The Development of Hypersensitivity Reactions in the Pediatric Population: A Review

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Abstract

Over the past several years, pediatric allergies have come to the forefront of many studies. Reports of immune-mediated hypersensitivity in younger patients have grown and led to an interest researching the causes of pediatric hypersensitivities. There are various risk factors that have been discussed that may lead to the development of allergies including genetic inheritance, genetic mutation, and environmental sensitization. It is important for all of these factors to be discussed in relation to the function of the immune system and its role in hypersensitivity reactions. If the causes of hypersensitivity reactions could be further studied and understood, treatments might be developed to reduce or eliminate these hypersensitivity reactions in younger pediatric populations. Much research has been done regarding the risk factors for pediatric hypersensitivity reactions and many recommendations have been made to combat this growing phenomenon. It is important to review the mechanisms of hypersensitivity reactions, the risk factors for developing them, and to research the incidences of pediatric hypersensitivity reactions and the recommended interventions for future diagnosis and treatment of hypersensitivity reactions in the pediatric population.

Keywords: Immune-mediated hypersensitivity reactions, pediatrics

Introduction

The mechanism behind hypersensitivity reactions lie in the immune system. The immune system is a fascinating and complicated organization of cells and organs that are designed to protect the body from foreign invading organisms that are potentially harmful (McKinley, O'Loughlin, & Bidle, 2016). Hypersensitivity reactions occur when the immune system overreacts to foreign organisms that present with specific antigens. This can cause a wide variety of negative effects from urticaria to angioedema and anaphylaxis. This occurs through a complex pathway mediated by the immunoglobulin E (IgE). When mast cells with the IgE surface antigen encounter an allergen or the triggering antigen, histamine is released from the mast cell causing a widespread reaction in the body. The smaller pathways that occur within this immunological response pathway are complex and intricate, and variations in these pathways can alter the type of allergic response displayed (Borzova & Grattan, 2013, pp. 506-521). It is important to study the details of these pathways so that a proper understanding might be reached and appropriate diagnosis and treatment recommendations might be made. Early diagnosis of allergic reaction is necessary because allergic reactions are so prevalent. A study done in 2006 revealed that 7.7% of children were diagnosed with a food hypersensitivity by the time they were three years old (Carina, Brett, Grundy, Clayton, & Roberts, 2006). Since that time, the incidence of allergies has only risen (Hockenberry, Wilson, & Rodgers, 2017). Hypersensitivity to food is not the only issue. Hypersensitivity reactions to drugs have also been noted to be on the rise, and identifying the allergies and treating them is imperative, especially in the healthcare setting (Ariza, Fernandez, Mayorga, Blanca, &

Torres, 2013). Because so much research is being done in the field, it is essential for those looking to work in pediatrics to understand the pathophysiology behind hypersensitivity reactions and the rationales behind current diagnostics and treatments.

The current literature is pointing to several factors leading to the development of hypersensitivity reactions in pediatric patients. Pediatric patients for this paper will be defined from birth to 21 years old. The foremost factor being researched is the role of genetics in the development of allergies. Alterations in the genetic code can lead to alterations in the immune response pathways thus leading to overreactions to specific antigens. For instance, a recent study revealed that allergies to beta-lactam antibiotics are often related to alterations in the interleukin (IL) 4, IL-3, and the IL-4 receptor-alpha-chain within the IgE-mediated pathway (Ariza, Fernandez, Mayorg, Blanca, & Torres, 2013). Ariza et al. (2013) also reported that previous studies had found a relationship between the differences in the HLA-B 1502 and the HLA-B 5801 alleles and the risk of developing hypersensitivity reactions to anti-epileptic drugs. The research seems to be pointing to the fact that genetics do in fact play a role in determining hypersensitivity reactions. Because of the prevalence of allergies, much of the literature has focused on diagnosis, prevention, and treatment. Newer research and studies are now beginning to change recommendations as they are finding out that older recommendations are unsuccessful. In the Longo et al. study (2013), restricting maternal diet during breastfeeding and then restricting the child's diet from allergenic foods failed to reduce the prevalence of hypersensitivity reactions, but rather led to an increase in these hypersensitivity reactions (Longo, Berti, Burks, Krauss, & Barbi, 2013). In recent years,

due to recommendations from healthcare providers and researchers, more studies have been done to research the risk factors for development, the genetic impact on hypersensitivity reactions, strategies for prevention, the necessity of early diagnosis, and the different types of treatment.

