Eczema in infants

The role of dietary manipulation

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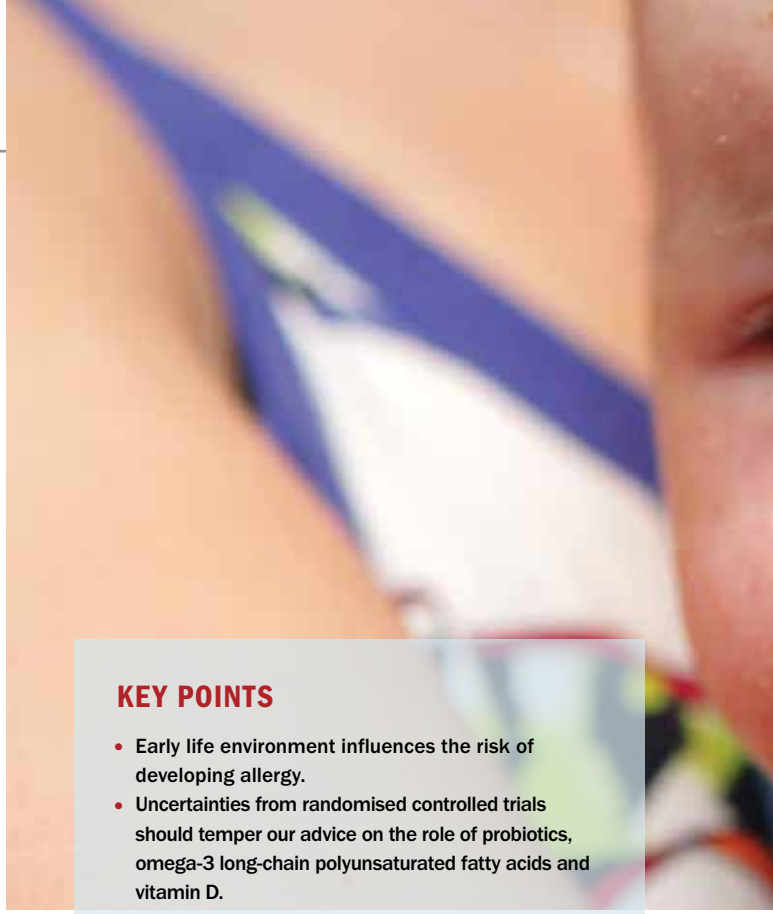
The internet and the health and wellbeing industry have multiple suggestions for dietary modification to prevent or treat eczema. Our evidence-based advice can help clinicians and parents discern between benefit and detriment of various dietary measures for the prevention and treatment of eczema in infants and children.



KEY POINTS

- Early life environment influences the risk of developing allergy.
- Uncertainties from randomised controlled trials should temper our advice on the role of probiotics, omega-3 long-chain polyunsaturated fatty acids and vitamin D.
- There is no role for specific serum IgE tests (previously called radioallergosorbant or RAST tests) or skin prick tests in most infants with eczema alone.
- Delayed introduction of foods and dietary exclusion may have a restricted role in treating some infants with eczema.
- Unnecessary dietary exclusion increases the risk of developing food allergy.
- Specialist referral is recommended if dietary modification is being considered in infants.

Atopic dermatitis or eczema is a chronic, itchy, inflammatory skin condition that is often associated with atopy.[1] Eczema is highly prevalent in Australia with a 25% cumulative incidence among 12-month-old infants in Melbourne.[2] Dietary modification is of interest because a child's early life environment influences the risk of developing allergy.[3] In addition, dietary modification is attractive for parents of infants with eczema because it appears to address an underlying 'cause', is nonmedical, presumed harmless and empowers parents to manage their children's eczema with independence from the medical profession. The health and wellbeing industry and complementary medicine practitioners are key stakeholders in this market. Unfortunately, there is also risk of harm from unnecessary or ineffective diet strategies.

