Prescribing guidelines of infant formula for infants with cows' milk protein allergy (CMPA) and guidelines for lactose intolerance.

Information for GPs

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Date Approved:
Review Date: November 2025

Approved by: Sheffield Area Prescribing Group

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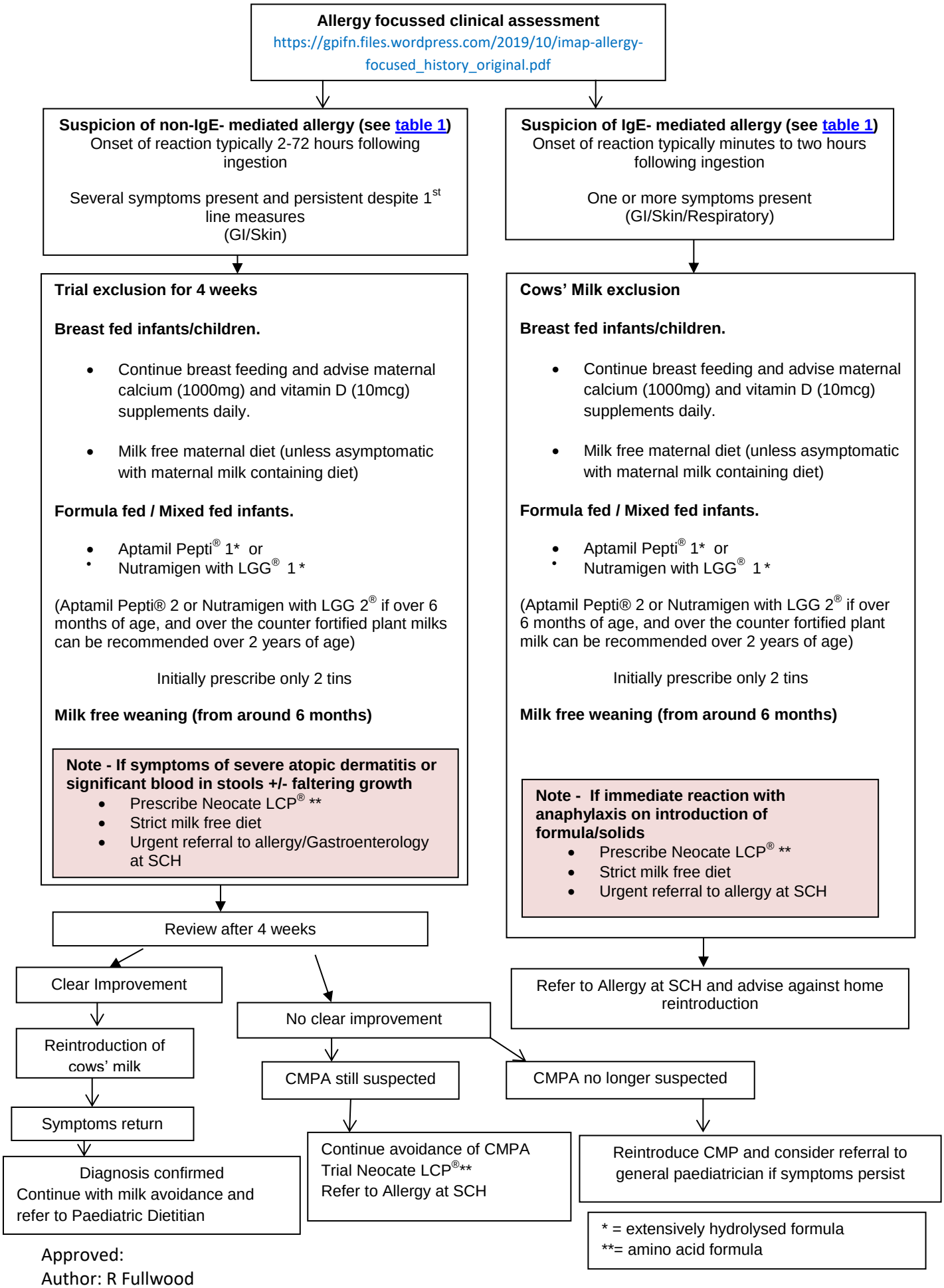
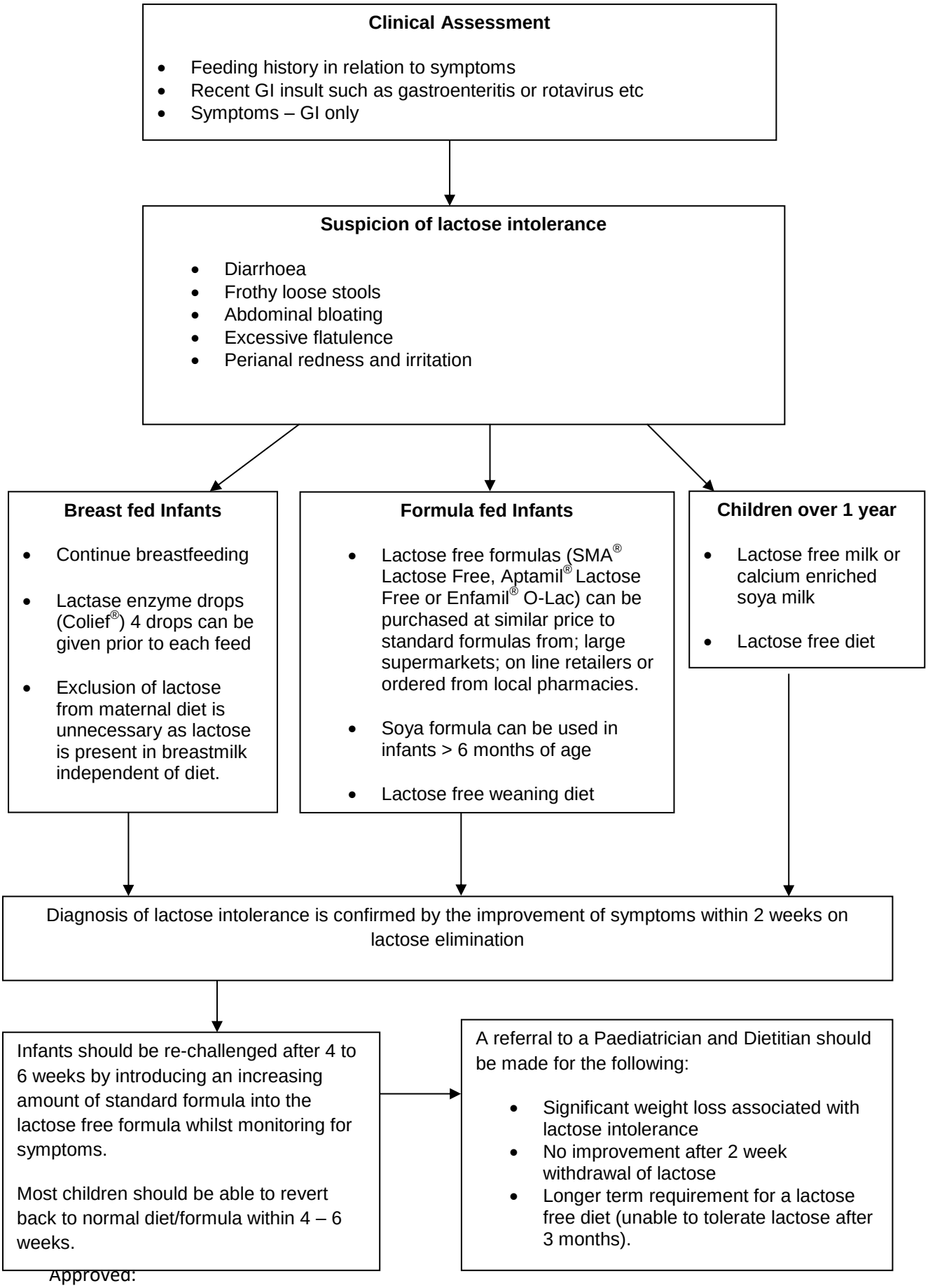


