A proposed standard defining acceptable food allergy testing was circulated for comment on July 6, 2011. The announcement of the proposed standard was sent to all clinical laboratories currently permitted by NYS or applying for a NYS permit (approximately 1017 facilities). This distribution was by e-mail to the facility, laboratory contact person, and the director's e-mail as provided on their certificate of qualification application. The documents were also posted to the CLEP website.

The comment period ended August 15, 2011. Nine commenters representing regulated parties, health care systems, private individuals, a manufacturer and a health care provider submitted comments to the proposed standard. The standard was modified based on comments received. Insightful comments to the proposed standard generally indicated that the IgG food allergy testing performed by laboratories is not intended as the sole indicator to diagnose a Food Allergy (FA) but to assist health care providers to design therapies for management of FA-diagnosed individuals that include elimination diets, which is an appropriate intended use of the testing.

However, a review of tests for IgG to food allergens approved under a now obsolete “investigational test” approval model revealed that tests approved under this model were not offered as explicitly intended for appropriate utilization and/or were not sufficiently clinically validated for diagnostic claims. Therefore, the standard is adopted with effective date three months after the date of this letter to give laboratories time to submit validation packages that comply with Submission Guidelines as outlined in the cover letter accompanying this package. The use of all allergen-specific immunoglobulin testing to food allergens except for IgE-based assays must cease unless a current validation package has been submitted by the effective date and CLRS has determined that the package is substantially complete. The submission must:

- be made using the current general assay approval checklist
  (http://www.wadsworth.org/labcert/TestApproval/forms/General_Checklist.pdf)
- include the explicit intended use, clinical claims, example patient reports, and marketing information, and
- conform to the validation requirements articulated in the attached correspondence.

CLRS will review the packages submitted and provide written correspondence that indicates the disposition of the assay for clinical testing. Laboratories that submit a validation package by the effective date may continue to provide testing until written notification is received indicating otherwise.
**Diagnostic Immunology Sustaining Standard of Practice 4 (DI S4): Food Allergy Testing**

The laboratory shall use IgE based assays for food allergy testing unless written approval to use other immunologic tests have been received from the Department.

Validation studies for other immunologic tests must be submitted for review and must be approved prior to offering testing. Please refer to the CLEP Submission Guidelines and the Guidelines for the Diagnosis and Management of Food Allergy in the United States when submitting a validation package. Validation Guidelines are posted on the CLEP website at www.wadsworth.org/labcert/clep/clep.html
Background and Definitions

National Institute of Allergy and Infectious Diseases of the National Institute of Health (NIAID) definition of food allergy (FA) testing is the ingestion of food that leads to a severe allergic reaction that may result in death. The allergic reaction is IgE mediated and involves systemic mediator release from sensitized mast cells and basophils. Clinical symptoms indicating FA are acute and include swelling of lips and/or tongue, tightness/closure of throat, hives, vomiting, diarrhea, intestinal cramps, shortness of breath, wheeze, weak pulse and dizziness.

It appears that labs performing IgE testing do so for the purpose of assisting in the design of treatment including elimination diets for patients already diagnosed with chronic gastrointestinal ailments such as chronic diarrhea or constipation. Commenters described the testing as an assessment of delayed Type 3 allergic-related reactions to food. Another commenter described that the ratio between IgE and IgG4 was useful to determining the likelihood of tolerance or desensitization to a food.

NIAID definition of food allergen is a specific component of, or ingredient, in a food (typically proteins, but sometimes also chemical haptens when bind with proteins), that are recognized by allergen-specific immune cells resulting in characteristic symptoms.

Comments and Responses

Comment:

We concur in the NYDH (food allergy testing) policy. We do not do it and do not refer it.

Response:

The writers agree with the recommendation and have modified the standard accordingly.

Comment:

I just have a comment on the wording of the standard:

"The laboratory shall use IgE based assays for food allergy testing....etc."

Response:

The writers agree with the recommendation and have modified the standard accordingly.

Comment:

The Department may wish to specify in vitro IgE testing unless they are also allowing laboratories to perform specific IgE skin testing for food allergies.

I would also like to suggest that guidance include IgA and/or IgG gliadin testing as some algorithms suggest first testing IgA first to determine if an IgA deficiency exists, then IgG. If IgA is sufficient then IgG testing isn’t necessary.

Response:

The Clinical Laboratory Evaluation Program issues laboratory permits under the authority of Article 5 Title V which defines a clinical laboratory as a facility that examination of materials
derived from the human body. Therefore, the oversight of skin allergy testing is not in the scope of a laboratory permit.

The guidance has been modified based on the comments received. The guidance indicates that assays not cleared or approved by the Food and Drug Administration (FDA) need to be validated and submitted to the Department for approval. However, submission for review of Standard Operating Procedures Manuals and validation for any test system used by the laboratory prior to April 24, 2003 is not required, unless specifically requested. Please refer to the Management of NPL Requests available on our website at http://www.wadsworth.org/labcert/clep/Administrative/ChangeForms.htm.

