

LRA by ELISA/ACT® CLINICAL UPDATE # 6

Milk and Children

Is there a need to prevent food allergy/intolerance in infants?

The answer to this question at first glance may be *no* since most physicians believe the frequency of food allergies/intolerances is quite low. Currently, however, the frequency of cow's milk allergy/intolerance (CMA/CMI) in infants with no special family antecedents is reported to range between 2.2 and 7% (2,4,8). Moreover, the frequency of such allergies may evolve, such that one food allergy provokes the development of additional food allergies. For example, an infant may present an allergy to cow's milk and then become sensitive to eggs, citrus, soy, and other foods (6,8,9). Thus, the frequency of multiple food allergies would also be quite high. Since treatment and prevention programs for diseases with frequencies much lower than 2% are currently in existence, the answer to the question, based on the latest scientific information, is *yes*.

Another critical question to ask prior to initiating a treatment/prevention program for infants with food allergies is "does the allergy pose a severe enough problem?" In the case of food allergies/intolerances, the severity of the symptoms depends in part on the type of immunological reaction and the organ system involved. The most common symptoms among infants are cutaneous, with eczema and urticaria; gastrointestinal with colic, vomiting, diarrhea, and/or constipation; and respiratory with wheezing and rhinitis (4,9). Other symptoms related to CMA/CMI include serous otitis media, musculoskeletal pains, and anorexia (4). In

our judgement, even the least serious of these symptoms justifies treatment and preventive approaches. Thus, the overall answer to the question is unequivocally *yes!* The Lymphocyte Response Assay (LRA) by ELISA/ACT® provides an advanced, individual, functional test for all delayed hypersensitivity pathways thus making accurate testing available and rapid.

What types of immune mechanisms are involved with food allergies/intolerances?

Food allergies/intolerances in infants are usually immunologic reactions or responses to specific food proteins. In the case of CMA/CMI, the proteins may be beta-lactoglobulin, casein, bovine IgG, or bovine albumin (3,13,15,19,20). The fact that the timing on the onset of symptoms varies suggests that more than one immunologic/pathogenic mechanism is involved. Some responses are immediate, with clinical manifestations apparent in less than one hour, whereas other symptoms may not be observed until after 24 hours. Other manifestations may be noted between one and 24 hours (2,4,8-12). Accurate diagnosis is thus dependent on whether the response is immediate, intermediate, or late.

The timing of the responses and the available data provide evidence that all four types of immune responses as described by Gell and Coombs are involved. Some infants clearly exhibit Type I, or immediate hypersensitivity reactions, as determined by elevated total serum IgE and milk-specific

IGE RAST values (4,8-12); they typically display cutaneous symptoms (12) and also demonstrate a significant increase in IgM-secreting cells after an oral milk challenge (11). Type II (delayed) responses have also been identified: infants exhibiting only GI symptoms show an increased capacity to induce antibody-dependent cell-mediated cytotoxicity (21), whereas infants with only cutaneous symptoms do not. The appearance of immune complexes in serum of children with food allergy has also been reported (10), an indication of Type III or immune complex-mediated hypersensitivity. Finally, T-cell mediated hypersensitivity has also been observed in infants with CMA/CMI (14). Thus, the spectrum of immune responses is broad and only served to confuse the physician trying to make a diagnosis before full range testing (LRA by ELISA/ACT) was available.

Interestingly, most infants with proven CMA/CMI do not fall into the category of Type I or IgE-mediated allergy, but rather exhibit delay-in-onset, or Types II through IV responses (4,8,9). The LRA by ELISA/ACT is currently the only test that can be

INDEX

Food Allergies in Infants.....	1
Types of Immune Mechanisms.....	1
Diagnosis of CMA/CMI.....	2
Health Consequences of Cow's Milk..	2
Ulcerative Colitis Success.....	4

used to identify allergens which evoke one or all of these delay-in-onset (Type II, III, or IV) immune responses. As such, it should be very useful in the treatment and prevention of food allergies/intolerances in children.

What methods are currently used in the diagnosis of CMA/CMI in infants?

