The Influence of Gluten: Weaning Recommendations for Healthy Children and Children at Risk for Celiac Disease

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Abstract

In most developed countries, gluten is currently most commonly introduced between 4 and 6 months of age, in spite of little evidence to support this practice. As for infants at risk of developing food allergies, there is clear evidence that introducing solid foods before the end of the 3rd month is detrimental and should be avoided. A recent growing body of evidence however challenges the notion that solids (and among them, gluten-containing foods) should be introduced beyond the 6th month of life. Another important aspect of gluten introduction into the diet has to do with its possible role in causing type-1 diabetes (IDDM). Recently, a large epidemiological investigation in a cohort of children at risk for IDDM found that exposure to cereals (rice, wheat, oats, barley, rye) that occurred early (≤3 months) as well as late (≥7 months) resulted in a significantly higher risk of the appearance of islet cell autoimmunity compared to the introduction between 4 and 6 months. As for celiac disease, the protective role of breastfeeding can be considered ascertained, especially the protection offered by having gluten introduced while breastfeeding is continued. Evidence is emerging that early (≤3 months) and perhaps even late (7 months or after) first exposure to gluten may favor the onset of celiac disease in predisposed individuals. Additionally, large amounts of gluten at weaning are associated with an increased risk of developing celiac disease, as documented in studies from Scandinavian countries. In celiac children observed in our center, we could show that breastfeeding at the time of gluten introduction delays the appearance of celiac disease and makes it less likely that its presentation is predominantly gastrointestinal. Based on current evidence, it appears reasonable to recommend that gluten be introduced in small amounts in the diet between 4 and 6 months, while the infant is breastfed, and that breastfeeding is continued for at least a further 2–3 months.
Introduction

Although no official recommendation from professional societies or academic bodies is available specifically on the timing of gluten introduction, with some exceptions [1], it would appear that most commonly gluten is introduced between 4 and 6 months of age. In fact, epidemiological surveys conducted in developed countries in the last couple of decades show a progressive trend toward shifting introduction of solid foods (even 15 years ago often still introduced with other cereals before 4 months) to a later age [2], and it is generally believed that the habit of introducing gluten into the diet around that time is justified [2–4]. In the United States, typically the first solid food to be introduced into the diet is rice cereal, followed by cereal grains (oats, barley, wheat and rye).

In the healthy child who does not belong to a group at risk for development of food allergy or celiac disease, there is a paucity of data to support or contradict such practice. From a purely digestive-absorptive viewpoint, it could be argued that gluten-containing cereals should be tolerated by the time the combined digestive abilities of pancreatic amylase, brush-border-bound glucoamylase and pancreatic and brush border-bound peptidases have reached the capacity of fully digesting ‘normal’ amounts of the starch and protein components of such food staples, i.e. at the remarkably early age of 4–6 weeks, in full-term babies [5]. It remains to be seen whether such an early introduction is advisable, and as mentioned no recommendations endorse such practice.

Gluten Introduction and the Risk of Food Allergy

In infants at risk for food allergy on the other hand, many studies have been conducted, and recommendations based on a large body of evidence are now available from the American Academy of Pediatrics (AAP) [6] and from a joint committee of the European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and of the European Society for Pediatric Allergy and Clinical Immunology (ESPACI) [7].

Both these recommendations are largely based on evidence that early introduction of solid foods (<3–4 months) may increase the risk of developing eczema and asthma, something that a subsequent study however does not appear to confirm [8]. According to both sets of recommendations, in infants at risk of developing food allergy breastfeeding should be exclusive for 4–6 months of age, with complementary food introduced during that time window [1, 6, 7]. However, it should be stressed that to date, only one very recent study has evaluated prospectively the timing of specific dietary exposures in relation to the development of specific food allergy in a population selected for being at risk of type-1 diabetes (IDDM) and/or celiac disease (see below for
more details on this cohort of children enrolled in the so-called ‘DAISY’ study, but not at risk of allergy [9]. Most previous studies, on which current recommendations are based, have in fact focused on eczema and asthma, complex disorders not always associated with food allergy. This specific study examined the association between cereal-grain exposure (wheat, barley, rye, oats) in the infant diet and development of wheat allergy in 1,612 children from birth until the mean age of 4.7 years. One percent of these children developed wheat allergy. Surprisingly, those who were first exposed to cereals after 6 months of age had an increased risk of wheat allergy compared with children first exposed to cereals before 6 months of age (see table 1).

