Infant Feeding: Swinging the Pendulum from Late to Early Introduction of Food

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Medical guidelines are constantly changing and some are even being reversed, as illustrated by a shift in focus from cholesterol numbers to a heart-healthy lifestyle, and cardiopulmonary resuscitation moving from a fixation on maintaining airway and breathing to sustaining circulation. There is no greater example of changing medical advice than what is currently emerging in the allergy field – a shift from avoiding exposure to furry pets (e.g., cats and dogs) to now emphasizing that early-life exposure to pets can be protective against the development of allergy. We review here the changing attitude towards the introduction of highly allergenic foods into the infant diet.

It is reasonable to assume that the anatomic, physiologic and metabolic requirements of human infants have not changed significantly during the last century, yet we, the medical community and authorities, are generating and issuing new infant feeding guidelines almost annually. Instructions that were the most updated medical information just years ago are now considered obsolete and possibly harmful. Fortunately, mothers have either ignored most medical advice or infants have survived despite it. However, in some cases, we may be paying for the mistakes.

Food allergy is mostly an iatrogenic disease

OPINION-BASED INFANT FEEDING GUIDELINES

It is notable that formal infant feeding guidelines issued by medical societies have only been in existence for the past five decades; before that, mothers and infants managed without formal guidelines [1]. The first reports of the American Academy Committee on Nutrition were educational and only in the mid-1960s did the Committee gain nutritional prominence through its assistance to the Food and Drug Administration (FDA) in defining nutritional requirements for infant formulas and setting policy for nutritional practices relating to infants, children and adolescents. The aims of the first guidelines were to address the metabolic and nutritional needs of newborns and infants. In 1985, the FDA published the minimum concentrations of 29 nutrients and maximum concentrations of 9 of these nutrients [2]. In 1998, an Expert Panel made recommendations for revision of the Code of Federal Regulations (CFR) as it applied to the nutrient content of infant formulas [3].

In the second half of the twentieth century in parallel to the emergence of the allergy epidemic, starting with respiratory and skin allergies [4], there was a focus on preventing allergic diseases through dietary manipulations. Cow's milk protein (CMP) was the "immediate suspect" for respiratory, skin and food allergies. Various approaches such as delaying introduction of CMP and/or introduction of modified CMP – extensively or partially hydrolyzed CMP – were investigated. While a detailed description and discussion of these studies is beyond the scope of this review, it is now well established that partially hydrolyzed CMP [5-8] is not protective against eczema [9,10], and a recent large scale meta-analysis concluded that there is no consistent evidence to support the use of hydrolyzed formula for the prevention of allergic or autoimmune disease [11]. The rationale for avoiding CMP in infancy in an attempt to change the course of asthma or eczema remains unclear.

The emergence of the food allergy epidemic, especially the increasing prevalence and associated morbidity and mortality of peanut allergy in the United States, Britain and Australia, fueled efforts to reverse this trend. In 1998, the British Committee on Toxicity of Chemicals (COT) in Foods published detailed dietary recommendations, including the following [12]:

> Pregnant women who are atopic, or for whom the father or any sibling of the unborn child has an atopic disease, may wish to avoid eating peanuts and peanut products during pregnancy. Breast-feeding mothers who are atopic, or those for whom the father or any sibling of the baby has an atopic disease, may wish to avoid eating peanuts and peanut products during lactation. During weaning of these infants, and until they are at least three years of age, peanuts and peanut products should be avoided.

In 2000, the American Academy of Pediatrics (AAP) adopted these recommendations [13]. In 2005, the Australian

Society of Clinical Immunology and Allergy published a position statement about allergy prevention in children [14], recommending avoidance of potentially allergenic foods such as egg and milk until 12 months of age, and peanuts, nuts and shellfish until after 2–4 years of age. While admitting the lack of evidence for these recommendations they justified this policy in the following statement: "there is no evidence that avoiding peanuts, nuts and shellfish during early life is harmful for high risk children."

