



Food Allergy in Infancy: A Practice Primer

Allergy Prevention from the Experts: Recommendations for Patients

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Food Allergy Diagnosis and History of Atopy

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Food Intolerance and Allergy in Infancy: A Parents' Guide to a Healthy, Happy Infant

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Practice Pearls for the Diagnosis and Management of Cow's Milk Protein Allergy

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Welcome to this special issue of *Health Odyssey* on Food Allergy in Infancy.

In the following pages, Canadian specialists share their expert opinions on how to identify infants at risk for food allergy and allergy to cow's milk protein in particular; how to minimize that risk; and how to intervene appropriately in infants if they do develop an allergy to cow's milk protein or symptoms of non-allergic intolerance to lactose in general.

Health Odyssey was developed as an educational supplement to help guide physicians and other healthcare professionals not unfamiliar with the literature or with this aspect of clinical practice towards making better choices for parents who are concerned their infant may be at risk for food allergies.

We hope you will find the following pages both informative and clinically relevant and that the overview of the subject provided by our expert panelists will help guide clinical decisions in the future.

Panel

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Allergy Prevention from the Experts: Recommendations for Patients

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It is estimated that approximately 6% of North American children younger than 3 years of age have some type of food allergy. The most common food allergens for infants and children in Canada are cow's milk, eggs, peanuts, tree nuts, sesame seeds, seafood, soy and wheat. In a study cited by editors of a core document on the diagnosis and management of food allergies entitled "Food Allergy: A Practice Parameter," approximately 80% of symptoms develop in the first year of life. Some food allergies remit in childhood. For example, many infants who are allergic to cow's milk protein outgrow it in the preschool years, although recent data suggest that IgE-mediated cow's milk allergy may last longer in more highly atopic children.

Parents with a history of atopic disease likely will want to know if allergies can be prevented in their newborn. The American Academy of Pediatrics (AAP) and the European Academy of Allergology and Clinical Immunology (EAACI) have made largely concordant recommendations that should help guide physicians in their parental counselling concerning allergy prevention in infants at high risk for allergies. The fact that these groups reached very similar conclusions is reassuring, as physicians can be confident that they are giving parents the best possible advice about allergy prevention in high-risk infants, i.e. infants with one parent and/or sibling with documented allergic disease. A comparative summary of their recommendations for high-risk infants follows.

AAP (2008)	EAACI (2004)
<p>Exclusive breastfeeding for at least 4 months compared with feeding infants intact cow's milk protein formula decreases the cumulative incidence of atopic dermatitis and cow's milk allergy in the first 2 years of life.</p> <p>Exclusive breastfeeding for at least 3 months protects against wheezing in early life but evidence that exclusive breastfeeding protects against allergic asthma occurring beyond 6 years is not convincing.</p> <p>There are insufficient data to support a protective effect of any dietary intervention against atopic disease after 4-6 months of age.</p>	<p>Feeding exclusively human milk for at least 4 months is associated with a lower cumulative incidence of cow's milk allergy until 18 months. (Updated 2008 EAACI review)</p> <p>The most effective dietary regimen is exclusively breastfeeding for at least 4-6 months. Evidence that such avoidance affects later allergic manifestations such as asthma and rhinitis is lacking.</p> <p>There is no evidence for a preventive effect of a diet after the age of 4-6 months. These preventive effects have only been demonstrated in high-risk infants.</p>
<p>There is a lack of evidence that maternal dietary restrictions during pregnancy play a significant role in the prevention of atopic disease in infants. Antigen avoidance during lactation does not prevent atopic disease either, with the possible exception of atopic eczema (although more data are needed to substantiate this).</p>	<p>No convincing evidence exists for a preventive effect of maternal diet during pregnancy or lactation.</p>
<p>For infants who are not breastfed exclusively for 4-6 months or who are formula-fed, there is modest evidence that atopic dermatitis may be delayed or prevented by the use of extensively or partially hydrolyzed formulas compared with cow's milk formula in early childhood.</p>	<p>A documented hypoallergenic formula (extensively hydrolyzed formula) combined with avoidance of solid foods for 4-6 months reduces the cumulative incidence of cow's milk allergy and eczema. (Updated 2008 EAACI review)</p> <p>In the absence of breast milk, formulas with documented reduced allergenicity for at least 4 months, combined with avoidance of solid food and cow's milk for the same period, may be considered.</p>
<p>Extensively hydrolyzed formulas may be more effective than partially hydrolyzed formulas in the prevention of atopic disease. Partially hydrolyzed formulas may have an effect in the prevention of atopic disease, although it seems to be less than that of an extensively hydrolyzed formula at present.</p>	<p>Partially hydrolyzed formulas may have an effect in the prevention of atopic disease, although it seems to be less than that of an extensively hydrolyzed formula at present.</p>
<p>Solid foods should not be introduced before 4-6 months of age but there is no convincing evidence that delaying their introduction beyond this period has a significant protective effect on the development of atopic disease. This includes foods considered to be highly allergic, including fish, eggs and foods containing peanut protein.</p>	
<p>For a child who has developed an atopic disease that may be precipitated or exacerbated by ingested proteins via human milk, infant formula or specific complementary foods, treatment may require specific identification and restriction of cause food proteins.</p>	