Interestingly, the results of this prospective study are in substantial agreement with the findings of another recent study: a large, population-based, prospective birth cohort study conducted in Germany [10], showing that delaying solid food introduction beyond the 6th month did not offer protection toward atopic dermatitis or atopic sensitization.

Thus, taken together these very recent observations support the recommendation of introducing solids between 4 and 6 months of age as endorsed by the joint European committee [7] and in agreement with the AAP Committee on Nutrition [1], whilst they do not support the widely diffused practice to recommend further delaying the introduction of cereal grains beyond that time.

### Gluten Introduction and the Risk of IDDM

Another important aspect of cereal (and hence gluten) introduction into the diet has to do with its role in causing IDDM. This condition results from the

### Table 1. Adjusted odd ratios for development of wheat allergy [from 9]

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Adjusted OR (95% CI)</th>
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<tr>
<td>Age exposed to cereal grains (wheat, barley, rye, oats)</td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>1.00</td>
</tr>
<tr>
<td>≥7 months</td>
<td>3.8 (1.18–12.28)</td>
</tr>
<tr>
<td>Age exposed to rice cereal</td>
<td></td>
</tr>
<tr>
<td>0–6 months</td>
<td>1.00</td>
</tr>
<tr>
<td>≥7 months</td>
<td>1.6 (0.46–5.23)</td>
</tr>
<tr>
<td>Breastfeeding duration, 1-month increase</td>
<td>1.05 (1.00–1.11)</td>
</tr>
<tr>
<td>Any food allergy before 6 months of age</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>7.6 (2.67–21.9)</td>
</tr>
<tr>
<td>Family history of allergic disorders</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1.00</td>
</tr>
<tr>
<td>Yes</td>
<td>3.9 (1.40–10.88)</td>
</tr>
</tbody>
</table>

*All variables were included simultaneously in the logistic regression model.*
destruction of the insulin-producing cells of the pancreas. Autoantibodies to the islet cells, or islet autoimmunity, which mark this destructive process, can be present for years prior to the diagnosis of IDDM. Exposure to cereal in the infant diet has been implicated, albeit inconsistently, in the etiology of IDDM. First it was cow’s milk that was associated with increased risk [11, 12], although different studies have yielded conflicting results. Studies of other foods in the infant diet have also been contradictory, with some investigations finding that IDDM cases had been exposed to solid foods earlier than controls [13, 14], others found no association [15, 16]. Recently, a role for cereals has been proposed as a result of the same large epidemiological investigation cited before (the DAISY study), conducted in a cohort of children at risk for IDDM followed prospectively from birth for a mean of 4.7 years [17]. This study documented that exposure to cereals (rice, wheat, oats, barley, rye) that occurred early (≤3 months) as well as late (≥7 months) resulted in a significantly higher risk of appearance of islet cell autoimmunity compared to introduction between 4 and 6 months. Figure 1 [from 17] shows the percentages of children developing islet cell autoimmunity in function of the age at first introduction of cereals. Interestingly, this study also showed that if cereals were introduced while the child was still breastfed, the risk of islet cell autoimmunity was reduced, independently of the age at introduction of cereals. A previous large study in Germany had also shown a similar increased risk of developing islet cell autoimmunity for children born to parents with IDDM when gluten is introduced during the first 3 months of life [18]. In both these studies, no effect of the duration of breastfeeding and/or age at introduction of cow’s milk was detected [17, 18].

**Gluten Introduction and the Risk of Celiac Disease**

Arguably the most central aspect of gluten introduction into the diet regards the issue of how this may influence the appearance and/or the presentation of celiac disease.