All these recommendations were based on an "opinion" rather than on solid evidence-based research. The experts in the various panels postulated that the infant immature immune system is "not ready" to successfully handle potentially allergenic proteins [14]. It did not take long before the medical community began to examine the outcome of these recommendations. In a sequential cohort from the same geographic location in the UK, peanut allergy increased from 0.5% in a cohort of 3–4 year old children born in 1989 to 1.4% in a cohort of similar aged children born between 1994 and 1996 [15]. Similarly, a twofold increase in the prevalence of peanut allergy among children in the USA (0.4% vs. 0.8%) was observed over a 5 year period (1997–2002) using random-digit telephone surveys [16].

The HealthNuts study, a population-based study conducted in Australia provided additional evidence for the rising prevalence of food allergy. More than 10% of infants born between 2006 and 2010 were diagnosed as having food challenge-proven immunoglobulin E (IgE)-mediated food allergy to egg (8.9%), peanut (3%) and sesame (0.8%). Moreover, 5.6% and 0.8% of the infants were sensitized to milk and shellfish, respectively [17]. Thus, evidence was emerging that the twentieth century Feeding Guidelines were clearly not successful in preventing food allergy.

The bright side of the story: we can reverse the trend of a food allergy epidemic

OBSERVATIONAL STUDIES

In a widely cited study published in 2008, there was a tenfold higher prevalence of peanut allergy found among 5171 Jewish schoolchildren in the UK (1.85%) compared with 5615 schoolchildren in Israel (0.17%) [18]. Early exposure of Israeli infants to peanut, via the peanut-based snack Bamba™, was hypothesized to contribute to the low prevalence of peanut allergy in Israel.

This study started a new era in the research of the relation between infant feeding and development of food allergy. At least four additional observational studies from different geographic regions supported the concept that early introduction of potentially allergenic food was associated with lower prevalence of food allergy. First, in a prospective population-based study of a large cohort, over 13,000 newborns were followed from birth until they consumed CMP regularly. Of over 6500 infants who were never breastfed or only partially breastfed (thus started on CMP during the first 14 days of life), only 3 developed milk allergy, compared with 63 who developed IgE-mediated cow's milk allergy (CMA) [19] from an equal-sized cohort exposed to cow's milk starting after 14 days of life. The finding that early introduction of CMP was associated with lower incidence of IgE-mediated CMA was confirmed in a retrospective study from Japan [20]. Analysis of the HealthNuts study (in Australia) showed that early introduction of egg was associated with a lower incidence of egg allergy [21]. A recent Canadian multicenter study found a lower rate of sensitization to milk, peanut and egg among children who consume these foods earlier [22]. Thus, several observational studies suggested that early exposure to potentially allergenic foods such as milk, peanut and egg was associated with protection against allergy to the introduced food.

RANDOMIZED CONTROL STUDIES

In order to substantiate the link between the age at which potentially allergenic food is introduced and the incidence of allergy, several interventional, randomized controlled trials (RCT) have been undertaken. Early introduction of peanut to 4–11 month old infants who were considered at high risk to develop peanut allergy, suffering from severe atopic dermatitis and/or egg allergy, was shown to be very effective [23]. The prevalence of peanut allergy at age 60 months was several-fold higher among infants who avoided peanut protein compared with infants who consumed peanut regularly. The protective effect of regular consumption of peanut was higher among those infants at the age of 60 months who were not sensitized (see below) at the randomization: 0.4% and 1.9% peanut allergy (per protocol and intention to treat, respectively, consumption group) vs. 13.9% and 34% (per protocol and intention to treat, respectively, avoidance group). Furthermore, the effect persisted even after a year of peanut avoidance in the consumption group [24].

