



Iron Requirements for Infants with Cow Milk Protein Allergy

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Impact of Cow Milk on Iron Status

Historically, cow milk has been used as a major source of protein and balanced nutrition for infants and children in resource-rich and resource-constrained countries. It is a rich source of energy, protein, and calcium. It is also an important source of fat; many of its fatty acids are readily metabolized to essential omega-3 fatty acids. Regular consumption of milk during childhood has been shown to enhance bone density later in life.^{1,2} However, reliance upon whole pasteurized cow milk as the sole or major source of nutrition for infants during the first year of life can increase the risk for iron deficiency and, in extreme cases, iron-deficient anemia (IDA) for a number of reasons.^{3,4} In 1972, Woodruff et al⁵ showed that 7 of 12 infants (ages 7-17 months) with IDA who ingested between 720 and 1920 mL whole milk daily had higher albumin turnover rates than a group of 5 normal infants. Parenteral iron had no effect on albumin turnover, but replacing whole milk with reconstituted evaporated milk or soy formula decreased the high albumin turnover rates to normal levels, suggesting that large amounts of cow milk protein could result in iron and protein loss in the gastrointestinal tract. Cow milk contains low levels of ascorbic acid, a factor that increases iron absorption,⁶ and certain proteins that negatively impact iron absorption.⁷ Cow milk contains about 4 times more calcium than human milk, and calcium negatively impacts iron absorption.⁸ Furthermore, cow milk has a higher protein concentration than human milk, and ingestion of large amounts can lead to metabolic and fluid imbalances, particularly in children with febrile illnesses. Thus, several entities have recommended against whole cow milk ingestion until 9-12 months and then, only when given in moderate amounts in conjunction with appropriate complementary foods.^{3,9-11}

Cow Milk Protein Allergy

Of greater concern with regard to cow milk is the risk for developing cow milk protein allergy, defined as a hypersensitivity reaction to one or more proteins contained in cow milk.¹² The incidence of cow milk protein allergy in resource-rich countries ranges from 2%-5% of infants at 1 year of age.¹² It has been shown to occur in resource-constrained countries such as India,¹³ Thailand,¹⁴ and Tanzania.¹⁵ It is not known if the incidence of cow milk protein allergy in resource-constrained countries is different from that in resource-rich countries because only limited studies are available.¹⁶ In resource-constrained countries, the presentation of bloodstained stool in infants and children is often assumed to be caused by infectious organisms rather than a food allergy.¹⁵ In addition, the diagnosis in resource-constrained countries is sometimes difficult to make because the resources necessary for a definitive diagnosis may not be readily available.^{13,17}

The incidence of allergic diseases, including those that involve the gastrointestinal tract, is increasing globally. This trend is especially pronounced in resource-rich countries and appears to coincide with improvements in sanitation and reduced exposure to pathogens during infancy.¹⁸ They also may be related to an increased awareness and subsequent diagnosis of the disease. The incidence appears to be rising significantly in resource-constrained countries as the environment changes but has not yet reached the levels present in resource-rich countries.¹⁴

Cow milk is comprised of 80% casein proteins, which include several different forms of casein, and 20% whey proteins, which include alpha lactoglobulin, beta lactoglobulin, bovine serum albumin, lactoferrin, and immunoglobulins. Both types of proteins are capable of eliciting IgE-mediated allergic responses to their linear and conformational epitopes, and polysensitization to several cow milk proteins is common in one individual. Proteins in the whey and casein fractions also appear to be responsible for eliciting the non-IgE-mediated inflammatory changes that are characteristic of enterocolitis and proctocolitis induced by cow milk proteins.

About 50%-60% of affected individuals display IgE-mediated reactions (eg, urticaria, nausea and vomiting, rhinoconjunctivitis, wheeze or asthma) up to 2 hours after exposure.^{12,19} Many do not have an IgE response and show a delayed hypersensitivity that develops hours or days after exposure, and many individuals display a mixture of the 2 types of responses. In small infants, allergic enterocolitis and allergic proctocolitis are the most common presentations in the gastrointestinal tract and are typically non-IgE-mediated disorders.²⁰⁻²⁷ These conditions are

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<http://dx.doi.org/10.1016/j.jpeds.2015.07.019>

IDA Iron-deficiency anemia

characterized by inflammatory changes in the small bowel and/or colonic mucosa. The most common histologic features are increased numbers of eosinophils in the lamina propria and increased lymphoid proliferation and numbers of visible lymphoid nodules.^{28,29} Endoscopically, one can see the edematous mucosa with poor visualization of the ramifying vascular patterns and erythematous patches often overlying or near the lymphoid nodules. It is important to remember that the histology of these lesions is nonspecific and may result from other pathologic conditions as well. Also, the lesions are often patchy, and large numbers of biopsies must be taken in order to definitively make the diagnosis by biopsy.

