

Cost effectiveness of extensively hydrolysed casein formula plus probiotic *Lactobacillus rhamnosus* GG (eHCF with LGG®) for the dietary management of cow's milk protein allergy

Summary

Newly diagnosed infants with IgE-mediated CMPA managed with Nutramigen with LGG® instead of eHCF alone improves patient outcomes, releases healthcare resources for alternate use, reduces NHS cost of patient management and thereby affords a cost-effective strategy to the NHS:

- Subjects using eHCF with LGG® compared to eHCF alone reduced the incidence of 1 or more other allergic manifestations by ~50% over 3 years & resulted in a faster return to cow's milk (tolerance acquisition)
- Reduction in NHS costs per patient of **-£497 and -£907** at 3 and 5 years respectively.

Medicines Optimisation

Medicines Optimisation (MO) looks at the value which medicines deliver, making sure they are clinically effective and cost effective.¹ The introduction of MO marks a move away from looking at processes and systems (and unit costs of a medicine/product) by focusing on patients and their experiences.² The ways in which MO aims to help patients and how this might apply to cow's milk protein allergy (CMPA) is shown in table 1.

Table 1:

Desired outcomes for prescribing for CMPA when applied to the medicines optimisation model

Medicines optimisation can help ²	Application to prescribing for CMPA
Improve outcomes	Relieve symptoms of CMPA Aid tolerance acquisition and return to a normal cow's milk diet as quickly as possible Reduce the risk of long-term allergic manifestations such as asthma
Taking correctly	Follow the manufacturers preparation instructions on making up the products Ensure that NICE & iMAP guidance is followed on the use of appropriate formulas for CMPA
Avoiding unnecessary prescribing	Avoiding other medications for symptomatic relief and allergic manifestations, when not appropriate Re-challenge with cow's milk at appropriate intervals. Ensure correct amounts of tins are prescribed for infants needs
Improving safety	Adherence to formula preparation and storage instructions

Hypoallergenic formula for managing cow's milk protein allergy:

Breast milk should always be encouraged but for formula fed infants, these products are normally based on cow's milk. CMPA is the most common childhood food allergy affecting 2–7.5% of infants.³ CMPA is a distressing condition for infants and their families. Symptoms can be immediate (IgE-mediated) or delayed (non IgE-mediated) and can affect the skin, GI tract and respiratory system and range from mild to severe reactions, such as anaphylaxis and failure to thrive.^{4,5}

Management of CMPA involves complete removal of cow's milk from the diet. Clinical guidelines recommend extensively hydrolysed formula (eHF) first-line for mild-moderate CMPA (suitable for up to 90% of infants).^{6,7} eHF are based on hydrolysed casein or whey protein. Amino acid formula (AAF) should be reserved for severe CMPA (up to 10% of infants) as they are considerably more expensive and may delay the development of oral tolerance (return to milk).⁸

Nutramigen with LGG® is an effective first line clinical choice for CMPA

There is increasing evidence that specific probiotics may play a role in regulating the immune system in children with allergy.⁹⁻¹¹ Not all probiotics are the same, the clinical benefit is dependent on strain specificity. *Lactobacillus rhamnosus* GG (LGG®) is one of the most extensively studied probiotic strain for allergy management.

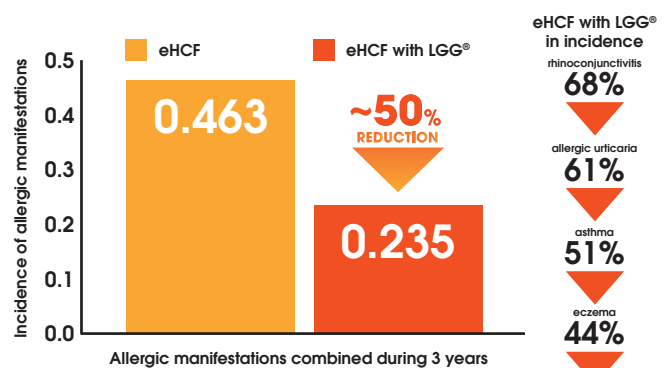
Several studies have found that Nutramigen with LGG®, an extensively hydrolysed casein formula with LGG® (eHCF with LGG®) resulted in a faster return to milk* (oral tolerance acquisition).^{8,12,13} After 12 months of dietary management 79%, 44% and 18% of infants on eHCF with LGG®, eHCF and AAF formula respectively were shown to return to cow's milk.⁸