At present, the diagnostic tests most frequently used to diagnose food allergies are the skin test and the RAST test (1,4). Both tests are intended to detect IgE-mediated reactions, and both have less than desirable predictive accuracy (1). Interestingly, Host et al (8,9) recently demonstrated that of 39 children meeting the criteria for CMA as determined by elimination/milk challenges, only 16 were classified as having IgE-mediated CMA; the remaining 23 had non-IgE-mediated reactions. Of the 39, 20 were also classified as "late responders", and 13 of these infants were non-IgE-mediated. This evidence clearly demonstrates the prognostic dilemma of current tests, since the two tests most commonly used reflect only immediate hypersensitivity immune responses.

Other tests that have been used on a limited basis that reflect other immune reactions include lymphocyte transformation, measurements of leukocyte inhibition factor, and neutrophil chemotactic activity (1). Renz et al (19,20) recently noted that determination of secretory IgA anti-casein might represent an additional method for screening infants with allergic disposition. However, none of these tests have been validated. In addition, small intestinal biopsies have also been proposed (1), but this is an invasive procedure that most parents would object to. One other test that has validity in children and adults is LRA by ELISA/ACT, and since this test measures Types II, III, and IV immune responses, unlike any of the other tests, it should be the test to consider in the future.

Only LRA by ELISA/ACT tests for all delayed types of immune response and can test for more foreign substances than any other test system. More important is the treatment plan unique to LRA by

ELISA/ACT that can help correct the cause and rebuild immune defense resilience.

What are the health consequences of feeding cow's milk and cow's milk products before the child is one year old?

Distinct health consequences of feeding an infant cow's milk to an infant with CMI are known, and health risks for providing cow's milk in the absence of CMA/CMI are also recognized (5,7,16-18,22). Infants who have undiagnosed, late responses to cow's milk may exhibit a variety of symptoms and have mixed health problems (4). As stated above, nasal congestion, asthma, serous otitis media, diarrhea, failure to thrive, eczema, and/or musculoskeletal aches are common. Unfortunately, infection rather than an allergic response may be suspected, and result in treatment with antibiotics which will not help cure the food allergy.

Another potential but real complication or health consequence relates to the subsequent development of other food allergies/intolerances (2,4,8,9). The gastrointestinal (GI) tract is a major barrier to foreign antigen entry and infants with CMA commonly demonstrate GI symptoms. Recently, Jalonen (12) reported intestinal permeability changes in children with CMA, and noted that the intestinal barrier was equally altered in immediate and late responders. Further, indirect evidence of local immune responses in the GI tract being activated after a milk challenge has been offered (11), an indication that hyperpermeability of the gut may evolve through reactions of the intestinal mucosa. When the function of the mucosal barrier is compromised by exposure to milk antigens, enhanced absorption of other potential antigens could lead to the development of multiple food allergies. In fact, it is very common for children with CMA to develop adverse reactions to other foods as they get older (2). Avoiding cow's milk does not guarantee freedom from other food allergies, but avoiding milk and milk products and identifying other reactive foods would be beneficial to the health of

the infant. The LRA by ELISA/ACT allows identification of such foods.

Other recognized health consequences of feeding infants cow's milk and milk products during the first year of life, even in the absence of CMA/CMI, are nutrient imbalances, a high renal solute load, and the development of anemia (5,7,16-18,22). Recent studies clearly indicate that when cow's milk is introduced prior to the first year, infants receive unnecessarily high intakes of protein, sodium, and phosphorous, and low intakes of iron and linoleic acid (5). Further, intakes of calcium and potassium are also higher for milk-fed infants as compared to infants fed formula or breast milk. These high protein and electrolyte intakes result in an unduly high renal solute load. Not only is this a load on the kidneys, but if water intake is reduced or water losses are elevated, the high solute load would lead to dehydration more rapidly (5). Additionally, numerous studies have shown that cow's milk feeding results in occult blood loss from the GI tract, an event that can lead to the development of iron deficiency anemia, even in the absence of CMA/CMI (7,16-18,22). Finally, recent evidence suggests an association between cow's milk feeding in infancy and insulin-dependent diabetes mellitus: the bovine protein albumin may act as to trigger the autoimmune response that ultimately results in the development of pancreatic beta cell dysfunction (13).

What preventive measures are available?

