



PROFESSOR PHILIPPE A EIGENMANN (Orcid ID : 0000-0003-1738-1826)

DR MOTOHIRO EBISAWA (Orcid ID : 0000-0003-4117-558X)

PROFESSOR MATTHEW GREENHAWT (Orcid ID : 0000-0002-2365-9372)

PROFESSOR JONATHAN HOURIHANE (Orcid ID : 0000-0003-4997-9857)

DR BENJAMIN C REMINGTON (Orcid ID : 0000-0001-5450-8334)

Article type : Rostrum

Addressing risk management difficulties in children with food allergies

Philippe A. Eigenmann¹, Motohiro Ebisawa², Matthew Greenhawt³, Jonathan O'B Hourihane⁴, Tamara T. Perry⁵, Benjamin C. Remington^{6,7}, Robert A. Wood⁸

¹ University Hospitals of Geneva, Department of Woman, Child and Adolescent, Pediatric Allergy Unit, Geneva, Switzerland.

² Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan.

³ Children's Hospital Colorado, University of Colorado School of Medicine, Aurora, CO, USA.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/PAI.13455](#)

This article is protected by copyright. All rights reserved

⁴ Paediatrics and Child Health, Royal College of Surgeons in Ireland, Children's Health Ireland, Temple St Hospital, Dublin, Ireland.

⁵ University of Arkansas for Medical Sciences and Arkansas Children's Research Institute, Little Rock, AR, USA.

⁶ Food Allergy Research and Resource Program, University of Nebraska, Lincoln, NE, USA.

⁷ Remington Consulting Group BV, Utrecht, The Netherlands.

⁸ Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA.

Correspondence to:

Philippe A. Eigenmann, Pediatric Allergy Unit, University Hospitals of Geneva, 6, rue Willy-Donze, CH-1211 Geneva 14, Switzerland

Phone +41-22-372 4531 Fax +41-22-372 4775

E-mail: Philippe.Eigenmann@hcuge.ch

Word count: 4304

Tables : 5 ; Figure : 1

Addressing risk management difficulties in children with food allergies

Pediatr Allergy Immunol 2020

Abstract

Risk is a concept inherent in every medical procedure. It can be defined as the probability of an adverse event in a defined population over a specified period of time. In the frame of food allergy management, it might be related to a diagnostic procedure, a treatment, or the consumption of foods. The risk of an adverse event can also be augmented by individual factors. This rostrum article discusses various aspects faced by children with food allergies in the light of risk, and their practical implications. Identifying personal risks for severe reaction, such as unstable asthma, and correcting them whenever possible also contributes to a reduction of the risk inherent to food allergy. Among the facets discussed, oral food challenges (OFC) are the most common diagnostic procedures implying an inherent risk. The risk of OFCs can be minimized by correct indication and timing of the test, a safe setting, as well as by ensuring that the patient is otherwise well without potential stressor potentially increasing the risk of a more severe reaction. Oral immunotherapy (OIT) has been studied as a potential treatment for increasing the threshold dose for reaction, and thus reducing the risk of accidental reaction. Nevertheless, the procedure is not devoid of risk as the patients may, and do often react, during the course of the procedure. Ingestion of trace amounts in processed foods, mainly in community settings such as restaurants, schools or day care, represent a potential risk of reactions, although for a minority of patients. Precautionary allergen labelling (PAL) is a wide spread strategy to reduce the potential risk of reactions due to traces. However, PAL is currently inefficient due to inconsistent labelling, also not indicating a clear maximum amount possibly present in the manufactured food. Finally, cost-effectiveness needs to be considered in risk management, as many risk-reduction procedures are clearly not cost-effective.

Keywords: food allergy, children, risk assessment, anaphylaxis, oral tolerance induction, oral food challenges, diagnosis.

Potential conflict of interests:

PAE received speaker's honoraria and research support from ThermoFisher Scientific, consultant fees from Nestlé, Abbott, DBV Technologies, reports royalty payments from UpToDate and Elsevier, and holds stock options in DBV Technologies.

ME received speaker's honoraria from DBV Technologies, and Mylan.

MG: is supported by grant #5K08HS024599-02 from the Agency for Healthcare Research and Quality; is an expert panel and coordinating committee member of the NIAID-sponsored Guidelines for Peanut Allergy Prevention; has served as a consultant for the Canadian Transportation Agency, Thermo Fisher, Intrimmune, and Aimmune Therapeutics; is a member of physician/medical advisory boards for Aimmune Therapeutics, DBV Technologies, Sanofi/Genzyme, Genentech, Glaxo Smith Kline, Merck, Nutricia, Kaleo Pharmaceutical, Nestle, Acquestive, Allergy Therapeutics, Allergenics, Aravax, and Monsanto; is a member of the scientific advisory council for the National Peanut Board; has received honorarium for lectures from Thermo Fisher, Aimmune Therapeutics, DBV Technologies, Before Brands, multiple state allergy societies, the American College of Allergy Asthma and Immunology, the European Academy of Allergy and Clinical Immunology; is an associate editor for the Annals of Allergy, Asthma, and Immunology; and is a member of the Joint Taskforce on Allergy Practice Parameters.