Parents often present to their GP for advice regarding the role of diet in the prevention and treatment of eczema. This article reviews high-quality evidence from randomised controlled trials (RCTs) and meta-analyses of these RCTs regarding dietary supplementation or elimination during pregnancy, lactation and infancy. It also highlights the significant change in practice in recent years as a result of the Learning Early About Peanut Allergy (LEAP) study and other studies.[4]

Primary prevention during pregnancy

Supplementation with probiotics

- Probiotics may have a role in reducing the risk of infantile eczema.
- Probiotics are probably ineffective if administered during pregnancy alone but may be effective if supplementation is continued throughout lactation and/or early infancy.
- *Lactobacillus rhamnosus* is the most common probiotic used in this context.
- There is low risk of harm from probiotic interventions.

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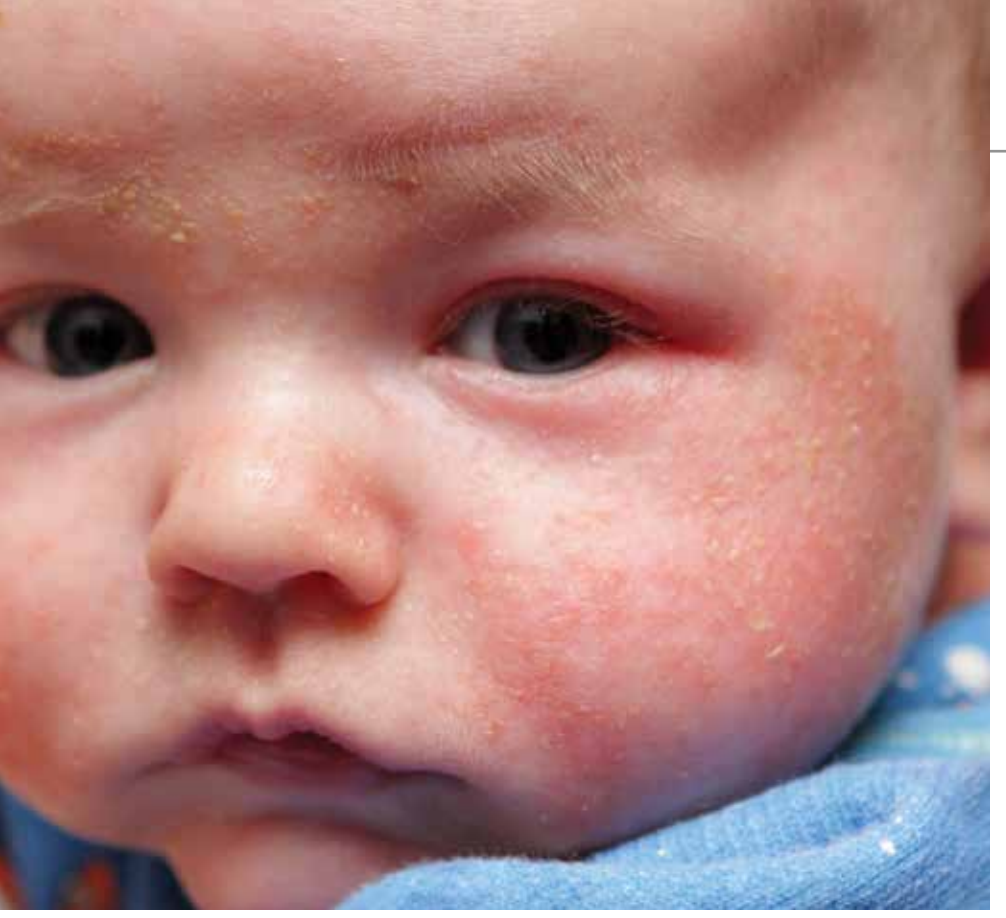

Mechanism

Children with eczema have less diverse skin flora and this appears to be more restricted during flares of disease. However, whether this relationship is causal is unclear.[5] Probiotics are given with the aim of improving gut bacterial diversity but may have other immunomodulatory effects on the baby. The clinical relevance of these other immunomodulatory mechanisms has yet to be verified.

Evidence

Some qualification is required regarding the evidence for probiotics in pregnancy. The only trial of probiotic supplementation in mothers during pregnancy alone did not show a reduction in eczema in their children.[6] This was a large, Australian trial of women at high risk of having atopic infants.

When multiple trials were evaluated in a meta-analysis, women taking probiotics in pregnancy had infants with a reduced incidence of eczema.[7] However, these studies also involved probiotics administered directly to the infant or to mothers during lactation in addition to during pregnancy. As such, the relative importance of probiotics during pregnancy is unclear.

