
The natural history of wheat allergy

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Background: Wheat allergy is 1 of the most common food allergies in children, yet few data are available regarding its natural history.

Objectives: To define the natural course of wheat allergy and identify factors that help predict outcome in a large referral population of children with wheat allergy.

Methods: Patients were included in the study if they had a history of a symptomatic reaction to wheat and a positive wheat IgE test result. Clinical history, laboratory results, and final outcome were recorded for 103 patients who met the inclusion criteria. Resolution of wheat allergy was determined based on food challenge results. Kaplan-Meier survival curves were generated to depict resolution of wheat allergy.

Results: Rates of resolution were 29% by 4 years, 56% by 8 years, and 65% by 12 years. Higher wheat IgE levels were associated with poorer outcomes. The peak wheat IgE level recorded was a useful predictor of persistent allergy ($P < .001$), although many children outgrew wheat allergy with even the highest levels of wheat IgE.

Conclusion: The median age of resolution of wheat allergy is approximately 6½ years in this population. In a significant minority of patients, wheat allergy persists into adolescence.

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INTRODUCTION

Wheat allergy is 1 of the most common food allergies in childhood, affecting 0.4% to 1% of children.^{1,2} Wheat is a major staple of the worldwide diet, and despite the popularity of low-carbohydrate diets, the average American still consumes more than 130 lb of it yearly.³ Consequently, wheat avoidance is exceedingly difficult and imposes major dietary restrictions.

Despite the high prevalence of wheat allergy, relatively little is known about its natural history. As many studies have demonstrated, the possibility of resolution of food allergy varies widely by the food.^{4–7} For example, milk and egg allergy have good prognoses, but in only approximately 20% of children is peanut and tree nut allergy resolved by adulthood. It is not clear where wheat falls on this spectrum. The natural course of only a handful of patients with wheat allergy has been reported in the literature, and in these studies one-fourth to one-third of patients became tolerant in a 1- to 2-year period.^{8,9} For other foods, predictors of resolution of food allergy have included specific IgE levels, presence of other atopic diseases and food allergies, and symptoms at presentation.^{4–7}

In this study we evaluated a large population of children with IgE-mediated wheat allergy to develop a better understanding of the natural history of this common disease. The purposes of this study were to determine the rate of acqui-

sition of oral tolerance to wheat and to identify clinical and laboratory predictors of tolerance development.

METHODS

We completed a retrospective medical record review of patients from the Johns Hopkins Pediatric Allergy Clinic who were diagnosed as having wheat allergy. The patients were under the care of 2 attending physicians (R.A.W. and E.C.M.) from 1993 to 2007. Records were abstracted by 3 reviewers (C.A.K., M.N.P., and G.D.). Patients were included in this study if they had a clinical history consistent with an IgE-mediated allergic reaction on wheat ingestion and a positive wheat IgE test result. Patients were excluded if they were older than 18 years at their first clinic visit, if they had only 1 clinic visit, or if they were no longer wheat allergic at the first clinic visit. Potential study participants were drawn from databases created for 2 previous studies of the natural history of food allergy,^{4,5} from our database of food challenges, and from a keyword search of all clinic notes from 1999 to 2006, which includes a total of approximately 5,000 children. Fifteen patients were excluded because they had non-IgE-mediated reactions to wheat, 4 patients were older than 18 years at their first clinic visit, and 34 had only 1 visit. The study was approved by the Johns Hopkins institutional review board, which did not require informed consent. The specific data collected included the patient's birth date, sex, presence of other atopic disease and food allergies, dietary history, symptoms at wheat allergy diagnosis, date and symptoms with unintentional exposures to wheat, wheat skin prick test results, other medical conditions, and wheat IgE levels.

The diagnoses of asthma, eczema, allergic rhinitis, and other food allergies were made by the attending physician. Allergy to other foods was defined as having had a clear

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symptomatic reaction to the food. Patients with food allergy treated in this clinic typically have food specific IgE levels evaluated annually using the ImmunoCAP system (Phadia, Uppsala, Sweden). ImmunoCAP IgE measurements ordered by other physicians were also included in the analysis when available.