It is important to understand the basic function and workings of the immune system so that the precise pathways by which hypersensitivity reactions occur might be comprehended. Understanding the IgE mediated pathways is essential for covering pediatric hypersensitivity reactions. This is essential because many of the genetic variations that have been studied with regards to hypersensitivity reactions are variations within the IgE pathway. It is important to understand how these function in the pediatric population, especially in infants. In the past, few studies have been done on these populations, but within recent years more research has been done. Recent studies have also shown that previous plans of prevention and treatment have not been as successful as hoped, and therefore further recommendations for prevention, diagnosis, treatment, and further research has been made. It is essential for pediatric healthcare providers to understand all of these factors and to be able to implement them in practice so that the best care can be provided to the pediatric population.

The Role of the Immune System in Hypersensitivity

Hypersensitivity reactions occur when the immune system identifies a particular protein as foreign to self and a potential danger. In food hypersensitivities, this happens when the immune cells within in the digestive tract identify a specific food protein as dangerous (Grosvenor and Smolin, 2015). According to the Gell and Coombs

Classification of allergic responses, allergic responses occur in four major ways. Type I allergic responses are governed through the IgE pathway. Type II is cytotoxic (Ariza, Fernandez, Mayorg, Blanca, & Torres, 2013). Cytotoxic reactions are mediated by IgG and IgM. This results in phagocytosis of the antigen and cellular injury (Moriber, 2014, pp. 329-360). Type III is the immunocomplex reaction (Ariza, Fernandez, Mayorg, Blanca, & Torres, 2013). Immunocomplex reactions are produced through the combinations of antigen-antibody immune complexes that form within the bloodstream. When these complexes embed themselves in the endothelium of the vasculature, systemic inflammatory response ensues (Moriber, 2014, pp. 329-360). Type IV is delayed type hypersensitivity (Ariza, Fernandez, Mayorg, Blanca, & Torres, 2013). Delayed type hypersensitivity is cell mediated and therefore is not immediate (Moriber, 2014, pp. 329-360).

The IgE-Mediated Pathway

Most immune responses to food allergens resulting in hypersensitivity are governed through the IgE-mediated pathway. There are several important cells within the immune system. B-cells are responsible for removing toxins and extracellular microbes and for developing memory to defend against future infections. B-cells also produce antibodies, which are also known as immunoglobulins. There are five different types of immunoglobulins: IgG, IgA, IgM, IgD, and IgE. Each of the immunoglobulins are responsible for producing a specific immune response. IgE is responsible for inflammation, allergic response, and fighting parasitic infections (Moriber, 2014, pp. 276-305). IgE production is promoted by interleukins, specifically IL-4 and IL-13

(Eisenstein, Sullivan, & Williams, 2011, pp. 769-754). Interleukins are types of cytokines. Cytokines are polypeptides that are produced by various cells that stimulate the function of immune and non-immune responses within the body (O'Shea, Gadina, & Siegel, 2013, pp. 108-135). IL-4 and IL-13 are produced by TH2 cells. TH2 cells are a specific type of CD4+ T helper cells. TH2 cells are essential for the acute hypersensitivity pathway as well as promoting the chronic and relapsing presentation of eosinophil chronic allergic inflammation (Eisenstein, Sullivan, & Williams, 2011, pp. 769-754). Normally, TH2 cells are inhibited by TH1 and Treg cells. TH1 and Treg cells are also CD4+ T helper cells. In IgE-mediated disorders, TH2 is inadequately regulated by TH1 and Treg cells and thereby the hypersensitivity reaction occurs. When IgE binds with an allergen and then comes in contact with the FcεRI high affinity receptor on mast cells and basophils, the mast cells and basophils release histamine which is the primary cause of immediate allergic symptoms (Bohle, 2013, pp. 543-549).

