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IgE antibodies and response to cow’s milk elimination diet in pediatric eosinophilic esophagitis

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Summary

Milk is a common cause of eosinophilic esophagitis. Allergy testing does not predict response to dietary therapy. In this study, patients with low or undetectable IgE antibodies to milk achieved histologic remission with milk elimination.

Keywords

eosinophilic esophagitis; children; food allergens; IgE assay; dietary treatment; remission

To the Editor

There are three lines of evidence supporting cow’s milk as a relevant problem food for pediatric patients with eosinophilic esophagitis (EoE). First, studies of the six-food elimination diet followed by reintroduction of food groups showed that when cow’s milk was reintroduced, symptoms or inflammation returned in up to 74% of patients. Second, it was subsequently reported in a retrospective analysis that a significant proportion of EoE patients (65%) responded to single food elimination of cow’s milk (1). In our own recent prospective study of patients treated with cow’s milk elimination, we also found that 65% of patients had <15 eosinophils/high power field (hpf) after 6-8 weeks of treatment (2). Finally, a striking proportion of pediatric EoE patients have low levels of serum IgE antibodies to cow’s milk (3). Our objective for the current analysis, was to evaluate the relationship between specific...
IgE antibodies to cow's milk, as well as other common problem foods, and histologic response after cow's milk elimination.

Through two separate studies, we have prospectively observed 27 patients who were treated with cow's milk elimination diet (2). In the first study, patients were treated with proton pump inhibitor (PPI) concurrently (2). Subsequent patients were treated with PPI prior to starting cow’s milk elimination diet. Twenty-one patients had repeat upper endoscopy after 6-8 weeks of treatment to evaluate histologic response. Serum analysis for total IgE and specific IgE antibodies to cow’s milk, egg, wheat, soy, and peanut was performed by ImmunoCAP (ThermoFisher Scientific/Phadia, Uppsala, Sweden). In nine patients, serum was available to perform additional studies and IgG4 antibodies to cow’s milk and IgE antibodies to milk components were also measured by ImmunoCAP. We analyzed the categorical variables IgE antibodies to food (≥0.35 IU/ml) and histologic response (yes or no) using the chi square test, and after testing for normality, we compared geometric mean levels of IgE antibodies in “responders” and “non-responders” using the t test. Levels of IgG4 antibodies to cow's milk were analyzed using the Mann Whitney U test. Log ratios of IgG4/IgE antibodies to milk were compared using a paired t test.

Thirteen patients (62%) were classified as “responders” to dietary elimination of cow's milk based on having <15 eosinophils/hpf on repeat esophageal biopsy. Peak esophageal eosinophil counts decreased from a mean of 59 [standard deviation (SD) 35] to 6.3 (SD 4.8) in responders compared with a mean of 56 (SD 31) to 34 (SD 11) in nonresponders. Levels of specific IgE antibodies to cow’s milk were <0.35 IU/ml for 8/13 responders (62%). In contrast, specific IgE antibodies to cow’s milk were <0.35 IU/ml for 2/8 non-responders (25%) (p=0.1) (Table IA). The geometric mean level of specific IgE to cow's milk among patients with detectable IgE antibodies was significantly lower in responders at 0.50 IU/ml [95% confidence interval (CI) .32-1.0] versus 2.6 IU/ml (95% CI 1.6-5.1) in non-responders (p=0.002) (Table IB). Furthermore, there was a direct correlation between levels of IgE antibodies to milk and the number of esophageal eosinophils found after treatment (R=0.46, p=0.04) (Fig E1). Among the nine patients who had analysis for IgE to milk component allergens, 0/6 responders had detectable IgE antibodies to any specific milk protein compared with 3/3 non-responders. Patients who did not respond to single food elimination of cow's milk also had IgE antibodies to wheat (p=0.006) and egg (Table IB). All patients tested, including those without specific IgE to cow's milk, had IgG4 antibodies to milk [median level 1420 mg/mL (range 17.6-2010)]. Overall log ratios of IgG4/IgE antibodies to milk decreased significantly with cow's milk elimination diet from 3.0 to 2.6 (p=0.05). The change in ratios was not different in responders and nonresponders (p=0.7).

