINITION, CLINICAL MANIFESTATION, PREVALENCE AND DIAGNOSIS

Definition and clinical manifestations
A food is defined as any substance—whether processed, semi-processed, or raw—that is intended for human consumption, and includes drinks, chewing gum, food additives, and dietary supplements.\(^1\) Although any food may cause a reaction, relatively few foods are responsible for the majority of food allergic reactions: cow’s milk, hen’s egg, peanut, tree nuts, (shell) fish, soy, celery, sesame seeds and wheat.\(^1\) Allergies for cow’s milk, hen’s egg, and peanut are the most common in children.\(^1\)

Food allergy is defined as an adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food.\(^1\) The term food allergy refers to a reaction to food that is initiated by immunological mechanisms and is most commonly IgE-mediated.

IgE-mediated food allergies cause a wide spectrum of clinical signs and symptoms. Food allergic reactions can cause oral allergy syndrome (e.g. local itching and/or mild swelling of lips, tongue, palate, throat, ears), rhino conjunctivitis (e.g. sneezing, blocked or running nose, itching and watering eyes), skin symptoms (e.g. worsening eczema, exanthema, pruritis, angioedema, urticaria), gastrointestinal symptoms (e.g. nausea, vomiting, abdominal pain, diarrhea), respiratory symptoms (e.g. asthmatic symptoms or laryngeal edema) or cardiovascular symptoms (e.g. dizziness, loss of consciousness, palpitations).\(^2\)

Prevalence of food allergy
Food allergy is a growing health issue in countries with a Western lifestyle. Food allergy affects about six to eight percent of children in the first year of life.\(^3\) Most children outgrow their sensitivity to certain foods, and approximately two to three per cent of the adult population still have food allergies.\(^3\)
It has been suggested that the prevalence of food allergy appears to have increased over the last decade. However, reliable population-based data are limited. Most studies have based their estimates only on patient perceptions of reactions to foods within the general population, showing prevalences of self-reported food allergy varying from three per cent to as high as thirty-five percent. A few studies have included double-blind, placebo-controlled food challenges (DBPCFCs), the gold standard to diagnose food allergy. These studies showed prevalences of approximately three per cent for all foods together. The prevalence of self-reported food allergy is higher than the prevalence of food allergy confirmed by DBPCFCs. This might be due to problems with determining the prevalence of food allergy, such as misclassification, biased participation, lack of simple diagnostic tests, rapid evolution of disease, large numbers of potential triggers, varied clinical phenotypes, or differences between populations. The prevalence of food allergy is also thought to be dependent on geographical differences (e.g. differences in dietary intake and eating habits) and demographic differences (e.g. age, sex, and ethnicity). With the prevalence increasing it is therefore important to improve food allergy awareness, to identify food allergic patients at high risk for anaphylaxis and to diagnose and to manage food allergy and anaphylaxis adequately.

**Diagnosis of food allergy**

The diagnosis of food allergy is primarily based on a detailed patient’s clinical history and can be supported by physical examination and diagnostic tests. Several diagnostic tests may be useful for the diagnosis of food allergy, including the skin prick test, intracutaneous or intradermal test, or determination of allergen-specific IgE (sIgE) test in serum. These tests detect sIgE to suspected food(s) and may assist in the identification of foods that may be the cause in specific cases of IgE-mediated food allergic reactions. However, although these tests can be used easily, are safe, quick and inexpensive, they cannot by themselves be considered to be diagnostic.

Another important diagnostic test is the oral food challenge. An oral food challenge can ascertain whether a clinical allergy is the result of ingesting a specific food. There are three different kinds of oral food challenges: (1) an open oral challenge (2) a single-blind oral challenge or (3) a double-blind, placebo-controlled challenge (DBPCFC). The gold standard to diagnose food allergy is a DBPCFC. An oral food challenge is always performed in a hospital setting under physician surveillance, with the possibility to administer emergency treatment. Although a DBPCFC is the gold standard, it is expensive, labor-intensive and can be time consuming for patients. However, it is an accurate and safe diagnostic test for food allergy, and, most importantly, undergoing a DBPCFC improves health-related quality of life (HRQL) of food allergic patients irrespective of the outcome of the test.
ANAPHYLAXIS: DEFINITION, CLINICAL MANIFESTATION, PREVALENCE AND DIAGNOSIS

