Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion

Andrew S Kemp,* David J Hill,* Katrina J Allen, Kym Anderson, Geoffrey P Davidson, Andrew S Day, Ralph G Heine, Jane E Peake, Susan L Prescott, Albert W Shugg and John K Sinn

ABSTRACT

- Three types of infant formula (soy, extensively hydrolysed and amino acid) may be appropriate for treating cows milk protein allergy.
- Selection of a formula depends on the allergy syndrome to be treated.
- Extensively hydrolysed formula is recommended as first choice for infants under 6 months of age for treating immediate cows milk allergy (non-anaphylactic), food protein-induced enterocolitis syndrome, atopic eczema, gastrointestinal symptoms and food protein-induced proctocolitis.
- Soy formula is recommended as first choice for infants over 6 months of age with immediate food reactions, and for those with gastrointestinal symptoms or atopic dermatitis in the absence of failure to thrive.
- Amino acid formula is recommended as first choice in anaphylaxis and eosinophilic oesophagitis.
- If treatment with the initial formula is not successful, use of an alternative formula is recommended.

MJA 2008; 188: 109–112

Various infant formulas — such as soy, extensively hydrolysed and amino acid-based formula — that can be used to treat cows milk protein allergy are available in Australia. An analysis of Australian formula-prescribing practices indicated that they did not appear to be in line with authoritative statements and position papers or the guidelines of the Australian Pharmaceutical Benefits Advisory Committee (PBAC).[1]

In 2000, the Committee on Nutrition of the American Academy of Pediatrics stated that soy formula was a suitable option for treating infants with cows milk protein allergy.[2] In April 2006, the Committee on Nutrition of the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) recommended that soy protein formulas should not be used in infants with cows milk protein allergy during the first 6 months of life, because few infants had been studied, and the reported rate of adverse reactions to soy protein was higher in infants under 6 months of age. This committee also recommended that, when soy formula is used to treat cows milk protein allergy in infants over 6 months of age, tolerance to soy formula be established by clinical challenge.[3]

The PBAC guidelines once restricted the use of extensively hydrolysed formula to infants with combined intolerance to cows milk protein and soy protein. It also restricted the use of amino acid formula to infants with combined intolerance to cows milk protein, soy protein and extensively hydrolysed formula. In November 2006, the PBAC accepted the advice of its Nutritional Products Working Party to ease the restrictions: the requirement to demonstrate intolerance to soy protein before treating infants with these products was removed.

In 2007, European proposals for treating cows milk protein allergy in formula-fed infants with extensively hydrolysed formula and amino acid formula were outlined in an algorithm.[4]

Consensus panel

In the light of these considerations, we constituted an Australian panel with representation from all states. The panel was put together by the two lead authors (A S K and D J H) to represent practising paediatric clinicians. The panel was composed to include clinicians with expertise in paediatric allergy, gastroenterology, neonatology and general paediatrics.

There were two face-to-face meetings, in November 2006 and June 2007, and four telephone conferences. Meetings were co-chaired by A S K and D J H. Panel members (but not the co-chairs) were assigned individual tasks to review practice with regard to treatment as it related to specific clinical syndromes. After this material had been discussed by the panel, a position was reached. The number of panel members agreeing with the position (in view of the evidence presented) was recorded.

The panel considered the issues and reached a consensus on the indications for use of soy, extensively hydrolysed and amino acid formulas in the treatment of cows milk protein allergy under Australian conditions in general and paediatric practice. As the selection of a formula depends on the syndrome to be treated, the panel has outlined the salient features of the different syndromes in breastfed and formula-fed infants. Selected references to the individual syndromes have been provided.

The spectrum of cows milk protein allergy

Cows milk protein allergy is defined as an immunologically mediated adverse reaction to cows milk protein. It affects about 2% of infants under 2 years of age.[5] In this document, we use the term "allergy" in accordance with the World Allergy Organization's definition (ie, allergy is a hypersensitivity reaction initiated by specific immunological mechanisms).[6] Mechanisms may be IgE mediated or non-IgE mediated. Cows milk protein allergy can also occur in exclusively breastfed infants.

