Theme Editorial

Striving for Evidence-Based Management of Food Allergies

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This issue of JACI: In Practice highlights several advances in food allergy diagnosis and management. It comes 7 years after Du Toit et al’s seminal randomized, double-blinded, clinical trial Learning Early About Peanut (LEAP) that has led to a revolution in our thinking about food allergy prevention. The LEAP study clearly demonstrated that, at least in high-risk infants and young children with eczema and egg allergy, food avoidance increases the prevalence of peanut allergy. The aim of this theme editorial is to highlight key take-home messages and ongoing challenges presented in this issue’s Rostrum and Review articles that clinicians currently face regarding the diagnosis and management of patients with suspected food allergies.

IS IT POSSIBLE TO REPLACE THE ORAL FOOD CHALLENGE AS THE GOLD STANDARD IN DIAGNOSIS?

Accurate diagnosis is critically important to avoid the adverse effects of inappropriately labelling patients with food allergy. In vitro immunoglobulin E (IgE)—based tests measure allergen sensitization and correlate less well with clinical disease where the positive predictive value can be as low as 10% to 30% in patients with no history of ingestion of the food. As such, these tests should not be used as a screening test, but rather to support the clinical diagnosis in patients presenting with a history of an allergic reaction to a specific food. Incorrect diagnosis and labelling of patients as food allergic can lead to unnecessary dietary and lifestyle restrictions, as well as increase the risk of new allergies developing. In this issue, Santos et al discuss bead-based epitope assay, basophil activation test (BAT) and mast cell activation test as potential next-generation food allergy diagnostics. They compare the accuracy of these tests with the gold-standard oral food challenge as well as with routinely available in vitro IgE-based tests. The authors outline a pathway to bring these next-generation tests to the clinic, involving standardization, technical and external validation, as well as solving practical and logistic issues such as the need for fresh peripheral blood to perform BAT, and regulatory approval. However, for peanut allergy, BAT is no more accurate than skin prick tests in predicting threshold of reactivity and has a similar accuracy to peanut Ara h2 in predicting severity (both 100% sensitive, BAT 97% specific compared with Ara h2 92%). The predictive value of these tests for most other foods is unknown. Thus, at present, oral food challenge remains the best method of diagnosing food allergy and the only accurate method of predicting threshold of reactivity.

DEATHS FROM FOOD-INDUCED ANAPHYLAXIS

The potential for anaphylaxis to compromise breathing and circulation is of concern for patients suffering from immediate allergic reactions to foods, as well as their caregivers and physicians. In a Clinical Commentary Review entitled Fatal food anaphylaxis: dissecting fact from fiction, Anagnostou et al highlight the fact that, although the perceived risk from food-induced anaphylaxis is high, deaths are rare with an incidence of 1 to 2 per million and have halved over the last 20 years. In comparison, the fatality rate from drug-induced anaphylaxis is 8 times greater.

Fatality rates are highest in adolescence and young adults. In a U.S. observational study of 63 patients dying from food-associated anaphylaxis, 57% of deaths were in those 16 to 30 years old; 29% were in children younger than 16 years; and 14% were in those older than 30 years. The reasons for the higher risk of death in young people are likely to be multifactorial and include greater risk-taking behavior. Asthma is a poor predictor of subsequent severe outcomes because it is a comorbidity in most patients with food allergy. Previous reaction severity, exercise, and intercurrent infection are also poor and inconsistent predictors of death.

Intramuscular epinephrine is the recommended first-line treatment for anaphylaxis. However, at least 80% of anaphylactic events resolve spontaneously. Subcutaneous epinephrine was recognized as an effective treatment for acute bronchospasm a century ago but, because of potential for cardiac complications, inhaled salbutamol is now the treatment of choice. Although not discussed in the accompanying reviews, we suggest that the relative effectiveness of intramuscular epinephrine and inhaled salbutamol might be actively explored in future clinical trials as primary treatment for patients with food-induced mild to moderate bronchospasm where there is no upper airway or circulatory compromise.

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COMPLEX INTERPLAY BETWEEN IMMEDIATE AND DELAYED FOOD ALLERGY

Although most allergy practices focus on treating patients with immediate hypersensitivity to foods, there is growing recognition of delayed reactions. For instance, it is well recognized that 10% to 20% of patients avoiding foods because of acute allergies develop delayed reactions when they are reintroduced. Similarly, 20% to 30% of patients avoiding foods because of delayed hypersensitivity reactions develop acute allergic reactions on attempted reintroduction. Skypala et al’s review highlights the complex interplay between these 2 types of hypersensitivity responses. They focus on food protein–induced enterocolitis syndrome and eosinophilic esophagitis, as well as the challenges of managing multiple food allergies and consequent food aversions.

