

FACULTY



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Managing cow's milk allergy in infants

The role of Aptamil AllerPro Syneo and Neocate Syneo

BREASTMILK IS BEST FOR BABIES:

Professional advice should be followed before using an infant formula. Introducing partial bottle feeding could negatively affect breast feeding. Good maternal nutrition is important for breastfeeding and reversing a decision not to breastfeed may be difficult. Infant formula should be used as directed. Proper use of an infant formula is important to the health of the infant. Social and financial implications should be considered when selecting a method of feeding.

INTRODUCTION

Cow's milk allergy (CMA) is an inflammatory response to milk proteins^{1,2} and is one of the most common food allergies that occurs in early childhood.³ It is estimated that CMA affects 2% of infants (or 1 in 50) in Australia and New Zealand, and while the majority outgrow this by the age of three to five years, it may occasionally persist into later childhood and/or adulthood.⁴ While some CMA cases during infancy are IgE mediated, others may be non-IgE mediated, with resulting differences in presentation and diagnostic approach.^{1,2,5} CMA is more common in formula-fed infants than in breast-fed infants.⁶

For infants with CMA, avoidance of cow's milk protein in the diet remains the only effective management strategy.¹ However, this can be associated with a number of nutritional implications, in particular, the risk of inadequate vitamin, calcium, protein and energy intake.¹ Thus, a timely and correct diagnosis of CMA in infants and toddlers in the primary care setting is critical so that dairy products can be safely removed from the diet with adequate dietetic supervision that ensures poor nutritional outcomes for growth and bone density are avoided.^{1,2,4,6}

Evaluating the irritable infant – could it be CMA?

CMA may present as a range of different symptoms reflecting a variety of different allergic disorders. However, a detailed history will usually enable GPs to arrive at the correct diagnosis in an infant presenting with irritability and other allergic symptoms.^{4,7} An overview of when to suspect CMA in the first year of life is provided in **Table 1**.



Practice tips

- CMA is an inflammatory response to milk proteins^{1,2} and is estimated to affect 2% of infants (or 1 in 50) in Australia and New Zealand.⁴
- Timely and correct diagnosis of CMA in infants and toddlers in the primary care setting is critical so that the dairy products can be removed from the diet with adequate dietetic supervision that ensures poor nutritional outcomes for growth and bone density are avoided.^{1,2,6}
- Food allergies should be suspected when the onset of symptoms occur in infancy or early childhood; there is patient or family history of atopy; and symptoms affect two or more systems (i.e. skin, gut, non-infectious respiratory symptoms).⁶
- For formula fed infants (aged <6 months), an eHF such as Aptamil AllerPro Syneo is recommended as a first-line management approach in infants with mild-to-moderate CMA.^{4,6,9} For the 1 in 10 infants who do not tolerate an eHF or have severe CMA, an AAF such as Neocate Syneo is recommended.⁹
- Both Aptamil AllerPro Syneo and Neocate Syneo contain a patented synbiotic blend of prebiotics and probiotics to help address the underlying gut dysbiosis of food-allergic infants.^{13,17}