Anaphylaxis
Fatal allergic reactions have been recognized for over 4000 years.20 Hieroglyphics suggest an anaphylactic death caused by a Hymenoptera sting.20 However, it was not until the last century that the syndrome of anaphylaxis was fully characterized. Anaphylaxis was first described in 1902 by Portier and Richet.21 In their classic studies they described the rapid death of several dogs that they were attempting to immunize against the toxic sting of the sea anemone. Since this reaction represented the opposite of their intended ‘prophylaxis’, they coined the term ‘anaphylaxis’, or ‘without or against protection’. From these studies, they concluded that anaphylaxis required a latent period for sensitization and re-exposure to the sensitizing material. Three years later, in 1905, Schlosser reported a patient who developed acute shock after the ingestion of cow’s milk.22 In 1969 Golbert et al. described ten cases of anaphylaxis following the ingestion of various foods.23 Thereafter, the reports by Yunginger et al., Sampson et al. and Bock et al. further characterized the natural course of near-fatal and fatal food-induced anaphylaxis.24-27

Definition and clinical manifestations
Anaphylaxis is defined as ‘a serious allergic reaction that is rapid in onset and may cause death’.28 Food is the most common elicitor of anaphylaxis in children and the second most common in adults.29,30 The proposed clinical diagnostic criteria for anaphylaxis are presented in Table 1.28 In brief, anaphylaxis is a probable diagnosis in the presence of symptoms from two or more organ systems after exposure to a likely allergenic food, or hypotension alone after exposure to a known allergenic food for that patient.

An anaphylactic reaction may be immediate and uniphasic, or may be delayed in onset, biphasic, or protracted. Biphasic anaphylaxis is defined as ‘a recurrence of symptoms that develops following the apparent resolution of the initial anaphylactic event not due to the given treatment’.31,32 Biphasic reactions have been reported to develop in 20% of food related anaphylactic reactions. These reactions typically occur within one to four hours following the resolution of the initial symptoms, although some cases have been reported up to 72 hours later.31 Protracted anaphylaxis is defined as ‘an anaphylactic reaction that lasts for hours or in extreme cases, for days’.31,33 These reactions may persist up to 32 hours after treatment.
Symptoms and signs of anaphylaxis can occur within minutes to hours after ingesting the culprit food. In a large case series of fatal anaphylaxis, the median time from the onset of symptoms to cardiac arrest was reported as 30 minutes for food allergy. Although nearly every organ system can be affected by an anaphylactic reaction, most effects involve the cutaneous, respiratory, cardiovascular, and gastrointestinal systems. Respiratory and cardiovascular symptoms or signs are potentially the most life-threatening features of anaphylaxis. Nausea and vomiting may also be associated with anaphylaxis.

**Diagnosis of anaphylaxis**

Anaphylaxis is a clinical diagnosis that is based on the criteria shown in Table 1. To date, there are no reliable tests to diagnose anaphylaxis. Retrospectively, the diagnosis may be supported if serum tryptase is elevated within a few hours after the reaction. This elevated serum tryptase level needs to be compared with the patient’s baseline levels. It is important to know that serum tryptase levels are often normal, especially in food-triggered reactions in children. A severity score can be helpful in the diagnosis and ensuring the timely administration of epinephrine (Table 2).
Table 2. Grading severity of anaphylaxis*

<table>
<thead>
<tr>
<th>Grade</th>
<th>Skin</th>
<th>GI tract</th>
<th>Respiratory</th>
<th>Cardiovascular</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Mild</td>
<td>Sudden itching of eyes and nose, generalized pruritus, flushing, urticaria, angioedema,</td>
<td>Oral pruritus, oral tingling, mild lip swelling, nausea or emesis, mild abdominal pain</td>
<td>Nasal congestion and/or sneezing, rhinorrhea, throat pruritis, throat tightness, mild wheezing</td>
<td>Tachycardia (increase &gt;15 beats/min)</td>
<td>Change in activity level plus anxiety</td>
</tr>
<tr>
<td>2. Moderate</td>
<td>Any of the above</td>
<td>Any of the above, crampy abdominal pain, diarrhoea, recurrent vomiting</td>
<td>Any of above, hoarseness, barking cough, difficulty swallowing, stridor, dyspnkea, moderate wheezing</td>
<td>As above</td>
<td>Light headedness feeling of impending doom</td>
</tr>
<tr>
<td>3. Severe</td>
<td>Any of the above</td>
<td>Any of the above loss of bowel control</td>
<td>Any of the above, cyanosis or Saturation &lt;92%, respiratory arrest</td>
<td>Hypotension** and/or collapse, dysrhythmia, severe bradycardia and/or cardiac arrest</td>
<td>Confusion, loss of consciousness</td>
</tr>
</tbody>
</table>