The long-term adverse effects of food allergies and food avoidance on the physical and psychosocial health of patients and their families should not be underestimated. Patients with multiple food allergies are at risk of nutritional deficiencies and poor growth, as well as social isolation owing to fear and embarrassment. Parents and their caregivers may become anxious, distressed, frustrated, and self-blaming. The harm caused by removing foods from children’s diet where food allergies have not been objectively proved may be difficult to reverse. Feeding skills develop early in childhood. Discomfort, irritation, or avoidance during these sensitive developmental stages can lead to life-changing maladaptive eating behaviors that are difficult to reverse. Regular follow-up to address nutritional and psychosocial needs is important to deal with maladaptive learned feeding behavior, build confidence, reduce anxiety, and normalize mealtime dynamics.

REDUCING THE BURDEN OF FOOD ALLERGY: PROMOTING TOLERANCE

Most management guidelines advocate avoidance as the standard for patients with food allergies. However, only a quarter of patients with peanut allergies react to 25 mg or less of the food, the remainder react to 100 mg or more. Two Clinical Management Reviews in this issue discuss recent advances and ongoing challenges in oral immunotherapy (OIT). Sicherer et al present the case for consuming foods in subthreshold amounts to maintain and promote tolerance in patients who do not react to trace amounts. Perrett et al focus on OIT for foods other than milk, egg, and peanuts; long-term management of patients; and strategies for managing patients who suffer allergic reactions during immunotherapy.

Allergists often assume that patients and their caregivers are too risk-adverse to consider OIT and that those who react will pursue legal proceedings. These reviews recommend that allergy management moves beyond these unilateral assumptions and a paternalistic approach by clinicians to treatment. Bidirectional decision making between health care professionals, the patients, and caregivers as equal partners should be the modern standard of care. Contraindications to instigating OIT include patient’s inability to cope with instructions, lack of time/commitment, uncontrolled asthma, and pregnancy.

Changes are already being made in the way we manage food allergies. Sixty to 80% of children with IgE-mediated milk and egg allergies tolerate these products when baked. As such, milk and egg OIT is standard practice in many allergy centers. Data from clinical trials and preliminary clinical practice also suggest that OIT is effective in some peanut-allergic patients. Thus, OIT may also be considered for other foods such as tree nuts, sesame, and fish, in a similar way that the principles of drug desensitization are already being applied to any drug. Where possible, OIT should be performed with food from the grocers to prevent medicalizing patient’s diets more than is necessary.

Risk of immediate allergic reactions during OIT remains a concern, with epinephrine administered to 14% of patients taking part in the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults (PALISADE). Clear home-dosing instructions are required, as are advice on avoiding exacerbating factors and treatment of reactions. The potential for delayed hypersensitivity reactions such as eosinophilic esophagitis that may have been subclinical before starting OIT should also be discussed. Real-life, follow-up studies are required to evaluate the practicalities, risks-benefits, compliance, length of treatment, and overall effectiveness of this
approach. The quantity of food that needs to be consumed to prevent allergic reactions and how often it should be ingested still need to be determined. Previous studies have shown that compliance declines as intake increases. One study showed a compliance rate of 94% when 4 peanuts were recommended, compared with 69% with 10 peanuts.17

PRIORITIZING EVIDENCE-BASED DIAGNOSIS AND MANAGEMENT OF FOOD ALLERGY

Progress in any field of medicine requires challenging dogma, particularly when it is not evidence based. There is now sufficient evidence to demonstrate that incorrect labelling of patients with food allergies and unnecessary food avoidance are detrimental to the physical and mental well-being of the patients and their families. In addition, unnecessary avoidance has helped to stoke the current food allergy pandemic. In this regard, the current food allergy pandemic parallels the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic, where long-term attempts at avoidance have largely failed at both an individual and a societal level, and the solution lies in inducing protective immunity/tolerance with immunotherapy. Health care professionals need to be rigorous in their diagnosis, and where possible, promote tolerance rather than avoidance particularly in young children, if the burden of food allergy is to be reduced (Figure 1).

REFERENCES