Algorithm for the treatment of lactose intolerance



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Contents

1.0 Overview of CMPA

The management of infants and children with suspected cows' milk protein allergy (CMPA) is complex. This guideline is aimed at supporting GPs and health visitors in primary care in the recognition, confirmation and management of infants and children presenting with suspected CMPA and to outline the recommendations for the prescribing of infant formula feeds for CMPA. The specific management of IgE-mediated CMPA and severe presentations of non IgE-CMPA such as food protein induced enterocolitis, eosinophilic oesophagitis and food protein induced enteropathy with faltering growth are not addressed.

Breastfeeding is the best form of nutrition for infants and this should be promoted, supported and protected where-ever possible

1.1 Objectives:

- Maintain awareness that breastmilk is considered the best for babies and not initiating an un-necessary change from breastmilk to formula.
- Provide a clear pathway for the diagnosis and management of CMPA
- Provide guidance of suitable quantities for prescribing, duration of supply, and guidance on stopping prescriptions of infant formula for infants and children with CMPA.

This guidance covers all infants; including those breastfed, formula-fed or those fed a combination of both. It is intended for health professional use only and not to be used for commercial or marketing purposes.

2.0 Background

Cows' milk protein allergy (CMPA) is an allergic response to proteins in milk. CMPA typically presents in the first year of life and affects approximately 2-3% of infants[1]. The majority of children will outgrow CMPA by 6 years of age however milk allergy can persist past school age and is more likely to persist in individuals with multiple food allergies and/or concomitant asthma and allergic rhinitis[2].

Diagnosis is a particular challenge as most of the typical symptoms are common in well babies. However in infants where these symptoms are multiple, significant and persistent as well as resistant to medical treatment, it is important to consider diagnosis of CMPA. At this point clinical judgement, together with discussion with parents, is required to decide if a diagnostic milk exclusion is appropriate[3].

The symptoms can vary and often, despite CMPA being classified as mild, presentation of symptoms are accompanied by high amounts of parental stress. This is often exacerbated by the lack of sleep associated with incessant itching and abdominal pain. The impact on quality of life for families with food allergy has been shown to be significantly worse than for those with chronic pain or diabetes[2]. It is therefore essential that a timely diagnosis is made and appropriate advice on management is given. NICE Clinical Guideline 116[4] recommends that many manifestations of food allergy could be managed in primary care, with GPs, dietitians, nurses and community based health professionals having up to date and correct knowledge. However as CMPA is the most clinically complex, guidelines are required to give more practical guidance for CMPA in primary care.

2.1 IgE and Non IgE mediated Cows' Milk Protein allergy

The response to cows' milk protein can be subdivided into IgE and non-IgE forms with respect to allergy testing and clinical manifestations (Table 1), although mixed phenotypes have been observed.

2.1.1 Table 1[3,4]

	IgE	**Non-IgE**
Onset of symptoms	Mostly within minutes (may be up to two hours) after ingestion of cows' milk protein	Mostly 2 – 72 hours after ingestion of cows' milk protein
	Usually one or more of these symptoms present	**Usually several of these symptoms present and persistent despite first line treatment**
Skin	Acute pruritus Erythema Urticaria Angioedema Acute 'flaring' of persisting atopic dermatitis	Pruritus 'itching' Erythema 'flushing' Non specific rashes Persistent atopic dermatitis +/- faltering growth
Gastrointestinal	Vomiting Diarrhoea Abdominal pain/colic	Persistent irritability 'colic' Vomiting 'reflux'/GORD Food refusal/aversion Diarrhoea Constipation Abdominal discomfort Blood and/or mucous in stools +/- faltering growth
Respiratory	Acute rhinitis Conjunctivitis	Nasal congestion, catarrh
Cardiovascular	Hypotension	Pallor
Neurological	Sense of impending doom, clingy, lethargic	Fatigue Persistent irritability