In the last few years, a robust new wealth of knowledge has accumulated, leading to the understanding of celiac disease as an autoimmune reaction to the ubiquitous enzyme tissue transglutaminase (tTG) in the intestinal mucosa, initiated by exposure to dietary gluten in genetically predisposed individuals. Many details of this reaction have been revealed, and a role for innate immunity in the early phases of the process has been suggested [19]. Yet basic questions about the amount of gluten needed to trigger celiac disease and the possible role of the timing of its introduction into the diet have remained unanswered.

Once the role of gluten had been clearly identified, the quest to find a relation between the timing of its introduction into the diet and the appearance of celiac disease began. At the same time, the search for a possible protective
The Protective Role of Breastfeeding

As for breastfeeding, as early as more than 50 years ago its protective role was already proposed [20]. The majority of subsequent investigations (though performed with different methodologies and thus somewhat hard to compare) did indeed find a negative correlation between its duration and the development of celiac disease [21–25], to the point that – also according to a very recent rigorous meta-analysis [26] – such a protective effect can now be considered universally accepted. For instance, the most recent study on this issue [24], a population-based case-referent study of Swedish children that examined 627

Fig. 1. a, b Risk of development of islet cell autoimmunity as function of the age at introduction of cereals [from 17]. The numbers in the tables below the graphs represent the number at risk.

role of breastfeeding was also unleashed, and the two were often conducted simultaneously.

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cases with celiac disease and 1,254 referents showed that in children less than 2 years old, the median (25th, 75th centile) duration of breastfeeding was 5 months (3, 7) for cases and 7 months (4, 9) for controls (p < 0.001).

Another intriguing aspect of the protective role of breastfeeding that has recently received a great deal of attention based on the notion that breast milk may provide passive as well as active mucosal immunity [27, 28] is the possibility that breastfeeding at the time of gluten introduction may also prove to be of protective value. To test this hypothesis, several observational epidemiological studies have been conducted and reviewed in a recent meta-analysis [26]. All of them, with only one exception found in a small study [29], showed that introducing gluten during breastfeeding reduces the risk of development of celiac disease. Figure 2 [from 26] shows in a graphical manner the odds ratio of developing celiac disease if breastfed at the time of gluten introduction.

In our recent, unpublished series of 162 celiac children studied at the University of Chicago [30], we found some evidence that breastfeeding at the time of gluten introduction delays the appearance of celiac disease: in fact (see fig. 3) the age at diagnosis was slightly but significantly higher in children who had been breastfed at the time of gluten introduction as compared to those who were not. Additionally, celiac children who were breastfed at the time of gluten introduction were just as likely to develop typical (i.e. gastrointestinal) as atypical (i.e. extraintestinal) celiac disease (see fig. 4), whereas children who were not breastfed when weaned with gluten had a much higher chance of developing mostly gastrointestinal symptoms (fig. 4).

Therefore, while the evidence is there, the actual mechanism through which breast milk protects against the development of celiac disease is unclear. On an entirely speculative basis, three main theories seem plausible: (1) Continuing

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds Ratio (95% CI)</th>
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<tr>
<td>Peters et al. [25]</td>
<td>0.46 (0.27, 0.78)</td>
</tr>
<tr>
<td>Faith-magnusson et al.</td>
<td>0.35 (0.17, 0.66)</td>
</tr>
<tr>
<td>Ivarsson et al.</td>
<td>0.50 (0.40, 0.64)</td>
</tr>
<tr>
<td>Ascher et al. [29]</td>
<td>1.54 (0.27, 10.56)</td>
</tr>
<tr>
<td>Combined (fixed)</td>
<td>0.48 (0.40, 0.59)</td>
</tr>
</tbody>
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**Fig. 2.** Odds ratio of the effect of breastfeeding at the time of gluten introduction on the development of celiac disease [from 26].
Breastfeeding at the time of weaning results in a lower amount of gluten given to the infant, and so reduces the chances of the child developing symptoms of celiac disease. (2) Breast milk could, by preventing gastrointestinal infections, reduce the chances that they trigger pathophysiological mechanisms that may influence the development of celiac disease.

**Fig. 3.** Breastfeeding at the time of gluten introduction results in delayed appearance of celiac disease. ■ = Celiac children nonbreastfed at time of gluten introduction; ◆ = celiac children breastfed at time of gluten introduction (n = 162).

