

One Child's Food Fight: A Case Study of Oral Immunotherapy Treatment for Food Allergies

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ABSTRACT

The prevalence of food allergy has risen dramatically in the last two decades. Primary care providers encounter food-allergic children on a daily basis. Although the standard of care has traditionally been strict avoidance of the allergen and advisement to carry an epinephrine autoinjector in case of an accidental exposure resulting in a severe reaction, food allergy research has progressed in the past decade concerning various immunotherapies that may provide an alternate treatment strategy. Oral immunotherapy (OIT), performed under the supervision of an allergist, is the most widely studied of these therapies. In the past, OIT has been available in the realm of clinical trials, but it is now being offered by a small but increasing number of allergists in private practice throughout the United States. Pediatric primary care clinicians should be aware of both the risks and possible benefits of this treatment, because they are likely to encounter patients who may inquire about OIT in their practices. In this case report, use of OIT will be reviewed in the treatment of a food-allergic child. *J Pediatr Health Care.* (2018) ■■, ■■-■■.

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Conflicts of interest: None to report.

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0891-5245/\$36.00

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<https://doi.org/10.1016/j.pedhc.2018.01.004>

KEY WORDS

Anaphylaxis, desensitization, epinephrine autoinjector, food allergy, oral immunotherapy

CASE PRESENTATION

A 10-year-old boy with a known history of food allergies presented to the primary care clinic with his parents. His past medical history was significant for a first reported allergic reaction, which occurred at 7 months of age after ingestion of pasta, in which he exhibited facial flushing and edema followed by one episode of emesis an hour after ingestion. After subsequent reactions to different foods, percutaneous prick testing at 9 months showed sensitization to wheat, eggs, peanuts, and tree nuts. Strict avoidance was recommended and initiated.

Continued additional food reactions with similar allergic symptoms led to broader categories of food avoidance, a second opinion with a different allergist, and a new recommendation to carry an epinephrine autoinjector. At age 3 years, the child experienced facial edema, generalized severe urticaria, and repetitive emesis after eating a peppermint patty candy with inadvertent egg ingestion. His mother administered an epinephrine autoinjector at home, followed by emergent medical care and overnight hospitalization. During the next 7 years, various food challenges were tried in conjunction with allergist recommendations, often met with mixed results, with the child passing a wheat challenge but failing a baked egg challenge.

DISCUSSION

Between 1997 and 2011, food allergies among children were estimated to have increased by 50% (Jackson, Howie, & Akinbami, 2013). Between 2010 and 2016,

peanut allergies alone rose 21% (American College of Allergy and Immunology, 2017). Insurance claims in the United States with the diagnosis of anaphylactic food reactions rose a staggering 377% between the years 2007 and 2016 (Gelburd, 2017). Current estimates in the United States identify approximately 8% of children, or 6 million, who suffer from some form of food allergy, with younger children disproportionately affected (Centers for Disease Control and Prevention, 2011; Gupta et al., 2011). Most food-induced allergic reactions in children occur from exposure to milk, eggs, and peanuts. Symptoms of food allergy may present with symptoms ranging from mild to severe in the skin, gastrointestinal and respiratory tracts, and/or cardiovascular system (Food Allergy Research and Education, 2017). The clinical diagnosis of food allergy is based on a combination of medical history, physical examination, and food allergy testing. Clinicians should consider referral to an allergist/immunologist for diagnosis and management of suspected food allergy (American Academy of Pediatrics, 2011).

