# Milk allergy guidelines for infants in England promote over-diagnosis: a cross-sectional survey

Timothy DH Smith1, Rebecca Townsend2, Haleema Sadia Hussain3, Miriam Santer4, Robert J Boyle 5,6

1. Mackenzie Clinical Research Institute, University of Central Lancashire, Preston, UK

2. School of Medicine, Dentistry and Biomedical Sciences, Queen’s University Belfast, Belfast, UK

3. THRIVE Research Centre, University of Central Lancashire, Preston, UK

4. Primary Care Research Centre, University of Southampton, Southampton, UK

5. National Heart and Lung Institute, Imperial College London, London, UK

6. Centre for Evidence-Based Dermatology, University of Nottingham, UK

**Keywords** Cow’s milk allergy, Breastfeeding, Primary Care, Guidelines, Prescribing

# Key Messages

* In 2019, we identified 70 English primary care guidelines for milk allergy diagnosis and management
* All guidelines promoted overdiagnosis by suggesting milk allergy diagnosis for common symptoms such as constipation
* All guidelines recommended maternal dietary restriction, only half indicated breastfeeding is best for milk-allergic infants

To the Editor,

Diagnosis of cow’s milk protein allergy (CMPA) in infants is based on reproducible symptoms and absence of symptoms on elimination of cow’s milk protein.1,2 Previous research has raised concerns that CMPA guidelines published by national or international organisations could be driving CMPA overdiagnosis1. CMPA overdiagnosis may reduce breastfeeding confidence, especially when maternal dietary restrictions are advised. Dietary restrictions are not likely to be needed for most breastfed infants with CMPA, since quantities of cow’s milk protein transferred to the infant via breastmilk are much smaller than thresholds of reactivity in children with CMPA.1-3 Data from England show that specialised formula prescriptions have been steadily rising, with a 5- to 6-fold increase in prescription costs in England between 2008 and 2018.7,8 There is no sign of a change in CMPA prevalence in the UK, Australia or US over the past 30 years to explain this trend.4-6

We sought to explore the role that local guidelines play in CMPA overdiagnosis, by performing a cross-sectional survey of all available local primary care guidelines endorsed or co-authored by the 191 clinical commissioning groups (CCGs) in England. CCGs are overseen by health commissioners who look after local health needs and manage the health budget for regions of England, each with a population of between a hundred thousand and a million people. Between April and September 2019, we searched all 191 CCG websites for guidelines on the diagnosis or management of infants with suspected CMPA . TS and RT extracted data independently from each guideline using a bespoke data extraction proforma. There was excellent agreement between the data extractors (e.g. κ=0.779 for stating breast milk is best for infants with CMPA), but in the small number of cases where there was a discrepancy in data extraction this was resolved by direct discussion, or arbitration by a third researcher, HSH. Data were analysed using Microsoft Excel 2016 and graphs developed within the package. Statistical analysis using the independent t-test was performed in SPSS version 27 (IBM, Armonk, New York).

One hundred and sixty (84%) health regions in England had accessible CMPA guidelines during the study period. There were 70 different guidelines, with 38 (54%) guidelines unique to a region and 32 (46%) used across more than one region. Out of 67 guidelines identifying date of authorship, 45 (67%) were from 2017 or later, with only 10 (15%) from 2015 or earlier. Fifty of 70 (71%) reported an update due date, with 18/50 (36%) having expired on or before the previous year.

Sixty-three (90%) guidelines addressed CMPA diagnosis, of which 43 (68%) reported separate criteria for non-IgE-mediated CMPA and 20 (32%) reported a single set of diagnostic criteria without discriminating non-IgE- and IgE-mediated CMPA signs and symptoms. As shown in Figure 1, a wide range of signs and symptoms were included in diagnostic criteria specific for non-IgE-mediated CMPA, covering most common signs and symptoms that occur in healthy infants. Only four symptoms (constipation, diarrhoea, colic, and eczema) were consistently reported by all 43 guidelines as suggestive of non-IgE mediated CMPA. Other symptoms commonly cited were reflux (98%), blood in stools and food refusal (both 95%), and mucus in stools, pruritus and erythema (each 88%). Symptoms and signs which were only rarely cited as indicators of non-IgE-mediated CMPA included nausea (2%) and breathlessness (9%).