**Fig. 4.** Introduction of gluten while nonbreastfed is more likely to induce typical (gastrointestinal) symptoms in celiac children. □ = Celiac children nonbreastfed at time of gluten introduction; ▼ = celiac children breastfed at time of gluten introduction. Celiac children who were breastfed at the time of gluten introduction were just as likely to develop typical (i.e. gastrointestinal) as atypical (i.e. extraintestinal) celiac disease, whereas children who were not breastfed when weaned with gluten had a significantly (p < 0.01) higher chance of developing predominantly gastrointestinal symptoms (n = 162). GI = Gastrointestinal.

Breastfeeding at the time of weaning results in a lower amount of gluten given to the infant, and so reduces the chances of the child developing symptoms of celiac disease. (2) Breast milk could, by preventing gastrointestinal infections, reduce the chances that they trigger pathophysiological mechanisms that may
be contributing factors to the development of celiac disease. In fact, infections of the gastrointestinal tract in early life could lead to increased permeability of the intestinal mucosa, allowing the abnormal entry of gluten into the submucosal compartment. Enteric infections can also increase the expression of tTG, thus possibly increasing the production of deamidated gluten peptides. (3) Breast milk may possess unique immunomodulating effects that, by interfering with the early phases of the interaction between toxic peptides and the innate immune system of the intestinal mucosa, allow for the development of gluten tolerance.

Whatever the mechanism underlying the protective effect of breast milk, the big question that has puzzled researchers from early times remains: is such protection effective in completely aborting the onset of celiac disease in predisposed individuals, or is it simply delaying its appearance and/or causing it to appear in more subtle, less overtly symptomatic forms? To date, we have essentially no data to answer this, and larger epidemiological studies are needed.

The Specific Role of Gluten

Does the timing of gluten introduction per se, independently of breast-feeding, influence the development of celiac disease in predisposed individuals? Theoretically, this is an attractive possibility, as there might well be an age interval during which humans have a decreased ability to develop oral tolerance to a newly introduced antigen.

In reality, the results of most previous studies suggest that the age at first gluten exposure – while affecting the age at onset of symptoms – had actually no bearing on the development of celiac disease [21–23, 25]. All of the studies so far examined however had been conducted retrospectively. A recent prospective, 10-year observational study [31] conducted in the USA that enrolled 1,560 children considered at increased risk of celiac disease or IDDM came to a different conclusion, showing that initial exposure to gluten in the first 3 months or at 7 months and later significantly increased the risk of subsequent celiac disease autoimmunity (CDA), defined as a positive tTG on two or more consecutive visits or a positive tTG once with a small bowel biopsy consistent with celiac disease. The data have been generated as part of the larger study already mentioned, the so-called project DAISY (Diabetes Autoimmunity Study in the Young), aimed at prospectively describing the natural history of IDDM and CDA in genetically predisposed children. In this study, the increased risk of celiac disease or IDDM was defined as having either HLA-DR3 or DR4 alleles or a first degree relative with IDDM. The majority of children studied were identified at birth and followed for a mean of about 5 years, with serum tTG measured at 9, 15 and 24 months and yearly thereafter. Fifty-one children developed CDA. Their mean age at first positive tTG was 4.7 years. Three were exposed to wheat, barley, or rye between 1 and 3 months, 12 (23%) at 4–6 months, and 36 (71%) at 7 months or later. Among CDA-negative children, only 40 (3%),

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574 (38%) and 895 (59%) were positive at the same time intervals. Adjusting for HLA-DR3 status, children exposed to gluten in the first 3 months of life had a 5-fold increased hazard of CDA compared with those exposed at 4–6 months. Figures 5 and 6 show the risk of CDA by month of exposure to gluten in the entire cohort and in those who were HLA-DR3 positive, respectively. Children not exposed to gluten until 7 months or later were at a slightly increased hazard of CDA compared with those exposed in the 4- to 6-month period (an only marginally significant difference, however).