Table 1. When to suspect CMA in the first year of life⁶

	IgE-mediated CMA		Non-IgE-mediated CMA	
	Mild-to-moderate	Severe	Mild-to-moderate	Severe
Onset of symptoms after ingestion of cow's milk protein	Immediate Mostly within minutes (may be up to 2 hours)	Immediate Mostly within minutes (may be up to 2 hours)	Delayed Mostly 2–72 hours	Delayed Mostly 2–72 hours
Symptoms	One or more of the following symptoms: <ul style="list-style-type: none"> • Skin (one or more is usually present): acute pruritus, erythema, urticaria, angioedema, acute 'flaring' of persisting atopic dermatitis • Gastrointestinal: vomiting, diarrhea, abdominal pain • Respiratory (rarely in isolation of other symptoms): acute rhinitis and/or conjunctivitis 	One or more of the following symptoms <ul style="list-style-type: none"> • Severe respiratory and/or cardiovascular signs and symptoms (rarely a severe GI presentation) • Severe unresponsive dermatological symptoms • Anaphylaxis 	Usually several of these symptoms will be present:* <ul style="list-style-type: none"> • Gastrointestinal: persistent irritability ('colic'), abdominal discomfort, vomiting ('reflux', GORD), food refusal or aversion, diarrhea (abnormally loose +/- more frequent), constipation (especially soft stools with excess straining), blood and/or mucus in stools • Skin: pruritus, erythema, non-specific rashes, moderate persistent atopic dermatitis 	One but usually more of the following persistent and treatment-resistant symptoms: <ul style="list-style-type: none"> • Gastrointestinal: diarrhea, vomiting, abdominal pain, food refusal or aversion, significant blood and/or mucus in stools, irregular or uncomfortable stools +/- faltering growth • Skin: severe atopic dermatitis +/- faltering growth

*The symptoms listed are very common in otherwise well infants or those with other diagnoses so clinical judgment is required. The presence of symptoms affecting multiple systems are more likely to be allergy related. GORD, gastro-oesophageal reflux disease.

Confirming the diagnosis of suspected CMA

A suspected diagnosis of CMA in the first year of life should be confirmed either by allergy testing (for IgE-mediated CMA) and/or exclusion then reintroduction of dietary cow's milk (for both IgE- and non-IgE-mediated CMA; **Table 2**).⁶ Breast milk is the ideal nutrition for infants with CMA and any decision to initiate a diagnostic elimination dietary trial must include measures to ensure that breastfeeding is actively supported.^{6,7}

Table 2. Confirming the diagnosis of suspected CMA in the first year of life⁶

	Suspected mild-to-moderate IgE-mediated	Suspected mild-to-moderate non-IgE-mediated	Suspected severe IgE- or non-IgE mediated
Dietary elimination for exclusive breastfeeding mothers	<ul style="list-style-type: none"> • Trial exclusion of all cow's milk protein from maternal diet for a 2-week period 	<ul style="list-style-type: none"> • Trial exclusion of all cow's milk protein from maternal diet for a 2–4 week period 	<ul style="list-style-type: none"> • Trial exclusion of all cow's milk protein from maternal diet for a 2–4 week period
Substitute formula for formula fed or mixed feeding infants	<ul style="list-style-type: none"> • An extensively hydrolysed formula (eHF) is generally first choice • Infant soy formula may be used in infants aged >6 months if not sensitised on IgE testing • Rice-protein based formula (rHF) may be used as an alternative to eHF or soy protein formula 	<ul style="list-style-type: none"> • An extensively hydrolysed formula (eHF) is generally first choice • Infant soy formula may be used in infants aged >6 months if not sensitised on IgE testing • Rice-protein based formula (rHF) may be used as an alternative to eHF or soy protein formula 	<ul style="list-style-type: none"> • Urgently consult and refer to paediatric allergy and/or paediatric gastroenterology to consider the appropriate choice of formula, usually an amino acid based formula (AAF)
Notes	<ul style="list-style-type: none"> • Ensure referral to paediatric allergy to confirm the diagnosis by IgE testing or perform a supervised challenge in the minority of cases • Daily calcium and vitamin D supplementation should be recommended to breastfeeding mothers 	<ul style="list-style-type: none"> • If symptoms improve, perform a reintroduction of cow's milk protein (challenge) at home. This step is critical to confirm the diagnosis 	<ul style="list-style-type: none"> • Daily calcium and vitamin D supplementation should be recommended to breastfeeding mothers • An urgent dietetic referral may be indicated

Take home messages



- CMA is one of the most common food allergies in early life, with most children outgrowing their CMA by 5 years of age.
- An allergy-focused clinical history including family history of allergy, sources of cow's milk and timing of presenting symptoms is essential in making the diagnosis.
- The majority of infants with non-IgE CMA can be confidently diagnosed and managed in primary care. Infants with mild-to-moderate IgE CMA can be initially managed in primary care, but will require a referral to paediatric allergy for ongoing management. Infants with anaphylaxis or severe non-IgE CMA require urgent referral.
- For formula fed infants with mild-to-moderate CMA, an extensively hydrolysed cow's milk based formula is a first choice in infants under 6 months of age.



