

Idiopathic anaphylaxis: What you do not know may hurt you

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ABSTRACT

Idiopathic anaphylaxis (IA), like immunologic and nonimmunologic anaphylaxis, is a life-threatening, sometimes fatal allergic disease. Although the priority is immediate recognition and initiation of treatment, long-term care planning is important to help reduce anxiety and promote healthy growth and development. Learning to recognize, manage, and stabilize the child is an essential part of improving the family dynamics. Despite advancements in the management of anaphylaxis, research has shown a need for continued patient education and training to improve timely recognition and treatment. This article focuses on elucidating the clinical presentation, theories of pathogenesis, and diagnosis, treatment, and management of IA.

Keywords: Allergy; anaphylaxis; idiopathic anaphylaxis; epinephrine; immunology; management; pediatric; prevention; primary care.

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Anaphylaxis is a multisystem allergic reaction that can be broken down into four subtypes—immunologic, non-immunologic, idiopathic (Lieberman, 2014), and exercise-induced (Montgomery, 2015). Idiopathic anaphylaxis (IA), like its other subtypes, is a life-threatening, sometimes fatal allergic disease. It is the most common (mis)diagnosis among patients following anaphylaxis of unknown origin. Patients can present with any combination of urticaria, pruritus, angioedema, nausea, vomiting, wheezing, stridor, upper and lower airway obstruction, hypotension, and/or shock, but must meet the diagnostic criteria for anaphylaxis (Table 1) (Moore, Kemp, & Kemp, 2015).

This article will present a case and review the epidemiology, theories of pathogenesis, clinical presentation, differential diagnosis, diagnostic workup, possible triggers, and management of IA. The role of the nurse practitioner (NP) will be discussed as a crucial part of the health care team in the reduction of the potential for an adverse outcome for the child as well as decreasing strain on the family.

Case study

MDC is a 9-year-old boy, born at 35-week gestation through repeat cesarean section secondary to a

nonreassuring fetal heart rate tracing and preterm labor. By 3 months of age, MDC had developed severe eczema requiring systemic steroids and antibiotics. MDC's first anaphylactic event followed a lick of ice cream at 9 months old. MDC was treated with epinephrine and diphenhydramine and was referred to an allergist for follow-up.

Over the next 2 years, MDC proceeded to have multiple allergic episodes that were confirmed to be allergies to eggs, shellfish, peanuts, tree nuts, tropical fruits, sesame, and soybeans. For a 3-month concentration period, MDC had eight episodes of anaphylaxis, two of which resulted in hospitalization and one event requiring intubation. Three episodes were classified as anaphylactic shock, unspecified.

MDC was diagnosed with IA after an extensive diagnostic workup, which included detailed history and multiple allergy testing modalities. Consistent with an allergy profile, MDC also developed seasonal allergies and food-dependent exercise-induced asthma.

Overview

First described by Bacal, Patterson, and Zeiss in 1978 (as cited in Kim & Khan, 2015), IA is a disease characterized by multiple episodes of anaphylaxis that have no known trigger. It is considered a diagnosis of exclusion. Idiopathic anaphylaxis is thought to account for 10% of children presenting with anaphylaxis to the emergency department (ED) (Greenberger & Lieberman, 2014). This estimate is expected to grow exponentially as noted by an increase in overall allergic reactions across the United States with a continued upward trend (Gupta, 2014).

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Table 1. Differential diagnoses for IA