The primary end point of interest was the development of oral tolerance to wheat. Oral wheat challenges were generally performed at least every 2 years if the child did not have an interval history of symptoms with unintentional exposure. Food challenges followed a protocol described by Perry et al.¹⁰ Home challenges were recommended for some children based on their clinical history.

We analyzed the data using 3 different definitions of outgrowing wheat allergy. Under the most stringent definition (definition 1), an individual was considered tolerant to wheat when he or she passed a home or office challenge and was then able to incorporate wheat into the diet. All other individuals were considered to have persistent wheat allergy. Because not all study participants underwent regular food challenges or had unintentional exposures to wheat, we also analyzed the data with 2 other definitions that imputed tolerance even in the absence of exposure. For definition 2, we assumed acquisition of tolerance when an individual had a wheat IgE level of less than 20 kU/L and had gone 1 year without a symptomatic reaction to wheat or when an individual passed a home or office food challenge. Under the least stringent definition (definition 3), an individual was defined as being tolerant when he or she had a wheat IgE level of less than 50 kU/L and had not had a symptomatic reaction to wheat in 1 year or had passed a home or office food challenge. In previous studies, no clear IgE level predicting clinical reactivity has been found, but challenge decision points of 20 to 100 kU/L have been proposed.^{10,11} Unless otherwise noted, definition 1 was used for all analyses. An additional 66 patients who had never had a symptomatic exposure to wheat but had at least 1 wheat IgE level greater than 20 kU/L were analyzed separately.

All analyses were performed with StataSE statistical software, version 8.0 (StataCorp, College Station, Texas). Wheat IgE levels were recorded as less than 0.35 kU/L or more than 100 kU/L, or, if between those values, the specific value was recorded. For purposes of statistical analysis, IgE levels less than 0.35 kU/L were assigned a value of 0.18 kU/L, and levels greater than 100 kU/L were assigned a value of 101 kU/L. The highest wheat IgE level obtained for each patient was considered their peak level, and these levels were stratified into 3 categories: less than 20 kU/L, 20 to 49 kU/L, and 50 kU/L or higher.

Kaplan-Meier curves were generated to depict the development of tolerance to wheat over time for each of the 3 definitions of wheat tolerance. Kaplan-Meier curves were also generated to depict the development of tolerance separately for the patients who had a symptomatic reaction to wheat and the patients who had been diagnosed as having wheat allergy on the basis of laboratory studies alone. The

log-rank test was used to compare the time to development of tolerance between groups with and without a particular characteristic. The Mann-Whitney test was used to compare wheat IgE levels between the patients with persistent allergy and the patients who developed tolerance, to compare wheat IgE levels for passed and failed food challenges, and to compare the number of allergies, initial visit age, and peak wheat IgE level between the patients who presented on the basis of symptoms and the patients whose conditions were diagnosed by laboratory testing only. The Pearson χ^2 test was used to compare demographic features between the groups. Nonparametric Lowess smoothed curves with a bandwidth of 0.8 were generated to depict the trend in wheat IgE levels over time. For all survival analyses, the data were left truncated to the first clinic visit.

RESULTS

Study Population

There were 103 patients with IgE-mediated wheat allergy on whom data were collected (Table 1). Of these, 42 initially had their conditions diagnosed on the basis of laboratory testing only, but all 103 had symptomatic wheat reactions during the observation period. Sixty-eight patients (66%) were male. At the first clinic visit, the median age was 19 months (interquartile range [IQR], 11–42 months). Patients were followed up for a median of 30.9 months (IQR, 16–51 months). Patients were highly atopic; 90 (87%) had eczema, 68 (67%) had asthma, and 62 (60%) had allergic rhinitis by the last clinic visit. Ninety percent were allergic to at least 1 other food allergen, 56% to egg, 70% to milk, 29% to peanut, 50%

Table 1. Demographic Characteristics of the Study Patients

Characteristic	No. (%) of patients ^a (N = 103)
Sex	
Male	68 (66)
Female	35 (34)
Other atopic disease	
Eczema	90 (87)
Asthma	68 (67)
Allergic rhinitis	62 (60)
Other food allergies	
Egg	58 (56)
Milk	72 (70)
Peanut	30 (29)
Soy	51 (50)
Tree nuts	15 (15)
Family history of atopy	77 (75)
Age at initial visit, mo (IQR)	19 (11–42)
Duration of follow-up, mo (IQR)	31 (16–51)
Median initial wheat specific IgE level, kU/L (IQR)	24 (5–69)
Median peak wheat specific IgE, kU/L (IQR)	73 (14–101)

Abbreviation: IQR, interquartile range.