Confusion between CMA and lactose intolerance is common!²

CMA is an inflammatory response to milk proteins that is distinct from lactose intolerance, which is a metabolic disorder characterised by a deficiency in the intestinal enzyme lactase.^{1,2} However, because the gastrointestinal (GI) symptoms of CMA, such as nausea, abdominal discomfort, bloating and diarrhoea, are similar to many symptoms of lactose intolerance, these conditions may be confused.^{1,2} A key difference between the conditions is that CMA usually first appears during infancy, while lactose intolerance usually starts after 4 years of age, in particular, in adolescence or adulthood.¹

Managing the infant with CMA

Breast milk is the first choice of nutrition for all infants including those with food allergy.⁸ For formula fed infants with CMA a specialised formula is recommended.⁸ In general, extensively hydrolysed formula (eHF) is the first choice for infants with mild-to-moderate CMA, with additional options including soy protein formula, amino acid based formula (AAF) and rice protein based formula (**Table 3**).⁶

Table 3. Formula options for infants with CMA (up to one year of age)⁴

Type of formula	Uses	Availability
Cow's milk based extensively hydrolysed formula (eHF)	<ul style="list-style-type: none"> • Usually the first choice of formula in infants with CMA. • Not suitable for infants who have had anaphylaxis to cow's milk. • Treated with enzymes to break down most of the cow's milk proteins. 	Without prescription or with PBS prescription
Soy protein formula	<ul style="list-style-type: none"> • Usually only recommended in babies over six months. • Tolerated by most infants with CMA, but unsuitable for those allergic to soy. 	Without prescription
Amino acid based formula (AAF)	<ul style="list-style-type: none"> • Usually prescribed when an eHF or soy protein formula is not tolerated (estimated to be necessary in around one in ten infants with CMA). • Tolerated by most infants with cow's milk and soy allergies. • Suitable for severe (anaphylaxis) CMA. 	PBS prescription required
Rice protein based formula (rHF)	<ul style="list-style-type: none"> • May be used as an alternative to eHF or soy protein formula, based on specialist advice. • Should not be used in infants with food protein induced enterocolitis syndrome to rice. 	Without prescription

The following formulae are either contraindicated or not recommended in infants with CMA:^{3,4,7,9}

- Standard cow's milk-based (including anti-regurgitation)
- Lactose-free cow's milk-based
- Partially hydrolysed cow's milk-based (commonly labelled HA)
- Goats milk-based formula

Advise parents starting their child on any hypoallergenic formula that these products have a different taste and smell to standard formula.⁸ For those infants who do not initially accept the switch to the new hypoallergenic formula, this can be progressively introduced into the infant's cow's milk formula feeds over several days.⁸

Aptamil AllerPro Syneo and Neocate Syneo – hypoallergenic formula options for infants with CMA

An eHF is recommended as a first-line management approach in infants with mild-to-moderate CMA.^{4,6,7,9} Aptamil AllerPro Syneo is an eHF based on cow's milk that is indicated for the dietary management of mild-to-moderate CMA.^{10,11} It has been shown to reduce the symptoms of CMA with no negative impact on growth and is well-tolerated among approximately 97% of children with CMA.^{10,11} While eHF products are available in pharmacies without a prescription, they should be used under medical supervision. These products are not suitable for infants with severe allergy or anaphylactic reactions to cow's milk protein.^{4,6}

