

Detection and management of milk allergy: Delphi consensus study

Hilary I. Allen¹ | Ursula Pendower¹ | Miriam Santer² | Marion Groetch³ | Mitchell Cohen⁴ | Simon H. Murch⁵ | Hywel C. Williams⁶ | Daniel Munblit⁷  | Yitzhak Katz⁸ | Neeraj Gupta⁹ | Sabeen Adil¹⁰ | Justine Baines¹¹ | Eefje G. P. M. de Bont¹² | Matthew Ridd¹³  | Victoria L. Sibson¹⁴ | Alison McFadden¹⁵ | Jennifer J. Koplin¹⁶  | Josephine Munene¹⁷ | Michael R. Perkin¹⁸  | Scott H. Sicherer⁴ | Robert J. Boyle¹ 

¹National Heart and Lung Institute, Imperial College London, London, UK

²Primary Care Research Centre, University of Southampton, Southampton, UK

³Department of Pediatrics, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, New York, New York, USA

⁴Department of Paediatrics, University of Alabama at Birmingham & Children's of Alabama, Birmingham, Alabama, USA

⁵University of Warwick, Coventry, UK

⁶Centre of Evidence Based Dermatology, School of Medicine, University of Nottingham, Nottingham, UK

⁷Department of Paediatrics and Paediatric Infectious Diseases, Institute of Child's Health, Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia

⁸Allergy and Immunology Institute, Assaf Harofeh Medical Center, Department of Paediatrics, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

⁹Division of Paediatric Allergy, Department of Paediatrics, Institute of Child Health, Sir Ganga Ram Hospital, Rajinder Nagar, New Delhi, India

¹⁰International Lactation Consultant Association, Raleigh, North Carolina, USA

¹¹Manchester Children's Community Centre, Manchester, UK

¹²Department of Family Medicine, CAPHRI School for Public Health and Primary Care, Maastricht University, Maastricht, The Netherlands

¹³Population Health Sciences, University of Bristol, Bristol, UK

¹⁴First Steps Nutrition Trust, London, UK

¹⁵Mother and Infant Research Unit, University of Dundee, Dundee, UK

¹⁶Murdoch Children's Research Institute, Parkville, Victoria, Australia

¹⁷Certified Lactation Educator, Kenya Association for Breastfeeding and La Leche League South Africa, Nairobi, Kenya

¹⁸Population Health Research Institute, St George's University of London, London, UK

Correspondence

Robert J. Boyle, National Heart and Lung Institute, Imperial College London, Norfolk Place, Wright Fleming Building, London W2 1PG, UK.
Email: r.boyle@imperial.ac.uk

Funding information

This study was funded through an Irish College of General Practice Research Fellowship awarded to Dr Allen.

Abstract

Background: There is significant overdiagnosis of milk allergy in young children in some countries, leading to unnecessary use of specialized formula. This guidance, developed by experts without commercial ties to the formula industry, aims to reduce milk allergy overdiagnosis and support carers of children with suspected milk allergy.

Methods: Delphi study involving two rounds of anonymous consensus building and an open meeting between January and July 2021. Seventeen experts in general practice, nutrition, midwifery, health visiting, lactation support and relevant areas of paediatrics participated, located in Europe, North America, Middle East, Africa, Australia

This is an open access article under the terms of the [Creative Commons Attribution](https://creativecommons.org/licenses/by/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2022 The Authors. *Clinical & Experimental Allergy* published by John Wiley & Sons Ltd.

and Asia. Five authors of previous milk allergy guidelines and seven parents provided feedback.

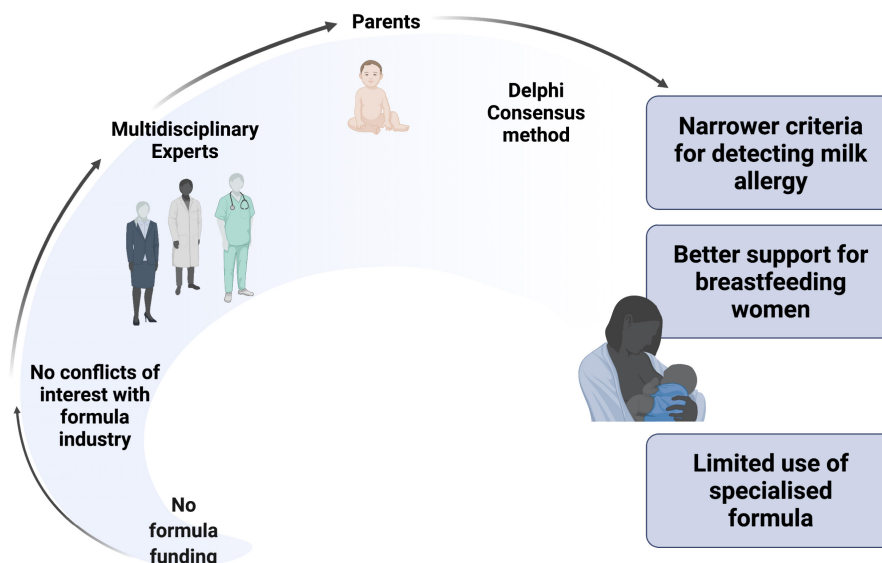
Findings: Participants agreed on 38 essential recommendations through consensus. Recommendations highlighted the importance of reproducibility and specificity for diagnosing milk allergy in children with acute or delayed symptoms temporally related to milk protein ingestion; and distinguished between children directly consuming milk protein and exclusively breastfed infants. Consensus was reached that maternal dietary restriction is not usually necessary to manage milk allergy, and that for exclusively breastfed infants with chronic symptoms, milk allergy diagnosis should only be considered in specific, rare circumstances. Consensus was reached that milk allergy diagnosis does not need to be considered for stool changes, aversive feeding or occasional spots of blood in stool, if there is no temporal relationship with milk protein ingestion. When compared with previous guidelines, these consensus recommendations resulted in more restrictive criteria for detecting milk allergy and a more limited role for maternal dietary exclusions and specialized formula.

Interpretation: These new milk allergy recommendations from non-conflicted, multidisciplinary experts advise narrower criteria, more prominent support for breastfeeding and less use of specialized formula, compared with current guidelines.

KEYWORDS

breastfeeding, Cow's milk allergy, Delphi consensus, overdiagnosis

Non-conflicted milk allergy guidance may prevent overdiagnosis



GRAPHICAL ABSTRACT

Milk allergy overdiagnosis is common in some regions and can potentially harm mothers and infants. We developed consensus recommendations for safe detection and management of milk allergy in young children. Recommendations aim to safely reduce overdiagnosis and better support breastfeeding women with suspected milk-allergic infants (graphic created with BioRender.com).

