IgG Testing: Is it All it's Cracked Up to Be?  
IgG for Foods: Fad or Fact?

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8:45pm - 10:00pm

Disclosures

David R. Naimi, DO  
- Employment: Northwest Asthma & Allergy Center (Seattle, WA)  
- Financial interests: Speaker's bureau - True, Prada  
- Research interests: Allergy/immune disease  
- Organizations: AAAAI, ACAAI, IACAI, WSIIAAI  
- Gifts: Nothing to disclose  
- Other: Medical advisory board - PPIES Foundation  
  Medical advisor - Washington FEAST

Megan T. Ott, MSN, RN, CPNP  
- Employment: The Children's Hospital of Philadelphia (Philadelphia, PA)  
- Financial interests: Nothing to disclose  
- Research interests: DBV technologies: using allergy patch testing for peanut allergy  
- Organizational: AAAAI, NAPSAR  
- Gifts: Nothing to disclose

Objectives

- Brief review of IgG  
- Review advertisements and community claims for the benefit of IgG testing for foods  
- Literature review of efficacy and interpretation of IgG testing  
- Group discussion

IgG Review

Major Immune System Components

* B- Lymphocytes produce antibodies (or immunoglobulins or gammaglobulins)  
* T- Lymphocytes  
* Phagocytes  
* Complement

Antibodies in brief

* IgA- produced near mucus membranes; present in breathing passages, GI tract, eyes  
* IgM- largest antibody; lymph fluid; made in response to infection  
* IgE- lungs, skin, mucus membranes; important for allergy  
* IgD- found in small amounts in chest and abdomen; function is unclear  
  * IgG - Smallest but most common antibody  
  - IgG is key to fighting bacteria and viral infections
IgG: In a few words...

- Binds to pathogens—viruses, bacteria and fungi
- One of five major immunoglobulins
- Most abundant antibody in circulation
- Half life about 23 days- the longest of any plasma protein
- Opsonizes bacteria to allow phagocytosis
- Activates complement cascade
- Binds to TRIM21 to allow intracellular antibody-mediated proteolysis

IgG

- Four sub-classes of IgG:
  - IgG 1- Most abundant
  - IgG 2
  - IgG 3
  - IgG 4- Least abundant

  Presence of IgG4 to a food indicates repeated exposure to a food (Normal reaction!)

(Aliberson, 2009)

Why is IgG a question related to food?

- 1980s studies suggested antigen specific IgG4 induces histamine release from basophils
  - Prior to knowledge of Th2
- 1990s commercial labs began to offer assays for detection of food immune complexes...

Now presume...

- As you desensitize to a food that one is IgE allergic, note an increase in IgG levels
  - Specifically IgG 4
- Thus, higher numbers of IgG 4 = better desensitized?
- Does it block the effect at mast cell level? Inhibit IgE mediated antigen presentation?

(Aliberson, et al., 2009; Stäpel, et al., 2000)

Community claims and Advertisements

- Pond's bitters
- Witch cream
- Cancer Cured at Home
Google IgG testing and food allergies—About 96,500 results (0.26 seconds)
  o Majority of results are labs offering testing

Direct to consumer labs offer the ability to identify an etiology and potential cure for symptoms
  o +/- Insurance coverage
  o Identify “Non-IgE hypersensitivity to foods”

In general, what is proposed is to test IgG levels to a panel of foods to determine which is triggering symptoms

One source claims: “Allergy Relief”

- Immediate-onset food allergies are frequently permanent and fixed allergies. Once you develop an allergy to peanuts or shellfish, for example, it’s for life.

- Delayed-onset food allergies are listed as commonly reversible. If you strictly eliminate the allergic foods for 3 to 6 months, you can bring most of them back into your diet and remain symptom-free.
  o Claim that they may lie behind many of chronic medical conditions of unknown cause.
  o These allergic people suffer for years, even decades, without ever suspecting that their health problems are rooted in what they eat.

- Testing of all IgG sub-classes is key per this site. By not screening for all sub-classes, treatment may only be partially effective.

- Testing available for the initial low price of $299.00.

Claim: “Must complete IgG testing to foods to determine:”

- A finger-prick blood test is analyzed by a specialized lab.

  Reported advantages:
  o Gives a clear outline of food intolerances and the severity of the intolerance.
  o Tests for a wide variety of commonly consumed foods.
  o Can be done in office or at home.

  Reported disadvantages:
  o Can be expensive.
  o Food must be consumed within 3 weeks prior to the test for an accurate reading.

