

Hypoallergenic formula prescribing practices in Australia

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Aim: To gain insight into the use of hypoallergenic formula in Australia by analysis of prescribing statistics.

Methods: Statistics on supply of amino acid and extensively hydrolyzed formula were obtained from the Health Insurance Commission web site. The number of prescriptions supplied in 2003 and 2004 per 1000 children aged 4 years and younger were calculated for each State and Territory. This was related to the numbers of paediatric physicians and paediatric allergists in each State.

Results: There was a marked rise in the use of amino acid formula (AAF) commencing in 2001. The Australian Capital Territory, New South Wales and Victoria had 6–7 times more AAF items per 1000 children prescribed than Western Australia. This did not appear to relate to the numbers of paediatricians or paediatric allergists in each State. In all States and Territories the prescribing of extensively hydrolyzed formula was less than that of AAF.

Conclusions: There are significant regional differences which do not appear to be related to the prevalence of allergic disease. In some States and Territories AAF may be frequently prescribed as a first line treatment for cows milk allergy and for prevention of allergic disease in contradistinction to current recommendations of the Pharmaceutical Benefits Scheme and authoritative statements and position papers. Re-examination of both the Pharmaceutical Benefit Scheme guidelines and the knowledge and perceptions of the prescribing community is indicated.

Key words: amino acids; food hypersensitivity; infant formula; infant nutrition; protein hydrolyzates.

In conjunction with a marked increase of allergic disease in the 20th century there has been an increase in infants and young children with cows milk allergy. A successful treatment strategy has been the modification of allergenic cows milk proteins by hydrolyzation to render them less allergenic. In the late 1980s papers were first published concerning the use of hydrolyzed formula for the treatment of cows milk allergy.¹ It was also suggested that these formulae may be of use for the prevention of allergic disease. There are two types of hydrolyzed formula partially and extensively hydrolyzed. In hydrolyzed formula milk proteins are broken down to peptide fragments by enzymic hydrolysis with a consequent reduction in allergenicity. In contrast to partially hydrolyzed formula (PHF), extensively hydrolyzed formula (EHF) does not contain peptides with a molecular

weight greater than 3000 Da. The amount of the allergenic protein *Beta lactoglobulin* in the EHF Pepti-Junior (Nutricia, Sydney, Australia) (13 µg/L) is comparable to that detectable in breast milk (5–150 µg/L) and much less than that detected in a PHF such as NAN HA (48 000 µg/L).² Subsequently formula containing only amino acids and no whole proteins were developed. As these formulae do not contain peptide fragments they are non-allergenic. The use of amino acid formula (AAF) for treatment of cows milk allergy was reported in the early 1990s.³

The use of hydrolyzed formula as a strategy for allergy prevention was postulated by an authoritative body in 1989 although it was also stated there was no clear evidence of the effectiveness of such an approach.¹ Extensively hydrolyzed formula (EHF) was recommended for prevention of allergic disease in high risk infants in 1993 in a position paper from The European Society of Pediatric Allergy and Clinical Immunology.⁴ Interestingly there have been no statements by authoritative bodies recommending AAF in preference to EHF for allergy prevention and there are no published trials examining the use of AAF as a primary preventative strategy. Currently primary prevention of allergy is not a recognized indication for an Australian Pharmaceutical Benefit Scheme (PBS) authority prescription.

A small proportion of cows milk allergic children, approximately (5%) will not respond to treatment with an EHF but will respond to AAF.⁵ The current PBS schedule and the Australasian Society of Clinical Immunology and Allergy recommend that only those cows milk allergic children who do not respond to treatment with an EHF should be given AAF. The aim of this study is to gain insight into the

Key Points

1. Prescribing practices for hypoallergenic formula appear to differ from established guidelines and authoritative statements.
2. There is a marked state based variation in the prescription of amino acid formula.

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use of hypoallergenic formulae in Australia by analysis of prescribing statistics as both EHF and AAF require a PBS authority prescription.