Soy-based Formulas

a) Prevention of allergy:

Both the AAP and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition concur that soy protein-based formula has no effect on the prevention of allergic diseases in high-risk infants. The EAACI suggests that soy formulas should not be recommended for prevention of food allergy.

b) Treatment of cow's milk allergy:

For the treatment of infants with cow's milk protein allergy, the ESPGHAN recommends the use of therapeutic formula based on extensively hydrolyzed proteins (or amino-acid formulas if extensively hydrolyzed formulas are not tolerated). They suggest that soy protein-based formula should not be used in infants with food allergy during the first six months of life. They state that after the age of six months, although soy may be considered for treatment of cow's milk allergy because of its lower cost and better acceptance, tolerance to soy protein should first be established by clinical challenge.

The AAP indicates that most infants with documented IgE-mediated allergy to cow's milk protein will tolerate soy protein-based formula (due to only a 10% to 14% crossover rate). The AAP cautions against the use of soy protein-based formula in infants with cow's milk protein-induced enteropathy or enterocolitis (non-IgE-mediated allergy), who frequently (30% to 64%) react to soy protein and cow's milk protein. Instead, they should receive formula derived from hydrolyzed protein or synthetic amino acids.

In Canada, the treatment of cow's milk allergy follows a combination of the recommendations from the ESPGHAN and AAP. There is acknowledgment of the lower cost and better acceptance of soy formulas, as identified by the ESPGHAN. Use of soy formula for cow's milk allergy is based on whether or not the allergy is IgE-mediated. If the allergy is IgE-mediated, soy protein-based formula is frequently acceptable (due to the 10% to 14% crossover rate). If the allergy is non-IgE-mediated, a soy protein-based formula is not acceptable because of extensive

cross-reactivity between soy and cow's milk protein. For non-IgE-mediated cow's milk allergy, extensively hydrolyzed formula (if tolerated) or amino acid-based formula (if not) is the treatment of choice.

c) Non-allergic uses of soy:

The two organizations provide other advice as to which infants may be considered for soy protein-based formula. In a 2006 review of the literature, the ESPGHAN recommended that soy protein-based formula should only be used in specified circumstances, including severe persistent lactose intolerance and galactosemia. They also suggested that soy protein-based formula can be considered in light of religious, ethical or other considerations that stipulate avoidance of cow's milk-based formula.

In 2008, the AAP stated that although isolated soy protein-based formulas may be used to provide nutrition for normal growth and development, there are few indications for their use in place of cow's milk-based formula. They noted that soy protein-based formulas are appropriate for infants with galactosemia, hereditary lactase deficiency (rare) and in situations in which a vegetarian diet is preferred. Soy protein-based formula may be considered for secondary lactose intolerance after gastroenteritis, but most previously well infants with acute gastroenteritis can be managed after rehydration with continued use of human breast milk or standard dilutions of cow's milk-based formulas.

The AAP also noted that with the exception of those cases described above, soy protein-based formula does not have any advantages over cow's milk protein-based formula as a supplement for breast milk. Furthermore, soy protein-based formulas are not designed or recommended for preterm infants. Both organizations are against the use of soy protein-based formula for either the prevention or management of colic.

Summary

Primary care physicians are frequently called upon to counsel parents about the prevention of allergies in their infant, and thus need to understand what parents may be able to do to prevent allergies from occurring in infants at high risk. Consensus now stands with a single dominant recommendation from expert committees in North America and Europe: exclusive breastfeeding for the first four to six months of age (and a delay of solid foods during

the same interval) is the single most important strategy parents can implement to help protect high-risk infants from allergic disease. For infants who cannot be breastfed, the same groups recommend the use of extensively hydrolyzed formulas over those that are partially hydrolyzed to reduce the likelihood infants will develop cow's milk protein allergy and eczema. Soy-based infant formulas have no role in allergy prevention. For treatment of cow's milk allergy, their role depends on whether the infant has IgE-mediated or non-IgE-mediated cow's milk allergy.

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Food Allergy Diagnosis and History of Atopy

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The incidence of atopic disease including food allergies has increased dramatically over the past several decades, especially in urban areas. Reasons for this are not clear but several hypotheses have been proposed that may explain in part the rising incidence of allergic conditions such as atopic dermatitis, asthma and peanut allergies.

One theory briefly discussed by the National Institutes of Health (NIH) expert panel on food allergy research in a 2006 report is the widely publicized “hygiene hypothesis.” At birth, the immune system is actually prone to become allergic. Over time, as infants are exposed to bacteria and viruses, the immune system shifts away from this atopic tendency and responds appropriately to pathogenic allergens. The relatively recent sanitation of home environments, the shift to smaller families and widespread use of antibiotics at onset of infection in infancy and childhood effectively reduces exposure to environmental pathogens, thereby keeping the immune system in its allergy-prone state in greater numbers of infants and children.