Cows milk protein is often the first food protein ingested by formula-fed infants, and allergies present as a range of syndromes. A correct diagnosis is critical and will often depend on appropriate immunological and morphological investigations. In all cases, the diagnosis is confirmed by observing remission of the symptoms following removal of the protein. If the diagnosis remains uncertain, further confirmation should be obtained by observing relapse following challenge with cows milk protein. As some of the conditions may remit with time, rechallenge with cows milk protein after a period of avoidance is indicated in some cases. A complete discussion of the diagnostic process and ongoing management[4] falls outside the scope of this guideline.

Consensus on the use of formulas

Three different types of formula (soy, extensively hydrolysed and amino acid) may be appropriate treatment in particular circumstances (Box 1). Some preparations are not recommended for treating cows milk protein allergy. The panel considers that there is no place for partially hydrolysed (known as HA) formulas nor other mammalian milks (such as goats milk)[7] in treating cows milk protein allergy. The consensus recommendations for using infant formulas to treat allergy syndromes are shown in Box 2. Breastfeeding may be continued, and recommendations are provided for eliminating maternal intake of cows milk protein.

The panel believes the information provided is a guideline for most cases. However, in severely affected infants or if the diagnosis is uncertain, it may be appropriate to start treatment with an extensively hydrolysed or amino acid-based formula which is not in accordance with this consensus.[8] Such a case should be managed by a paediatrician with particular expertise in these disorders.

1 Preparations available for treating cows milk protein allergy

Suitable

- Soy formulas
- Extensively hydrolysed formulas
  - Alfaré (Nestlé)
  - Pepti-Junior (Nutricia)
- Amino acid formulas
  - EleCare (Abbott)
  - Neocate (SHS)

Contraindicated or not recommended

- Formulas
  - Cows milk-based (including anti-regurgitation)
  - Lactose-free cows milk-based (eg, Karicare De-Lact, Digestelact [Nutricia], S-26 LF [Wyeth])
  - Partially hydrolysed cows milk-based (eg, Karicare SensiKare [Nutricia], NAN HA [Nestlé])
  - Goats milk-based formula
- Other preparations
  - A2 milk (A2 Australia)
  - Rice milk
  - Oat milk
  - Other mammalian milks (camel, mare, ass, goat and ewe) ◆

Cows milk protein allergy syndromes

The syndromes are classified as reactions which develop over minutes, hours or days. The recommendations include advice about the necessity for mothers to eliminate dietary intake of cows milk protein while breastfeeding. In some situations, failure to thrive affects the choice of formula. Recommendations provide for an alternative formula if treatment with the initial formula is not successful.

Immediate allergic reactions[9]

Cows milk protein allergy may manifest with erythema, angioedema, urticaria or vomiting. Some infants may have contact urticaria where protein has touched the skin. Typically, there will be evidence of IgE sensitisation (positive skin prick test or an allergen-specific IgE antibody test [RAST] to cows milk). Symptoms develop within minutes of ingestion of small volumes of milk. Infants with cows milk protein allergy often have other food allergies, in particular to egg and peanut products.

Anaphylaxis is a severe immediate reaction with respiratory tract involvement and/or hypotension. Features of anaphylaxis may be difficult to identify in infants. It may be suggested by coughing, wheezing, severe distress, floppiness or collapse.

Food protein-induced enterocolitis syndrome (FPIES)[10]

FPIES is an uncommon disorder which usually presents with acute onset of repeated projectile vomiting, hypotonia, pallor and sometimes diarrhoea 1 to 3 hours after ingestion of cows milk protein. FPIES may be mistaken for acute gastroenteritis, sepsis or intestinal obstruction, and multiple presentations before the diagnosis is established are not uncommon. Typically, FPIES occurs at the first introduction of cows milk protein into the diet. It has not been reported in exclusively breastfed infants. FPIES may also be caused by other food proteins (eg, soy, wheat, rice and chicken). Despite the onset within hours of ingestion, the disorder is not IgE mediated. Remission has usually occurred by the third year of life.