^a Data are number (percentage) of patients unless otherwise indicated.

Table 2. Types of Wheat Reactions

Reaction type	No. (%) of patients
Symptoms at presentation (N = 103)	
Skin (except eczema)	31 (30)
Eczema	23 (22)
Gastrointestinal	12 (12)
Lower respiratory tract	11 (11)
Upper respiratory tract	4 (4)
Oral erythema	3 (3)
No exposure or unclear history	42 (41)
Symptoms with unintentional exposures (N = 88)	
Skin (except eczema)	51 (58)
Eczema	8 (9)
Gastrointestinal	12 (14)
Lower respiratory tract	36 (41)
Upper respiratory tract	11 (13)
Oral erythema	4 (5)
Anaphylaxis ^a	40 (45)

^a Two or more body systems or lower respiratory tract involvement.

to soy, and 15% to tree nuts. Eight (8%) had eosinophilic gastrointestinal disease. Seventy-seven (75%) had a recorded family history of atopy. The median initial wheat specific IgE level was 24 kU/L (IQR, 5–69 kU/L), and the median peak wheat IgE level was 73 kU/L (IQR, 14 to >100 kU/L).

In those presenting with a clinical reaction, rash was the most common initial symptom (Table 2). Patients had an average of approximately 1 unintentional exposure every 4 years at risk, of which 78 of 88 (89%) resulted in symptoms. Forty of 88 unintentional exposures (45%) resulted in anaphylaxis, defined as either lower respiratory tract symptoms or at least 2 body system involvements¹² (Table 2). Seventy-six (86%) of the exposures were due to ingestion of wheat, and 12 (14%) were due to contact or inhalational exposures. Of the unintentional ingestions, 45 of 76 (59%) were caused by foods clearly containing wheat, such as bread, cake, cookies, cereal, and wheat flour. Breaded products and candies were other common sources of unintentional exposure.

Resolution of Wheat Allergy

Sixty-three of 103 study participants (61%) underwent a food challenge during the study period, and 24 (23%) underwent more than 1. Overall, 40 of 95 food challenges (42%) were passed, including 20 of 40 home challenges (50%) and 20 of 55 office challenges (36%). Symptoms during failed office challenges tended to be more severe than during home challenges. For example, lower respiratory tract symptoms were present in 13 of 35 failed office challenges (37%) compared with 1 of 20 failed home challenges (5%). Nine of 20 failed home challenges (45%) were due to eczema flare.

The median age of acquisition of tolerance was 79 months (IQR, 42–190 months). The percentage of study participants who had achieved tolerance to wheat was 29% by the age of 4 years (95% confidence interval [CI], 19%–43%), 45% by the age of 6 years (95% CI, 34%–59%), 56% by the age of 8 years (95% CI, 43%–69%), 62% by the age of 10 years (95% CI, 48%–75%), 65% by the age of 12 years (95% CI, 51%–78%), and 70% by the age of 14 years (95% CI, 55%–84%) (Table 3).

In addition, sensitivity analyses were performed that evaluated the effects of alternative definitions of resolution of wheat allergy. When patients were assumed to have resolved their allergy after 1 year without symptoms and a wheat IgE level of less than 20 kU/L (definition 2), the median age of resolution was 66 months (IQR, 33–122 months). Under definition 3, the least stringent definition, requiring a wheat IgE level of less than 50 kU/L and 1 year without symptoms, the median age of resolution was 57 months (IQR, 32–99 years) (Table 3 and Fig 1).