Comment:

Our laboratory requests clarification regarding testing performed by us related to the attached draft standard. Attached is a copy of the approval letter received in 1997 for allergen-specific IgG testing. Please advise us of the status of the current approval for allergen-specific IgG testing. Is the approval for testing NY specimens affected by the proposed standard for food allergy testing using IgG subtypes or total IgG to food allergens?

Response:

All previous letters and/or permits issued by the Department for IgG and IgG subtypes for food allergy testing will be rescinded three months after the date of the adoption of the standard unless the laboratory submits a complete validation package. This includes "investigational test" approvals given to laboratories in the late 1990s for the purpose of identifying IgG to food allergens as part of the information in an allergic pathologic process. The "investigational test" approval model no longer exists.

Comment:

Thank you for the opportunity to submit a response with regards to both the letter of notification and the publication. As your letter of recommendation currently stands the reader may interpret your advice that all total IgG, IgG4 and IgG subclasses and allergen specific IgG4 are prohibited. However the guidelines published by Boyce et al recommend simply that allergen specific IgG4 does not have an established role in the diagnostic assessment of food allergies. To avoid confusion for the reader we believe the following points may therefore warrant consideration:

1. Under section 4.2.2.9 Non standardised and unproven procedures (pg 1112), guideline 12 states a list of tests that have been deemed "non standardised" and are therefore not recommended by the Expert Panel for the routine evaluation of IgE mediated food allergies. Among this list is the test or tests for allergen specific IgG4 levels. Within the document there is no reference to the use of total IgG subclass levels only to the levels of allergen specific IgG4. The terms "IgG", "IgG4" and "IgG subclasses" and "allergen specific IgG, IgG4 and IgG subclasses" appear to be interchangeable in the letter of notification. We would request that the distinction between total non-allergen specific assays and allergen specific assays are clarified for the reader and therefore please consider removing reference to either total IgG and IgG4 assays in the absence of specifying that it is allergen specific.
2. In paragraph 2 of the letter of notification there is the following sentence "To date, professional societies of allergists and immunologists in North America and Europe have advised against the use of IgG subclass assays for diagnosing food allergies."

With reference to point 1 above this sentence requires clarification for the reader. We believe that the advice in North America and Europe, such as that stated in the publication and AAAI, March 2008: 100 (3), Supplement 3, is in fact in reference to allergen specific IgG subclasses and is not pertinent to non-allergen specific IgG subclasses. Again, please consider removing reference to IgG subclass assays in the absence of specifying that it is allergen specific.

3. Section 1.5 (pg 1108) Summary states "that this guidance does not override their (the clinicians) responsibility to make decisions appropriate to the circumstances to the individual". And, paragraph 3 of the letter of notification states "we will prohibit the use of IgG4 and tests for other IgG subclasses or total allergen specific IgG for specimens accepted from New York State". To our knowledge elevated levels of total human IgG subclasses do not appear to be measured as part of allergy testing however, during some clinical investigations into a suspected allergy the levels of IgG subclasses may be determined if the clinician suspects they can identify the underlying cause, e.g., a primary immunodeficiency disease (J Investig Allergol Clin Immunol. 2010;20(3):185-94). We request again that actual use of total IgG subclasses in and during allergy testing is fully clarified to the reader. Also, we request that the potential interpretation, of the letter, on prohibiting total IgG subclass testing rather than limited to allergen specific subclass testing be removed.

Response:
The final standard clarifies that laboratories using assays measuring allergen-specific levels of IgG and IgG subtypes must submit a complete validation package for Department review. The standard does not apply to non-allergen IgG assays.

Comment:
We are responding to your letter of June 30, 2011 regarding the NYS DOH Standard 6 Proposed Revision in which you seek to eliminate physician and patient access to IgG (and all subclasses) food-specific antibody testing. Your letter references the document, “Guidelines for the Diagnosis and Management for Food Allergy in the United States,” J. Allergy Clin Immunol 126:1106-1118 (“Guidelines”). However, your letter misstates and misinterprets those guidelines in several regards:

Your letter states: “To date, professional societies of allergists and immunologists in North America and in Europe have advised against the use of IgG subclass assays for diagnosing food allergy. Of note in these guidelines is the determination that allergen specific IgG4 assays are not recommended for the routine evaluation of food allergies.”

Guideline 12 advises against using IgG for the routine evaluation of IgE-mediated food allergies only. Your letter misstates the Guideline by leaving out the very significant phrase, IgE-mediated. Nowhere in the Guideline is it stated that IgG assays are not recommended for any other purpose. The overview section states that the “Guidelines focus on diseases that are defined as FA [food allergy] and include both immunoglobulin E (IgE)-mediated reactions to food and some non-IgE-mediated reactions to food.” It does not address several areas of physiological responses to food, including IgG. You have misappropriately construed it to be used as a position paper on IgG food antibody testing.
Beyond the inappropriateness of using the Guideline to eliminate IgG testing in general, it is further inappropriate to present it as a basis for a regulatory issue, when the document expressly states that it is NOT to be used to dictate clinical practice and override clinical judgment. The Summary in section 1 of the Guideline specifically states the following:

- The guidelines are not fixed protocols that must be followed.
- Health care professionals should take the guidelines into account when exercising their clinical judgment.
- The guidance does not override clinician responsibility to make decisions appropriate to the circumstances of the individual patient.
- Clinical judgment on the management of individual patients remains paramount.
- The document is intended as a resource to guide clinical practice.
- The document is not an official regulatory document of any government agency.