Children with CMPA have an increased risk of other allergic manifestations, such as eczema, asthma, urticaria or rhinoconjunctivitis, later in life.¹³

Managing CMPA with appropriate formula milks may reduce the incidence of longer term allergic manifestations. A study found that subjects using eHCF with LGG® compared to eHCF alone reduced the incidence of 1 or more allergic manifestations by ~50% up to 3 years of age (figure 1).

Figure 1:

Incidence of allergic manifestations of eHCF versus eHCF with LGG® showing a statistical clinical benefit of eHCF with LGG®.¹³



Adapted from Canani et al. 2007. This figure depicts the main study outcome under complete case analysis. Absolute risk difference for eHCF with LGG® vs. eHCF alone = -0.23 (95% CI: -0.36 to -0.10; P<0.001)

*Vs an extensively hydrolysed casein-based formula without LGG® or formulas based on soy or amino acids.



Evidence that Nutramigen with LGG® is a cost effective strategy

A cost effectiveness analysis aims to study the costs and health gains of alternative strategies.¹⁴ The cost effectiveness analysis by Guest et al aimed to answer whether eHCF with LGG® (Nutramigen with LGG®) is more cost effective versus eHCF alone in infants with IgE-mediated CMPA.¹⁵

The Guest paper showed that eHCF with LGG® is proven to improve patient outcomes, release NHS resources and reduce NHS costs vs eHCF alone.

The primary measure of clinical effectiveness was the probability of being symptom free of allergic manifestations (i.e. urticaria, eczema, asthma and rhinoconjunctivitis) up to 5 years of age. The secondary clinical effectiveness measure was the probability of developing tolerance to cow's milk. From these outcomes cost effectiveness of eHCF with LGG® was determined.

Resources for CMPA management in the NHS were determined by interviewing GPs who managed CMPA according to local and NICE guidance. Costs for the NHS were assigned to each resource. Resource use included:

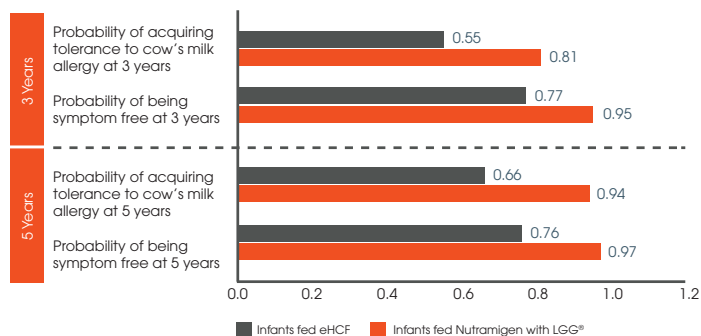
- Usage of formula feed up to 24 months of age
- GP, paediatric specialists, dietitian visits
- A&E attendance
- Hospital admissions
- Medicines for treating symptoms (PPIs; systematic corticosteroids; antihistamines; emollients; inhaled corticosteroids and salbutamol) over 3 and 5 years from starting formula feeding.

eHCF with LGG® is the dominant strategy

The primary clinical outcome - probability of being free of allergic manifestations and the secondary outcome - probability of acquiring tolerance to cow's milk at 3 and 5 years were the dominant strategy for eHCF with LGG® (figure 2).