*The severity score should be based on the organ system most affected. Bold face symptoms and signs are mandatory indication for the use of adrenaline (epinephrine).36

** Hypotension defined as low systolic blood pressure (age-specific): 1 month–1 year <70 mm Hg; <1–10 years [70 mm Hg + (2 × age)]; <11–17 years 90 mm Hg or greater than 30% decrease in systolic blood after exposure to known allergen for that patient. Modified from Sampson.36

Risk and co-factors of anaphylaxis

Risk factors for anaphylaxis include individual patient related aspects and circumstances, and the severity of the reaction depends on a complex interplay between various factors.37-43

Epidemiological risk factors for a food-induced anaphylactic reaction are defined as (a) a previously severe anaphylactic reaction to a food requiring emergency treatment or hospitalization as a result, (b) asthma or asthmatic reactions to food, (c) adolescent or young adult age, (d) systemic reaction to traces of the food allergen, and (e) having a peanut or nut allergy.44 When the first factor is present or when at least two of the other risk factors are present in the context of suspected or proven food allergy, food allergic patients are considered high-risk patients, and candidates for an epinephrine auto-injector (EAI).2
Co-factors, also called augmenting factors, increase the risk of an allergic reaction occurring or its severity.² Co-factors are life style factors (alcohol and physical exercise); medication (NSAIDs, ACE inhibitors, β-blockers); patient specific factors (adolescence, infections, hormonal status, psychogenic stress); and pre-existing conditions (asthma and other IgE dependent diseases, cardiovascular diseases, mastocytosis and/or increased basal tryptase). Other factors that are known risk factors for fatal food-induced anaphylaxis are not recognizing an allergic reaction, delayed or no administration of epinephrine or inadequate use of an epinephrine auto-injector.³⁴,⁴⁵

**The prevalence of anaphylaxis**

Estimates of the actual prevalence of anaphylaxis are uncertain. For ethical reasons, it is not possible to conduct randomized, placebo-controlled trials in anaphylaxis. With anaphylaxis being a syndrome with variable symptoms, signs and time course, none of the definitions are ideal and impede accurate epidemiological study.⁴⁶ Comparisons of epidemiologic data are often complicated due to differences in anaphylaxis definitions, methodologies, and characteristics of the study population.⁴⁷ It has been reported that the life-time prevalence of anaphylaxis in Europe is 0.3% (95% CI 0.1-0.5).⁴⁷ Fatalities due to food-induced anaphylaxis are rare. Overall, the case fatality ratio from anaphylaxis is estimated at under 0.0001%.⁴⁷

**Acute management and long-term management of food allergy and anaphylaxis**

The care for patients with food allergies and anaphylaxis may be subdivided into acute, or emergency and long-term management. It is very difficult to predict the severity of an allergic reaction and, in fatal reactions, death may occur within minutes of onset. Therefore effective, acute management is important. However, long-term management is also important which provides the best quality of life for the food allergic patients.

**Acute management**

The first step in the acute management of food-induced anaphylaxis is the intramuscular injection of epinephrine.⁴¹,⁴⁸-⁵⁰ The initial treatment should include a rapid assessment to determine the extent and severity of the allergic reaction, the adequacy of oxygenation, cardiac output and tissue perfusion, any potential confounding medications, co-existing diseases and the suspected cause of the reaction.⁴⁸-⁵⁰ The patient should be placed in the supine position with the legs elevated, if tolerated, to help maintain adequate perfusion and blood pressure. Initial therapy should be directed at the maintenance of an effective airway and circulatory system.⁴⁸-⁵⁰
**Epinephrine and epinephrine auto-injectors**