3.0 Recommendations

3.1 Assessment

Assess the likelihood of IgE or non-IgE mediated allergy by taking an allergy focussed clinical history which is the cornerstone of diagnosis. It should be undertaken in all children where history, signs and symptoms are suggestive of CMPA. In non-IgE-mediated CMPA, it is essential to exclude IgE-mediated mechanisms as exclusion and subsequent re-introduction may result in an immediate and potentially life-threatening allergic reaction[5]. See link to the iMAP allergy focused Clinical History for Suspected Cow's Milk Allergy in Infancy – the Cornerstone of the diagnosis.

An allergy focussed history should include:

- A physical examination of the child to exclude any differential diagnoses and check for signs of allergy related co-morbidities eg. atopic eczema
- Weighing and measuring the child to assess growth, looking at previous weight and length/height trajectories and asking about any concerns with feeding difficulties or poor growth
- Family history of atopic disease (atopic dermatitis, asthma, allergic rhinitis, or food allergy in parents/siblings) as this may make IgE-mediated allergy more likely
- Feeding history including sources of cows' milk protein and how much was/is ingested
- Symptom history including age of first onset, speed of onset and severity following milk ingestion.
- Any changes in the diet or previous management (including medication) and any response.

3.2 Initial treatment

If IgE-mediated CMPA is suspected, advice should be given on strict dairy avoidance and the child should be referred to the specialist allergy service at Sheffield Children's Hospital; specialist allergy dietitians form part of this service.

The diagnosis of non-IgE CMPA is based on clinical symptoms during periods of elimination and reintroduction therefore children should undergo a 2 – 6 week period of strict cows' milk elimination[4]. After this time, all dairy products should be re-introduced 2 – 3 times weekly for a period of 2 – 3 weeks. Improvement in symptoms during cows' milk dietary elimination associated with a relapse of symptoms following the re-introduction of cows' milk will confirm the diagnosis.

Verbal and written advice should be provided on the avoidance of foods containing cows' milk protein (https://www.bda.uk.com/resourceDetail/printPdf/?resource=milk-allergy) and breastfeeding should be actively supported where possible (https://gpifn.files.wordpress.com/2019/10/imap-supporting-breastfeeding-factsheet.pdf).

If an exclusively breastfed child is symptomatic, the mother should be advised to exclude cows' milk protein from her diet. A maternal substitute should be advised in addition to a daily supplement of 1000mg calcium and 10micrograms vitamin D.

If the child is fed with formula +/- breastmilk, a replacement of cows' milk based formula should be advised with an extensively hydrolysed formula (eHF) as first line (see 3.4 Formulary for Specialist Formula for preferred choice of formula in Sheffield).

Amino acid formula (AAF) should only be prescribed first line in the following situations[6]:

- Severe atopic dermatitis +/- faltering growth
- Severe, persistent and treatment resistant gastrointestinal symptoms +/- faltering growth
- Eosinophilic oesophagitis
- Food protein-induced enterocolitis/enteropathy
- Significantly symptomatic breast fed infants requiring supplemental formula

For prescriptions of eHF, 2-3 tins should be prescribed initially until tolerance/compliance is established then, if necessary, a second prescription with enough to last 4-6 weeks can be issued.

For mixed fed infants, if symptoms occur only with the introduction of top up formula feeds, these should be replaced with eHF top ups. The mother can continue to consume foods containing cows' milk protein.

If on solids advice should be given to parents to exclude all cows' milk protein from the child's diet and advice given on a suitable milk alternative. Milk free solids should be commenced no earlier than 17 weeks unless otherwise indicated.

Over 12 months of age, suitable dairy alternatives depend on patient preference and any associated food allergies. These include soya, oat, rice, coconut and nut milks. Soya milk is not suitable as a first line dairy substitute under 6 months of age and rice milk should not be used as a main dairy alternative under 4 and a half years of age due to its naturally occurring arsenic content.