JOBH receives consultant fees and research funding from Aimmune Therapeutics, research funding from DBV Technologies and from Johnson & Johnson

TTP receives research grant funding from the National Institutes of Health.

BCR received research support and consultant fees from DBV Technologies.

RAW receives research funding from NIAID, Aimmune, Astellas, DBV technologies, Regeneron, Sanofi, and Genentech, and royalties from Up To Date.

Accepted Article

Introduction

The concept of risk is present in all human activity, and as health care providers we are aware that any procedure or treatment may involve an “inherent” risk. Nevertheless, the presence of risk is in contradiction with the dogma that “each health-related intervention needs to be safe and efficient”. In our specialty, one common procedure highlighting this is allergen-specific immunotherapy for venoms and environmental allergens, the most efficient treatment available to date to durably down-regulate allergy. Although it is a procedure not devoid of risk.

As a general rule, the decision of initiating a treatment is obvious when the risk of mortality or morbidity is high as in cancer therapy, even with a high risk of significant adverse events. However the decision is often less obvious when the absence of intervention objectively has less effect on the patient, even when the risk is less important. And it becomes evident that the benefit of the procedure must be weighed against the risk of renouncing. In recent years new treatments for more and more diseases have become available, and their “efficiency” has improved. More interventions also inevitably introduce new potential risks, a fact sometimes denied by the patient who might only perceive the positive aspects of a new treatment.

Risk can be a confusing topic with its varying definitions, timeframes and perceptions, but it can be defined as *the probability of an adverse event in a defined population over a specified period of time*. Thus it is important to clearly define the risk being presented and discussed. First, is the risk being evaluated within the allergic population or for a specific allergic individual? Second, is the risk under investigation (or being communicated) defined as a risk due to:

- Diagnostic procedures,
- Treatment / immunotherapy,
- Consumption of food...
 - Prepared by the allergic individual,
 - Prepared by others...
 - At home,
 - At a friend's or relative's house,

- In a restaurant / catering setting,
- A prepackaged food?

Third, what is the actual risk being presented? Is it the risk of an allergic reaction, a severe allergic reaction, a fatal allergic reaction, or something completely else? And fourth, what is the specified timeframe for the risk being evaluated (i.e. risk per eating occasion, per week, per month, per year, per lifetime)? Each of these multilayered “definitions” fit into the presentation a singular “risk”, which highlights the need for clear and consistent communication.

Finally, it is important to be aware that while everyone has the best interest of a food allergic individual in mind, the perception of risk for a food allergic individual can and will vary between different stakeholders [food allergic individual, parent or caregiver of a food allergic individual, healthcare providers, food safety and regulatory authorities (public health risk managers), pharmaceutical companies investigating therapeutic products, food business operators (restaurants, caterers, prepackaged food producers, etc)].

Perceptions of risk will be influenced by previous knowledge and experience, or lack thereof, with allergic reactions (1). In addition, the perception of risk might be very much different from the real risk of various events as shown in Figure 1. Subsequent differences in the perception of risk between these stakeholders can lead to different actions or outcomes for a scenario, all of which can lead to confusion and contradictory recommendations for the food allergic individual (1).

In this article, we aim to discuss various aspects involving the concept of risk, either individual factors, diagnostic or therapeutic procedures, specific risk-associated situations and include the benefit, and the objective and perceived risks. In addition, economic aspects in relation to risk management are discussed.

Predictors of severe reactions

Although the majority of food-induced reactions are not life-threatening, severe reactions can occur with exposure to food allergens. Severe reactions include those involving life-threatening symptoms such as respiratory or cardiovascular compromise; however,

predicting the prevalence of severe food reactions is difficult due to differences in criteria used to define severe reactions and variable methods used to collect data regarding food reactions (i.e. billing codes, self-report, etc). Further, reports on the severity of food-induced reactions may be inconsistent due to variability in the perception of severity or failure to seek treatment for food reactions by patients/caregivers, as well as variability in recognition of severe food-induced food reactions among healthcare providers (1,2).

Fatal anaphylaxis is rare as depicted in Figure 1 with a recent systematic review estimating the risk of fatal anaphylaxis among food-allergic individuals as 1.81 per million person-years (95% CI 0.94-3.45) (3). Although the actual risk of fatal reactions is low the perceived risk is typically very high and adversely affects the quality of life of patients with food allergies and is a source of considerable anxiety for patients and families (4).

