The importance of achieving healthy growth in infants and children with Cow Milk Allergy: **Evidence supporting use of Neocate®**

Summary box: In addition to supporting symptom resolution in cow milk allergy (CMA), a hypoallergenic formula must also promote healthy growth. Nutricia presents an overview of the extensive clinical evidence demonstrating that Neocate supports healthy growth in infants and children with food allergies.

Key Learning Points:

1. Healthy growth is an important clinical outcome for infants and children with conditions requiring a hypoallergenic formula such as an amino acid-based formula (AAF). Growth deficits should be addressed as early as possible to optimize long-term outcomes.
2. Infants and children with CMA are at risk of faltering growth (FG*), particularly poor linear growth. An AAF is recommended where there is FG in CMA, arising from extensively hydrolyzed formula (eHF) failure, severe gastrointestinal symptoms and multiple food allergy (MFA).
3. There is an extensive, high-quality, published evidence-base from studies on Neocate carried out over the last 25 years demonstrating efficacy in achieving normal and catch-up growth.

The importance of adequate growth in the early years in CMA

The provision of adequate nutrition in the first two years of life is critical to ensure healthy growth, ideally provided by breast milk where possible. Nutritional deficits in the early years due to chronic illness may have long-term consequences for growth, developmental and cognitive outcomes. Dietary management of food allergy aims to significantly improve symptoms while also ensuring nutritional adequacy to meet infants' requirements for growth and development[1]. If breastfeeding with a maternal avoidance diet is not possible, a subset of infants may require an AAF[2], with 100% free amino acids in place of protein. Allergic symptoms will improve on an eHF in most infants, however due to the residual peptides in an eHF, symptoms may not fully resolve in up to 10% of children with IgE mediated allergy and a higher failure rate (up to 40%)[2] is likely in non-IgE mediated CMA[2,3].

Expert bodies[4,5] and clinician-led guidelines variously recommend an AAF as the formula of choice[2,3,6,7] where there is poor symptom resolution on an eHF, FG, severe gastrointestinal symptoms, eosinophilic esophagitis (EoE), food protein-induced enterocolitis syndrome (FPIES), severe eczema, MFA and anaphylaxis. Current guidelines recommend that a suitable substitute formula should be continued until the age of two years[5,8] to provide essential energy and nutrients for growth and development.

Infants with CMA are at increased risk of FG, particularly poor linear growth, with studies reporting between 7-24%[2,9,10] of children with food allergy present with stunting (height-for-age z score < -2). A systematic review of the literature concluded that children with MFA have a higher risk of growth impairment[9]. It has been speculated that poor growth may persist in some children due to low grade inflammation with incomplete antigen elimination. This may affect gastrointestinal barrier function resulting in suboptimal nutrient absorption[11]. Infancy is a critical developmental stage, therefore choosing an effective hypoallergenic formula is important to avoid growth deficits and optimize long-term outcomes.

Extensive evidence base and history of use by infants and children taking Neocate

As the first hypoallergenic AAF available globally, there is an extensive evidence base reporting growth on > 1,000 infants and children fed Neocate from studies undertaken worldwide over the last 25 years. These studies, discussed below, demonstrate that Neocate supports growth, promotes catch-up growth and meets nutritional requirements.

* Faltering growth is also known as failure-to-thrive or growth failure.

Observational studies reporting growth outcomes for infants with CMA fed Neocate

Several key studies, summarized in table 1, demonstrate that use of Neocate promotes healthy growth and catch-up growth in infants and children with incomplete symptom resolution ("failure") on an eHF, severe (gastrointestinal) symptoms and MFA accompanied by FG[12-19]. Early work by Vanderhoof et al in 1997[19] identified 28 infants with ongoing symptoms including gastrointestinal symptoms and poor weight gain while taking an eHF who were switched to Neocate for a minimum of 2 weeks. As well as symptom resolution, all infants achieved appropriate weight gain on Neocate. Hill et al[15] reported the long-term follow-up of 18 infants with MFA and eHF failure, of which 4 infants presented with significant FG (mean weight-for-age z score of -2.4). These infants achieved catch-up growth within 6-12 weeks of commencing feeding with Neocate; the mean height-for-age z-score also improved during the follow-up.