Diagnosis	Differential
Somatoform event	• A psychiatric disorder that can mimic anaphylaxis • Symptoms of vocal cord dysfunction and panic attacks • Lack of response to prednisone and increasing anaphylaxis events on prednisone • No urticaria • Account of the event is more severe than in presentation • Inconsistent in the history versus the actual presentation • Consider when presenting with syncope without abnormal blood pressures or heart rate (Kim & Khan, 2015) • Empirical treatment with prednisone can increase the number of episodes as opposed to decrease in IA
Self-induced (variation of Munchausen syndrome)	• Patient or family member deliberately causes anaphylaxis
Hidden allergen	• Positive or confirmatory diagnostic testing
Scombroidosis (ingestion of spoiled fish)	• Related to eating fish of the scombroid variety (mahi-mahi, bluefish, salmon, sardines, herring, amberjack) • Histamine poisoning due to a bacterial derivative histidine decarboxylase, which converts histidine to histamine, causing a reaction that is anaphylaxis-like (Greenberger & Lieberman, 2014)
Exercise-induced Anaphylaxis	• Occurs after a person has ingested a particular food and then exercises • Ingestion of the allergen can be from 6 hr earlier with anaphylaxis presenting within 45 min of exercise initiation (Montgomery, 2015)
Carcinoid syndrome	• Order urine studies for 5-HIAA • Does not present with urticaria or angioedema (Blatman & Ditto, 2012).
Vasointestinal polypeptide secreting tumors	• Does not present with urticaria or angioedema (Blatman & Ditto, 2012)
Paradoxical pheochromocytomas	• Order urine studies for metanephrines • Does not present with urticaria or angioedema (Blatman & Ditto, 2012)
Medication	• Recent exposure to NSAIDs, ACE inhibitors
Latex	• Route and amount must be considered
Hereditary or acquired angioedema	• Autosomal dominant disorder in which the patient has lower levels of protein C • Three types of hereditary angioedema, differentiated by genetic testing and abnormal complement levels • Presentation includes edema of the skin and mucous membranes with facial swelling, upper airway swelling that can involve the larynx and abdominal organ • Does not respond to epinephrine (Fenny & Grammer, 2015) • Complement levels (C4 as screening to rule out)
Indolent systemic mastocytosis	• Skin or bone marrow biopsy, especially if serum total tryptase level is >20 ng/mL
Hereditary acquired C1 esterase inhibitor deficiency	• Complement levels (C4 as screening to rule out)
Alpha-Gal delayed-onset anaphylaxis	• Eliminate if no ingestion of meat within 3–6 hr (Greenberger & Lieberman, 2014; Kim & Khan, 2015) before reaction or no tick bite exposure (Commings, Jerath, Cox, Erickson, & Platts-Mills, 2016)

Note: 5-HIAA = 5-hydroxyindoleacetic acid; ACE = Angiotensin converting enzyme; Alpha-Gal = galactose- α -1, 3-galactose; IA = idiopathic anaphylaxis; NSAID = nonsteroidal anti-inflammatory drug.

Epidemiology

The overall prevalence of IA is unknown. Patterson (1995) wrote a landmark article that estimated the incidence in the United States to be between 20,592 and

47,024 cases/263,000,000 (as cited in Greenberger & Lieberman, 2014). At the time of the study, the total number of identified cases of IA was 1,020. Wright, Longjohn, Lieberman, and Lieberman (2017) reported a

17% incidence of IA among 40 ED. Similarly, Gonzalez-Estrada et al. (2017) reported a rate of 13.6% of IA in a survey of 730 patients of all ages presenting to the ED with anaphylaxis.

Current but limited data show a prevalence of IA more in female patients than in male patients, and in adults versus children (Greenberger & Lieberman, 2014). Higher incidence of IA in women suggests a correlation of estrogen/progesterone effects on basophil activation and lowering the threshold for degranulation, supporting the theory of hormone-related IA (Greenberger & Lieberman, 2014).

Although the financial impact of IA is not fully appreciated, research on the effects of food allergies, both direct and indirect, estimates the impact on the general population to be \$24.8 billion annually (Sclar & Lieberman, 2014). Idiopathic anaphylaxis is a significant financial burden even if it is only a fraction of this estimate.

Theories of pathogenesis

The caveat, if the pathogenesis can be understood, the diagnosis of IA, is no longer valid. Because of the lack of data and ethical concerns surrounding testing, theories regarding the pathogenesis of IA are difficult to study and thus find quantifiable data.