Anaphylaxis

Histamine is a vasoactive amine that causes increased capillary permeability, vasodilation, and bronchoconstriction (Delany, Baker, Bastardi, & O'Brien, 2017, pp. 738-785). The increased capillary permeability causes fluid leakage into the interstitial space leading to interstitial edema and decreased vascular volume. This massive systemic response is called anaphylaxis and must be treated rapidly to avoid deterioration into anaphylactic shock. The interstitial edema leads to laryngeal edema. Laryngeal edema combined with bronchoconstriction leads to respiratory distress. Rapid vasodilation leads to circulatory collapse that can lead to circulatory failure. Symptoms

include chest pain, dizziness, incontinence, pruritus, flushing, angioedema, urticaria, anxiety, wheezing, stridor, and swelling of the lips and tongue. These symptoms are generally the same regardless of the age of the patient (Seckel, 2017, pp. 1587-1608).

Class 1 and Class 2 Food Allergies

There are two types of food allergies mediated by IgE. Class 1, also known as primary, is a true food allergy that often arises in early childhood or infancy. This reaction results from the interaction of food proteins and the immune cells within the digestive track. This results in a variety of symptoms from symptoms specific to the gastrointestinal track to anaphylaxis and urticaria. Class 2, also known as secondary, describes the reactions that result from cross-sensitivity to respiratory allergens. This type of reaction mostly occurs in the adolescent and adult population, and thus will not be discussed. Allergens that cause primary reactions pass through the stomach without being broken down by pepsin and hydrochloric acid. Once in the intestines, the food proteins come in contact with the gut-associated lymphoid tissue (GALT). GALT is responsible for distinguishing between normal GI flora, harmless food proteins, and pathogens. M cells are responsible for transporting the antigens and presenting them to the lymphoid tissue for discrimination. Some antigens come in direct contact with dendritic cells without being transported by M cells. Some antigens cross into the lymphoid tissue without any transportation assistance. Once the antigen presenting cell (APC) comes in contact with the antigen, it brings it to the appropriate T-cell for determination. Any disorder involving the determination of the particular T-cells can

lead to an immediate immune response leading to hypersensitivity reactions (Bohle,

2013, pp. 543-549).

When the T-cells appropriately recognize food proteins as harmless the inhibition

of further immune response is called oral tolerance. There are several theories regarding

the development of oral tolerance or lack thereof relating to genetic factors, gut epithelial

barrier integrity, and the degree of concurrent local immune activation. Primary food

allergy occurs when oral tolerance fails to develop and a hypersensitivity reaction occurs.

Because there are so many factors within the pathway through which food proteins are

presented to the T-cells within the GALT, it is very difficult to determine exactly why

food allergies develop. Oral tolerance can only develop when immune homeostasis has

been achieved. Immune homeostasis can only develop during specific windows of

opportunity during the coordination of innate and adaptive immunity through APC

orchestration with microbial products and dietary constituents (Bohle, 2013, pp. 543-

549).

Genetic Risk Factors

There is some evidence that shows that the development of hypersensitivity

reactions could be related to various genetic risk factors. According to *The Health

Professional's Guide to Food Allergies and Intolerances,* children can inherit allergic

reactions from their parents. This inheritance, however, is not an inheritance of a specific

allergy, but rather an inheritance of the potential to develop an allergy through the

abnormal function of TH2 cells (Joneja, 2013). Pregnant mothers pass on

immunoglobulins to their babies through the placenta and through breastmilk (Davidson,

London, & Ladewig, 2016). Most of the time, these immunoglobulins that are passed on

are IgG1 and IgG3. Mothers who already have a hypersensitivity reaction pass on IgE

and IgG4. IgG4 is not able to pass the placenta, and thus the baby developing in the

womb receives a high concentration of IgE. This may lead to an increased change of

development of a hypersensitivity reaction (Joneja, 2013).

Some children may also have a genetic predisposition to developing

hypersensitivity reactions not through their parents, but rather through chromosomal

anomalies. In a 2013 study, several children were tested for IL-17 production from

CD4+ T cells. This test was conducted both in vivo and ex vivo. In both scenarios,

children who were later diagnosed with a food hypersensitivity reaction were found to

have decreased levels of IL-17. IL-17 is important for the repression of TH2 cytokines

and the TH2-recruiting chemokine production (Dhuban, D'hennezel, Ben-shoshan,

Mccusker, Clarke, et al. 2013). As shown above, abnormal TH2 function leads to over-

reaction of the IgE-mediated pathway thus causing the systemic hypersensitivity

response. Thus, decreased production of IL-17 can predispose a patient to the

development of a food allergy.