1 | INTRODUCTION

Cow's milk allergy affects up to 1% of European children in their first 2 years.¹ Prescriptions for specialized formula used by bottle-fed infants with cow's milk allergy have increased in Australia, England and Norway exceeding expected volumes by up to 10-fold.²

Milk allergy diagnosis can be difficult, making the condition vulnerable to overdiagnosis – and formula milk company sponsorship of milk allergy guidelines, their authors and healthcare professional education is thought to contribute to milk allergy overdiagnosis.^{2,3} Current milk allergy guidelines appear to promote overdiagnosis by labelling common symptoms of infancy as allergy indicators, and there is concern that guideline recommendations undermine breastfeeding.²⁻⁴

We undertook a Delphi consensus study to develop practical guidance for healthcare practitioners working in community and hospital settings on the safe detection and management of milk allergy in children under 2 years old. We specifically addressed the prevention of overdiagnosis or underdiagnosis, supporting breastfeeding women and the role of specialized formula products. We used the Delphi consensus method due to the lack of high-certainty research evidence to guide clinical practice in this field.⁵

2 | METHODS

This Delphi study is reported according to Conducting and REporting DELphi Studies (CREDES) guidance.^{6,7} Detailed methods and the study protocol are shown in the Supplement. Ethics approval was given by the Imperial College Research Governance and Integrity Team (reference 21IC6572) and all participants gave written, informed consent. Throughout this manuscript, “milk” refers to any non-human, mammalian milk such as that from cows, sheep, or goats, and “milk allergy” refers to both IgE-mediated and non-IgE mediated milk allergy. In order to define the scope of the Delphi consensus study, we searched Medline and Embase to identify relevant literature including milk allergy epidemiology, guidelines for diagnosis and management of milk allergy, and discussion of milk allergy overdiagnosis.^{5,8-20}

2.1 | Participants

We identified experts by searching Medline and Embase using MeSH term “Milk hypersensitivity,” asking identified experts to nominate other relevant experts, and contacting experts affiliated with relevant professional organizations including the International Board Certified Lactation Consultants and societies associated with the World Allergy Organization. Inclusion criteria were clinical and/or research expertise in general practice, dietetics, infant nutrition, health visiting, midwifery, lactation support, general paediatrics, paediatric allergy, paediatric gastroenterology, paediatric dermatology, paediatric allergy nursing or food allergy. Exclusion criterion

Key Messages

- Milk allergy overdiagnosis is common in some regions and can potentially harm mothers and infants
- We developed consensus recommendations for safe detection and management of milk allergy in young children
- Recommendations aim to safely reduce overdiagnosis and better support breastfeeding women with suspected milk-allergic infants

was a recent conflict of interest related to the formula (breastmilk substitute) industry, defined as activities in the previous 3 years or anticipated to occur in the next year. We aimed to include experts from diverse geographical and cultural settings.

2.2 | Study procedure

Through literature review we identified three key questions to address:

1. What aspects of milk allergy detection are important to ensure the condition is not overdiagnosed or underdiagnosed?
2. In a fully or partially breastfed child who has milk allergy, what aspects of management are important to ensure breastfeeding is not undermined?
3. What aspects of milk allergy management are important to prevent unnecessary use of specialized formulas such as amino acid formula, extensively hydrolysed formula, soya or rice-based infant formula?

Formal diagnosis of milk allergy was considered out of scope, so the term “detection” is used for the questions addressed by this manuscript, to indicate that the guidance deals with clinical interpretation of children presenting with different symptoms and signs, rather than the application of formal diagnostic tests such as oral food challenge or skin prick tests for confirmatory diagnosis of milk allergy. We conducted two anonymous electronic Delphi survey rounds followed by an online consensus meeting summarized in the Appendix S1. Delphi questionnaires were piloted among research team members and three independent assessors with expertise in survey methodology, general practice and allergy. Each survey round lasted 3 weeks and used Qualtrics XM electronic software (Qualtrics, London, England). Participants were required to rank the importance of each statement using a nine-point scale. Table S1 shows the approach used to classify consensus as “Essential,” “Recommended” and “No Consensus.” At the independently chaired consensus meeting, participants discussed statements where no consensus had yet been reached and were given the opportunity to comment on statements which had reached consensus. The meeting was recorded and carefully reviewed by the study team to finalize

the recommendations, which were developed into flowcharts to support safe detection and management of milk allergy in children under 2 years. Flowcharts were reviewed and piloted by the participants and also by independent paediatric allergists, community and hospital-based dieticians, general practitioners, health visitors and community midwives before being refined and receiving final approval by the participants.

2.3 | External commentary and patient involvement

To include the views of experts who could not contribute due to conflicts of interest, we invited authors of high-profile milk allergy guidelines or awareness tools to comment on the study proposal and again prior to the consensus meeting.^{11,18,20,21}

We invited parents, with experience of cow's milk allergy diagnosis and management in their child, to comment on the study scope and draft first-round survey and provisional recommendations. We specifically asked whether recommendations captured all early signs of milk allergy in their child, and whether the role of health-care practitioners in providing support, diagnosis and management including maternal dietary advice and breastfeeding promotion was fully addressed. Feedback from external experts and parents was summarized for the consensus meeting and two parents attended the consensus meeting.

3 | RESULTS

The study commenced on 1st January 2021 and concluded with a consensus meeting on 9th July 2021. Twenty-eight experts from 11 countries were invited, of whom 17 were eligible and agreed to participate (Table S2). All 17 participants completed both Delphi survey rounds, 12 attended the consensus meeting. Five authors of milk allergy guidelines or awareness tools participated in both stages of the external consultation and seven parents provided feedback on at least one stage of the project – four mothers with experience of milk allergy overdiagnosis and three mothers with experience of delayed milk allergy diagnosis in their child. Figure 1 summarizes the outcomes at each stage of the Delphi consensus process. An initial 38 statements were included in the first round, which expanded to 72 statements in the second round, mainly through splitting and adaptation of the original statements. Consensus was reached for 38 “essential” statements, shown in Tables S3–S5 with detailed explanatory notes, and summarized in Figures 2, 3 and 4. There were no “recommended” statements and the remaining statements were removed because of lack of consensus. Four key areas were discussed at the consensus meeting: symptoms suggestive of milk allergy in an exclusively breastfed infant, maternal dietary elimination, infants presenting with blood in the stool and agreed terminology.

3.1 | Milk allergy detection

Recommendations highlight the distinction between acute, delayed or chronic symptoms in relation to milk protein ingestion. For children with acute or delayed symptoms, recommendations highlighted the importance of reproducibility and specificity of symptoms in relation to milk protein ingestion (Table S3; Figure 2). For chronic symptoms without any obvious temporal relationship to milk protein ingestion, recommendations highlighted the distinction between children directly ingesting milk protein and those who were exclusively breastfed (Table S3; Figure 3).²² Consensus was reached that milk allergy does not need to be considered for changes to colour, frequency or consistency of stool, aversive feeding, occasional spots of blood in stool, nasal or respiratory symptoms, in the absence of a temporal relationship with milk protein ingestion. Exceptions to this were biopsy-proven eosinophilic gastrointestinal disorders or protein-losing enteropathy or, in a child ingesting milk protein, faltering growth or daily visible blood in stools.