CMA and MFA are chronic conditions which can persist beyond infancy[20,21]. Rates of growth on Neocate have been investigated among those who are more severely allergic with MFA and multisystem involvement. de Boissieu et al[14] published the long term outcome for 52 infants (5.2 ±3.8 months) with CMA who, due to symptoms persisting on eHF, switched to Neocate. After an average of 11.4 ± 7.9 months on Neocate, mean z-scores for weight (-1.04 ± 1.45 to -0.02 ± 1.16) and length (-0.86 ± 1.37 to 0.16 ± 1.38) for age increased significantly ($p<0.001$), demonstrating satisfactory catch-up growth after long term use of Neocate. Similarly, Isolauri and Sampson[16] reported improved relative weight-for-height (mean scores -3.1 ± 6.9 to -1.2 ± 7.9) after 6 months of feeding with Neocate. These early observational studies in children with CMA taking Neocate helped to identify the need for a hypoallergenic AAF where symptoms persisted on an eHF. These studies also demonstrated catch-up growth, particularly linear growth in these infants and children.

Table 1: Growth outcomes in key observational studies with Neocate in CMA and MFA

Author, year	Indication for use of AAF	Intervention; Subjects (number and age)	Length of follow-up	Growth outcome
Vanderhoof et al, 1997[19]	Continued food allergy symptoms on an eHF	Neocate; n=28 Infants; 22-173 days of age	2 wks followed by challenge with eHF	All gained weight during the intervention
Hill et al, 1999[15]	CMA with eHF failure and persisting multiple allergic symptoms	Neocate; n=18 Age at presentation; 7.3±0.76 mos	Up to 3 years	All infants with significant FTT (mean weight-for-age z-score -2.4; n=4) achieved catch-up growth
Isolauri et al, 1999[22]	Continued atopic eczema symptoms while breastfeeding	Neocate; n=100 Age at enrolment; 2-10 mos	2 mo	Significant improvement in relative length in the group after switching to Neocate
Kanny et al, 2002[18]	MFA with persistent symptoms including poor growth	Neocate; n=26 Infants and young children	6-19 mo	Weight gain with catch-up growth in 4 of 5 subjects with poor growth
de Boissieu et al, 2002[14]	CMA with eHF failure and persisting clinical symptoms	Neocate; n=52 Infants followed into early childhood	3.5-41 mo	Significant catch-up growth in weight and length in all subjects
Isolauri and Sampson, 2004[16]	Use in children with CMA and MFA	Neocate; n=31 At entry 14 mo to 8 yrs of age	6 mo	Improvement in mean relative weight-for-height
Colson et al, 2013[13]	CMA	Neocate; n=102 eHF; n=32 Infants aged 6+ mo	>15 mo	Long-term appropriate growth

Randomized controlled trials reporting growth outcomes for infants with CMA fed Neocate

Several multi-center randomized controlled trials (RCTs) in infants taking Neocate have reported normal and/or catch-up growth compared to an appropriate control or reference population[17,23-28]. The findings are summarized in table 2.

An early RCT by Isolauri et al[17] compared the efficacy and safety of an eHF and AAF (Neocate) in 45 infants with CMA. Atopic eczema symptoms improved in both groups, however, there was also improved growth in the AAF group, with increased relative length during the 9-month follow-up. The authors concluded that an AAF may be preferable in infants with MFA in achieving normal growth. Subsequently in a multi-center RCT, Niggemann et al[28] compared the growth and efficacy of Neocate (n=42) and an eHF (n=31) in infants (1.6-9 months of age) with CMA. The authors reported a significant increase in the length z-score in infants taking Neocate compared to the eHF group.

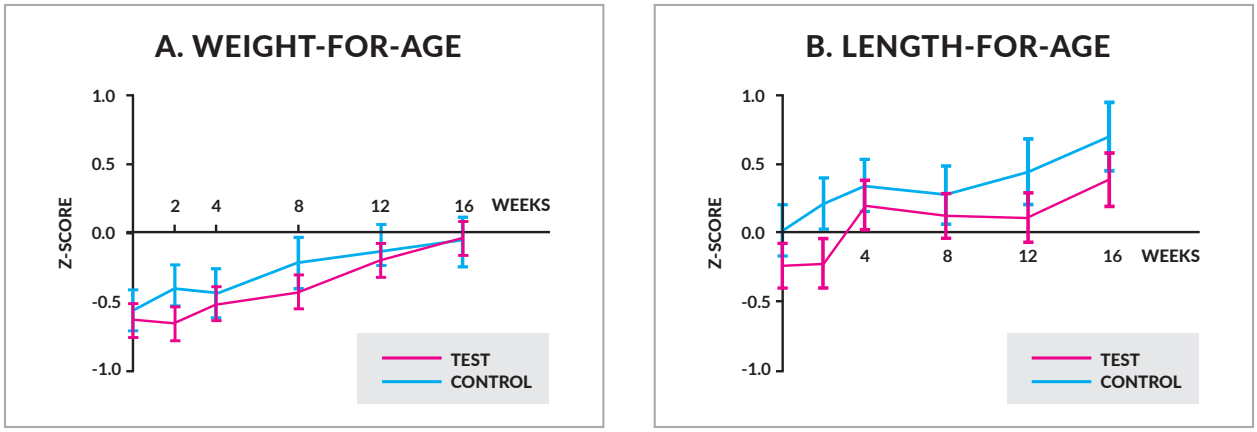
More recently as part of the clinical trial program for Neocate® Syneo® Infant, Burks et al[23] compared the growth of infants (< 8 months) with IgE or non-IgE CMA fed Neocate with (n=54) or without (n=56) a synbiotic over a 4-month period. The study demonstrated similar growth between the two AAF formulas and, as shown in figure 1, both AAF formulas were also effective in promoting catch-up growth where weight-for-age was below population norms at study entry. A further publication[26] of the same study population as in Burks et al also showed mean blood concentrations of all minerals were within reference ranges for infants at baseline (n=82) and after 16 weeks (n=66). Harvey et al[27] demonstrated that the same Neocate and Neocate with sybiotics studied in Burks et al, when taken as a sole source of nutrition in 115 healthy infants, supported normal growth compared to the WHO 2006 growth standards.

