

The Prevention Pendulum: Avoidance or Introduction

David W. Hauswirth^a Elizabeth A. Erwin^b

^aDivision of Pulmonary, Allergy, Critical Care and Sleep Medicine, The Ohio State University Medical Center/Nationwide Children's Hospital, and ^bDepartment of Pediatrics, Section of Infectious Diseases and Immunology, Nationwide Children's Hospital, Columbus, Ohio, USA

The treatment and diagnosis of allergic disease continues to evolve; however, the definitive cure would be prevention. There are many different ways to intervene in the natural history of a disease; the most common strategies describe disease prevention using the terms primary, secondary, and tertiary. Primary prevention aims to prevent the disease from ever occurring; secondary prevention happens after the pathologic origin of the disease, but prior to clinical recognition, and tertiary prevention occurs after the discovery of disease, preventing further suffering and disability [1].

In clinical allergy, primary prevention seems obtainable as the human allergic response is based upon exposure. The formation of allergen-specific IgE occurs, by definition, after exposure to the offending allergen. The timing, route, and amount of allergen exposure are often varied. The concept remains simple: modify exposure and prevent disease. It would seem 'easy' to avoid one offending allergen and limit disease; however, the aim of primary prevention in allergy is not to prevent one sensitivity or limit disease from one allergen. The ultimate goal is to prevent atopy and the myriad of diseases and comorbidities that are associated with atopic disease. To further complicate matters, allergen sensitization is not the only variable that relates to allergic disease; atopy has complex and varied origins. Genetics, environmental ir-

ritant/toxin exposures, and immune responses to infectious agents or components (e.g. viral infections and endotoxin) all impact the beginnings of atopic sensitization. As we continue to grow in our understanding of the origins of atopy, we learn that single-antigen avoidance may not be the key to primary prevention.

In this issue of *International Archives of Allergy and Immunology*, Kuo et al. [2] have put forth a very well-done study of primary prevention. The concept was straightforward: in a large group of formula-fed infants, they were hoping to prevent the onset of atopic disease. Infants with a family history of allergy who were unable to breast feed were offered the opportunity to be enrolled and randomized to a hydrolyzed milk protein-based formula or a standard cow's milk formula for the first six months of life. The children were then followed until 36 months of life to evaluate dietary avoidance of milk proteins as a primary prevention measure against general atopic disease.

Unfortunately, their results are similar to those found in so many primary prevention studies. Avoidance of one specific allergen may lead to decreased sensitization to that particular allergen (in this case milk), but has no bearing on the overall development of atopic disease. Importantly, in the study by Kuo et al. [2], the authors were able to demonstrate a significant reduction in milk pro-

tein sensitization at age 36 months (12.7% in those fed hydrolyzed formula vs. 23.4% in those fed cow's milk; $p = 0.048$). Thus, in an at-risk group with a very high prevalence of milk protein sensitization, they were able to almost cut in half the number of children who were sensitized. However, they were not able to show a reduction in the rate of sensitization to other allergens or decrease the development of other atopic conditions (atopic dermatitis, allergic rhinitis, or wheezing).

Many others have fallen victim to the same outcome as was found in the current prevention trial. Avoidance of one or two allergens can lead to a modest decrease in sensitization but no overall impact on atopy. A number of the major allergy prevention trials are discussed in an excellent review by Simpson and Custovic [3]. One of the most talked-about prevention studies is the Isle of Wight primary prevention study [4]. Here, the investigators looked at a defined cohort in the UK. High-risk infants were randomized to dietary avoidance and dust mite control in the home. This highly restrictive approach did result in lower sensitization to mite and a lower prevalence of clinical allergic disease [4]. Overall, this is one of the most successful attempts at the primary prevention of allergies. Other investigators have looked at similar interventions and have obtained mixed results. Groups have gone to the ends of the earth and beyond to implement avoidance. In the Study on the Prevention of Allergy in Children in Europe (SPACE trial), investigators looked at only house dust mite avoidance and its impact on atopy [5]. Unfortunately, this was a negative intervention trial with no difference between the control and the active-avoidance group at 24 months [5].