An unexpected finding of this study was the lack of evidence for a protective effect of prolonged breastfeeding. This finding is in contradiction to the

Fig. 5. Risk of CDA by months of exposure to gluten in entire cohort [from 31]. The numbers in the table below the graph represent the number at risk. Wilcoxon p = 0.04.

Fig. 6. Risk of CDA by months of exposure to gluten in HLA-DR3-positive children [from 31]. Wilcoxon p = 0.004.
previous studies from Europe already commented upon. The discrepancy, besides being possibly due to different methodologies (most studies were done retrospectively and in populations including children not at genetic risk for celiac disease), may also be related to differences inherent in infant diets across studies, reflecting infant diet practices different from those of the United States.

But what about the amount of gluten in the diet? Does this factor also play a role? While this study completely leaves out this parameter [31], previous studies seem to suggest that indeed the amount of gluten may be a determinant in the risk of developing celiac disease. Ivarsson et al. [24] could demonstrate in their epidemiological investigation of 627 cases of celiac children and 1,254 referents that cases received a larger amount of flour, and that at 7 months of age, cases still consumed larger amounts of flour than referents. Another classical example is provided by the so-called Scandinavian paradox. In fact, it is known that a profound difference in the prevalence of celiac disease exists between the neighboring countries of Denmark, where a very low prevalence has repeatedly been found [32], and Sweden, where a much higher prevalence is reported. The explanation given for this is a striking difference in the diet of infants, who apparently receive much less gluten in Denmark [32]. Further evidence supporting the idea that the quantity of gluten is important comes again from Sweden where a so-called epidemic of celiac disease has been observed [33]. A sharp increase in symptomatic celiac disease in young children was thought to be related to a sudden increase in the consumption of gluten in infancy as a result of new dietetic guidelines (later changed for this reason). In analyzing the data from the ‘epidemic’ of the 1980s, and comparing them to the prevalence recorded subsequently in the same geographical areas, Carlsson et al. [34] found (see table 2) that the prevalence of celiac disease before the rules were changed (i.e. during a time of a higher amount of gluten at weaning) was overall 1.03% [35], including asymptomatic cases detected at screening and cases with gastrointestinal symptoms. This compared to a prevalence of only 0.39% in subsequent years [34], thus suggesting that indeed higher quantities of gluten in the diet of the weaning infant lead to a higher rate of appearance of celiac disease in the first 2 years of age. Although the story may be more complex than this, as new epidemiological data show that other factors have influenced the fluctuation in the prevalence of this condition in Sweden [36], we can conclude from the available evidence that the amount of gluten may be a major factor in the appearance of celiac disease.

Conclusions and Final Recommendations

It seems reasonable to conclude the following:
Certainly early (0–3 months) and possibly late (>6 months) introduction of wheat into the diet is likely to increase the risk of wheat allergy.

Early (0–3 months) and possibly late (>6 months) introduction of gluten into the diet is likely to increase the risk of IDDM in genetically predisposed children.

Breastfeeding is likely to reduce the risk of celiac disease and/or to delay its onset.

Introduction of gluten during breastfeeding reduces the risk of celiac disease (and/or significantly delays its onset) and influences the time and the type of presentation.

Infants nonbreastfed at the time of gluten introduction seem to be more likely to develop typical (gastrointestinal) celiac disease.

Introducing gluten at 4–6 months seems to be associated with the lowest risk of celiac disease.

Introduction of ‘large amounts’ of gluten increases the risk of celiac disease.

From all of the above, the following final recommendations can be drawn for the prevention of celiac disease:

- Breastfeeding should be conducted for at least 6 months.
- Gluten should be introduced while the infant is breastfed between the age of 4 and 6 months.
- Gluten should be introduced in ‘small amounts’.
- Breastfeeding should be conducted for at least 2–3 months after gluten introduction.

### References


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Influence of Gluten Weaning

Dr. Seidman: You talked about the risk of type 1 diabetes and its relationship to gluten but there is also the notion that untreated celiac disease is associated with an increased risk for other autoimmune diseases, particularly thyroiditis.

