Clinical Trials in Infant Nutrition: The Role of the American Academy of Pediatrics and the Committee on Nutrition

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The American Academy of Pediatrics (AAP) is committed to the attainment of optimal physical, mental, and social health for all infants, children, adolescents, and young adults (1). To this end, the members of the Academy dedicate their efforts and resources. The Academy has established approximately 30 committees that help in developing guidelines to assist health care professionals, governmental agencies, and industry in the care of infants, children, and adolescents. The Committee on Nutrition (CON) is the group appointed to help in the development of AAP policy concerning nutrition.

RECENT COMMITTEE ON NUTRITION STATEMENTS

Statements from the CON are reviewed by individuals with expertise in the subject matter of the statement, circulated to the individual Committee members, amended and modified, and finally reviewed and approved by the board of directors of the AAP. This can be a lengthy process. The time interval from when it is realized that there is a need for a statement on a given subject to when the statement is finally published in Pediatrics can be up to 2 to 3 years. In some instances, a subcommittee of CON or a special work group will be established to accelerate the process for a given subject. The following are brief summaries of the seven statements published by the CON or work groups of the CON since 1990 (Table 1).

Statement 1: Practical Significance of Lactose Intolerance in Children

This statement was prompted in part by a major comprehensive report that concluded that it is unwise to discourage the use of milk in children from a population with a high rate of lactose malabsorption unless these children are suffering from
severe diarrhea or show a definite intolerance to milk or milk products. This clinical conclusion is similar to the one reported by the AAP/CON in 1978. In general, evidence for malabsorption of lactose as a clinical problem is not manifest until after 5 to 7 years of age, although this age can be variable. Nondigesters (adults) who continue to drink milk might tolerate as much as 240 ml of whole milk. This adaptation is presumed to be a result of a change in the intestinal flora.

The CON concluded in this statement that individuals can increase their tolerance to dairy products by ingesting fermented products such as yogurt, hard cheeses, cottage cheese, and acidophilus milk. The Committee noted that there are also enzyme preparations on the market that predigest the lactose in the milk and render it almost lactose-free (2).

Statement 2: Statement on Cholesterol

The AAP and the National Cholesterol Education Program both endorse the principle that the diet of children and adolescents should be adequate to support normal growth and development. A varied diet including foods from each of the major food groups provides the best assurance of nutritional adequacy. Dietary guidelines that restrict fat and cholesterol should not apply to infants from birth to age 2 years. This CON statement gives recommendations for screening children 2 years of age and older for hypercholesterolemia (3).

Statement 3: The Use of Whole Cow’s Milk in Infancy

Optimal nutrition of infants involves selecting the appropriate milk source and eventually introducing infant solid foods. To achieve this goal, in this statement, the AAP recommends that infants be fed breast milk for the first 6 to 12 months. The only acceptable alternative to breast milk is iron-fortified infant formula. Appropriate solid foods should be added between the ages of 4 and 6 months. Consumption of breast milk or iron-fortified formula, along with age-appropriate solid foods and juices, during the first 12 months of life allows for more balanced nutrition. The AAP recommends that whole cow’s milk and low-iron formulas not be used during the first year of life (4).
Statement 4: Infant Feeding Practices and Their Possible Relation to the Etiology of Diabetes Mellitus

This statement was written by a Work Group and then cleared by the CON and approved by the board of directors of the AAP (5). The Work Group’s recommendations are as follows:

1. Breast-feeding is strongly endorsed as the primary source of nutrition during the first year of life for all infants.
2. In families with a strong history of insulin-dependent diabetes mellitus (IDDM), particularly if a sibling has diabetes, breast-feeding and avoidance of commercially available cow’s milk and products containing intact cow’s milk protein during the first year of life are strongly encouraged.
3. Because the antigenicity of infant formulas and cow’s milk may be different, and there is no evidence against the use of formula for infants whose mothers do not breast-feed, commercial infant formulas utilizing cow’s milk protein remain the approved alternate.
4. The substitution of soy-based formulas for milk-based formulas is not advised for either general or high-risk infant feeding practices because of animal studies linking the ingestion of soybean protein intake to the development of diabetes.
5. The substitution of elemental formulas for milk-based formulas has intellectual appeal, as potential antigenically harmful large proteins have been replaced by dipeptides, tripeptides, and oligopeptides. However, because no scientific studies in humans confirming their benefit are yet available, this feeding option cannot be endorsed.
6. A prospective randomized trial in which genetically susceptible infants avoid the ingestion of cow’s milk should be developed through collaborative national and international arrangements.

Following publication of the statement, a letter was submitted to the editor of Pediatrics (6). The letter noted that

in the statement by the American Academy of Pediatrics (AAP) Work Group on Cow’s Milk Protein and Diabetes Mellitus, it was concluded that “The substitution of soy-based formulas for milk-based formulas is not advised for either general or high-risk infant feeding practices because of animal studies linking the ingestion of soy protein intake to the development of diabetes.” This AAP statement leaves the impression that there is evidence that soy protein causes insulin-dependent diabetes mellitus (IDDM) and that it is sufficient to conclude that soy formulas should no longer be fed to human infants. Based on our reading of literature cited in the statement and additional studies that do not appear to have been considered, we do not believe this to be the case. . . . We believe this statement should be clarified to recommend that given our current state of knowledge, no changes in feeding practices during infancy are warranted to avoid IDDM. (6)

The response of the chairman of the Work Group to the above letter was:

The American Academy of Pediatrics appointed and directed the Work Group on Cow’s Milk Protein and Diabetes Mellitus to undertake a review of the available research and
### TABLE 2. Fluoride supplementation\(^a\) for children: Interim policy recommendations

<table>
<thead>
<tr>
<th>Age</th>
<th>Water fluoride content (ppm)</th>
<th>0.3–0.6</th>
<th>&gt;0.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth–6 mo</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6 mo–3 yr</td>
<td>0.25</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3–6 yr</td>
<td>0.50</td>
<td>0.25</td>
<td>0</td>
</tr>
<tr>
<td>6–16 yr</td>
<td>1.0</td>
<td>0.50</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Fluoride daily doses are given in milligrams (11).

publications on possible connections between childhood nutrition and the development of IDDM. The purpose of this activity was to bring to the pediatric community a position paper that would provide interim conclusions while providing direction for future research into the important area. This has been accomplished. After a period of approximately 18 months of review, deliberation, and multiple reediting, the position paper was finally published in *Pediatrics* in November 1994. Our final conclusion and recommendation deserves reemphasis. Research directed toward further defining the possible relationship between infant feeding practices and the development of IDDM is needed. A prospective randomized trial in which genetically susceptible infants avoid the ingestion of cow’s milk should be developed through collaborative national and international arrangements. (7)

It should be noted that two other letters were written in response to the statement (8,9).

### Statement 5: Reimbursement for Medical Foods for Inborn Errors of Metabolism

It is the position of the AAP that special medical foods that are used in the treatment of amino acid and urea cycle disorders are medical expenses that should be reimbursed (10).

### Statement 6: Fluoride Supplementation for Children: Interim Policy

Fluoride supplementation is no longer recommended from birth, and doses have been decreased during the first 6 years of life because of an increased incidence of dental fluorosis in children living in the United States (11; Table 2).

### Statement 7: Aluminum Toxicity in Infants and Children

The recommendations of the CON in this statement are as follows:

1. Aluminum-containing phosphate binders should not be given to infants and children with renal failure.
2. Continued efforts should be made to reduce the levels of aluminum in products that are added to intravenous solutions used for premature infants and infants and children with renal failure.

3. Continued efforts should be made to reduce the aluminum content of all formulas used for infants, but especially soy formulas and formulas tailored specifically for premature infants.

4. In infants at risk for aluminum toxicity (renal failure and prematurity), attention should be paid to the aluminum content of the water used in reconstitution of infant formulas (12).