In a large study, Ma et al[29] compared the efficacy of Neocate to a soy protein-based formula in 240 infants with CMA or MFA over 12 weeks and found significantly superior weight gain (p=0.002) in infants on Neocate (n=124) compared to the infants on soy protein-based formula (n=124). In a longer-term study, Berni Canani et al[24] investigated the growth of 40 infants with confirmed CMA that were randomly allocated to take an eHF or age-appropriate Neocate formula over 12 months compared with a healthy control group. Catch-up growth was achieved by both the Neocate and eHF fed children with similar z-scores in the two feeding groups compared to healthy controls by the 6-month visit for weight-for-age and by the 12-month visit for length-for-age.

Table 2: Growth outcomes from RCTs with Neocate in subjects with CMA

Author, year	Subjects (number and enrolment age)	Length of intervention	Growth outcome
Isolauri et al, 1995[17]	eHF; n=22 Neocate; n=23 Age range; 4-7 mo	9 mo	At baseline, relative length was -0.3 SD in both groups of infants with CMA, with a length-for-age increase in the AAF group compared to the eHF group
Niggemann et al, 2001[28]	eHF; n= 31 Neocate; n= 42 Age range; 1.6–9 mo	6 mo	Significant increase in length-for-age (standard deviation score) in the AAF group compared to eHF group, despite similar energy intakes
Ma et al, 2012[29]	Soy formula; n= 124 Neocate; n= 124 Age range; 1 – 10 mo	3 mo	From 4 weeks, significantly better weight gain in infants on AAF compared to soy-protein based formula
Burks et al, 2015[23]	Neocate; n=56 Neocate with synbiotics; n=54	4 mo	Neocate with/without synbiotics promotes catch-up growth compared to population norms (see Figure 1)
Berni Canani et al, 2017[24]	eHF; n=19 Neocate; n=21 Standard formula; n=25 Age range: 5-12 mo	12 mo	Long-term management with age-appropriate AAF supports catch-up growth and adequate protein status in young children with CMA
Candy et al, 2018[25]	Neocate; n=36 Neocate with synbiotics; n=35	2 mo	Growth parameters were within the expected ranges for age

Figure 1.



Weight-for-age (A) and length-for-age (B) Z-scores over time. Test = Neocate with synbiotics; Control = Neocate. Z-scores were calculated by using the WHO growth standards. Values are given as mean ± SEM. Reprinted with permission from John Wiley and Sons. Article publicly available at https://onlinelibrary.wiley.com/doi/epdf/10.1111/pai.12390

Conclusion

It is beneficial to optimize growth in the first two years of life to ensure adequate long-term developmental outcomes. Infants with CMA are at increased risk of FG, particularly poor linear growth. A significant body of high quality published evidence, including RCTs and observational studies, demonstrates that Neocate has been repeatedly shown to promote healthy growth or catch-up growth in infants and children with CMA and MFA.

