

EDITORIAL

Early Allergen Introduction for Preventing Development of Food Allergy

Matthew Greenhawt, MD, MBA, MSc

In 2000, the American Academy of Pediatrics (AAP) recommended that “solid foods should not be introduced into the diet of high-risk infants until 6 months of age, with dairy products delayed until 1 year, eggs until 2 years, and peanuts, nuts, and fish until 3 years of age” in “infants at high risk for



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developing allergy, identified by a strong (biparental, parent, and sibling) family history of allergy” to help prevent food allergy from developing.¹ In 2008, the AAP revised this guidance, stating that new evidence raised “serious questions about the benefit of delaying the introduction of solid foods that are thought to be highly allergic.” A recommendation to not delay solid food introduction beyond 4 to 6 months of life was issued but offered no guidance regarding an optimal timing of introduction.² However, the estimated prevalence of food allergy in the United States nearly doubled (from 3.4% to 5.1%) between 1999 and 2009, and the estimated prevalence of peanut allergy tripled (from 0.4% to 1.4%) between 1999 and 2011, although it is unclear if guidance regarding delayed introduction of allergenic foods contributed to these increases or how well the 2008 guidance has been followed.³⁻⁵

Since the mid-2000s, additional data have demonstrated that early introduction of some dietary allergens may have protective effects against the development of food allergy. This evidence, some of which prompted the 2008 revised recommendations, has evolved from large observational cohorts to more targeted randomized clinical trials.⁶ In this issue of *JAMA*, Ierodiakonou and colleagues⁷ report findings from a systematic review and meta-analysis evaluating this evidence, concluding there is “moderate-certainty” evidence supporting the association between introduction of peanut between ages 4 and 11 months and egg between ages 4 and 6 months and reduction in the risk of developing peanut allergy (risk ratio [RR], 0.29; 95% CI, 0.11-0.74 based on 2 randomized clinical trials with 1550 children) or egg allergy (RR, 0.56; 95% CI, 0.36-0.87 based on 5 trials with 1915 children). The authors also found low-certainty evidence that early fish introduction was associated with reduced allergic sensitization and high-certainty evidence that early gluten introduction was not associated with celiac disease risk. No evidence was found for any effect of the early introduction of other foods or for other allergic or autoimmune outcomes.⁷

The meta-analysis by Ierodiakonou and colleagues provides statistical support for the concept that early introduc-

tion of egg and peanut is associated with reducing the risk of developing these food allergies, but this conclusion should be cautiously interpreted. Even though the analysis found moderate-certainty evidence for a protective association for early dietary introduction of both peanut and egg, the authors were appropriately guarded in support of these findings based on the trial sequential analysis. This analysis was unable to be performed for peanut introduction because of insufficient data. For egg introduction, thousands of additional trial participants would be needed to confirm with reasonable certainty that early egg introduction has an effect size of a 30% risk reduction. Moreover, the individual studies contributing to the pooled estimates have concerns regarding generalizability and unknown effectiveness in clinical populations.

Of the 2 peanut trials, only 1 evaluated exclusive peanut introduction. The Learning Early About Peanut Allergy study, which included 641 children, showed strong risk reduction for preventing peanut allergy (RR, 0.19; 95% CI, 0.10-0.36) but was conducted in a very narrowly selected high-risk population (infants 4 to 11 months of age with severe eczema, egg allergy, or both).⁸ The study used the unconventional approach of stratifying children based on screening for peanut sensitization using skin testing before randomization, an approach that is not recommended in clinical practice given that false-positive test results are common and that identification of sensitization alone does not indicate allergy without a corroborating history of symptomatic ingestion. Furthermore, the necessity and efficacy of the screening approach were never proven or empirically tested in the trial. Lack of replication of the data preclude determination of whether the definition of high risk could be expanded to include other food allergies more likely to be present in the first 4 to 6 months of life than egg allergy (eg, milk, wheat, or soy) or to infants with a family history of atopy.⁹