Many others have come along with primary prevention studies. Some of these studies have employed food allergen avoidance and others have tried environmental control, but the results have been consistently inconsistent. As many of these authors would, we hope, agree, one of the reasons for variable results is that the people and surroundings for prevention studies are inconsistent. Looking at the Childhood Asthma Prevention Study (CAPS), one sees house dust mite sensitization rates above 30% in both the control and intervention groups [6]. As a result, the outcomes are inevitably different from those of a study like SPACE where dust mite avoidance was the primary tool but where the rates of sensitization are only about five percent, even in the control group [5]. So, as many look for strategies to prevent allergies, asthma, and other atopic conditions, we see that the environments studied and the results are inconsistent. As any student of evidence-based medicine will tell you, one of

the first keys to applying the results of a study is to determine whether the patients in the study are similar to the patient you are trying to treat. If mite sensitization rates are extremely high in a given practice area, results may be vastly different if one limits exposure. However, if 'home' is a climate that doesn't breed high levels of dust mite allergen, then mite avoidance may not work as a strategy to decrease sensitization and atopy.

A striking finding in the results presented by Kuo et al. [2] is the high prevalence of dust mite sensitization at age 36 months. It would seem in their local environment that dust mite exposure is highly relevant and likely related to the presence of atopic diseases in these children. Recently, it has been proposed that there may be a hierarchy of allergens defined by the impact on total IgE and/or relationship to allergic disease [7, 8]. In those studies, total IgE and titers of specific IgE were measured in children and adults living in three different areas of the world with strikingly different allergen exposures and asthma prevalence. In those environments, titers of specific IgE to dust mite and grass were related to total IgE while titers of specific IgE to cat were not. The implication is that high exposure to dust mite (and grass) in certain environments could be associated with a higher prevalence of asthma. With the high prevalence of mite sensitivity in the Kuo et al. [2] study, avoidance of this key allergen may have boosted the impact of their prevention measures.

Avoidance may or may not be the answer; many authors have shown inconsistent results. For centuries, it has been argued that allergic diseases are less common in the working class. As a society, we now have a decrease in some infections, components related to infection, and exposure to soil microbes, as well as increased exposure to antibiotics [9]. The Hygiene Hypothesis, as it is known, would suggest that living in a less sterile environment may decrease atopy. Based on this theory, more and varied environmental exposures may decrease atopic responses. However, if our exposure pattern is off a little (i.e. we are exposed to too much or not enough of certain infectious components), we risk increasing our chances of harm. Endotoxin exposure may hold the real key to the prevention of atopic disease. As was elegantly shown by Braun-Fahrlander et al. [10], the clues to decreasing atopy, at least in the farming environment they studied, may be hidden in the dirt.

With environmental avoidance showing mixed results, it would seem that food avoidance should then be simple. It could certainly be a strategy to decrease food allergy, if not overall atopy. Again, a major problem comes

from the environment and the confounding factors. In the example of peanut allergy, Fox et al. [11] have shown that it may not be consumption that is driving early allergy, but rather environmental exposure to peanut. In this report, families of peanut-allergic children were found to have a significantly elevated level of environmental peanut protein. The authors submit that this is driving the early sensitization and increased rates of allergy. Current dietary guidelines from the American Academy of Pediatrics published in 2008 suggest that avoidance of high risk foods may still be the right course to reduce food allergy [12]. This, however, is in direct conflict with evidence from countries and cultures where there is a lower prevalence of peanut allergy. A 2003 analysis of nut allergy in Israel, where peanut exposure occurs in early life, found that the rates of peanut sensitivity were significantly decreased [13]. Whether this is due to the alternate form ingested, the processing used, or the early age of introduction is still a matter of debate. The ongoing Learning Early About Peanut Allergy (LEAP study, www.leapstudy.com) study, funded through the Immune Tol-

erance Network, is a look at the question of early introduction (as opposed to avoidance) as an alternate strategy. Many await these important results.