Severe food-induced allergic reactions are multifactorial and variable (5), and a prior severe reaction cannot predict the risk of future reactions. Although severe reactions can be unpredictable, reducing these risks may be facilitated by recognizing factors that have been related to increased risk. These risks can be divided into two large categories, risks associated with patient factors and risks related to food allergens. Underlying patient factors include age, uncontrolled asthma, and sensitization status (1,2). Risks associated with the food allergen include the type of food and presentation of the allergen. For patient-related risks, individuals in the 2nd-3rd decade of life are at highest risk due to increased risk-taking behaviors including poor dietary compliance and failure to adequately treat allergic reactions (6,7). Patients with uncontrolled asthma are also at increased risk of lower respiratory symptoms which may be life-threatening (8). Serum and skin IgE testing are not predictive of reaction severity, however, sensitization to certain allergens has been related to increased risk of severe reactions such as Ara h 2 for peanut in some patient populations (9) although this has not been proven for all populations (10). Allergen-specific risk factors include type and presentation of the food allergen. Peanut and tree nuts are more likely to induce severe and fatal food reactions compared to other foods (6). Also, the preparation (cooked vs. raw) and bioavailability of the food can increase severity risk. For example, milk and egg allergens have reduced allergenicity when extensively heated and incorporated with wheat (i.e. baked goods) (1). Other factors that can alter the presentation of the allergen include exercise and ingestion

of alcohol or NSAIDs which may increase severity risk. (11). While it is impossible to reliably predict severe reactions, clinicians should counsel patients about these patient- and allergen-related risks in addition to ensuring they are adequately prepared to treat allergic reactions and have an emergency management plan. Table 1 provides a summary of the main aspects for possible risk reduction strategies in patients identified as presenting an increased risk for severe reactions.

Trace exposures and risk management

Accidental allergic reactions have occurred in a number of situations (i.e. consumption of packaged foods, meals outside the home, among others), with causes of reactions being attributed to both allergic individuals and their caregivers (i.e. forgetfulness, intentionally ignoring potential for risk, errors in reading a label, reduced supervision, errors in meal preparation), as well as the production of food by food business operators (i.e. cross-contact during production, use of wrong ingredient, manufacturer labeling errors). Due to reactions potentially being caused by a number of sources, a clear distinction must be made between food allergen management and food allergy management. Food allergy management (diagnostic procedures, initiation of an avoidance diet, instruction on reading labels, etc.) by an allergic individual and their caregivers should be conducted in an informed manner after consultation with, and education from their allergist and other healthcare providers (12). In contrast, food allergen management is conducted by food safety and regulatory authorities (public health risk managers) and food business operators. In a number of countries, food business operators are required to label the use of foods or ingredients derived from the most common allergenic foods (13). However, current regulations do not cover the management of unintended allergen presences (UAP) that can occur in “trace amounts” because of cross-contact during the production process. Further, “trace amounts” are not defined in regulations, with Japan being the notable exception (14). As such, precautionary allergen labelling (PAL) and its various forms (i.e. may contain, manufactured on shared equipment, manufactured in a shared facility) are voluntary in nature and can vary widely in wording or application (13,14). According to EU Regulation No. 1169/2011, voluntary food information shall not mislead the consumer, shall not be ambiguous or confusing, and where appropriate, it shall be

based on relevant scientific data. However, in practice the application of PAL is inconsistent and PAL does not correlate to the actual risk of an allergic reaction (13,14). These inconsistencies diminish the overall added value of PAL (15). It has been agreed upon by various stakeholders that PAL should bear a relationship to the actual risk and the decision-making criteria for application of such labelling should be transparent to all stakeholders (13,14,16). The need for transparent, risk-based labelling is further highlighted by the fact that allergens have been analytically detected in similar frequencies and in similar concentrations for prepackaged foods, regardless of whether PAL for a specific allergen was present or not (13,17). Additionally, allergic reactions and anaphylaxis have been reported at similar frequencies to foods with or without PAL (17,18). The need for PAL, or its absence, should be based on a consistent allergen risk assessment framework which utilizes quantitative benchmarks or “reference doses” in a such as those proposed by the VITAL ® Program (19). If transparent, risk-based PAL could be widely applied, it could reduce the burden of reading and interpreting labels for food allergic consumers & their caregivers, and provide an added value when trying to make informed food choices (13). Table 2 provides a summary of the main aspects for possible risk reduction strategies related to trace-management, and their potential benefits to the patient.

Nevertheless, PAL is currently not effective, no matter the threshold, due to the inconsistent application. Also, PAL does not always mean a low exposure, so while unlikely, it is still possible that a product with PAL contains over 1000mg of the allergenic protein.