Although it might be attractive to take any probiotics regardless of the species, especially in more enjoyable and natural ways such as eating yoghurt, some trials comparing two different probiotics showed that only some species were effective.[8] Although all probiotic species in these studies were safe, we recommend supplementation with *L. rhamnosus* during pregnancy because it is supported by the most data and was included in most trials that found protective effects. Doses varied between 5 and 50 billion colony-forming units and commercial products typically contain 20 billion colony-forming units.

Supplementation with omega-3 long-chain polyunsaturated fatty acids (LCPUFA)

- **There is no evidence to recommend supplementation with omega-3 LCPUFA in pregnancy for the prevention of eczema in infants.**
- **Omega-3 LCPUFA may reduce the risk of eczema with concomitant sensitisation. However, the clinical significance of such an intervention is uncertain.**
- **Although safe, any potential benefits have to be balanced against the significant pill burden.**

Mechanism

Omega-3 long-chain polyunsaturated fatty acids (LCPUFA) have anti-inflammatory properties. They are thought to alter lipid components in cell walls used to produce prostaglandins, but a clinically relevant mechanism for reducing the risk of eczema has not been established. Some studies have implicated metabolites of LCPUFA in activating mast cells.[9]

Evidence

Three large trials of fish oil in pregnancy did not identify a reduction in eczema incidence in infants.[10-12] These included a large Australian study of women at high risk of having atopic infants.[12]

Trials of omega-3 LCPUFA have been conducted in the prevention of other disorders, but it is not within the scope of this article to discuss all allergic outcomes in trials of fish oil. However, some studies did identify a reduction in allergic sensitisation to egg and, consequently, a reduced proportion of children with eczema and skin sensitisation.[10,11] This is occasionally labelled 'atopic eczema', which is an unhelpful classification in paediatrics, especially when the infants in these trials, by nature of their family history, are already 'atopic'. A preventive strategy that reduces the prevalence of 'atopic eczema' but not eczema in general has limited value at a population level.

Although fish oil is considered safe in pregnancy, the theoretical risk of increased bleeding was not specifically tested in these trials. Any potential benefits must be weighed against the large pill burden, fishy aftertaste and potential heartburn and diarrhoea. As such, we do not recommend fish oil supplementation in pregnancy for the prevention of eczema alone.

Dietary exclusion

- **We strongly recommend not excluding any allergenic foods from the maternal diet during pregnancy.**

A meta-analysis of two small studies of women at high risk of having atopic infants and who avoided eating allergenic foods during pregnancy did not show reduced eczema rates.[13] One of the studies showed reduced maternal weight gain during pregnancy in mothers on the avoidance diets.[14] Although the current evidence is poor, it indicates that risks associated with dietary exclusion in pregnancy outweigh any potential benefit.

Primary prevention during lactation

Supplementation with probiotics

- **Probiotics are probably ineffective in reducing the incidence of eczema in infants if taken by the mother during lactation alone but may be effective if supplementation is also given to the mother during pregnancy and/or to the infant in early infancy.**

The evidence for probiotics during lactation is similar to that for pregnancy. The only trial of probiotics during breastfeeding alone did not show a reduction in eczema incidence among infants.[15] This trial was small, included healthy rather than atopic women and used a different *Lactobacillus* species to the other studies.

Two meta-analyses of RCTs of probiotics in lactation (in addition to probiotics during pregnancy or probiotics in infancy) showed a reduction in eczema incidence.[7,16] Probiotics during lactation appear to be relatively important when comparing the effect sizes of probiotics in pregnancy, lactation and infancy.[7]

Supplementation with omega-3 LCPUFA

- **Maternal omega-3 LCPUFA supplementation during lactation does not reduce the risk of eczema in the infant.**
- **Any potential benefits have to be balanced against the significant pill burden.**

Only one trial of fish oil in pregnancy extended maternal supplementation into lactation. This trial did not show a reduced incidence of eczema in infants.[17,18] However, in this study fish oil was associated with a reduced risk of IgE sensitisation to egg by skin prick test and, consequently, a reduced risk of atopic eczema.[17,18] Again, the clinical significance of reducing the number of patients with IgE sensitisation but not eczema is uncertain. There are conflicting results about whether omega-3 LCPUFA supplementation influences other allergic outcomes, and further trials are being conducted that include supplementation during lactation. Currently, there is not enough evidence to support recommending fish oil during lactation to reduce the risk of eczema alone.