OTHER STATEMENTS AND/OR REPORTS

Reports prepared under FDA contracts do not necessarily constitute AAP policy. A recent report concerning cow and soy milk allergy was prepared for the FDA. It did not undergo Board of Directors review. This technical advisory report was prepared by Dr. Ronald E. Kleinman, Chairman of the CON, and a subcommittee on nutrition/allergic disease. The report was not published in a peer-reviewed journal. It is summarized as follows (13):

Allergic, immune-complex, and cell-mediated immune reactions to cow milk and other dietary proteins encountered during infancy are responsible for some of the adverse symptoms and syndromes observed in infants intolerant to cow milk, infant formulas, and occasionally human milk. Iron deficiency anemia associated with gastrointestinal blood loss, protein-losing enteropathy, enterocolitis, colitis, and malabsorption syndrome are examples of nonallergic (i.e., non-IgE-mediated), putative immune-mediated reactions to dietary antigens that occur in infancy. However, the immunopathogenesis of these syndromes remains to be elucidated and confirmed. A number of symptoms referable to the gastrointestinal tract, such as vomiting, colic, and chronic nonspecific diarrhea, occur in infants both with and without immune-mediated reactions to dietary antigens. None of these gastrointestinal symptoms are pathognomonic for food allergy or immune-mediated reactions to dietary antigens in infancy.

Verification of adverse reactions to dietary antigens, including allergic reactions, should be accomplished through the use of double-blind, placebo-controlled food challenge, with the dietary antigen to be tested presented in a liquid vehicle or, in older children, in capsule form. Most of the symptoms and adverse effects of offending dietary antigens are reversed within days after removal of the offending antigen from the diet. For the most part, except for those infants and young children with malabsorption syndrome (an increasingly rare consequence of milk allergy), nutritional support remains the same as for an otherwise healthy infant.

Dietary proteins that retain their antigenicity when tested by in vitro methods or in vivo cannot be considered hypoallergenic. Approximately 8% to 25% of children with immediate hypersensitivity to cow milk have been found to be allergic to soy products. Soy and other intact protein substitutes for cow milk, such as beef- and lamb-based formulas, have produced anaphylactic reactions both in human infants and in animal models. Few scientifically valid studies have been published evaluating the sole use of alternative formulas in the prevention of cow milk allergy or allergic disease.

Preclinical testing of infant formulas is necessary to characterize the molecular properties of the protein or peptide to be used in the hypoallergenic formula. This includes physicochemical tests, such as gel permeation chromatography and sodium dodecylsulfate
polyacrylamide gel electrophoresis (SDS-PAGE), and immunochemical tests conducted both in vivo, e.g., guinea pigs, mouse, or rat, and in vitro, e.g., ELISA and RIA. The sine qua non, however, for defining and declaring an infant formula as hypoallergenic requires clinical testing of the formula in human infants and children. This should be performed as a double-blind placebo-controlled challenge followed by open challenge in an appropriate number of infants or young children with milk allergy proven by oral challenge within 2 months of the new formula challenge. The number of infants or children should be sufficient to project with 95% confidence that 90% of milk-allergic infants will not react to the product. The studies should be conducted on at least 24 subjects at a minimum of two centers, and each center should contribute at least six subjects. Open challenge should follow the successful completion of the double-blind, placebo-controlled challenge, and in this open challenge the test formula should be fed for at least 24 hr to subjects who are under the direct supervision of the investigator. Further observation should occur for 6 days at home, and the subjects should be assessed by a clinical scoring system for allergic responses.

Finally, it is theoretically possible that formulas might prevent or delay allergy. Clinical testing to support a claim for delay or prevention of atopic disease should include infants from families with a strong history of allergy who are fed the product for at least 6 months under the conditions of a blinded controlled and randomized study. These infants should be followed for at least 1 year after the blinded study and must demonstrate a statistically significantly lower prevalence of allergy than infants fed a standard milk-based control formula over the same 6-month period of time. Formulas that successfully produce these clinical results with 1-year follow-up may be claimed by manufacturers to delay food allergy, and with 2- to 3-year follow-up to prevent food allergy, but cannot be termed hypoallergenic (13).