Food challenges

An Oral Food Challenge (OFC) is the standard definitive test to confirm or refute a diagnosis of allergy to food, usually performed under supervision in an experienced medical facility. Patient selection has a significant impact on OFC outcome rates, with conservative (relatively risk averse) criteria leading to most OFCs (up to 90%) being negative, less conservative (relatively risk amenable) having a 50:50 positive-negative split, and research protocol-based OFCs studies (e.g. qualifying for a treatment study)

having a very high rate of reaction. An OFC may be offered at the first presentation if there is sufficient uncertainty of the presumed diagnosis or may be used to confirm a previously confirmed allergy has resolved or persisted over time. There are well accepted protocols and set criteria to determine the outcome of an OFC. Clearly the best outcome from a food challenge is “passing”/ a negative result, which allows the specific allergy diagnosis to be removed, with predictable changes in patients’ quality of life. It is well known in the specialty but not widely understood in the community that a “failed”/positive challenge can have nearly as great a positive impact, because it removes uncertainty and addresses the common, unfounded fear that each reaction inevitably escalates in severity. It also gives families an opportunity to be guided through how they could manage a similar reaction in the community and to have specific and focused dietary and lifestyle advice. And now as food allergy treatments become more widespread, it can also help determine which patients are most likely to benefit from treatment. An intermediate or inconclusive outcome from OFC is usually due to a combination of a child’s developmental stage or anxiety of the child or their parents’. These can be mitigated by rescheduling and offering interim review or support from other health care services.

Anaphylaxis is the greatest risk in OFC but it is uncommon. Any unit doing OFC must be fully resourced to deal with such cases.

OFC is a controlled incremental exposure to a food allergen and as such is quite different to exposures in the community. In OFC most augmentation/cofactors are controlled and OFC is terminated as soon as the set criteria are met. This is quite different to community reactions, with which OFC outcome do not correlate strongly. EAACI guidelines 2014 suggest low dose reactivity is an indication for adrenaline kit prescription but it appears dose has only a small influence on outcome of an OFC, compared to other factors such as asthma status and previous reaction severity (20).

The decision if and when to challenge is a good example of shared decision making between clinicians and families. OFC-proof of allergy can be required for reimbursement reasons in some health economies and in others access and resources are so poor that careful selection becomes more a medical decision. Babies with milk or egg allergy may

need challenges relatively soon after diagnosis to ensure the food allergy hasn't already completely or partly resolved. For more persistent or already confirmed food allergies like peanut, OFC can be delayed, pending interim review over several years, seeking reports of community exposures, and evaluation of changes in SPT and sIgE levels. It is vital to note that children who have simply had blood tests done for whatever reason but who have never eaten the food being avoided, may need OFC irrespective of the test results, as decision points/ values for SPT and sIgE that many non-specialists rely upon were not derived in such populations. Oral and epicutaneous immunotherapy options may require an entry OFC, irrespective of other factors, to set the eliciting dose which can then be compared with the post OIT eliciting dose. Table 3 provides a summary of the main aspects for possible risk reduction strategies related to oral food challenges, and their potential benefits to the patient.

No medical procedure is without risk. OFC risk can be minimized by correct timing of the test and by ensuring the patient is otherwise medically well and without other stressors such as fatigue, lack of sleep or viral infections, on the day of challenge.

Oral immunotherapy

What is Oral Immunotherapy (OIT)?

OIT involves mixing an allergenic food into a vehicle and consuming it in gradually increasing doses (21). OIT protocols vary in the type of food and vehicle used, with some using commercially available foods in their natural forms while others use specifically prepared products such as the first FDA approved OIT product, AR101 for the treatment of peanut allergy. Most OIT protocols include an initial escalation phase, followed by dose build-up phase and maintenance phases with considerable variability depending on the study. The initial escalation phase is typically conducted over one to two days, using rapid up-dosing starting from a very small dose - that is extremely unlikely to cause any adverse reaction - and progressing to a dose that is still likely safe for home administration. If tolerated, the dose is escalated incrementally (usually biweekly or weekly) until a target maintenance dose is reached or the subject reaches

dose-limiting symptoms. There is considerable variation between studies regarding the target maintenance dose, ranging from 300 to 4000 mg of proteins. At the lower maintenance doses, such as that used with AR101, the goal of treatment is protection from small, accidental exposures, while higher dose therapies are more likely to allow ingestion of the larger amounts of the food in a dietary form.

The potential efficacy of food OIT depends on the defined endpoints, including the ability to tolerate the treatment, the induction of desensitization alone, and/or the development of a more durable state of clinical tolerance, which is often referred to as “sustained unresponsiveness” (SU). Desensitization is defined as a temporary increase in the threshold for reactivity, with maintenance of the desensitized state requiring continued consumption of the allergenic protein. While all studies have demonstrated that the majority of patients treated with OIT can be successfully desensitized, SU is less commonly achieved. Thus, as far as we know at this time, the vast majority of patients will need to be treated indefinitely to maintain protection, or at least ingest some form of the food on a regular basis.