Dietary exclusion

- **We recommend continuing to eat allergenic foods during breastfeeding.**

The only trial of dietary exclusion during late pregnancy and lactation is limited by its small size, exclusion of important data, varying results across different time periods and high risk of bias.[13,19] As the data are low quality, we recommend that mothers continue to eat allergenic foods during lactation.

Treatment during lactation

Dietary supplementation

- **There are no studies of maternal dietary supplementation in breastfeeding for the treatment of established eczema in infants.**

Dietary exclusion

- **There is no evidence to recommend maternal dietary exclusion during lactation to treat established eczema in infants.**

A small trial of exclusively breastfed infants with eczema was conducted to assess the effect of maternal dietary exclusion in lactation. In this randomised double-blind placebo-controlled cross-over trial, there was no reduction in eczema area or severity when mothers excluded cow's milk or egg from their diet for four weeks.[13] Although data are limited, there is no evidence that maternal dietary exclusion during lactation improves eczema in infants.

Primary prevention in infancy

Supplementation with probiotics

- **Probiotics are ineffective if administered in infancy alone but may be effective in reducing the incidence of eczema if maternal supplementation is also given during pregnancy and/or lactation.**

The evidence for probiotics in infancy is similar to probiotics in lactation and pregnancy. A meta-analysis and a more recent trial in infants at high risk of allergy did not find that probiotics in infancy reduced the risk of eczema.[7,20] However, when these trials were combined with others that involved probiotics in either pregnancy or lactation, a decrease in eczema was noted.[7] The dose of *L. rhamnosus* for children is usually lower, at 5 to 10 billion colony-forming units daily.

Supplementation with prebiotics

- **Although prebiotics may be promising, studies in infants are too few and heterogeneous to recommend this intervention for the prevention of eczema.**

Mechanism

Prebiotics are simple, nondigestible carbohydrates such as galacto-oligosaccharides and fructo-oligosaccharides. They promote the growth of some commensal bacterial species such as *Bifidobacterium* species and can be fermented into short-chain fatty acids, which

have anti-inflammatory properties. As such, prebiotics may promote more gut diversity and tolerance than probiotics. Again, the clinical relevance of these mechanisms in reducing eczema is not established.

Evidence

Two large trials that compared prebiotic-supplemented extensively hydrolysed formula with cow's milk formula in infants at high risk of allergy produced differing results. One study showed a reduced risk of developing eczema and an increase in *Lactobacillus* and *Bifidobacterium* species in the stools of infants.[21] The subsequent, larger Australian Prevention of Allergy Through Cow's Milk Hydrolysate (PATCH) study did not show a significant difference in eczema incidence.[22] Given the conflicting results, currently there is not enough evidence to recommend prebiotics in infancy to prevent eczema.

Supplementation with omega-3 LCPUFA

- **There is no evidence that omega-3 LCPUFA supplementation in infancy reduces the risk of eczema or allergic outcomes.**

A meta-analysis of seven studies of infants given fish oil in infancy did not show a reduction in the incidence of eczema.[23]

Hydrolysed infant formula

- **The role of hydrolysed infant formula in the prevention of eczema is controversial with most authorities now concluding that it is not useful.**
- **The German Infant Nutritional Intervention (GINI) trial identified a reduced incidence of eczema with some hydrolysed formulas.**
- **However, until there is further evidence to corroborate this finding, we do not recommend hydrolysed formula for the prevention of eczema.**

The role of hydrolysed formula in reducing the risk of eczema is controversial. The greatest evidence to support hydrolysed formula comes from the GINI trial. This study compared different formulas at cessation of breastfeeding in infants at high risk of allergy. The formulas used were a partially hydrolysed formula from the whey fraction of milk (pHF-W), an extensively hydrolysed formula from the whey fraction (eHF-W), another extensively hydrolysed formula from the casein fraction (eHF-C) and ordinary cow's milk formula. At various time points, two of the formulas (pHF-W and eHF-C) were associated with either a reduced cumulative incidence of eczema or reduced point prevalence of eczema.[24] There is no mechanism to explain why this effect was observed in only two out of three of the formulas.