Predictors of Prognosis

There were 397 wheat IgE levels recorded. Wheat IgE level was correlated with resolution of allergy (Table 4 and Fig 2), and the peak wheat IgE level predicted the rate of resolution ($P < .001$ for trend). The median age of acquisition of tolerance was 31 months for the group with a peak wheat IgE level of less than 20 kU/L, 54 months for those with a peak IgE level between 20 and 49 kU/L, and 145 months for those with a peak IgE level of more than 50 kU/L (Fig 3). By the

Table 3. Incidence of Wheat Allergy Resolution

Age, y	Criteria for outgrown allergy		
	Definition 1: passed food challenge, % (95% CI) [number at risk]	Definition 2: passed food challenge or had a wheat IgE level <20 kU/L and no symptoms in 12 months, % (95% CI) [number at risk]	Definition 3: passed food challenge or had a wheat IgE level <50 kU/L and no symptoms in 12 months, % (95% CI) [number at risk]
2	11 (4–24) [53]	11 (4–24) [53]	11 (2–24) [53]
4	29 (19–43) [49]	35 (24–48) [47]	40 (28–52) [46]
6	45 (34–59) [29]	55 (43–67) [28]	60 (49–72) [26]
8	56 (43–69) [18]	67 (55–78) [18]	72 (60–82) [18]
10	62 (48–75) [11]	74 (61–84) [10]	83 (72–91) [8]
12	65 (51–78) [8]	78 (66–88) [7]	85 (74–92) [6]
14	70 (55–84) [5]	82 (70–91) [5]	85 (74–92) [5]

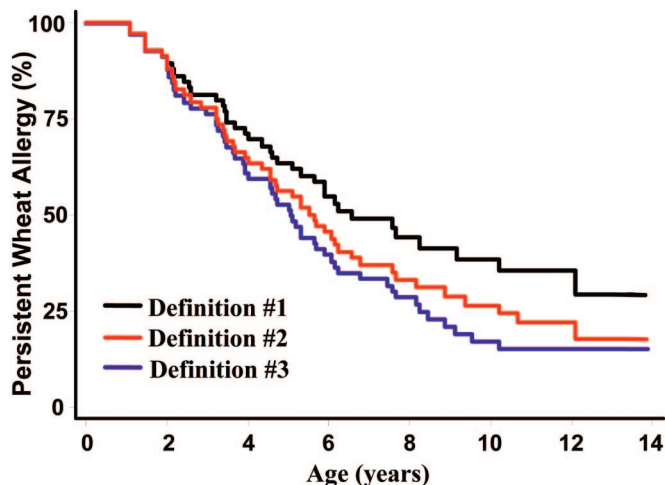


Figure 1. Resolution of wheat allergy over time. Kaplan-Meier curves depicting resolution of wheat allergy over time under 3 definitions of resolution: passing a food challenge (black line, definition 1), having gone 1 year without symptoms with a wheat IgE level of less than 20 kU/L or passing a food challenge (red line, definition 2), or having gone 1 year without symptoms with a wheat IgE level of less than 50 kU/L or passing a food challenge (blue line, definition 3).

Table 4. Median Wheat IgE Levels in Patients With Persistent vs Resolved Wheat Allergy

Age, y	Wheat specific IgE, kU/L		P value ^a
	Persistent	Outgrown	
<2	28	13	.05
2-4	69	21	.04
4-6	70	24	.006
6-8	62	25	.05
8-10	68	14	.09

^a Mann-Whitney test.

end of analysis, 56% of those with a peak wheat IgE level of less than 20 kU/L had outgrown their allergy, compared with 44% with a wheat IgE level between 20 and 49 kU/L and 27% for those with a wheat IgE level of 50 kU/L or higher. Twenty-one percent of those whose peak wheat IgE level was more than 100 kU/L had resolved wheat allergy. In general, the peak wheat IgE level occurred before 4 years of age (Fig 2). The rate of acquisition of tolerance did not vary by the patient's sex ($P = .89$), number of other food allergies ($P = .48$), or the presence of eczema ($P = .46$), allergic rhinitis ($P = .22$), or asthma ($P = .43$).