IMPACT OF STATEMENTS

Several points should be considered when assessing the impact of CON statements. First, the tragic error that resulted in some infants suffering when the infants were fed formulas low in chloride could have been averted by closer regulation and more open lines of communication among the AAP, industry, and the FDA. This error occurred during 1978 and 1979, when two infant formulas deficient in chloride were marketed in the United States by Syntex, Inc. Some of the children who ingested these formulas developed a variety of problems including failure to thrive, lethargy, anorexia, and weakness. In addition, severe metabolic derangements including hypochloremia, alkalosis, hypokalemia, hyponatremia, hyperaldosteronism, and increased plasma renin activity were present in some of these children. The aggregation of these signs, symptoms, and laboratory findings has been termed the chloride depletion syndrome or the dietary chloride deficiency syndrome. Although resolution of these acute problems occurred following the restoration of a diet adequate in chloride, the question of whether these children would experience long-term effects has been raised. In one study, 21 of these exposed children were developmentally evaluated at 2 years of age, and 18 of these returned for reexamination at 4 years of age (14). When other known predictors of developmental outcome were taken into account by means of multiple linear regression analyses, exclusive formula use emerged as an important predictor of the children’s cognitive functioning at 2 years and of quantitative, perceptual,
and fine motor ability at 4 years of age. These data raise concern about the developmental outcome of the children exposed to the chloride-deficient formula (14).

In another study of infants who ingested one of these chloride-deficient formulas, a representative sample of such children was identified in a southern county in the Southeastern United States through a mailing to the homes of 3639 first- and second-grade children in the public schools (15). Of the 2329 (64%) who responded, 56 reported use of deficient formula and were invited to have developmental testing by one of four study psychologists at their school. Of the 310 users of other soy formulas, 112 were selected for testing as matched controls on the basis of their sex, feeding history, age, birth weight, and socioeconomic status (as indicated by school attended). Children who used chloride-deficient formula were found to average 4.9 IQ points less than the controls. The largest difference was in the quantitative subscale. The data showed a statistically significant although small effect of chloride-deficient formula on the long-term developmental outcome of exposed children; however, further study of the results is needed for full confirmation (15).

A second point to address concerns whether statements are accepted and whether they have any impact on how physicians or industry performs. In 1985, the AAP published a policy statement on the treatment of infants with acute diarrhea complicated by mild to moderate dehydration (16). To determine how closely physicians in the United States followed this statement, a questionnaire was sent to 457 pediatricians and 360 family practitioners (17). The questionnaire presented a hypothetical infant with acute diarrhea complicated by mild to moderate dehydration and included questions regarding the number of such patients seen yearly, length of time used to rehydrate the infant, and how formula or solids are introduced following rehydration. Overall, the findings suggest that very few pediatricians and family practitioners follow all aspects of the AAP’s treatment guidelines for infants with acute diarrhea complicated by mild to moderate dehydration (17).

These examples point out first that the CON, industry, and the FDA should cooperate to better regulate formulas and foods for infants and children. Second, more should be done to disseminate recommendations to physicians and interested parties so they may be better utilized.

COMMITTEE ON NUTRITION AND INDUSTRY INTERACTIONS

There are a various ways the CON and industry may work together to improve the health of infants, children, adolescents, and young adults according to whether a topic of interest is CON or industry driven (Table 3).

Committee-Driven Interests

The CON should keep industry updated in areas that they feel need research. When the CON is developing policy statements, it should also confer with appropriate qualified representatives of industry. These individuals may have information
TABLE 3. Suggestions for CON and industry

CON-driven interests
The CON should keep industry appraised of areas of nutrition that need research.
The CON, when developing policy statements related to nutrition, should confer with
appropriate qualified representatives of industry for expertise otherwise not available
to the CON.