Epinephrine is the medication of choice in the emergency treatment of anaphylaxis in the community.\(^{49,51}\) Epinephrine is a natural body constituent, comprising approximately 80% of the catecholamines in the human adrenal medulla.\(^{48}\) During sudden frightening or life-threatening situations, endogenous epinephrine is released from this site and exerts its action via sympathomimetically innervated structures all over the body.\(^{48}\) Heart rate accelerates and the force of cardiac contractions increases. Blood pressure rises. Blood flow is redistributed from the skin and subcutaneous tissue to the skeletal muscles, splanchnic circulation, and brain.\(^{48}\) The bronchi and pupils dilate.\(^{48}\) Oxygenation increases, blood glucose rises, and the body is prepared for ‘fight or flight’\(^{48}\).

For food allergic patients at high risk of anaphylaxis in the community, epinephrine should be prescribed in the form of an auto-injector.\(^{52}\) Intramuscular epinephrine should be given at a dose of 0.01 mg/kg of body weight to a maximum total dose of 0.5 mg for a large adult and 0.3 mg for most adults and older children.\(^{48}\) This is based on tradition and clinical consensus rather than on randomized controlled trials.\(^{48}\) After using an EAI the patient should be transported to a hospital as soon as possible for further anaphylaxis treatment. The time during which children are observed following an (severe) allergic reaction varies in clinical practice. Recommendations vary from between two to twenty-four hours.\(^{28,32,53-56}\)

Bronchodilators such as albuterol (salbutamol) and other medications, including antihistamines, or oral corticosteroids, although useful adjuncts in the treatment of anaphylaxis, but are not a substitute for epinephrine.\(^{41,49}\) On the basis of clinical consensus, the epinephrine dose can be repeated every five to fifteen minutes, as needed.\(^{41,48,49}\)

**Available epinephrine auto-injectors**

EAIIs are not in every country available to food allergic patients.\(^{57}\) An EAI is a single use, disposable, prefilled automatic injection device (auto-injector) with a fixed dose of epinephrine. There are several auto-injectors: EpiPen\(^\text{®}\), Jext\(^\text{®}\), Emerade\(^\text{®}\), Anapen\(^\text{®}\), Intelliject\(^\text{®}\), Twinject\(^\text{®}\), Adrenaclick\(^\text{®}\), and Auvi-Q\(^\text{®}\). This thesis will focus on EAIIs available in the Netherlands: EpiPen\(^\text{®}\), Jext\(^\text{®}\), and Emerade\(^\text{®}\). Anapen\(^\text{®}\) was previously available in the Netherlands, but not after June 2012.\(^{58}\) Intelliject\(^\text{®}\), Twinject\(^\text{®}\), Adrenaclick\(^\text{®}\), and Auvi-Q\(^\text{®}\) are not available in the Netherlands. EAIIs differ significantly with regard to size, ease of carrying, ease of use, needle protection, and robustness.\(^{39}\) They are not inter-changeable.\(^{59}\) Descriptive characteristics of available EAIIs in the Netherlands are shown in Table 3.

In the Netherlands there are different fixed epinephrine doses available (0.15 mg, 0.30 mg and 0.50 mg). Food allergic children between 7.5 kg and 25 kg of weight should be prescribed an EAI containing 0.15 mg epinephrine.\(^{41}\) Food allergic children and adolescents over 25 kg of weight should be prescribed an EAI containing 0.30 mg of
There is no fixed epinephrine dose available for food allergic infants and children <7.5 kg. Currently, health care providers must choose between two alternatives for these children at risk for anaphylaxis: prescribing a user-friendly EAI (0.15 mg) and potentially overdosing the food allergic infants and children of <7.5 kg, or prescribing an epinephrine ampule along with a sterile syringe/needle and instructions. Although for the first-aid treatment of anaphylaxis in food allergic infants and children of <7.5 kg, the goals of precise epinephrine dosing of 0.01 mg/kg is preferable, Simons et al. demonstrated that many of the parents felt uncomfortable using an epinephrine ampule along with a sterile syringe/needle. Prescribing an EAI (0.15 mg) for use in food allergic infants and children of <7.5 kg, the threefold epinephrine overdose to those weighing approximately 5 kg and a twofold epinephrine overdose to those weighing approximately 7.5 kg appears to be a preferable alternative to the epinephrine ampule/syringe/needle technique. An EAI for this age group or additional premeasured or pharmacy preset sterile epinephrine doses of 0.05 mg and 0.1 mg in user-friendly formulations are urgently needed. All devices are also produced as training devices. These are needleless replicas of the actual devices that patients can use to practice using the device with a trainer.