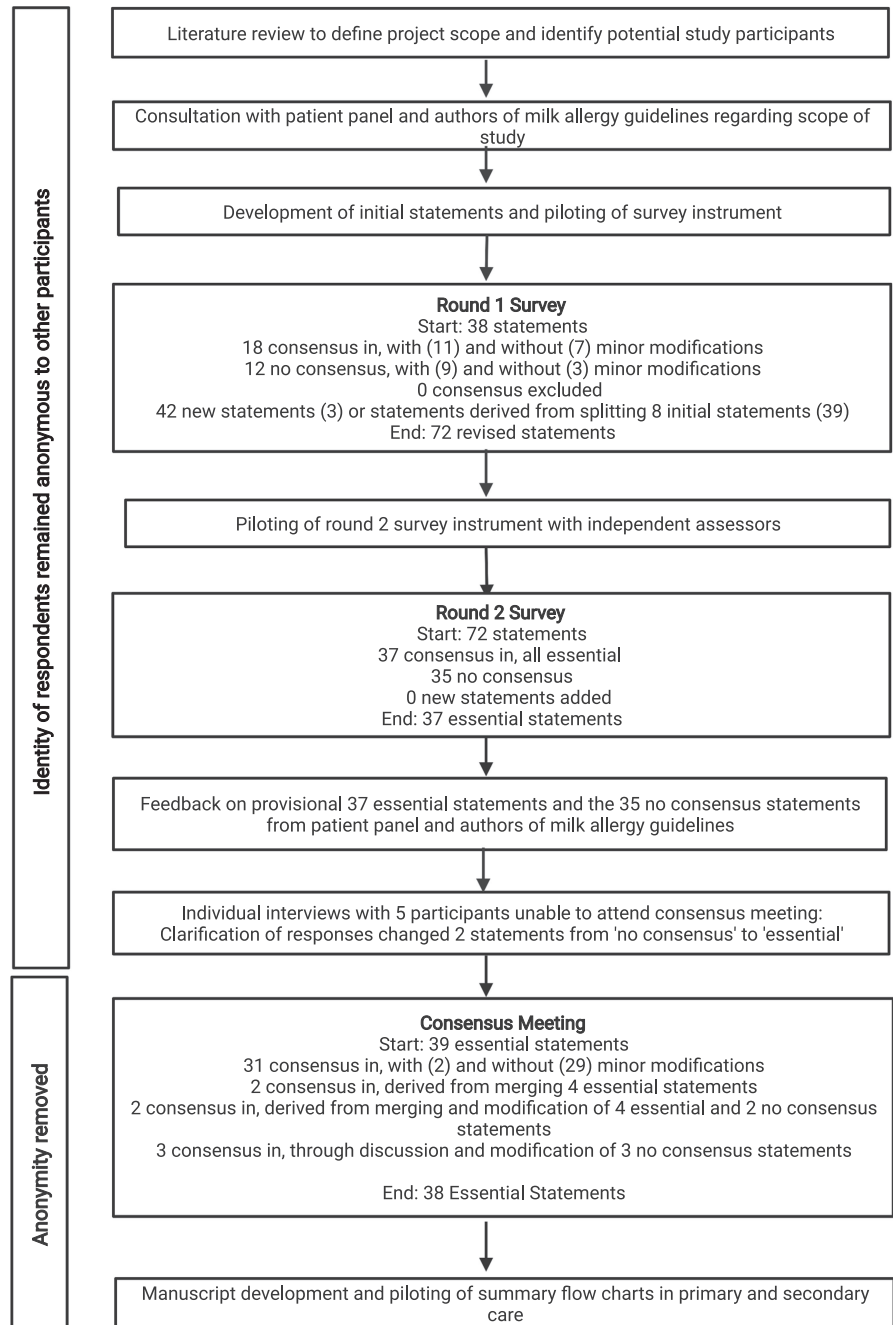
Participants reached consensus on recommendations for detecting food protein-induced allergic proctocolitis (FPIAP) in a child with chronic symptoms consuming milk protein (Table S3; Figure 3). Consensus could not be reached on diagnosing FPIAP in an exclusively breastfed infant with recurrent visible blood in the stool. It was acknowledged that many food allergy guidelines consider milk allergy in the differential diagnosis of blood in stools, but participants noted that visible blood in the stool in an exclusively breastfed infant is usually self-limiting, with many possible causes including infection and fissures. A parent highlighted the potential harms of a milk allergy diagnosis in an exclusively breastfed infant with blood in the stools, such as unnecessary or unsupervised maternal dietary elimination. Participants did not reach consensus that severity of crying should trigger consideration of a milk allergy diagnosis. Consensus was reached that milk allergy diagnosis should be considered in a child with reproducible crying after milk protein ingestion. There was consensus that differential diagnoses need to be considered for bile-stained vomiting, faltering growth, blood in the stool, colic and crying.

3.2 | Milk allergy management

Consensus was reached that breastfeeding should be supported in line with World Health Organization²³ or local recommendations by signposting to local breastfeeding support and reassuring families that breastmilk is the most appropriate milk for children with or without milk allergy. The only absolute medical contraindication to breastfeeding or use of donor breastmilk is classic galactosaemia.²³ The panel commented that carers who make a fully informed decision to use a breastmilk substitute should be supported, and advice about safe formula feeding should be given where needed (Table S4).

Consensus was reached that maternal dietary restriction is not usually necessary to manage milk allergy, but may be supported if mother has noticed a clear relationship between her own dietary

FIGURE 1 Summary of Delphi consensus process. A summary of the actions taken during each step of the Delphi consensus process is shown



intake and eczema symptoms in her child, but consensus was not reached for other symptoms (Table S4). The panel reached consensus that maternal dietary restriction may be advised by healthcare professionals in the unusual circumstance of a breastfed infant with faltering growth and protein-losing enteropathy (Table S4). The panel did not reach consensus that healthcare professionals should advise maternal dietary restriction in any other circumstances. The panel reached consensus on a number of important considerations for supporting families who are practicing maternal dietary restriction (Tables 1; S4).

Consensus was reached that specialized formula should not be advised or continued in children who are breastfed or can return to full breastfeeding; for preventing the development of atopic conditions; or for children aged over 12 months with a good, mixed diet

and normal growth pattern (Table S5; Figure 4). The panel reached consensus that specialized formula should be used in infants aged under 12 months who require formula milk and have confirmed milk allergy, usually confirmed using history, allergy tests or a trial of elimination and re-introduction. The panel advised that the suitability and safety of using plant-based milk alternatives in a child's diet should be assessed by a paediatric dietitian.

