LEARNING PLAN

1. Set the scene – define the problem
2. Understand the normal process of tolerance
3. Understand where this can go wrong – who is at risk
4. Discuss strategies to improve
    a. Hydrolysed formula – discuss what it is
    b. Probiotics
    c. Timing of weaning foods
5. Evidence of these strategies
6. Reflection

Dietary Prevention of Food Allergy.

Food allergies contribute to significant morbidity, particularly in the very young, where food allergy occurs in 5-8% of the population. In Australia we have seen rises in allergic conditions such as eczema, where in a similar population and survey instrument the rate of eczema in children under 5 years has risen from 3% in the 1960's to 17% in 1999[1]. This is concordant with recent ISAAC studies[2]. The rate of food anaphylaxis in Australia has increased 5 fold in a 10 year period[3] and this is also reflected globally with rises reported in the UK and USA. Current dietary prevention strategies are clearly not working to prevent food allergy.

Cows milk allergy is the most common food associated with allergy affecting 2-3% of infants in Australia, with other foods including hen egg, soy, wheat, tree-nut, peanut, sesame, fish and shellfish. There are regional variations in food allergy that reflect antigen exposure such as corn in South America, high proportions of children with shellfish allergy in Singapore, Thailand and the Phillipines[4] and sunflower seed, carrot and celery in France. The ongoing increases in peanut and tree-nut allergy that is being observed in the US, Australia and the UK have largely not been observed in continental Europe, South America and most of Asia, although a recent report indicates peanuts now comprise a component of serious food allergies in Singapore[5].

Understanding the structure of food allergens and how they are processed is useful in appreciating where this process of tolerance may go awry. Dietary antigens, particularly the more soluble antigens are processed and absorbed via high specialised micro-fold "M" cells which then excrete peptide chains from their baso-lateral surface to dendritic cells. Dendritic cells can present antigen to T lymphocytes and the efficacy and the pattern of signalling of this communication will depend on the expression of co-stimulatory molecules and the micro-environment. Ideally, tolerance will develop to dietary proteins, however if there is insufficient immunological development such a lack of Forkhead box protein 3 (FoxP3) T regulatory cells, this can result in poor tolerance and either IgE or cell mediated intolerances. Animal models of a sterile environment appear to result in non-tolerance of food and inhalant allergens[6]. Studies have also related low cord blood FoxP3 expression with risk of food and inhalant allergen sensitisation[7,9] and higher blood levels of FoxP3 with likelihood of milk allergy resolution[10].

Ideally for tolerance dietary antigens should be soluble. It is worthwhile noting that caseins are relatively insoluble, whereas whey proteins are soluble. Breast milk contains less casein than cow's milk and in addition it contains oligosaccharides (prebiotics) which promote the growth of beneficial bacteria (probiotics) such as bifidobacteria and lactobacillus.

The main strategies in the dietary prevention of food allergy are:

1. Enteric gut enhancement through probiotics, prebiotics or the combination of these.
2. Breast-feeding, however if breast-feeding is not possible, the use of hypoallergenic formula is recommended in those deemed at high risk.
3. Timing of complementary feeding
4. Increasing dietary omega 3 fatty acids and vitamin D

The main background on enteric gut enhancement appears in 2 comprehensive recent reviews[11,12]. It appears that enhancing growth of probiotic bacteria such as lactobacilli and bifido bacteria in formula fed infants; the microflora can develop in a similar pattern to breast fed infants. Probiotic type bacteria have been reported to have effects on both the innate and adaptive immune response, and in particular the development of the gut associated lymphoid tissues including antigen-processing cells. The literature on pre-biotics remains scant, whereas the probiotic literature is confounded by strain, dose and viability variation and varying trial outcomes (reviewed by Prescott and Bjorksten[12]). The most recent Cochrane review on Probiotics suggested:

"There is insufficient evidence to recommend the addition of probiotics to infant feeds for prevention of allergic disease or food hypersensitivity. Although there was a reduction in clinical eczema in infants, this effect was not consistent between studies and caution is advised in view of methodological concerns regarding included studies. Further studies are required to determine whether the findings are reproducible"[13].