If avoidance has shown mixed results and we do not know which foods to eat when or which inhalant allergens to avoid, then maybe we need to allow the pendulum to swing the other direction. The allergy and clinical immunology community needs to take a significant look at the results from many of the trials of primary prevention and see where we are heading. So much (but definitely not all!) of the evidence would point away from clean bedrooms and restrictive diets. Instead, children need to spend time outside playing in the dirt and interacting. Maybe we need to increase the exposure to allergens and endotoxin and let our children eat whatever comes naturally to their diet. Time, and well-done prospective, controlled, interventional studies of early (dietary) allergen exposure like LEAP, will guide the allergy community. Our patients are begging for guidance. Once and for all, we need to tell them what to do: live cleanly or eat, drink, and get dirty.

References

- Gordon RS Jr: An operational classification of disease prevention. *Public Health Rep* 1983;98:107–109.
- Kuo H, Liu C, Ou C, Hsu T, Wang C, Huang H, Chuang H, Liang H, Yang KD: Partial protein hydrolyzed infant formula decreased food sensitization but not allergic diseases in a prospective birth cohort study. *Int Arch Allergy Immunol* 2011;154:310–317.
- Simpson A, Custovic A: Prevention of allergic sensitization by environmental control. *Curr Allergy Asthma Rep* 2009;9:363–369.
- Arshad SH, Bateman B, Sadeghnejad A, Gant C, Matthews SM: Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J Allergy Clin Immunol* 2007;119:307–313.
- Horak F, Matthews S, Ihorst G, Arshad SH, Frischer G, Kuehr J, Schwieger A, Forster J, SPACE study group: Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study – 24 months results of the Study of Prevention of Allergy in Children in Europe. *Clin Exp Allergy* 2004;34:1220–1225.
- Marks GB, Mihrshahi S, Kemp AS, Tovey ER, Webb K, Almqvist C, Ampon RD, Crisafulli D, Belousova EG, Mellis CM, Peat JK, Leeder SR: Prevention of asthma during the first 5 years of life: a randomized controlled trial. *J Allergy Clin Immunol* 2006;118:53–61.
- Erwin EA, Ronmark E, Wickens K, Perzanowski MS, Barry D, Lundback B, Crane J, Platts-Mills TA: Contribution of dust mite and cat specific IgE to total IgE: relevance to asthma prevalence. *J Allergy Clin Immunol* 2007;119:359–365.
- Erwin EA, Hosen J, Pollart SM, Reid MJ, Platts-Mills TAE: High-titer IgE antibody specific for pollen allergens in northern California is associated with both wheezing and total serum IgE. *J Allergy Clin Immunol* 2009;123:706–708.
- Liu AH, Leung DY: Renaissance of the hygiene hypothesis. *J Allergy Clin Immunol* 2006;117:1063–1066.
- Braun-Fahrlander C, Riedler J, Herz U, Eder W, Waser M, Grize L, Maisch S, Carr D, Gerlach F, Bufe A, Lauener RP, Schierl R, Renz H, Nowak D, von Mutius E, Allergy and Endotoxin Study Team: Environmental exposure to endotoxin and its relation to asthma in school-age children. *N Engl J Med* 2002;347:869–877.
- Fox AT, Sasieni P, du Toit G, Syed H, Lack G: Household peanut consumption as a risk factor for the development of peanut allergy. *J Allergy Clin Immunol* 2009;123:417–423.
- Greer FR, Sicherer SH, Burks AW, American Academy of Pediatrics Committee on Nutrition, American Academy of Pediatrics Section of Allergy and Immunology: Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. *Pediatrics* 2008;121:183–191.
- du Toit G, Katz Y, Sasieni P, Mesher D, Maleki SJ, Fisher HR, Fox AT, Turcanu V, Amir T, Zadik-Mnuhin G, Cohen A, Livne I, Lack G: Early consumption of peanuts in infancy is associated with a low prevalence of peanut allergy. *J Allergy Clin Immunol* 2008;122:984–991.