3.3 | Comparison with milk allergy guidelines

Tables S6–S9 show a comparison between the characteristics and recommendations of this Delphi consensus study and nine leading

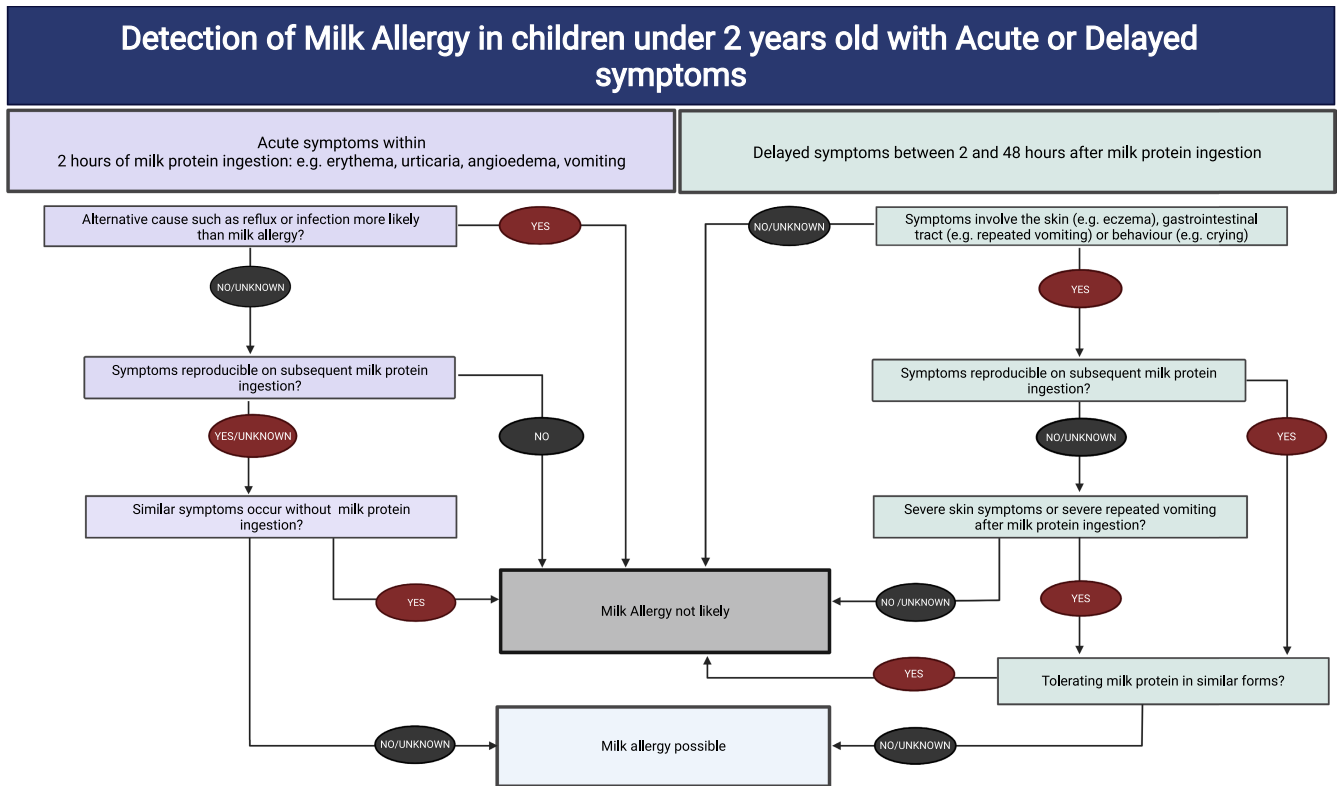


FIGURE 2 Detection of milk allergy in children under 2 years old with acute or delayed symptoms. Tolerating milk protein in similar forms means consuming milk protein in similar forms to that which triggered a reaction(s) on other occasions, but without any symptoms or signs of an allergic reaction. Age, previous milk protein exposure/tolerance and duration of symptoms after an exposure to milk protein are all relevant to considering whether an alternative cause is more likely. Bile-stained vomiting can indicate intestinal malrotation, so requires urgent assessment. Eczema management includes avoiding physical triggers, using moisturizers and topical anti-inflammatories. Colic and crying are common in healthy infants, but if severe, these can be related to a wide range of health issues in the infant or their carer (graphic created with BioRender.com)

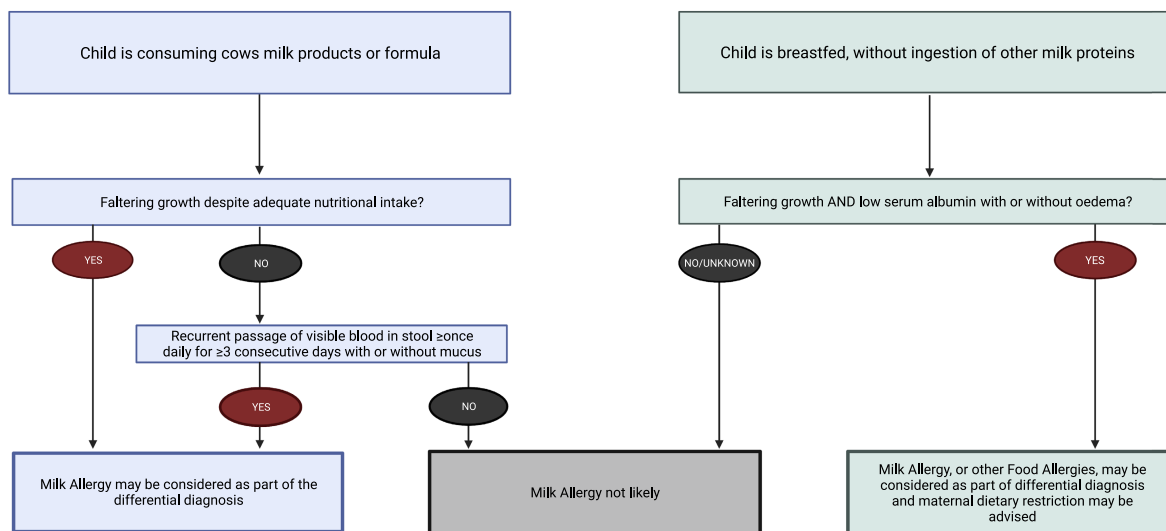
milk allergy guidelines.⁸⁻¹⁹ Only three guidelines^{8,9,16} included both primary care and patient representation and only one guideline¹⁹ declared no financial conflicts of interest in relation to the formula industry (Table S6). Consistent with our consensus, five of nine guidelines emphasized the importance of reproducibility in making a milk allergy diagnosis (Table S7).^{8,9,11,14,19} However, only one guideline distinguished between formula fed and breastfed infants in diagnosis, and only one guideline provided differential diagnoses for vomiting, blood in stools or faltering growth (Table S7).⁹ In contrast to our recommendations, most guidelines recommended considering milk allergy diagnosis for stool changes, respiratory symptoms or aversive feeding in the absence of a temporal relationship with milk ingestion or a history of faltering growth (Table S7).⁸⁻¹⁹ Only two guidelines^{12,16} specified the duration of exclusive and total breastfeeding recommended by WHO,²³ with others not stating the recommendations or stating shorter durations (Table S8). Four guidelines did not explicitly state that breastfeeding or breastmilk is the best milk for infants with milk allergy (Table S8).^{8,11,13,19} Guidelines recommended broader indications for maternal dietary restriction than the Delphi consensus, and five guidelines^{11-13,15,16} recommended total or strict milk exclusion from mother's diet, while only one limited the degree of maternal dietary restriction (Table S8).¹⁶