Atopic eczema[11]

Atopic eczema is a chronic, relapsing, pruritic inflammatory disease of the skin, usually associated with allergic sensitisation. Food allergy plays a role in some cases of eczema in children. It should particularly be considered in infants with moderate to severe eczema. It is usually associated with high levels of IgE antibodies to common foods (eg, milk, egg and peanut). Egg is the most frequently involved allergen, followed by cows milk protein. Although IgE antibodies have been implicated in most cases of cows milk protein-induced eczema, about 10% of cases are not IgE associated.

Gastrointestinal syndromes

Infants with cows milk protein allergy may present with vomiting, chronic diarrhoea, malabsorption and failure to thrive. Most of the syndromes are not IgE associated and have other pathogenic immune mechanisms. Cows milk protein allergy is the most commonly identified food allergen sensitivity; however, in some cases, hypersensitivity to multiple food proteins is involved. Gastrointestinal biopsy may be required to define the disorder.

Gastro-oesophageal reflux disease (GORD)[12]

About 40% of infants referred for specialist management of GORD have allergy to cows milk protein. These allergic reactions are typically not IgE mediated. In these infants, intestinal biopsy commonly shows partial villous atrophy.

Allergic eosinophilic gastroenteritis[13]

Common features include weight loss and failure to thrive associated with postprandial vomiting, diarrhoea and, occasionally, blood loss. In more severe cases, the infants may have iron deficiency anaemia and oedema due to hypoproteinaemia and protein-losing enteropathy.

Food protein-induced enteropathy[14]

Infants with allergic enteropathy due to cows milk protein may present with diarrhoea, failure to thrive, various degrees of vomiting and, sometimes, hypoproteinaemia and anaemia. Some cases have an associated soy allergy. The clinical signs of secondary lactose intolerance, including perianal excoriation from acidic stools, may be present.

Constipation[15]

Whether constipation is a clinical manifestation of cows milk protein allergy in infants and young children is controversial. Constipation is a common symptom in early childhood and, in some cases, resolves after removal of cows milk protein from the diet. Cows milk protein-induced constipation is often associated with anal fissures and rectal eosinophilia.

2 Formula feeding in syndromes associated with cows milk protein allergy*

Syndrome	Onset of reaction	Maternal elimination of CMP if breastfeeding?	Choice of formula			NHMRC level of evidence‡	Consensus panel agreement§
			First†	Second (if first not tolerated)	Third (if second not tolerated)		
Immediate reaction							
Immediate food allergy	< 1 h	Yes	eHF (< 6 months)	AAF	—	II	11/11
			Soy (> 6 months)	eHF	AAF		
Anaphylaxis	< 1 h	Yes	AAF (followed by urgent consultation with paediatric allergist)	—	—	IV	11/11
Food protein-induced enterocolitis syndrome	1–3 h	No	eHF	AAF	—	IV	10/11
Delayed reaction							
Atopic eczema	Hours to days	Yes¶	eHF (< 6 months or > 6 months with FTT)	AAF	—	IV	11/11
			Soy (> 6 months, no FTT)	eHF	AAF		
Gastrointestinal syndromes, GORD, allergic eosinophilic gastroenteritis, food protein-induced enteropathy, constipation, severe irritability (colic)	Hours to days	Yes¶	eHF (< 6 months or > 6 months with FTT)	AAF	—	I (severe irritability), III (GORD), IV (others)	11/11
			Soy (> 6 months, no FTT)	eHF	AAF		
Food protein-induced proctocolitis							11/11
Formula-fed	> 24 h	—	eHF	AAF	—	IV	
Breastfed	> 24 h	Yes¶	—	—	—		
Eosinophilic oesophagitis in infants	Days to weeks	Yes	AAF	—	—	IV	11/11

CMP = cows milk protein. NHMRC = National Health and Medical Research Council. eHF = extensively hydrolysed formula. AAF = amino acid formula.
FTT = failure to thrive. GORD = gastro-oesophageal reflux disease. — = no further alternative choice.
* If restriction of multiple or common foods is indicated, advice from a dietitian on implementation may be required.
† Complementary to breastfeeding or exclusive formula feeding.
‡ NHMRC levels of evidence for intervention studies: I = systematic review of level II studies; II = randomised controlled trial; III = non-randomised experimental trial; IV = case series with either post-test or pretest–post-test outcomes.
§ Number of panel members in agreement with decision. ¶ May also need maternal elimination of other foods. ◆

Severe irritability (colic)[16]

The mechanisms of infant colic are poorly understood. Colic is not mediated by IgE, and the role of dietary factors is controversial. Persistent crying is a common problem that may affect about a third of young infants and gradually abates by 4 months of age without specific treatment in most cases. In infants with unremitting distress persisting beyond the typical colic period, an underlying organic cause may be more likely. Exclusion of cows milk protein helps in some cases, but these cannot be identified by allergy tests.