Patients Whose Conditions Were Diagnosed by a Positive Test Result Only

An additional 66 patients had a wheat IgE level greater than 20 kU/L and had never been exposed to wheat before their first clinic visit. Patients who did not have a history of symptomatic exposure to wheat had more concurrent food allergies ($P = .03$) and eczema ($P = .02$) and tended to

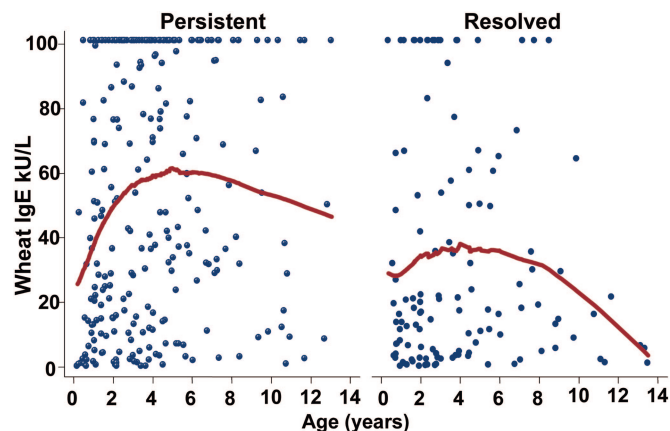


Figure 2. The relationship of wheat IgE level to age. The blue dots show the scatterplot of all wheat IgE levels recorded to the age of 14 years for those patients with (A) persistent wheat allergy (266 values) and (B) resolved wheat allergy (124 values). The red lines depict the locally weighted running means (Lowess curves) of wheat IgE level by age (bandwidth, 0.8).

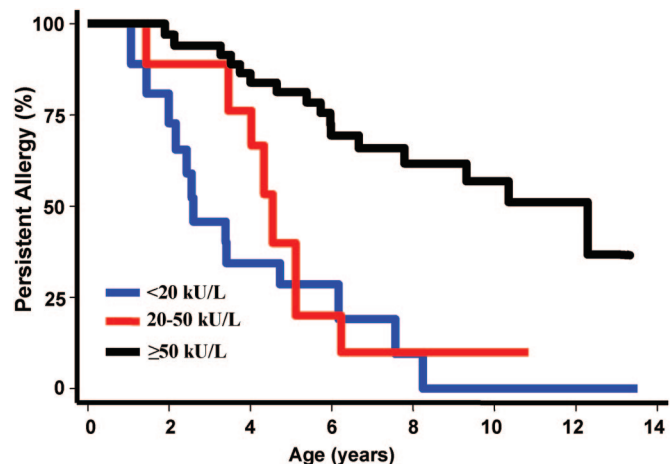


Figure 3. Relationship of peak wheat IgE level to persistence of wheat allergy during the first 14 years of life. The blue line represents patients with a peak wheat IgE level of less than 20 kU/L (27 patients), the red line represents those with peak wheat IgE level of 20 to 50 kU/L (16 patients), and the black line represents those with a peak wheat IgE level greater than 50 kU/L (60 patients). Log-rank test for trend, $P < .001$.

present at an earlier age (median, 15 vs 19 months; $P = .11$) than those who had a history of symptomatic wheat allergy. The rate of resolution of wheat allergy did not vary between this group and the group diagnosed as having wheat allergy based on symptoms ($P = .55$).

DISCUSSION

In this study we describe the natural history and other clinical characteristics of the largest population of wheat allergic patients that has yet been described. We found that within this referral population, the median age at resolution was approximately 6½ years. By 4 years of age, 29% had become

tolerant, and by the age of 10 years, 62% had become tolerant. Thirty-five percent remained allergic into their teenage years.

We found that wheat IgE level was an important prognostic factor predicting resolution of wheat allergy. Wheat IgE levels differed overall in the groups that outgrew wheat allergy compared with those individuals who remained allergic by the end of follow-up, and wheat IgE levels predicted the rate of resolution of allergy. For example, children with a peak wheat IgE level of less than 20 kU/L had a median age of resolution of 2½ years compared with 4½ years for children with a peak between 20 and 49 kU/L and 12 years for children with a peak of 50 kU/L and higher. As a practical matter, it can be hard to evaluate when a child's peak wheat IgE level has been reached, especially when the child is young. For patients and physicians with a laboratory value at a discrete point in time, these results can be used as a best case scenario to classify the patient into prognostic groups, realizing that the wheat IgE level can continue to increase.