Neocate Syneo is an AAF that is recommended as a first-line management approach for the dietary management of infants with severe CMA (including anaphylaxis).⁹ Neocate Syneo has been studied in three clinical trials including 266 patients evaluated over 8 years, with results demonstrating effective resolution of food allergy symptoms, while supporting normal growth and development.^{12–16}

Aptamil AllerPro Syneo and Neocate Syneo both contain synbiotics to help address gut microbiota dysbiosis

Both Aptamil AllerPro Syneo and Neocate Syneo contain a patented synbiotic blend of prebiotics and probiotics to help address the underlying gut dysbiosis of food-allergic infants.^{13,17} This includes prebiotic oligosaccharides, which stimulate the growth and activity of beneficial bacteria, and a probiotic *Bifidobacterium Breve* M16V.¹⁷

Dietary management of CMA includes the use of hypoallergenic formula to resolve symptoms. While this approach is recommended, it does not address the gut microbiota, which is widely recognised to play an important role in immune development.^{18–20} Gut microbiota dysbiosis is often associated with the development of CMA.^{21–23} Indeed, the gut microbiota composition in allergic infants has been found to have a low diversity of microbiota species thought to be beneficial for immune function (i.e. lower levels of infant-like *Bifidobacteria*) as well as higher levels of adult-like *Clostridia* and *Eubacteria*.¹² Synbiotics have been developed to address this gut microbiota dysbiosis in allergic infants.^{13,17,24} These include a combination of prebiotics and probiotics that work synergistically to target microbial gut dysbiosis in the dietary management of CMA.^{13,17,24}



In a study comparing infants randomised to receive standard AAF (control) or AAF with synbiotics (test) for 8 weeks, after which infants could continue study product until 26 weeks, with age-matched, healthy, breastfed infants, the AAF with synbiotics positively modified faecal microbiota by increasing levels of *Bifidobacteria* and decreasing levels of *Eubacterium rectale* and *Clostridium coccooides* at 8 weeks to be closer to that of healthy, breastfed infants versus the standard AAF.^{12,14,24} The beneficial effects of AAF with synbiotics on microbiota composition continued to be observed over 26 weeks.²⁴ Thus, selecting a hypoallergenic formula that contains synbiotics, such as Aptamil AllerPro Syneo or Neocate Syneo, can help promote a gut microbiota balance closer to that of a breast fed infant.^{12,14}

Course resource centre

Clinical papers

- [Australian Society of Clinical Immunology and Allergy \(ASCIA\). Information for Health Professionals. Guide for Milk Substitutes in Cow's Milk Allergy. 2020](#) [cited 2020 November 1].
- [Australian Society of Clinical Immunology and Allergy \(ASCIA\). Information for Patients, Carers and Consumers. Cow's milk \(dairy\) allergy. 2019](#) [cited 2020 May 5].
- Crittenden RG, Bennett LE. [Cow's Milk Allergy: A Complex Disorder](#). J Am Coll Nutr. 2005;24(sup6):582S-591S.
- Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, et al. [World Allergy Organization \(WAO\) Diagnosis and Rationale for Action against Cow's Milk Allergy \(DRACMA\) Guidelines](#). World Allergy Organ J. 2010;3(4):57–161.
- Fox A, Brown T, Walsh J, Venter C, Meyer R, Nowak-Węgrzyn A, et al. [An update to the Milk Allergy in Primary Care guideline](#). Clin Transl Allergy. 2019;9(1):40.
- Kemp AS, Hill DJ, Allen KJ, Anderson K, Davidson GP, Day AS, et al. [Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion](#). Med J Aust. 2008;188(2):109–12.
- [The Milk Allergy in Primary Care \(MAP\) Guideline 2019. Healthcare Professional Factsheet—on the use of iMAP guideline](#) [cited 2020 May 5].
- Venter C, Brown T, Meyer R, Walsh J, Shah N, Nowak-Węgrzyn A, et al. [Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP—an international interpretation of the MAP \(Milk Allergy in Primary Care\) guideline](#). Clin Transl Allergy. 2017;7(1):26.

