

The left side of the slide features a decorative design consisting of several vertical elements: a thin dark green line, a wider light green bar with a fine grid pattern, another thin dark green line, and a cluster of five solid dark green circles of varying sizes. The largest circle is at the top left, with others of decreasing size arranged below and to its right.

FOOD REACTIONS

The Facts

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WHAT'S IN A NAME?

○ Food Allergy

- Only IgE reactions are considered true food allergies.

○ Food Intolerance

- Not a true food allergy : could be enzyme deficiency, chemical reactions, aversion. May also refer to IgG-mediated reactions or other immune reactions to food.

○ Food Sensitivity

- Not true food allergy: could be enzyme deficiency, chemical reactions, aversion. May also refer to IgG-mediated reactions or other immune reactions to food.



DEFINITIONS

- **Antigen** is any substance that elicits antibody production
- **Allergen** is any substance that causes an allergy (IgE)
- **Immunoglobulin** and **antibody** are terms used interchangeably. There are 5 major immunoglobulins:
 - IgE – only 1 to 2 % of immunoglobulins are IgE
 - IgG – most abundant in serum, crosses placenta
 - IgA – immunoglobulin produced in greatest numbers in a day. Found in mucous membranes
 - IgM - produced at onset of infections
 - IgD – function not well understood



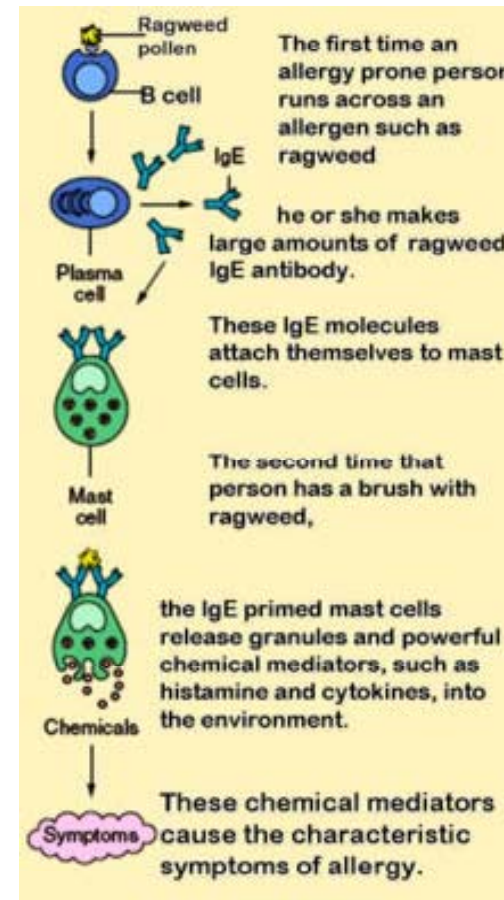
Major immunoglobulin-mediated food reactions

- **IgE** – Type I hypersensitivity reaction (Immediate)
- **IgG** – Type III hypersensitivity reaction (Delayed)
- **IgA** – mucosal damage (Delayed)



FOOD ALLERGY : TYPE I HYPERSENSITIVITY

- IgE mediated
- Rapid onset
 - Immediate onset
 - Immediate plus late phase
- Observable reactions
 - hives
 - anaphylaxis



Wiki - public

SYMPTOMS ASSOCIATED WITH IgE FOOD REACTIONS

Respiratory

- laryngeal edema
- asthma / wheezing
- rhinitis, ↑ mucous secretion
- lip, tongue swelling
- oral allergy syndrome
- sneezing