Dr. Guandalini: For those of you who are not too familiar with celiac disease, this is an autoimmune condition that is significantly associated with type 1 diabetes but also, as Dr. Seidman mentioned, with thyroiditis and other autoimmune conditions. In 1999 Ventura et al. [1] published a multicenter study in Gastroenterology showing that the later the diagnosis of celiac disease is made in time (i.e. the longer gluten was being eaten while having celiac disease), the higher the cumulative prevalence of other associated autoimmune disorders. This appears as an interesting piece of evidence in favor of some link between celiac disease and the development of other autoimmune conditions. There are, however, no data that I am aware of regarding the timing of gluten and the onset of other autoimmune conditions aside from celiac disease and type 1 diabetes. As for thyroiditis, the prevalence of celiac disease in this condition is certainly higher than in the normal population, and is estimated to be around 3–4% [2, 3]. In this specific case, there are still doubts that celiac disease is really acting as a trigger [4].

Dr. Krebs: I am curious about the findings in relation to the introduction of complementary food in that the most common cereal introduced first in the US is rice. How carefully has it been documented that there are other sources of gluten and what are those sources? Norris et al. [5] have good dietary data.

Dr. Guandalini: Indeed rice is the cereal most commonly introduced first, followed then by grain cereals like wheat mostly; rye, barley and oats are uncommonly used early in life. In the paper by Norris et al. [5] the data refer to any cereal introduction, and they do comment, however, that even considering those who only have wheat as the first cereal, the same results hold true. It doesn’t have to be gluten per se, for instance there is a very recent paper by Mojibian et al. [6] showing that individuals who have type 1 diabetes have higher levels of antibodies against a wheat storage
protein called glb1 than patients who do not have type 1 diabetes, suggesting there may be other wheat storage proteins.

**Dr. Ziegler:** Can you enlighten us on the relationship between wheat allergy and celiac disease?

**Dr. Guandalini:** Very simply stated, there is no relationship. Wheat allergy is one of the many food allergic conditions, mostly of transient nature, that frequently affect babies, while celiac disease is a permanent, autoimmune-induced sensitivity to gluten.

**Dr. Seidman:** I was intrigued by your comments on rotavirus infection and the onset of celiac disease. Are you saying that individuals who are already on gluten when they have a rotavirus infection are more likely to develop celiac disease afterwards?

**Dr. Guandalini:** I included rotavirus among the possible environmental factors because of a recent epidemiological investigation by the Denver group [7], retrospectively showing a significantly higher prevalence of rotavirus infection in the second semester of age in patients who then develop celiac disease versus matched controls. The authors’ speculation is that the enteritis, which is well know to cause a profound disruption in small intestinal permeability, might have favored the onset of celiac autoimmunity in predisposed individuals by allowing a much higher entry of toxic gluten epitopes.

**Dr. Seidman:** One of the focuses of this workshop is childhood exposure to foods and the onset of disease later in life. It is fair to say that most celiac patients are diagnosed as adults, not as children or infants, yet most human beings have rotavirus infection during childhood and infancy. We know that these patients have predisposing genes, HLA DQ2 or DQ8, and that they ingest gluten and yet they present with celiac disease in adulthood, long after a rotavirus infection.

**Dr. Guandalini:** Your point is well taken. However, we should note that it takes time for celiac autoimmunity to develop. In fact, even in the study by the same Denver group that prospectively followed genetically predisposed babies from birth, it was apparent that nobody actually had any detectable antibody levels before the age of 3 and half or so. Of course I understand your point, it is difficult to accept the concept that you have a rotavirus infection when you are 6 months old and then you develop celiac disease at 25 years. However, not much is known about the timing of the development of autoimmunity in any such condition.

**Dr. Seidman:** Is there any evidence that the feeding practices you discussed, breastfeeding and introduction to gluten, in fact have an impact on adult onset of celiac disease?

**Dr. Guandalini:** Very good question that I am afraid cannot be answered yet. I had the opportunity to discuss this issue with Dr. Peter Green at Columbia University in New York. His group is now looking into the relationship between early feeding habits and the development of celiac disease in adulthood. A major undertaking, as you can imagine, given the uncertainty about lucid history after many years.