Industry-driven interests
Industry should work with the CON to help set guidelines for formulas.
Industry should advise the CON when introducing new formulas, components of formulas,
or alternatives to currently commercially available food products for infants, children,
adolescents, and young adults.
Industry should confer with the CON concerning the marketing of potentially controversial
products.

concerning the production, storage, and/or use of formulas and foods for children
that the CON would not otherwise be able to gain access to.

Industry-Driven Interests

Industry should work with the CON to set guidelines for formulas and advise the
CON when they introduce new formulas, components of formulas, or new food
products for infants, children, adolescents, and young adults. Industry should confer
with the CON when they market potentially controversial products, for example,
bovine somatostatin or fat and sugar substitutes.

It is hoped that with better cooperation and lines of communication among the
CON, industry, and the FDA, improved nutritional products for infants, children,
adolescents, and young adults will be made available. In addition, it is hoped that
errors in formula and food composition will be eliminated, and tragedies such as the
dietary chloride deficiency syndrome resulting from formulas inadequate in chloride
content will be averted. Because young infants are totally dependent on breast and/or
bottle formulas, there is little leeway for human error.

REFERENCES

5. American Academy of Pediatrics. Infant feeding practices and their possible relationship to the
etiology of diabetes mellitus: work group on cow’s milk protein and diabetes mellitus. Pediatrics
1994;94:752–754.


DISCUSSION

Dr. Iber: The failure of the majority of your members to undertake your recommendations on diarrhea suggests that, perhaps, the committee is a specialized or elite fraction of the society that may not be representative. I would be interested in your comments on that.

Dr. Udall: Classically, the treatment of acute diarrhea in the otherwise normal child was to fast the child for 12 to 24 hr and then keep the child on clear liquids for 2 to 3 days or longer. Gradually, dilute formulas and later solid foods were reintroduced. What the Committee did in 1985, when they made the recommendations for the treatment of acute diarrhea, was to condense this sequence and suggest that the rehydration take not 24 hr but 4 to 6 hr, with the child being reintroduced to foods within 24 hr of seeing the physician. It wasn’t a case of dramatically altering the recommendation but of having the infant progress through the sequence much more rapidly. I think that one of the problems we had was breaking down the barriers of the traditional approach. It takes time to do that.

Dr. Perman: You have shown us in reviewing the statements over the past 5 years that at least some of them, or components of the statements, are open to challenge. Has the entire production of statements from the Committee on Nutrition over the years been scrutinized to see how these statements have withstood the test of time? By and large, do you find that the Committee’s work has been supported by subsequent scientific evidence?

Dr. Udall: To my knowledge, there is no mechanism to evaluate the success of each of the statements in terms of their acceptability, or how they are used in the field. I think one of the disappointments to the members of the Committee on Nutrition is that the Technical Advisory Group from industry has been abolished from the Committee. Is that correct, Dr. Klish?

Dr. Klish: It has not been totally abolished, but it has been more difficult to request the interaction with industry over the past year or so.

Dr. Udall: Your point about tracking the statements to see how successful they are is something that we might consider. It has not been done.

Dr. Klish: Can I address that question. I think there is a misconception about what the Committee on Nutrition of the American Academy of Pediatrics is really supposed to be doing. Primarily, the Academy of Pediatrics is a professional organization that is intended to educate its own membership, so these policy statements are not national policy statements,
they are recommendations given to the membership of the Academy about how they should deal with particular issues that happen to have public relevance. We do get asked at times to become involved in policy issues, and I think sometimes the Committee recommendations are used in that way. But that is not always the intent for these particular statements. The Committee on Nutrition is made up of people from all over the United States—they are selected not only for their scientific expertise but also for the region of the country that they come from. There is a selection process that allows the Academy to select certain individuals who we think are going to be able to respond to issues that we know are coming along. We have no mechanism to force anybody to follow our statements because they are in essence educational statements rather than policy statements.