Systemic

- anaphylaxis

World Allergy Organization

Skin

- eczema
- angioedema
- acute urticaria

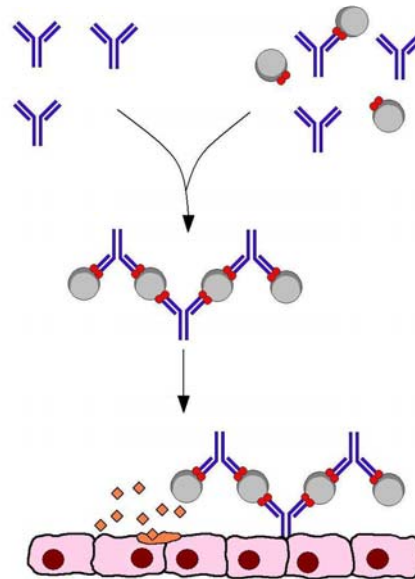
Digestive

- abdominal cramping
- nausea
- vomiting
- diarrhea



FOOD SENSITIVITY : TYPE III HYPERSENSITIVITY - IgG

- Type III hypersensitivity is an IgG mediated reaction caused by the deposition of antigen : antibody immune complexes at tissue sites.
- With excess antigen, small complexes tend to deposit in blood vessel walls where they can cause tissue injury.



Circulating IgG antibodies encounter food antigens & form

circulating immune complexes (CICs)

CICs can deposit in tissue and release inflammatory cytokines

Immunobiology : The Immune System in Health and Disease. 5th ed Janeway CA Jr, Travers P, Walport M, et al. New York: Garland Science: 2001



FOOD SENSITIVITY : TYPE III HYPERSENSITIVITY - IgG

- Half-life of IgG is 23 to 96 days in serum
- IgG antibodies form ~ 30 days after antigen recognition
- 4 sub-types of IgG:
 - IgG₁ IgG₂ IgG₃ IgG₄
 - IgG₄ may be protective against IgE reactions

Trevino S, Dixon H. Food Allergy. Thieme Medical Publishing. 1997

Mullin G et al. Nutr Clin Pract. 2010;25(2):192-98



SYMPTOMS ASSOCIATED WITH IgG FOOD REACTIONS

Systemic

- Fever
- Fatigue
- Sweating
- Chills
- Weakness
- Reduced tolerance for exertion

Nutr Clin Pract. 2010;25(2):192-98

Skin

- Rashes
- Redness
- Swelling
- Scaling (eczema, psoriasis)
- Thickening of skin
- Pruritis

Lungs

- Food-induced bronchitis, asthma



SYMPTOMS ASSOCIATED WITH IGG REACTIONS

Digestive

- Abdominal pain
- Bloating
- Nausea
- Vomiting
- Diarrhea

Nutr Clin Pract. 2010;25(2):192-98

Brain

- Disordered thinking/feeling
- Memory disturbances
- Behavioural problems

Musculoskeletal

- Food-allergic arthritis
- Pain
- Stiffness
- Swelling



COMPARING IGE AND IGG

Consideration	Immunoglobulin E	Immunoglobulin G
Onset of reaction	Rapid	Delayed
Duration of reaction	Brief (hours)	Prolonged (days to weeks)
Origin of response	Mast cells	Circulating immune complexes (CICs) macrophage overload
Food that trigger	Any food	Commonly consumed foods
Food quantity	Small amount of food can trigger response	Dose dependent - more reactive food means bigger reaction
Patient awareness	Subject usually aware of food trigger	Subjects usually unaware of food trigger
Persistence	Reactions may persist for life or resolve spontaneously	Symptoms may occur for months after elimination of reactive foods

LABORATORY TESTS FOR FOOD ALLERGY / SENSITIVITY

- IgE
 - *In vivo*
 - *In vitro*
- IgG
 - *In vitro*



TESTING FOR FOOD REACTIONS – IGE

In vivo

- Skin prick test
 - Looking for histamine response
 - 90% sensitivity, 50% specificity
- Oral food challenge (DBPCFC)
 - Hospitals or allergy clinics only



Waserman and Watson *Allergy, Asthma & Clinical Immunology* 2011, 7(Suppl 1):S7



TESTING FOR FOOD REACTIONS – IgE

In vitro

- ImmunoCAP is highly sensitive and specific quantitative analysis
 - Provocation unnecessary
 - Antihistamine use is acceptable
- Food specific IgE via ELISA
 - Only **unbound** IgE is measured in serum.
 - Half-life of IgE antibodies is short (approx 1 day).



