Prevention of Food Allergy in Infants and Children

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The presence in a family of an infant or a child with immunologically mediated adverse responses to food causes important feeding problems. Prevention in at-risk populations and early treatment of food allergy in infants and children include the identification of the mechanisms which are involved in pathogenesis.

At the present time, the prevention of food allergy—frequently mediated by IgE reactions to food and by other mechanisms not involving IgE mediation—might be limited to the following possibilities:

1. Avoidance of potentially allergenic foods during the last trimester of pregnancy and during lactation in infants at risk.
2. Encouragement of breast-feeding, which has the dual benefit of eliminating some of the potential allergenic proteins and providing important immune defenses.
3. Use of pharmacologic agents when food allergic disease is present.

These preventive possibilities will now be discussed in detail (1,2).

AVOIDANCE OF POTENTIALLY ALLERGENIC FOODS

Immunogenicity of potentially allergenic proteins depends on the foreignness, the exposure dose, the frequency of exposure, the age of exposure, the molecular structure, the molecular size and shape, and the multiplicity binding sites (3). Some of the physical properties of the proteins are the heat resistance and the resistance to denaturation and to digestion (4). Very few food-allergenic proteins have been isolated and characterized, but some have been purified. Milk, for instance, is composed of a large number of antigenic components. Most of the 16 antigens found in cow’s milk (5), as well as most of the 32 antigens found in bovine whey, are serum proteins; only a few are milk-specific (6).

The major milk proteins—namely, alpha-lactalbumin, beta-lactoglobulin, and casein—have been purified and tested for allergenicity. Denaturation of alpha-
lactalbumin, beta-lactoglobulin, and casein modify their properties so that they are less allergenic.

We know that food allergens from the mother's diet can cross the placenta and can be excreted in the breast milk. Casein, and particularly beta-lactoglobulin and ovoalbumin, can be easily demonstrated in the breast milk after ingestion from the mother (7). It is well established that the presence of these substances in breast milk may be responsible for the manifestations of food allergy in some nursing infants. The hypersensitivity phenomena are not dissimilar to the symptoms produced by artificially fed infants.

Therefore, evidence tends to favor the conclusions that the avoidance of highly allergenic food proteins must be considered by the mothers who are in the last trimester of pregnancy and during the period of lactation, to prevent placental or breast milk passage of food antigens from the mother to the infant. However, problems of compliance sometimes occur.

For the infant reacting to cow's milk, there are problems in selecting appropriate feeds without allergenic components. The use of soybean formulas and casein hydrolysate mixtures is indicated in infants and children with symptoms and signs of cow's-milk-protein allergy. However, nearly 25% of the children affected by cow's milk allergy who are fed exclusively with soy formula, as well as nearly 18% who are fed with casein hydrolysate, develop hypersensitivity reactions to these substitutes over weeks or months. Elimination diets are often not easily followed, resulting in lack of compliance. Alternatively, a specialized elemental diet may be useful in selected patients who do not tolerate mother's milk substitutes. Special diets with selected cow's milk substitutes are sometimes refused or are difficult to maintain for a long period of time. Therefore, special care must be taken to avoid suboptimal nutrition and malnutrition.

BREAST-FEEDING

Breast-feeding for the first 4 to 6 months has been claimed as an effective tool in preventing the early development of symptoms of sensitization, especially in high-risk infants.

During the last 50 years, numerous articles have been published addressing the question, Does the exclusion of cow's milk from the infant diet reduce the risk of allergy? In 1983, Burr reviewed 24 articles on this subject (8). In 13 of these 24 studies, allergic diseases were positively associated with cow's milk or mixed feeding, whereas 10 showed no convincing relationship with infant feeding. After Burr's article, there have been seven others published on the subject. Three of them confirm the question under consideration, three do not provide evidence against it, and one presents positive results regarding breast milk (9–13). Some defects are present in many of these studies; very few have been conducted as randomized controlled trials, and sufficient information has not usually been collected regarding early supplementary feeds given to breast-fed infants (Table 1).
In conclusion, the results of these studies tend to favor the hypothesis that giving infants cow's milk or the early introduction of solid foods increases the risk of allergic disease.