The reduced incidence of eczema was reproduced in a Singaporean study but not in a larger Australian study, both of which used the same brand of pHF-W as the GINI trial.[25,26] The PATCH study did not reproduce the GINI findings using a different brand of pHF-W.[22] Some may argue that not all pHF-W are alike and findings from the PATCH study need not discount those from the GINI trial.[27] However, it is also important to note that the pHF-W product used in the GINI trial has changed substantially over time. Due to greater degrees of hydrolysation, the current formula more closely resembles the ineffective eHF-W than the original pHF-W.[28]

The only other methodologically sound study of hydrolysed infant formula found a trend to reduced eczema incidence with eHF-C formula compared with cow's milk, but this was only statistically significant in one of five time points.[29] The uncertainty around eHF-C is academic as it is not commercially available in Australia.

Given these controversies, we do not recommend hydrolysed formula for prevention of eczema in infants unless further studies corroborate the GINI trial findings. This coheres with current Australian Society of Clinical Immunology and Allergy (ASCIA) guidelines on infant feeding and allergy prevention.[30]

Dietary exclusion

- **There is no evidence that dietary avoidance of allergenic foods in infancy reduces the risk of eczema.**
- **Early introduction and regular consumption of allergenic foods likely reduces the risk of food allergy, and unnecessary avoidance incurs risk of harm.**

Evidence

Two trials have compared the effect of egg avoidance and egg supplementation in infancy on the incidence of eczema. The first was the Australian Starting Time of Egg Protein (STEP) trial, which was a large study of infants at risk of allergy.[31] There was no reduction in eczema incidence in the avoidance group compared with the group who ate egg powder daily. The Beating Egg Allergy Trial (BEAT) had a baseline incidence of eczema of 26% but showed no reduction in the prevalence or severity of eczema at eight or 12 months in the avoidance group compared with the group who ate egg powder daily.[32]

Findings from the LEAP trial and the per-protocol analysis in the Enquiring About Tolerance (EAT) trial showed that early and regular consumption of peanut and egg reduced the risk of infants developing food allergy.[4,33] This may be a more important strategy in children with moderate to severe eczema compared with children in the general population at lower risk of developing allergy. As such, unnecessary avoidance of food in an attempt to prevent eczema could cause harm and is not recommended. The consumption of allergenic solid foods in infants at risk of allergy is also encouraged in the current ASCIA guidelines on infant feeding and allergy prevention.[30]

Testing for food allergy

Although the American National Institute of Allergy and Infectious Diseases have suggested that high-risk infants be screened for food allergies with skin-prick testing or serum specific IgE testing followed by food challenge, this practice is

not currently supported by ASCIA. Adopting such a screening practice would result in an overwhelming increase in referrals to allergy services in Australia.

Furthermore, because most sensitised infants identified by food allergy screening tests are tolerant of the foods, this could lead to an unnecessary and detrimental delay in the introduction of peanut and other allergenic foods. Most reactions in this age group are mild with a low risk of anaphylaxis. However, as the risk of anaphylaxis cannot be obviated completely, ASCIA's *Guide for Introduction of Peanut to Infants with Severe Eczema and/or Food Allergy* recommends a cautious graded introduction of allergenic solids, beginning with a smear on the lip, to further minimise the risk of severe reactions at introduction.[34]

Treatment in infancy

Dietary supplementation with vitamin D and other supplements

- **Vitamin D may be of value in children who are vitamin D deficient. The value of this intervention in the Australian environment is yet to be evaluated.**
- **There is no evidence to support using supplements other than possibly vitamin D for the treatment of children with established eczema.**

A study of Mongolian children with eczema flares in winter showed that vitamin D supplementation was associated with reduced eczema area and severity.[35] However, vitamin D deficiency is endemic in Mongolia and the relevance of these findings to the Australian context is debatable.

A meta-analysis of other dietary supplements such as fish oil, zinc sulfate, selenium, vitamin E, pyridoxine, sea buckthorn seed oil, hempseed oil, sunflower oil and docosahexaenoic acid did not support any of these interventions.[36] Similarly, there are no trials to support hydrolysed infant formula in the treatment of eczema in infants.

