THE INSTITUTE FOR FUNCTIONAL MEDICINE®

Food Allergy, Hypersensitivity, and Intolerances: Diagnosis and Treatment

DAN LUKACZER, ND

Applying Functional Medicine in Clinical Practice

Disclosure

Dan Lukaczer, ND has no financial relationships to disclose.

Evidence Icons: Key

Clinical Disclaimers:

Association, not causation

Lab test
(Labs not generally accepted in conventional care)

Clinical experience
(Intervention warranted by historical clinical experience of educator and/or functional medicine community of practitioners in the context of evidentiary paucity)

Clinical judgment
(Intervention warranted by clinical judgment of educator and/or functional medicine community of practitioners in the context of evidentiary paucity)

Conflict of interest

Study Types:

Animal study

In vitro study

n of 1, or single-case study

In silico *(Computerized molecular modeling)*

Performance Objectives

Following this activity, successful participants will be able to…

1. Identify the differences between food allergy, food sensitivity, and food intolerance.
2. Differentiate between IgG and IgE food testing, benefits and disadvantages.
3. Recognize the differences between celiac disease, wheat allergy, and non-celiac gluten sensitivity.
4. Outline a rationale for evaluating and testing for food reactions.

FUNCTIONAL MEDICINE TIMELINE

Mediators/Perpetuators

Weight gain in college

Antecedents

Fam Hx of IBS, Diverticulitis

History of Depression

Triggers or Triggering Events

Solid foods at 6 months

Parents divorced

Bottle fed @ 4wks

Mother remarried

Married

Vag delivery

Vag delivery

"Post partum depression" after each; no treatment

Divorced

Preconception

Vag Birth, prolonged ABX, membrane rupture (PROM)

Mother SAD diet

Prenatal

Birth 3 4 7 9 10 25 27 29 34 44

Current Concerns

Colic @ 6 weeks

Abdominal Pain
- > Missed school
- > GI eval, no scopes

Gas & Bloating, Frequent non-bloody stools, "sensitive stomach", Feeling of incomplete voiding.

Tonsillectomy @4yo

3-5 bouts of OM treated with ABX

Dx as lactose intolerance partial improvement.

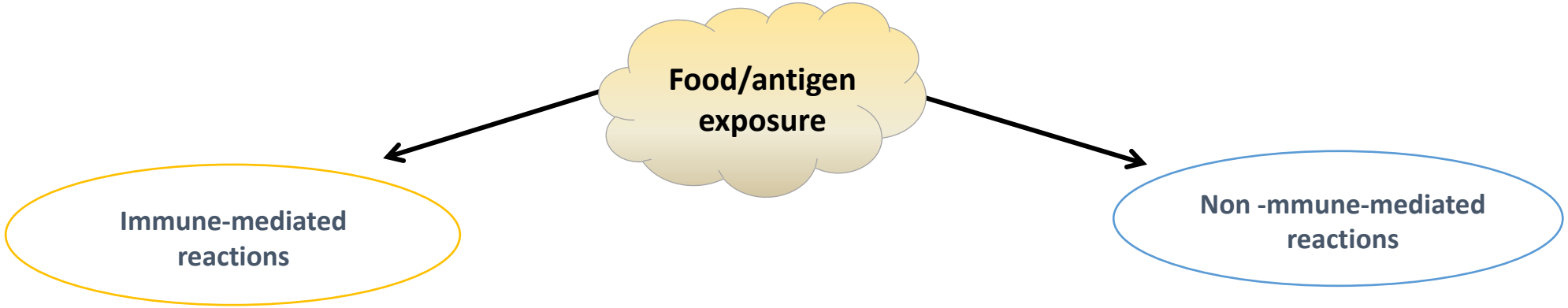
Signs, Symptoms or Diseases Reported

Name: _____ Date: _____ CC: _____

IFM

Putting Food Reactions Into Your Differential

Reactions to Food



National Institute of Allergy and Infectious Disease Definition Of Food Allergy

- Adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food
- **Type 1 hypersensitivity (IgE)**

NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-S58. doi:10.1016/j.jaci.2010.10.007

An estimated **4-8%** of the US population have food allergies.

1. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1–S58. doi:10.1016/j.jaci.2010.10.007
2. Gupta RS, et al. Prevalence and Severity of Food Allergies Among US Adults. JAMA Netw Open. 2019 Jan 4;2(1):e185630. doi: 10.1001/jamanetworkopen.2018.5630.

According to the NIAID, there are additional groups of patients with food reactions.

Approximately 12% of the US population can be diagnosed with reactions to food.

NIAID-Sponsored Expert Panel, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58. doi: 10.1016/j.jaci.2010.10.007.

