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Update on Food Allergies

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Non-IgE mediated food allergies
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Abstention or tolerance?
The importance of lactose
New discoveries on food allergies

Nowadays, allergies are one of the most common diseases. In infancy and early childhood, these are mainly adverse reactions to food. A burden on the child, their parents and their carers.

Around 20% of the population have indicated that they are affected by one or several allergies or intolerances to food. Studies have shown that they affect 1–4% of adults and around 6–8% of infants and small children, of which 2–3% concerns cows’ milk protein. Other studies have suggested that this value is up to 5%. Recent data from the EuroPrevail Study shows that Germany is affected 0.5% less.

Gastrointestinal symptoms affect up to 50% of patients. These are typical for non-IgE mediated allergies, for which finding proof is much more complex and can lead to delayed or false diagnoses. A specially developed tool, the CoMiSSawareness tool should, in the case of unclear symptoms, bring attention to a possible food allergy.

It is important to note that food allergies can also affect breastfeeding children, as allergens can be ingested through the mother’s milk. This also applies to Cows’ Milk Protein Allergies (CMPA).

An already classic study indicated that severe colic is an effect of a CMPA – this disappeared as long as the breastfeeding mother stopped consuming cows’ milk (Fig. 2: Jacobsson 1978). Since then, this reaction has been confirmed many times.

Editorial

Dear readers,

The number of those affected by allergic diseases have increased massively over the last few years. Infants and small children are most affected, which, for the small patients as for their parents, is a burden with a profound impact on all areas of life. Allergic reactions to foodstuffs are most common during the first weeks and months of an infant’s life, during which an allergic reaction to cows’ milk protein has the greatest impact.

There has been a fundamental paradigm change in the approach to preventing these diseases: It was believed that avoiding all allergens, such as cows’ milk, eggs, peanuts and wheat, for as long as possible was fundamental, and in the meantime, conducting more and more early exposure tests to develop a tolerance to all suspect foods. International long-term studies have documented the success of such methods, which led to numerous recommendations for allergy prevention being changed.

There is continuously more research being carried out on this complex topic, on everything from early detection to effective treatment for food allergies and intolerances. On the next few pages, we would like to present some recent findings and their practical applications.

I hope you enjoy the articles and find them inspiring – happy reading!

Dr. med. Mike Poßner
Medical Director Europe
Nestlé Nutrition Institute

Update

Symptoms

- Restlessness, frequent crying
- Distended abdomen, meteorism
- Spitting up or vomiting
- Refusing to drink
- Diarrhoea, partially bloody
- Failure to gain weight
- Seldom, but not to be ruled out: Constipation

Allergies and breastfeeding

It is important to note that food allergies can also affect breastfeeding children, as allergens can be ingested through the mother’s milk. This also applies to Cows’ Milk Protein Allergies (CMPA).

An already classic study indicated that severe colic is an effect of a CMPA – this disappeared as long as the breastfeeding mother stopped consuming cows’ milk (Fig. 2: Jacobsson 1978). Since then, this reaction has been confirmed many times.

1: Cows’ Milk Protein Allergy (CMPA)

- Anamnesis, examination findings and laboratory diagnosis
- Diagnostic elimination diet (with eHF or AAF)
- Late reaction (e.g. atopic eczema): 1–2 weeks
- Gastroint. Symptoms (e.g. diarrhoea, vomiting): 2–4 weeks
- IgE-specific negative or clear immediate reaction
- Improvement of clinical symptoms
- Standardised oral provocation
- Negative
- Specific elimination
- Positive
- No improvement of clinical symptoms
- No diet
- Negative
- Positive

Kolotko S et al. 2009
Allergies

In infancy, cows’ milk, soya and eggs (not orally, but ingested through the skin) can trigger allergies and for small children, also wheat, nuts and fish. It is important to differentiate between IgE mediated allergies – which mainly present in an immediate gastrointestinal reaction – and those that are non-IgE mediated. Protein-induced proctocolitis and Food Protein-Induced Enterocolitis Syndrome (FPIES) and enteropathy can appear in these cases. Not infrequently but in one case IgE mediated and non-IgE mediated forms appeared.