One guideline¹³ recommended using specialized formula in a fully breastfed infant if symptoms failed to respond to maternal dietary exclusion (Table S9), no guideline stated formula is unnecessary after age 1 year, and two^{11,15} recommended specialized formula up to 2 years (Table S9).

4 | DISCUSSION

In this Delphi consensus study, we generated guidance which aims to safely reduce milk allergy overdiagnosis and unnecessary use of specialized formula products, and to support breastfeeding women in the context of suspected milk allergy. To our knowledge, this is the first guidance for milk allergy detection and management generated by experts with a wide range of relevant topic expertise, without financial conflicts of interest with formula companies. The guidance differs from previous milk allergy guidelines by stating when symptoms and signs are not likely to be due to milk allergy, so that criteria for milk allergy are more restrictive. This is likely to reduce the risk that normal infant symptoms are labelled as milk allergy. Our consensus guidance also places limits around the settings where healthcare practitioners should advise breastfeeding women

Detection of Milk Allergy in children under 2 years old with Chronic symptoms



In breastfed or formula-fed children without acute or delayed symptoms or the chronic symptoms described here, milk allergy does not need to be considered as a diagnosis for the following symptoms, either alone or combined:

- Frequency changes in stool
- Consistency changes in stool
- Aversive feeding
- Nasal or respiratory symptoms
- Occasional spots of blood in the stool, without any daily, visible blood
- Other colour changes in stool

FIGURE 3 Detection of milk allergy in children under 2 years old with chronic symptoms. Chronic symptoms means symptoms without obvious temporal relationship to milk protein ingestion for example crying, vomiting and eczema. Cow's milk products include cheese, yoghurt and cream – products made with sheep or goat milk are also relevant due to cross-reactivity with cow's milk. Faltering growth is slower weight gain than expected for age, gender and current weight of child and has a wide range of causes including insufficient protein/calorie intake. Protein-losing enteropathy is a rare condition characterized by low serum albumin with or without oedema due to intestinal protein loss and has a wide differential diagnosis. Blood in the stool can also be caused by infection, clotting disorders or intestinal abnormalities. Endoscopic biopsy is not usually appropriate for food allergy diagnosis in children due to need for general anaesthetic and frequency of non-specific histological findings, and should only be undertaken in specialist paediatric gastroenterology centres. Milk allergy may be considered as part of the differential diagnosis in an exclusively breastfed child, or child consuming cow's milk products, in those rare circumstances that biopsy is performed and confirms findings of eosinophilic gastrointestinal disorders associated with non-IgE mediated milk allergy, such as eosinophilic oesophagitis (graphic created with BioRender.com)

to restrict their diet, and aligns closer to international infant feeding recommendations.^{23,24}

Milk allergy guidelines have generated controversy due to their potential to promote overdiagnosis and undermine breastfeeding. Analysis of one guideline suggested 74% of infants could be assigned a diagnosis of mild–moderate, and 9% severe non-IgE mediated milk allergy in the first year.⁴ Guidelines typically have broad diagnostic criteria covering common symptoms of infancy, and recommend strict maternal dietary exclusions.^{8–19}

Milk elimination diets can be burdensome, and dietary exclusion advice may cause maternal anxiety or depression, weight loss, reduced breastfeeding confidence and early breastfeeding cessation.²⁵ In some high-income countries, there is up to 10-fold excess prescription of specialized formula for managing milk allergy in formula fed infants which is costly to public health systems.^{2,3} Unnecessary exposure to specialized formula could potentially have deleterious effects for young children, although long-term

outcomes have not yet been fully characterized. Such products can affect taste perception and impact growth trajectory, and have been associated with micronutrient deficiencies.^{26–28} Many specialized formula products contain free sugars such as glucose in place of milk lactose, and may thereby increase risk of dental decay and childhood obesity.^{29,30}

Our new consensus guidance provides narrower criteria for identifying milk allergy in young children, by emphasizing reproducibility and specificity of reactions, and setting very limited circumstances in which chronic symptoms without temporal relationship to cow's milk ingestion might indicate milk allergy. Milk allergy guidelines usually consider blood in the stool to be a sign of milk allergy,^{8–19} without reference to the mode of infant feeding, and two current guidelines specify specks, streaks or flecks of blood to be indicators of FPIAP.^{11,14} However, most infants presenting with blood in the stools do not have milk allergy, and the condition is generally of short duration without serious

