

Review article

Factors influencing the incidence and prevalence of food allergy

Food allergy is an increasing problem in Europe and elsewhere and severe reactions to food are also becoming more common. As food allergy is usually associated with other forms of allergic sensitisation it is likely that many risk factors are common to all forms of allergy. However the potential severity of the disease and the specific public health measures required for food allergy make it important to identify the specific risk factors for this condition. Food allergy is unusual in that it often manifests itself very early in life and commonly remits with the development of tolerance. Hypotheses that explain the distribution of food allergy include specific genetic polymorphisms, the nature of the allergens involved and the unique exposure to large quantities of allergen through the gut. Progress has been made in developing more specific and testable hypotheses but the evidence for any of these is still only preliminary. Further collaborative research is required to develop an appropriate public health response to this growing problem.

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There is now substantial evidence that the prevalence of sensitization to common allergens has increased markedly over the last half century, with a consequent increase in the prevalence of atopic disease. There is also some evidence that sensitization to food has increased (1–3). This is important because reactions to food allergens can be particularly severe and there are implications for food safety.

There is no clear understanding yet of the reasons for the increase in sensitization, though there are several active lines of enquiry, nor is it clear whether sensitization to foods is a special case or whether the causes of food

allergy are the same as those for allergy in general. There is, however, circumstantial evidence that there may be specific causes of food allergy over and above the general causes of allergic sensitization.

This study reviews what is known about the causes of food allergy. We have avoided discussing the general causes of sensitization. For the purposes of this publication, the term food allergy is confined to IgE-mediated reactions to food and the study is strongly focused on findings from studies of humans. We refer to sensitization where there is evidence of IgE to a food, and allergy where there is also evidence of clinical response to the food.

Food allergy in relation to other atopic diseases

Atopic diseases, such as asthma, allergic rhinoconjunctivitis, atopic dermatitis and food allergy are closely related. Their manifestations often present in a characteristic sequence that has been named the 'atopic march' (4). The first signs of atopic diseases are usually food allergies and atopic dermatitis, with their greatest incidence during the first three years of life.

The natural course of food allergy is a dynamic process that is different for each allergen. The prevalence of disease is determined by the accumulation of new cases (incidence) and the removal of cases by the development of tolerance or, rarely, by death. Most infants with cow's milk allergy develop symptoms in the first year of life, often before one month of age, but about 85% become clinically tolerant by the third year of life (5). Hypersensitivity to hen's egg is more often recognized in the second year of life, and appears to be more persistent than cow's milk allergy, with approximately half of the patients becoming tolerant in 3 years and up to 66% of children in 5 years (6). As opposed to cow's milk and hen's egg allergies, peanut allergy tends to persist throughout adulthood. However, it has been reported in recent years that up to 20% of the peanut allergic children lose their allergy and there is some evidence, for peanut at least, that to maintain tolerance continual exposure of the immune system to the food may be necessary (7–9). Respiratory allergies such as asthma and allergic rhinoconjunctivitis often start after the age of 3 years and are usually associated with sensitization to inhalant allergens.

Family history of atopy is a strong risk factor for the development of atopic diseases as shown in several studies (10, 11). Having one atopic disease is a risk factor for developing another atopic disease. The mechanism behind this progress is poorly understood but many birth cohort studies describe this phenomenon. There are several studies that have indicated that identification of specific IgE to food allergens is related to expression of different atopic diseases or a risk factor for their development. Typically 20–40% children with atopic dermatitis have been reported to demonstrate sensitization to food allergens, with sensitization correlating with both the severity and age of onset of atopic dermatitis (12, 13) and clinically relevant food allergy is reported in a similar percentage of children with atopic dermatitis (AD) (12, 14).

There are many studies that have indicated a relationship between sensitization to food in infancy and consecutive development of atopic diseases such as atopic dermatitis (15, 16), asthma (17, 18), allergic rhinoconjunctivitis (15, 19) and sensitization to inhalant allergens (20, 21). Food allergy early in life seems to be a distinct predictor for developing atopic diseases later in childhood.

The sequential appearance of atopic diseases is unlikely to be because one disease causes the other but rather that

certain individuals are prone to manifest these atopic disorders under the influence of environmental factors within a particular time-frame.