Non-IgE: Allergies Heterogeneous Group

- Celiac disease
- Eosinophilic esophagitis
- Eosinophilic gastroenteritis

Food Intolerances:
Non-Immune Mediated Reactions

- **Lactose intolerance** (lactase deficiency)
- **Tyramine, histamine** (monoamines)
- **MSG, aspartame, sulfites**
- **Salicylates** (eicosanoid metabolism)
- **Lectins** (indirect immune stimulation)

See References: Food Intolerances: Non-Immune Mediated Reactions

References:
Food Intolerances: Non-Immune Mediated Reactions

Tyramine, Histamine:

Comas-Basté O, Sánchez-Pérez S, Veciana-Nogués MT, Latorre-Moratalla M, Vidal-Carou MDC. Histamine Intolerance: The Current State of the Art. Biomolecules. 2020;10(8):1181. Published 2020 Aug 14. doi:10.3390/biom10081181

Andersen G, Marcinek P, Sulzinger N, Schieberle P, Krautwurst D. Food sources and biomolecular targets of tyramine. Nutr Rev. 2019;77(2):107-115. doi:10.1093/nutrit/nuy036

Ruiz-Capillas C, Herrero AM. Impact of Biogenic Amines on Food Quality and Safety. Foods. 2019;8(2):62. Published 2019 Feb 8. doi:10.3390/foods8020062

Salicylates:

Tuck CJ, Biesiekierski JR, Schmid-Grendelmeier P, Pohl D. Food Intolerances. Nutrients. 2019;11(7):1684. Published 2019 Jul 22. doi:10.3390/nu11071684

Skypala IJ, Williams M, Reeves L, Meyer R, Venter C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. Clin Transl Allergy. 2015;5. doi:10.1186/s13601-015-0078-3

Lectins:

Barre A, Damme EJMV, Simplicien M, Benoist H, Rougé P. Are Dietary Lectins Relevant Allergens in Plant Food Allergy? Foods. 2020;9(12):1724. Published 2020 Nov 24. doi:10.3390/foods9121724

Brouns F, van Rooy G, Shewry P, Rustgi S, Jonkers D. Adverse Reactions to Wheat or Wheat Components. Compr Rev Food Sci Food Saf. 2019;18(5):1437-1452. doi:10.1111/1541-4337.12475

Approximate Incidence of NIAID-Recognized Food Reactions

- **IgE food allergies: 4-8%**
- **Non-IgE food allergies: 3%**
  - Celiac disease: 1+%
  - e.g., eosinophilic esophagitis/gastroenteritis: ~2%
- **Food intolerances: 1-2%**

1. NIAID 2010 Guidelines J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58. 2008 An exploration of food intolerance in the primary care setting: The general practitioner's experience *Social Science & Medicine*, Volume 67, Issue 6, Pages 1038-1045; www.emedicine.com (celiac sprue; pediatric eosinophilic esophagitis)
2. Messina M, Venter C. Recent surveys on food allergy prevalence. Nutrition Today. 2020;55(1):22-9. doi:10.1097/NT.0000000000000389

BUT

Conservative Estimates Suggest That **1/3 of the U.S. Population** Believe They Have a Reaction to Some Food.

1. Chafen, S. The Journal of the American Medical Association. May 12, 2010; vol 303: pp 1848-1856.
2. Turnbull JL, Adams HN, Gorard DA. Review article: the diagnosis and management of food allergy and food intolerances. Aliment Pharmacol Ther. 2015;41(1):3-25. doi:10.1111/apt.12984

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IFM Definitions

- **Food allergy**: Immunologic IgE-mediated type 1 hypersensitivity
- **Food sensitivity**: Immunologic reaction to food (IgA or IgG-mediated delayed hypersensitivity)
- **Food intolerance**: Non-immunologic reaction to food (e.g., lactose intolerance)

American Academy of Allergy, Asthma & Immunology. Food Intolerance Definition. https://www.aaaai.org/conditions-and-treatments/conditions-dictionary/food-Intolerance Retrieved March 8, 2021.

Adverse Food Reactions

Many people who experience adverse reactions to food don't realize that a specific food is causing symptoms. Food reactions are often overlooked as a contributor to chronic health issues. Adverse reactions to food can be broken down into three categories: allergies, intolerances, and sensitivities.