“IgG testing will improve:”

<table>
<thead>
<tr>
<th>Condition</th>
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</thead>
<tbody>
<tr>
<td>ADHD</td>
<td>Diabetes</td>
<td>Heartburn</td>
<td>Psoriasis</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Digestive Disorders</td>
<td>Irritable Bowel Syndrome (IBS)</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Autism</td>
<td>Ear Infections</td>
<td>Joint &amp; Muscle Pain</td>
<td>Skin Disorders</td>
</tr>
<tr>
<td>Asthma</td>
<td>Eczema</td>
<td>Leaky Gut</td>
<td>Weight Loss</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>Fibromyalgia</td>
<td>Mental Fatigue</td>
<td>Yeast Infections</td>
</tr>
<tr>
<td>Celiac</td>
<td>GERD</td>
<td>Migraines</td>
<td>Poor Memory</td>
</tr>
<tr>
<td>Chronic Fatigue Syndrome (CFS)</td>
<td>G.I. Disorders</td>
<td>Obesity</td>
<td>Sinusitis</td>
</tr>
<tr>
<td>Depression</td>
<td>Headaches &amp; Migraines</td>
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Provider Claims:

- “Our goal is to find the cause of symptoms of illness and disease. In some people the cause is the food we eat, and a sensitivity or allergy to those foods. Food allergies and sensitivities can have an incredibly wide range of symptoms.”

- “Symptoms of food sensitivity include acne, arthritis, depression, psoriasis, colitis, allergies, sinusitis...”

- “Considerable evidence for IgE testing, but there is also abundant evidence that IgG. It is an important marker for allergy testing. IgG and IgG-complexes are involved in 80% of all food allergy reactions.”
  o IgG is involved in delayed immune responses which are more common in food intolerance.

An online lab offers a panel direct to patient

- “The newest development which only needs a small amount of blood for testing of 95 food antigens.”
  o Can be done at home or in the office

- “Provides results based on concentrations – safe, moderately safe or avoid.”
  o These results can then be used to design therapeutic elimination or rotation diets.

- “Food IgG levels increase in response to the presence of the food antigens in the bloodstream, especially those foods eaten often such as corn, wheat, soy, and egg. IgG responses may cause delayed symptoms, such as joint or muscle pain, chronic headaches, fatigue, eczema, and psoriasis.”

- Free consultation and free shipping!
Additional Claims

- "People with food sensitivities have non-allergic food reactions and increased IgG antibodies to food due to inflammation."
- "Nutritional interventions based on IgG circulating antibodies against food antigens affects stool frequency, abdominal pain and well being."
- "IgG represents the pro-inflammatory effect of food intake."

Claims have merit?

Improved headaches:
- "Elimination diet based solely on IgG will decrease frequency of headache and number of headache days."
- "Rotary diet of introducing one new food per cycle of food identified can prevent headaches."

Obesity:
- "Anti-food IgG is linked to low grade inflammation and atherogenesis."

GI Symptoms:
- "Food specific IgG4 guided exclusion diet improved symptoms of bloating, severity, depression and improved quality of life."
- "Serum IgE level does not capture mucosal allergy response in intestine."
- "IgG4 may be physiologic response of the gut immune system to a dietary antigen challenge."
- "Elimination diet based on IgG antibodies in migraine patients with IBS can relieve symptoms in both groups."

Allergy Office response to questions about testing:

What is IgG4 or IgG testing?
- IgG4 or IgG testing (often named "food allergy panel") is a screening blood test that has gained popularity in the past several years.
- Its supporters believe the test can determine the foods to which you are allergic or sensitive. When you stop eating those foods, your symptoms, whichever they may be, will go away. In reality, it is probably not so simple.
- For unknown reasons, the immune system also makes IgG antibodies to many of the foods we eat. IgG directed at a food isn’t necessarily harmful. Healthy individuals can have elevated IgG levels to a particular food(s), yet have no symptoms at all.
- In fact, food allergy researchers are finding that higher IgG levels may actually protect against food allergy. It goes to show that there is still much to learn about food allergy/sensitivity and the immune system.