This principle appears to be borne out by several studies cited by the NIH panel. One such study showed that immunotherapy with airborne allergens prevented or delayed onset of asthma in a group of at-risk European children. Another group found that high levels of exposure to dog and cat allergens in early childhood reduced the development of allergy later on. As the panel observed, the protective effect seen in this study might have been elicited by the allergens themselves or they might have been attributable to microbial products, such as endotoxins, carried by pets and farm animals. Endotoxins are potent activators of innate immune responses that can skew the immune system away from the development of atopic

diseases. High levels of exposure to pets and farm animals may in fact “inoculate” the immature immune system and condition it towards a non-allergic state.

Another relatively compelling hypothesis cited by the NIH panel suggests that exposure to peanuts relatively early on in infancy is associated with remarkably low rates of peanut allergy. In Israel, 90% of young children consume a popular peanut snack beginning in the first year of life. The prevalence of peanut allergy in Israel is 0.04%, about ten- to 20-fold lower than it is in the US, Europe and Australia, where parents discourage young children from eating peanuts. Immunological response to peanuts may also depend on how they are prepared: roasting peanuts at high temperatures as they often are in the US appears to alter the structure of allergens and may make them more allergenic, panel members pointed out. It is quite plausible that significant exposure to allergens early in life may prevent the development of IgE antibody responses to sensitizing allergens, providing perhaps a novel approach to the prevention of atopic disease in infancy and childhood.

- **Overdiagnosis of food allergy is best avoided by ruling out atopic disease in at least one parent or one sibling.**
- **IgE-mediated allergy to cow’s milk protein causes symptoms immediately and can involve the skin, gastrointestinal (GI) tract and respiratory system.**
- **Non-IgE-mediated allergic reactions to cow’s milk protein typically occur more than two hours after feeding and are usually confined to the GI tract.**
- **Infants who develop recurrent vomiting or gastroesophageal reflux unresponsive to standard treatment may have a different type of allergy to cow’s milk known as eosinophilic esophagitis or gastritis.**

Avoid Overdiagnosis

Given the increasing incidence of atopic disease—food allergies among them—primary care physicians are likely to encounter a considerable number of patients who present with symptoms suggestive of food allergy, and in infancy, to cow’s milk protein in particular. Here, the caution is to avoid overdiagnosing food allergy when there is none present. In a Medline search by Brazilian investigators, overdiagnosis of food allergy was found to be quite prevalent based on their literature review. An inappropriate diagnosis triggers unnecessary avoidance of nutritionally important foods and potentially long-term sequelae in terms of eating disorders and other psychological issues.

To reduce the likelihood of overdiagnosing food allergies, physicians always need to take a careful history from the parents. Infants born into a family where at least one parent or one sibling has any type of allergic disease (and not necessarily food allergy) have a markedly greater risk for developing atopic disease, including food allergy, than infants born into families with no history of atopy. In the absence of a positive family history, chances that symptoms initially believed to be suggestive of an allergic reaction to cow’s milk protein are reduced. If the infant has an atopic predisposition because of family history, parents need to be queried closely as to the precise nature of the infant’s symptoms.

IgE-mediated allergy to cow’s milk protein gives rise to symptoms immediately. Reactions to cow’s milk protein are generally not life-threatening but in some severe cases, they can involve multiple organs, including the skin, the gastrointestinal (GI) tract and the respiratory system, as well as systemic reactions in the form of anaphylaxis. (Alternative sources of mammalian milk, such as goat or sheep, will cause the same types of reaction in children with cow’s milk allergy.)

Non-IgE-mediated allergic reactions to cow’s milk protein are still allergic in nature but they

typically occur more than two hours after feeding and are usually confined to the GI tract, where they manifest as severe, protracted diarrhea and vomiting and bloody stools. In non-IgE-mediated reactions, the gut wall becomes leaky in reaction to cow's milk protein. As a consequence, the infant's ability to absorb food is reduced and valuable proteins are lost through the gut wall.

If the family history is positive and the symptoms are suggestive of an IgE-mediated allergy, it is always recommended that physicians carry out a skin prick test which is both more sensitive and specific for food allergy than the UniCAP (ELISA test for blood-specific IgE measurement). With the skin prick test, physicians can directly observe whether the infant has an IgE-mediated allergy to cow's milk protein. For infants with this allergy, soy protein-based formula is a very convenient alternative because the risk of cross-reactivity between cow's milk and soy protein is about 15%. Moreover, when weighed against the cost of the hydrolysates, it is more economical.

The UniCAP test detects the presence of IgE in the blood, which does not necessarily mean the infant has a clinical allergy. If the infant has eczema or the skin is otherwise sensitive, the UniCAP test may be used to identify allergy to cow's milk protein.

- Physicians should carry out a skin prick test in infants with suspected IgE-mediated allergy.
- A food patch test that produces a localized dermatitis helps confirm suspected non-IgE-mediated allergy.
- Always interpret test results in the context of the family history of atopy.