EVIDENCE OF EFFICACY - IgE

○ ImmunoCAP

- Specific IgE useful to identify potential allergens, but not considered diagnostic. *J Allergy Clin Immunol. 2010; 126(6):S1-S58*
- ImmunoCAP IgE antibody levels predicted clinical reactivity (positive food challenge) with >95% certainty for egg, milk, peanut, and fish. *J Allergy Clin Immunol. 2010; 125:S116-25*

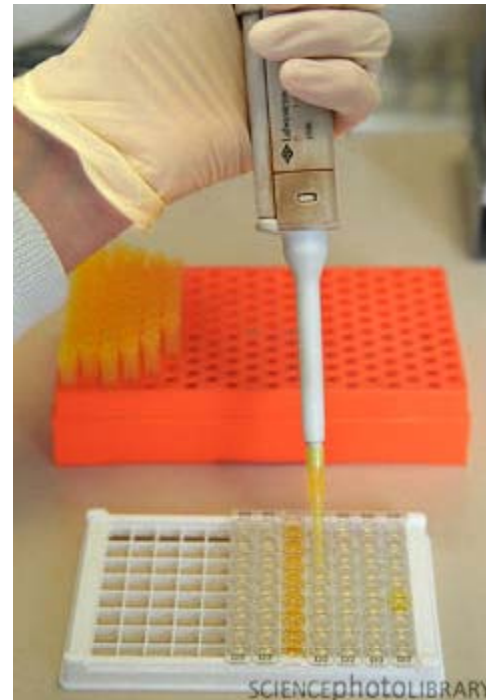
○ Total IgE

- Helminths stimulate IgE production *World Allergy Organization*
- Chronic intermittent hive reactions may be due to parasite infection. *J Parasitol. 2003 Jun;89(3):490-2. Eur Rev Med Pharmacol Sci. 2004 May-Jun;8(3):117-20. Rev Cubana Med Trop. 1980 May-Aug;32(2):149-53*



TESTING FOR FOOD SENSITIVITY

- measures levels of IgG antibodies to food antigens via ELISA
 - Total IgG (all four subclasses)
 - Studies showing clinical relevance most often use total IgG
 - IgG4 subclass only
 - 10 to 15% of healthy patients have IgG4 deficiency.
 - IgG4 testing for food allergy is questionable *Int Arch Allergy Immunol.* 2011;155(1):52-6. Epub 2010 Nov 26.



IS FOOD SENSITIVITY A CLINICAL CONDITION

- Gluten sensitivity is a recognized diagnosis
 - the 14th International Celiac Symposium June 2011 recognized gluten sensitivity as a diagnosis separate from wheat allergy or celiac disease
 - Criteria for diagnosis include elevated IgG and IgA antibodies to gliadin (gluten protein), negative celiac sera and biopsy and symptoms consistent with either celiac disease or wheat allergy.
- Evidence continues to evolve regarding the clinical relevance of IgG food sensitivity reactions.



FOOD SENSITIVITY TEST : CLINICAL BENEFITS

- GI Conditions:
 - Irritable Bowel Syndrome (IBS)
 - Crohn's
 - Dyspepsia
- Migraine Headaches
- Obesity



FOOD SENSITIVITY IgG - IBS

- 150 outpatients tested for food-specific IgG
 - Randomized to 'true' diet or 'sham' diet
 - After 6 weeks, 10% reduction in symptoms. (p=0.024)
 - After 12 weeks, 26% reduction. (p<0.001)

Atkinson J. et al. Gut 2004;53:1459–1464.