Food allergies	True food allergies are immune reactions to food. These reactions begin to cause symptoms immediately after a trigger food is eaten. Symptoms can range from mild to severe, and may include a rash, swollen or itchy tongue, runny nose, hives, abdominal pain, vomiting, trouble breathing, coughing, wheezing, or a closed airway. Common sources of food allergies are peanuts, tree nuts, wheat, soy, milk, fish, and shellfish. However, many other foods can also cause allergic reactions.
Food intolerances	Food intolerances are non-immune reactions to certain food components (e.g., lactose, histamines, alcohol, etc.) that occur when a person is lacking the digestive enzyme or nutrient responsible for breaking down those food components. Intolerances can cause flushing, cold or flu-like symptoms, inflammation, and general discomfort, because the body lacks the appropriate tools to break down trigger foods. Common trigger foods and ingredients include dairy products, sulfites, histamines, lectins, preservatives, artificial colors, fillers, flavorings, chocolate, citrus fruits, and acidic foods.
Food sensitivities	Food sensitivities can cause reactions that are delayed by hours or even days. These food reactions are usually caused by an imbalance in the gastrointestinal system that is affecting the immune system. One such imbalance is intestinal permeability, or "leaky gut syndrome." Symptoms of food sensitivities differ from person to person, and can depend on the type of food eaten. Some symptoms are migraines, headaches, dizziness, difficulty sleeping, mood swings, depression, anxiety, unintentional weight loss or gain, dark under-eye circles, asthma, irregular heartbeat, irritable bowels, bloating, wheezing, runny nose, sinus problems, ear infections, food cravings, muscle or joint pain, indigestion, nausea, vomiting, hives, rashes, dry skin, excessive sweating and acne, bladder control issues, fatigue, hyperactivity, hives, rashes, dry skin, excessive sweating and acne. Common sources of food sensitivities are cow's milk (and dairy products), eggs, gluten (from wheat, rye, spelt, and barley), soy, shellfish, and tree nuts.

Identifying Adverse Reactions to Food

If you suffer from a food allergy, you are likely aware of the allergy and already avoid trigger foods. If you or your healthcare practitioner suspects that you have a food intolerance or sensitivity, the best way to identify the foods that cause negative symptoms is eliminate those foods from your diet for a certain period of time, then reintroduce those foods one by one, paying close attention to your body's reaction. There are some laboratory tests that can be helpful to assess for food sensitivities and intolerances, although an elimination diet is likely the most accurate way to proceed. Consult your healthcare provider for further explanations.

IFM's comprehensive Elimination Diet, Food Reintroduction Symptoms Tracker, and Diet, Nutrition, and Lifestyle Journal are some of the tools your practitioner may give you to help you in this process.

References

1. American Gastroenterological Association. Food Allergies and Intolerance: Food Allergy vs. Food Intolerance. https://[illegible]. Accessed April 2, 2020.
2. American Academy of Allergy Asthma and Immunology. Food Intolerance versus Food Allergy. https://www.aaaai.org/conditions-and-treatments/library/allergy-library/food-intolerance. Accessed April 2, 2020.

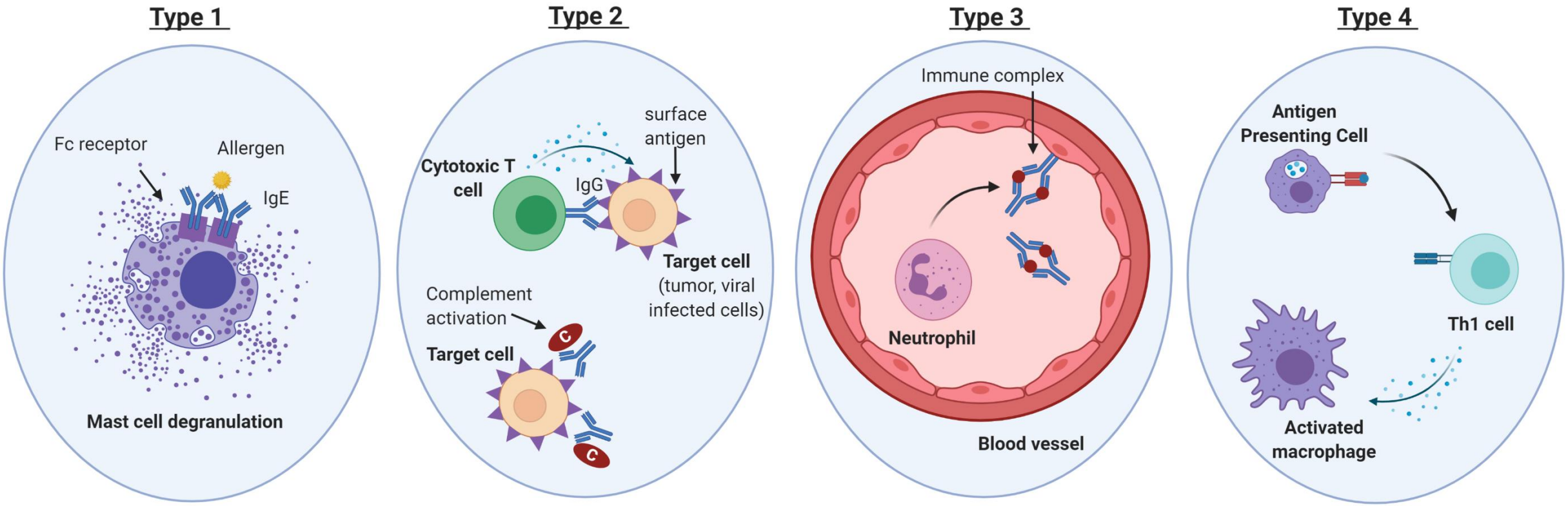
Version 3

In your Toolkit

Gell and Coombs Classification

- **Type 1**: IgE-mediated allergies
- **Type 2**: Cytotoxic (IgG, IgM, complement)
- **Type 3**: Delayed hypersensitivity IgG-mediated reactions
- **Type 4**: Cell Mediated (celiac disease, eosinophilic esophagitis)