We have polled New York clinicians who use this test in patient care. Many clinicians noted that not having access to this testing would place an unnecessary burden on treatment of their patients. There was a consensus that the test and the treatments based upon it do not cause financial, medical or emotional harm to patients; rather, the discontinuation of the test would cause the harm. The test is inexpensive, and the recommendations are benign and quite often result in positive outcomes in treating a wide range of conditions such as gastrointestinal problems, fibromyalgia, eczema, chronic infections and headaches – conditions for which other treatment options are often limited and/or ineffective. Denial of access to the testing could prolong patient suffering and increase costs. Many clinicians feel that, if New York were to restrict access, patients would seek treatment in other states.

Your letter states: “IgG subclasses indicate an antibody is present but these levels are not diagnostic of a disease process.”

The Guidelines do not make this statement, and you have not documented the source in your letter. This statement implies that NYS DOH requires that a laboratory test must be diagnostic of a disease process. Where is this documented? Many laboratory tests are not: IgE, the test you are recommending in Standard 6 for food allergy testing, is not by itself diagnostic of food allergies. Guideline 7 recommends allergen-specific serum IgE tests to identify foods that potentially provoke IgE-mediated food-induced allergic reactions, but states that by themselves these tests are not diagnostic of FA. Therapeutic drug monitoring, drug screening, sex hormone levels and even cholesterol levels are other examples of widely used tests that are not diagnostic of disease. There is a long list of tests that are used in patient care that fall in this category.

Your letter states: “Until such time as the peer-reviewed medical literature supports serological food allergy testing and these professional societies endorse such testing, or a laboratory provides evidence of analytical and clinical validity in a validation package submitted for review, we will prohibit the use of IgG4 and tests for other IgG subclasses or total allergen specific IgG for specimens accepted from New York State.”

We are not familiar with any NYS DOH standards that require professional societies’ endorsement of a test as a prerequisite for it to be offered. We have also not been notified of the requirement of submission of validation packages for tests that have previously been approved under our licensure. Unless you can demonstrate that these requirements exist and that we have been notified of them, it is inappropriate for you to attempt to enforce them.
Enclosed are references to several peer-reviewed documents that support the use of serological IgG food antibody tests for use in patient care.

**Your letter states:** “Although laboratory developed tests . . . for IgG to food allergens have been submitted for review to the Department, the validation materials have not contained acceptable evidence of analytical or clinical validity.”

NYS DOH has reviewed our methods for IgG4 food antibody testing and has not indicated to us that they do not have acceptable analytical validity. If we were required to submit a full validation package after your review, this should have been indicated to us.

**In summary:**
- The Guidelines were written for IgE-mediated (Type I) food reactions and a few, limited non-IgE-mediated reactions to foods. It does not attempt to address other types of reactions to foods, including Type III, which is related to IgG antibody testing.
- The Guidelines were not intended to be used for regulatory purposes; they do, in fact, state that clinical judgment remains paramount.
- There is substantial scientific and clinical support for the benefit of IgG food antibody testing in patient care.
- A test does not need to be diagnostic to be clinically relevant and useful.
- Restricting NY physicians from using IgG4 testing at their discretion in treatment of their patients would be to the detriment of NY citizens, which is contrary to the mandate of the department.

Our recommendations regarding the proposed standard are as follows:
“The laboratory shall use IgE for IgE-mediated food allergy testing. Assays for IgA, IgG and IgG subclasses are permitted for non-IgE-mediated responses to foods since there is a significant literature supporting the use.”

*(The references provided by the commenter are at the end of this document)*

**Response:**

*We agree that the reference used as a basis for the proposed standard provides a definition of food allergy testing that included IgE mediated response. A clear description of the intended use is required by CLRS when reviewing and evaluating all validation packages submitted to the department for review and approval. A review of the literature has not provided defensible peer-reviewed evidence-based clinical validation directly supporting the use of IgG levels for evaluation of food allergies. Sound evidence-based analytical and clinical validation must be submitted for review to demonstrate that the assays are sensitive and specific for diagnosis of food allergy.*

**Comment:** The Clinical Laboratory Evaluation Program (CLEP) is considering the adoption of a new standard largely because of guidelines for the diagnosis and management of food allergy that were published by the National Institute of Allergy and Infectious Diseases of the National Institute of Health in 2010. However, we believe that the proposed standard goes beyond the recommendation in the guidelines, which recommended against using a number of tests, including allergen-specific IgG4 testing for the "routine" evaluation of food allergies. The guidelines did not conclude that IgG, IgG4 and IgA testing have no place in patient management, and if CLEP rescinds the approval for these tests that ViraCor-IBT has been offering in New York since they were approved in 1997, our physician clients will lose access to
a test that, when used in conjunction with other tests and examinations, provides them with helpful information for patient management.