Skin prick tests in the non-IgE-mediated allergic infant as well as in those with eosinophilic-mediated disease are likely to be

negative. In these two situations, it is possible to do a food patch test to see if localized dermatitis occurs when the skin is exposed to milk. Blood tests can also be carried out to look for very high eosinophil counts. If eosinophilic-mediated disease is suspected, stool samples should be sent for analysis to look for pus cells; if the gut is inflamed, the presence of pus cells is supportive of a non-IgE-mediated allergy.

Regardless of the test used, results must be interpreted in the context of the family history of atopy and the infant's likelihood to be similarly atopic. This point cannot be overemphasized, as Montreal-based researchers have shown that up to 50% of skin tests are false positive if they are carried out in the absence of a positive family history. Patch tests are never used in the diagnosis of IgE-mediated food allergies, although their use is being explored in non-IgE-mediated allergies as well as eosinophilic enterocolitis. An oral challenge is the optimal test that may be performed under medical supervision to determine if the infant reacts to the suspected protein on exposure. This test is used to confirm the resolution of the disease or the diagnosis.

Infants who are suspected of having a non-IgE-mediated reaction, especially if the infant has bloody stools, should be investigated for potential complications arising from their reaction to cow's milk protein. Complications arising from food-induced enterocolitis, a non-IgE-mediated food reaction, include dehydration, hypotension, anemia and poor growth. Food-induced colitis is also a non-IgE-mediated reaction to food but is generally characterized only by the presence of gross or occult blood in the stool.

Cow's Milk Alternatives

For infants who are diagnosed with an IgE-mediated reaction to cow's milk protein, alternatives should be recommended. Prior to the reintroduction of cow's milk into the diet, physicians should repeat the skin prick test: if

negative, parents may safely give cow's milk or cow's milk formula to their infant at home. Infants who are diagnosed with a non-IgE-mediated allergic reaction almost always outgrow it by 12 to 18 months of age. For these infants, parents should continue using alternatives to cow's milk until 12 months of age, at which point they may gradually reintroduce it into the diet as tolerance.

Lactose intolerance may be prevalent in parts of the country where there is a high concentration of individuals of Asian descent who are often lactose-intolerant but it is not common in provinces such as Quebec, where the majority of residents are still of European descent and better able to tolerate milk. However, if parents are lactose-intolerant, then symptomatic infants should be exposed to lactose-free milk products to see if symptoms resolve.

Summary

Food allergies, especially allergy to cow's milk protein, are not uncommon in infants; physicians need to identify which type of allergy is present in order to counsel parents on its appropriate management. Allergy tests used to confirm the diagnosis of cow's milk protein allergy must always be driven by the genetic predisposition of the infant to develop allergies. In the absence of an atopic family history, infants are unlikely to be allergic to cow's milk protein. Once the diagnosis has been made, physicians should counsel parents to adopt recommended alternatives for infants with cow's milk protein allergy, which are detailed in the accompanying editorials.

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Food Intolerance and Allergy in Infancy: A Parents' Guide to a Healthy, Happy Infant

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Parents are understandably concerned when their infant develops symptoms of either lactose intolerance or food allergy. Physicians need to reassure them that there are steps they can take to ensure their infant receives optimal nutrition without adverse consequences. Parents need to understand that there are several different reasons why infants react to either breast milk or, much more commonly, to their first exposure to cow's milk. Explaining the difference between the various types of reactions to milk can be very helpful.

When infants are allergic to cow's milk, they are allergic to the protein in the milk, clearly very different from milk sugar. However, infants can react to protein in the milk in two distinctly different ways. Classic food allergy involves the allergy antibody, referred to as IgE, that is responsible for this type of allergic reaction to milk. Infants with IgE-triggered reactions develop symptoms very quickly after they have ingested the milk—often within minutes but definitely within hours. Symptoms of a classic milk allergy include red, raised, itchy rash (urticaria), swelling of the lips or the eyes (angioedema), difficulty breathing (asthma), and abdominal pain and vomiting. Infants who have a more severe allergic reaction may also become lethargic. Small amounts of milk protein may also trigger this particular type of IgE-mediated reaction.

The other type of allergic reaction to cow's milk protein does not involve the allergy antibody but instead involves other cells of the immune system. Infants with the non-IgE-mediated allergy to cow's milk protein generally need significantly more milk to trigger symptoms than infants with IgE-mediated allergies. These symptoms occur more insidiously over a longer period of time and are mostly limited to the gastrointestinal (GI) tract. These include reflux, vomiting, and abdominal pain and diarrhea,

which may be either faintly bloody or contain occult blood. Infants with severe and/or persistent forms of non-IgE-mediated allergy may also fail to thrive.

Importantly, eczema does not distinguish between the two types of allergic reactions, as infants with both IgE- and non-IgE-mediated reactions to cow's milk protein can develop eczema. Lactose intolerance tends to present with a much milder clinical picture. These babies can experience fussiness and gas, and may also have a watery acidic diarrhea, which can cause significant diaper dermatitis.

These are clearly not trivial risks and raise a very practical question: can the mother do anything to reduce the likelihood that a high-risk infant will develop allergies at some point in infancy or childhood?