Clinical Papers

- Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, et al. [Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants](#). ISME J. 2016;10(3):742–50.
- Burks AW, Harthoorn LF, Van Ampting MTJ, Oude Nijhuis MM, Langford JE, Wopereis H, et al. [Synbiotic-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants](#). Pediatr Allergy Immunol. 2015;26(4):316–22.
- Candy DCA, Van Ampting MTJ, Oude Nijhuis MM, Wopereis H, Butt AM, Peroni DG, et al. [A synbiotic-containing amino acid-based formula improves gut microbiota in non-IgE-mediated allergic infants](#). Pediatr Res. 2018;83(3):677–86.
- Fox AT, Wopereis H, Van Ampting MTJ, Oude Nijhuis MM, Butt AM, Peroni DG, et al. [A specific synbiotic-containing amino acid-based formula in dietary management of cow's milk allergy: a randomized controlled trial](#). Clin Transl Allergy. 2019;9(1):5.

Professional associations

- [Allergy & Anaphylaxis Australia](#).
- [Australian Breastfeeding Association for Health Professionals](#).
- [Australian Paediatric Society](#).
- [Australian Society of Clinical Immunology and Allergy \(ASCIA\)](#).
- [Food Standard Australia New Zealand \(FSANZ\)](#).

Resources for parents

- [Allergy & Anaphylaxis Australia](#).
- [Australian Breastfeeding Association](#).
- [Australian Government Department of Health: Get Up and Grow: Infant Formula](#).
- [Australian Society of Clinical Immunology and Allergy \(ASCIA\)](#).
- [Nutricia website](#).