Methods

Statistics on PBS items supplied were obtained from the Health Insurance Commission web site (http://www.hic.gov.au/statistics/dyn_pbs/forms/pbs_tab1.shtml). Data on EHF, Alfar (Nestle, Sydney, Australia) and Pepti-Junior (item Nos. 2676W and 8259Q) and AAF, Neocate (Scientific Hospital Supplies, Sydney, Australia) and EleCare (EleCare Abbot Australasia, Sydney, Australia; item Nos. 3066J, 87574G, 87575H, 8754R, 8755T and 8433J) were obtained. From 2002 Alfar and Pepti-Junior were the only EHF supplied on the PBS as other EHF preparations (Nuramigen and Pregestemil; Mead Johnson, Evansville) were withdrawn from the PBS in 2001. Population statistics for the numbers of children aged 4 years or younger in each State and Territory were obtained from the Australian Bureau of Census figures 2001. The numbers of paediatric physicians per State were obtained from the Royal Australasian College of Physicians in 2004. The numbers of paediatric allergists per State were derived from the Australian Society of Clinical Immunology and Allergy Handbook 2003. EHF and AAF prescriptions supplied per 1000 children aged 4 years and younger were calculated.

Results

There was a marked rise in the use of AAF (Fig. 1) commencing in 2001. For the 3 years 2002–2004, the numbers of prescribed items of AAF increased by 41% while that those of EHF increased by only 9%. The rise in AAF observed is largely due to increased Neocate usage as Neocate Advance (introduced in 2002) and EleCare (introduced in 2004) made up only 1.4% and 6.6%, respectively, of the AAF formula prescribed from January 2003 to January 2005.

Table 1 shows AAF and EHF prescriptions per 1000 children aged 0–4 years from January 2003 to January 2005 by individual States and Territories. This is compared with the numbers of paediatric physicians and allergists per 1000 children aged 4 years or younger. Prescribing practices varied markedly between States and Territories. The Australian Capital Territory, New South Wales and Victoria had 5–6 times more AAF items per 1000 children prescribed than Western Australia. This did not appear to relate to the numbers of paediatricians or paediatric allergists as Western Australia had a

similar number of paediatricians and more paediatric allergists per 1000 children than NSW and Victoria. The state-based discrepancy was also not related to the practice in Western Australia of encouraging the dispensing of AAF for hospital patients from the paediatric hospital pharmacy rather than an outside PBS script. Inclusion of the number of items of AAF dispensed from the Princess Margaret Hospital Perth in 2003 and 2004 only increased the items per 1000 children to 8.9. This discrepancy in prescribing practice is reflected to a lesser extent for EHF. In all States and Territories the prescribing of EHF was less than that of AAF. The relative amounts of AAF compared with EHF varied from a high of 3.7 times as much in New South Wales to a low of 1.1 times as much in Queensland. The rate of EHF prescription in Victoria was twice that in NSW.

Discussion

Hypoallergenic (EHF and AAF) formulae are supplied on the PBS and it is unlikely that that significant amounts are utilized outside this scheme. Thus the PBS statistics may be assumed to provide an accurate reflection of prescribing practices within Australia. AAF (Neocate and EleCare) are recommended on authority for an initial prescription for combined intolerance to cows milk, soy and protein

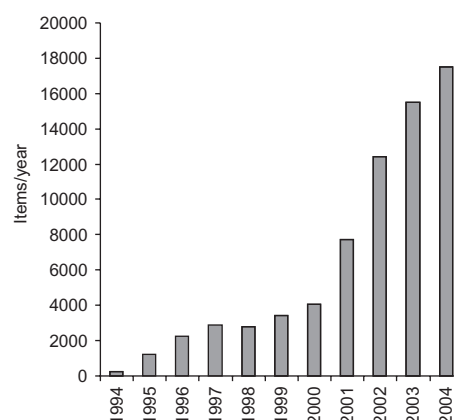


Fig. 1 Amino acid formula (Neocate and EleCare) prescription items/year.