The current standard of care for food allergies is to practice strict avoidance of the allergen and carry self-injectable epinephrine for emergency use in case of an accidental exposure and subsequent anaphylaxis (Kulis, Wright, Jones, & Burks, 2015). This practice contributes to a diminished quality of life for these children and their families. One in three children report being bullied or teased because of their food allergy, with increased frequency of bullying corresponding to lower quality of life measures (Shemesh et al., 2013). Greater numbers of allergens also correlate to decreased quality of life measures (Warren, Otto, Walkner, & Gupta, 2016). Feelings of dissatisfaction with diminished quality of life can lead some patients and their caregivers to explore other treatment options (Lanser, Wright, Orgel, Vickery, & Fleischer, 2015). After 7 years of traditionally recommended allergen avoidance, the reported social health impacts of a food allergy diagnosis for this child's family included mild generalized anxiety; perceived stigma from requiring an "allergy safe spot" at school; feelings of social isolation when excluded from parties or other social events, which often revolved around food; restriction of airline travel because of exposure concerns; limitations to a small group of restaurants for social eating; and maternal anxiety over potential exposures, which did

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inadvertently happen in the school setting. Because of the continued allergy and significant social and emotional impact, the boy's family began seeking treatment options and learned about oral immunotherapy (OIT).

EMERGING TREATMENTS

Several forms of immunotherapy are currently being explored as a treatment for food allergies. Epicutaneous immunotherapy (EPIT) is a treatment in which a patch containing the offending allergen is placed on the skin each day for a year or longer, thereby aiming to induce desensitization to the allergen (DBV Technologies, 2017; Jones et al., 2017). EPIT recently failed to meet its primary endpoint for a Phase 3 trial, with only 35.3% of patients responding to treatment, but it is still proceeding with the U.S. Food and Drug Administration (FDA) approval process (DBV technologies, 2017). A second option available to the general pediatric population and currently being studied in clinical trials is sublingual immunotherapy (SLIT), in which drops of allergen extract are placed under the tongue daily for a period of months to sometimes years, with the goal of inducing desensitization (Lanser et al., 2015). A third treatment option is OIT, available to children in private practice and undergoing continuing clinical trials. The offending food allergen is fed orally to the patient, first in minute amounts and then slowly increased over the course of months until the patient is able to tolerate a prespecified target dose of the food (Kulis et al., 2015). Although all three forms of immunotherapy have shown promise, OIT is the most widely studied food allergy treatment (Warren et al., 2016). The safety profile of both EPIT and SLIT are more favorable than OIT, producing few, if any systemic reactions. OIT, however, to date supersedes both EPIT and SLIT in efficacy (Kulis et al., 2015). In a randomized, double-blind, placebo-controlled study comparing peanut SLIT versus OIT in 21 children ages 7 to 13 years, after 12 months of treatment the median tolerated dose of peanut protein among those receiving SLIT therapy was 496 mg, or about two peanuts, whereas the median tolerated dose of those receiving OIT for 12 months was 7,246 mg of peanut protein, or about 29 peanuts (Narisety et al., 2015).

OIT protocols vary among providers but share some commonalities (Wasserman et al., 2014). OIT treatment is commonly divided into three stages: a rapid desensitization day at the onset of treatment, a gradual dose increase phase lasting for a period of several months, and a final maintenance phase continued indefinitely (Kulis et al., 2015). Although protocols vary by allergen and treatment provider, the rapid desensitization day usually begins with the patient ingesting micrograms of the allergenic proteins in question and ends with the consumption of several milligrams of the allergen. The second phase of treatment begins when the dosing amount achieved during the rapid desensitization day is consumed at home either daily or twice

daily for a set amount of time (often 1-2 weeks), depending on the protocol. If the patient does not experience any symptoms, the patient returns to the clinic for a medically supervised dose increase. That new dose is administered at home daily or twice daily for a set amount of time before returning for another dose increase. Dose increases continue over the course of months until a maintenance dose is achieved, which varies depending on the protocol. The patient is instructed to consume the maintenance dose daily for the foreseeable future (Wasserman et al., 2014).