In the fall of 2016, the National Institute of Allergy and Infectious Diseases (NIAID)-sponsored policy will be released that formally recommends early peanut introduction for high-risk children as early as 4 to 6 months of age.¹⁰ Screening for peanut sensitization is being recommended to counter perceived reluctance of families to introduce peanut at home to high-risk infants despite its limitations and although its use raises challenges of practicality and resource utilization. The forthcoming NIAID-sponsored guideline reflects confidence in the evidence suggesting potential benefit of early peanut introduction with minimal risk, is supported by the findings of the meta-analysis by Ierodiakonou and col-

leagues, and reflects a reasonable starting point to help deter the recent increase in prevalence of peanut allergy.

The data for early dietary introduction of egg also have limitations. Among 5 trials of early egg introduction, 4 trials failed to show any protective effect supporting early vs delayed egg introduction, although 3 of these 4 studies had nonsignificant findings suggesting possible protection. In 1 trial, early egg introduction was associated with a nonsignificant finding suggesting a net potential increased risk of developing egg allergy and a high rate of anaphylactic reactions among patients with preexisting presence of egg serum-specific IgE.¹¹ In addition, it is unclear if the single trial showing benefit of early egg introduction is an outlier.¹² The varying findings may be attributable to using different egg vehicles—the 4 trials showing no benefit used raw, pasteurized egg powder, whereas the single trial showing benefit used heated egg, which is less allergenic than raw egg. Egg contains many heat-labile allergenic proteins, and higher-temperature egg preparations are better tolerated among allergic individuals.¹³ Including the heated egg trial may have leveraged the overall protective effect for egg, and such differences in the specific vehicle form must be better reconciled through additional trials to understand the relationship between the timing of egg introduction and the development of egg allergy. The NIAID-sponsored expert panel is not making any changes to existing guidance for the timing of egg introduction, which is currently the 2008 general recommendation to not delay the introduction of any food (including egg) past 4 to 6 months.² However, the strength of the pooled findings should reasonably reassure caregivers and clinicians that egg introduction need not be delayed, in particular for infants without eczema.

Early introduction of foods may not be a panacea to address the food allergy epidemic. Implementation barriers (eg, caregiver or clinician willingness to recommend early introduction; logistical ability to screen high-risk infants), questions about the exact dose and duration of allergen exposure necessary to confer protection, and a narrow window of

opportunity may limit any potential effect. In addition, it is not clear that it is the specific early introduction of an allergenic food that renders immunological protection, rather than the accompanying increased diversity in the diet that occurs as a by-product.¹⁴

The rigorous, comprehensive meta-analysis by Ierodiakonou and colleagues is an important addition to the evidence regarding food allergy prevention. The authors were precise in their methods and forthcoming in describing the limitations of the study, cautioning that “these systematic review findings should not automatically lead to new recommendations to feed egg and peanut to all infants.” Nonetheless, their conclusions highlight that the 2008 guidelines to not delay introduction were correct. Delay of introduction of these foods may be associated with some degree of potential harm, and early introduction of selected foods appears to have a well-defined benefit. These important points should resonate with allergy specialists, primary care physicians, and other health care professionals who care for infants, as well as obstetricians caring for pregnant mothers, all of whom are important stakeholders in effectively conveying the message that guidance to delay allergen introduction is outdated.

Food allergy is a difficult disorder without a cure or treatment and with negative health and economic outcomes for the entire family.¹⁵ The potential to prevent disease occurrence and related negative consequences through an inexpensive and simple intervention is exciting. Careful evaluation of the effect of the forthcoming NIAID-sponsored guideline for early inclusion of peanut in an infant's diet on development of food allergy will be important, as there is always uncertainty involved in translating any research finding into a policy. Investment in additional trials involving peanut, egg, and perhaps other allergens is needed and requires commitment from sponsors such as the NIAID, the Immune Tolerance Network, or the UK Food Standards Agency to enhance the existing evidence base regarding early allergen introduction.