Since the time that the IgG test was first offered, physicians have had ample opportunity to study its usefulness in making treatment decisions. We note that the guidelines state that food-specific IgG testing has been suggested for use in diagnosing non-IgE mediated reactions, and we are aware of publications that report on the use of IgG testing for a variety of indications. We also have discussed the proposed standard with several of our long-time physician clients, and we would like to share some of this information with you.

Recent literature has found that food-specific IgG assays can be used to establish an elimination diet for patients with Crohn's disease. Additionally, food specific-IgG4 testing has been used not to diagnose IgE-mediated food allergy, but to assess the severity of the allergy and to monitor children and assist in determining whether or not they will outgrow the allergy.

A recent discussion with an independent thought leader from the state of New York, confirmed the use of food-specific IgG testing for reasons other than food allergy. He uses "the testing to evaluate patients with bowel symptoms, such as diarrhea or bloating, and/or any clinical manifestations associated with extra-intestinal manifestations of bowel inflammation, including various skin rashes, arthritis, uveitis and unexplained fatigue. We have had a very high success rate in identifying foods with the IgG-RAsT test which when eliminated lead to improvement and/or complete resolution of symptoms."

We also discussed the proposed standard with a pediatric allergist who has been in practice for 30 years. He acknowledged that most studies have shown that total IgG4 testing for individual foods is not useful, but noted that in the last 10 years, IgG4 has been helpful in determining whether a patient is developing desensitization or oral tolerance induction. "We have found that measuring the ratios between IgE and IgG4 for a particular food protein is extremely helpful in determining when we can move up to a higher dose for a patient increasing the likelihood of tolerance or desensitization. The addition of IgG4 testing has made the whole process of food allergy challenge in children and adults with egg allergy and milk allergy much safer, and there is increasing evidence that it is also helpful with ingestion of peanut and tree nut allergy, as well. These results have allowed us to introduce the foods back to children and adults when we would not have been able to have done this before." Furthermore, research from multiple investigators including those at Mt. Sinai, Duke and Children's Hospital of Arkansas demonstrating the utility of adding IgG4 testing for foods.

Our perspective is based on over 25 years of providing diagnostic testing to physicians across the United States. We have discussed this type of testing with numerous physicians over the years as they deal with patients that suffer from adverse food reactions that are non-allergic in nature, and we believe this standard is not necessary, nor practical. One difficulty with the proposed standard is that reference laboratories do not typically know why a physician is ordering a test. Therefore it will be impractical to determine if a physician is attempting to diagnosis food allergy or some other food intolerance. Because of this it will be unrealistic to police this standard. We believe that laboratories should continue to make the tests available to physicians and that the determination of whether a test is medically necessary for a specific patient should be addressed in a discussion between the ordering physician and the patient.

We respectfully request that the proposed standard be rescinded.
Response:
We agree that the reference used as a basis for the proposed standard provides a definition of food allergy testing that included IgE mediated response. A clear description of the intended use is required by CLRS when reviewing and evaluating all validation packages submitted to the department for review and approval. A review of the literature has not provided defensible peer-reviewed evidence-based clinical validation directly supporting the use of IgG levels for evaluation of food allergies. Sound evidence-based analytical and clinical validation must be submitted for review to demonstrate that the assays are sensitive and specific for diagnosis of food allergy.

Comment: We have recently been informed that the decision-makers for New York regulatory licensing of medical laboratories is favoring a decision to restrict allergy related testing to IgE and continue to ban IgG testing. We are opposed to this idea and would appreciate your careful consideration of the information we are providing within this brief letter. In addition to the letter, we have completed an extensive validation packet as per earlier requests from your office and we are prepared to forward that upon your request. Please consider the following

- Our laboratory is licensed in New York to perform a limited number of Immunodiagnostic tests since 2008. We are participating in New York State’s Quality Control Survey Program.
- We have been performing hundreds of thousands of IgG food sensitivity tests throughout the United States (except in New York) for approximately 30 years!
- Our laboratory is CLIA and CAP certified and licensed to perform IgG food sensitivity testing in Florida, California and other States in the USA. Our laboratory bi-annually performs IgG comparison studies with another permitted laboratory.
- While the subject of IgG food sensitivity testing may be controversial, there are excellent studies published on its reliability and clinical validity.
- The University of Miami has recently completed a study of 189 patients with our laboratory’s IgG test results as the only information used to assist patients with chronic conditions. The results were statistically significant measured by means of widely accepted instruments such as the IBS-36 and SF36. Professional papers are forthcoming and the first of several is now being submitted for publication.
- Our laboratory was one of the first labs to introduce IgG testing and the only lab over these past 30+ years to remain focused on offering this test as a cornerstone to assist physicians in diagnosing and treating chronic, costly, unresolved conditions such as obesity, migraines, irritable bowel and more.
- While foods may not be the only contributing factor, physicians have found time and time again, the right food can be their first and best medicine and their method for detecting the ‘right foods’ is our laboratory’s IgG test.
- The performance and interpretation of the tests are in total compliance with patient safety and wellbeing. In other words, there is great benefit to this testing and no harm has ever been reported.
- We are so confident in the exceptional outcomes our testing provides, we offer a written money-back guarantee to physicians and their patients. It's a simple, straightforward promise - either the patient gets significant benefit or we refund their test fee. This is unprecedented in laboratory testing and is our way to raise confidence in the value of what we contribute.
Our successful IgG testing has not only helped hundreds of thousands of patients throughout the USA, it’s also been of great benefit to helping physicians conquer their own chronic unsolved conditions. We have on file, over 300 such case studies from physicians reporting their own, personal benefits from IgG food sensitivity testing.