Reviewing the Evidence

- **Exclusive breastfeeding for at least four to six months of age and delayed introduction of solids for the same period of time is the only way mothers can reliably try to prevent allergies in high-risk infants.**
- **An extensively hydrolyzed infant formula may reduce the risk of high-risk infants from becoming allergic to milk or developing eczema if mothers cannot breastfeed.**
- **Soy formulas, tolerated by most infants who have an IgE-mediated allergy to cow's milk protein, are a reasonable substitute.**

The answer to that question has been thoroughly explored by international expert panels, including the American Academy of Pediatrics (AAP), from whom Canadians take their cue. In 2008, the AAP reviewed evidence questioning whether certain forms of dietary restrictions during pregnancy, including exclusion

of cow's milk and eggs, may make high-risk infants less prone to the development of atopic disease. Having reviewed a series of studies, the AAP concluded that evidence generally does not support a preventive benefit of dietary restriction during pregnancy.

Several recent reviews cited by the AAP indicated that there was no convincing evidence that high-risk infants are better protected against atopic disease if mothers eliminate offending allergens from their diet during lactation. The only current evidence that allergies can be prevented in high-risk infants is for exclusive breastfeeding for at least four to six months of age—along with delayed introduction of solids for the same period of time—as the AAP now recommends. If a mother cannot breastfeed, and the infant is at high risk to develop allergies, an extensively hydrolyzed infant formula such as Alimentum or Nutramigen may reduce the risk of the infant becoming allergic to milk or developing eczema.

It is important for parents to know that even if the infant is exclusively breastfed for the recommended period of time, it may not be protective against the development of many allergic diseases over a longer period of time and does not even seem to protect infants from long-term food allergies. Indeed, some recent studies with a longer follow-up period seem to suggest that breastfeeding may not be protective against asthma, and that it may actually increase the long-term risk of asthma, although this observation is still controversial.

Treatment Recommendations

Allergies are hereditary; if either parent has any type of atopic disease, be it allergic rhinitis, asthma, eczema or food allergy, their offspring have a 20% to 40% risk of developing some form of allergy themselves. If both parents are allergic, their offspring have a 40% to 70% risk of developing allergy.

Making a distinction between the types of allergy an infant has to cow's milk protein is not an academic exercise, as treatment recommendations differ significantly, depending on whether the infant has an IgE- or a non-IgE-mediated allergy. Mothers whose infants develop abdominal pain and diarrhea in response to breast milk and who have a non-IgE-mediated allergy to cow's milk protein should be counseled to eliminate dairy products from their own diet and then observe whether or not the baby seems better without any exposure to cow's milk protein through breast milk.

Some 30% of infants with a non-IgE-mediated allergy to cow's milk protein may also react to soy protein so for these infants, the first choice is an extensively hydrolyzed infant formula—not a partially hydrolyzed formula as this, too, can trigger the allergic reaction. In the small percentage of infants who cannot tolerate an extensively hydrolyzed formula, an elemental formula (amino acid) may be used as a substitute.

In IgE-mediated cow's milk allergy, what mothers should do depends on the type of symptoms an infant develops in response to breast milk. If the breastfeeding mother is consuming dairy in her diet, and the infant has no symptoms while being breastfed but reacts on its first exposure to milk, mothers do not need to remove milk from their own diet as the infant tolerated the breast milk well until then.

Conversely, if the infant has eczema as a sign of their allergic reaction to cow's milk, mothers should remove milk from their own diet to see if the infant's eczema improves. If it does, then mothers should eliminate dairy from their diet as long as they continue to breastfeed. If the eczema does not change at all, then mothers can continue to drink milk.

The development of hives, however, necessitates a different approach. If a breast-fed baby develops hives every time mothers consume dairy, mothers should definitely remove all dairy from their diet as long as they continue to breastfeed.

Soy protein-based formulas are tolerated by all but about 15% of infants who have an IgE-mediated allergy to cow's milk protein so for the majority of this group of infants, a soy protein-based formula can be a reasonable substitute as well. But again, if an infant is also allergic to soy, an extensively hydrolyzed formula may be recommended, followed again by an elemental formula for those with dual allergies to cow's milk protein and soy who do not tolerate an extensively hydrolyzed formula.

Lactose Intolerance

- **Lactose intolerance occurs because infants are missing the enzyme that digests milk sugar and once fermented, sugar causes bloating, burping, flatulence and diarrhea.**
- **Most infants with non-IgE milk allergy tolerate milk by the age of one year, and almost all by the time they are three.**
- **Resolution of an IgE-mediated milk allergy takes longer but most children will tolerate milk by the ages of four to six.**

In some ethnic groups, the lactase enzyme that digests milk sugar is missing from certain cells, known as border cells, in the intestine. As the milk progresses through the intestine, the infant is unable to fully digest the sugar or lactose in the milk and the sugar ferments in the intestine rather than being absorbed. It is this fermentation that causes the cardinal symptoms of lactose intolerance including abdominal pain, bloating, burping, flatulence and diarrhea.