- Open label, 20 IBS patients
 - Food specific IgG testing done
 - Significant reduction in # stools/day and pain scale (p<0.05) after 1 year

Drisko J. et al. J Am Coll Nutr. 2006;25(6):514-22



FOOD SENSITIVITY IgG - CROHN'S DISEASE

- 40 Crohn's patients
 - IgG levels to specific foods measured
 - Symptom diary kept
 - Randomized (blinded) to true or sham diet for 6 weeks then crossover to alternate diet.
 - Decreased stool frequency, abdominal pain and increased overall well being in patients that adhered to diet excluding IgG reactions (true diet) compared to sham diet group.

Bentz S et al. Digestion 2010;81:252–264



FOOD SENSITIVITY IgG - MIGRAINE

- Elimination of IgG reactive foods led to improvement in migraine headaches:
 - 43/56 migraine patients reported no migraine after one to six months of elimination diet (removing reactive foods from diet)
 - Most common reactive foods in migraineurs: dairy, wheat, eggs, yeast

Arroyave-Hernandez C. et al. Revista Alergia Mexico. 2007;54(5):162-8



FOOD SENSITIVITY IgG - MIGRAINE

- Double-blind randomized cross-over trial of 30 patients
 - 6 week baseline diet
 - IgG food testing
 - Randomized to either exclusion diet or inclusion diet, 2 week washout, then cross-over to opposite diet
 - In elimination diet phase there was statistically significant reduction in attack count, # headache days, number of attacks requiring acute medication and total medication use.
 - No significant difference in attack severity or attack duration

Alpay K et al. *Cephalalgia*. 2010; 30(7): 829–837



FOOD SENSITIVITY IgG - OBESITY

- Obese juveniles have significantly elevated C-reactive protein, and greater intima media thickness and elevated IgG antibodies to foods compared to normal weight controls
- Tight correlation between elevated IgG antibodies and increased CRP/intima media thickness.
- Findings raise “**possibility, that anti-food IgG is pathogenetically involved in development of atherosclerosis and obesity.**”

Wilders-Truschnig et al. Exper Clin Endocrinol Diabetes 2008;116:241-45.



FOOD SENSITIVITY – IgG : CLINICAL PEARL

○ Suspected IgG reaction

- Omit suspected food for approximately 5 days. Food antigen is cleared, but IgG antibodies are still being produced and present in high numbers.
- On day 6 – consume a large amount of the suspected food. If food is truly IgG reactive, it will provoke a large immune response and an exacerbation of symptoms.

Reference: Trevino R, Dixon H. Food Allergy. American Academy of Otolaryngic Allergy. Thieme Publishing 1997. pp. 8-9



REPRODUCIBILITY OF RESULTS

- Hodsdon looked at the reproducibility of IgG food test from a CLIA accredited laboratory RMA refers testing to
 - Two samples from same patient (split sample) – 100% within one reactivity level
 - Four samples from one patient on 4 different days over the course of a week - 99% within one reactivity level

Result	Split Sample	Four samples / 1 week
Identical	95%	82%
Within one reactivity level	5%	17%

Hodsdon W, Zwickey H. NMJ.2010;2(3):8-13



LABORATORY TEST SUMMARY

- No *in vitro* test is considered diagnostic for food allergy, sensitivity or intolerance.
- Reproducibility of results and evidence of clinical benefits are the only measures of 'accuracy' of non-diagnostic tests.



USEFUL REFERENCES

- Trevino R. Dixon H. *Food Allergy*. 1997 Thieme Medical Publishers. American Academy of Otolaryngic Allergy Monograph Series.
- Mullin G, Swift K, Lipski L. et al. *Testing for Food Reactions: The Good, the Bad, and the Ugly*. 2010;25(2):192-198.



SUMMARY

- IgE food reactions are the only true food allergies.
- *In vitro* tests are **not** considered diagnostic of food allergy.
- The terms food sensitivity and food intolerance are not universally defined.
- *In vitro* tests for food sensitivity/food intolerance include IgG and non-specific immune testing (leukocytotoxic / neutrophil degranulation)