References

1. Venter C, Laitinen K, Vlieg-Boerstra B. Nutritional aspects in diagnosis and management of food hypersensitivity-the dietitians role. J Allergy (Cairo). 2012;2012:269376.
2. Hill DJ, Murch SH, Rafferty K, et al. The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review. Clin Exp Allergy. 2007;37:808-22.
3. 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. 2018;6:383-99.
4. 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;55:221-9.
5. Luyt D, Ball H, Makwana N, et al. BSACI guideline for the diagnosis and management of cow's milk allergy. Clin Exp Allergy. 2014;44:642-72.
6. Ludman S, Shah N, Fox AT. Managing cows' milk allergy in children. BMJ. 2013;347:f5424.
7. Vandenplas Y, Koletzko S, Isolauri E, et al. Guidelines for the diagnosis and management of cow's milk protein allergy in infants. Arch Dis Child. 2007;92:902-8.
8. Fiocchi A, Brozek J, Schunemann H, et al. World Allergy Organization (WAO) Diagnosis and Rationale for Action against Cow's Milk Allergy (DRACMA) Guidelines. Pediatr Allergy Immunol. 2010;21 Suppl 21:1-125.
9. Sova C, Feuling MB, Baumler M, et al. Systematic review of nutrient intake and growth in children with multiple IgE-mediated food allergies. Nutr Clin Pract. 2013;28:669-75.
10. Vieira MC, Morais MB, Spolidoro JV, et al. A survey on clinical presentation and nutritional status of infants with suspected cow' milk allergy. BMC Pediatr. 2010;10:25.
11. Isolauri E, Sutas Y, Salo MK, et al. Elimination diet in cow's milk allergy: risk for impaired growth in young children. J Pediatr. 1998;132:1004-9.
12. Ammar F, de Boissieu D, Dupont C. Allergy to protein hydrolysates in 30 infants. 1999.
13. Colson D, Michaud Benedicte, Soulaines P, Dupont C. . Long term nutritional outcome of children fed by an amino acid formula. J Allergy Clin Immunlogy. 2013.
14. de Boissieu D, Dupont C. Allergy to extensively hydrolyzed cow's milk proteins in infants: safety and duration of amino acid-based formula. J Pediatr. 2002;141:271-3.
15. Hill DJ, Heine RG, Cameron DJ, et al. The natural history of intolerance to soy and extensively hydrolyzed formula in infants with multiple food protein intolerance. J Pediatr. 1999;135:118-21.
16. Isolauri E, Sampson H.A. Use of an amino acid based formula in the management of cows milk allergy and multiple food protein intolerance in children. Paper presented at: 2004.
17. Isolauri E, Sütas Y, Mäkinen-Kiljunen S, et al. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. J Pediatr. 1995;127:550-7.
18. Kanny G, Moneret-Vautrin DA, Flabbee J, et al. [Use of an amino-acid-based formula in the treatment of cow's milk protein allergy and multiple food allergy syndrome]. Allerg Immunol (Paris). 2002;34:82-4.
19. Vanderhoof JA, Murray ND, Kaufman SS, et al. Intolerance to protein hydrolysate infant formulas: an underrecognized cause of gastrointestinal symptoms in infants. J Pediatr. 1997;131:741-4.
20. Host A, Halken S, Jacobsen HP, et al. Clinical course of cow's milk protein allergy/intolerance and atopic diseases in childhood. Pediatr Allergy Immunol. 2002;13 Suppl 15:23-8.
21. Santos A, Dias A, Pinheiro JA. Predictive factors for the persistence of cow's milk allergy. Pediatr Allergy Immunol. 2010;21:1127-34.
22. Isolauri E, Tahvanainen A, Peltola T, et al. Breast-feeding of allergic infants. J Pediatr. 1999;134:27-32.
23. Burks AW, Harthoorn LF, Van Ampting MT, et al. Synbiotics-supplemented amino acid-based formula supports adequate growth in cow's milk allergic infants. Pediatr Allergy Immunol. 2015;26:316-22.
24. Berni Canani R, Nocerino R, Frediani T, et al. Amino acid-based formula in cow's milk allergy: long-term effects on body growth and protein metabolism. J Pediatr Gastroenterol Nutr. 2017;64:632-8.
25. Candy DCA, Van Ampting MTJ, Oude Nijhuis MM, et al. A synbiotic-containing amino-acid-based formula improves gut microbiota in non-IgE-mediated allergic infants. Pediatr Res. 2018;83:677-86.
26. Harvey BM, Eussen S, Harthoorn LF, et al. Mineral Intake and Status of Cow's Milk Allergic Infants Consuming an Amino Acid-based Formula. J Pediatr Gastroenterol Nutr. 2017;65:346-9.
27. Harvey BM, Langford JE, Harthoorn LF, et al. Effects on growth and tolerance and hypoallergenicity of an amino acid-based formula with synbiotics. Pediatr Res. 2014;75:343-51.
28. Niggemann B, Binder C, Dupont C, et al. Prospective, controlled, multi-center study on the effect of an amino-acid-based formula in infants with cow's milk allergy/intolerance and atopic dermatitis. Pediatr Allergy Immunol. 2001;12:78-82.
29. Ma L sK, et al. A clincial multi-centre study of the efficacy and safety of an aminoo acid based formula in the treatment of infants with food protein allergy. Chinese Jounal of Practical Pediatrics. 2012;27.