3.3 Re-assessment for further treatment

In suspected non-IgE mediated CMPA **only**, a cows' milk exclusion trial MUST be followed by reintroduction of cows' milk, if the diagnosis is to be confirmed or excluded – this is now a NICE quality standard and failure to do this will lead to un-necessary over-diagnosis[3]. Parents should be informed why the reintroduction phase is essential.

If there is a clear improvement during the elimination trial, home reintroduction should be undertaken either using cows' milk formula if formula fed or by the mother reverting to a normal diet containing cows' milk containing foods.
https://gpifn.files.wordpress.com/2019/10/home_reintroduction_protocol_to_confirm_or_exclude_diagnosis_original.pdf

If there is no clear improvement during the elimination trial but CMPA is still suspected, the child should be referred to the specialist paediatric allergy service at Sheffield Children's Hospital. If breastfed, an exclusion of other maternal food (soya, egg) should be considered with specialist advice. If the child is formula fed, a trial of amino acid formula should be initiated.

If there is no return of symptoms following home reintroduction, CMPA can be ruled out and normal feeding can resume.

If symptoms return after home reintroduction CMPA can be confirmed.

3.4 Formulary for specialist formula

It is essential to use every possible opportunity to promote breastfeeding amongst the mothers of infants suspected of milk allergy. Mothers should be supported to breastfeed as long as they wish to and this support can be particularly important when mothers are following a dairy free diet[3].

If breastfeeding is not possible, specialist formulas are required for infants with cows' milk protein allergy.

The recommendations of specialist formula to be prescribed first line in Sheffield is based on cost in addition to other factors such as how the formula is made up, suitability for the age it is it marketed for, and whether it has added pre/probiotics.

Extensively hydrolysed formula should be used first-line. At least 90% of children with proven CMPA should tolerate these feeds[7].

3.4.1 Extensively Hydrolysed Formula (eHF)

	Concentration	Size of tin	Cost per tin	Cost per 28 days*	Notes
First line eHF in Sheffield					
Aptamil Pepti® 1	13.64%	400g 800g	£9.87 £19.73	£47.04	Whey based, contains lactose therefore more palatable for infants who have started weaning. Contains prebiotic oligosaccharides
Aptamil Pepti® 2 (over 6 months)	14.43%	400g 800g	£9.41 £18.82	£47.46	
Nutramigen with LGG® 1	13.5%	400g	£11.21	£52.92	Casein based lactose free. Contains probiotics therefore not suitable for premature or immunocompromised infants.
Nutramigen with LGG® 2 (over 6 months)	14.2%	400g	£11.21	£55.58	
Alternative eHF formulas					
SMA Althera®	13.2%	400g	£9.86	£45.50	Whey based, contains lactose therefore more palatable for infants who have started weaning. Marketed for up to 3 years of age which, in volumes to meet calcium requirements may compromise intake from solids
Similac Ailimentum®	14%	400g	£10.01	£49.05	Casein based, lactose free.

*****Based on 500ml of formula per day (ref. cBNF, accessed November 2020)

3.4.2 Amino Acid Formula (AAF)

Amino Acid Formula should only be prescribed for: severe IgE-mediated allergy; severe atopic dermatitis +/- faltering growth; severe, persistent and treatment resistant gastrointestinal symptoms +/- faltering growth; symptoms persisting despite a 4 week trial of an eHF; eosinophilic oesophagitis; food protein-induced enterocolitis/enteropathy; and significantly symptomatic breast fed infants requiring supplemental formula[6].

	Concentration	Size of tin	Cost per tin	Cost per 28 days*	Notes
First line AAF in Sheffield					
Neocate LCP®	13.5%	400g	£22.98	£108.50	Cost is now in line with other AAF
Alternative AAF formulas					
Neocate Syneo®	14.4%	400g	£29.56	£148.40	Contains pre and pro biotics. Not suitable for premature or immunocompromised infants.
SMA Alfamino®	13.8%	400g	£22.98	£110.99	Higher vitamin A content therefore to use fat soluble vitamins with caution
Nutramigen Puramino®	13.6%	400g	£22.98	£109.38	

*Based on 500ml formula per day (ref. cBNF, accessed November 2020)

3.4.3 Formula for over 1 year of age

Most well infants with an appropriate and varied diet can be moved from prescription formula onto widely available dairy free milk substitutes at the age of 1 year. It is important to remember that children under 4.5 years should not be given rice milk, and replacement milks should be fortified with 120mg calcium: parents should be encouraged to check this when buying from the supermarket[3]. In some circumstances, a formula will be required for children over 1 year of age; these should not be routinely prescribed as a follow on formula.