The design of currently available EAI has not changed significantly in the last decade. A previous study showed that treatment failures and unintentional needle-stick injuries have been reported which may be attributed to EAI design. However, unintentional needle-stick injuries may decrease as EAI with improved design, including a needle protection feature, are being introduced. Several new devices and alternative delivery systems have been developed. The new devices of EpiPen®, Jext® and Emerade® available in the Netherlands.

### Table 3. Characteristics of epinephrine auto-injectors available in the Netherlands

<table>
<thead>
<tr>
<th>EAI</th>
<th>EpiPen®</th>
<th>Jext®</th>
<th>Emerade®</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Doses (mg)</strong></td>
<td>0.15; 0.30</td>
<td>0.15; 0.30</td>
<td>0.15; 0.30; 0.50</td>
</tr>
<tr>
<td><strong>Excipients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>1.8mg; 1.8mg</td>
<td>Present; mg n/a*</td>
<td>Present; mg n/a*</td>
</tr>
<tr>
<td>Sodium metabisulfite (E223)</td>
<td>0.5mg; 0.5mg</td>
<td>Persent; mg n/a*</td>
<td>Present; mg n/a*</td>
</tr>
<tr>
<td>Other</td>
<td>Hydrochloric acid, water</td>
<td>Hydrochloric acid, water</td>
<td>Disodium edetate, hydrochloric acid</td>
</tr>
<tr>
<td><strong>Exposed needle length (mm)</strong></td>
<td>12.7; 15.02</td>
<td>13; 15</td>
<td>16; 23; 23</td>
</tr>
<tr>
<td><strong>Needle gauge (G)</strong></td>
<td>22</td>
<td>22</td>
<td>n/a</td>
</tr>
<tr>
<td><strong>Needle protection</strong></td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td><strong>Length (cm)</strong></td>
<td>±15.6</td>
<td>±19.5</td>
<td>±22.0</td>
</tr>
<tr>
<td><strong>Shelf-life (months)</strong></td>
<td>18</td>
<td>18</td>
<td>30</td>
</tr>
<tr>
<td><strong>No. of doses per auto-injector</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>Manufacturer/Distributor</strong></td>
<td>Meda-Pharma</td>
<td>ALK-Abelló</td>
<td>Bausch&amp;Lomb</td>
</tr>
</tbody>
</table>

*n/a: information not available*
Netherlands have needle guards following use to protect against needle stick injury. Patients not carrying their EAI at all times may also be due to its design and/or inadequate training. Patients reported that an EAI is difficult to carry and impractical because of its size. To date no studies seem to have been undertaken to evaluate EAI’s together with patients.

**When to use an EAI: mild, moderate and/or severe allergic symptoms**

Food allergic patients are instructed to use their epinephrine auto-injectors if they have signs of an allergic reaction. However to recognize the start of an allergic reaction and to distinguish between mild, moderate or severe allergic symptoms can be quite difficult for a patient or their parent(s)/caregiver(s). There are different recommendations given by health-care professionals and manufacturers of EAI’s as to when an EAI should be administered. Administering an EAI after a patient has ingested the culprit food but is not yet experiencing allergic symptoms is unlikely to be necessary. In our center we advise food allergic patients to administer their EAI for any (reasonably definite) allergic symptoms in the context of being reasonably sure of possibly having accidentally ingested the culprit food, and we stress to call the emergency number immediately after such administration. It has been proposed that the use of an EAI for initial, mild allergic symptoms may lead to overtreatment of an allergic reaction, and possible subsequent unavailability of a second dose for the event that symptoms worsen. However, the progress after the onset of an allergic reaction is uncertain. Previous studies on fatalities caused by anaphylactic reactions to food suggest that there is only a brief window of time during which the first dose of epinephrine is effective. Early administration of an EAI may therefore be justified.