There is currently much research being conducted on the relationship between

different types of HLA (human leukocyte antigen) and the development of

hypersensitivity reactions. While not enough research has been done to link specific

types of HLA with different allergens, it has been shown that all ethnic groups who have

variations on the HLA-B*1502 and HLA-B*5801 alleles have an increased risk of

developing hypersensitivity reactions to antiepileptic drugs like carbamazepine or

allopurinol (Ariza, Fernandez, Mayorg, Blanca, & Torres, 2013).

Prevalence

The prevalence of hypersensitivity reactions can be difficult to identify because

there is such a wide variety of types and timings of the reactions (Hernandez, Ponce,

Busquets, Hernandez, & Oliva, 2016). For instance, infants may present with atopic

eczema, gastroesophageal reflux, or infantile colic (Ho, Wong, & Chang, 2012). There is

also a plethora of allergens that may induce a hypersensitivity reaction. In pediatric

patients, the most common allergens are the result of egg, milk, wheat, soy, tree nuts,

peanuts, fish, and shellfish. Children will often outgrow their allergies to eggs and milk,

however allergies to peanuts and tree nuts are not usually outgrown (Ho, Wong, &

Chang, 2012).

There are many estimates regarding the percentage of infants and children who

suffer from food hypersensitivity reactions. According to a recent study, "In spite of

many articles dealing with this issue, the true prevalence of allergic drug reactions is not

well known, and the associated morbidity, mortality and economic cost are often

underestimated" (Ariza, Fernandez, Mayorg, Blanca, & Torres, 2013). A 2013 study

estimated that approximately 3-8% of children are affected by food hypersensitivity

reactions (Long, Berti, Burks, Krauss, & Barbi). It has been noted that the number of

children who are being diagnosed with food hypersensitivity reactions worldwide has

been increasing in recent years (Ho, Wong, & Chang, 2012). This has driven public

health official to label food hypersensitivity as an evolving public health issue (Long,

Berti, Burks, Krauss, & Barbi. 2013).

Even though the effects of food hypersensitivity reactions are often

underestimated, very often the reported number of food hypersensitivity reactions is

lower than the actual number of food hypersensitivity reactions. In a 2012 study, out of

20-30% of parents who reported a food allergy in their child, only 6-8% of those children

have been diagnosed with an actual food allergy (Ho, Wong, & Chang). More education

is needed about what a food allergy is, the symptoms associated with a true food allergy,

and how to diagnose a food allergy.

Recommendations for Prevention

For many years, the recommendation for the prevention of food allergies was for

breastfeeding and pregnant mothers to avoid consuming foods like fish, eggs, and cow's

milk. These foods are potentially allergenic, and it was thought that delayed exposure to

these foods would allow the infant's immune system enough time to develop so that

sensitization would not develop. However, in a 2012 Cochrane review, five trials found

that avoidance of such food did not decrease the development of hypersensitivity

reactions, but rather negatively impacted the nutritional health of both the mother and the

baby. It is, however, still possible for an infant to experience hypersensitivity reactions

to food that the mother ingests while breastfeeding. According the guide, *Counseling the*

Lactating Mother, "An infant is rarely, if ever, allergic to the mother's milk. At the same

time, the infant may show allergic symptoms in response to foods ingested by the mother

and passes through her milk. Allergens pass through the mother's milk and may cause

reactions such as spitting, vomiting, gas, diarrhea, colicky behavior, or skin rash"

(Lauwers, & Swisher, 2016, p. 199). Further symptoms include angioedema, urticaria,

pruritus, erythema, abdominal pain, vomiting, hoarse voice, persistent cough, stridor,

wheeze, nasal congestion, or respiratory distress (Longo, Berti, Burks, Krauss, & Barbi,

2013).