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	Concentration	Size of tin	*Price per tin	Notes
Nutramigen with LGG 3®	13.7%	400g	£11.21	EHF
Neocate Junior®	21.1%	400g	£30.62	AAF, generally recommended when an infant has multiple food allergies and/or faltering growth.

*Based on 500ml formula per day (ref. cBNF, accessed November 2020)

Feeds containing probiotics (Nutramigen with LGG® and Neocate Syneo®) should be prepared with boiled water cooled down to room temperature, as per manufactures guidance. Note, this is currently not in line with DH guidance on safe preparation of infant formula which recommends that feeds should be prepared with boiled water cooled to 70°C, however this temperature would denature the probiotic.

Evidence based summaries of formula can be found here (https://www.firststepsnutrition.org/infant-milks-health-workers)

3.4.4 Suggested monthly quantities of formula to be prescribed.
All milk formulations are defined as Borderline substances. Any prescription written needs to be endorsed 'ACBS'.

Age	Formula quantity	Notes
Under 6 months	12 x 400g or 6 x 800g	Exclusively formula fed 150ml/kg/day of standard concentration formula.
6-12 months	7-13 x 400g or 3-6 x 800g	Infants may require less formula as solid food increases
Over 12 months	6 x 400g or 3 x 800g	To meet calcium requirements of 350mg per day

3.4.5 Private Prescriptions
If the infant has been seen by a private Paediatrician and prescriptions are being requested on the NHS, GPs are advised to ensure that the prescribing recommendations are in line with these guidelines. This is to ensure equity for all patients.

3.5 Soya

Soya based formulas are not recommended for infants under 6 months of age due to isoflavonoids and the phyto-oestrogen content; in theory, this could pose a risk to the longterm reproductive health of these infants when given as the sole source of nutrition. Furthermore, soya formula also contains phytate which may affect nutrient absorption.

An eHF should ideally be chosen rather than soya formula in the management of CMPA. Soya can be used in infants older than 6 months if eHF is not accepted or tolerated, or if there are strong parental preferences. Babies of vegan mothers who choose not to breastfeed may use soya formula which can be purchased over the counter, the above risks should be highlighted to the parent.

3.6 Reintroduction of cows' milk protein

3.6.1 Suspected IgE-mediated CMPA or history of immediate symptoms

Home reintroduction is not indicated and the child should be referred to the specialist paediatric allergy service at Sheffield Children's hospital for testing and a supervised food challenge if necessary.

3.6.2 Confirmed non-IgE mediated CMPA

Tolerance should be assessed with home reintroduction using the cows' milk ladder https://gpifn.files.wordpress.com/2019/10/imap_final_ladder-may_2017_original.pdf when infants are 9-12 months of age or 6 months after their most recent symptomatic exposure to dairy. This is generally repeated every 3 – 6 months until tolerance is induced. Re-introduction should be guided and managed by a paediatric dietitian.

3.7 Referrals and seeking advice

When the diagnosis is confirmed, every child with CMPA should have a nutritional assessment with a registered paediatric dietitian.

Referrals can also be made to a paediatric dietitian: if parents are having difficulty with the infant refusing to take a milk free formula for the elimination trial; if parents require support to eliminate milk free solids during the initial elimination trial; and for breastfeeding mothers requiring support with milk elimination.