Food protein-induced proctocolitis[17]

Infants with allergic proctocolitis due to cows milk protein allergy usually present with mild diarrhoea and low-grade rectal bleeding. If the infant is fully breastfed (breast milk colitis), symptoms may be caused by protein transferred via the breast milk. The bleeding is usually observed as stools containing mucus and flecks of blood rather than as frank rectal bleeding. Other systemic features (such as failure to thrive or anaemia) are usually absent, and the infants appear generally well. Rectal biopsies are not usual, but may be required to confirm the diagnosis in more severe or atypical cases.

Eosinophilic oesophagitis[18]

Eosinophilic oesophagitis is more often identified in older children than in infants, but may occur in both groups. In infancy, typical symptoms are refusal of food, difficult feeding, poor weight gain and poor response to standard antireflux measures. Older children may present with dysphagia or episodes of impacted food bolus. Endoscopy is necessary to establish the diagnosis, which is based on eosinophilia of the upper and lower oesophagus. Eosinophil numbers are typically lower in infants with peptic reflux oesophagitis. Hypersensitivity to multiple foods may be seen in infants with eosinophilic oesophagitis. In older children and adults, aeroallergens may also be implicated. Therapy may include hypoallergenic diets and swallowed steroid aerosol.

Other conditions associated with eosinophilic infiltration of the small and large bowel require specialist diagnosis and treatment, and may respond to elimination of cows milk protein.

Acknowledgements

The panel gratefully acknowledges the support of SHS/Nutricia, which funded the teleconferences and face-to-face meetings for the preparation of this consensus. None of the panel members received any remuneration for their participation.

Competing interests

Andrew Kemp has spoken at a clinical update sponsored by Nutricia and received a speaker fee, and his department has held a clinical update meeting sponsored by Abbott. David Hill has received support from SHS/Nutricia for clinical research, to attend scientific meetings, for consultations and to speak at sponsored meetings. Ralph Heine has been a member of the scientific advisory boards of Nutricia Australia and the Nestlé Nutrition Institute Oceania, and has received travel assistance and speaker fees from both companies to present at or attend scientific meetings. Jane Peake has been a speaker at meetings sponsored by SHS/Nutricia, Nestlé and Wyeth, and has had some travel expenses reimbursed. Susan Prescott has received an honorarium from Mead Johnson and is a member of the independent Scientific Advisory Board of Nestlé.

Author details

Andrew S Kemp,* PhD, FRACP, Professor of Paediatric Allergy[1]
David J Hill,* FRACP, Senior Allergist[2]
Katrina J Allen, FRACP, PhD, Paediatric Gastroenterologist–Allergist[3]
Kym Anderson, FRACP, Paediatrician[4]
Geoffrey P Davidson, FRACP, Gastroenterologist[5]
Andrew S Day, MD, FRACP, Head of Gastroenterology[6]
Ralph G Heine, MB ChB, Paediatric Gastroenterologist–Allergist[3,7]
Jane E Peake, FRACP, DTM&H, Senior Lecturer and Paediatric Immunologist and Allergist[8]
Susan L Prescott, BMedSc, PhD, FRACP, Professor and Paediatric Allergist–Immunologist[9]
Albert W Shugg, DCH, FRACGP, FRACP, Director of Paediatrics and Senior Lecturer[10]
John K Sinn, MMed(ClinEpi), FRACP, Senior Lecturer and Paediatrician[11]
* Equal first authors.