- See handouts

Studies & References Sited to Validate IgG to Foods

Irritable Bowel Syndrome (IBS)
Results of studies of IgG antibody elimination diets for migraine headaches

<table>
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<tr>
<th>Author</th>
<th>Subjects</th>
<th>Trial</th>
<th>Results</th>
</tr>
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<tr>
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Average mean score of migraine with chronically high tea was 24.1±1 against 24.5±1. Compared in baseline, there was statistically significant difference in B (B = 24.1±1 vs. 24.5±1, P < 0.001) and C (B = 24.1±1 vs. 24.5±1, P < 0.001) in the elimination diet group. These differences were not statistically significant in the prevention diet group. There was no significant difference in B (B = 24.1±1 vs. 24.5±1, P > 0.05) and C (B = 24.1±1 vs. 24.5±1, P > 0.05) in the elimination diet group. These differences were not statistically significant in the prevention diet group. There was no significant difference in B (B = 24.1±1 vs. 24.5±1, P > 0.05) and C (B = 24.1±1 vs. 24.5±1, P > 0.05) in the elimination diet group. These differences were not statistically significant in the prevention diet group.

Results of studies of IgG antibody elimination diets for migraine headaches

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Results of studies of IgG antibodies in irritable bowel syndrome: a randomized controlled trial

- Double blind, randomized, parallel design
- 150 patients in IBS randomized to receive, for 3mo, either a "true diet" excluding all foods to which they had raised IgG antibodies (IgG1, IgG2) or a "sham diet" excluding the same number of foods but NOT those to which they had antibodies.
- Primary outcome measures: change in IBS symptom severity & global rating scores. Secondary outcome measures: Neuroendocrine symptomatology, QOL, and anxiety/depression.
- Obtained IgG also specific to 29 different food antigens.
- Most patients found to be (+) to 6-7 foods (range 1-19).
- Sham diet eliminated same # of foods but not those particular foods in the True diet.
- Adherence was lower in those on the true diet (14% patients withdrawn from the study in the true diet group mainly b/c of difficulty in following the diet).

Table 3

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<thead>
<tr>
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<th>Sham group</th>
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</tr>
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Figure 2: Mean change in symptom severity score of 12 weeks with and without elimination diet (95% CI for difference between groups shown). There was a significantly lower score in the elimination diet group at 12 weeks (P < 0.05). There was no significant difference between the groups at 6 weeks (P = 0.79).

Figure 3: (a) Changes in symptom severity score from baseline at 12 weeks with and without elimination diet (95% CI for difference between groups shown). There was a significantly lower score in the elimination diet group at 12 weeks (P < 0.05). There was no significant difference between the groups at 6 weeks (P = 0.79).

- Content of food elimination diets in true & sham groups were NOT similar. Dietary restrictions in one group are NOT controlled for by the other group.
- Treatment group excluded significantly different foods to the control group, particularly those foods which appear in exacerbation symptoms of IBS.
- "True diet": 38% avoided milk products, 39% avoided wheat (both foods are known to be common offenders in IBS). Total number of foods avoided by this group = 498.
- "Sham diet": 13% avoided milk, 8% avoided wheat. Total number of foods avoided = 143.
- These differences between the diets could explain the modest differences in outcome between the two diet groups.
- More care needs to be taken to match them not just for number of food types excluded but also for types of food.

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- Effectiveness of blinding is questionable.
- Does the test add specificity?
- Would patients with IBS gain as much symptomatic improvement if recommended to exclude the top four foods (cabbage, milk, whole egg, and wheat) compared with an IgG antibody test based diet?
- 86.7% in treatment group avoided yeast.
- "Yeast exclusion" diet is not a recognized diet in standard textbooks of diet & nutrition. This diet may sometimes entail exclusion of a wide range of foods (e.g., bakery products, alcoholic beverages, commercial fruit juices, cereals, condiments, dairy produce, legumes, meat products, canned food, dried fruit, etc).

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**Conclusions from the IBS studies**

**IBS**

- May indeed be true, proven benefits from dietary change.
- Trials that appropriately blind interventions in irritable bowel syndrome are difficult to design and implement.
- IgG to the food may reflect foods commonly consumed rather than those contributing to symptoms.
- There may be other food-specific immune effects, immune dysregulation, peptide effects or effects of dietary components on gut microbiota composition, irrespective of IgG values.

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**What does this mean?**

- Elevated IgG to certain foods in patients with IBS, inflammation/obesity & migraine?
- Elevated IgG antibodies to food could be secondary to inflammation and therefore be of more an epiphenomenon rather than a true delayed allergic reaction.
What we do know: IgG4 & the Development of Clinical Tolerance in OIT and SLIT Trials

- 30 subjects with CM allergy. After therapy, 1 of 10 subjects in the SLIT group, 6 of 10 subjects in the OIT/OTIT group, and 6 of 10 subjects in the OTIT group passed the 8 g challenge (p = 0.02 SLD vs OIT).
- By the end of therapy, titrated CM skin prick test results and CD4+ and CD20+ expression decreased and CM-specific IgG4 levels increased in all groups, whereas CM-specific IgE and spontaneous histamine release values decreased in only the OIT group.