Figure 2:

Expected clinical outcomes using eHCF and eHCF with LGG®.¹⁵



* Incremental cost or incremental cost effectiveness ratio (ICER) represents the economic value of one intervention compared to another (comparator). An ICER is calculated by dividing the difference in costs between the intervention and comparator with the measure of health outcome to provide a ratio of "extra cost per extra unit of health effect" for the more expensive therapy versus the alternative. Costs are usually described in monetary terms (£), and effects can be measured in terms of health status or another patient orientated outcome measure. In this instance the outcomes were probability of tolerance to cow's milk and probability of being symptom-free, both measured at 3 and 5 years.¹⁴

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IMPORTANT NOTICE: Breastfeeding is best for babies. The decision to discontinue breastfeeding may be difficult to reverse and the introduction of partial bottle-feeding may reduce breast milk supply. The financial benefits of breastfeeding should be considered before bottle-feeding is initiated. Failure to follow preparation instructions carefully may be harmful to your baby's health. Parents should always be advised by an independent healthcare professional regarding infant feeding. Products of Mead Johnson must be used under medical supervision. *Trademark of Mead Johnson & Company, LLC. © 2018 Mead Johnson & Company, LLC. All rights reserved. LGG® is a registered trademark of Chr Hansen A/S..

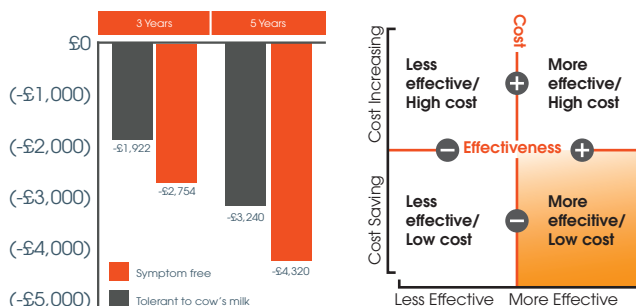
Nutramigen with LGG® is not recommended for premature and immunocompromised infants unless directed and supervised by a healthcare professional.

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The estimated total healthcare cost over 5 years for infants initially fed eHCF with LGG® was less than eHCF (£4,229 vs. £5,136 per patient) with a reduction in NHS costs per patient of -£497 and -£907 at 3 and 5 years respectively using eHCF with LGG®. The incremental cost* analysed for each additional infant who was tolerant to cow's milk or who was symptom free showed cost effectiveness of the eHCF with LGG® strategy at 3 and 5 years (figure 3).

Figure 3:

Incremental cost effectiveness ratio (ICER)¹⁶ for each additional infant who was tolerant to cow's milk or symptom free at 3 and 5 years. Showing eHCF with LGG® to be a cost effective strategy¹⁵



Adapted from Guest et al 2019

Sensitivity analysis

The sensitivity analysis (a method for exploring the impact of potential sources of bias and uncertainty) showed that eHCF with LGG® remained cost effective for the 2 outcome measures (incremental cost for each additional infant who was tolerant to cow's milk and was symptom free). The effects of a number of parameters being changed on the outcome measures were tested e.g. they looked at:

- Reducing the costs of the comparator eHCF from £11.21 to £9.20/400g (lowest eHCF at time of paper and is cheaper than any other eHCF in the market today)
- Changing the amount of resources needed to manage allergic manifestations by 25%.

In all scenarios eHCF with LGG® remained cost effective.

Conclusion

First line dietary management of newly diagnosed infants with IgE-mediated CMPA with Nutramigen with LGG® instead of eHCF alone **improves patient outcomes, releases healthcare resources** for alternate use, **reduces NHS cost of patient management** and thereby affords a cost-effective strategy to the NHS.

In order to achieve cost effective prescribing, systems need to be in place using a medicines optimisation approach. These systems include development and implementation of local guidance. Guidelines need to detail how and when review will occur enabling an opportunity to reintroduce cow's milk and to ensure formula feeds are not continued beyond a point when the infant may have outgrown their allergy to cow's milk.