Dietary exclusion

- **There is no evidence that untargeted dietary exclusion has a role in the treatment of eczema.**
- **There is no role for specific serum IgE tests (previously called radioallergosorbent or RAST tests) or skin prick tests in most children with eczema alone.**
- **Delayed introduction of foods and dietary exclusion may have a restricted role in treating some infants and children with eczema and egg sensitisation.**
- **Unnecessary dietary exclusion increases the risk of developing food allergy and compromising nutrition.**
- **Ineffective dietary exclusion misdirects parents from conventional and effective therapies.**
- **Specialist referral is recommended if dietary modification is being considered in infants and children.**
- **If dietary modification is prescribed a dietitian can provide a valuable contribution to management.**

Evidence

A Cochrane review and a more recent trial in children with eczema showed that dietary exclusion of common allergens such as egg did not improve eczema.[37,38] It is possible that dietary exclusion may improve eczema in infants and children who are sensitised to a particular food. A small trial found egg exclusion reduced the eczema severity score and the eczema area in children with egg sensitisation.[39] This has not been reproduced in any subsequent study.

Testing

Although many parents request diagnostic tests for their children, there is no test to determine who will respond to dietary exclusion. Skin-prick testing and serum-specific IgE testing are designed for investigating IgE-mediated food allergy or aeroallergy. In children with eczema, allergy tests may detect sensitised children who might possibly benefit from an avoidance diet.[39] However, these tests are also nonspecific and much more likely to identify sensitised children who are completely tolerant to the food.

Furthermore, some children who react to food with an eczema flare may not have evidence of sensitisation, as the mechanism of the flare may more closely resemble a delayed-type hypersensitivity reaction that cannot be diagnosed on skin-prick testing or specific IgE testing. Testing can also cause harm because parents often misinterpret the results and pursue unnecessary dietary exclusions. As such, we do not recommend testing unless there is a history of IgE-mediated food allergy or aeroallergy.

Recommended management approach

The cornerstone of therapy for infants with eczema remains generous use of emolients and adequate use of topical corticosteroids, which must be instituted first to optimally control eczema. Children with severe, uncontrolled eczema are more likely to have significant day-to-day variations in severity, making it difficult to monitor the association of flares with food. This difficulty is well described in double-blind placebo-controlled food challenges. Although placebo reactions are uncommon (in 2.8 to 5.4%), the most common reaction to placebo is worsening eczema, and this is more common in children with poorly controlled eczema, in which fluctuating disease is part of the natural history.[40,41] To emphasise this difficulty, children with eczema and a history of food-induced flares reacted as often to placebo as to the food in one study of double-blind placebo-controlled food challenges.[42] Given these constraints, a history of food causing a flare of eczema is best taken when the

disease is optimally controlled with standard-of-care therapies. Furthermore, repeated exposures to the food with consistent flares of eczema should be noted to support a convincing association.

Given these complexities and the risk of harm from unnecessary dietary avoidance, we do not recommend prescribing diets for children with eczema in primary care without involving a specialist. If an avoidance diet is commenced with a specialist, it is important that close follow up within four weeks is arranged to assess the response. Given the potential harm, avoidance diets that are ineffective for an individual patient should not be continued for longer than four weeks.

Role of the specialist dietitian

For children who require dietary manipulation for any reason, a dietitian's input is useful in several respects:

- to identify sources of food antigens that may not be obvious in a child's diet;
- to ensure adequate growth and development is achieved during any period of dietary exclusion;
- to eliminate nonrequired food avoidances;
- to provide practical, affordable and sustainable strategies for food avoidance.

These important principles of dietetic management are addressed individually and with consideration of the child's age, developmental stage of feeding skills and social environment.

Conclusion

The GP plays a crucial role in assisting parents and carers to navigate through an overwhelming volume of information and misinformation regarding the role of dietary manipulation for children with eczema. Focusing parental attention on skin barrier protection, reducing infection and prompt management of flares with topical corticosteroids is key to gaining control of eczema. Although early life environment influences the risk of developing allergy, uncertainties from RCTs should temper our advice on the role of probiotics, omega-3 LCPUFA and vitamin D. Although dietary exclusion may have a restricted role in treating some infants and children with eczema, it is best performed in consultation with a specialist as unnecessary dietary exclusion increases the risk of developing food allergy. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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