The promotion of breast-feeding is advised by pediatricians because it seems to offer the dual benefit of eliminating one of the most common sensitizing food antigens while providing important immune defenses. Colostrum and breast milk provide important immune defenses for the infant's gastrointestinal tract, especially during the early neonatal period (14). They contain a number of factors that contribute to its beneficial effect, including nonspecific anti-infective components such as lysozyme, lactoferrin, gastrointestinal mucosal growth factor, and B-cell proliferation factor (15) (Table 2). On the other hand, the transient deficiency or absence of secretory IgA, along with the maturational delay of the gut mucosa during the neonatal period, may predispose the vulnerable infant to macromolecular absorption of intact food protein and absorption of partially degraded food products (13).

According to the previously presented data (Fig. 1; Table 2), there is no doubt about the advantages of breast-feeding. However, in some cases, despite dietary prevention, the symptomatology of food allergy appears.
TABLE 1. Review of 31 studies that showed epidemiologic evidence for the following: a relationship between allergy and cow’s milk feeding (CMF) or mixed feeding; a relationship between allergy and breast-feeding (BF); and the absence of a convincing relationship between allergy and infant feeding

31 Reported Studies

- 16 positive for CMF or mixed feeding
- 2 positive for BF
- 13 no convincing relationship

![Graph showing Hb and Serum Iron levels](image)

**FIG. 2.** DSCG effect (100 mg x 4) on the occult blood loss from the intestine in a child with iron-deficiency anemia due to milk intolerance. (From ref. 27.)

TABLE 2. Immunoglobulins and other factors present in colostrum and human milk

<table>
<thead>
<tr>
<th>IgA, IgG, IgM</th>
<th>Lysozyme</th>
<th>Lactoferrin</th>
<th>Growth factor gastrointestinal mucosa</th>
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<tr>
<td></td>
<td>B-cell proliferation factor</td>
<td>T, B cells and macrophages</td>
<td>Lactobacillus bifidum</td>
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PHARMACOLOGIC AGENTS

Pharmacologic agents may be useful in the management of specific cases of food allergy (which does not profit by dietary prevention) as well as in treatment of prophylaxis, especially in children when strict avoidance of the offending food cannot be attained. However, the benefit cannot be predicted (16).

The pharmacologic agents are anti-H₁-receptor antihistamines, H₂-receptor antagonists, cinnarizine, pirenzepine, steroids, oral disodium cromoglycate, ketotifen, and inhibitors of prostaglandin synthesis (Table 3).

The mode of action of antihistamines is through competitive inhibition with histamine for receptors on target cells. All antihistamines act best when administered prior to the release of histamine, but the doses of antihistamine needed to control symptoms are large enough to provoke secondary effects such as drowsiness. Only some of the new antihistamines having minimal side effects might be useful in treating food allergy (16).

H₁-receptor antihistamines alone or in association with H₂-receptor antagonists must be given before the exposure to the offending food to prevent symptoms. But despite the good clinical improvement with anti-H₂, several side effects (endocrinologic, hematologic, gastroenteric, and immunologic) have been observed (16).

Food allergens are believed to stimulate mediator release from mast cells in the gastrointestinal tract, thus causing adverse reactions such as, for instance, increased permeability of the gut with absorption of potential allergenic protein into the blood. Sodium cromoglycate acts primarily by inhibiting mediator release at the surface of mast cells. Originally used by inhalation and aerosol to prevent allergic asthma, oral sodium cromoglycate has been used with favorable results in controlling adverse symptoms in many patients suffering from food allergy not managed by dietary restriction. The drug is effective in preventing gastrointestinal symptoms and amelioration of other symptoms of IgE-mediated food allergy. Oral sodium cromoglycate is a safe drug; however, adverse reactions such as abdominal pain, vomiting, headache, rhinorrhea, and insomnia have been reported (16–21) (Fig. 2).