**Possible side-effects of epinephrine and EAI use**

There are no absolute contra-indications to treatment with epinephrine in a patient experiencing anaphylaxis. Side-effects of epinephrine in general are associated with the α- and β-receptor activity of epinephrine. Transient pharmacologic effects of epinephrine, such as pallor, tremor, anxiety, palpitations, headache, and dizziness, that occur within five to ten minutes after injection are usually mild and confirm that a therapeutic epinephrine dose has been given. Serious adverse effects are rare with intramuscular use. The majority of serious adverse effects occur when epinephrine is given intravenously or incorrectly dosed, which is unlikely to happen when using an autoinjector with a single fixed dose of epinephrine. When epinephrine is given intravenously, this should be done by experienced health-care professionals, and should be monitored with continuous cardiac monitoring, pulse oximetry and frequent non-invasive blood pressures. EAI’s contain sodium metabisulphite, which may rarely cause severe hypersensitivity reactions. There is also the risk of accidentally injecting epinephrine into a digit.
Figure 2. Pictures of available epinephrine auto-injectors in the Netherlands

1. Epipen®

2. Jext®

3. Emerade®
(Under)prescription of EAIs

All food allergic patients at high risk for anaphylaxis should carry an EAI at all times. However, previous studies have shown that many high-risk food allergic patients do not have an epinephrine auto-injector (EAI). A previous study by Flokstra-de Blok et al. showed that there is an alarming under-prescription of EAIs in high-risk food allergic adolescents (11-20 years) in Dutch high schools. Less than 1 in 30 of these adolescents had actually been prescribed an EAI. This study highlights the shortcoming to effective management of anaphylaxis in adolescents in the Netherlands. Fatality studies also show that some patients dying from anaphylaxis had unfortunately not been prescribed an EAI. It might be possible that these patients did not visit a health-care professional.

To identify patients who are at high risk for anaphylaxis and to assess the need for an EAI is important. A risk factor assessment based on the guidelines of the European Academy of Allergy and Clinical Immunology (EAACI) can be used for any patient who experienced allergic symptoms due to food.

In the Netherlands general practitioners (GPs) play an important role in diagnosing, treating food allergic patients and prescribing EAIs. However, primary care guidelines in the Netherlands, the NHG (Nederlandse Huisartsen Genootschap) guidelines, recommend that an EAI should only be prescribed to patients after a previous anaphylaxis. Significantly, risk factors for a life-threatening food-induced anaphylactic reaction are mentioned, but are not put forward as a reason to prescribe an EAI in the absence of a previous anaphylactic reaction.

Previous studies also show that GPs are not always knowledgeable about food allergic patients at high risk for anaphylaxis. These studies show that there is a lack of allergy knowledge in primary care, especially the recognition and treatment of anaphylaxis are problematic and that national guidelines are often not followed. Therefore, the prescription of EAIs is an important issue and there is a need for improvement of the quality of care for high-risk food allergic patients in primary care. The incomplete data might be due to under-reporting of patients (or their parents), under-documentation of clinical information by GPs or lack of knowledge and/or practice behavior gaps experienced by GPs.

How many EAIs to prescribe?

There is no consensus among experts about how many EAIs to prescribe for each food allergic patient. There is data about absolute indications for a prescription of an EAI, however there is no high quality data to help decide how many EAIs should be available to individual patients. Previous studies showed that the percentage of patients who required a second dose of epinephrine after having used an EAI to treat allergic symptoms varied between zero to 32%. A decision to prescribe one, two or more devices is influenced by a number of factors. Some authorities advise that patients should have...
one EAI at each site that they regularly attend (e.g. kindergarten, school, work). Others advise there should be two EAs at each location, in case one is defective or misfires, or a second injection is needed before emergency help arrives. This would be particularly important if the patient is going to a remote location where prompt medical attention is unavailable. There may be practical, psychological or policy considerations as to why an individual patient needs more than one EAI. However, prescribing more than one EAI may negatively influence compliance and burden of treatment.

It is important is to identify the patients who need to have access to more than one EAI. The EAACI has suggested indications for prescription of a second EAs, namely (1) co-existing unstable or moderate to severe, persistent asthma and a food allergy, (2) co-existing mast cell diseases and/or elevated baseline tryptase concentration, (3) lack of rapid access to medical assistance to manage an episode of anaphylaxis due to geographical or language barriers, (4) previous requirement for more than one dose of epinephrine prior to reaching hospital, (5) previous near fatal anaphylaxis, (6) if available EAI dose is much too low for body weight.