Breastfeeding

Counseling the Lactating Mother states*,* breastmilk is the best option for

prevention of development of hypersensitivity reactions. While breastfeeding does not

fully prevent the development of all hypersensitivity reactions, the use of formula has

been linked to an increase in the risk of development of hypersensitivity reactions. This

is because the infant's intestinal tract has not yet fully matured and requires

immunoglobulins from the mother for the infant's immune system to appropriately

function (Lauwers, & Swisher, 2016, p. 199). While breastfeeding does seem to prevent

the development of allergies, prolonged breastfeeding may promote the development of

hypersensitivity reactions. Recent studies have found that exclusive breastfeeding

beyond four months no longer has a major effect on preventing food allergies. Exclusive

breastfeeding after 6 months has no impact on the development of hypersensitivity

reactions (Longo, Berti, Burks, Krauss, & Barbi, 2013). The American Academy of

Pediatrics has stated that exclusive breastfeeding for the first few months of life have

been shown to be helpful in preventing the development of hypersensitivity reactions.

"There is a protective effect of exclusive breastfeeding for 3-4 months in reducing the

incidence of clinical asthma, atopic dermatitis, and eczema by 27% in a low-risk

population and up to 42% in infants with positive family history" (American Academy of

Pediatrics, 2012).

Food Avoidance

Along with the advice to pregnant and breastfeeding mothers to avoid allergenic

foods, it was recommended to avoid introducing the most allergenic foods during the first

year of life and perhaps even later. This was because it was believed that the later the

allergenic food was introduced, the better. The idea was to reduce the incidence of food

hypersensitivity reactions later in life. The result was the opposite of what was

anticipated. Newer research has instead indicated that introducing allergenic food earlier

on in life may promote tolerance in the infant's immune system and thus reduce the

incidence of hypersensitivity reactions. This should be done carefully, but the hope is

that if this is introduced, fewer children may develop hypersensitivity reactions (Joneja,

2013).

A 2013 meta-analysis reviewed several earlier studies that tracked the

introduction of allergenic foods into children's diets and the incidence of food

hypersensitivities. The study found that Israeli children who had been given peanut

butter beginning at six months of age were ten times less likely to develop a

hypersensitivity reaction to peanuts than their United Kingdom Jewish counterparts who

were not give peanut butter until they were older as suggested by public health

campaigns. Because the Israeli and Jewish children had the same genetics, the most

likely explanation is that the early introduction to the peanut allergy actually prevented sensitization and reduced the incidence of a peanut allergy (Longo, Berti, Burks, Krauss, & Barbi, 2013). The same meta-analysis found that development of tolerance might be promoted by exposure to allergens during critical time windows in early development. These time windows are between three and four months of age and six and seven months of age. Further research is still required to find the best route forward with regards to early feeding practices. (Longo et al., 2013).

Recommendations for Diagnosis

The number of reported food hypersensitivity reactions is far greater than the actual number of real food hypersensitivity reactions. Thus, it is imperative that healthcare providers know how to diagnose food allergies. Health care professionals should be familiar with what constitutes a food hypersensitivity leading to an allergic reaction and what is simply a food intolerance. According to an article entitled, *Incidence of Parentally Reported and Clinically Diagnosed Food Hypersensitivity in the First Year of Life,* "Food hypersensitivity can be divided into either food allergy if immunologically mediated or nonallergic food hypersensitivity, previously referred to as food intolerance. The gold standard in establishing food hypersensitivity is the double-blind, placebo-controlled food challenge (DBPCFC)" (Venter, et al., 2006).

DBPCFC

The DBPCFC is used to determine whether the food in question is causing the allergic reaction. If the patient has an allergic reaction to the tested food, the patient is most likely allergic to that particular food protein, though additional testing might be

needed to develop a definitive diagnosis (Venter, et al., 2006). The elimination and

challenge procedure may also be used to determine specific foods or food products that

are causing allergic reactions. This involves eliminating the suspected foods from the

diet and then slowly reintroducing the foods one at a time into the diet. Selection of these

suspected foods is based on a careful medical history, testing if appropriate, and food

intake diaries. If the foods cause a reaction, the food is withdrawn, and an appropriate

dietary guideline is then drawn (Joneja, 2013).

Skin Testing

Alternative testing involves skin testing. Skin testing may take several forms,

though all forms of testing have the same positive and negative results (Joneja, 2013).

According to *The Healthcare Professional's Guide to Food Allergies and Intolerances,*

"[skin testing] is designed to reveal the IgE, which is fixed to the skin mast cell. When

the allergen bridges to IgE molecules on the surface of the cell, inflammatory mediators

(particularly histamine) are released that cause edema (swelling) and erythema

(reddening) – the "wheal and flare reaction"" (Joneja, 2013, p. 58). The three methods of

skin testing are the prick test, the scratch test, and the intradermal test.