Hidden allergens

According to Greenberger and Lieberman (2014), the most prevalent theory of IA is that there is an undiagnosed allergy that the health care team is unable to identify. The complexity of this thought is that the spectrum of allergic triggers is infinite, making it problematic to diagnose. The diligent process of elimination and clinical investigation requires oversight by an allergy/immunology (AI) specialist. Even with the expansive diagnostic tools currently available, there are documented limitations.

Mast cell activation disorders

Mast cells theoretically contribute to IA through activation and release of their contents into circulation. Many patients with IA are noted to have atopy-related to the increase in type 2 cytokines (Th2), which can lead to a lower threshold for mast cell degranulation and anaphylactic reactions (Greenberger & Lieberman, 2014).

Distinguishing between IA, mast cell activation syndrome, and its various subtypes is difficult because the clinical features as well as their response to treatment are identical (Kim & Khan, 2015). Greenberger and Lieberman (2014) demonstrated in acute reactions, patients with IA have elevated serum tryptase levels, which subsequently returned to baseline. Patients exhibiting both elevated tryptase levels at baseline and during critical responses require evaluation for mast cell disorders (Matito & Carter, 2015).

Lymphocyte activation

Patients diagnosed with IA have an increase in circulating activated T cells during acute reactions and not at baseline (Greenberger & Lieberman, 2014). An increase in activated B-cells is also noted and remains elevated even at baseline (Fenny & Grammer, 2015). When treated with prednisone, the total lymphocyte count decreases, consistent with expected steroid response. It suggests that IA is a steroid-responsive disorder with possible autoimmune etiology (Fenny & Grammer, 2015).

Clinical presentation

Idiopathic anaphylaxis is a multisystem allergic reaction with the same presentation as other forms of anaphylaxis. Patients present with a combination of urticaria, pruritus, angioedema, nausea, vomiting, wheezing, stridor, arrhythmia, upper and lower airway obstruction, hypotension, and/or shock (Moore, et al., 2015). However, 10–20% of patients present without cutaneous symptoms (Nowak & Macias, 2014). Children typically present with respiratory symptoms. In contrast, adults typically present with cutaneous manifestations (Nowak & Macias, 2014). Even a mild-appearing reaction can change and become severe, either suddenly or delayed in a biphasic response, all with possible fatal outcome (Gupta, 2014).

Differential diagnosis

Anaphylaxis remains a clinical diagnosis based on pattern recognition and requires further differentiation from nonallergic food reactions such as food intolerance and/or exercise-induced anaphylaxis (Table 1). Idiopathic anaphylaxis is a diagnosis of exclusion confirmed by a detailed patient history, physical examination, and comprehensive diagnostic testing.

Diagnostic tests aim to rule out conditions such as C1 esterase inhibitor deficiency, mast cell activation syndrome, monoclonal mast cell activation syndrome, systemic mastocytosis, and chronic inflammatory or autoimmune disease (Fenny & Grammer, 2015; Greenberger & Lieberman, 2014; Kim & Khan, 2015). In particular allergies such as galactose-alpha-1, 3-galactose, often presents as a delayed reaction, and must be considered before making the diagnosis of IA. Table 1 lists differential diagnoses and their clinical presentation.

Diagnostic evaluation

Diagnosis of IA cannot be made in the acute situation. If a primary care provider is suspicious of IA after two or more documented events of anaphylactic shock, unspecified, the patient must be referred to an AI specialist for a comprehensive workup. A detailed history that includes past interactions with suspected trigger and response to date, evaluation of underlying predisposing factors, birth history, and familial comorbidities should be collected in combination with allergy testing (Table 2).