The STAR (Solids Timing for Allergy Research) study (Australia) included high risk infants (e.g., those with eczema) with a high proportion (~35%) who were sensitized and clinically reactive to hen's egg [25]. Among those who completed the study, there was a trend for a lower, but not significant, proportion of infants in the egg group who were subsequently given a diagnosis of IgE-mediated egg allergy compared with the control group. The HEAP study (Hen's Egg Allergy Research) in Germany examined non-sensitized infants, aged 4–6 months with egg-specific IgE < 0.35 kU/$_A$L, who were assigned to two treatment groups. At the age of 12 months, a higher proportion of the verum (pasteurized egg white powder) group were sensitized (5.6%) and egg allergic (2.1%) compared to the placebo group (2.6% and 0.6% respectively). The differences between the groups did not reach significance in either case, $P = 0.24$ and 0.35 for sensitization and allergy,

respectively [26]. In the STEP study (Starting Time of Egg Protein) (Australia), infants aged 4–6 months (actually 4.5–6.5) with hereditary risk of allergy (atopic mother) but without eczema were randomized to consume hen's egg or to avoid egg up to 10 months of age. At age 12 months, 7% of the egg group and 10.3% of the control group had IgE-mediated egg allergy. The difference did reach statistical significance [27]. In Japan the PETIT study (Prevention of Egg Allergy with Tiny Amount InTake) randomly assigned 5–7 month old infants with atopic dermatitis to receive cooked egg powder or placebo at age 6 to 12 months. The prevalence of hen's egg allergy was 37.7% in the placebo group and 8.3% in the intervention group ($P = 0.0013$) [28]. Finally, In the BEAT study (Beating Egg Allergy Trial), infants with at least one first-degree relative with allergic disease and skin prick test (SPT) < 2 mm to hen's egg white were randomized at age 4 months to receive whole-egg powder or placebo. At the age of 12 months, 20% of the placebo group and 11% of the infants in the egg group showed sensitization to egg white ($P = 0.03$). However, 8.5% of the "egg group" infants (n=14) reacted to egg within 1 week of its re-introduction [29].

Israel has contributed a great deal to the new trend in infant feeding

The EAT study (Enquiring About Tolerance) yielded mixed and somewhat disappointing results. The study population comprised 1303 exclusively breastfed infants (for 3 months) who were randomly assigned to receive early introduction of six allergenic foods (peanut, cooked egg, cow's milk, sesame, whitefish, wheat) [30]. The primary outcome was food allergy to one or more of the six foods between age 1 and 3 years. Significant benefit was demonstrated for egg (1.4% vs. 5.5%) and peanut (0 vs. 2.5%). The rate of non-compliance was high: "only 42.8% of the participants in the early-introduction group …adhered to the protocol" (pp 1738) and the low number of participants probably contributed to the negative outcome with other foods.

HOW EARLY IS EARLY INTRODUCTION OF POTENTIALLY ALLERGENIC FOOD?

Several lines of evidence, with three different foods – milk, peanuts and hen's egg – indicate that the age of 4 months or above may not be suitable for the term "early supplementation of potentially allergenic foods" in order to prevent or reduce the rate of development of food allergy. Firstly, in the observational study by Katz et al. [19], only 0.05% (3/6500) of the infants who started to regularly consume a milk-based formula during the first 14 days of life developed CMA, compared with a tenfold higher prevalence of CMA in the entire study group (> 13,000 newborns). Secondly, in the LEAP study [23,24], older age at food introduction was associated with less effective prevention. It is notable that ~12% (76/640) of infants aged 4–11 months were excluded from the intervention (consuming peanut) and control (avoiding peanut) groups because of significant sensitization to peanut: SPT > 4 mm. Another 51 (8%) were sensitized to a lesser extent, e.g., had positive SPT but the wheal size was less than 4 mm. These infants were included in the study unless they had clinical allergy, but had a less favorable outcome compared with the non-sensitized [23]. Furthermore, it was noted that older age at screening was associated with a higher rate of sensitization (1–4 mm SPT) or exclusion because of "significant sensitization" (SPT > 4 mm). At age 4 months, 91.4% of the candidates (infants with severe atopic dermatitis) had negative SPT to peanuts and 8.6% had mildly positive SPT (up to 4 mm), but none had SPT > 4 mm. At the age of 10 months 15.4%, and an additional 16.2% had SPT > 4 mm, or up to 4 mm, respectively, and only 68.2% had negative SPT (G. Lack, Oral presentation AAAAI Meeting, San Antonio, TX, USA, February 2015) [31]. Thirdly, in three prospective interventional studies on "early" introduction of egg where infants aged 4–6 months were exposed to egg (e.g., the HEAP [25], STEP [27] and BEAT [29] studies), 4–10% were already sensitized and about 4% exhibited allergy upon initial exposure. In two of these studies, infants with some degree of "high risk" were chosen: infants of atopic mothers (STEP) or infants with first-degree atopic relatives (BEAT). In the third study (HEAP), 23 infants (5.7%) were excluded on the basis of positive SPT (wheal ≥ 2 mm). Taken together, we raise the point that 4–6 month old infants are likely "too old" for "early" intervention to prevent allergy.