OIT RESEARCH AND PEDIATRIC CLINICAL TRIALS

The first report of OIT occurred in 1908, published in the *Lancet*, entitled “A Case of Egg Poisoning.” In this case report, a 13-year-old boy who suffered from severe egg allergy (then deemed *egg poisoning*) was successfully desensitized to egg over the course of more than 6 months, beginning with 1/10,000 of an egg and slowly increasing to daily consumption of an entire egg by the end of treatment (Schofield, 1908). A century later, with rapidly rising food allergy prevalence, OIT research began to accelerate. Although OIT has a fairly high reaction rate, most reactions are mild, transient, and require no intervention. Some reactions do require treatment, however, including treatment with antihistamines and epinephrine-treated reactions (ETRs). The results, adverse effects, and safety profile of several OIT pediatric clinical trials are summarized in the Table.

Another potential adverse effect of OIT treatment is the development of eosinophilic esophagitis (EoE), a chronic allergic/immune condition caused by proliferation of eosinophils in the esophagus. It causes inflammation and can result in narrowing of the esophagus to the point of food impaction (American Academy of Allergy, Asthma, and Immunology, 2017). Younger children who present with EoE may refuse food or exhibit signs of failure to thrive. School-aged children with EoE may experience gastrointestinal discomfort or vomiting. School-aged children and teenagers may present with dysphagia. The only way to diagnose EoE is through an endoscopy and biopsy of the esophagus (American Academy of Allergy, Asthma, and Immunology, 2017).

A meta-analysis found that 2.7% of OIT-treated patients developed EoE during treatment (Lucendo, Arias, & Tenias, 2014). More recently, Silvers et al. (2017) characterized eosinophilic esophagitis-like OIT-related syndrome (ELORS) after a chart review of 427 OIT patients in a single private practice setting. ELORS is characterized by vomiting, either with or without gastric pain or nausea, 2 to 6 hours after consuming an OIT dose and at least a 25% increase in peripheral blood eosinophils from a pretreatment baseline level. The rate of ELORS during OIT was approximately 8.7%. Of these patients, 51% chose to discontinue OIT. The patients who continued with OIT reduced the allergen dose and then continued dose increases after a period of time. Of the 18 patients (49%) who continued treatment, 10 achieved the target maintenance dose (Silvers et al., 2017).

TABLE. Clinical endpoints and reaction rates of pediatric oral immunotherapy (OIT) research

Study type	Population (treatment arm)	Endpoint (treatment arm)	Reaction rates (treatment arm)	Intervention needed
Peanut OIT randomized, double-blind, placebo-controlled study (Varshney et al., 2011)	19 patients Hospital setting Median age = 7 years	84% ingested 4,000 mg of peanut protein	Initial escalation day: 9 (47%) reacted Build-up doses: 1.2% reaction rate out of 407 doses At-home doses: no ETR	Initial escalation day: 9 needed antihistamine, and 2 of those had an ETR Build-up doses: antihistamine, no ETR
Milk OIT randomized, double blind, placebo-controlled study (Skripak et al., 2008)	13 patients Hospital setting Mean age = 9.3 years	Median change in milk dose threshold was 5,100 mg	45.4% of doses produced a reaction	10.2% of doses needed antihistamine 0.2% of doses had an ETR
Egg OIT randomized, double-blind, placebo-controlled study (Burks et al., 2012)	40 patients Hospital setting Median age = 7 years	75% ingested 10,000 mg of egg protein	14.3% of doses produced mild symptoms, and 0.7% of doses produced moderate symptoms; no severe reactions	3.6% of doses were treated for mild or moderate symptoms
Chart review, peanut OIT (Wasserman et al., 2014)	327 patients from five practices, four community-based practices in the United States and one hospital in Israel Median age at each site ranged from 5 to 9 years	85% reached target maintenance dose for their practice (targets varied by practice from 415 mg of peanut protein to 8,000 mg of peanut protein)	Only ETR-treated reactions were recorded	0.7 out of 1,000 doses required ETR during escalation phase 0.2 out of 1,000 doses required ETR during maintenance phase

Note. ETR, epinephrine-treated reaction; OIT, oral immunotherapy.