Table 2. Diagnostic tests for differential diagnosis

Diagnostic Test	Differential/Notes
Skin prick test	• First-line testing, results within 15–20 min (Stukus & Mikhail, 2016) • Must have emergency medical equipment available • Confirm hidden allergens • Negative skin tests do not exclude the suspected allergen if a clinical reactivity can be documented • Reactions may be non-IgE-mediated or caused by a reagent lacking relevant protein (Sicherer & Sampson, 2014) • Discontinue antihistamines 2–3 days before for accuracy • Risk of death in patients with a history of severe reactions (Moore et al., 2015)
In vitro testing	• Not recommended, less sensitive and specific, false positives
Patch test	• Useful in detecting delayed reactions
Blood tests include ELISA, EIA, ISAC, and ImmunoCAP Pharmacia CAP	• Must be used in combination with a comprehensive history • Eliminates safety or ethical concerns because of the risk of anaphylaxis with skin testing • ImmunoCAP is less sensitive and specific to false positive • ISAC tests 103 allergies • ELISA, EIA can have false-positive results because patients with allergies/asthma have higher baseline IgE
Double-blind placebo-controlled oral challenge testing	• The gold standard for diagnosis of IgE-mediated anaphylaxis (Allen & Koplin, 2012) • Time-consuming and risk is higher due to introduction to allergen • History, with positive oral challenge test supported by laboratory tests confirms the diagnosis (Boyce et al., 2010) • Terminate immediately if any reaction is elicited (Stukus & Mikhail, 2016)
Serum Alpha-Gal anti-IgE	• Patients who have confirmed tick bites with 2–3 weeks of pruritus, edema, and or swelling, as a result, should be evaluated for IgE antibodies to alpha-gal, a mammalian oligosaccharide that has been associated with delayed-onset anaphylaxis (Commins, Jerath, Cox, Erickson, & Platts-Mills, 2016) • Transmission can also occur through ingestion of pork, beef, or lamb and should be added to the differential if ingestion happened in the 3–6 hr postprandial (Greenberger & Lieberman, 2014; Kim & Khan, 2015)
Serum tryptase	• Elevated tryptase levels occur in systemic mastocytosis • Peak tryptase levels occur 2–4 hr after acute event • Patients with IA have elevated serum tryptase levels during acute reactions with a return to the baseline level (Greenberger & Lieberman, 2014) • Optimal timing for Tryptase concentration is 1–2 hr after, but no later than 6 hr after an acute episode because the peak serum concentration occurs at 2–4 hr and declines from there
Complement test	• Decreased level of C4, CH50, and C1 esterase inhibitor concentration or function confirms diagnosis of IA and rules out hereditary angioedema and C1 inhibitor deficiency (Fenny & Grammer, 2015; Blatman & Ditto, 2012)
24-hr urinary prostaglandin D2	• Patients with mast cell activation disorders can present with elevated metabolites of histamine, prostaglandins, and leukotrienes, and should have a 24-hr urinary metabolite analysis done (Greenberger & Lieberman, 2014)
D816V Kit mutation	• More than 80% of patients diagnosed with systemic mastocytosis, which is commonly diagnosed as IA, are carriers of the D816V mutation (Schuch & Brockow, 2017) • Positive result adds MCAS to differential
Bone marrow biopsy	• Continuous elevations in serum tryptase level are >20 ng/mL in all states, which is an indication for a bone marrow biopsy to rule out systemic mastocytosis or urticaria pigmentosa (Schuch & Brockow, 2017) • If the patient presents with IA, an elevated serum tryptase, and urticaria pigmentosa, a bone marrow biopsy should be performed (Kim & Khan, 2015)

Note: Alpha-Gal = galactose-alpha-1, 3-galactose; EIA = enzyme immune assay; ELISA = Enzyme-Linked Immunosorbent Assay; IA = idiopathic anaphylaxis; ISAC = Immuno Solid Phase Allergen Chip; MCAS = Mast cell activation syndrome.

Patients will often have known food allergies, asthma, atopic dermatitis, and allergic rhinitis (Greenberger & Lieberman, 2014). A single testing methodology does not establish the diagnosis of IA. Test results do not predict the severity of the allergic reactions (Stukus & Mikhail, 2016). Table 3 outlines the advantages and disadvantages of diagnostic testing.