To deny New York physicians and consumers of the option to order IgG testing is not in the best interests of their health or wellbeing at a time when cost effective solutions for improving the healthcare of Americans is in desperate short supply.

While IgG testing is no panacea, it’s an overlooked and underappreciated assessment of delayed, Type 3 allergic-related reactions in patients with chronic symptoms. The therapeutic utilization of the test is used in conjunction with a personalized food avoidance program. The test, food plan and physician's applicable treatment protocols are producing outstanding results; often when all previous more conventional and widely accepted attempts have failed to work.

We are appealing to the decision-makers to provide New York physicians and their patients the freedom to choose IgG testing by granting written approval to provide this option under our New York license.

Response:
We agree that the reference used as a basis for the proposed standard provides a definition of food allergy testing that included IgE mediated response. A clear description of the intended use is required by CLRS when reviewing and evaluating all validation packages submitted to the department for review and approval. A review of the literature has not provided defensible peer-reviewed evidence-based clinical validation directly supporting the use of IgG levels for evaluation of food allergies. Sound evidence-based analytical and clinical validation must be submitted for review to demonstrate that the assays are sensitive and specific for diagnosis of food allergy.

Comment: The IgG food sensitivity tests were of great help to me. I was feeling depressed and anxious and found out from the tests that I was sensitive to gluten and casein. I eliminated them from my diet and felt much better in a few weeks.

Response:
We agree that the reference used as a basis for the proposed standard provides a definition of food allergy testing that included IgE mediated response. A clear description of the intended use is required by CLRS when reviewing and evaluating all validation packages submitted to the department for review and approval. A review of the literature has not provided defensible peer-reviewed evidence-based clinical validation directly supporting the use of IgG levels for evaluation of food allergies. Sound evidence-based analytical and clinical validation must be submitted for review to demonstrate that the assays are sensitive and specific for diagnosis of food allergy.

Comment: I have been evaluating the total IgG RAST test in my patients over the last two years. I order this testing in patients with bowel symptoms, such as intermittent diarrhea, and an extra-intestinal manifestation of bowel inflammation, such arthritis (involving predominantly hands, wrists and ankles), uveitis, skin rashes such as pyoderma gangrenosum and dermatitis herpiformis, and generalized fatigue associated with eating particular foods. I have identified
over 30 patients in whom the identification and elimination of a food or foods by IgG RAST testing has led to a dramatic improvement in symptoms. I am in the process of writing up my experience and evaluating these issues in a prospective manner.

At the present time, I would not eliminate the IgG RAST test as I believe it has value. It may be an indicator of cell-mediated reactivity to particular foods.

Response:
We agree that the reference used as a basis for the proposed standard provides a definition of food allergy testing that included IgE mediated response. A clear description of the intended use is required by CLRS when reviewing and evaluating all validation packages submitted to the department for review and approval. A review of the literature has not provided defensible peer-reviewed evidence-based clinical validation directly supporting the use of IgG levels for evaluation of food allergies. Sound evidence-based analytical and clinical validation must be submitted for review to demonstrate that the assays are sensitive and specific for diagnosis of food allergy.

The effective day of the standards is three months from the day of adoption in order for laboratories to submit complete validation packages to the department. Further explanation is provided in the cover letter.
Evidence-Based Clinical Relevance of Food Specific Serum IgG Antibodies

It has been proposed that food-specific IgG antibodies are involved in the delayed, Type III hypersensitivity reaction. This mechanism does not utilize IgE. Pathologic consequences stem from the formation of IgG immune complexes and initiation of the complement system in the blood. [http://pathmicro.med.sc.edu/ghaffar/hyper00.htm](http://pathmicro.med.sc.edu/ghaffar/hyper00.htm). A recent assessment of the validity of using food-specific IgG4 testing found significant evidence of its benefit in clinical settings. (Bernardi, Borghesan et al. 2008)