References

1. Crittenden RG, Bennett LE. Cow's Milk Allergy: A Complex Disorder. J Am Coll Nutr. 2005;24(sup6):582S-591S.
2. Fiocchi A, Brozek J, Schünemann H, Bahna SL, von Berg A, Beyer K, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. World Allergy Organ J. 2010;3(4):57–161.
3. Venter C, Brown T, Meyer R, Walsh J, Shah N, Nowak-Węgrzyn A, et al. Better recognition, diagnosis and management of non-IgE-mediated cow's milk allergy in infancy: iMAP—an international interpretation of the MAP (Milk Allergy in Primary Care) guideline. Clin Transl Allergy. 2017;7(1):26.
4. Australian Society of Clinical Immunology and Allergy (ASCIA). Information for Patients, Carers and Consumers. Cow's milk (dairy) allergy, 2019 [cited 2020 May 5]. Available from: https://allergy.org.au/images/pcc/ASCIA_PCC_Cows_milk_dairy_allergy_2019.pdf.
5. Allen KJ, Hill DJ, Heine RG. Food allergy in childhood. Med J Aust. 2006;185(7):394–400.
6. Fox A, Brown T, Walsh J, Venter C, Meyer R, Nowak-Węgrzyn A, et al. An update to the Milk Allergy in Primary Care guideline. Clin Transl Allergy. 2019;9(1):40.
7. Kemp AS, Hill DJ, Allen KJ, Anderson K, Davidson GP, Day AS, et al. Guidelines for the use of infant formulas to treat cows milk protein allergy: an Australian consensus panel opinion. Med J Aust. 2008;188(2):109–12.
8. The Milk Allergy in Primary Care (MAP) Guideline 2019. Healthcare Professional Factsheet—on the use of iMAP guideline [cited 2020 May 5]. Available from: https://gpifn.files.wordpress.com/2019/10/imap-additional_tool_for_hcps-5rm_tb_original.pdf.
9. Australian Society of Clinical Immunology and Allergy (ASCIA). Information for Health Professionals. Guide for Milk Substitutes in Cow's Milk Allergy, 2020 [cited 2020 November 1]. Available from: https://www.allergy.org.au/images/stories/pospapers/ASCIA_HP_Guide_CMA_Milk_Substitutes_2020.pdf.
10. Verwimp JJ, Bindels JG, Barents M, Heymans HS. Symptomatology and growth in infants with cow's milk protein intolerance using two different whey-protein hydrolysate based formulas in a Primary Health Care setting. Eur J Clin Nutr. 1995;49 Suppl 1:S39-48.
11. Giampietro PG, Kjellman N-IM, Oldaeus G, Wouters-Wesseling W, Businco L. Hypoallergenicity of an extensively hydrolyzed whey formula. Pediatr Allergy Immunol. 2001;12(2):83–6.
12. Michaelis LJ, Wopereis H, Van Ampting MTJ, Nijhuis M, Candy DCA, Butt AM, et al. An amino acid-based formula with synbiotics affects faecal microbiota in non-IgE mediated cow's milk allergic infants. Allergy. 71(S102):58(114).
13. Candy DCA, Van Ampting MTJ, Oude Nijhuis MM, Wopereis H, Butt AM, Peroni DG, et al. A synbiotic-containing amino acid-based formula improves gut microbiota in non-IgE-mediated allergic infants. Pediatr Res. 2018;83(3):677–86.
14. Nutricia Advanced Medical Nutrition. Unpublished preliminary report on the primary outcome and safety findings of the ASSIGN trial: Data on file. 2016.
15. Harvey BM, Langford JE, Harthoorn LF, Gillman SA, Green TD, Schwartz RH, et al. Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics. Pediatr Res. 2014;75(2):343–51.
16. Burks AW, Harthoorn LF, Van Ampting MTJ, Oude Nijhuis MM, Langford JE, Wopereis H, et al. Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants. Pediatr Allergy Immunol. 2015;26(4):316–22.
17. van der Aa LB, Heymans HS, van Aalderen WM, Sillevius Smitt JH, Knol J, Ben Amor K, et al. Effect of a new synbiotic mixture on atopic dermatitis in infants: a randomized-controlled trial. Clin Exp Allergy. 2010;40(5):795–804.
18. Gensollen T, Iyer SS, Kasper DL, Blumberg RS. How colonization by microbiota in early life shapes the immune system. Science. 2016;352(6285):539–44.
19. Jo J, Garssen J, Knippels L, Sandalova E. Role of Cellular Immunity in Cow's Milk Allergy: Pathogenesis, Tolerance Induction, and Beyond. Mediators Inflamm. 2014;2014:1–10.
20. Tan J, McKenzie C, Vuillermin PJ, Gervere G, Vinuesa CG, Mebius RE, et al. Dietary Fiber and Bacterial SCFA Enhance Oral Tolerance and Protect against Food Allergy through Diverse Cellular Pathways. Cell Rep. 2016;15(12):2809–24.
21. Berni Canani R, Sangwan N, Stefka AT, Nocerino R, Paparo L, Aitoro R, et al. Lactobacillus rhamnosus GG-supplemented formula expands butyrate-producing bacterial strains in food allergic infants. ISME J. 2016;10(3):742–50.
22. Ling Z, Li Z, Liu X, Cheng Y, Luo Y, Tong X, et al. Altered Fecal Microbiota Composition Associated with Food Allergy in Infants. Appl Environ Microbiol. 2014;80(8):2546–54.
23. Thompson-Chagoyan OC, Vieites JM, Maldonado J, Edwards C, Gil A. Changes in faecal microbiota of infants with cow's milk protein allergy- a Spanish prospective case-control 6-month follow-up study. Pediatr Allergy Immunol. 2010;21(2p2):e394–400.
24. Fox AT, Wopereis H, Van Ampting MTJ, Oude Nijhuis MM, Butt AM, Peroni DG, et al. A specific synbiotic-containing amino acid-based formula in dietary management of cow's milk allergy: a randomized controlled trial. Clin Transl Allergy. 2019;9(1):5.

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