Genetics and food allergy

The initial observation of an underlying genetic susceptibility to the development of allergic diseases stems from the investigation of first degree relatives of affected individuals (22–24). These studies showed that the prevalence of allergic disease in first degree relatives of affected individuals was significantly higher than in relatives of unaffected individuals. Subsequent studies involving asthma, hay fever, atopic dermatitis and allergic conjunctivitis, assessed over three generations and involving thousands of families, clearly indicated that each of these phenotypes are significantly overrepresented in relatives of atopic individuals. As these studies were performed in different populations, it is likely that the impact of genetics on expression of allergic disease is present in different geographical areas (25–27).

Frequently, reports of a strong positive association of one or several genetic markers with a particular allergic phenotype (e.g. asthma or atopic dermatitis) are subsequently counterbalanced by another report that fails to establish such an association (28). So far no asthma or allergy gene has been found in all tested populations although several gene associations have now been replicated more than 10 times (29).

Among the genes with a potential role in allergy investigated so far are genes within the cytokine cluster on chromosome 5q31; the α and β chain of the Fc ϵ RI receptor, IFN γ , STAT6 and interleukin (IL)-4R.

To date, there is no segregation analysis available nor is the population based sibling recurrence risk known. Furthermore, only a small number of studies have investigated the association between genetic traits (e.g. SNPs) and susceptibility to food allergy.

Woo et al. (30) assessed the promoter polymorphism (159 C/T) in the CD14 gene (cytokine cluster on chromosome 5) for a potential relationship with both atopic and nonatopic asthma as well as with food allergy. They found the –159 T allele to be more common among patients with nonatopic asthma and food allergy than among control subjects.

Kabesch et al. (31) described in a population of German school children a significant association between the homozygote for 420Lys polymorphism in SPINK5 and asthma while a Japanese group described a higher prevalence of food allergy in children with atopic dermatitis related to polymorphism in SPINK5.

Amoli et al. (32) investigated the genetic background of nut allergy in a Caucasian population by assessing the STAT6 2964 G/A 3' UTR polymorphism in a cohort of 71 nut-allergic, 45 atopic patients without nut-allergy and 184 healthy controls. They found that STAT6 G allele

frequency was significantly increased in nut allergy patients compared with blood donor controls but not in atopic patients without nut allergy.

Hand et al. (33) investigated a potential association of HLA-class I and HLA-class II alleles (HLA-A & B and HLA-DRB1 & DQB1, respectively) and the susceptibility to nut allergy. They found that the frequencies of two alleles (HLA-B and DRB1) were increased in nut-allergic patients when compared to atopic controls but not in comparison to 'non-allergic' blood donors.

Finally, Blanco et al. searched for underlying genetic traits in latex and latex-fruit allergic patients by assessing genetic markers in the HLA Class II, IL 4 and FcεRI-βca gene (34). They found that latex-fruit allergy was associated with loci HLA-DQB1*0201, DRB1*0301 and *0901, as well as with HLA-DR functional group E.

These results highlight some preliminary research into the genetics of food related allergy. A literature research indicates a wealth of studies related to asthma but nearly none to food-related disorders. A first goal could therefore be a description of the genetic epidemiology. If recurrence risks for food-related allergy are high enough some of the already known allergy genes may be retested. However, other genes may also be responsible for food related allergy.

Characteristics of food allergens

Given the large number of foreign proteins and the variety of potential allergens encountered by the gut immune system, the ability to avoid serious reactions to food must reside largely in the way that these potential allergens are handled in the gut, how they are presented to the immune system and how the immune system responds to them. Breakdown in the mechanisms for coping with these problems are likely to be the proximal causes of food allergy. In elucidating how food allergy might differ from inhalant or contact allergy, it is important to consider the particular properties of food allergens and how they interact with the immune system.

Most plant and animal food allergens belong to very few protein families indicating that certain conserved structures play a role in determining or promoting allergenic properties. Additionally, the level of exposure and the physico-chemical properties of an allergen itself contribute to the allergenic potential although the molecular basis for these effects is still not well understood. Consequently, the allergenicity of a food protein is determined by its membership of a certain protein family, its abundance, and the stability to processing and digestion.