A growing body of medical literature supports the clinical value of measuring food-specific IgG antibodies to guide therapeutic dietary changes. A number of studies involve IBS patients. These are cited below with full abstracts in the reference section. (Atkinson, Sheldon et al. 2004) (Zar, Mincher et al. 2005; Drisko, Bischoff et al. 2006; Yang and Li 2007; Zuo, Li et al. 2007; Ou-Yang, You et al. 2008) In all studies, significant clinical improvement was gained by using IgG testing to screen for foods for dietary exclusion. Irritable Bowel Syndrome (IBS) is estimated to occur in 12% to 22% of the US population and is a disorder of high direct and indirect medical costs. (Mertz 2003) Any improved treatment and management would be of significant benefit not only to patient outcome, but also to the reduction in health care costs. Others studies looking at a variety of conditions showed IgG testing to be clinically useful in ameliorating symptoms. (Dixon 2000; Wilders-Truschnig, Mangge et al. 2008; Alpay, Ertas et al. 2010)

References


INTRODUCTION: It is well-known that specific foods trigger migraine attacks in some patients. We aimed to investigate the effect of diet restriction, based on IgG antibodies against food antigens on the course of migraine attacks in this randomised, double blind, cross-over, headache-diary based trial on 30 patients diagnosed with migraine without aura. METHODS: Following a 6-week baseline, IgG antibodies against 266 food antigens were detected by ELISA. Then, the patients were randomised to a 6-week diet either excluding or including specific foods with raised IgG antibodies, individually. Following a 2-week diet-free interval after the first diet period, the same patients were given the opposite 6-week diet (provocation diet following elimination diet or vice versa). Patients and their physicians were blinded to IgG test results and the type of diet (provocation or elimination). Primary parameters were number of headache days and migraine attack count. Of 30 patients, 28 were female and 2 were male, aged 19-52 years (mean, 35 +/- 10 years). RESULTS: The average count of reactions with abnormally high titre was 24 +/- 11 against 266 foods. Compared to baseline, there was a statistically significant reduction in the number of headache days (from 10.5 +/- 4.4 to 7.5 +/- 3.7; P < 0.001) and number of migraine attacks (from 9.0 +/- 4.4 to 6.2 +/- 3.8; P < 0.001) in the elimination diet period. CONCLUSION: This is the first randomised, cross-over study in migraineurs, showing that diet restriction based on IgG antibodies is an effective strategy in reducing the frequency of migraine attacks.


BACKGROUND: Patients with irritable bowel syndrome (IBS) often feel they have some form of dietary intolerance and frequently try exclusion diets. Tests attempting to predict
food sensitivity in IBS have been disappointing but none has utilised IgG antibodies. AIMS: To assess the therapeutic potential of dietary elimination based on the presence of IgG antibodies to food. PATIENTS: A total of 150 outpatients with IBS were randomised to receive, for three months, either a diet excluding all foods to which they had raised IgG antibodies (enzyme linked immunosorbant assay test) or a sham diet excluding the same number of foods but not those to which they had antibodies. METHODS: Primary outcome measures were change in IBS symptom severity and global rating scores. Non-colonic symptomatology, quality of life, and anxiety/depression were secondary outcomes. Intention to treat analysis was undertaken using a generalised linear model. RESULTS: After 12 weeks, the true diet resulted in a 10% greater reduction in symptom score than the sham diet (mean difference 39 (95% confidence intervals (CI) 5-72); p = 0.024) with this value increasing to 26% in fully compliant patients (difference 98 (95% CI 52-144); p<0.001). Global rating also significantly improved in the true diet group as a whole (p = 0.048, NNT = 9) and even more in compliant patients (p = 0.006, NNT = 2.5). All other outcomes showed trends favouring the true diet. Relaxing the diet led to a 24% greater deterioration in symptoms in those on the true diet (difference 52 (95% CI 18-88); p = 0.003). CONCLUSION: Food elimination based on IgG antibodies may be effective in reducing IBS symptoms and is worthy of further biomedical research.


BACKGROUND: The usefulness of serum antibodies to common food antigens (immunoglobulin G4; IgG4) assay in management of patients suffering from food intolerance was assessed. METHODS: A total of 22 asymptomatic healthy subjects and 68 patients with symptoms referred for suspected food intolerance were studied. Serum IgG4 to 19 common foods was measured by an automated immunoassay. RESULTS: The area under the receiver operating characteristic curve was 0.92 (standard error 0.04) and, at a threshold value of 2.3 U/mL, the IgG4 determination had a sensitivity of 0.81, with a specificity of 0.87. With a pre-test probability of 5% and 20%, the post-test probability of having disease was found to be 24% and 61%, respectively, and 1.1% and 5% if the result was negative. Cohen's K value (0.83) indicated a good agreement between symptoms and IgG4 concentrations. CONCLUSION: Serum IgG4 assay may play a role in ruling out food intolerance, because of its satisfactory negative predictive value (0.99).


This preliminary, descriptive study after extensive clinical experience demonstrates specific IgG food RASTs done in 114 consecutive patients with strong positive histories for delayed food allergy. Elimination of the positive foods was the sole means of treatment. The symptoms leading to the test are detailed, and the method of workup is reviewed. The overall results demonstrated a 71% success rate for all symptoms achieving at least a 75% improvement level. Of particular interest was the group of patients with chronic, disabling symptoms, unresponsive to other intensive treatments. Whereas 70% obtained 75% or more improvement, 20% of these patients obtained 100% relief.