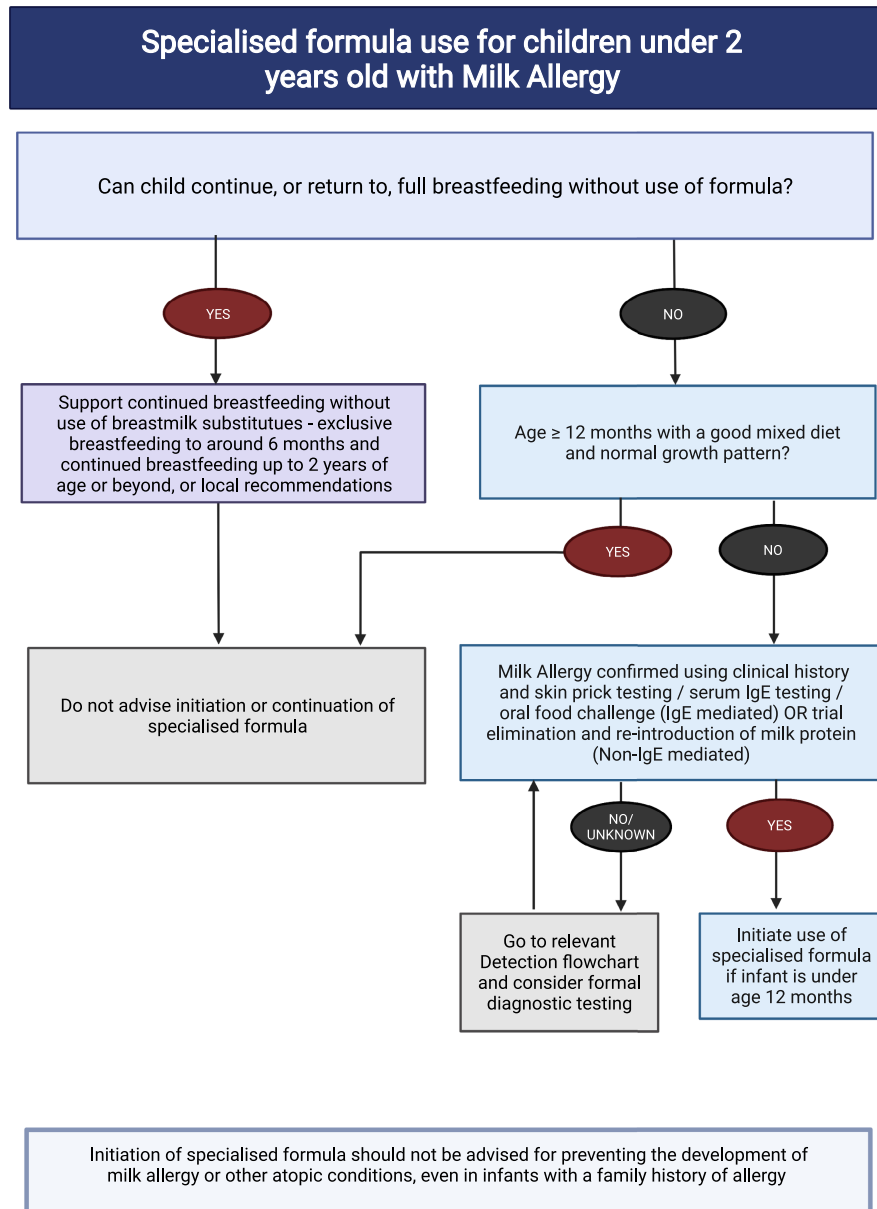


FIGURE 4 Specialized formula use for children under 2 years old with milk allergy. Reassure families that breastmilk is the most appropriate milk for all children, with and without milk allergy, and if necessary signpost to local breastfeeding support services, including referral to a lactation specialist, where available. The only absolute medical contraindication to breastfeeding or use of donor breastmilk is classic galactosaemia – however, carers who make a fully informed decision to use a breastmilk substitute should be supported and given advice about safe formula feeding, where needed. For milk allergic children over age 12 months who require a breastmilk substitute, calcium-fortified plant-based milk alternatives or milk from animals with low cross-reactivity with cow's milk such as donkey or mare milk may also be considered, guided by a paediatric dietician, where available. A good mixed diet was defined by participants as at least two-thirds of energy intake being provided by a varied solid food diet (which may be vegetarian or vegan), consuming a nutritionally appropriate milk or milk alternative at an age-appropriate volume and able to consume adequate macro and micronutrients from this diet. Oral food challenge may not be required for the diagnosis of Food Protein Induced Enterocolitis Syndrome if the diagnosis is clear or the initial reaction(s) was severe. (graphic created with BioRender.com)

health consequences.^{31,32} There is particular uncertainty about management of rectal bleeding as cow's milk FPIAP in an exclusively breastfed infant, where the infant is not directly exposed to cow's milk.³ In contrast to existing guidelines,⁸⁻¹⁹ our consensus recommendations clearly distinguish between diagnosis of FPIAP in an exclusively breastfed infant, where parent contributions

highlighted the potential for harmful consequences when maternal dietary exclusions are advised; and FPIAP diagnosis in children directly consuming cow's milk protein, where we reached consensus on clinical criteria for considering a diagnosis of FPIAP.

A recent survey of 70 primary care milk allergy guidelines in England found all recommended consideration of non-IgE milk

TABLE 1 Consensus recommendations for advising and supporting women practicing dietary restrictions during lactation**Advising maternal dietary restriction during lactation**

Maternal dietary restriction is not usually necessary for a breastfed infant with suspected or proven milk allergy, but may be advised in an exclusively or partially breastfed child with faltering growth and low serum albumin, with or without oedema

For mothers avoiding cow's milk, goat and sheep milk protein should be avoided as well, due to cross-reactivity

Supporting mother's own decision to restrict her diet during lactation

Maternal dietary restriction is not usually necessary for a breastfed infant with suspected or proven milk allergy, but may be supported if mother has noticed a clear relationship between her own dietary intake and symptoms of eczema in her child, and wishes to restrict her diet

Address the need for an exclusion diet, taking into consideration the physical and psychological burden of elimination diets on the family

Advise re-introduction of milk into the maternal diet if a 2-week trial of exclusion has not resulted in resolution of symptoms

Advise a trial of re-introducing milk into the maternal diet if symptoms of concern have subsided for at least 2 weeks

Advise that avoidance of baked products^a containing milk is unlikely to be necessary, due to the very small quantity of maternal dietary milk protein transferred to breastmilk.

General support for mothers who restrict their diet during lactation

Ensure adequate maternal dietary intake of calcium and vitamin D

^aBaked products refers to foods containing milk as a minor ingredient that are baked in an oven, for example bread, cakes, muffins, scones and biscuits. This statement may also be relevant for other foods containing only minor quantities of milk protein.

allergy in constipated infants, and this is consistent with some published milk allergy guidelines.³³ Participants reached consensus that reproducible and specific gastrointestinal symptoms related to milk protein ingestion are a sign of possible milk allergy, and these could potentially include constipation, but in the absence of temporally related symptoms, there was consensus that changes in stool consistency or frequency were not a sign of milk allergy. While some studies have suggested responses to milk exclusion diets in a subset of children with treatment-resistant constipation, most participants in this study felt that the evidence for allergy is limited in patients with these responses.³⁴ Trial of an exclusion diet may however be considered for children with treatment-resistant constipation who are referred for specialist paediatric gastroenterology assessment.³⁴

WHO breastfeeding recommendations are only referred to by a minority of milk allergy guidelines,^{9,12,16} but our recommendations align closely with international infant and young child feeding guidance.^{23,24} Maternal decisions on breastfeeding are influenced by maternal confidence, healthcare practitioner advice and ability to resolve feeding difficulties.³⁵ Our consensus recommendation that breastfeeding is the most appropriate nutrition for children with milk allergy may help to support breastfeeding women in the

context of suspected cow's milk allergy. Our consensus recommendations advise against the initiation or continuation of specialized formula in a child beyond 12 months old with normal growth pattern and nutritionally adequate diet. This contrasts with some published milk allergy guidelines,^{11,15} but is consistent with European Food Standards Agency recommendations, which advise against use of infant formula over 12 months old.²⁴ Our participants also reached consensus that specialized formula should not be advised for preventing the development of allergic conditions, a practice recommended for several decades but now largely withdrawn from guidelines.