The commonest symptoms and signs used as diagnostic criteria by the 20 guidelines not separating non-IgE- from IgE-mediated CMPA were eczema, reflux and constipation (all 100%), diarrhoea (95%), colic, vomiting and blood in stools (90%). Anaphylaxis was cited as an indicator of CMPA in 16 (80%) of these guidelines. Out of all 63 guidelines on diagnosis of suspected CMPA, 15 (24%) stated that there were usually a few or several symptoms present, and 55 (87%) mentioned that in order to reach a definite diagnosis, infants need to be rechallenged with cow’s milk protein after a period of two to six weeks to see whether symptoms return.

The management of suspected CMPA was addressed by all 70 guidelines. Sixty-four (91%) addressed management in breastfed infants, summarised in Figure 2. They all advised exclusion of cow’s milk products from the maternal diet; the remaining 6 guidelines only addressed management in formula-fed infants and did not address breastfeeding a child with CMPA. A possible need to avoid other mammalian milk was suggested by 11/64 (17%), and non-milk products by 12/64 (19%). Out of the 64 guidelines for management of breastfed infants with suspected CMPA, 32 (50%) stated that breast milk is the best milk for infants with suspected CMPA, with a further 12 (19%) advising encouragement to continue breastfeeding without stating any reason for this. Only 5 (8%) suggested referral to a breastfeeding support advisor. No guidelines suggested that there should be any differences in diagnostic criteria for CMPA (e.g. types or numbers of symptoms/signs) between breastfed and bottle-fed infants. Only 9 (13%) stated more generally that CMPA was less common in breastfed infants or required a different diagnostic approach.

All 70 guidelines recommended that the less expensive extensively hydrolysed formula (EHF) was used in uncomplicated mild/moderate cases of CMPA in formula-fed infants, and included recommendations for when to use the more expensive amino acid formula (AAF). The most common reasons for recommending AAF were severe IgE-mediated reaction to CMPA such as anaphylaxis (64, 91%), and severe non-IgE-mediated CMPA (59, 84%). Fifty-four (77%) guidelines suggested using AAF if EHF was unsuccessful, and a further 6 (9%) stated AAF was indicated if at least two EHFs were unsuccessful. Other stated indications for AAF were if infants had previously reacted to cow’s milk protein in maternal breastmilk (34, 49%), multiple food allergies (20, 29%), and mild/moderate non-IgE reactions (4, 6%).

This is the first cross-sectional survey of English milk allergy guidelines produced by regional commissioners for the diagnosis and management of CMPA. We extracted and analysed data from 70 unique guidelines. The guidelines all appear to promote over-diagnosis of CMPA, as they list multiple symptoms and signs that occur in many infants without underlying pathologies, and have little established relationship with CMPA. Guidelines also fail to support breastfeeding, with universal recommendations to restrict maternal diets, a practice which is unlikely to be necessary in most breastfed infants with CMPA; and a notable lack of advice that breastmilk is the best milk for infants with CMPA in many guidelines.

A previous review of existing national and international guidelines raised concerns that they could lead to an over-diagnosis of CMPA and a reduction in breastfeeding.3 Our findings suggest a similar risk arising from guidelines approved by local commissioners in England. Together, these two studies may help to explain the significant over-prescription of specialist formulas for managing CMPA in England.6-8 The guidelines we reviewed also showed significant regional variations in recommendations for using AAF in place of EHF, which likely reflect a wider lack of consensus on this issue.9

Strengths of our study are that we reviewed guidelines from most health regions in England, and data were extracted consistently, with good agreement between the data extractors. A limitation of this work is that guidelines were only evaluated for one country, and local guidelines are not the only source of information that guides community practice in England. Thus, other guidelines, cultural norms, practices and patient expectations may also be relevant to the over-diagnosis and overtreatment of CMPA.