**Compliance and burden of treatment of EAs**
A number of studies show that food allergic patients, adolescents in particular, are often poorly compliant and do not always carry their EAI. The reluctance to carry an EAI may be the result of the perception of patients that such treatment is burdensome. It has been previously shown that the burden of treatment (BoT) of an EAI in vespid allergic patients is high. Additionally, regularly replacing devices, the need to educate about how and when to use an EAI, the potential stigma associated with requiring an EAI as well as the cost of devices might contribute to being poorly compliant and the burden of treatment.

**Non-use of EAs**
EAs are underused by patients for a variety of reasons. In some countries, EAs are not available or not prescribed when indicated, or they are not affordable. Another reason is that many patients do not have their EAs with them at the time of accidental ingestion of the allergic food. In adolescents, this may be caused by problems occurring at the time of the transfer of responsibility for managing their food allergy from parents to themselves. Other reasons of non-use may be that patients do not think that their allergic reaction is severe enough to use an EAI, anxiety, use of other medication, peer pressure, feeling ashamed, or practical problems.
**How to use an EAI?**
Several studies showed that a significant proportion of patients and their parents (or other caregivers), and even health-care professionals, do not know how to correctly use an EAI. Anaphylaxis usually occurs in the community, and therefore, all food allergic patients at risk for anaphylactic reactions as well as their parents (and other caregivers) should be provided with educational resources. Training should cover avoidance strategies, recognition of symptoms, and when and how to administer an EAI. Health-care professionals prescribing and/or dispensing an EAI should provide such training, although it has been shown that failure to provide this is commonplace.

**Long-term management**
The only way to avoid an allergic reaction is to avoid the food(s) that cause the allergic reaction. However, accidental ingestion is common and can cause a severe allergic reaction, and because of the life-threatening nature of anaphylaxis the cornerstone of therapy is prevention. Consequently, an accurate diagnosis is very important in order to identify which foods should be avoided, and it is also important to identify risk- and co-factors for the individual patient. It is also of importance to provide food allergic patients and their families with comprehensive information on food allergen avoidance, and prompt recognition and management of allergic reactions in order to manage his or her food allergy.

**Quality of life in food allergy and anaphylaxis**

**Impact of food allergy and having to carry an EAI on quality of life**
Food allergy and anaphylaxis carries with it the additional psychological burden of daily dietary restriction in a variety of settings (e.g. home, restaurants, schools, social gatherings) and having to carry an EAI at all times. Usually, food allergic children do not have objective allergic symptoms until exposed to the allergenic food, and this may cause confusion and misunderstanding in people in the child’s environment about the severity or occasionally even the existence of the child’s allergy.

Also, food allergic children, especially adolescents, have the desire to be ‘normal’ and are afraid of the embarrassment encountered in certain social situations when having an allergic reaction. The burden of avoidance and fear of an accidental exposure, and having to carry an EAI at all times are all associated with poorer quality of life (QoL).

QoL is a broad concept and the term is used to denote the general well-being of individuals. QoL means different things to different people in different cultures, and many definitions of this concept have been proposed. The World Health Organization (WHO) has defined quality of life as ‘the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations,
The component of overall quality of life that pertains to an individual's health is called health-related quality of life (HRQL) and is defined by the WHO as 'a state of complete physical, mental, and social well-being and not merely the absence of disease and infirmity.'

**Food allergy health-related quality of life measures**

QoL can be measured with generic or disease-specific questionnaires. Generic QoL questionnaires are useful for evaluating and comparing different diseases, and they are also sensitive to co-morbidities. The limitations of generic QoL questionnaires are that they are less sensitive and responsive to change than disease-specific instruments. Hence potentially important differences or changes may be missed. This is particularly relevant in the context of food allergy, where, unless individuals are exposed to the allergenic food, they may have no symptoms or problems other than the direct and indirect psychological effects resulting from the need for the constant vigilance of continued avoidance. Disease-specific questionnaires have been developed for this purpose, and are therefore significantly more sensitive and are able to detect small but potentially (clinically) important differences. The previously mentioned disease-specific questionnaires are significantly more sensitive in measuring the response to interventions or future treatments as well as estimating the general burden of food allergy.