OBJECTIVE: In Irritable Bowel Syndrome, the gut-associated immune system may be up-regulated resulting in immune complex production, low-grade inflammation, loss of Class I bacteria, and translocation of inflammatory mediators and macromolecules outside of the GI lumen. Since food intolerance may be one of the reasons for this upregulation, our goal was to investigate the role of food intolerance in IBS patients.

METHODS: In this open label pilot study, we enrolled 20 patients with IBS by Rome II criteria (15 women, ages 24-81) who had failed standard medical therapies in a tertiary care GI clinic. Baseline serum IgE and IgG food and mold panels, and comprehensive stool analysis (CSA) were performed. Breath-hydrogen testing and IBS Quality-of-Life (QOL) questionnaires were obtained. Patients underwent food elimination diets based on the results of food and mold panels followed by controlled food challenge. Probiotics were also introduced. Repeat testing was performed at 6-months. We followed up with this cohort at 1 year after trial completion to assess the reported intervention and for placebo effect.

RESULTS: Baseline abnormalities were identified on serum IgG food and mold panels in 100% of the study subjects with significant improvement after food elimination and rotation diet (p < 0.05). Significant improvements were seen in stool frequency (p < 0.05), pain (p < 0.05), and IBS-QOL scores (p < 0.0001). Imbalances of beneficial flora and dysbiotic flora were identified in 100% of subjects by CSA. There was a trend to improvement of beneficial flora after treatment but no change in dysbiotic flora. The 1-year follow up demonstrated significant continued adherence to the food rotation diet (4.00 +/- 1.45), minimal symptomatic problems with IBS (4.00 +/- 1.17), and perception of control over IBS (4.15 +/- 1.23). The continued use of probiotics was considered less helpful (3.40 +/- 1.60). CONCLUSION: These data demonstrate that identifying and appropriately addressing food sensitivity in IBS patients not previously responding to standard therapy results in a sustained clinical response and impacts on overall well being and quality of life in this challenging entity.


OBJECTIVE: The causes of chronic diarrhea in children are complex. At present, food allergy is generally viewed as an important cause of this disorder, and IgG-mediated delayed allergy plays a major role in this process. This study aimed to explore the link between food specific IgG and chronic diarrhea in children, as well as the value of food allergens-specific IgG antibody detection in the management of this disorder.

METHODS: Eighty-two children with chronic diarrhea and 30 healthy controls were enrolled. Serum levels of specific IgG antibody to 14 kinds of food were detected using ELISA. The results were classified into four grades: Grade 0 (negative), Grade 1 (mild allergy), Grade 2 (moderate allergy) and Grade 3 (severe allergy). The patients received a diet treatment based on the results of food specific IgG antibody detection. Children with negative IgG antibody were allowed to continue their current diet. In children with Grade 1 allergy, the food responsible for the IgG antibody positive test was given only at an interval of four days. In children with Grade 2 or 3, the offending food was eliminated from the diet. RESULTS: Of the 82 children with chronic diarrhea, 79 (96.2%) had increased specific IgG levels for one or more of the 14 foods tested compared to 8
(26.7%) of the controls (P <0.01). The majority of patients showed increased specific IgG levels for milk (68.3%) and egg (62.2%). A low proportion of patients (2.4%) was allergic to chicken, and no patient was allergic to pork. The symptoms were improved in 65 patients (79.3%) after 1 week to 3 months of diet treatment. CONCLUSIONS: Food allergy is one of major causes of chronic childhood diarrhea. Food specific IgG antibody detection may assist in the dietary management of this disorder.


OBJECTIVE: Systemic low grade inflammation may contribute to the development of obesity, insulin resistance, diabetes mellitus and atherosclerotic vascular disease. Food intolerance reflected by immunoglobulin G (IgG) antibodies may predispose to low grade inflammation and atherogenesis. We examined the relationship between IgG antibodies specific for food components, low grade inflammation and early atherosclerotic lesions in obese and normal weight juveniles. RESEARCH METHODS AND PROCEDURES: We determined IgG antibodies directed against food antigens, C-reactive protein (CRP) and the thickness of the intima media layer (IMT) of the carotid arteries in 30 obese children and in 30 normal weight children. RESULTS: Obese juveniles showed a highly significant increase in IMT (p=0.0001), elevated CRP values (p=0.0001) and anti-food IgG antibody concentrations (p=0.0001) compared to normal weight juveniles. Anti-food IgG showed tight correlations with CRP (p=0.001/r=0.546) and IMT (p=0.0001/r=0.513) and sustained highly significant in a multiple regression model. DISCUSSION: We show here, that obese children have significantly higher IgG antibody values directed against food antigens than normal weight children. Anti-food IgG antibodies are tightly associated with low grade systemic inflammation and with the IMT of the common carotid arteries. These findings raise the possibility, that anti-food IgG is pathogenetically involved in the development of obesity and atherosclerosis.