4.1 | Limitations

Some milk allergy experts could not be invited to participate due to conflicts of interest with the formula industry. We tried to address this by including anonymous comments from authors of guidelines with author conflicts of interest during the consensus process. Parent participation was limited to commentary rather than voting, because the objective of the study was to develop clinical guidance for healthcare practitioners. The parental representatives were a small group and from two countries. It is possible that a more diverse parent panel would have had different perspectives. Our study is not a formal milk allergy guideline, so did not address areas such as interpreting allergy tests or food challenges to diagnose milk allergy, timing of allergenic food introduction for primary prevention of milk allergy, interventions to promote breastfeeding, optimal specialized formula selection for use in different settings or oral immunotherapy. In clinical practice, some infant symptoms may improve with specialized formula in the absence of an allergic mechanism. For example, specialized formula can have physiological effects such as early satiation that may change infant symptoms.^{28,36} For this reason, some practitioners and carers may still wish to try a specialized formula in case there are physiological effects which relieve infant symptoms. However, it should be noted that development and regulatory approval of specialized formula has largely been in the context of supporting adequate nutrition and avoiding symptoms of milk allergy, rather than for any physiological effects on common infant symptoms unrelated to milk allergy.

5 | CONCLUSIONS

These new consensus recommendations on the safe detection and management of milk allergy in children under 2 years aim to reduce harms associated with milk allergy overdiagnosis. Implementation of this new guidance may better protect young children and their carers from receiving an inappropriate diagnosis of milk allergy or specialized formula prescription, and from advice which may undermine breastfeeding. However, further work is needed in order to formally evaluate the safety and effectiveness of using this guidance to prevent milk allergy overdiagnosis in practice.

AUTHOR CONTRIBUTIONS

Dr Boyle had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Concept and design: Boyle, Allen, Pendower, Santer, Acquisition, analysis or interpretation of data: Allen, Pendower, Boyle. Drafting of the manuscript: Allen, Boyle. Critical revision of the manuscript for important intellectual content: All authors. Statistical analysis: Allen, Boyle. Administrative, technical or material support: Allen, Pendower, Boyle, Perkin. Supervision: Boyle, Santer.

ACKNOWLEDGEMENTS

This study was funded through an Irish College of General Practice Research Fellowship awarded to Dr Allen. JJK is supported by a fellowship from the Australian National Health and Medical Research Council (GNT# 1158699). The authors are grateful to Kate Henaghan-Sykes, Ruth O'Malley and the five other parents for providing helpful comments to them throughout this study. The authors are grateful to milk allergy guideline authors Hania Szjaweska, Adam Fox, David Luyt, Alessandro Fiocchi and Michael Kuitinen for providing helpful comments to them regarding the project scope and provisional Delphi consensus recommendations.

CONFLICT OF INTEREST

RJB declares consultancy payment from Cochrane, John Wiley and sons and the British Society for Allergy and Clinical Immunology for editorial work, payment for expert witness work in cases involving food anaphylaxis and a disputed infant formula health claim, and payment for membership of a Prota Therapeutics advisory board concerning the development of food allergy immunotherapy treatments. MEG receives royalties from UpToDate and the Academy of Nutrition and Dietetics; serves on the Medical Advisory Board of IFPIES, as a Senior Advisor to Food Allergy Research and Education, and as a Health Sciences Advisor for the American Partnership for Eosinophilic Disorders; and has no commercial interests to disclose. SHS reports royalty payments from UpToDate and from Johns Hopkins University Press; grants to his institution from the National Institute of Allergy and Infectious Diseases, from Food Allergy Research and Education, and from HAL Allergy; and personal fees from the American Academy of Allergy, Asthma and Immunology as Deputy Editor of the *Journal of Allergy and Clinical Immunology: In Practice*, outside of the submitted work. SHS Served on the expert panel for the Addendum guidelines for the prevention of peanut allergy in the United States: Report of the National Institute of Allergy and Infectious Diseases-sponsored expert panel. AMcF is in receipt of a NIHR grant to develop guidance for breastfeeding support in the United Kingdom (HS&DR Project: NIHR130995). All other authors declare no conflicts of interest in relation to this study.

DATA AVAILABILITY STATEMENT

Detailed summary data are presented in the Supplementary Material. Individual responses and comments during Delphi rounds and a recording of the consensus meeting are stored at Imperial College London. Requests for access to this information should be

directed to the corresponding author, and reasonable requests for data sharing will be considered but would require explicit permission of all study participants before any individual responses or recording could be shared.

ORCID

Daniel Munblit  <https://orcid.org/0000-0001-9652-6856>

Matthew Ridd  <https://orcid.org/0000-0002-7954-8823>

Jennifer J. Koplin  <https://orcid.org/0000-0002-7576-5142>

Michael R. Perkin  <https://orcid.org/0000-0001-9272-2585>

Robert J. Boyle  <https://orcid.org/0000-0002-4913-7580>

REFERENCES

- Schoemaker AA, Sprikkelman AB, Grimshaw KE, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children--EuroPrevall birth cohort. *Allergy*. 2015;70(8):963-972.
- [Under review] Mehta S, Allen HI, Campbell DE, Fagerli Arntsen K, Simpson MR, Boyle RJ. Trends in use of specialised formula for managing cow's milk allergy in young children. *Clin Exp Allergy*. 2022. Online ahead of print.
- Munblit D, Perkin MR, Palmer DJ, Allen KJ, Boyle RJ. Assessment of evidence about common infant symptoms and cow's milk allergy. *JAMA Pediatr*. 2020;174(6):599-608.
- Vincent R, MacNeill SJ, Marrs T, et al. Frequency of guideline-defined cow's milk allergy symptoms in infants: Secondary analysis of EAT trial data. *Clin Exp Allergy*. 2022;52(1):82-93. doi:10.1111/cea.14060
- Stróżyk A, Horvath A, Meyer R, Szjaweska H. Efficacy and safety of hydrolyzed formulas for cow's milk allergy management: A systematic review of randomized controlled trials. *Clin Exp Allergy*. 2020;50(7):766-779.
- Junger S, Payne SA, Brine J, et al. Guidance on Conducting and REporting DELphi Studies (CREDES) in palliative care: Recommendations based on a methodological systematic review. *Palliat Med*. 2017;31(8):684-706.
- Enhancing the QUALity and Transparency Of health Research. <https://www.equator-network.org/reporting-guidelines/>. [Accessed 31st October 2021].
- National Institute for Health and Care Excellence. Food allergy in under 19s: assessment and diagnosis. Clinical Guideline [CG116]. 2011. Available from: <https://www.nice.org.uk/guidance/cg116>. (Accessed 19th November 2021).
- Meyer R, Chebar Lozinsky A, Fleischer DM, et al. Diagnosis and management of Non-IgE gastrointestinal allergies in breastfed infants-An EAACI Position Paper. *Allergy*. 2020;75(1):14-32.
- Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI Food Allergy and Anaphylaxis Guidelines: diagnosis and management of food allergy. *Allergy*. 2014;69(8):1008-1025.
- Fiocchi A, Brozek J, Schünemann H, 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.
- Vandenplas Y, Abuabat A, Al-Hammadi S, et al. Middle east consensus statement on the prevention, diagnosis, and management of cow's milk protein allergy. *Pediatr Gastroenterol Hepatol Nutr*. 2014;17(2):61-73.
- Koletzko S, Niggemann B, Arato A, et al. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI committee practical guidelines. *J Pediatr Gastroenterol Nutr*. 2012;55(2):221-229.
- Sampson HA, Aceves S, Bock SA, et al. Food allergy: A practice parameter update—2014. *J Allergy Clin Immunol*. 2014;134(5):1016-1025.e43.