Management

The most important diagnostic methods after anamnesis are symptom and nutrition diaries for the child – and for breastfed children, also the mother! – examination of blood count according to IgE and specific IgE. This naturally allows no statement to be made on non-IgE mediated food allergies. The method of choice is therefore an elimination diet and subsequent provocation testing. If a food allergy is ascertained, elimination and then administration of special foods such as extensively hydrolysed formula (eHF) or less frequently, of amino-acid based formula (AAF) is necessary. To confirm a diagnosis, re-exposure to an allergen after a few months is necessary (see Fig. 1).

A study on breast milk-associated allergic proctocolitis (Lake, JPGN 2000) can also be applied in the case of other food allergies: 95 fully breastfed infants were examined retrospectively. The symptoms comprised blood-tinged stools, partially painful passing of stools and mild eczema as well as some diarrhoea. The majority were subjected to elimination of cows’ milk or egg on the part of the mother, the rest found success with special formulas (11.6% – of which 7.4% were on eHF and 4.2% on AAF).

Prognosis

The positive aspect of food allergies is that, in the large majority of cases, they are limited in time. For non-IgE mediated forms, the prognosis is even better, as after one year, 100% of those affected lost their allergy, and for those affected by a IgE mediated allergy, this was 56.5% (Shoemaker et al., EuroPrevall, 2015).

Conclusion

- Gastrointestinal symptoms such as colic, vomiting, diarrhoea and dysphagia can be an effect of a food allergy.
- For infants, this is often due to a Cows’ Milk Protein Allergy (CMPA).
- Food allergies - including CMPA (!) – can also appear in breastfed children.
- In the case of primarily gastrointestinal symptoms, there is usually no ‘typical’ IgE mediated allergy.
- Allergy despite unremarkable ‘allergy test’ (IgE testing) >> Non-IgE mediated.
- Treatment by allergen avoidance, application of therapeutic formulas (extensive hydrolyze, amino acids) and, if necessary, medicine.
- Current allergy prevention guidelines:
  - exclusively breast-feeding (4 months),
  - no delayed introduction (after 5 months) to solid foods
  - and no early introduction to solid foods.
- Good prognosis for most non-IgE mediated food allergies.

The presentation is based on a report by Prof. Stephan Buderus, to be found online here:


2: Colic as a manifestation of a cows’ milk allergy

Crying (hours/day)

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Jacobsson et al., Lancet 1978
CoMiSS – important aid for CMPA

An international group of experts has developed a special CoMiSS symptom score, which improves cognition of a Cows’ Milk Protein Allergy (CMPA). It can also substantiate changes in symptoms during treatment.

Diagnosing a CMPA is always a challenge because the symptoms are mainly unspecific. Therefore, the patient’s path to a correct diagnosis is often delayed (Koletzko S, 2015).

The CoMiSS symptom score is not an instrument for diagnosis, but should raise awareness of the possibility of a CMPA. It also allows the development of symptoms during treatment to be evaluated and quantified.

This was demonstrated in a summary of three separate clinical studies. The patients had very similar characteristics, the average age was 2.5 months, the majority had a high CoMiSS score at the beginning (median = 13), which sank to a median value of 5 after 1 month of elimination and using extensively hydrolysed therapeutic formulas. However, the children were at risk of a positive provocation test (OR 0.83; 95% confidence interval).

The data suggests that the changes in CoMiSS on the basis of 1 month of CMPA symptoms can be predicted, in light of the outcome of a provocation test.

When to introduce allergenic solid foods

Abstention from possible allergens such as cows’ milk, eggs and peanuts, for as long as possible, as well as delaying the movement to solid foods, have been measures for allergy prevention up until now. This approach has fundamentally changed.