- SLIT vs hazelnut: 33 patients, half randomized to active treatment and half to placebo. 30% of those on active treatment were able to tolerate 30 g of hazelnut at the end of the trial and showed increases in hazelnut-specific IgG4.

- Egg oral immunotherapy in seven children with IgE-mediated egg allergy, all of whom improved during the course of the study. Two were able to reach a state of complete oral tolerance. Hen's egg-specific IgG rose significantly in those subjects, IgE did not.

What we also know: IgG is increased in healthy controls

- 13 healthy lab workers. IgG4 and IgG5 obtained to specific foods.
- Positive results for IgG4 against different foods found in all samples, and did not significantly coincide with positive IgE.
- Increased IgG4 results were, in some of the subjects, related to clinical problems by intake of foods.
- "Positive IgG4 tests to foods therefore do not indicate the presence of food allergy, but are probably reflecting prolonged exposure to food components."

(+ IgG ... then what?

- Some companies construct a "rotary diet" for the patient to follow at home, though most laboratories do not get involved in the practice of medicine in this way.
- Such dietary prescriptions can be hard to follow & may cause nutritional deficiencies especially in children.

ANY testing...

- Allergy tests (SPT, serum IgE, patch testing, etc) MUST be interpreted in the context of the patient's specific clinical history, and the diagnosis of an allergy disorder CANNOT be based solely on a laboratory result.
- Food Allergy: Accurate diagnoses VERY important - to prevent unnecessary avoidance of foods & potentially harmful diets.

Testing in General: Can be a "Dangerous Weapon"

- All Physicians must educate themselves & their patients about the clinical utility of ANY test.
- The "Danger" - misdiagnosis, unnecessary specialist consults, wasted time & $$$.
- Panels for food allergy may be seen by some patients & physicians as a substitute for a thorough history & physical exam.
- Nonspecific use of large panels of allergens can lead to false positives and misinterpretation of the results, particularly in food allergy.

We need to utilize our testing wisely & responsibly.
American Academy of Allergy, Asthma & Immunology

Five Things Physicians and Patients Should Question

Don't perform unproven diagnostic tests, such as immunoglobulin G (IgG) testing or an indiscriminate battery of immunoglobulin E (IgE) tests, in the evaluation of allergy.

Appropriate diagnosis and treatment of allergies requires specific IgE testing (either skin or blood) and is based on the patient's clinical history. The use of other tests in attempts to diagnose allergies is approved and is not considered appropriate diagnosis and treatment. Appropriate diagnosis and treatment of both conditions is essential for optimal patient care.

Don't order sinus computed tomography (CT) or indiscriminately prescribe antibiotics for uncomplicated acute rhinosinusitis.

Many patients with suspected food intolerance/sensitivity are disappointed by the negative results of IgE testing. They often look elsewhere for testing that might be "more in line" with their expectations.

Sherer et al. Allergy. 2003

What NOT to Say

I have a food allergy... Look at these test results! What should I do?

You don't have a food allergy... Don't do ANYTHING. That testing is hogwash.

www.ericdopplemier.com

A More Appropriate Response

Oh... let's talk about what these results mean and what we know about IgG testing...

www.ericdopplemier.com

What I tell my patients

- IgG testing is controversial and is/should be used for research purposes. IgG is elevated in many foods in healthy individuals.
- IgG panels almost always come back (+) to what most of us eat a lot of: Wheat/Grains, Dairy, and Egg.
- If food intolerance/sensitivity is suspected:
  - Best way to diagnose this is avoidance of these foods for a certain duration (few/several weeks) followed by re-introduction.
  - Consultation with dietitian if continued avoidance of foods is done.

www.ericdopplemier.com

Final Thoughts

- Have an open mind & healthy skepticism
- IgG to foods needs further research.
- Too early to encourage patients or insurers to spend $ on panels that are not clinically validated/used.
- IgG could be a sign of clinical tolerance, normal response to food, or prolonged food exposure.
- IgG elevated in IBS, migraines, and inflammation? What is the link?
- IgG to foods is "NOT ready for prime time."

Sherer et al. Allergy. 2003