The Pfam protein family database (35) whose version 19.0 contains 8183 protein families, classifies these on the basis of protein sequence homology which is related to conserved three-dimensional structures. The majority of

plant food allergens are either storage or defence-related proteins (36). The Pfam database was used to assign sequences of clinically proven food allergens to 27 protein families (37). Strikingly, only three dominating plant food allergen protein families/superfamilies were identified, the prolamin and the cupin superfamily, and the Bet v 1 family. Animal proteins are even less diverse and belong to just eleven Pfam families. The most important animal-derived food allergens belong to the tropomyosins, the calcium-binding EF hand proteins, the glycosyl hydrolase family, the lipocalins and the Kazal type serine protease inhibitors.

Many common food allergens are not easily altered either by heat, pH changes or by proteolytic digestion. They are therefore more likely to be presented to the immune system of the gut as well conserved three dimensional protein structures that the immune defences will recognize as potentially harmful foreign proteins. The major exception to this is the group of allergens that is related to the birch pollen allergen Bet v 1. Such proteins are found in many plants but are unstable when heated and easily digested. Primary sensitization to Bet v 1-like allergens is usually through contact between the Bet v 1 in pollen and the respiratory tract, and it is noted that cross-reactions with foods are often confined to oral allergy syndrome.

Regarding genetically modified foods (GM-foods), risk assessment for their sensitizing capacity is based on knowledge of the source of constituents/antigens and their possible cross-reactivity with known allergens. Database searches are used to compare new antigens with already well characterized allergenic products (38).

The gut immune system and food allergy

Hitherto, due to ethical and technical problems very little is known of the role of the gut immune system in humans, and most, if not all the observations have come from animal studies.

The exact route of primary sensitization to food allergens is currently unknown, but it is generally accepted that the gut immune system plays an important role in the genesis of adverse IgE-mediated allergic reactions to food components (39).

The gut represents the largest immunologic organ in terms of numbers of lymphocytes it can accommodate at any given time and without doubt is a unique immunological environment. Indeed, this branch of the immune system is exposed to a daily antigenic load that probably surpasses what the systemic immune system encounters in a life time. The gut epithelium is in direct contact with the external environment, including dietary components but despite this only a small percentage of individuals develop food allergy. This is related to the onset of oral tolerance to dietary protein, a state of active inhibition of immune responses to a specific antigen following exposure to that

antigen via the oral route (39). Although the gut immune system is pivotal in controlling immunity to food components, many basic cellular and molecular events involved in food (allergen)–gut interactions remain largely unknown. For example, very little is known of the route via which food components and allergens in particular, cross the intestinal barrier and reach the gut immune system. As the route of transport strongly influences the way the intestinal immune system reacts (40) this aspect of food–gut interaction is of fundamental relevance to the ensuing immune responses. The intestinal epithelial cells (IEC) take up and process food antigens mainly by fluid-phase transcytosis involving two functional pathways, one minor direct pathway without degradation and another major lysosomal degradative pathway (41). Recently, it has been shown in nonsensitized mice that the rapid *in vivo* transport of digested allergen (peanuts) occurs almost exclusively via Microfold (M) cells (42). This observation was surprising as it is known that M cells are relatively inefficient at transporting soluble protein. Although the real biological relevance of this transport remains to be fully understood, it is important to highlight that the M cell-mediated transport favours the initiation of an active immune response rather than the establishment of oral tolerance (43). In contrast, postsensitization transport of allergen across intestinal epithelial cells has received considerable attention in the past few years. Indeed, IL-4-dependent IgE-CD23 mediated transport of allergens has been identified in both animals and humans (44, 45). Finally, other cell types, such as dendritic cells (DCs), may actively participate in delivery of allergen to the gut immune system but this has not been determined yet.

The potential of DCs in regulating IgE allergen-specific responses has been highlighted by experiments carried out using a mouse model of food allergy. First, adoptive transfer of a specific subpopulation of DCs (CD11c⁺/hiB220⁺) from cow's milk (CM) allergic mice into naïve syngeneic recipients induced the production of CM-specific antibody even in the absence of allergenic challenge (46). DCs from allergic mice also showed an increased resistance to antigen-specific T cell mediated apoptosis in allergic mice (47). T cell-mediated apoptosis of DCs occurs following DC-T cell cognate interaction in antigen-specific manner and it has been described in several experimental models as an effective downregulatory mechanism that prevents an otherwise uncontrollable activation of T cells by antigen-loaded DCs (48). Indeed, these apoptosis-resistant DCs induce specific IgE and TH2 responses when transferred into syngeneic recipients (49). It is likely that allergy-associated alteration of the finely balanced regulation between these two cell types, which play a central role in regulating immune responses, has a profound effect on the genesis and maintenance of adverse reaction to food. More recently, the role of gut-DCs has been further highlighted by the observation that IL-4-dependent production of IL-12