Table 1 Amino acid and extensively hydrolyzed formula prescription rates/1000 children January 2003 to January 2005

	Amino acid formula Items/1000 children	Extensively hydrolyzed formula items/1000 children	Paediatric physicians/ 1000 children	Paediatric allergists/ 1000 children
ACT	44.4	20.5	0.79	0
New South Wales	37.6	10.2	1.02	0.033
Victoria	37.0	22.1	1.00	0.030
Tasmania	25.5	18.7	0.53	0.033
Northern Territory	21.4	12.3	0.92	0
South Australia	19.9	13.9	1.01	0.067
Queensland	12.4	11.4	0.72	0.008
Western Australia	7.1	5.8	0.99	0.049

hydrolyzate up to the age of 2 years. Further authorities can be obtained up to the age of 2 years or beyond 2 years where the child is assessed by suitably qualified allergist or paediatrician. These items can also be supplied on authority for rare conditions such as short bowel syndrome or substituted for parental nutrition. EHF (Pepti-Junior and Alfare) are authorized for treatment of intolerance to both cows milk and soy protein for both initial treatment or continuing treatment beyond the age of 2 years where the child is assessed by qualified allergist or paediatrician. The EHF may also be used for a number of rarer conditions involving the liver and gastrointestinal tract. Owing to the high prevalence of cows milk allergy as compared with other conditions for which hypoallergenic formulae are authorized it is likely that the great majority of items are prescribed for management of allergic conditions. It is also likely that paediatricians rather than paediatric allergists authorize the majority of items as there are 20–30 times as many paediatricians as there are paediatric allergists. Although general practitioners can authorize an initial prescription subsequent prescriptions must be authorized by a paediatrician or paediatric allergist and the number of items prescribed under item numbers for continuing usage is approximately four times the amount prescribed under the initial authority. The cost to the PBS of feeding an infant from 3 months to 12 months on AAF is approximately \$3500 compared with \$800 with an EHF and the current yearly cost to the PBS of AAF of approximately \$7 million is 10 times that of EHF.

Pharmaceutical Benefit Scheme guidelines restrict the use of AAF to combined intolerance to cows milk protein, soy protein and protein hydrolyzate formulae. Among children who are allergic to cows milk only 10% or less are intolerant of EHF. The figure of 10% appears to be derived from the statement that for a formula to be considered hypoallergenic at least 90% of cows milk allergic children must tolerate the product and the actual proportion of children intolerant to EHF may be less than this.⁵ Thus the combined results of three studies of EHF in children with IgE-mediated or non-IgE-mediated cows milk protein allergy found that 97% (126/130) tolerated EHF.^{5–7} There is a small group of children with multiple food protein hypersensitivity some of whom do not tolerate EHF; however, it is unclear what proportion of the total cows milk allergic patients this comprises. A hospital-based specialist paediatric allergy unit identified approximately 60 such patients over 10 years with suspected late

adverse reactions to formulae including cows milk, soy and protein hydrolyzate.⁸ As about 5% of cows milk allergic children are not improved by extensively hydrolyzed formula if PBS guidelines were followed one might expect the use of EHF to be approximately 20 times of the use of AAF. The differences in prescribing are unlikely to relate to variations in the prevalence of cows milk or combined milk, soy protein and hydrolyzate intolerance as the prevalence of allergic disease does not differ markedly between Australian States.⁹ It would also seem unlikely that 80% of the cases of combined cows milk and EHF intolerance are being missed in Western Australia in view of the numbers of paediatricians and paediatric allergists in that State.

A longitudinal analysis indicates a marked rise in prescription of AAF commencing in 2001. This may reflect both an increased awareness and the increasing prevalence of allergic disease. It is also possible that the increase in prescription of AAF commencing in 2001 may be partly related to the withdrawal of two of the EHF preparations (Nutramigen and Pregestimil) in 2001 resulting in the substitution by AAF rather than another EHF preparation. This increase in use of AAF is far greater than the rate of increase of allergic disease and does not appear to parallel recommendations in the paediatric literature (Table 2). Papers describing the use of EHF for the treatment and prevention of allergic disease began to appear in the late 1980s^{16–18} and in 1989 the American Academy of Paediatrics Stated that hydrolyzed formula may be useful both for prophylaxis and elimination of symptoms in sensitized infants¹ and reconfirmed this opinion in 2000.¹³ In 1993 the European Society of Paediatric Allergy and Clinical Immunology published a position paper recommending EHF for treatment of IgE mediated cows milk allergy and prevention of cows milk allergy and associated atopic dermatitis in high risk infants.⁴ In 1997 an editorial in the *Journal of Paediatric Gastroenterology and Nutrition* suggested that exclusive feeding with EHF for 6 months might prevent allergic disease in early life.¹⁰ In 1998 a Cochrane review recommended a 1-week trial of a hydrolyzed hypoallergenic formula for infantile colic,¹¹ however, prescription for this indication has been specifically prohibited in the current PBS guidelines. A further position paper in 1999 published from the *European Society of Paediatric Allergy and Clinical Immunology* and the *European Society of Paediatric Gastroenterology* again recommended that children at high risk of allergic disease be