In the last few years, different studies have been conducted to find the ideal point in time for introducing foods that are considered to be allergens. The results show that there is no reason for delaying the introduction of such foods. The current recommendation is therefore to introduce these foods after 4 months. However, three recent studies have highlighted that some children are sensitised before the first exposure to food allergens (Palmer, 2017). Therefore, future studies should focus more on the prevention of sensitisation at such young ages than on the introduction of solid foods.

Observational studies also show that the introduction of solid foods before 4 months is linked with an increased risk of allergies. However, the results of two recent studies (DIPP cohort and PASTURE/EFRAIM cohort) could be misinterpreted to the effect that believing that the feeding infants solid foods before 4 months has a positive effect on the development of immunotolerance. Although both of the studies do not rule out reverse causality, it is recommended to keep to the existing guidelines of the ESPGHAN and AAP, as long as no randomised, controlled intervention studies suggest a different procedure (Heinrich, 2014): Solid foods should be introduced between 17 and 26 weeks.


Until this point, such quantifiable data did not exist. A prospective validating study is still required. CoMiSS can be used by doctors and experts as a helpful awareness tool for CMPA.
“With the **Prevall Study**, we could demonstrate **clear differences in the frequency of Cows’ Milk Protein Allergies**”

**Professor Beyer, food allergies, especially adverse reactions to cows’ milk protein, frequently arise in infancy. The recent EuroPrevall study, which you of course worked on, shows differing results in the different participating European countries. Is there an explanation for this?**

That is a very interesting question. The meta-analysis had already given indications that the frequency of occurrence of cows’ milk allergies can differ greatly from country to country. The question remains, however, whether the differing study designs were responsible for such differences. The EuroPrevall study was first conducted to investigate the frequency of food allergies with the same study design in each of the 9 European countries. In total, 12,049 newborns were included in the study, and then followed up 2 years later. The study was funded by the European Union. Even then, we could demonstrate a clear difference in the frequency of cows’ milk allergies, with Holland the most affected and Greece the least affected. The causes for this are now being investigated.

**In general, the numbers of recorded cases were significantly lower than expected. Did that surprise the authors?**

We went into the study without any presupposed outcomes. We already knew that a lot more parents believe that their child has a cows’ milk allergy than has actually been confirmed. These children often have problems with their skin, their respiratory system or the gastrointestinal tract and, in the case of a suspected cows’ milk allergy, a differential diagnosis is important. Alongside indications of sensitisation through blood or skin tests, an oral provocation test using cows’ milk can confirm a cows’ milk allergy. This process was applied in the study, so that we had a really reliable diagnosis. Our data concerning England could recently be confirmed by an English study.

**The EuroPrevall study is the largest study on the topic. In the near future, will there we a similar fundamental screening with participants from other nations?**

We would be delighted if the same study design were also to be used in other countries to enable a real comparison. There is already very good data concerning other countries, especially Australia and the Scandinavian countries, but a direct comparison is difficult, because the study designs are different.

**In the last few years, there has been a profound change in the prevention of food allergies from avoidance to developing tolerance. Is this already being done in practice or do you think more explanatory work is necessary?**

Large numbers of studies have already been conducted on the topic of preventing food allergies, especially concerning egg and peanut allergies. The biggest problem, however, is the generalisability of study findings. A study in England has shown that the chance of developing an allergy to peanuts could be reduced by 80% if a child with a high risk of developing such an allergy is exposed early to products containing peanuts. To what extent these results can be used in other countries that barely eat peanuts and also have a small population allergic to peanuts, such as Greece, is yet to be clarified. Similarly, regarding egg allergies, there are still no uniform recommendations and there are even indications that early exposure without previous allergy tests could possibly lead to even more allergic reactions.

**When it comes to gastrointestinal symptoms, the cause can be a non-IgE-mediated food allergy. However, these are famously hard to diagnose. What do you recommend in practice?**

If a non-IgE-mediated gastrointestinal intolerance is suspected, a paediatric gastroenterologist must be included in the process of diagnosis. The guidelines on food allergies also stipulate this. In these cases, important diagnostic procedures include elimination and provocation and if necessary, endoscopic procedures.