1 Department of Allergy and Immunology, Children's Hospital at Westmead, Sydney, NSW.
2 Murdoch Childrens Research Institute, Royal Children's Hospital, Melbourne, VIC.
3 Department of Allergy and Clinical Immunology, Royal Children's Hospital, Melbourne, VIC.
4 Alice Springs Hospital, Alice Springs, NT.
5 Department of Gastroenterology, Women's and Children's Hospital, Adelaide, SA.
6 Department of Gastroenterology, Sydney Children's Hospital, Sydney, NSW.
7 Department of Gastroenterology and Clinical Nutrition, Royal Children's Hospital, Melbourne, VIC.
8 Department of Paediatrics and Child Health, University of Queensland, Royal Children's Hospital, Brisbane, QLD.
9 School of Paediatrics and Child Health, University of Western Australia, Princess Margaret Hospital, Perth, WA.
10 University of Tasmania Rural Clinical School, Burnie, TAS.
11 Department of Neonatology, Royal North Shore Hospital, Sydney, NSW.

Correspondence: AndrewK5@chw.edu.au

References

1 Kemp A. Hypoallergenic formula prescribing practices in Australia. *J Paediatr Child Health* 2006; 42: 191-195.
2 American Academy of Pediatrics, Committee on Nutrition. Hypoallergenic infant formulas. *Pediatrics* 2000; 106: 346-349.
3 Agostoni C, Axelsson I, Goulet O, et al. Soy protein infant formulae and follow-on formulae: a commentary by the ESPGHAN Committee on Nutrition. *J Pediatr Gastroenterol Nutr* 2006; 42: 352-361.
4 Vandenplas Y, Brueton M, Dupont C, et al. Guidelines for the diagnosis and management of cows milk protein allergy in infants. *Arch Dis Child* 2007; 92: 902-908.
5 Heine RG, Elsayed S, Hosking CS, Hill DJ. Cows milk allergy in infancy. *Curr Opin Allergy Clin Immunol* 2002; 2: 217-225.
6 Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organization, 2003. *J Allergy Clin Immunol* 2004; 113: 832-836.
7 Muraro MA, Giampietro PG, Galli E. Soy formulas and nonbovine milk. *Ann Allergy Asthma Immunol* 2002; 89: 97-101.
8 Vanderhoof JA, Murray ND, Kaufman SS, et al. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. *J Pediatr* 1997; 131: 741-744.
9 Sampson HA. Update on food allergy. *J Allergy Clin Immunol* 2004; 113: 805-819.
10 Nowak-Wegrzyn A, Sampson HA, Wood RA, Sicherer SH. Food protein-induced enterocolitis syndrome caused by solid food proteins. *Pediatrics* 2003; 111: 829-835.
11 Niggemann B, Sielaff B, Beyer K, et al. Outcome of double-blind, placebo-controlled food challenge tests in 107 children with atopic dermatitis. *Clin Exp Allergy* 1999; 29: 91-96.
12 Iacono G, Carroccio A, Cavataio F, et al. Gastroesophageal reflux and cows milk allergy in infants: a prospective study. *J Allergy Clin Immunol* 1996; 97: 822-827.
13 Chehade M, Magid MS, Mofidi S, et al. Allergic eosinophilic gastroenteritis with protein-losing enteropathy: intestinal pathology, clinical course, and long-term follow-up. *J Pediatr Gastroenterol Nutr* 2006; 42: 516-521.
14 Savilahti E. Food-induced malabsorption syndromes. *J Pediatr Gastroenterol Nutr* 2000; 30 Suppl: S61-S66.
15 Iacono G, Cavataio F, Montalto G, et al. Intolerance of cows milk and chronic constipation in children. *N Engl J Med* 1998; 339: 1100-1104.
16 Lucassen PL, Assendelft WJ. Systematic review of treatments for infant colic. *Pediatrics* 2001; 108: 1047-1048.
17 Lake AM. Food-induced eosinophilic proctocolitis. *J Pediatr Gastroenterol Nutr* 2000; 30 Suppl: S58-S60.
18 Liacouras CA, Eosinophilic esophagitis: treatment in 2005. *Curr Opin Gastroenterol* 2006; 22: 147-152.

(Received 1 Jul 2007, accepted 4 Oct 2007) ❑