Although CMA is the most common food allergen among infants and children, many other foods also pose problems. One reasonable solution is for the mother to avoid eating all potentially antigenic foods so the breast fed baby is not sensitized or exposed through the mother's milk. Since it is well established that food proteins are found in breast milk, this approach is sound. However, such approaches may disrupt a household, impose substantial emotional and social stress on the family, and prove to be unsatisfactory. Additionally, the nutritional status of the mother may be compromised if adequate nutrition

education is not provided. A similar approach can be followed with the infant: no potentially antigenic foods would be given at least during the first year. Again this may not be optimal, and allergies may have already evolved prior to introducing solids. The most effective approach would be for the mother to obtain results from LRA by ELISA/ACT and then assume that her food sensitivities reflect those of the child. The LRA by ELISA/ACT allows specific identification of food allergies/sensitivities so that only reactive foods must be avoided. Nursing mothers would then avoid reactive foods since it well established that breast milk contains a variety of bovine proteins (3,15). In addition, mothers would restrict the reactive foods from their infant's diet for at least one year. Thereafter, one reactive food could be introduced each week to the child, and potential late symptoms would be carefully observed. Such approaches also free the mother from subjecting their infant to numerous invasive procedures.

It is clear that some measures must be taken in the future. Many mothers have reported health problems with their infant and minimal or no success after numerous trips to their pediatrician. Only after removing cow's milk from their diet did the infant begin to thrive and behave in normal fashion. No mother wants her infant to suffer needlessly, undergo useless therapies or invasive procedures when straightforward approaches are available. LRA by ELISA/ACT can be of tremendous value and save health, time and money for mother with newborns, infants, and toddlers.

References

1. Bahna SL. New aspects of diagnosis of milk allergy in children. *Allergy Proc* 1991;12 (4):217-20.
2. Bishop JM, Hill DJ, and Hosking CS. Natural history of cow milk allergy: clinical outcome. *J Pediatr* 1990;116 (6) 862-7.
3. Clyne PS and Kulczycki A Jr. Human breast milk contains bovine IgG. Relationship to infant colic? *Pediatrics* 1991;87 (4): 439-44.
4. Deamer WC, Gerrard JW, and Speer F. Cow's milk allergy: a critical review. *The J Fam Practice* 1979;9(2):223-232.

Common signs and symptoms of cow's milk sensitivity

- Allergic "shiners" and rhinitis
- Abdominal colic, diarrhea, recurrent "belly aches"
- Recurrent infections, particularly middle ear "otitis"
- Eczema or psoriasis
- Mood or behavior swings
- Joint and muscle pains
- Asthma or recurrent bronchitis
- Sinusitis
- Headaches
- Easy fatigability

5. Ernst JA, Brady MS, and Rickard KA. Food and nutrient intake of 6 to 12 month-old infants fed formula or cow milk: a summary of four national surveys. *J Pediatr* 1990;117 (2 Pt 2): S86-100.

6. Guesry PR, Secretin MC, Jost R, Pahud JJ, and Monti JC. Milk formulae in the prevention of food allergy. *Allergy Proc* 1991;12 (4):221-6.

7. Haschke F and Javaid N. Nutritional anemias. *Acta Paediatr Scand Suppl* 1991;374:38-44.

8. Host A. Importance of the first meal on the development of cow's milk allergy and intolerance. *Allergy Proc* 1991;12 (4): 227-32.

9. Host A and Halcken S. A prospective study of cow milk allergy in Danish infants during the first 3 years of life. Clinical course in relation to clinical and immunological type of hypersensitivity reaction. *Allergy* 1990;45 (8): 587-96.

10. Husby S, Host A, Teisner B, and Svehag SE. Infants and children with cow milk allergy/intolerance. Investigation of the uptake of cow milk protein and activation of the complement system. *Allergy* 1990; 45 (7):547 -51.

11. Isolauri E, Virtanen E, Jalonen T, and Arvilommi H. Local immune response measured in blood lymphocytes reflects the clinical reactivity of children with cow's milk allergy. *Pediatr Res* 1990; 28 (6):582-6.

12. Jalonen T. Identical intestinal permeability changes in children with different clinical manifestations of cow's

13. Karjalainen J, Martin JM, Knip M, Ilonon J, et al. A bovine albumin peptide as a possible trigger of insulin-dependent diabetes mellitus. *New Eng J Med* 1992;327:302-307.