The medical literature contains some references to the use of oral ketotifen in controlling food allergy. Ketotifen decreases the responsiveness of the autologous mixed lymphocyte reaction in vitro, and it seems to be of some utility in the man-

<table>
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<th>Table 3. Pharmacologic agents in food allergy</th>
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<tr>
<td>Sodium cromoglycate</td>
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<tr>
<td>Ketotifen</td>
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<tr>
<td>H₁ receptor antagonists</td>
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<tr>
<td>H₂ receptor antagonists</td>
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<tr>
<td>Cinnarizine</td>
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<tr>
<td>Pirenzepine</td>
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<td>Prostaglandin inhibitors steroids</td>
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agement of patients with food allergy, even if it lacks carry-over effects. Ketotifen seems to be a simple and effective drug, but at present it requires more investigation because an inhibitory effect on lymphocyte proliferation has been reported (22,23).

Steroids for long-term medication should not be used, especially if other drugs can be effective.

Prostaglandins seem to play a role in mediating adverse reactions—especially in the gastrointestinal tract—to certain foods. Inhibitors of prostaglandin synthesis—for example, aspirin and other nonsteroid drugs (indomethacin, ibuprofen)—have prevented symptoms of food intolerance in a group of patients, but there have been some failures (24,25). Pirenzepine, an anticholinergic drug which acts by modulating gastric secretion, seems to be useful in the treatment on gastroenterologic adverse reactions to foods because it defends the intestinal mucosa and controls enteric motility.

NEW APPROACHES TO THE PREVENTION

The prevention of IgE-mediated disorders could be approached by intervention at the lymphokine level to modify IgE production. A search for the "designer gene" to produce lymphokines is in progress.

In summary, the various strategies described above may be useful in the prevention or treatment of the adverse reactions to foods in infants and children.

However, a great deal is still to be learned about the various mechanisms that operate in adverse reactions. Investigations are necessary in order to identify the structure and immunologic properties of food antigens and their relationship to food allergy.

Although pharmacologic agents are of potential value, their effectiveness seems unpredictable. These drugs must be more precisely investigated, not only for their therapeutic benefits but also for adverse reactions and possible side effects.

REFERENCES


DISCUSSION

Dr. Strobel: I am always very impressed when I see your data on the use of disodium cromoglycate (SCG) in the treatment of gastrointestinal food allergy. It is difficult to conceive that SCG could work in this situation since it does not seem to affect the intestinal mast cell, either in vivo or in vitro, and there is no really sound evidence that it stabilizes mast cells or exerts an anti-IgE effect. There are some conditions where it will reduce antigen uptake, and I suppose it is also possible that it may form complexes with food antigens in the gut, but I have had very variable responses when using SCG under controlled clinical conditions.

Dr. Scadding: I should like to comment on that. We have often failed with SCG as well, but we do find that it is more effective when given after an exclusion diet. Whether this reflects the change in the mast cell population in the gut or some other mechanism, I don't know. We have recently been trying Nedocromil, which is Fison's new drug which is said to have an effect on intestinal mast cells. When used prophylactically in patients with eczema, migraine, and irritible bowel syndrome in a small open trial, there is some evidence of efficacy despite persevering with a full diet.
Dr. Strobel: We have used Nedocromil, and it does not prevent mediator release from rat intestinal mast cells assessed by measuring rat mast-cell protease release (RMCPII). I cannot comment on its effect in children.

Dr. Durand: We use SCG in certain patients who have not been helped by any other treatment. I have no experience about its specific effects on mast cells, but in some cases it has a very good clinical effect, and there may be considerable improvement in the histological appearance of the mucosa.