OIT EXCLUSIONS

Currently, the only exclusions from OIT treatment include non-immunoglobulin E (IgE)-mediated food allergies, pre-existing eosinophilic esophagitis, and uncontrolled asthma (Levy, Elizur, Goldberg, Nachshon, & Katz, 2014; Lucendo et al., 2014). Recent data have shown that OIT is most effective in the preschool population, although that does not diminish its effectiveness on older children and adults (Vickery et al., 2017). Recent data also show that patients with lower food-specific IgE tend to fare better with peanut and egg OIT (Hague et al., 2017).

OIT TREATMENT EXPERIENCE

After carefully weighing the risks and benefits of SLIT and OIT treatment, the child's family decided to pursue OIT. They first approached the director of a peanut OIT clinical trial at a large children's hospital in their area, but the patient was excluded because of past medical history significant for asthma. His parents then decided to pursue OIT in a private practice setting. The boy first underwent egg OIT, completing the initial escalation day and then dosing with egg white powder twice daily at home and going for weekly appointments to increase his dose. It took a total of 6.5 months to desensitize to a whole egg. Although he did not experience an ETR, he did have several episodes of emesis during OIT treatment. After egg OIT, the patient successfully completed multi-nut OIT to peanut and hazelnut simultaneously. Like his experience with egg OIT, he had several episodes of emesis after dosing during the 7-month time period it took him to reach the maintenance phase of OIT. It is important to note that the patient was successful in OIT despite high IgE levels for egg white (52 kU/L) and for peanut and hazelnut (> 100 kU/L; reference range: elevated allergen-specific IgE level ranges from ≥ 0.35 kU/L to > 100 kU/L) and being an older child, two factors that often make OIT more difficult.

OIT AND QUALITY OF LIFE MEASURES

Although OIT treatment is not without risk, multiple studies have noted significant improvements in food allergy-specific quality of life for those who have completed OIT treatment (Factor, Mendelson, Lee, Nouman, & Lester, 2012; Otani et al., 2014). One 2012 study (Factor et al., 2012) measuring the quality of life of peanut-allergic children and their caregivers both before and after OIT found that quality of life improved on 100% of the questions on the food allergy quality of life survey when parents answered for their children ages 5 to 12 years. Quality of life also improved on nearly 92% of questions answered by children ages 8 to 12 years and on nearly 67% of questions answered by teenagers (Factor et al., 2012). Another OIT quality of life study found that caregivers' quality of

life significantly improved after multiple allergen OIT (Otani et al., 2014).

OIT AVAILABILITY, AFFORDABILITY, AND FDA APPROVAL

Although clinical trials for EPIT, SLIT, and OIT are ongoing, SLIT and OIT are being offered by a small but growing number of private practice allergists and otolaryngologists. The National Institute of Allergy and Infectious Diseases does not recommend food allergen-specific immunotherapy in clinical private practice (Boyce et al., 2010).

Since 2010, the debate both for and against OIT in private practice has continued. In 2014, a group of physicians from five different private practices published an

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article on the use of OIT in clinical practice stating that OIT protocols and information are widely available to the public and that restricting OIT to the realm of clinical trials may result in patients attempting to self-treat (Wasserman et al., 2014). They concluded, "Practicing allergists may consider offering this treatment to patients with peanut allergy" (Wasserman et al., 2014, p. 95). This prompted an editorial response from Robert Wood and Hugh Sampson (2014), two of the nation's leading allergists, stating that they "remain convinced that food OIT is not ready for clinical practice" (p. 98). Although OIT recommendations in the United States have not been officially updated since 2010, the European Academy of Allergy and Immunology recently updated its guidelines on the practice of OIT, concluding that OIT could be performed both in research facilities and in clinical sites that have substantial experience with OIT (Pajno et al., 2017). In a work group report issued by the American Academy of Allergy Asthma and Immunology, 28 U.S. and Canadian allergists reported using OIT in a nonacademic setting (Greenhawt & Vickery, 2015). That number has grown since 2015. The nonprofit, pro-OIT Web site OIT101.org (OIT 101, 2017) now lists nearly 70 board-certified allergists in the United States who offer OIT in private practice. Because OIT is a process and not a drug, it is not under purview of the FDA and therefore cannot gain FDA approval. The FDA can, however, approve a drug product associated with OIT (Greenhawt & Vickery, 2015). A peanut OIT product, AR101, is currently in Phase 3 clinical trials, with anticipated FDA approval possibly as early as 2018 (Gagné, 2016). AR101's Phase 2 results were promising, with 79% of subjects, ages 4 to 26 years old, meeting their primary endpoint of tolerating at least two peanuts after treatment (Bird et al., 2017). The approval of a product like AR101 will standardize peanut OIT and make OIT more