The prick test involves dropping an allergen onto the skin and then pricking the

skin underneath the drop with a lancet. The scratch test involves scratching the skin with

a sterile instrument and then dropping the allergen onto the excoriated skin. The

intradermal test involves injecting the allergen directly into the skin using a syringe.

With all of these tests, two controls must be used. The first control is a specific amount

of histamine. The second control is the solution in which the allergen is place and is

called the negative control; this is normally saline. The test is ruled invalid if the

histamine fails to produce a wheal less than 3mm in diameter or if the negative control

triggers a reaction. A positive reading is defined as a wheal that is at least 3mm larger

than the negative control. If it is suspected that the patient has a delayed hypersensitivity

reaction, a patch test may be used in which the allergen is introduced to the body through

patch that remains on the skin for a set period of time. If the physician wishes to test for

specific food antibodies, a blood test may be used. Blood tests must be only be used if

accompanied by a physical examination and careful history (Joneja, 2013).

Elimination Diets and Challenges

Elimination diets and challenges must be performed carefully so that an

appropriate diagnosis may be made. In order for a proper diagnosis to be made an

elimination diet must be performed to remove the suspected foods that contain the

allergens. Once the symptoms have subsided, the foods may be introduced one at a time

into the diet. If the food causes a reaction, then a diagnosis of food allergy may be made

(Joneja, 2013).

There are three basic kinds of elimination diets: Selective elimination diets, few

food elimination diets, and elemental diets. Selective elimination diets involve removing

one or a few numbers of foods from the diet. Few foods elimination diets involve

avoiding all foods except for a select number for a specified time period. Elemental diets

eliminate all solid foods and allow only an amino acid-based formula. This may

occasionally involve considerably hydrolyzed formula, especially for children and

infants. The specific elimination diet to be used must be carefully chosen. The decision-

making process is governed by results of previous allergy testing, a 7-day food exposure

diary, a detailed medical history, identification and exclusion of any other possible causes

of symptoms (Joneja, 2013).

Selective elimination diets.

Selective elimination diets are best used when it is believed that a specific food

ingested is causing a specific reaction. Normally, the specific foods are avoided for four

weeks. This time frame was chosen because it allows enough time for the patient to be

free of the symptoms that the food is potentially causing. This also allows enough time

to appropriately challenge the allergen. Even though the symptoms might be eliminated,

the circulating levels of IgE remain unchanged, and thus when the food is reintroduced, a

reaction will be provoked, thus confirming the diagnosis. Selective elimination diets may

also show that a specific food is not responsible for the symptoms. "If the symptoms

persist after specific foods have been eliminated, the assumption can be made that the

foods avoided are not causing the reaction" (Joneja, 2013, p. 75). There are several

advantages to the selective elimination diet. It is relatively quick, easy to diagnose, and

does not normally adversely affect nutritional status (Joneja, 2013).

Few foods elimination diet.

A few foods elimination diet is useful for reactions in which a specific food

cannot be identified. In this case, the diet eliminates most foods except those which are

thought to be the least likely to trigger an allergic reaction. Because this diet has negative

nutritional benefits, it should never be used for more than fourteen days, and extreme

caution must be used when using this diet in the pediatric population. Pediatric patients

are at high risk for nutritional deficiencies because of their growth rate, and thus

restricting their nutritional intake may adversely affect their growth and development.

These patients must be monitored very closely. Thus, it is not recommended that this diet

be used before the onset of puberty; normally a selective elimination diet is capable of

diagnosing food hypersensitivities in the pediatric population. If it is used for children

under 7 years old, a period of 7-10 days should not be exceeded. If symptoms are

reduced during the duration of the diet, it may be assumed that some type of food protein

is the cause of the symptoms. If, however, the symptoms do not respond to the

elimination, two conclusions may be drawn. The first is that the patient is allergic to one

of the foods that was not removed. The second is that the patient's symptoms are not due

to food proteins at all. Further eliminations and challenges may be performed in order to

distinguish which of the conclusion is accurate (Joneja, 2013).

Elemental diet.