by Peyer patch, but not systemic DCs, is severely impaired in allergy-susceptible mice (50); this appeared to be critical for the development of food allergy. Although no data are available so far on the role of gut-derived DCs in humans, the latter finding would suggest that a reduced production of IL-12 by DCs may play a pivotal role in the development of food allergy in humans as well (51).

The importance of timing, dose and route of allergen exposure in the development of food allergy

Whether a person becomes sensitized or tolerized to an allergen depends on the timing and dose of the allergen as well as the route of exposure. Allergen exposure, allergic sensitization and allergic disease manifestation are sequential characteristics of allergic diseases. Allergen exposure takes place repeatedly, under some circumstances permanently and thus defined allergen levels directly involved and responsible for promotion of allergic sensitization remain unclear.

Information on threshold doses of allergens in general and food allergens in particular initiating an allergic immune response is scarcely available. This may be due the numerous factors being involved in the beginning of an immune response: allergen dose, allergen nature, genetic background, defined environment at the time of allergen encounter. Largely open questions in this context are

1. How much allergen is necessary in general to initiate an immune response in humans? and
2. How much allergen is necessary in atopy prone individuals to sensitize rather than to tolerize?

These two immunological outcomes seem to be closely related since not only does the same food allergen in a certain dose sensitize one individual and not another, but it may also tolerize if applied in a certain time frame while sensitizing at another time point. These questions largely challenge research activities in that field. In allergen-specific immunotherapy this bimodal effect of allergen exposure is clearly highlighted and used therapeutically. It is thus of crucial importance to discriminate sensitizing from tolerizing allergen doses. Attempts to define low zone and high zone tolerance inducing allergen levels remain occasional and only refer to defined food and inhalant allergens (52–54). However, such levels have not been established for substantial relevant food sources and only inconclusively for inhalant allergens, thus there is little information on which levels might be relevant for sensitization:

- Is it the prenatally delivered allergens in < ng levels (55, 56)?
- Are these the cumulative breast-milk delivered cow's milk allergens (ng) (57, 58) egg allergens (0.2–4 ng/l) (59, 60) peanut allergen (200 ng/ml) (61) or wheat

allergen (~ng) (62) or the adapted supplied milk (63) allergens as well as the hydrolysed residual amounts of milk proteins (64, 65)?

- Or is it the inhaled food allergen (~ng) (66, 67)?

Animal models, mainly in rodents, readily reveal allergen doses sufficient to sensitize and tolerize animals employing different routes of application (i.p., s.l., i.v., and epicutaneous) (68–70). It is however questionable, whether such allergen doses can be extrapolated to humans, and therefore due to ethical limitations only indirect and retrospective calculations/estimations can be employed to assess sensitizing threshold levels.

Concerning the timing of allergen exposure and subsequent allergic sensitization, it appears quite clear from cohort studies, that though environmental food allergen exposure is quite constant over time, allergic sensitization follows a certain sequential rule, starting with food allergens and followed by inhalants (71). It is thus pertinent to learn more about maturational changes of the immune system from the foetal period through infancy to adulthood before fostering new dietary habits (i.e. food allergen avoidance). Apparently, avoiding allergen exposure in the development of the immune system is not mandatory for efficient allergy prevention. The protection against allergy afforded by living on a farm shows the time frame of such an effect (72). This may be operative during the foetal period and through early infancy but not beyond that period. In addition to the dose and timing the route of allergen exposure might be important for the development of tolerance or sensitization. As discussed above the gut immune system in response to dietary antigens plays an important role. In addition, other potentially important routes of exposure, both with regard to driving sensitization to food allergens and eliciting reactions, are the skin and respiratory tract. Using data from the Avon Longitudinal Study of Parents and Children (ALSPAC), a cohort study of 13 971 preschool children, Lack et al. (73) showed a significant independent relation of peanut allergy with the use of skin preparations containing peanut oil. The authors concluded from their data that sensitization to peanut might occur in children through the inflamed skin. Although there are supporting data from animal models, further research is necessary to prove this concept. Similarly, the question whether aerosolized food allergens could play a role in primary sensitization may be answered with further research (74). Finally, the clinical relevance and sustainability of immune responses raised by the fetus or newborn or infant to a food protein in terms of specific IgE production needs to be established, since transient appearance of specific IgE to food and inhalant antigens in early infancy has been documented repeatedly (75–79). The early presence of specific IgE-antibodies might predict the course of the atopic phenotype, but appears to be less predictive of the development of a particular allergy.