The four types of allergy (1) hypersensitivity reaction (2-4)



IgE Mediated Hypersensitivity

Cytotoxic/Antibody Mediated Hypersensitivity (IgG/IgM)

Immune Complex Mediated Hypersensitivity

Cell Mediated Hypersensitivity

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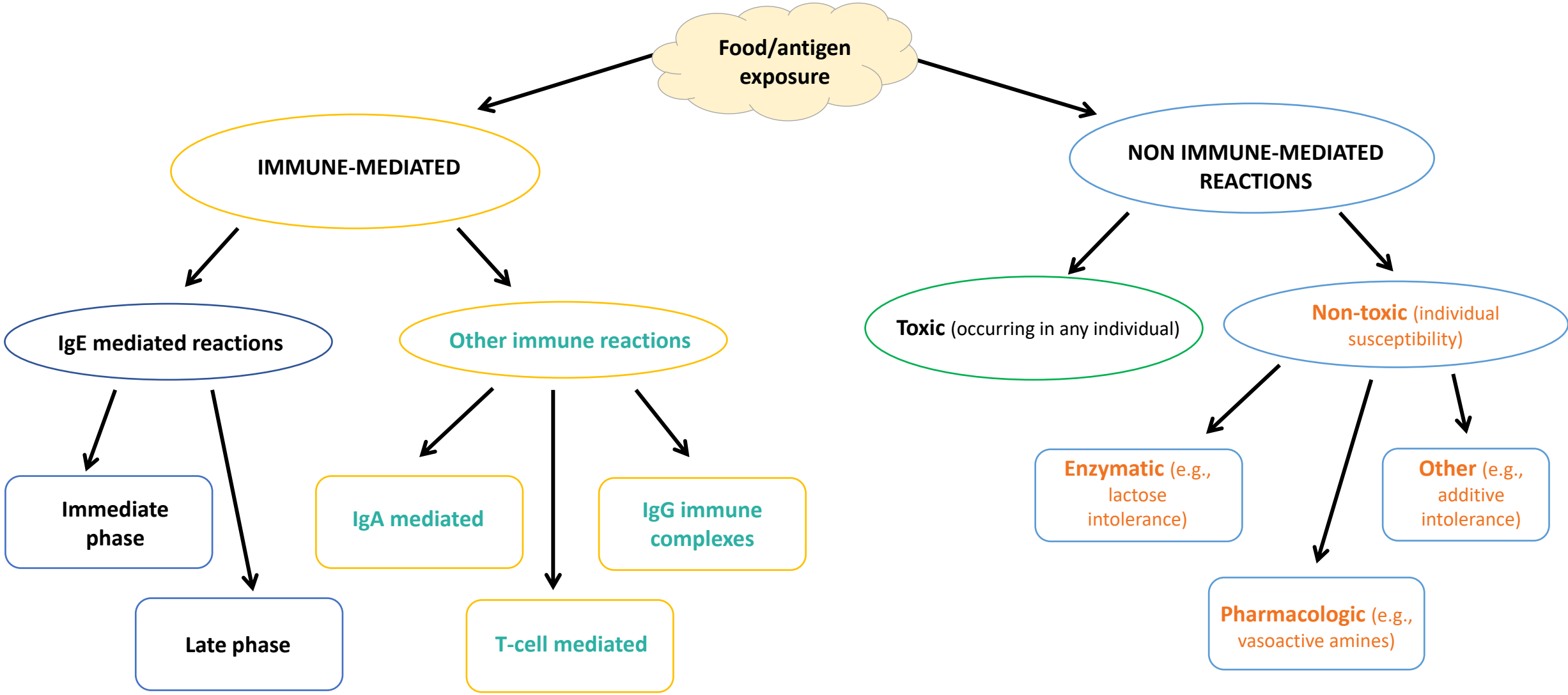
Justiz Vaillant AA, Vashisht R, Zito PM. Immediate Hypersensitivity Reactions. [Updated 2020 Sep 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2020 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK513315/

MECHANISMS OF IMMUNE AND NON-IMMUNE MEDIATED REACTIONS TO FOOD



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The Immunoglobulin Isotypes

CLASS	FEATURES	MAJOR ACTIVITY
IgE	Attaches to Mast Cells	Extreme Sensitivity
	Contact with Allergen	Gatekeeper for IgA
	Causes Release of Histamine, etc.	Antiparasitic
	t1/2: **2.3 Days**	
IgG	Complement Activation	Protects Tissues
	Transplacental	
	t1/2: **23 Days**	
IgA	Two Forms	Protects Mucosa
	Serum – Monomer	Clears Absorbed Food
	Secretions – Dimer	Antigens - Biliary System