Safety of OIT

Adverse reactions are very common with OIT, with overall rates similar for peanut, milk, egg, and wheat. Reactions are generally mild and local symptoms such as oral itching are most common. Abdominal pain is the most common symptom leading to withdrawal from treatment, and moderate reactions, such as wheezing, vomiting, and urticaria occur in a small percent of all doses. However, given that doses are given daily over an extended period of treatment, the risk for each patient is substantial. A recent systematic review found that peanut OIT significantly increases the risk of anaphylaxis compared to avoidance alone (22). It is especially concerning that most severe reactions occur unpredictably, with a dose that has been previously tolerated, often associated with co-factors such as infection, exercise, anxiety, or allergen co-exposure (23–26).

A major impediment in moving OIT to widespread clinical practice is the high percent of patients who cannot tolerate the treatment. Overall, 10-20% of subjects have dropped out of OIT trials, with rates as high as 36%. While some participants have withdrawn due to anaphylaxis or other acute reactions, the vast majority of withdrawals are due to

chronic abdominal pain. Eosinophilic esophagitis has been documented in some of these cases and it is not clear how frequently undiagnosed disease may complicate OIT (27,28). Further studies directed at minimizing adverse reactions are therefore critically important to move these treatments forward in clinical use. Table 4 provides a summary of the main aspects for possible risk reduction strategies and benefits related to OIT.

Eating out (restaurants / schools...)

It is a burden for food allergy sufferers to eat out, especially when they are allergic to common foods, hard to avoid, such as milk and egg. Current legal requirements for allergens labeling in processed foods are most helpful for identifying definite ingredients, nevertheless it is often difficult to identify potential contamination during the food preparation process. In addition, getting accurate information about ingredients when eating out is most often challenging. Food allergy sufferers also have difficulty when traveling as they eat dishes they do not consume usually. These conditions may vary greatly from country to country, and are require continuous adaptation. Also, when traveling, language barriers are additional difficulties increasing the risk of accidental reactions. In order to overcome these hurdles, patients with food allergies and their families eating out and travelling need to seek appropriate information and adapt to local rules, when available, for food allergy.

School and day care

Food allergy is the most common cause of anaphylaxis in childhood (29), and schools and day care are places of increased risk of reaction. Food allergy and anaphylaxis prevention measures in school and day care vary greatly from country to country, and even between schools of a same area. Whether meals are provided by the institution at school and day care, or brought from home may largely influence the risk of reaction. Most often, large facilities deliver foods to schools increasing the inherent risk of contamination by an allergen. Thus, accidental ingestion are a real threat at school, rendering proper emergency treatment plans necessary. Legislation for treatment plans

may vary between countries. In the United States of America, most states allow school nurses to use self-injectable adrenaline at school when any student develops anaphylaxis due to food allergies or other causes. In Japan, school personnel are allowed to use self-injectable adrenaline but only for the students who are prescribed self-injectable adrenaline. In Europe, anaphylaxis treatment plans at schools vary in-between countries and regions. For example, teachers in Germany are not allowed to use self-injectable adrenaline. Furthermore, there are many developing countries where self-injectable adrenaline kits are not available. Table 5 provides a summary of the main aspects for possible risk reduction strategies related to meals in "non-safe" places, and their potential benefits to the patient.

How economic aspects influence risk management

Managing risk in food allergy can be viewed through the lens of cost and value. Risk in food allergy is mainly focused on fatality risk, given concerns that severe reactions can become fatal ones, and our policies are intended to protect against fatal reactions. However, as stated earlier, the risk of fatal food induced anaphylaxis is actually exceedingly low, though cases happen annually. While uncomfortable to contemplate, risk management strategies have to have value, and the cost to save one life or prevent one death cannot be excessive—a standard governments and payers apply to judge and prioritize interventions. Cost-effective interventions produce maximal quality-adjusted life-years (QALY) (e.g., a year of perfect health relative to a condition, measured by quantifying what a patient may be willing to sacrifice to maximize healthy life with their condition) at the lowest cost, within an economy-specific cost/QALY threshold. Low-value care exists where alternative options provide superior outcomes at lower costs (30). What the data suggest from recently published analysis is that despite noble intentions, our risk management strategies may be of low value.

Surprisingly, our most common option, the epinephrine auto-injector (EIA) is low-value and costly at preventing fatality. EIAs retail at approximately \$700 US/twinpack. When simulating how effective devices are at reducing the risk of fatality (estimating devices reduce the risk between 10-1000-fold), EIAs were only cost-effective at a ceiling price of

\$24 US/twinpack (31). Placing these devices in schools as part of stock epinephrine policy (same risk-reduction range) is cost-effective vs. not doing so. However, the model of having all students supply their own twinpack in addition to two undesignated units at the school costs \$7419/student and produces fewer qualities than purely sharing the devices across all students at the school, without requiring anyone to supply their own individual units (32).