Acidity of the gut and food allergy

The susceptibility of most food allergens to acid digestion in the stomach has raised the possibility that changes in the acid content of the stomach may make subjects more susceptible to sensitization or, if already sensitized, to responses to allergen. Studies on mice have shown that they are more likely to be sensitized to fish allergens (80) and hazelnut allergens (81) if treated with antacids, and similar findings have been demonstrated in patients taking antacids (82, 83). It has been speculated that the relatively high pH in the stomach of infants may make them more susceptible to sensitization by ingested allergens (84).

Food allergy, breastfeeding and diet

The dietary approach to prevent allergic disease is evolving from passive allergen avoidance to active stimulation of the immature immune system, to support the establishment of tolerance. This may involve the use of probiotics, prebiotics, polyunsaturated fatty acids and antioxidants (84).

To prevent the development of allergic diseases including food allergy an expert group of the European Academy of Allergology and Clinical Immunology (EAACI) recommends exclusively breastfeeding preferably for 6 months but at least four months for all infants irrespective of atopic heredity (85). For infants at increased risk of allergic disease, defined as at least one first-degree relative, extensively hydrolysed formula is recommended if a supplement is needed. After the age of 4 months those children at risk can be nourished like low risk children.

As concerns the introduction of solid foods, cow milk and other products to infants at high risk of developing allergy, several studies have shown that the delayed introduction of these foods is associated with higher risk of allergic diseases such as food allergy, eczema, atopic dermatitis and atopic sensitization. For example, a recent prospective birth cohort did not find evidence to support a delayed introduction of solids beyond the sixth month of life for the prevention of atopic dermatitis and atopic sensitization (86). Moreover, recent data from wheat allergic patients showed that children who were exposed to cereals before six months of age had a lower risk of wheat allergy than children who were first exposed to cereals after 6 months of age (87). Another recently published study showed that delay in introduction of both cow's milk and other food products (i.e. pasteurized milk, porridge, dairy products and yogurts) was associated with higher risk of eczema. Moreover, in the same work, it was reported that a delayed introduction of other food groups tended to be related with a higher risk for recurrent wheeze, atopic dermatitis and atopic sensitization (88). These findings lead the Nutritional Committee

from the American Academy of Pediatrics (AAP) to update the recommendations regarding the age threshold of introduction of solid foods and whole cow's milk. In particular, although this Committee in previous reports had proposed that infants at high risk of developing allergy may benefit from late introduction of eggs (after 2 years of age), peanuts, nuts and fish (after 3 years of age) (89), now it recommends that solid foods should not be delayed further than 4–6 months of age and whole cow's milk should not be delayed further than 12 months of age (90).

There is accumulating evidence that early colonization of the intestinal tract by an appropriate intestinal microbiota is important for the healthy maturation of the immune system, including appropriate programming of oral tolerance to dietary antigens (91, 92). Additionally, differences in certain bacterial populations within the intestinal tract have been noted between allergic and nonallergic infants (93). Dietary interventions to augment the intestinal microbiota of infants using probiotics (94) and prebiotics (95) have therefore been explored as a means of decreasing allergic disease.