IgG

IgM

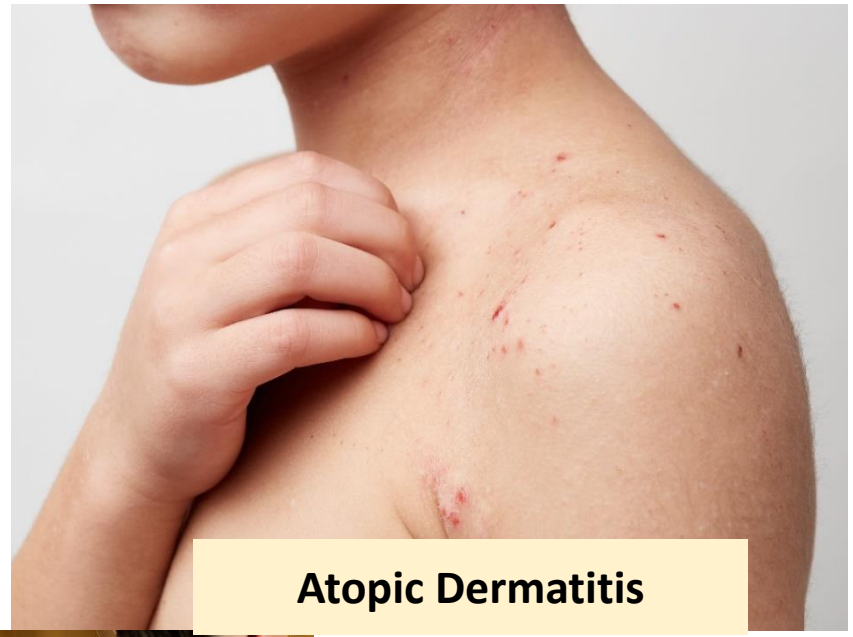
Dimeric IgA

IgE

The Many Faces of Allergy

Contact Dermatitis

Allergic Conjunctivitis



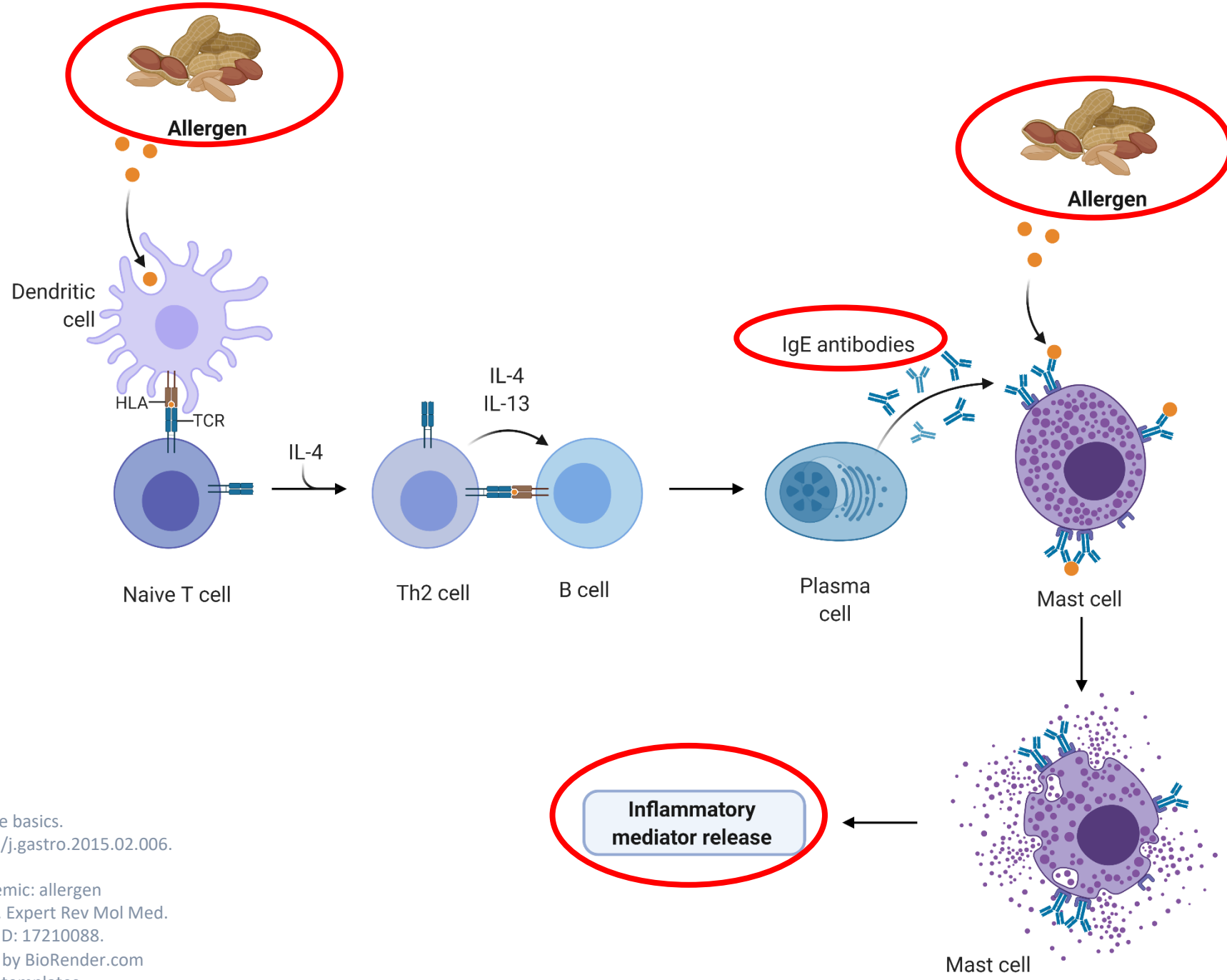
Atopic Dermatitis

Skin Testing IgE Reaction

“Classic” Food Allergy Presentation

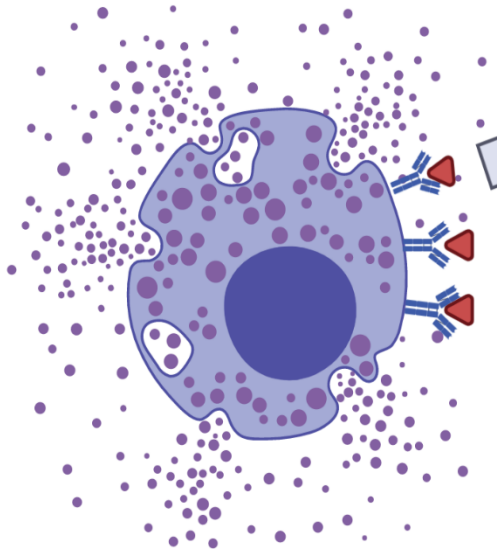
Organ System	Symptoms
Skin	Pruritus, flushing, urticaria, angioedema
Gastrointestinal	Oral pruritus, abdominal pain, cramping, vomiting, diarrhea
Respiratory	
Upper airway	Sneezing, nasal congestion, coughing, hoarseness, throat pruritus/tightening, difficulty swallowing
Lower airway	Wheezing, shortness of breath, cyanosis, respiratory arrest
Cardiovascular	Early tachycardia, late hypotension, dysrhythmia, bradycardia, cardiac arrest
Neurologic	Change of activity level, anxiety, feeling of doom, dizziness, loss of consciousness
Other	Metallic taste in mouth, uterine cramping, urinary urgency

The Immune Response to an Allergen



1. Valenta R, Hochwallner H, Linhart B, Pahr S. Food allergies: the basics. Gastroenterology. 2015 May;148(6):1120-31.e4. doi: 10.1053/j.gastro.2015.02.006. Epub 2015 Feb 11. PMID: 25680669; PMCID: PMC4414527.
2. de Leon MP, Rolland JM, O'Hehir RE. The peanut allergy epidemic: allergen molecular characterisation and prospects for specific therapy. Expert Rev Mol Med. 2007 Jan 9;9(1):1-18. doi: 10.1017/S1462399407000208. PMID: 17210088.

Adapted from "Novel Pathway of IgE-Mediated Drug Allergy", by BioRender.com (2021). Retrieved from https://app.biorender.com/biorender-templates



Mast cells are involved in various immune processes.
Increased histamine, cytokines, prostaglandins, leukotrienes, chymase, trypatase, etc. lead to:

- Acute and chronic inflammation
- Increased mucus secretion and bronchoconstriction
- Vasodilation, edema, tissue swelling
- Increased fluid secretion and peristalsis

Mast cell activation and granule release can affect the GI tract, airways and blood vessels as well as increase both acute inflammation and chronic inflammation.

The Immunoglobulins

CLASS	FEATURES	MAJOR ACTIVITY
IgE	* Attaches to Mast Cells * Contact with Allergen Causes Release of Histamine, etc. * 0.0002 mg/mL * **1 % Total Immunoglobulin** * **t1/2: 2-3 Days** * **Memory (IL-4): up to years**	* Extreme Sensitivity * Gatekeeper * Antiparasitic

Hostoffer RW, Joseph N. Immunoglobulin E. In: StatPearls. Treasure Island (FL): StatPearls Publishing; May 11, 2020. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK482212/

ATMs Involved in Food Allergy

- Genetics
- Epidermal permeability
- Medications
- Environmental toxins
- Nutrient deficiencies
- Hypochlorhydria
- Microbiota
- Stress
- Intestinal permeability

See References: ATMs Involved in Food Allergy

References: ATMs Involved in Food Allergy

Environmental Toxins:

Gilles S, Akdis C, Lauener R, et al. The role of environmental factors in allergy: A critical reappraisal. Exp Dermatol. 2018;27(11):1193-1200. doi:10.1111/exd.13769

Nutrient deficiencies:

Skypala IJ, McKenzie R. Nutritional Issues in Food Allergy. Clin Rev Allergy Immunol. 2019;57(2):166-178. doi:10.1007/s12016-018-8688-x

Meyer R. Nutritional disorders resulting from food allergy in children. Pediatr Allergy Immunol. 2018;29(7):689-704. doi:10.1111/pai.12960

Hypochlorhydria:

Plotnikoff GA. Assessment for Adverse Food Reactivity. A Clinician's Guide. Minn Med. 2016;99(6):36-39.