3.7.1 Contact details for Paediatric Dietitians

Paediatric Dietitians Department of Dietetics Sheffield Children's Hospital Western Bank Sheffield S10 2TH Tel: 0114 2717212	Paediatric Dietitian Community Dietitians Manor Clinic 18 Ridgeway Road Sheffield S12 2ST Tel: 0114 3078440 **Mild to moderate non-IgE mediated CMPA only**

3.7.2 Referrals to specialist paediatric allergy service

Referrals should be made to the specialist paediatric allergy service (which includes specialist paediatric allergy dietitians) for the following:

- Clinical history strongly suggestive of IgE-mediated CMPA
- An acute systemic reaction
- A severe delayed reaction
- A history of reacting to multiple foods
- Suspected CMPA and asthma
- Suspected CMPA with symptoms not responding to cows' milk exclusion.

4.0 Lactose Intolerance

4.1 Background

Lactose intolerance occurs as a result of a deficiency of the lactase enzyme in the intestine. Lactose intolerance produces some similar symptoms to CMPA, however these two conditions are two different entities and the terms should **not** be used interchangeably.

There are 3 main types of lactose intolerance:

- **Congenital lactose intolerance:** a rare condition where infants are born with a genetic defect resulting in an absence of the lactase enzyme (alactasia). Lactose has to be completely avoided from birth.

- **Primary lactose intolerance:** a rare and genetically inherited condition associated with a developmental decline of the lactase enzyme. This normally becomes apparent after 5 years of age. Primary lactose intolerance may more commonly present in adulthood.

- **Secondary lactose intolerance:** a temporary (usually lasting 4 to 6 weeks), **but much more common** condition which may affect infants as a result of transient lactase deficiency caused by damage to the lining of the gut following, for example, gastroenteritis or rotavirus infection. If the symptoms settle within two weeks of lactose exclusion, this diagnosis is likely.

- Lactose intolerance is defined as a non-immune mediated reaction to food i.e. it is not due to an allergy but to a lack of the lactase enzyme. Patients can present with symptoms of loose and/or watery stools, abdominal bloating and pain, increased flatus and nappy rash.

- Treatment should consist of a lactose free formula **not a hypoallergenic formula**. From the age of 1 year, infants continuing to require lactose free milk should be weaned onto proprietary lactose free milk purchased from supermarkets.

- Lactose free milk is more cariogenic than standard formula as it contains glucose in place of lactose therefore, dental hygiene should be stressed.

4.2 Managing lactose intolerance

Breast fed infants

- Breast milk is the ideal choice for infants with lactose intolerance.

- Exclusion of lactose from the maternal diet is unnecessary as lactose is present in breast milk independent of the diet.

- Lactase enzyme drops (Colief®) should be used with feeds. Recommendations are to give 4 drops prior to each feed for the period of 4 to 6 weeks.

Bottle fed infants

- Lactose free formulas such as SMA® Lactose Free, Enfamil® O-Lac, or Aptamil Lactose Free® can be purchased at a similar cost to standard infant formula therefore prescribers should not routinely prescribe. Healthy Start vouchers can be exchanged for lactose free formulas. See link for where vouchers can be used.

- Symptoms usually resolve on a lactose free formula in 2 to 3 days. As lactose intolerance is often temporary, infants should be re-challenged after 4 to 6 weeks by introducing an increasing amount of standard formula into the lactose free formula whilst monitoring for symptoms.

- Soya formula can be used in infants older than 6 months of age.

Children over 1 year of age

- Lactose free milk can be purchased from supermarkets and used for children over 1 year of age.

- Calcium enriched soya, oat, coconut, hazelnut or almond milks are also suitable.

- Children should be challenged to dairy by gradual reintroduction, after following a lactose free diet for 3 months. Long term use of lactose free products is not usually necessary for secondary lactose intolerance.

4.3 Referral to a Paediatrician and Dietitian

A referral to a paediatrician and/or dietitian should be made for the following:

- significant weight loss associated with lactose intolerance
- no improvement after a 2 week withdrawal of lactose
- longer term requirement for a lactose free diet; unable to tolerate lactose reintroduction after 3 months

5..0 References

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