Our results confirm that patients with levels of milk specific IgE less than 0.35 IU/ml, or even undetectable antibodies (i.e. <0.1 IU/ml), can respond to cow's milk elimination diet alone. In addition, the levels of IgE antibodies to cow’s milk were paradoxically lower in responders compared with quantities in those children who did not respond to the elimination diet (p=0.01) (Fig 1A). Taken with clear evidence that food can cause eosinophil-rich inflammation in the esophagus, our results are in keeping with a model where the disease is primarily driven by a T cell response, including T cells producing cytokines that are responsible for the eosinophil recruitment. However, we would
hypothesize that those T cells produce relatively little IL-4 and IL-13. The evidence that
these patients have IgG4 antibodies is in keeping with the production of IL-10 together with
IL-4 (4).

The low levels of IgE antibodies to milk in EoE seem distinct from other food allergy
syndromes. Levels of IgE antibodies to peanut or alpha-gal are typically much higher in
patients presenting with peanut anaphylaxis or with the alpha-gal syndrome, respectively (5).
Instead the low levels of IgE relative to IgG4 ab appear most similar to three different forms
of “tolerance”; i) beekeepers who have received multiple stings, ii) individuals who live with
a cat, and iii) sustained unresponsiveness in patients treated with peanut orally (6-8).
However, the response in EoE cannot be regarded as a form of tolerance since it is clearly
associated with a symptomatic form of inflammation in the esophagus.

The low levels of IgE antibodies with increased IgG4 antibodies to milk are in keeping with
existing evidence for the pathogenesis of EoE. Prussin and colleagues found that patients
with eosinophilic gastrointestinal disease (EGID) had a similar frequency of peanut specific
IL-4 producing T cells associated with an increased number of IL-5 producing T cells
compared with peanut allergic patients (9). Kottyan et al recently reported gene expression
results that are also in keeping with this form of inflammation (10).

Although the results we report are retrospective and need to be confirmed in a larger group
of patients, we feel that analysis of levels of IgE antibodies may be useful for patients with
EoE. From a clinical standpoint, the data from our studies suggest that IgE antibody levels to
milk may be a biomarker that is helpful for predicting response to cow’s milk elimination
diet with patients with low levels of IgE antibodies having the greatest drop in eosinophils
(Fig 1B). The IgE response may also be helpful in identifying the components of cow’s milk
that are relevant to the immune response, even in those patients who don’t have detectable
IgE antibody. Our recent paper on component analysis suggests that IgE antibodies to Bos d
4 and Bos d 5 correlate best with IgE to milk in EoE patients (3).

Supplementary Material
Refer to Web version on PubMed Central for supplementary material.

Acknowledgments
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Appendix
Additional Commentary
Although PPI non-responsiveness has been regarded as an important criterion for the
diagnosis of EoE, recent evidence has argued against that view (1). That paper argues
strongly that the subjects who respond to PPI are genomically and clinically similar to the
subjects who do not respond to PPI. Our own data has consistently suggested the
immunological responses to food in patients are independent of PPI responsiveness. The
importance of the response to cow’s milk, was first identified during the successive reintroduction of foods after successful treatment with six food elimination (1-3).

Additional References


References

Fig 1A.
Histologic response to cow’s milk elimination diet in EoE patients grouped by level of IgE antibodies to milk.

* Chi square test for trend
Fig 1B.
Esophageal eosinophil counts before and after treatment with cow’s milk elimination diet in EoE patients grouped by level of IgE antibodies to milk.
Table IA

Levels of specific IgE antibody (IU/ml) to foods and distinct milk components at baseline.