Other things we do to reduce fatality risk from a food allergic reaction also are low-value. First, advising strict avoidance of precautionary labelling (PAL, using the same 10-1000 fold risk-reduction) was associated with an incremental cost of \$182,434,277 per life saved vs. allowing PAL consumption, but the most cost-effective strategy was to perform a “one-shot” ED5 (dose eliciting a reaction in 5% of allergic individuals) peanut challenge to determine if PAL avoidance was necessary (33). Secondly, some anaphylaxis action plans advocate pre-emptively injecting epinephrine immediately upon known or suspected ingestion, before symptoms emerge, to prevent severe reactions (34). However, treating pre-emptively had an incremental cost of \$110,270,820 per death prevented and only reduced the fatality rate by <0.0001 over a 20-year modelled horizon, irrespective of past reaction history compared to treating only after symptoms emerge—again, low value (33). Third, automatically calling emergency medical services for transportation to the emergency department (ED) after using epinephrine (recommended on most anaphylaxis action plan), compared to watchful waiting and only activating this path if the person fails to stabilize, is also low-value and associated with incremental costs of \$1,349,335,651 per death prevented (35).

Taking this one step further, even certain prevention and treatment strategies may also have low-value. In comparing the United States National Institute of Allergy and Infectious Disease (NIAID) early introduction policy model to those recommended by the UK, European Society of Allergy and Clinical Immunology, Australasian Society of Clinical Immunology and Allergy models, the NIAID strategy (screening of high-risk infants with peanut skin testing, and advising against introduction this is $>8\text{mm}$), vs. a non-screening approach was associated with incremental costs of approximately \$654,000,000 and prevented 3,200 fewer peanut allergy cases over a 20-year horizon (36). Similar screening models applied to early egg introduction or introducing peanut to

the younger sibling of a peanut allergic child resulted in higher costs and fewer cases of allergy prevented (37,38). Finally, the potential cost-effectiveness of a commercially approved peanut oral immunotherapy product and a peanut epicutaneous immunotherapy product awaiting a decision on approval are somewhat narrow, and dependent on annual price, rates of attaining sustained unresponsiveness, rates of reduction in the risk of anaphylaxis, and gain in health utility that have yet to be demonstrated (38).

Collectively, when exploring policies, treatment strategies, and recommended actions to help prevent food-induced fatality, most actions are costly and have limited effectiveness. In trying to understand how this may have evolved, it may be in part that fatality is rare outcome, very difficult outcome to shift, and unlikely altered by most strategies we recommend. Morbidity is potentially a more modifiable outcome and perhaps a better focus, but many management strategies may artificially increase morbidity indicators, such as Emergency Department utilizations epinephrine use, creating noise around a critical signal.

A rational approach of risk management in food allergy

Food allergy is a disease with objectively moderate morbidity (effects on quality of life, significant reactions infrequent), but a very low mortality. Nevertheless, the perception of the inherent overall risk of the disease is perceived as high in the community, and may significantly leverage decision-making and policy.

- Strategies to diminish the risk inherent to food allergy must combine personal & cultural acceptance of risk, along with scientifically established management of food allergy (diagnosis, follow-up, and management).
- Risk assessment related to food allergy needs to consider strategies that are justified on the basis of health economics.
- Efficiently defined personalized risk management strategies related to food allergy can only be established at a personal level with the agreement of the patient, based on accurate information provided by a knowledgeable health professional.

- Accepted Article
- New treatment approaches may be of both psychological and medical benefit for some patients / families but may actually increase the overall risk of reactions in the short term.
 - Finally, as “next-generation” treatment approaches emerge over the next 10 – 20 years the risk:benefit profile of food allergy may change dramatically.

References

1. Turner PJ, Baumert JL, Beyer K et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy* 2016: **71**:1241–1255.
2. Dubois AEJ, Turner PJ, Hourihane J et al. How does dose impact on the severity of food-induced allergic reactions, and can this improve risk assessment for allergenic foods?: Report from an ILSI Europe Food Allergy Task Force Expert Group and Workshop. *Allergy* 2018: **73**:1383–1392.
3. Umasunthar T, Leonardi-Bee J, Hodes M et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy* 2013: **43**:1333–1341.
4. van der Velde JL, Dubois AEJ, Flokstra-de Blok BMJ. Food allergy and quality of life: what have we learned? *Curr Allergy Asthma Rep* 2013: **13**:651–661.
5. Boyce JA, Assa'ad A, Burks AW et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. *J Allergy Clin Immunol* 2010: **126**:S1-58.
6. Burks AW, Tang M, Sicherer S et al. ICON: food allergy. *J Allergy Clin Immunol* 2012: **129**:906–920.
7. Pouessel G, Tanno LK, Claverie C et al. Fatal anaphylaxis in children in France: Analysis of national data. *Pediatr Allergy Immunol* 2018: **29**:101–104.
8. Wang J, Liu AH. Food allergies and asthma. *Curr Opin Allergy Clin Immunol* 2011: **11**:249–254.
9. Asarnoj A, Movérare R, Ostblom E et al. IgE to peanut allergen components: relation to peanut symptoms and pollen sensitization in 8-year-olds. *Allergy* 2010: **65**:1189–1195.