**Dr. Domellöf:** Ivarsson [8] is currently performing a screening study of schoolchildren born before and after the Swedish celiac epidemic, and the preliminary results show that children born before the change in dietary recommendations have a high prevalence of celiac disease. The interesting part is the screening of the children born after the change in recommendations, and we are still awaiting those results.

**Dr. Shahkhalili:** What is the prevalence of celiac disease and type 1 diabetes in developing and developed countries? Should we have different recommendations for the introduction of gluten-containing cereal for different ethnic groups?

**Dr. Guandalini:** Basically all of my presentation was related to the situation in developed countries, all of these data have been generated there. I am not aware of data on type 1 diabetes, but to answer your question in terms of celiac disease, the disease is so strongly associated with HLA DQ2 and DQ8 that the current thinking is that,
in practical terms, there is no celiac disease outside these haplotypes. Now these haplotypes are found in about 30–35% of the white population regardless of where in the world they were born. However, if you then go to the black population the prevalence of these haplotypes is close to zero, so the current thinking is that you cannot develop celiac disease in those areas.

Dr. Haschke: What you are saying is in contradiction to the WHO recommendations, so we need a debate on this. Do you think that, at the present time, the data are strong enough to be transferred to scientific committees for evaluation, and then to enter into discussion whether in the respective developed countries with Caucasian populations the feeding recommendations should be modified? The WHO recommendations are for the sake of the children in the whole world, therefore they are being introduced in Europe and in the United States. If there are good reasons in this cost-benefit ratio calculation, how many children more will suffer from celiac disease if gluten is introduced later versus earlier, say 4–6 months; this has to be taken into consideration. Are we far enough advanced in our understanding to start such a debate?

Dr. Guandalini: Of course it is not for me to propose changes to the WHO guidelines. I will simply give you my opinion. Firstly, one needs to consider that actually, whether we want it or not, whether our official academic bodies want it or not, in developed countries children are weaned before 6 months in spite of current WHO recommendations. I believe this is not going to change significantly. Secondly, I think we have sufficient evidence that if children in developed countries are weaned after 6 months according to the WHO recommendations, this would expose us to the obvious risk of introducing gluten at a time when breastfeeding is no longer given. In all the most recent studies the prevalence of celiac disease autoimmunity has been estimated to be close to 1% [9], so we are probably talking about the most common genetic condition of the white population. Thus, it does not appear trivial. Additionally, studies have shown that if gluten is introduced after 6–7 months of age the amount of gluten is larger [10]. So not only do we end up introducing gluten after breastfeeding has stopped, but it is also given in a larger amount. In my humble opinion I think that the time has arrived for academic panels to discuss this and possibly carve out a slightly different set of recommendations for Caucasian children. Rather than going ‘against’ the WHO recommendations, here the matter is to suggest a rethinking of recommendations for a specific, albeit very large part of the world population. This is something that, for example, has already been successfully done with the composition of oral rehydration solutions (ORS). I was on the panel that in 1992 recommended a new low osmolality ORS for developed countries then promulgated by ESPGHAN [11]. It took the WHO 12 years, and in 2004 they essentially accepted the same composition for ORS that we recommended, even for children with cholera [12]. It seems to me that large bodies such as the WHO, that have a global vision, are by definition slower in adopting new recommendations. I think nevertheless that whenever the scientific evidence is there, and especially if it were endorsed, as has been the case for ORS, by scientific societies like ESPGHAN, even the WHO should feel the need to examine all the evidence and come up, if necessary, with a revised set of recommendations that again might be applicable to only part of the world, in our case the Caucasian population that is at a significant risk for celiac disease. I repeat, after all, current practices already do follow such a pattern for the most part.

Dr. Gailing: Last year during the nutrition CODEX committee meeting we adopted the CODEX standard on cereal-based food with the recommendation to start at 6 months and to have these accordingly labeled on the products so it will be now translated into all the regulations throughout the world. How do you recommend managing this issue? We will be discussing this again next week in the CODEX committee.
meeting in Thailand. We will also discuss the gluten-free food standard and again we will probably have the same results with the introduction after 6 months.

*Dr. Guandalini:* I hear your urgency but I am not a political man, I am not a representative who can make decisions. So unfortunately it is not me you should ask.