Hypoallergenic (HA) formula involves degradation of the milk proteins by heat, enzymes and or pressure. There are two main categories of HA formula, either a standard hydrolysed (HA) or extensively hydrolysed hypo-allergenic (eHA) formula. Hydrolysis can alter potentially allergic proteins, however reactive peptide chains can still remain and caution should be taken using these supplements in infants with acute IgE mediated reactivity or continued use in an infant who is failing to grow. The 2006 Cochrane review on HA formula concluded:

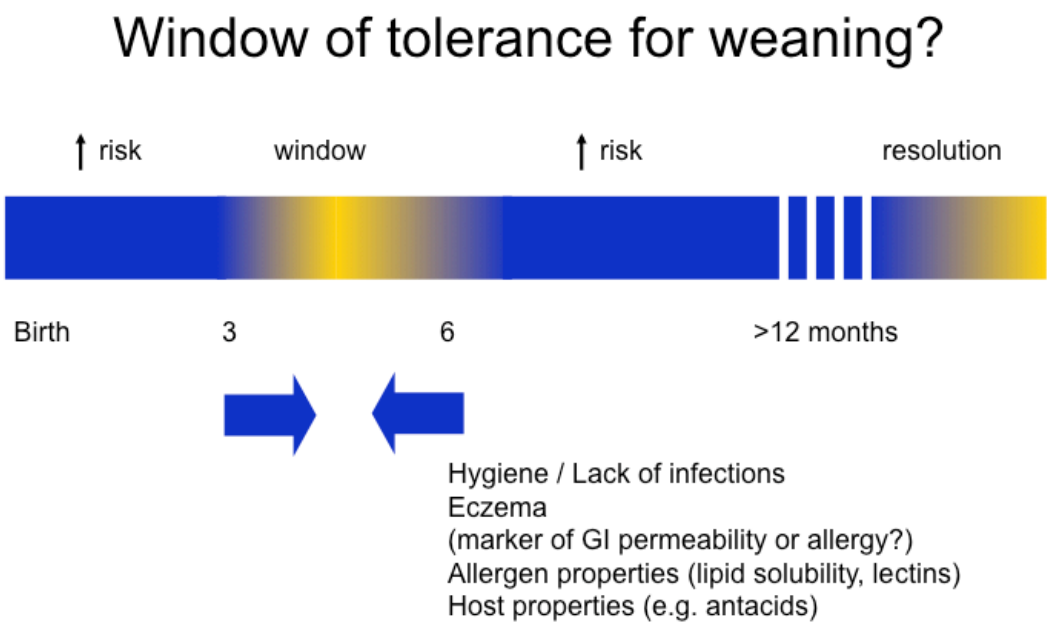
*"In high risk infants who are unable to be completely breast fed, there is **limited** evidence that prolonged feeding with a hydrolysed formula compared to a cow's milk formula reduces infant and childhood allergy and infant CMA.*

In view of methodological concerns and inconsistency of findings, further large, well designed trials comparing formulas containing partially hydrolysed whey, or extensively hydrolysed casein to cow's milk formulas are needed[14]."

Subsequent to this review, new data from German Infant Nutrition Intervention (GINI) study of 2252 infants have been published, indicating benefit of hydrolysed whey and casein formulas in the prevention of eczema at 3[15] and 6[16] years. At both time points, there was not a reduction in asthma.

In 2008, three reviews have summarized the data indicating that both early (less than 3-4 months) and late (>7 months) introduction of solid foods into the diet is a risk for the development of food allergy[17-19]. Early exposure to an un-prepared gut or immune system appears to increase risk for food allergy and other autoimmune conditions, whereas late exposure may represent risk to under-developed gut tolerance mechanism through adequate antigenic stimulation. We summarized these principles in a putative "Window of tolerance for weaning"

There is no evidence that soy formula or animal formulas other than cows milk, prevent the development of atopic disease.



In Summary:

Recommendations for dietary measures to reduce allergic manifestations (with levels of evidence
Cease strict elimination diets during pregnancy (Level I)
Ideally, exclusively breastfeed for 3-4 months (Level III)
Consider Lactobacillus probiotic supplements (before and after delivery)* (Level II)
Introduce weaning foods at 4-6 months (Level II).

If breastfeeding is not possible:
Consider Lactobacillus probiotic supplements* (Level II)
Protein hydrolysed formula (for 6-12 months)* (Level I)

*Data relate to atopy only, not asthma.

An expert review committee published un update on the dietary prevention of allergic diseases in early life in 2008 and this is an excellent, contextual analysis of the topic[22]. It remains to be seen if the cumulative effect of these recommendations will have on feeding practices and abating the increasing burden of food allergy in young children.

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