CURRENT STATUS AND EXPECTATIONS

As an immediate consequence of the LEAP study [23], 10 international medical societies (American Academy of Allergy Asthma and Immunology, American Academy of Pediatrics, American College of Allergy Asthma and Immunology, Australian Society of Clinical Immunology and Allergy, Canadian Society of Allergy and Clinical Immunology, European Academy of Allergy and Clinical Immunology, Israel Association of Allergy and Clinical Immunology, Japanese Society of Allergology and Clinical Immunology, Society for Pediatric Dermatology, and World Allergy Organization) issued a consensus communication calling for early peanut introduction and the prevention of peanut allergy in high risk infants, rendering earlier guidelines obsolete [12-14]. This consensus communication was co-published in the relevant journals of these organizations [32] and was considered as a limited interim report until wider recommendations are to be published by the forthcoming Expert Panel meeting sponsored by the National Institute of Allergy and Infectious Diseases [31] of the U.S. National Institutes of Health.

The Israeli infant feeding guidelines have omitted the recommendation to remove potentially allergenic foods from pregnant and lactating mothers.

What about other foods? A recent Cochrane library review considered the evidence for the benefits of adding allergenic

food at the age of 4–6 months and did not find a reason to change the current recommendation [33]. In an even more recent review and meta-analysis Lerodiakonou et al. [34] concluded that there is evidence in favor of "early" introduction of CMS, peanuts and egg proteins. One of the above cited studies [27] was not included, probably because it was published too late. However, this study would support the conclusion of the meta-analysis.

While the World Health Organization (WHO) recommends exclusive breastfeeding for at least 6 months, this recommendation is based mainly on increased infant mortality from respiratory and gastrointestinal infection in infants on other forms of feeding [35]. These reports were from low-income and middle-income countries. However, while two of the three reports showed increased mortality in the non-exclusive breastfed group, there was no difference between exclusively breastfed and predominantly breastfed infants [36], or only a borderline difference [37,38].

Furthermore, the risk of severe allergic reaction in the first weeks or months of life are very small. Without being bound by theory, it is stipulated that there is not even a single case of food allergy-related death in the first months of life even though this is the age at which allergenic food is introduced to the diet. Food allergy-related deaths occur usually in the second decade of life or later, and the earliest age "real danger" is the second half of the first decade of life [39]. Furthermore, in the LEAP study, even infants with sensitization (up to 4 mm) who had a positive oral food challenge (OFC) only experienced mild cutaneous reactions; in contrast, there were much more severe allergic responses (24.5% had respiratory symptoms and 16% required treatment with epinephrine) in the 5 year old children who had an OFC at the end of the trial (G. Lack, Oral presentation AAAAI Meeting, February 2015).

Many physicians share the wonder of Dr. Bobrow from New York, who pondered: "When my daughters visited I could not feed my grandchildren bananas at 6 weeks of age, even though their mothers enjoyed them in their infancy. An entire generation attests to the safety and the benefits of early introduction…" [40].

Thus, as the pendulum has started to change direction as the body of evidence is moving toward early introduction of potentially allergenic foods to prevent food allergies, the authors of this article hope that reading this will help hold up the pendulum in the direction of adding allergenic food in the infant diet.

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