Table 2 Authoritative recommendations on the use of hypoallergenic formulae

1989	Position paper	Casein and whey hydrolyzates may be useful in the prophylaxis or treatment. ¹
1993	Position paper	Hydrolyzed formula for IgE-mediated cows milk allergy and for prevention of cows milk allergy and associated atopic dermatitis in high risk infants. ⁴
1997	Editorial	Preliminary data suggest exclusive feeding for 6 months with hydrolyzed formula for prevention of allergic disease. ¹⁰
1998	Cochrane review	A one week trial with a hydrolyzed formula recommended for colic. ¹¹
1999	Position paper	Infants with cows milk protein allergy who are not breast fed should receive a dietary product with highly reduced allergenicity based on extensively hydrolyzed protein. ¹²
2000	Position paper	Treat cows milk allergy with extensively hydrolyzed formula. Infants at high risk for developing allergy, may benefit from extensively hydrolyzed formula or possibly a partial hydrolyzate formula. ¹³
2003	Cochrane review	For infants at high risk of allergy who cannot be exclusively breast fed, there is some evidence that prolonged supplementation with hydrolyzed formula reduces the risk of allergy. ¹⁴
2004	Position paper	For infants with a high risk for allergic disease if supplement is needed extensively hydrolyzed formula is recommended until 4 months of age. ¹⁵

given EHF¹² and a similar opinion was restated in 2004.¹⁵ A Cochrane review in 2003 recommends the use of hydrolyzed formula in high risk infants for the prevention of atopic disease but highlights that it is unclear whether extensively hydrolyzed formula have benefits over partially hydrolyzed formula.¹⁴ Thus recommendations by authoritative bodies do not support the preferential use of AAF formula over EHF revealed in the present study.

It is possible that AAF is prescribed for infants with symptoms of atopic disease such as atopic dermatitis with the aim of both treating the dermatitis and for prevention of further development of atopic disease. Apart from those children with cows milk allergy who do not tolerate EHF there is no clear evidence that AAF are more effective than EHF for the treatment of other manifestations of allergic disease. Two studies which examined the benefit of AAF and EHF formula for children with atopic dermatitis showed no significant benefit for AAF as compared with EHF.^{19,20} There are no studies which compare the use of AAF with EHF for prophylaxis of allergic disease. None of the position papers editorials and Cochrane reviews listed in Table 2, recommend AAF in preference to EHF for the primary prevention of allergy.

Why are AAF formulae used more extensively than EHF? As a proportion (approximately 5%) of cows milk protein intolerant children may not respond to EHF, it is possible that practitioners feel that the use of a formula which eliminates this possibility of non-response is a preferable therapeutic alternative. Another possibility to be considered is that the marketing of one brand of AAF to Australian paediatricians as 'the simple solution for food allergies' has influenced them to favour its use over that of EHF. An additional issue may be a perception that AAF is the formula of choice where allergic reactions involve the gastrointestinal tract. However, a recent text book on paediatric allergy recommends EHF as the treatment of first choice for dietary protein proctocolitis, enterocolitis and dietary protein enteropathy.²¹ AAF are only recommended as first line treatment for diseases with significant eosinophilic infiltration such as biopsy proven eosinophilic oesophagitis and eosinophilic gastroenteritis.²²

It seems that the prescribing population is not comfortable with the PBS guidelines for the use of hypoallergenic formulae although these guidelines in recommending the use of EHF before AAF appear to be in line with authoritative statements and position papers. That prescribing practices appear to be significantly at odds with PBS guidelines and that there are significant regional differences suggests that re-examination of both the PBS guidelines and the knowledge and perceptions of the prescribing community in the light of the best available evidence is required.

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