These mucosal inflammatory changes result in blood loss, the extent of which indicates the severity and location of the inflammatory changes. Infants with distal proctocolitis may have bright red blood in the stools but rarely become anemic. More proximal inflammatory changes, especially in the small bowel, may lead to more extensive erosions with greater degrees of blood loss. In older children, the syndrome of protein-losing enteropathy or exudative enteropathy has been described with increased gastrointestinal blood loss, anemia, hypoproteinemia, and even pulmonary hemosiderosis known as Heiner syndrome. In these patients, IDA can be quite severe. Eosinophilic inflammatory changes in the esophagus and the stomach can result in chronic gastrointestinal blood loss.

Breastfeeding

Breastfed infants also are capable of developing allergic enterocolitis and proctocolitis.^{30,31} In many instances, this is because very small amounts of protein antigens escape digestion and are transported from the gastrointestinal tract to the mammary gland and secreted into the milk by the lactating mother. It is quite likely that this mechanism for delivering antigens to the gastrointestinal tract of the infant evolved to help the baby's gut develop immune tolerance to the various food antigens. In animal models, exposure to very small quantities of antigens or very large quantities of antigen may induce tolerance, whereas exposure to intermediate quantities from the diet may induce an allergic reaction. Indeed, cow milk proteins as well as other food antigens are present in human milk in very small quantities for several hours after the mother eats. As a result, some breastfed infants may be responding to these small quantities of cow milk proteins with an allergic inflammatory response.

Treatment

Classically, treatment for cow milk protein allergy has been to eliminate exposure to the offending antigen. In non-IgE-mediated disease, inflammatory changes will resolve in 1-2 weeks following the elimination of the antigen in most infants. Once the inflammatory changes have healed, no more gastrointestinal blood loss occurs and iron requirements essentially revert to those of the normal infant. In IgE-mediated disease, the response is, of course, much faster.

One effective approach is to provide formula that contains extensively hydrolyzed cow milk proteins. This type of formula contains small 2-5 amino acid peptides and amino acids that are nonallergenic. Unfortunately, preparations of extensively hydrolyzed formula also can contain larger peptide fragments that are capable of inducing inflammatory changes in the mucosa as well as IgE-mediated responses. In these instances, amino acid-based infant formulas appear not to elicit a reaction in most infants.

There are instances, however, when persistent mucosal injury may occur. These include multiple food protein intolerance syndromes in which an allergic response to more than one food antigen exists. These children may have many foods that cause mucosal injury, and identifying each one can be difficult. This is especially true because these are largely non-IgE allergies that can only be identified by elimination and re-challenge. Finally, some persistent mucosal injury may occur despite appropriate dietary management, and the cause is often unclear.

Treatment in the breastfed infant is especially challenging.^{31,32} European guidelines have stated that cow milk elimination from the maternal diet for up to 4 weeks should be the first step in managing these infants.^{17,33} Most clinicians prefer to keep the child breastfeeding if at all possible. This requires eliminating the suspected offending antigens from the maternal diet, and, again, identification is often difficult. Removal of all cow milk protein from the diet is usually the first step, and, if clinical remission does not result, removal of other common food antigens from the diet may be attempted with judicious reintroduction following clinical remission. Removal of cow milk, eggs, wheat, soy, fish, shellfish, peanuts, and tree nuts is usually attempted. The diet is hard to follow and, although many mothers are highly motivated, they often become frustrated and run the risk of developing nutritional deficiencies. If formula is given, it should be hypoallergenic (ie, extensively hydrolyzed or amino acid based formula).

The prognosis for infants with cow milk protein allergy is good. In most instances, the mucosal lesions heal quickly following removal of the offending antigens. Most children will tolerate some cow milk protein by 12-18 months of age, although the age of tolerance development is often later in children with IgE-mediated disease than it is with non-IgE-mediated disease. Above a certain threshold in some children, cow milk ingestion may cause symptoms to recur or inflammatory lesions to reappear elsewhere in the gastrointestinal tract. In these instances, chronic iron loss, protein-losing enteropathy, and constipation may predominate. Eosinophilic esophagitis also may present in this manner. Recent evidence suggests that some of the infants with allergic colitis, especially those who are clearly non-IgE, may resolve even before the end of the first year of life.³⁴