ARTICLE INFORMATION

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Conflict of Interest Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and reported receiving support from grant 1-K08-HS024599-01 from the Agency for Healthcare Quality and Research; being a coauthor and work group member for the International Consensus Communication on Early Peanut Introduction; being a member of the scientific advisory council for the National Peanut Board;

receiving honoraria for talks regarding early peanut allergy prevention from multiple state and regional allergy societies and medical schools, the American College of Allergy, Asthma, and Immunology, and the Canadian Society of Allergy and Clinical Immunology; serving as a consultant for the government of Canada regarding peanut allergy risk and health care policy; and being a member of the NIAID expert panel on peanut allergy prevention.

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Introducing JAMA Performance Improvement

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Somewhat sensationalized¹ claims are still made that there is a crisis in health care, with many patients needlessly dying due to medical errors.² It is unlikely that medical care is as bad as



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is sometimes portrayed in the media, but because the prospect of poor-quality care and anecdotal reports of unac-

ceptable patient outcomes receive so much public attention, there must be greater transparency and open discussion about the quality of health care delivery and how to improve it. Public discussion is dominated by statistically aggregated data and many quality improvement efforts relying on assessment of those data.

Health care quality has improved with time, but not all of the improvement can be explained by collecting and analyzing large amounts of data. For example, the National Surgical Quality Improvement Program (NSQIP) is intended to improve surgical care via the analysis of high-quality clinical data maintained in a registry. By enabling hospitals to compare outcomes, it is assumed that they can identify less-than-optimal care and subsequently improve it. In addition to collecting the data, NSQIP helps hospitals and surgeons share information about quality improvement via communication networks, discussion of quality improvement at various meetings, and publications in the surgical literature.

The NSQIP program is very expensive because it relies on trained, dedicated data abstractors and maintenance of the database. However, recent analyses have demonstrated that surgical mortality has been steadily decreasing and that the rate of decreasing mortality was unaffected by the adoption of NSQIP at participating hospitals.³⁻⁵ Quality is improving, but more likely as a result of the efforts of individual clinicians who are committed to excellence and make improvements when they find deficiencies. Statistical aggregation of process and outcomes data appears to have little direct effect on quality improvement. Nonetheless, current performance improvement efforts tend to follow the statistical aggregation approach rather than emphasizing improvement of individual fundamental skills.

Reaching the next level of performance improvement in health care will require concentrating on fundamentals, such as communication, error identification and reporting and process improvement, and not on statistical aggregation of data. To help provide information about the fundamentals, in this issue of *JAMA* we launch a new series of articles entitled JAMA Performance Improvement. In developing this new series, thought leaders on performance improvement were interviewed to get their sense of what should be done to improve quality. Quality officers at various institutions were approached to find out what problems they encounter. Front-line clinicians played a major role by describing problems they encounter and how they think they should be addressed and corrected. The common denominator of these conversations was the need to address the fundamentals and not rely on performance measures or outcomes reports. Consequently, the problems addressed in the first few articles of this series included faulty communication among clinicians, ineffective checklists and time-out procedures, and improper informed consent.

Learning about how the fundamentals affect clinical outcomes is best done by analyzing individual cases. Consequently, JAMA Performance Improvement articles will be case-based and will summarize the results of investigations of clinical care gone awry. Based on these experiences and how physicians and other health care practitioners have successfully addressed the problems, recommendations will be provided about how to improve the quality of care in ways that *JAMA* readers can adopt in their own clinical practices.

The general approach to these articles will be similar to the recently launched JAMA Professionalism series.⁶ A 2-page article in the journal will have an accompanying podcast on the *JAMA* site enabling in-depth analysis of the case and its resolution. JAMA Performance Improvement articles will start with a summary of a clinical situation and report of suboptimal care. Incidents that have undergone a root cause analysis will be used for these articles. After summarizing the case, readers will be presented with 4 options for how they might address the quality of care problem. A discussion of