Dr. Udall: These statements go through many layers of review, and people come at them from different points of view. That is one of the reasons it can take so long to get them out, but as Dr. Klish mentioned, they are really to help the practitioner in the field more than anything else.

Dr. Klish: We do review every statement every 3 years though, and we retire those that are no longer relevant. Unfortunately, they are all published, and not everybody recognizes the fact that some of them may be retired statements.

Dr. Hamburger: You probably could avoid some of the problems that you create by floating the statements as drafts first in the publications of the Academy to allow a response from the general membership, because that is how you discover whether you were either premature or taking too strong a position one way or another. It would be sensible to put them out as a draft, wait about 3 months, and then come back with a definitive statement after you have allowed for much wider criticism than the multiple layers that you are using now.

Dr. Udall: That is a very good comment. However, I would be a little concerned because some individuals have their own very strong opinions and their own agenda—that is one of the problems with developing these statements. My concern would be that you are going to get many diverse comments, and it will be very difficult to respond to them all without alienating some people.

Dr. Klish: There actually is now a mechanism for publicizing the issues in advance of a statement, and that is the use of AAP News. We are publishing articles there about issues that we know are somewhat controversial, to test the waters with the membership and try to see what kind of response we get. We did that with fluoride, and we are doing it in the next issue with the long-chain polyunsaturated fatty acids. I agree there wasn’t a mechanism in the past, but we are now in the process of developing that mechanism.

Dr. Rey: I have a comment about fluoride. It seems paradoxical to recommend not adding fluoride between birth and 6 months and then adding it after 6 months, because after 6 months is the time when the child starts to absorb toothpaste with a high fluoride content. I would like to know the basis of this recommendation.

Dr. Udall: The fluoride statement evolved over a number of months. The American Dental Association convened a group to discuss this. Dr. Susan Baker from the Committee on Nutrition of the AAP attended those meetings. There was considerable discussion pro and con for fluoride supplementation in the first 6 months of life. Water is not fluoridated to a uniform level throughout the United States, and young children ingest significant but variable amounts of fluoride while brushing their teeth with fluoride-containing toothpaste. Because both these sources of fluoride are difficult to control, attention has been directed at the dosage of fluoride supplements to prevent dental fluorosis.

Dr. Rey: I have two other comments. The first is that, in France at least, and probably in Europe as a whole, we very much appreciate the publications from the Committee on Nutrition.
They are an excellent source of information for everyone, are very well presented and discussed, and it is a real pleasure to read them. I am not absolutely sure whether you read the recommendations of ESPGAN (European Society for Gastroenterology and Nutrition), but we read yours and we try to quote them. My last comment is about relations with industry. I think your proposal is very wise. For the past 2 or 3 years, we have had a Committee on Nutrition in France, not as important as yours, of course, but we meet the Association of Infant Food Producers twice a year and discuss our problems with them. They reveal their own difficulties, and we give them our papers before they are published to obtain their comment. We also have representatives of industry in the Subcommittee on Foods for Special Dietary Use, and they are consulted before any decision is taken. When they don’t agree with a decision, they can come and explain to the Subcommittee why they disagree. It is very important to have this type of exchange among nutritionists, pediatricians, and industry. It is a source of profit for everybody.

Dr. Udall: In regard to the Committee on Nutrition and the American Academy of Pediatrics cooperating with industry, I agree wholeheartedly with your thoughts. Personally, I feel that this is a matter of communication. When I was asked to come here and address this particular topic, I sent a copy of the paper to Dr. Klish, the current chair of the Committee on Nutrition, to Dr. Ron Kleinman, the previous chair of the Committee on Nutrition, and also to the American Academy of Pediatrics. I wanted them to review it and did not want to publish a manuscript that they were not in agreement with. They had an opportunity to make changes in the manuscript and suggested some alterations that were incorporated. So when we talk about industry and the Committee on Nutrition and the American Academy of Pediatrics working together, we need to stress communication and make sure that the lines of communication remain open.