10. Nicolaou N, Poorafshar M, Murray C et al. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J Allergy Clin Immunol* 2010; **125**:191-197.e1-13.
11. Sicherer SH, Sampson HA. Food allergy: A review and update on epidemiology, pathogenesis, diagnosis, prevention, and management. *J Allergy Clin Immunol* 2018; **141**:41–58.
12. Muraro A, Werfel T, Hoffmann-Sommergruber K et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014; **69**:1008–1025.
13. Allen KJ, Taylor SL. The Consequences of Precautionary Allergen Labeling: Safe Haven or Unjustifiable Burden? *J Allergy Clin Immunol Pract* 2018; **6**:400–407.
14. Manning L, Soon JM. An alternative allergen risk management approach. *Crit Rev Food Sci Nutr* 2017; **57**:3873–3886.
15. Graham F, Caubet J-C, Eigenmann PA. Can my child with IgE-mediated peanut allergy introduce foods labeled with “may contain traces”? *Pediatr Allergy Immunol* 2020; **31**:xx.
16. DunnGalvin A, Chan C-H, Crevel R et al. Precautionary allergen labelling: perspectives from key stakeholder groups. *Allergy* 2015; **70**:1039–1051.
17. Blom WM, Michelsen-Huisman AD, van Os-Medendorp H et al. Accidental food allergy reactions: Products and undeclared ingredients. *J Allergy Clin Immunol* 2018; **142**:865–875.
18. Zurzolo GA, Allen KJ, Peters RL et al. Self-reported anaphylaxis to packaged foods in Australia. *J Allergy Clin Immunol Pract* 2019; **7**:687–689.
19. Taylor SB, Christensen G, Grinter K et al. The Allergen Bureau VITAL Program. *J AOAC Int* 2018; **101**:77–82.

20. Pettersson ME, Koppelman GH, Flokstra-de Blok BMJ et al. Prediction of the severity of allergic reactions to foods. *Allergy* 2018: **73**:1532–1540.
21. Wood RA. Food allergen immunotherapy: Current status and prospects for the future. *J Allergy Clin Immunol* 2016: **137**:973–982.
22. Chu DK, Wood RA, French S et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. *The Lancet* 2019: **393**:2222–2232.
23. Skripak JM, Nash SD, Rowley H et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008: **122**:1154–1160.
24. Hofmann AM, Scurlock AM, Jones SM et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 2009: **124**:286–291, 291.e1-6.
25. Narisety SD, Skripak JM, Steele P et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2009: **124**:610–612.
26. Anagnostou K, Islam S, King Y et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet Lond Engl* 2014: **383**:1297–1304.
27. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol Off Publ Am Coll Allergy Asthma Immunol* 2011: **106**:73–74.
28. Sánchez-García S, Rodríguez Del Río P, Escudero C et al. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol* 2012: **129**:1155–1157.

29. Nagakura K-I, Sato S, Asaumi T et al. Novel insights regarding anaphylaxis in children - with a focus on prevalence, diagnosis, and treatment. *Pediatr Allergy Immunol* Published Online First: 10 June 2020. doi:10.1111/pai.13307
30. Shaker M, Greenhawt M. A primer on cost-effectiveness in the allergy clinic. *Ann Allergy Asthma Immunol* 2019; **123**:120-128.e1.
31. Shaker M, Greenhawt M. Association of Fatality Risk With Value-Based Drug Pricing of Epinephrine Autoinjectors for Children With Peanut Allergy: A Cost-effectiveness Analysis. *JAMA Netw Open* 2018; **1**:e184728.
32. Shaker MS, Greenhawt MJ. Analysis of Value-Based Costs of Undesignated School Stock Epinephrine Policies for Peanut Anaphylaxis. *JAMA Pediatr* 2019; **173**:169–175.
33. Shaker M, Greenhawt M. The Health and Economic Outcomes of Peanut Allergy Management Practices. *J Allergy Clin Immunol Pract* 2018; **6**:2073–2080.
34. Turner PJ, DunnGalvin A, Hourihane JO. The Emperor Has No Symptoms: The Risks of a Blanket Approach to Using Epinephrine Autoinjectors for All Allergic Reactions. *J Allergy Clin Immunol Pract* 2016; **4**:1143–1146.
35. Shaker M, Kanaoka T, Feenan L et al. An economic evaluation of immediate vs non-immediate activation of emergency medical services after epinephrine use for peanut-induced anaphylaxis. *Ann Allergy Asthma Immunol* 2019; **122**:79–85.
36. Shaker M, Stukus D, Chan ES et al. ‘To screen or not to screen’: Comparing the health and economic benefits of early peanut introduction strategies in five countries. *Allergy* 2018; **73**:1707–1714.
37. Shaker M, Verma K, Greenhawt M. The health and economic outcomes of early egg introduction strategies. *Allergy* 2018; **73**:2214–2223.
38. Shaker MS, Iglesia E, Greenhawt M. The health and economic benefits of approaches for peanut introduction in infants with a peanut allergic sibling. *Allergy* 2019; **74**:2251–2254.