Noland D, Drisko JA, Wagner L, editors. Integrative and Functional Medical Nutrition Therapy: Principles and Practices. Springer Nature; 2020.

Microbiota:

Shu SA, Yuen AWT, Woo E, et al. Microbiota and Food Allergy. Clin Rev Allergy Immunol. 2019;57(1):83-97. doi:10.1007/s12016-018-8723-y

Ali A, Tan H, Kaiko GE. Role of the Intestinal Epithelium and Its Interaction With the Microbiota in Food Allergy. Front Immunol. 2020;11:604054. Published 2020 Dec 7. doi:10.3389/fimmu.2020.604054

Intestinal permeability:

Farré R, Fiorani M, Abdu Rahiman S, Matteoli G. Intestinal Permeability, Inflammation and the Role of Nutrients. Nutrients. 2020;12(4):1185. Published 2020 Apr 23. doi:10.3390/nu12041185

Samadi N, Klems M, Untersmayr E. The role of gastrointestinal permeability in food allergy. Ann Allergy Asthma Immunol. 2018;121(2):168-173. doi:10.1016/j.anai.2018.05.010

Triggers of Increased Intestinal Permeability

- Alcohol
- Additives
- Gliadin protein
- High fat diet
- Simple sugars
- HIIT
- Zinc deficiency
- Antibiotics
- Concussions (TBI)
- Night shift work
- Oral contraceptives
- Diarrhea
- Constipation
- Gastroenteritis
- Hypochlorhydria
- Autoimmune disease
- Food allergies
- NSAIDS
- Stress/elevated cortisol
- Obstructive sleep apnea
- Cadmium exposure

See References: Triggers of Intestinal Permeability

References: Triggers of Intestinal Permeability

Dietary choices: Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress related psychiatric disorders. *Frontiers in Cellular Neuroscience*. 2015;9:392. doi:10.3389/fncel.2015.00392.

Stress: Vanuytsel T, van Wanrooy S, Vanheel H, et al. Psychological stress and corticotropin releasing hormone increase intestinal permeability in humans by a mast cell dependent mechanism. *Gut*. 2014 Aug; 63(8):12939. doi: 10.1136/gutjnl 2013305690.

Infection: Kukuruzovic R, Robins, Browne RM, Anstey NM, Brewster DR. Enteric pathogens, intestinal permeability and nitric oxide production in acute gastroenteritis. *Pediatr Infect Dis J*. 2002 Aug;21(8):730-9.

Dysbiosis: Brown K, DeCoffe D, Molcan E, Gibson DL. Diet induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients.* 2012;4(8):1095-1119. doi:10.3390/nu4081095

Inflammation: Michielan A, D'Incà R. Intestinal Permeability in Inflammatory Bowel Disease: Pathogenesis, Clinical Evaluation, and Therapy of Leaky Gut. *Mediators of Inflammation*. 2015;2015:628157. doi:10.1155/2015/628157

Systemic Disease: Arrieta MC, Bistritz L, Meddings JB. Alterations in intestinal permeability. *Gut*. 2006;55(10):1512-1520. doi:10.1136/gut.2005.085373.

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References: Triggers of Intestinal Permeability

Toxins: Pinton P, Nougayrède JP, Del Rio JC, et al. The food contaminant deoxynivalenol, decreases intestinal barrier permeability and reduces claudin expression. Toxicol Appl Pharmacol. 2009 May 15;237(1):41-8. doi: 10.1016/j.taap.2009.03.003.

Nutritional Deficiencies: Tran CD, Hawkes J, Graham RD, et al. Zinc-fortified oral rehydration solution improved intestinal permeability and small intestinal mucosal recovery. Clin Pediatr (Phila). 2015 Jun;54(7):676-82.doi: 10.1177/0009922814562665.

Medications: Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A*. 2011 Mar 15;108 Suppl 1:4554 61. doi: 10.107 3/pnas.1000087107.

Food Allergy: Järvinen KM, Konstantinou GN, et al. Intestinal permeability in children with food allergy on specific elimination diets. *Pediatr Allergy Immunol*. 2013 Sep;24(6):589-95. doi: 10.1111/pai.12106.

Malnutrition: Norman K, Pirlich M, Schulzke JD, Smoliner C, Lochs H, Valentini L, Bühner S. Increased intestinal permeability in malnourished patients with liver cirrhosis. Eur J Clin Nutr. 2012 Oct;66(10):1116-9. doi: 10.1038/ejcn.2012.104.