**Do you have any words of comfort for the parents of affected infants and children?**

Well, an allergy to cows’ milk has a very good prognosis. In the EuroPrevall study we could demonstrate that 69% of children with cows’ milk allergies developed a natural tolerance and so therefore could stomach cows’ milk again.
Managing a food allergy

For food allergies, a strict elimination of respective allergenic foodstuffs is important. For this reason, there are special formulas for infants and small children that contain sufficient amounts of all of the nutrients required for healthy development.

Extensively hydrolysed milk formula for infants (eHF) In eHF, the proteins from cows’ milk have been split up into peptides that have a low allergic potential. These can be stomached easily by most people affected. In contrast to eHF formulas, partially hydrolysed formulas (pHF) cannot be used for prevention or for treatment, because they will still be recognised as allergens by the immune system.

Amino acid based formulas (AAF) are used in the case of severe symptoms or obvious intolerance reactions to eHF. They do not contain proteins derived from milk, such as peptides, but rather exclusively synthetically manufactured free amino acids, the non-allergenic building blocks of protein.

If fully breastfeeding, strictly avoiding allergens in the mother’s diet is necessary. Despite this, mothers should be encouraged to continue breastfeeding.

Management Algorithms (Fig. 1) can be found here www.nestlehealthscience.de/marken/aaa-fachkreisangeh hoeverige/entscheidungsbau f-ernahrungstherapie

Recovering the cost of special formula

For food allergies, a diet of elimination is the method of choice. Therefore, special formulas are necessary and pursuant to the Medicinal Products Directive (Chap. I §§ 18–23 – www.gba.de/informationen/richtlinien/3/) are therefore are prescribable, paid by statutory health insurance.

This is on the condition that a modified normal diet or any other medical, nursing or nutritional therapy recommended measures for the improving the infant’s nutrition are not sufficient. Alongside Foods for Special Medical Purposes, used as the only source of nutrition, FSMPs with highly hydrolysed proteins or amino acids for infants and small children with cows’ milk protein allergies or with multiple food allergies should be prescribable.

If these special products are a burden on the pharmaceutical budget of the practice, it must be ascertained whether the diagnosis as a special prescribed need can be authorised. The specific requirements should be clarified with the responsible Association of Statutory Health Insurance Physicians.
A recent study, alongside other data, suggests that peanut allergies can be prevented through early exposure to products containing peanuts.

Since 2008, the American National Institute of Allergy and Infectious Diseases has worked together with other organisations to develop clinical recommendations for diagnosis and management. Three supplementary recommendations for the prevention of peanut allergies have been developed on the basis of new data.

The topic in discussion brings together the definition of groups at risk, appropriate testing (measuring specific IgE, skin prick-tests, oral provocation) and the time at which peanut products should be introduced into the diet.

### Summary of the supplementary recommendations 1, 2 and 3

<table>
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<tr>
<th>Recommendation</th>
<th>Childhood criteria</th>
<th>Recommendations</th>
<th>Earliest age for exposure to peanuts</th>
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<tr>
<td>1</td>
<td>Severe eczema, egg allergy or both</td>
<td>Evaluation through sIgE measurement and/or skin prick-test, if necessary oral provocation</td>
<td>4-6 months</td>
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<tr>
<td>2</td>
<td>Mild to slight eczema</td>
<td>Exposure to peanut products</td>
<td>Approximately 6 months</td>
</tr>
<tr>
<td>3</td>
<td>No eczema or food allergies</td>
<td>Introduction of peanut products in accordance with family preferences and cultural use</td>
<td></td>
</tr>
</tbody>
</table>


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A **cereal** that can be easily tolerated to fulfil requirements in the case of allergies

A strict elimination diet is prescribed for food allergies, but that carries the risk of an essential nutrient deficiency. The tolerability of a specially developed cereal was investigated.

Sinlac is appropriate for moving children with food allergies to solid foods, and is made of carob flour and non-hydrolysed rice proteins. Pre-clinical trials have demonstrated the anti-allergic properties of polyphenols; clinical trials showed that apple polyphenols (AP) reduced the occurrence of the symptoms of allergic rhinitis.