14. Khoshoo V, Bhan MK, Kumar R, Arora NK, and Stintzing G. Is cow's milk protein sensitive enteropathy a cell mediated immunological phenomenon? *Acta Paediatr Scand* 1991; 80 (11); 1092-3.

15. Magnusson K. Breast milk antibodies to foods in relation to maternal diet, maternal atopy and the development of atopic disease in the baby. *Int Arch Allergy Appl Immunol* 1989; 90:297-300.

16. Oski FA. Whole cow milk feeding between 6 and 12 months of age? Go back to 1976. *Pediatr Rev* 1990;12 (6):187-9.

17. Penrod JC, Anderson K, and Acosta PB. Impact on iron status of introducing cow's milk in the second six months of life. *J Pediatr Gastroenterol Nutr* 1990; 10 (4):462-7.

18. Pizarro F, Yip R, Dallman PR, Olivares M, Hertrampf E, and Walter T. Iron status with different infant feeding regimens: relevance to screening and prevention of iron deficiency. *J Pediatr* 1991;118(5):687-92.

19. Renz H, Brehler C, Petzoldt S, Prinz H, and Rieger CH. Breast feeding modifies production of SIgA cow's milk-antibodies in infants. *Acta Paediatr Scand* 1991; 80 (2):149-54.

20. Renz H, Vestner R, Petzoldt S, Brehler C, Prinz H, and Rieger CH. Elevated

concentrations of salivary secretory immunoglobulin A anti-cow's milk protein in newborns at risk of allergy. *Int Arch Allergy Appl Immunol* 1990; 92 (3):247-53.

21. Saalman R, Carlsson B, Fallstrom SP, Hanson LA, and Ahlstedt S. Antibody-dependent cell-mediated cytotoxicity to beta-lactoglobulin-coated cells with sera from children with intolerance of cow's milk protein. *Clin Exp Immunol* 1991; 85 (3): 446-52.

22. Ziegler EE. Milks and formulas for older infants. *J Pediatr* 1990;117 (2 Pt 2):S76-9.

LRA by ELISA/ACT Program success in Progressive Ulcerative Colitis. Case report:

AA is a 35 yo 67.5 Kgm WMF, BP 132/68. She has a 10-year history of Ulcerative Colitis (UC) first established by biopsy and barium enema in 1983 with continuous clinical activity until 1990 despite intensive medical management including azulfidene (0.5 gm QID). Annual sigmoidoscopies repeatedly confirmed persisting "cobblestone granuloma" lesions from 8-25 cm. Barium enemas in 12/83, 9/86, and 11/89 were all diagnostic for UC. The patient reports excellent compliance with all treatment plans. In 11/90 the patient was clinically symptomatic with a ESR of 60 (otherwise multiphasic 24 item chemistry panels and routine hematology tests were within usual ranges). The patient elected to have a lymphocyte response delayed type hypersensitivity (DTH) cell culture (LRA by ELISA/ACT) for 235 antigens. On initial testing, the patient showed an unusually high 45 reactions. Avoidance of reactive antigens was associated with complete symptom remission. Repeat DTH cell culture in 11/91 showed a 54% reduction in reactive epitopes (from 45 to 20), and on 10/92 the same assay showed a further reduction (from 20-17) items. Intertest confirmation of antigen reactants had an R = 0.928. The patient remains asymptomatic for the past 27 months.

Discussion: Ulcerative Colitis is the superficial and Crohn's disease the full thickness inflammatory bowel disease.

Some research GI specialists (gastroenterologists) now consider these conditions "two ends of a disease spectrum" (46), while other scientists consider these distinct entities. It is widely agreed that all significant IBD is autoimmune. By identifying the individual immunotoxins, allowing substitution for immunoreactive items, along with targeted supplementation to stimulate repair and healthy habit practices to stimulate the human healing response, the LRA by ELISA/ACT program helped this lady and many like her.

Thanks to the physicians who share well-documented case successes in treatment-resistant patients.

Contact

If you have any questions or would like more information about LRA by ELISA/ACT testing, please contact EAB's Client Services Department at 800-553-5472.