Primary lactose intolerance, where infants are born without lactase, is extremely rare. For the great majority of lactose-intolerant infants, the condition is secondary to either inflammation or infection of the GI tract. The border GI cells that normally digest lactose in milk lose the enzyme and consequently their ability to digest milk, at

least temporarily. In this situation, what parents need to do depends on what is causing the lactose intolerance. If, for example, the infant has developed lactose intolerance because of gastroenteritis, parents may choose either a lactose-free formula or a soy-based one. If they have non-IgE-mediated allergy to cow's milk protein, then infants will need an extensively hydrolyzed formula which will likely have to be continued for a relatively protracted interval if the gut has suffered a significant insult.

When parents may reintroduce cow's milk-based products into the infant's diet depends on whether infants have IgE-mediated or non-IgE-mediated milk allergy. The majority of babies with the non-IgE variant tolerate milk by the age of one year and almost all of them by the time they are three. In contrast, resolution of an IgE-mediated milk allergy tends to occur at a later age, between the ages of four and six years, where approximately 80% of previously IgE-mediated allergic children will be able to tolerate cow's milk. A more recent study has shown lower rates of resolution; however, it also showed that the milk allergy may be outgrown at a later age than was previously thought possible. IgE-mediated allergic infants should be followed with an annual skin prick test but if it remains positive, physicians may also use UniCAP radioallergosorbent testing (RAST) to measure the level of specific IgE antibody to cow's milk protein in their blood. IgE levels help predict if children will outgrow their milk allergy or not. An oral challenge to cow's milk protein may also be offered to parents in the clinic to see if the child has outgrown their allergy to cow's milk protein.

Summary

Many parents who have food allergies of their own are anxious not to pass along the same atopic tendency to their children and will ask physicians how best to avoid this. The best advice is for mothers to exclusively breastfeed from birth to four to six months of age if possible and to delay the introduction of solids for the same period of time. By following this recommendation they would be doing everything they can to prevent allergies in their infants. Delaying the introduction of solids after this time does not seem to be protective against the development of allergies. Parents should also be reassured that if one infant has the IgE form of cow's milk protein allergy, other siblings do not necessarily develop any food allergies at all, although their risk is slightly higher than that of the general population. This is not quite the case for infants who develop the non-IgE-mediated form of cow's milk protein allergy, where a second sibling may develop the same symptoms more often. Exclusive breastfeeding for four to six months is the best that any mother can do for their infant, regardless of whether the infant is at risk for atopic disease.



Practice Pearls for the Diagnosis and Management of Cow's Milk Protein Allergy

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Physicians who manage pediatric allergies often rely on small pearls of wisdom gained over the years, in combination with new discoveries in the field, to arrive at a decisive diagnosis. Faced with a symptomatic high-risk infant, the first of these pearls that helps distinguish different types of allergies to cow's milk protein is: How immediate is the infant's reaction to the milk? Infants with an immediate reaction to cow's milk—and keep in mind that breastfed infants can be allergic to “breast” milk, too, if the mother has dairy in her diet—develop hives, diarrhea, vomiting or respiratory distress with wheezing usually within 20 minutes or so of being exposed. (Eczema is also one of the earliest clinical manifestations of food allergy in infants, and in milk-related allergy, the eczema is commonly on the face. Eczema is more commonly identified as a manifestation of delayed food allergy.)

Immediate reactions to cow's milk protein are typical of all IgE-allergic conditions and help identify the presence of an IgE-mediated allergy.

On the other hand, infants who present with diarrhea or specks of blood in their stool, or vomiting, are unlikely to have an IgE-mediated reaction to cow's milk protein. Occurring more slowly than IgE-mediated reactions, the gut wall becomes “leaky” in the non-IgE-mediated reaction secondary to localized mucosal inflammation due to contact with a major food protein, frequently to cow's milk. Consequently, the infant's ability to absorb food is reduced, resulting in the loss of valuable protein and changes in stool pattern. When inflammation occurs in the lower bowel and rectum, infants will usually have loose, mucousy or bloody stools. Commonly, infants with lower bowel involvement to cow's milk protein do not appear very sick, even though they have upsetting symptoms.

However, if more of the gut is involved, infants will have much looser stools, they lose weight, they look sicker and they may become severely dehydrated—all signs of a more generalized inflammation from major food protein allergy, which is referred to as the food protein-induced enterocolitis syndrome (FPIES).

A third manifestation of food allergy in infants allergic to cow's milk protein is Eosinophilic Esophagitis (EE) or Eosinophilic Gastritis (EG). Infants who develop this particular type of allergy have recurrent vomiting or gastro-esophageal reflux disease (GERD) and the key here is that standard approaches to the treatment of reflux are ineffective. In eosinophilic EE or EG, inflammation occurs in the upper GI track and there is an intense build-up of eosinophils. As with the other two types of allergic reactions, this reaction can also be triggered by cow's milk protein. Here, the pediatrician or treating physician should ask the parents whether they have a history of difficult-to-control GERD or dysphagia, which if they have, may well be a symptom of eosinophilic-mediated disease and not classic reflux.