Studies in animals have shown that feeding probiotics and prebiotics can normalize intestinal barrier function, redress Th1/Th2 imbalances, induce regulatory T cell activity (96, 97) and reduce the development of allergy (98–100). In humans, a number of randomized controlled trials have shown a preventative effect of probiotic or prebiotic feeding on the development and severity of atopic dermatitis in infants (101–108). However, other recent clinical studies of probiotic supplementation to at-risk infants have failed to demonstrate clear benefits (109–112) with one study even reporting that probiotic intervention increased sensitization to allergen (109). Explanations for the varied results among studies include differences in the bacterial strains and doses used, host factors (i.e. genetic predisposition to allergic disease, polymorphism in microbial recognition pathways, etc.) that could influence responsiveness and allergic propensity and other environmental factors such as diet, treatment with antibiotics and general microbial burden (113). Although there is a sound theoretical basis for benefits of probiotics on prevention of atopic eczema, there are insufficient data to recommend probiotics as a part of standard therapy in any allergic conditions. This has resulted in an increased interest in dietary substrates that could have a more global effect on gut microbiota called prebiotics. At this stage, the data that confirm the immunologic or therapeutic effects of prebiotic supplements are lacking but several studies are underway. Therefore, further clinical results are required before recommendations on the use and effectiveness of prebiotics and probiotics in allergy prevention can be made. Nonetheless, both prebiotic and probiotic ingredients are currently incorporated by numerous infant milk manufacturers into specialized formulas to replicate the bifid-

ogenic effect of breast milk and may have benefits besides allergy prevention.

Other variables that can effect microbial colonization of the intestinal tract and could be related to the development of IgE mediated food allergy include mode of delivery and use of antibiotics. To date there has been just one study investigating the correlation between caesarian section (C-section) and risk of allergic disorders in childhood, reporting that children born by C-section have an increased risk of developing allergic rhinoconjunctivitis and in girls, asthma. Due to the small number of children in the cohort with a diagnosis of food allergy no meaningful statistical analysis could be carried out for this allergic disorder and therefore the influence of mode of birth of the subsequent development of food allergy is still unknown (114). The early use of antibiotics has been linked to atopic disorders such as asthma, atopic eczema and rhinoconjunctivitis (115–117); however there are currently no published data on antibiotic use as a risk factor for food allergy.

Beyond changing gut microflora, other nutrients and medications could affect the gastrointestinal tract such that they may prove to be important co-factors in the development of IgE mediated hypersensitivities to food. For example, vitamin D has a number of known immunomodulatory effects such as the inhibition of Th1 immune responses. However, vitamin D status as a risk factor for food allergy has yet to be investigated.

Conclusions

There is a clear association between food allergies and the general susceptibility to allergic disease and it can be assumed that many of the risk factors are in common. The evidence is unclear as to what specific factors are important in determining the likelihood of an individual developing food allergy. However these factors are of importance given that food allergy may cause very severe reactions and has its own specific problems in relation to the development of policies for its control.

An important characteristic of food allergy is that many of the common problems in infancy remit thereafter. Understanding persistent food allergy requires an understanding both of the mechanisms that promote sensitization and symptoms in the first place and remission of disease subsequently.

Some genes have been identified as possibly having a specific role in allergic responses to foods and there is some biological plausibility to these associations. The findings are however largely unreproduced and the research in this area has been sporadic and unsystematic.

Exposure to allergen is rarely the rate limiting step in the development of allergic disease but the nature of food allergens may give some clues as to susceptibility to food allergy. In particular:

1. Some food allergens are cross-reactive with inhalant allergens; in these cases primary sensitization is likely to be to the inhalant allergen and the response to the food, often confined to local symptoms in the mouth and throat, is a secondary response.
2. Other food allergens associated with more systemic effects are poorly digestible and less likely to be denatured in the upper digestive tract.
3. Some food allergens are readily denatured by prior treatment (for instance by cooking and freezing).

Primary food allergens are unique in the way that they are presented to the immune system, being presented in very high quantities through the gut. This raises the possibility that local changes in the gut may be important in the development of IgE mediated responses to foods. Specifically:

1. Changes to the pH of the gut might facilitate the persistence of allergen and lead to increased sensitization or response to allergens.

2. Changes to the microflora of the gut might alter the integrity of the gut or the immunological responses in the gut.
3. Other changes to the gut's transport of foods and proteins, such as changes to the M-cells, might change susceptibility.
4. Nutritional or pharmacological co-factors may also be important for example broad spectrum antibiotics (changing the bacterial ecosystem) and vitamin D (suppressing normal gut Th1 development).

The aetiology of food allergy poses specific problems which have been hard to investigate but for which answers are needed. Several hypotheses have been proposed but have little information currently to support them.

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