CMPA over-diagnosis is important, due to the impact on infants, families and health care services, and due to the potential for over-diagnosis to undermine breastfeeding.2,3 The diagnosis of CMPA is predominantly made in primary care in England and there is a need for greater support to reduce the current level of over-diagnosis and overtreatment. More evidence-based CMPA guidelines would be a first step towards this, plus greater support for primary care, health visiting and community dietician services. Provision of help for families whose infants have common, self-limiting symptoms may be important in addressing dynamics that make incorrect diagnosis more likely.

# Conflicts of interest

RB declares personal consultancy payments from Cochrane and Prota Therapeutics, expert witness fees for giving evidence in cases related to food anaphylaxis and infant formula health claims, and payments from Public Health England for membership of the UK Nutrition and Health Claims Committee and the UK Scientific Advisory Committee on Nutrition’s Subgroup on Maternal and Child Nutrition. All other authors report no conflicts.

# Author contributions

TS led and designed the study; MS and RB advised on study design and interpretation; TS, RT and HSH extracted data and performed initial delivery and interpretation of the findings. TS wrote the first draft of the research letter with assistance from RB and MS. All authors reviewed, commented and approved the final manuscript.

**References**

* + - 1. Flom JD, Sicherer SH. Epidemiology of Cow’s Milk Allergy. Nutrients 2019;11(5),1-14
			2. Van Tulleken C. Overdiagnosis and industry influence: how cow’s milk protein allergy is extending the reach of infant formula manufacturers. BMJ 2018;363:k5056.
			3. Munblit D, Perkin MR, Palmer DJ, et al. Assessment of Evidence About Common Infant Symptoms and Cow’s Milk Allergy. JAMA Pediatr. 2020;174(6):599-608.
			4. Peters RL, Koplin JJ, Allen KJ, et al. The Prevalence of Food Sensitization Appears Not to Have Changed between 2 Melbourne Cohorts of High-Risk Infants Recruited 15 Years Apart. J Allergy Clin Immunol Pract 2018;6(2):440-48 e2. doi: 10.1016/j.jaip.2017.11.018 [published Online First: 2017/12/19]
			5. McGowan EC, Peng RD, Salo PM, et al. Changes in Food-Specific IgE Over Time in the National Health and Nutrition Examination Survey (NHANES). J Allergy Clin Immunol Pract 2016;4(4):713-20. doi: 10.1016/j.jaip.2016.01.017 [published Online First: 2016/05/03]
			6. Bassegio Conrado A, Ierodiakonou D, Gowland H, Boyle RJ, Turner PJ. Food anaphylaxis in the United Kingdom: analysis of national data, 1998-2018. *BMJ*2021;372:n251
			7. NHS Digital. Prescription cost analysis— England, 2018. https://digital.nhs.uk/data-and-information/publications/statistical/prescription-cost-analysis/2018.
			8. PrescQIPP Community Interest Group. Appropriate prescribing of specialist infant formulae (foods for special medical purposes). 2016;B146:2.1.
			9. Meyer R, Groetch M, Venter C. When should infants with cow’s milk protein allergy use an amino acid formula? A practical guide. J Allergy Clin Immunol Pract. Mar-Apr 2018;6(2):383-399.

# Figure legends

## Figure 1. Guideline recommendations for diagnosis of non-IgE mediated milk allergy.

Data shown are the frequency with which specific skin (A), gastrointestinal (B), respiratory (C) or general (D) symptoms or signs were cited as indicators of possible non-IgE mediated milk allergy, in the 43 community infant milk allergy guidelines in England which specifically addressed symptoms and signs of non-IgE mediated milk allergy in 2019.

## Figure 2: Guideline recommendations for breastfed infants with suspected milk allergy.

Data shown are the frequency of specific recommendations for managing breastfed infants with suspected milk allergy in the 64 community infant milk allergy guidelines in England which specifically addressed the management of breastfed infants with suspected milk allergy. Data shown represent recommendations made for either all, or a subset, of breastfed infants with suspected milk allergy. 1Guidelines that contained a general statement about breast milk being best for infants with CMPA were included (n=32), along with those suggesting encouraging continuation of breastfeeding without a reason stated (n=12). 2Other than for reason of parental choice.