Triggers of idiopathic anaphylaxis

Recent exposure to a nonsteroidal anti-inflammatory drug (NSAID) has been shown to increase the intensity of anaphylactic reactions and could potentially be the causative agent (Fenny & Grammer, 2015). Response to NSAIDs are not IgE-mediated and are considered anaphylactoid, not anaphylaxis (Jarvinen & Celestin, 2014). When obtaining the history, it is important to remember many combination medications such as Children's Dimetapp Multi-Symptom Cold and Flu or Children's Mucinex Multi-Symptom Cold and Fever Relief Liquid that contains acetaminophen.

Specific angiotensin-converting enzyme inhibitors can cause angioedema, a common symptom of anaphylaxis (Greenberger & Lieberman, 2014). Onset can be sudden, within weeks of initiation or delayed in patients who have been on years of treatment, making the correlation more challenging.

The most severe reaction to latex is anaphylaxis. The severity of a latex allergy is dependent on the amount, patient threshold, and route of exposure (Jarvinen & Celestin, 2014). β -Lactam antibiotics such as penicillin, radiocontrast media, and chemotherapeutic agents can be added to the differential (Jarvinen & Celestin, 2014). Ironically, biologic response modifiers such as omalizumab (Xolair) used in the treatment of associated conditions such as asthma and chronic idiopathic urticaria list anaphylaxis as an adverse reaction (Baker, Nakamura, Lowman, & Fischer, 2015). Monoamine oxidase inhibitors and tricyclic antidepressants are known to decrease the effects of epinephrine by interrupting the catabolism pathway (Greenberger & Lieberman, 2014). Alcohol

consumption can increase the rate at which an allergen is absorbed (Gupta, 2014).

Age and other considerations

Specific allergies are more prevalent in different age subgroups and should be considered in the overall evaluation of the patient even if history has shown no previous reactions. Studies show that allergies to milk and egg can be seen more in younger children, whereas allergies to shellfish and finfish are more prevalent in adolescents (Gupta, 2014; Jarvinen & Celestin, 2014).

To further complicate diagnosis, severity in the presentation of anaphylaxis to a specific allergen can differ with each patient, and each patient can also present differently in severity to the same allergen. There is no predictive pattern to an allergic reaction—what presents as severe in presentation can present mildly another time and severe on a subsequent occasion (Simons et al., 2011).

Treatment

A tailored treatment plan (Table 3) should be initiated because of the life-threatening nature of IA. Family understanding is enhanced by using the teach-back method to make sure that they understand what they should do in case of a reaction.

Acute anaphylaxis

Intramuscular injection of epinephrine remains the first-line treatment and should be administered without hesitation if there is a suspicion of anaphylaxis (Moore et al., 2015). The benefits of epinephrine administration outweigh the side effects (Nowak & Macias, 2014). A delay in epinephrine administration has shown to contribute to biphasic anaphylaxis or even worse, death (Brown et al., 2013).

Patients should receive adjuvant diphenhydramine, an H₁ antihistamine at 1–2 mg/kg per dose. Antihistamines should never be the first and only treatment as it can take over 80 minutes to induce a 50% reduction in histamine flare (Lieberman, 2014).

Once the patient is stable, initiation of glucocorticoid therapy such as methylprednisolone should be considered for prevention of a biphasic (within 1–72 hours) anaphylaxis or protracted reaction (persist for up to 32 hours) (Moore et al., 2015). Glucocorticoids can take several hours to work. Patients should be monitored for at least 6–8 hours from stabilization before discharge using clinical judgment (Lieberman, 2014).

Patients with a history of severe featured anaphylaxis, asthma, and/or biphasic or protracted reactions should be started on glucocorticoid therapy immediately and monitored for a minimum of 24 hours (Moore et al., 2015).