15. Montijo-Barrios E, Lopez-Ugalde MV, Ramirez-Mayans J, et al. Guia latinoamericana para el diagnostico y tratamiento de alergia a las proteinas de la leche de vaca (GL-APLV). *Rev Invest Clin*. 2014;66(Suppl 2S9-S72):S9.
16. Fox A, Brown T, Walsh J, et al. An update to the milk allergy in primary care guideline. *Clin Transl Allergy*. 2019;9:40. doi:10.1186/s13601-019-0281-8
17. Venter C, Brown T, Meyer R, 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. doi:10.1186/s13601-017-0162-y
18. Venter C, Brown T, Shah N, Walsh J, Fox AT. Diagnosis and management of non-IgE-mediated cow's milk allergy in infancy – a UK primary care practical guide. *Clin Transl Allergy*. 2013;3(1):23. doi:10.1186/2045-7022-3-23
19. Ebisawa M, Ito K, Fujisawa T, et al. Japanese guidelines for food allergy 2020. *Allergol Int*. 2020;69(3):370-386.
20. Luyt D, Ball H, Makwana N, et al. BSACI guideline for the diagnosis and management of cow's milk allergy. *Clin Exp Allergy*. 2014;44(5):642-672.
21. Vandenplas Y, Dupont C, Eigenmann P, et al. A workshop report on the development of the Cow's Milk-related Symptom Score awareness tool for young children. *Acta Paediatr*. 2015;104(4):334-339.
22. Gamirova A, Berbenyuk A, Levina D, et al. Food proteins in human breast milk and probability of IgE-mediated allergic reaction in children during breastfeeding: a systematic review. *J Allergy Clin Immunol Pract*. 2022;10:1312-1324.e8. doi:10.1016/j.jaip.2022.01.028
23. World Health Organisation, UNICEF. Acceptable medical reasons for use of breast-milk substitutes. WHO Press. Report number: WHO/FCH/CAH/09.01, 2009. Available from: https://apps.who.int/iris/bitstream/handle/10665/69938/WHO_FCH_CAH_09.01_eng.pdf. [Accessed 26th September 2021]
24. European Food Safety Authority (2013). Scientific opinion on nutrient requirements and dietary intakes of infants and young children in the European Union. Available from: <http://www.efsa.europa.eu/en/efsajournal/pub/3408.htm> [Accessed 23rd November 2021].
25. Yilmaz O, Kacar AS, Gogebakan E, Can C, Neced I, Mutluer T, et al. The relationship between dietary elimination and maternal psychopathology in breastfeeding mothers of infants with food allergy. *Pediatr Allergy Immunol*. 2022;33(1):e13670. Available from: [10.1111/pai.13670](https://doi.org/10.1111/pai.13670)
26. Gonzalez Ballesteros LF, Ma NS, Gordon RJ, et al. Unexpected widespread hypophosphatemia and bone disease associated with elemental formula use in infants and children. *Bone*. 2017;97:287-292.
27. Mennella JA, Lukasewycz LD, Castor SM, Beauchamp GK. The timing and duration of a sensitive period in human flavor learning: a randomized trial. *Am J Clin Nutr*. 2011;93(5):1019-1024.
28. Mennella JA, Inamdar L, Pressman N, et al. Type of infant formula increases early weight gain and impacts energy balance: a randomized controlled trial. *Am J Clin Nutr*. 2018;108(5):1015-1025.
29. First Steps Nutrition. Specialized milks marketed for infants with allergies in the UK. London: 2021. Available from: https://infantmilkinfo.org/wp-content/uploads/2021/03/Specialised_Milk_Allergies_Jan21a_240321SW.pdf. [Accessed 30th December 2021].
30. World Health Organisation Nutrition and Food Safety Team. Guideline: sugars intake for adults and children. Report number: ISBN: 9789241549028, 2015. Available from: <https://www.who.int/publications/i/item/9789241549028>. [Accessed 7th January 2022].
31. Elizur A, Cohen M, Goldberg MR, et al. Cow's milk associated rectal bleeding: a population based prospective study. *Pediatr Allergy Immunol*. 2012;23(8):765-769.
32. Lemoine A, Lemale J, Aroulandom J, Tounian P. Rectal bleeding and cow's milk protein-induced allergic proctocolitis: A prospective study. *Clin Exp Allergy*. 2021;51(9):1242-1245.
33. Smith TD, Townsend R, Hussain HS, Santer M, Boyle RJ. Milk allergy guidelines for infants in England promote over-diagnosis: a cross-sectional survey. *Clin Exp Allergy*. 2022;52(1):188-191. doi:10.1111/cea.14053
34. National Institute for Health and Care Excellence. Constipation in children and young people: diagnosis and management. Clinical guideline [CG99]. 2010. Available from: <https://www.nice.org.uk/guidance/cg99/chapter/1-Guidance#clinical-management>. [Accessed 4th December 2021]
35. Radzimirski S, Callister LC. Mother's Beliefs, Attitudes, and Decision Making Related to Infant Feeding Choices. *J Perinat Educ*. 2016;25(1):18-28.
36. Staelens S, Van Den Driessche M, Barclay D, et al. Gastric emptying in healthy newborns fed an intact protein formula, a partially and an extensively hydrolysed formula. *Clin Nutr*. 2008;27(2):264-268.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Allen HI, Pendower U, Santer M, et al.. Detection and management of milk allergy: Delphi consensus study. *Clin Exp Allergy*. 2022;00:1-11. doi: [10.1111/cea.14179](https://doi.org/10.1111/cea.14179)