*Dr. Solomons:* Returning to the point of preventing gluten exposure at an inappropriate time for susceptible individuals, and referring back to the screening issue. Since it is all HLA subtype-related, presumably people without that subtype can have gluten anytime or never without any effect. Therefore what is the cost of a plan in which a susceptible population, i.e. Europeans, would be screened prior to 4 months, let’s say, and depending upon their positive/negative HLA appropriate type how should they be advised specifically by their pediatricians? So that means that anyone else who is immune, who doesn’t have the HLA, can just do whatever nature and their mothers want.

*Dr. Guandalini:* There are a lot of implications to your question, and two come to mind, one is the issue of cost. At least in the United States, checking for HLA DQ2 DQ8 is very expensive, in the order of several hundred dollars for one test. So if you want to extend these to every newborn, the cost would be prohibitive. On the other hand, restricting HLA testing to the offspring of celiac patients might be a more reasonable approach because then you would identify those who are at a direct risk for celiac disease and only they will have to follow the recommendations. As an alternative, dietetic advice for each newborn could be given to every parent with celiac disease.

*Dr. Solomons:* Is there a possibility to lower the cost?

*Dr. Guandalini:* From a technical standpoint, perhaps.

*Dr. Solomons:* You said the prevalence is 1 in 150.

*Dr. Guandalini:* The prevalence of celiac disease is currently estimated to be around 1% [9].

*Dr. Solomons:* You could calculate the annual cost based on the birth rate in a country multiplied by the current cost, and you could calculate the cost burden for that kind of screening. Obviously again technological solutions are needed to get a cheaper screening because the implications of everyone following the recommendations for only 1 in 100 is relevant. It is another ethical issue.

*Dr. Guandalini:* I totally understand. I think the issue is well raised and the answer might come from looking more in depth at cost-benefit ratios before making new recommendations. That said, however, I frankly fail to see a great risk in following the dietetic recommendations of the sort I indicated.

*Dr. Solomons:* The risk is following recommendations that violate the dictums of the WHO in a ‘politically correct’ sense of the word, and that is to the extent that you are suggesting that the black or the brown or the yellow or the red pigmented ethnic groups are exempted from the same recommendations. This could set up a situation of suspicion among those groups excluded from your preventive considerations.

*Dr. Vieira:* It is interesting that you did not mention oats. Here in Brazil and probably in some other countries, mothers add oats to fruits or other complementary foods. Although oats have been shown not to be damaging for celiac patients in vitro and in vivo, do you think we should stick to the idea of not recommending oats in the diet of these infants?

*Dr. Guandalini:* From data, not only in vitro but also in vivo, and from a number of papers over the last 12 years or so, I have a strong conviction that oats are perfectly safe for the vast majority of celiac children. All my patients eat oats, and to the best of my knowledge, none of them has unexpectedly developed high levels of autoantibodies or anti-gliadin antibodies or has experienced any side effect. One needs to be aware, however, that there is the remote possibility, well documented in a paper by Arentz-Hansen et al. [13], that a tiny subset of, probably extremely rare, celiac patients may react to a chronic ingestion of large amounts of oats. More commonly,
the issue with oats is that one must be sure that there is no cross-contamination in the manufacturing line between wheat-containing flours and oats because this might be the case.

Dr. Uy: I am wondering about autoimmunity in the development of type 1 diabetes. Were those children screened for DQβ? I understand that they were screened for DR3 but were they screened for DQβ Asp57, and was it positive or negative?

Dr. Guandalini: In Caucasians, the susceptibility to type 1 diabetes strongly correlates with the absence of aspartic acid at position 57 on the DQβ chain. The formation of a putative DQ susceptibility molecule (such as DQβ Asp57–) accounts best for the disease association. That said, I am not aware if the children described in the studies by the Denver group were also screened for DQβ Asp57–. They certainly were assessed for their HLA DR3 status.

Dr. Uy: If they are positive, they are more protected from having the autoimmunity.

Dr. Guandalini: As mentioned, my recollection of the paper is that they were HLA DR3 positive, I am not sure if the DQβ status was checked.

References