Despite the predictive value of the wheat IgE level, it is important for physicians and patients to realize that the prognosis is not uniformly bleak even for children with the highest wheat IgE levels. During the study period, one-fourth of children with a peak wheat IgE level of more than 50 kU/L outgrew their allergy. Indeed, one-fifth of children with a peak wheat IgE level of more than 100 kU/L had resolution of their allergy by food challenge during the observation period. Compared with other food allergies, wheat specific IgE level is less helpful in predicting clinical reactivity and prognosis.^{4,5} Despite attempts in several studies, clear cutoffs for wheat IgE levels that predict clinical reactivity have not been established.^{10,11} One reason may be that grass pollens and wheat can be cross-reactive *in vitro*, creating false-positive wheat IgE test results.¹³ In our experience, children passed wheat challenges with even the highest levels of wheat IgE. As our understanding of the epitopes most responsible for reactivity to wheat increases, an improved *in vitro* test with greater predictive qualities might be developed. In the meantime, although imperfect, the wheat IgE level provides some guidance regarding prognosis.

In contrast to other studies of the natural history of food allergy,^{4,5} we did not find that the presence of other food allergies or atopic disease predicted the rate of resolution of allergy. This finding may be because of the highly atopic nature of this population; 41% of patients had at least 3 other possible food allergies. Our study may not have been powered to detect differences between the small group without other allergies and the much larger multiallergic group.

As a retrospective study, this analysis has several potential limitations. We see a highly allergic population that may not be generalizable to the larger food allergic population. For example, 8% of patients had eosinophilic gut disease, likely reflecting the referral patterns of our clinic. Although the median age at first visit was only 19 months, patients may present to our clinic because they are already showing signs of persistent allergy. In our analyses, we adjusted for the

possibility that some patients may have outgrown their wheat allergy before the time when they would have been referred to our clinic.

Because we could not be certain that they were truly allergic to wheat, we excluded patients who were never exposed to wheat, even if they had high wheat IgE levels. By excluding these children, who tended to present at a younger age with more concurrent allergies, we may have introduced bias to our estimates of persistence. However, including patients with a wheat IgE level greater than 20 kU/L and no evidence of tolerance at the initial visit did not change the rates of resolution of wheat allergy or its relationship to wheat IgE level.

In a study of this kind, data regarding acquisition of tolerance are by necessity imprecise. Home challenges were unsupervised and unblinded and may have been stopped earlier than they would have in a research challenge setting. Because we relied on clinic medical records, it is likely that some unintentional exposures and other data were not captured. Although we generally follow a schedule of every year or every other year challenges, family preference may result in less frequent challenges. Because of the uncertainty in our accounting of tolerance acquisition, we created 2 alternative definitions of tolerance by assuming that patients with a wheat IgE level below 20 kU/L (definition 2) or 50 kU/L (definition 3) and no symptoms in 1 year were no longer wheat allergic. On the basis of our own data, we expect that definitions 2 and 3 overestimate the rate of resolution because 40% of all patients with a wheat IgE level of less than 20 kU/L failed their challenges, as did 50% of those with a wheat IgE level of less than 50 kU/L (data not shown). Nonetheless, these definitions permit an estimation of the sensitivity of the results to the challenge patterns of our clinic. Whether analyzed under the most stringent definition of tolerance or the least, our data suggest that the median age of resolution of wheat allergy is by the school-age years.

This places wheat allergy as 1 of the most easily outgrown of the common food allergies. Compared with recent analyses using our clinic population that found a median age of 8 to 12 years for outgrowing egg and milk allergy and that only 20% of peanut allergic children ever outgrow their allergies, the prognosis for wheat allergy is good.⁴⁻⁶ Nonetheless, wheat allergy persists into teenage years for a significant minority of children. In addition, our data on wheat reactions in this population demonstrate that reactions are frequently severe, with 45% of unintentional exposures resulting in anaphylaxis. Because of the unpredictable nature of reactions to wheat exposure, caution should be exercised when recommending home introduction of wheat.

In conclusion, we found in this analysis of a large cohort of children with wheat allergy that half of children outgrew their allergy by 6½ years of age. The level of wheat specific IgE can be helpful in counseling wheat allergic patients about their chances of outgrowing wheat allergy. Despite the utility of the wheat IgE level, our results also highlight the impor-

tance of periodic food challenges regardless of wheat IgE level in children with wheat allergy.

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