Iron Supplementation in Cow Milk Protein Allergy

The risk of developing iron deficiency is of particular concern for any lesions in the gastrointestinal tract associated with

chronic bleeding. For this reason, patients with allergic inflammation, such as patients with any other form of inflammatory disease of the gastrointestinal tract, are at risk of iron deficiency and may need iron supplementation. However, although the occurrence of IDA is one of many possible manifestations of cow milk protein allergy cited in various guidelines and review papers on the diagnosis and management of cow milk protein allergy,^{12,33,35-37} the reported incidence of IDA in infants and children with cow milk protein allergy is similar to that in normal children. In a population of 100 children with a mean age of 16 months presenting with manifestations of cow milk protein allergy, only one child (1%) had IDA.³⁸ In another study of 382 children with a diagnosis of cow milk protein allergy in Thailand, the incidence of anemia reported was 2.8%.¹⁴ These incidences are similar to the incidence of IDA in the general population of infants and children reported in resource-rich countries^{9,39} and lower than that reported in resource-constrained countries.⁴⁰⁻⁴² The most recent guidelines of the American Academy of Pediatrics and the World Health Organization on iron deficiency and IDA do not include cow milk protein allergy among the causes of iron deficiency or IDA,^{9,43} suggesting that cow milk protein allergy is an uncommon cause of IDA. Thus, it appears that relatively few children with cow milk protein allergy will be iron deficient and, therefore, iron should only be administered for repletion, based on measurements of iron deficiency such as reduced hemoglobin, red cell indices, or ferritin level.

In allergic diseases, removal of the offending antigen, usually cow milk, promptly heals the inflammatory process in most instances. After the lesions heal, there are no ongoing micronutrient losses and, consequently, no further need for supplementation. Thus, when the lesions heal, the need for iron and other micronutrients is no different than that in the healthy child, and this should be true as long as the disorder remains under control. In the event that dietary compliance or multiple unidentified allergies are problematic, more supplementation may be indicated, not only for iron but also for other nutrients.

Understanding that the properly treated intestinal mucosa in a child with food allergy is functionally normal is crucial to avoid over supplementation. This is of special concern in the formulation of hypoallergenic infant formulas as they are often the sole source of nutrition for small infants with food allergy. Infant formulas are specifically designed to provide nutritional adequacy. This is true for vitamins, minerals, long chain polyunsaturated fatty acids, and macronutrients. A large volume of data have accumulated over the years regarding appropriate formulation for infant formulas, and these data direct formulation of current products. Indeed, infant formulas designed those with allergies are primarily used when mucosal function is normal, as a means for limiting or eliminating allergen exposure. This assures that mucosal function will remain normal, and the infant will remain healthy.

During the short period of time when formulas are used initially and the mucosal surfaces are healing, absorptive

function is abnormal and nutrient deficiencies may exist. In most infants, supplementation may be required. However, this period is as short as a few weeks in most instances, and it is unlikely that supplementation would be needed for long periods of time. As such, providing specific nutrients such as vitamins, iron, and other minerals for short periods of time is the best approach.

Iron supplementation is beneficial in some instances, but over supplementation can be detrimental.⁴⁴ Over supplementation of iron may increase risk of infections in areas where malaria is endemic⁴⁵ and impair growth.⁴⁶ Thus, providing iron supplementation only during the period when iron losses are elevated or when iron insufficiency exists is a much safer and wiser treatment strategy for the infant whose iron deficiency is associated with cow milk protein allergy.

In summary, allergic disorders of the gastrointestinal tract can be associated with malabsorption and loss of protein and iron from the gastrointestinal tract. This may occasionally result in IDA that must be treated along with strategies to limit antigen exposure and induce tolerance. Supplementation is probably best provided only during the period of time when it is needed in appropriate dosage and format designed for the individual patient, rather than as a long-term over supplementation in hypoallergenic infant formulas. Most gastrointestinal allergies in infants can be easily treated by allergen elimination, and normal gastrointestinal function resumes when the inflammatory lesions have been treated. Hypoallergenic infant formulas are used for actual treatment of inflammatory lesions in the gut for only a short time, primarily to prevent recurrence over a much longer period of time. When effectively treated, most infants will outgrow cow milk protein allergy and, potentially, other food allergies fairly early in life, and most are able to tolerate a normal diet somewhere between 2 and 5 years of age. ■

Author Disclosures

J.V. is a part time employee of Mead Johnson Nutrition. R.K. received an honorarium to chair the Mead Johnson Pediatric Nutrition Institute Iron Expert Panel and serves as Guest Editor for this Supplement; the sponsor had no involvement in preparing the manuscript.

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