Skin prick tests help guide the diagnosis of IgE-mediated milk allergy. The UniCAP RAST, which measures specific IgE to milk, not only supports the allergy diagnosis, but also identifies the likelihood of immediate reactivity with future immediate exposures. Skin prick tests in the non-IgE-mediated allergic infant as well as in those with eosinophilic-mediated disease are likely to be negative. If non-IgE, T-cell-dependent disease is suspected and stool samples should be sent for analysis to look for pus cells; if the gut is inflamed, the presence of pus cells, although not specific, is supportive of this form of food allergy. Finally, an oral challenge may be performed under medical supervision to see if the infant reacts to the suspected protein on exposure.

- **Inclusion of vitamin D and omega-3 fatty acids in the mother's diet during pregnancy and beyond may reduce the risk of allergy in high-risk children.**
- **Food allergies can start at any time during infancy, even during breastfeeding, as dairy is transmitted in breast milk.**

If eosinophilic-mediated allergy is suspected, both bloodwork and patch testing has been used for objective evidence of this condition. Complete blood counts frequently reveal elevated eosinophil counts on differential cell counting. In the food patch test, an amount of milk is applied on a filter paper adhered to a Finn chamber on the child's back for a period of 48 hours, compared to a negative control. Identification of an inflamed red patch is suggestive of a delayed allergy.

Unlike the variants of immunologically induced food allergies, lactose intolerance is not an immune-mediated disorder but rather the inability of an infant to absorb lactose sugar in dairy products. In this case, unabsorbed lactose serves as an osmotic agent in the colon; consequently, stools become loose and the sugar undergoes fermentation, thereby expanding the walls of the colon. Symptoms of lactose intolerance are quite different from those of cow's milk protein allergy. There are no classic allergic-type rashes or other manifestations of IgE-mediated allergy, nor is there significant failure to thrive or fluid loss. On the other hand, infants with lactose intolerance present with loose stools, bloating and irritability. Lactose intolerance is largely a function of genetic background, with Caucasians having a relatively low risk of being lactose-intolerant, usually acquiring it post-infectiously. Individuals of Asian descent are highly prone to lactose intolerance as are Blacks and First Nations people.

Eliminate Food Allergens

- **All food allergies should be initially managed by eliminating the triggering food allergen.**
- **Infants who have a delayed allergic reaction should not receive a soy protein-based formula because the risk of cross-reactivity is too high.**
- **An extensively hydrolyzed formula may be recommended, followed by an amino acid formula if infants react to both soy and cow's milk protein.**

All food allergies are initially managed by eliminating the triggering food allergen. For infants with cow's milk protein allergy, management takes two separate tacks. Only a small percentage of infants are allergic to both cow's milk protein and soy, therefore a soy protein-based formula is generally safe for the majority of children with IgE-mediated milk allergy. For those who react to soy as well, an extensively hydrolyzed formula may be recommended, followed by an amino acid formula if the extensively hydrolyzed formula is not tolerated by the infant.

Infants who have a delayed allergic reaction should not receive a soy protein-based formula because the risk of cross-reactivity is too high. For infants with non-IgE-mediated milk allergy, parents need to go directly to an extensively hydrolyzed formula, with the same proviso for an amino acid replacement if the first-line choice proves unacceptable. When eosinophilic disease is in question, either type of hypoallergenic formula may be used as well.

Contrary to concerns that infants will dislike these formulas because they have a bitter taste, parents can expect their infant will feel better when they no longer receive cow's milk protein

and they typically do not resist these formulas because they know the formula agrees with them.

Optimal Nutrition for Infants

Universal recommendations from expert societies around the world suggest mothers breastfeed exclusively for four to six months to guarantee optimal nutrition for their infant. However, when mothers either cannot or choose not to breastfeed—and if there is a family history of atopic disease (i.e. one parent or sibling with documented allergic disease)—then they may wish to introduce their infants to an extensively hydrolyzed formula at the onset to reduce the risk of infants developing allergic disease as they grow.

As a child progresses through infancy, the decision of when to start solids, i.e. cereals has recently undergone review. Previous recommendations in high-risk atopic infants, i.e. either already diagnosed with atopic dermatitis or with either parent atopic, were to delay introduction of cereals. A recent policy review by the American Academy of Pediatrics, section of Allergy and Immunology, has identified no benefit in delaying solids and in fact supports earlier introduction of infant cereals.

There is also new and exciting information about vitamin D deficiency in pregnancy and subsequent development of allergic disease—the lower the levels of maternal vitamin D, the more likely the high-risk child will have allergic disease. If this link proves to be causal, then recommendations could include the simple and inexpensive inclusion of vitamin D in the mother's diet during pregnancy and beyond.

Similarly intriguing evidence is emerging that low levels of omega-3 fatty acids are implicated in the development of pediatric atopic disease; again, the lower the omega-3 fatty acid levels in the mother, the more likely the at-risk child will

develop atopic disease. While this association needs further confirmation, initial evidence would suggest benefits for expectant mothers to consume both vitamin D and omega-3 fatty acid supplements to reduce the risk of atopic disease in their newborn.