Accepted Article

Table 1: **Aspects of risk reduction for severe reactions**

Strategy	• Reducing/suppressing factors increasing the risk of severe reactions • Provide treatment plans for accidental reactions
Effectiveness	• High when risk factors (e.g. co-factors such as exercise) are identified • Treatment plans with emergency medications made available to the patients may save lives
Costs	• Cost of emergency care / medications Necessitates a well-trained health professional team
Benefits	• Reduced number of reactions • Reduced severity of reactions, decreased morbidity and mortality
Efficient?	• Yes, significant decrease of risk, but need to consider the cost of emergency care / medications

Table 2: **Aspects of risk reduction with traces**

Strategy	• Avoidance of foods labeled with “may contain...”
Effectiveness	• Low for all patients due to the inconsistent application of PAL and no correlation of PAL (presence or absence) with the actual risk • Potentially high for patients with a low threshold of reactivity • Potentially still low for most patients with food allergies, as their threshold of reaction is above trace amounts
Costs	High due to reduced quality of life, with little “return on investment” for patients with a high threshold of reactivity
Benefits	• Less reactions in patients with a low threshold of reactivity • Feeling of safety for all food allergic patients/families • Reduced risk of litigations for the food industry
Efficient?	• Efficient only if food choices are broadened though the consistent application of PAL which correlates with the actual risk, and egregious PAL is removed from products that do not present a risk.

Table 3: **Aspects of risk reduction with oral food challenges**

Strategy	• Performing a food challenge
Effectiveness	• Gold standard for the diagnosis and persistence assessment of food allergy
Costs	• Cost of the diagnostic/food allergy follow-up procedure, including the cost of a food challenge • Necessitates a well-trained health professional team • Risk of significant reactions
Benefits	• Better quality of life from a clear diagnosis • Reduced social and health costs after negative challenge
Efficient?	• Yes, OFC provide a clear benefit with either outcome, no reaction or reaction

Table 4: **Aspects of risk reduction with OIT**

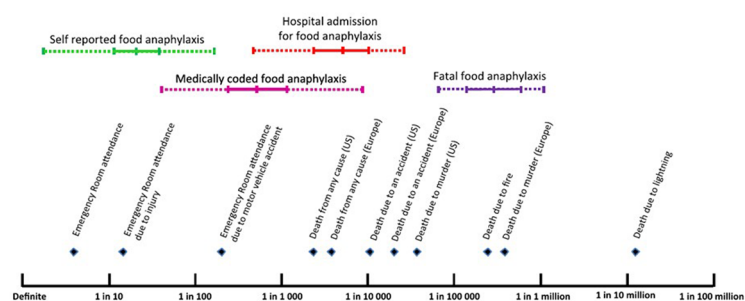
Strategy	• Successfully induce desensitization
Effectiveness	• Effective in most but comes with a significant risk of adverse reactions
Costs	• Costs are significant, due to: • Medical care needed to provide the treatment • Heavy burden on the patient / family • Caring for patients during treatment related reactions
Benefits	• Possibly improved quality of life • Possibly reduction in adverse reactions due to accidental exposures over time
Efficient?	• No, this is a slow, burdensome process that may need to be continued indefinitely given limited data regarding sustained unresponsiveness

Table 5: **Aspects of risk reduction for “eating out”**

Strategy	• School and community emergency care plan
Effectiveness	• High when standardized and well instructed, and implemented
Costs	• Significant burden of community organization • Increases the stress of care takers
Benefits	• Reduced number of reactions • Reduced severity of reactions, decreased morbidity and mortality
Efficient?	• Yes, significant decrease of risk, but with a substantial cost for the community

Legend of Figure 1

Annual incidence rate for different events in patients with food allergies aged 0-19 years, in comparison with other events. Continuous bars represent means with 95% CI and dotted bars the range of point estimates. Reproduced and adapted with permission from (3).



pai_13455_f1.tif