OBJECTIVE: To explore the therapeutic effects on irritable bowel syndrome (IBS) by eliminating the allergic foods according to food-specific IgG antibodies and to clarify the etiopathological role and mechanism of food allergy. METHODS: The food-specific IgG antibodies to a panel of 14 different food antigens in serum were detected with ELISA in fifty five cases with diarrhea-dominant IBS, thirty two with constipation-dominant IBS and eighteen normal controls. The frequency and severity index of symptoms and scores of Irritable Bowel Syndrome Quality of Life (IBS-QOL) in thirty five cases with positive food-specific IgG were observed before and after elimination of allergic foods for two months. RESULTS: The positive rate of serum food-specific IgG antibodies was 63.6 percent in patients with diarrhea-dominant IBS and 43.8 percent in constipation-dominant IBS. Both were higher than that in normal controls. After eliminating allergic foods for four weeks according to the levels of serum food-specific IgG antibodies, the frequency of symptoms decreased from (3.79 +/- 1.58) to (1.67 +/- 0.70) per week and the severity from 3.18 +/- 1.46 to 1.52 +/- 0.67 with significant differences. After eight weeks, the frequency of symptoms decreased from (3.79 +/- 1.58) to (1.53 +/- 0.69) per week and the severity from 3.18 +/- 1.46 to 1.45 +/- 0.66, also with significant differences. After eliminating allergic foods, the overall health score and the eight dimensionality integrals of QOL except avoiding food in patients with IBS increased significantly than those
before treatment. At the end of eight weeks, the symptoms relieved completely in 31.4 percent of the cases and remarkably in 34.3 percent. CONCLUSIONS: Abnormal immune reactions mediated by IgG antibodies coexisted in patients with IBS. It is of great significance in treating IBS by eliminating the allergic foods according to the serum level of food-specific IgG antibodies.


OBJECTIVE: Dietary modification improves symptoms in irritable bowel syndrome (IBS). Identification of offending foods by dietary elimination/re-challenge is cumbersome. IgG4 antibodies to common food antigens are elevated in IBS. The aim of this article was to evaluate the effect of exclusion diet based on IgG4 titres on IBS symptoms and rectal sensitivity and compliance. MATERIALS AND METHODS: The study comprised 25 patients with IBS (3 M, 22 F, mean age 43 years, Rome II criteria). IgG4 titres to 16 foods (milk, eggs, cheese, wheat, rice, potatoes, chicken, beef, pork, lamb, soya bean, fish, shrimps, yeast, tomatoes and peanuts) were measured. Foods with titres >250 microg/l were excluded for 6 months. Symptom severity was assessed with a previously validated questionnaire at baseline, at 3 months and at 6 months. Rectal compliance and sensitivity were measured in 12 patients at baseline and at 6 months. RESULTS: IgG4 antibodies to milk, eggs, wheat, beef, pork and lamb were commonly elevated. Significant improvement was reported in pain severity (p < 0.001), pain frequency (p = 0.034), bloating severity (p = 0.001), satisfaction with bowel habits (p = 0.004) and effect of IBS on life in general (p = 0.008) at 3 months. Symptom improvement was maintained at 6 months. Rectal compliance was significantly increased (p = 0.011) at 6 months but the thresholds for urge to defecate/discomfort were unchanged. CONCLUSIONS: Food-specific IgG4 antibody-guided exclusion diet improves symptoms in IBS and is associated with an improvement in rectal compliance.


BACKGROUND: Post-prandial worsening of symptoms as well as adverse reactions to one or more foods are common in the patients with functional gastrointestinal diseases, such as irritable bowel syndrome (IBS) and functional dyspepsia (FD). However, the role played by true food allergy in the pathogenesis of these diseases is still controversial and there are no well-established tests to identify food allergy in this condition. OBJECTIVE: To investigate serum food antigen-specific IgG, IgE antibody and total IgE antibody titres in controls and patients with IBS and FD, and to correlate symptoms with the food antigen-specific IgG titres in IBS and FD patients. METHODS: Thirty-seven IBS patients, 28 FD patients and 20 healthy controls participated in this study. Serum IgG and IgE antibody titres to 14 common foods including beef, chicken, codfish, corn, crab, eggs, mushroom, milk, pork, rice, shrimp, soybean, tomatoes and wheat were analysed by ELISA. Serum total IgE titres were also measured. Last, symptomatology was assessed in the study. Results IBS patients had significantly higher titres of IgG antibody to crab (P=0.000), egg (P=0.000), shrimp (P=0.000), soybean (P=0.017) and wheat (P=0.004) than controls. FD patients had significantly higher titres of IgG antibody to egg (P=0.000) and soybean (P=0.017) than controls. The percentage of individuals with detectable positive food antigen-specific IgE antibodies of the three groups did not show any significant differences (P=0.971). There were no significant differences between IBS
patients, FD patients and controls in the serum total IgE antibody titres (P=0.978). Lastly, no significant correlation was seen between symptom severity and serum food antigen-specific IgG antibody titres both in IBS and FD patients. CONCLUSION: Serum IgG antibody titres to some common foods increased in IBS and FD patients compared to controls. But there is no significant correlation between symptom severity and elevated serum food antigen-specific IgG antibodies in these patients.