An elemental diet is used after a selective elimination diet and a few foods

elimination diet have failed to identify the source of the hypersensitivity reaction and it is

suspected that the symptoms are the result of multiple food allergies. This diet is rarely

used because it is difficult to tolerate. It is more easily tolerated in infants than in any

other population. A nasogastric tube may be used because the elemental formula is not

appetizing. All the essential micro and macro nutrients and calories are provided in the

form of an amino acid-based formula. This diet must have a physician's approval and should not be continued for a prolonged time period (Joneja, 2013).

Challenge.

Following the elimination diet, the challenge step is begun. "This is achieved by careful challenge with precise quantities of each food component and careful monitoring of symptoms development, looking for immediate reactions (within a 4-hour period) or delayed reactions (from 1 to 4 days) following ingestion" (Joneja, 2013, p. 85). There are several different methods of conducting a challenge. The first is a double blind placebo controlled food challenge (DBPCFC) and is the gold standard for diagnosis (Venter, et al., 2006). In this challenge, neither the physician nor the patient know which capsule contains the suspected food protein and which capsule contains the control substance. A reaction to the suspected food protein is recorded (Joneja, 2013). A single-blind food challenge may be used as well, in which only the patient does not know when he or she is receiving the suspected food protein (Joneja, 2013). The third type of challenge is the most common food challenge carried out at home by the patient. This involves the patient controlling when foods are introduced and then noting the subsequent reactions (Joneja, 2013). If the patient demonstrates a hypersensitivity reaction to the foods introduced in the challenge, a positive diagnosis of food allergy can be made, and the food can be avoided in the future. If the food does not produce a hypersensitivity reaction, then it may be safely reintroduced into the diet (Joneja, 2013).

Recommendations for Treatment

The best treatment for hypersensitivity reactions that result in anaphylaxis for any patient regardless of age is avoidance of the allergen. It has been shown that children may outgrow some of their food allergies, and it is advised that foods may be reintroduced to the diet after a specific period of avoidance. This should usually be about one year. As certain allergens tend to result in life-threatening anaphylaxis and are rarely outgrown, it is not recommended that these foods be reintroduced into the diet (Rodgers, 2017, pp. 330-353). The most commonly outgrown allergies are milk, eggs, soy and wheat. Allergens like peanuts, tree nuts, fish and shellfish are rarely outgrown especially if they result in life-threatening anaphylactoid reactions. Patients who demonstrated high levels of IgE to wheat, milk, and egg are also not likely to develop tolerance and outgrow their allergies. Patients who are likely to outgrow their allergies should be tested after every few years of abstinence to see if tolerance has developed. According to a study 2013 study,

> For allergy to milk, egg, soy, or wheat, testing every 12-18 months is standard practice in the first 5 years of life. If the food allergy has not resolved by age 5 years, the interval for follow-up testing is extended to every 2-3 years. Although the likelihood of resolution of peanut allergy is low, resolution occurs most commonly by 5 years of age. Therefore, retesting for peanut allergy could follow a similar course as for allergy to milk, egg, soy, or wheat. Retesting can be done every 2-4 years for allergies to tree nuts, fish, and crustacean shellfish (Longo, Berti, Burks, Krauss, & Barbi).

During the intervals between testing, the allergen should be avoided to prevent recurrence

of the hypersensitivity reactions. Because treatments cannot provide assurance of

complete recovery, diet management and education about avoidance of allergens is

essential. This must include planning with a nutritionist and involvement of the family in

the case of pediatric patients. If the family is not involved, it is much harder for children

to eat a healthy diet and completely avoid the allergen. Thus, healthcare providers must

be sure to investigate family life and health education to be able to identify resources that

may best improve the child's quality of life despite they hypersensitivity reactions

(Joneja, 2013).

Oral Immunotherapy

Recent research has focused on the use of oral immunotherapy to produce

desensitization to the allergens. Further testing is required to prove the efficacy of this

therapy. This research found that children who had been diagnosed with egg allergies

treated with oral immunotherapy showed a lack of hypersensitivity reactions (Longo,

Berti, Burks, Krauss, & Barbi, 2013).