accessible to patients. That accessibility, however, comes at a cost. Analysts estimate that a year's worth of AR101 peanut pills could cost \$5,500 (Greenhawt & Vickery, 2015; Penumudi, 2015).

Many private practice OIT providers currently have patients source their own peanuts in the aisles of the local grocery store, making the treatment product much more affordable (Wasserman et al., 2014). Although there have not been extensive studies conducted on insurance coverage for OIT, a report issued in 2015 by the American Academy of Allergy, Asthma, and Immunology indicates that 43.5% of physicians offering OIT, both in private practice and in research facilities, were receiving insurance reimbursement for OIT, and only 13% of physicians stated that patients paid out of pocket for the treatment. The remaining funds for treatment came from research or grant funding and from pro bono work (Greenhawt & Vickery, 2015).

PATIENT OUTCOME

Because private practice OIT was not accessible in his metropolitan area, our patient traveled to a city several hundred miles away for treatment. In all, the patient and his family completed 51 appointments for OIT over the course of about 18 months. All of these appointments were covered by insurance, and the family paid only their specialist co-pay for each visit. After completing OIT for egg, peanut, and hazelnut, the patient and his family report greatly improved quality of life, including being able to eat out without speaking to restaurant staff and being able to attend social functions without worry about the food that would be present. At age 13 years, the boy continues to consume 8 g of peanuts, 7 g of hazelnuts, and a single scrambled egg daily to maintain his desensitization. He has not had any reactions to his maintenance doses or due to intentional or accidental ingestion of his allergens since completing treatment over a year ago. He follows up with the allergist once every 6 months to ensure compliance with dosing and to check allergen testing levels.

CLINICAL IMPLICATIONS

With the recent dramatic change in recommendation from the American Academy of Pediatrics advocating for early introduction of peanuts starting at age 6 months, early studies have suggested a decrease in the incidence of peanut allergy (Togias et al., 2017). For those patients already diagnosed with food allergies, nurse practitioners should be educated on the risks and benefits of food allergen therapies as families seek professional advice from trusted sources for therapy options. With a higher risk of ETR during the dose increase phase of treatment, they should help their patients weigh the risks and benefits of OIT treatment carefully (Wasserman et al., 2014). It is also clinically relevant for pediatric primary care providers to be able to recognize the symptoms of EoE and ELORS in patients

who may be undergoing treatment with OIT. Because of the delayed nature of these reactions, often occurring hours after a dose is consumed, patients may present to their primary care provider with intermittent nausea or vomiting, unaware that these symptoms could be related to OIT treatment (Silvers et al., 2017). Additionally, pediatric primary care providers may consider educating patients on the availability of OIT treatment if families are experiencing a significant reduction in their quality of life because of food allergies, with careful consideration of the risks and benefits involved. As patient demand and the body of favorable research about OIT grows, more allergists are offering the treatment. Social media is proving key in connecting both parents and children with OIT support groups, helping parents locate OIT providers, and providing emotional support during OIT treatment. All of these recent developments create great promise for children with food allergies and their families.

Nurse practitioners should be educated on the risks and benefits of food allergen therapies as families seek professional advice from trusted sources for therapy options.

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