The development and validation of disease-specific HRQL measures applicable to all age groups and parents and/or caregivers has provided important means of assessing the global impact of food allergy on patients and families' lives. There are several *Food Allergy Quality of Life Questionnaires* (FAQLQs) currently validated and used for research and clinical evaluation (Table 4).

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Target population</th>
<th>Respondent</th>
<th>Developed in</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAQLQ-adult form (AF)</td>
<td>adults (≥18 years)</td>
<td>patient</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>FAQLQ-teenager form (TF)</td>
<td>adolescents (13-17 years)</td>
<td>patient</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>FAQLQ-child form (CF)</td>
<td>children (8-12 years)</td>
<td>patient</td>
<td>The Netherlands</td>
</tr>
<tr>
<td>FAQLQ-parent form (PF)</td>
<td>children (0-12 years)</td>
<td>parent/caregiver</td>
<td>Ireland</td>
</tr>
<tr>
<td>FAQLQ-parent form teenager (PFT)</td>
<td>adolescents (13-17 years)</td>
<td>parent/caregiver</td>
<td>United Kingdom</td>
</tr>
</tbody>
</table>
These instruments were developed as part of the Europrevall project, a multi-center research study on food allergy. One of the aims of the Europrevall was to investigate the impact of food allergy on HRQL of patients throughout Europe. The FAQLQs were originally developed and validated in the Netherlands, Ireland and United Kingdom. The translation of FAQLQs was performed using established methods. The FAQLQs are now available in multiple languages. Other disease-specific instruments have been developed and validated in the United Kingdom for children and adolescents: You and Your Food Allergy and Paediatric Food Allergy Quality of Life Questionnaire (PFA-QL).
Aims of the thesis

The three major aims of this thesis are to investigate the reasons for the under-prescription of auto-injectors in food allergic patients at high risk for anaphylaxis, and the reasons for non-compliance and non-use of epinephrine auto-injectors by this group of patients. The first part of this thesis describes the prevalence of food allergy and under-prescription of epinephrine auto-injectors. The second part of this thesis describes the reasons for non-compliance, the burden of treatment with having to carry an EAI at all times and the impact of food allergy, anaphylaxis and carrying an EAI at all times on the health-related quality of life in food allergic patients. The third part of this thesis describes the reasons for non-use of an EAI in case of (severe) allergic reactions. This part also describes late reactions after double-blind, placebo-controlled food challenges.

Outline of the thesis

Part I. Prevalence of food allergy and under-prescription epinephrine auto-injectors

Chapter 2 estimates the prevalence of probable and self-perceived food allergy, EAI need and ownership in adolescents aged 11-20 in Dutch high schools. The results of this study are compared with the findings by Flokstra-de Blok et al. in 2009.

Chapter 3 describes and evaluates the practice in EAI prescriptions by general practitioners to food allergic patients in the Netherlands.

Part II. Non-compliance, burden of treatment and HRQL

Chapter 4 determines the burden of treatment (BoT) of an EAI and examines the relationship between this burden and compliance. It also analyzes which factors contribute to the BoT of the EAI as perceived by food allergic adolescents and their parents.

Chapter 5 investigates which factors predict health-related quality of life in food allergic patients. The influence of participant characteristics, experiencing anaphylaxis and being prescribed an EAI were investigated in this context.

Part III. Non-use

Chapter 6 investigates the knowledge, attitudes, and beliefs regarding food allergy and anaphylaxis among pharmacists in the Netherlands. It also investigates how accurately pharmacists demonstrate how and when to use an EAI to patients.

Chapter 7 determines the prevalence, severity and clinical characteristics of late reactions in food allergic children and adolescents after DBPCFC, and ascertains which factors are associated with and may predict late reactions.
Finally, Chapter 8 is a general discussion of the findings presented in this thesis and some future perspectives concerning food allergy, anaphylaxis and epinephrine auto-injectors.

In Chapter 9 the findings are summarized in English, Dutch, and Mandarin-Chinese.
REFERENCES


General introduction and outline of the thesis


General introduction and outline of the thesis


Part I

Prevalence of food allergy and under-prescription of epinephrine auto-injectors

Chapter 2
The prevalence of food allergy and epinephrine auto-injectors in Dutch food-allergic adolescents

Chapter 3
Epinephrine auto-injector prescriptions to food-allergic patients in primary care in the Netherlands