Other experts have also called for further research for oral immunotherapy, also

known as allergen-specific immunotherapy (SIT). SIT works by regularly exposing the

patient to the allergens to which they are sensitized. This is done with the hope that the

patient might become sensitized over time to the repeated exposure of the allergen. If

successful, patients will experience the ability to be exposed to allergens without

experiencing a hypersensitivity reaction. Because SIT alters the function of the immune

system, the positive effects of SIT can be seen long after the treatment has stopped,

potentially even life-long. This occurs because the TH2 response responsible for the

hypersensitivity reaction has been inhibited by the SIT and the TH1 response that is

responsible for identifying allergens as safe has been promoted. SIT also inhibits the

hypersensitivity reactions through introducing allergen-specific Treg cells. These Treg

cells produce IL-10 and TGF-β; these are cytokines that help to produce IgG1, IgG4, and

IgA antibodies. These antibodies are called blocking antibodies and they inhibit IgE by

binding to allergens before IgE. The third way that SIT inhibits hypersensitivity

reactions is through modulating the function of APC and effector cells. This successfully

decreases the amount of mast cells and thus reduces the mediators released by the mast

cells. SIT also successfully reduces the numbers of eosinophils and neutrophils that are

sent to respond to allergen exposure (Bohle, 2013).

SIT works differently for Class 1 food allergies and Class 2 food allergies. In

class 1 food allergies, SIT is often less successful and may even be dangerous because the

risk of anaphylactic reactions is very high. This risk was found to be even higher with

subcutaneous administration of SIT. SIT, however, is still being studied in these patients

to help improve the quality of life for patients. Recent studies have shown that oral

administration of SIT and sub-lingual administration of SIT may be safer than

subcutaneous SIT. Further research needs to be done as any form of SIT in patients with

class 1 food allergy carries with it a high risk of anaphylaxis and thus should be

monitored very closely (Bohle, 2013). Effective SIT in patients with class 2 food allergy

often required treatment with both the respiratory allergen and the food allergen. This is

because studies found that treatment with the respiratory allergen alone did not reduce

hypersensitivity to the associated food allergen. Likewise, treatment with the food allergen alone did not reduce hypersensitivity to the associated respiratory allergen, though it was more successful than sole treatment with the respiratory allergen (Bohle, 2013).

Recommendations for Healthcare Providers

Because hypersensitivity reactions are such a growing health problem, it is essential that healthcare providers, especially those working in the pediatric field, be familiar with all the aspects of care for hypersensitivity reactions. This includes how the immune system functions, how hypersensitivity reactions occur, how to diagnose food hypersensitivities, and how to treat those hypersensitivities. This could be accomplished through continuing education classes and participation in research projects aimed at learning more about how the immune system works with regards to hypersensitivity reactions.

Healthcare providers should not only be familiar with how to treat anaphylaxis, but also with how to safely administer immunotherapy or SIT. This will help to improve the quality of life of patients with food hypersensitivities and will also increase safety and efficacy of treatment. If more healthcare providers are trained in properly treating hypersensitivity reactions, more children will have access to adequate treatment leading to better outcomes (Hernandez, Ponce, Busquets, Hernandez, & Oliva, 2016; Bohle, 2013).

Because so much research has already been done on how to treat food allergies, further research should be done to build on the foundation already built. There are few

treatments available and none are as effective as complete avoidance which is difficult at

best and often impossible. Some research is currently being done to develop a vaccine

for both the prevention and the treatment of hypersensitivity reactions to food. This

research is going hand in hand with research in developing safer ways to perform

immunotherapy treatments (Bohle, 2013).

Pediatric healthcare providers include any physician, nurse, therapist, or any other

provider in the healthcare field caring for patients from the neonatal stage through the end

of adolescence. Pediatric healthcare providers should also actively participate in

research. More research is especially needed in the realms of prevention and treatment

(Longo, Berti, Burks, Krauss, & Barbi, 2013; Bohle, 2013). This includes further

research into breastfeeding and formula feeding and their link to development of

hypersensitivity reactions; genetic testing for genetic predisposition to hypersensitivity

reactions, and recommendations for when to begin introducing highly allergenic food into

the diet (Longo, Berti, Burks, Krauss, & Barbi, 2013). This also includes further research

into how to make SIT safer for those with class 1 food allergies, how to make SIT more

effective for those with class 2 food hypersensitivities, and how a vaccine might be

developed for prevention and treatment (Bohle, 2013).

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