Prophylactic maintenance

Patients diagnosed with IA should be managed as a chronic condition (Sclar & Lieberman, 2014). They are

Table 3. Idiopathic anaphylaxis plan of care in the primary care setting

Management of Acute Anaphylaxis

Administer IM epinephrine

Monitor response

Administer IM epinephrine every 5–15 min if necessary

Administer H₁ and H₂ antihistamines if available

Consider systemic glucocorticoids, i.e., prednisolone

Immediate transport to ED

Note: ED = emergency department; IM = intramuscular.

further classified as IA-frequent (IA-F) with either more than six times per year or more than once in a 2-month period; or IA-infrequent with less than six times per year or less than once in 2 months (Blatman & Ditto, 2012).

Preventive Therapy is vitally important and associated with good prognosis. Patients diagnosed with IA-F should begin a regimen of H₂ antihistamines such as cetirizine, fexofenadine, or hydroxyzine in combination with a glucocorticoid such as prednisolone for a minimum of 3 months but can continue for as long as 9–12 months (Fenny & Grammar, 2016). Cetirizine 10 mg should be taken daily for maintenance therapy following cessation of prednisolone (Blatman & Ditto, 2012). Eight percent of patients find cetirizine to be slightly sedating and prefer an alternative drug levocetirizine dihydrochloride (Xyzal), which are both available over the counter (Snidvongs, Seresirikachorn, Khattiyawittayakun, & Chitsuthipakorn, 2017). Mast cell stabilizers, anti-leukotrienes, and anti-IgE may be considered to reduce long-term use of steroids. A personalized medical kit should be created for every patient diagnosed with IA and should accompany them in any situation (Table 4).

According to Greenberger and Lieberman (2014), an empirical regimen of prednisolone should be initiated in children with IA-F with a suggested dosing of 1–2 mg/kg every morning for 1–2 weeks, then alternating mornings for one month, tapering 5–10 mg every month. If breakthrough symptoms occur during tapering, daily prednisone dosing should be increased again for two weeks, then tapered. If the patient is unable to taper off prednisone, ketotifen that is both an H₁ antihistamine and mast cell stabilizer can be used to effectively reduce steroid dependence but it does have a severe sedation profile as well as weight gain as a side effect (Fernandez & Akin, 2014). Oral cromolyn and anti-leukotrienes are also steroid sparing (Kim & Khan, 2015).

Role of the nurse practitioner Practice

The NP needs to understand the differential diagnosis of IA and the need for an AI referral. By recognizing the signs

of clinical anaphylaxis and appropriately initiating an acute treatment plan, lives can be saved (Stone & Choi, 2016). The NP is responsible for providing holistic and preventive care to the patient diagnosed with IA. The NP should start with collecting a thorough episodic history, comprehensive medical history.

The NP should autonomously provide a medical home for the child and assume the role as liaison between the subspecialists involved in the care of the patient (Table 5). The NP is responsible for initiation of a management plan until the child sees an allergist. Specific medication should be avoided, for example, beta blockers which decrease response to epinephrine (Greenberger & Lieberman, 2014). Additional referral to a dietician is equally vital with discussions focused specifically on a histamine-free diet and avoidance of allergens (Jarvinen & Celestin, 2014).

As part of the plan, routine yearly evaluation of the patient's history is recommended (Simon et al., 2014). Any changes in treatment plan including medication modifications such as the transition to higher dose epinephrine auto-injector (EpiPen) at 30 kg or the addition of omalizumab for treatment of severe asthma should be communicated to all members of the multidisciplinary team (Baker et al., 2015).

As the patient ages, the NP needs to be aware the child may feel socially isolated and may take risks as adult supervision decreases, which can lead to fatalities (Gupta, 2014). A referral to a mental health professional is important due to the increased stress related to having a life-threatening condition.

Education

Patients and their caretakers must understand and recognize the signs of anaphylaxis to decrease the risk of fatality. Expiration dates of essential lifesaving medications need constant and vigilant monitoring. The family should understand the indication, dosing, and side effects of these medications. The NP should use the

Table 4. Emergency medical kit

Item	Description
Medical ID jewelry	With diagnosis, emergency contact, and list of allergens
Epinephrine auto-injector duo pack	Ensure appropriate auto-injector based on your weight
Diphenhydramine	Use a syringe and cup for exact dosing based on weight
Prednisone	Use as instructed by your AI specialist for adjuvant therapy for moderate to severe reactions
Ventolin HFA (albuterol sulfate inhalation aerosol)	For patients with coexisting asthma profile
Allergy action plan	Assembled by your AI specialist and distributed to all parties active in the patient's life (school, family, extracurricular activities)

Note. AI = allergy/immunology; HFA = hydrofluoroalkane; ID = identification.