<table>
<thead>
<tr>
<th>Age (y)</th>
<th>Gender</th>
<th>Milk</th>
<th>Bos d 4</th>
<th>Bos d 5</th>
<th>Bos d 8</th>
<th>Bos d 6</th>
<th>Egg</th>
<th>Wheat</th>
<th>Soy</th>
<th>Peanut</th>
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<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>D001</td>
<td>13</td>
<td>M</td>
<td>&lt;0.10</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
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<td>&lt;0.10</td>
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<tr>
<td>D015</td>
<td>2</td>
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<td>&lt;0.10</td>
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<td>&lt;0.10</td>
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<td>D011</td>
<td>10</td>
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<td>nd</td>
<td>nd</td>
<td>0.33</td>
<td>33.2</td>
<td>26.0</td>
<td>18.5</td>
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<td>&lt;0.10</td>
<td>0.12</td>
<td>&lt;0.10</td>
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<td>&lt;0.10</td>
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<td>0.26</td>
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<td>0.17</td>
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<td>0.19</td>
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<td>nd</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
</tr>
<tr>
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<td>0.34</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
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<td>&lt;0.10</td>
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<td>nd</td>
<td>nd</td>
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<td>&lt;0.10</td>
<td>0.17</td>
<td>0.14</td>
<td>nd</td>
</tr>
<tr>
<td>Diet5</td>
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<td>F</td>
<td>1.67</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>0.25</td>
<td>0.24</td>
<td>0.11</td>
<td>nd</td>
</tr>
<tr>
<td>Diet7</td>
<td>14</td>
<td>F</td>
<td>0.26</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>&lt;0.10</td>
<td>0.35</td>
<td>0.18</td>
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</tr>
<tr>
<td><strong>Non-responders</strong></td>
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<td></td>
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<td></td>
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<td>16</td>
<td>M</td>
<td>3.65</td>
<td>2.67</td>
<td>2.88</td>
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<td>0.82</td>
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<tr>
<td>D013</td>
<td>14</td>
<td>M</td>
<td>2.53</td>
<td>2.37</td>
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<td>0.56</td>
<td>0.60</td>
<td>0.27</td>
<td>0.39</td>
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<td>1.58</td>
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<td>0.96</td>
<td>0.75</td>
<td>0.43</td>
<td>0.17</td>
<td>0.39</td>
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<td>D006</td>
<td>11</td>
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<td>nd</td>
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<td>nd</td>
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<td>&lt;0.10</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
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<tr>
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<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>0.38</td>
<td>0.72</td>
<td>0.14</td>
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<td>Diet3</td>
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<td>F</td>
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<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>2.57</td>
<td>1.69</td>
<td>0.84</td>
<td>1.33</td>
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<td>Diet4</td>
<td>3</td>
<td>F</td>
<td>8.08</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>0.78</td>
<td>1.58</td>
<td>0.31</td>
<td>0.18</td>
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<tr>
<td>Diet6</td>
<td>5</td>
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<td>&lt;0.10</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>0.28</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
<td>&lt;0.10</td>
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Table IB

Analysis of IgE antibodies based on histologic response to cow's milk elimination diet.

<table>
<thead>
<tr>
<th></th>
<th>Responders n=13</th>
<th>Non-responders n=8</th>
<th>p value</th>
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<tbody>
<tr>
<td>Cow's milk IgE Ab ≤0.35 IU/ml, n (%)</td>
<td>8 (62%)</td>
<td>2 (25%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Cow's milk IgE Ab level, IU/ml</td>
<td>0.50</td>
<td>2.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Milk component IgE Ab, n/number tested</td>
<td>0/6</td>
<td>3/3</td>
<td>---</td>
</tr>
<tr>
<td>IgE Ab ≤0.35 IU/ml to other foods, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egg</td>
<td>0</td>
<td>4 (50%)</td>
<td>---</td>
</tr>
<tr>
<td>Wheat</td>
<td>2 (15%)</td>
<td>6 (75%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Soy</td>
<td>1 (7.7%)</td>
<td>3 (38%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Peanut</td>
<td>1 (7.7%)</td>
<td>2 (25%)</td>
<td>0.3</td>
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<tr>
<td>IgE Ab levels to other food, IU/ml</td>
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<td></td>
<td></td>
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<tr>
<td>Egg</td>
<td>0.28</td>
<td>0.52</td>
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<tr>
<td>Wheat</td>
<td>0.60</td>
<td>0.93</td>
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Ab=antibody