A randomised clinical trial proved the tolerability of Sinlac with or without AP. Typical allergenic foods were compared – wheat, milk, eggs, potatoes ( = WMEP) – using participants between 4 and 40 months with severe food allergies.

The occurrence of allergic symptoms after administration of foods in 30-minute-intervals was recorded and observed over the following 24 hours. Of 51 participants, 13 were analysed for Sinlac and 12 for Sinlac AP (PP Population – Fig. 1). Both Sinlac variants (with or without AP) were tolerated significantly better than other allergy-triggering foods.

In total there were 83 allergic reactions, that are not associated with the product in study. The main allergen was wheat in 11.8% of participants, 7.8% potatoes, 23.5% milk and 21.5% egg. Sinlac and Sinlac AP caused inflammatory skin irritation for only 2 participants (despite negative values for rice and carob specific IgE); both trial participants did, however, also react to eggs.

Due to the low risk of allergy, Sinlac is a safe alternative for infants with food allergies (except for those with a rice or carob allergy). The benefits of an AP supplementation is to be found in further studies.


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### 1: Appearance of allergic reactions

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<td>Allergic reaction</td>
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<td></td>
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<td>Yes</td>
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<tr>
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<td>51% (26)</td>
<td>49% (25)</td>
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<tr>
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<td>51</td>
<td>98% (50)</td>
<td>2% (1)</td>
<td>25</td>
</tr>
<tr>
<td>Sinlac AP</td>
<td>51</td>
<td>98% (50)</td>
<td>2% (1)</td>
<td>25</td>
</tr>
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</table>
Calcium and lactose deficiency caused by allergy-free diets?

In the case of a Cows’ Milk Protein Allergy (CMPA), severe gastrointestinal disorders and multiple food allergies in infancy, a switch to special formula is prescribed as a rule. However, this can have an effect on growth.

Most specialised formulas contain distinctly more protein than formula for healthy infants, but still a reduced nitrogen uptake and retention. From this, it can be concluded that the quality of protein is not equivalent to that of intact protein. While high levels of protein in conventional infant formulas can be a risk factor for obesity in later life, it is a prerequisite for age-appropriate growth in therapeutic foods.

Special formulas – including when the mother is still breast-feeding – can only ensure a sufficient supply of nutrients in the first months of life. The increasing need for many micro-nutrients is to be compensated by solid foods, which is not always possible for infants affected by allergies.

The problem is exemplified with calcium. The lack of lactose in many therapeutic formulas is also critically examined, as it has many advantages and an important influence on the development of intestinal flora (see box).

The necessary conversion to special formula does not guarantee – depending on age and nutritional status – a sufficient supply of macro- and micro-nutrients. Cooperation with a nutrition expert is therefore recommended.

Reese I, Schäfer C: Use of special therapeutic diets in infancy – fulfilling changing needs and requirements. Allergology, 36, 2013: 1–8

After fat, lactose is the most important source of energy for breastfeeding infants. Breast milk contains 8.2–10.4 g/100 kcal and therefore makes up 40% of energy content (EFSA, 2014). In the small intestine, lactose is broken down by the enzyme lactase into absorbable building blocks, glucose and galactose.

- Lactose improves the absorption of calcium and its use in mineralising the bones. (Abrams et al., 2002).
- Lactose encourages the growth of bifidus bacteria in the colon and has probiotic qualities (Haschke et al., 1997).
- Breast milk contains lactose although it is no longer active or only slightly active in the majority of the adult population worldwide. This indicates their particular importance for infants, likely to go far beyond their role as a source of energy and the recently-discovered functions of lactose.

In their recent publication, the EFSA expressed the opinion that: Infant formula and follow-on formula for healthy infants should contain lactose as a carbohydrate, modelled on the mother’s milk.

EFSA: Scientific opinion on the essential composition of infant and follow-on formulae. EFSA Journal 2014; 12(7):3760