Table 5. Treatment plan and primary care role

Plan	Role
Prescription for epinephrine auto-injector (duo pack)	Standard of care for patients with a history of allergic reactions
Prescription for daily H ₁ antihistamine	For prophylactic management of IA
Referral to AI specialist	Follow-up every 1–2 weeks until seen by the specialist. Role changes to liaison between the entire medical team at that point
Referral to nutritionist	As patient's allergy profile expands related to diagnostic testing at the AI specialist, nutritional deficits may occur and growth curve can be affected
Referral to mental health professional	IA is not only stressful for the patient, it continues to represent a significant contributor to family stressors and medical health care costs. Both patient and family would benefit from care
Allergy action plan	A personalized allergy action plan should be developed and reviewed with the patient and caregivers. Included in this plan should be the complete list of prescribed medications, contact information for emergencies, and provider contacts

Note. AI = allergy/immunology; IA = idiopathic anaphylaxis.

teach-back method to evaluate the patient and family's understanding (Blatman & Ditto, 2012). Patients should have their allergy action plan and a personalized medical kit with them at all times. Medical alert jewelry provides vital information in case of an attack because the majority of anaphylactic reactions and related deaths occur outside of the home (Gupta, 2014). All caregivers including coaches and teachers must understand the allergy action plan.

Research

It is imperative that the NP remain abreast of the latest research on anaphylaxis including IA. Monoclonal antibodies are gaining ground in the successful use of the treatment in several allergic diseases. Rituximab has been shown to cause remission of IA (Borzutzky, Morales, Mezzano, Nussbaum, & Burks, 2014), which reduces circulating B cells (Kim & Khan, 2015). The National Institute of Allergy and Infectious Diseases is currently conducting the first IA-related randomized control study, on the use of omalizumab for treatment of IA.

Denouement

A treatment plan was developed using shared decision making. MDC receives daily doses of cetirizine 10 mg every morning as well as two puff of beclomethasone dipropionate HFA (QVAR) 80 µg twice a day. Acute allergic reactions are classified in response to three questions. Is the reaction mild, moderate, or severe? Is there a suspicion, confirmed or unknown allergen trigger? If suspicious for or confirmed, is this related to ingestion, contamination, or contact? With mild suspicion, MDC will receive an immediate dose of diphenhydramine 25 mg with monitoring

for 8 hours. If the reaction increases in severity, epinephrine will be administered followed by initiation of glucocorticoid therapy and administration of an H₁ antihistamine. For moderate to severe reactions, MDC will receive epinephrine as well as initiation of prednisolone therapy and then be transported to the nearest emergency room because of his history of biphasic reactions and airway closure. MDC's episodes have been noted to be most common in the late evening, which leads to the hypothesis that circadian rhythm may be an important consideration. A patient's immune response can be diminished when a patient is exhausted or in the late evening (Nakamura et al., 2016). Although not evidence based, adequate sleep should be included as an essential part of the plan.

Conclusion

When a patient presents with anaphylaxis of unknown origin, IA should be considered. While IA is a diagnosis of exclusion, it makes evaluation on a regular basis, at minimal annually, crucial as new understanding and advancements in allergy and immunology being discovered.

Idiopathic anaphylaxis continues to represent a significant contributor to family stressors and medical health care costs. Despite the knowledge gap in the underlying pathogenesis of IA, the prognosis remains optimistic despite the life-threatening nature of the disease. Studies demonstrate patients' quality of life improves with a treatment plan in place, and remission is possible. However, the mechanism for which remission is achieved is still not fully understood, making the definitive prognosis difficult.

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