Summary

Food allergies are common in infants and children, especially allergy to cow's milk protein, which may start any time during infancy, both during breastfeeding and initiation of cow's milk-based formula at four to six months. Parents can be understandably alarmed at these reactions and physicians need a firm diagnosis not only to direct management of these allergies

but also to reassure parents that their infant will thrive and be well as soon as exposure to cow's milk protein is eliminated. Either soy protein-based formulas in classic IgE-mediated milk allergy or extensively hydrolyzed formulas are appropriate first-line choices for most infants, although some will react to soy protein as well. For these infants, and for infants with non-IgE-mediated cow's milk protein allergy, an extensively hydrolyzed formula is the treatment of choice, followed by an amino acid-based formula in those extremely rare cases when an infant does not tolerate the extensively hydrolyzed variant. Research continues to be directed to help the high-risk parent to prevent development of atopy to their children.

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Food Reactions and Your Infant: A Parental Guide*

■ Risk factors for food allergy

- If either one parent or one sibling has a history of allergic disease—and this includes any type of allergy including hay fever, asthma, or food allergies—infants are at greater risk for becoming allergic themselves, often first to cow's milk protein in formula, or less often, cow's milk protein from the mother's diet that is excreted in breast milk.

■ How infants may react

- There are two types of allergic reactions: one in which symptoms appear immediately after the infant has been fed and the second reaction that occurs more slowly over a longer period of time.
- Symptoms of the first type of reaction include eczema (often on the infant's face); hives; wheezing and signs of respiratory distress; swelling of the lips and eyes and abdominal pain and vomiting. Infants only need to be given small amounts of milk to develop these immediate symptoms.
- Symptoms of the second type of reaction usually involve the GI tract and include reflux (spitting up), vomiting, abdominal pain and diarrhea. Blood in the stools is a key symptom of a more delayed allergic reaction to cow's milk protein. In severe forms of this type of reaction, infants fail to thrive.

■ Prevention of allergies in infants

- Only infants who have a family history of allergies are at a higher risk for developing allergies themselves, including food allergies. Infants without a family history can develop allergies but are at a lower risk.
- There is little evidence that mothers can prevent allergies in at-risk infants by eliminating cow's milk and eggs from their own diet during pregnancy or lactation.
- The best protection against allergies in an allergy-prone infant is to breastfeed exclusively for four to six months.
- If a mother cannot breastfeed, and the infant is at high risk to develop allergies, an extensively hydrolyzed infant formula such as Alimentum or Nutramigen may reduce the risk of the infant becoming allergic to food or other allergens.
- Partially hydrolyzed formulas may have an effect, in the prevention of atopic disease, although it seems to be less than that of an extensively hydrolyzed formula at present.
- Solid foods should not be introduced into the infant's diet before four to six months of age; after this period, the timing of the introduction of foods such as dairy, eggs and nuts does not seem to affect the development of allergies.
- Even fruits and vegetables which are not likely to cause allergies should be introduced one at a time to make sure infants can tolerate each individual ingredient.

- When introduced individually, fruits and vegetables should be introduced in their cooked form, which is less likely to provoke allergies when cooked.

■ **Treatment of cow's milk allergy in infants who develop immediate symptoms**

- Infants who develop immediate symptoms on being fed cow's milk may be switched to a soy-protein formula such as Isomil, as only about 15% of infants with allergy to cow's milk are also allergic to soy protein.
- Infants who develop immediate symptoms to both cow's milk and soy protein should be switched to an extensively hydrolyzed formula such as Alimentum or Nutramigen.
- If Alimentum or Nutramigen are not tolerated, infants may be switched to an amino acid-based formula.
- Infants with immediate reactions to cow's milk usually do not outgrow the allergy until they are four to six years of age. For those with delayed reactions, most babies outgrow symptoms by the age of one year and almost all by three years of age.
- Parents should consult with their pediatrician or allergist before introducing cow's milk to previously allergic infants, as they should be tested to see if they are still allergic to it.

■ **Treatment of cow's milk allergy in infants whose symptoms to cow's milk are delayed:**

- Infants who have delayed symptoms to cow's milk protein that are largely confined to the GI tract should not be switched to a soy protein-based formula as they are likely to react to the soy protein as well.
- For infants with this type of allergic reaction, parents should use an extensively hydrolyzed formula such as Alimentum or Nutramigen amino acid-based formula if the extensively hydrolyzed formula is not tolerated.
- Most infants with this type of allergy outgrow it by the age of one and almost all of them by the time they are three years of age, at which point they should tolerate cow's milk.

■ **Symptoms of lactose intolerance**

- Symptoms of lactose intolerance include diarrhea, gas and bloating.
- Lactose intolerance is not an allergy but rather an inability to digest milk sugar, leaving the sugar to ferment inside the GI tract, which leads to symptoms.
- Lactose intolerance is most likely in those of Asian descent, First Nations people and Blacks and least likely to occur in people of European descent.

■ **Treatment of lactose intolerance**

- Infants who are lactose-intolerant should receive a lactose-free formula to improve tolerability.

*This parental guide can be accessed at www.mednet.ca/2008/ho08-002pge

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