Systematic Reviews:

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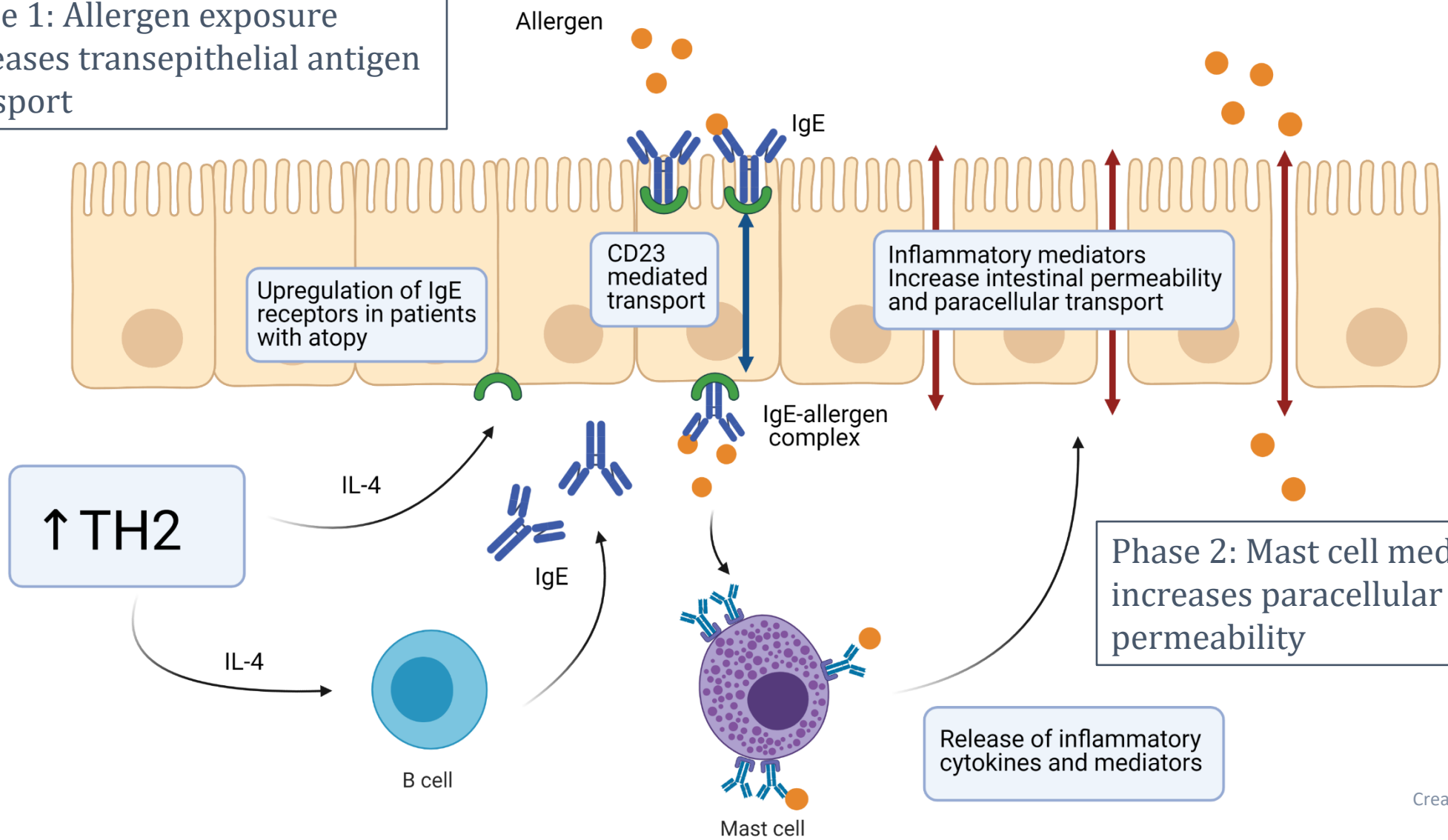
Leech B, Schloss J, Steel A. Association between increased intestinal permeability and disease: A systematic review. Advances in Integrative Medicine. 2019;6(1):23-34. doi: https://doi.org/10.1016/j.aimed.2018.08.003

Gut Permeability and Food Allergies

Phase 1: Allergen exposure increases transepithelial antigen transport



Phase 2: Mast cell mediator release increases paracellular epithelial permeability

Created with BioRender.com

1. Yu LC. Intestinal epithelial barrier dysfunction in food hypersensitivity. J Allergy (Cairo). 2012;2012:596081. doi: 10.1155/2012/596081. Epub 2011 Sep 8. PMID: 21912563; PMCID: PMC3170794.
2. Perrier C, Corthésy B. Gut permeability and food allergies. Clin Exp Allergy. 2011 Jan;41(1):20-8. doi: 10.1111/j.1365-2222.2010.03639.x. Epub 2010 Nov 11. PMID: 21070397.

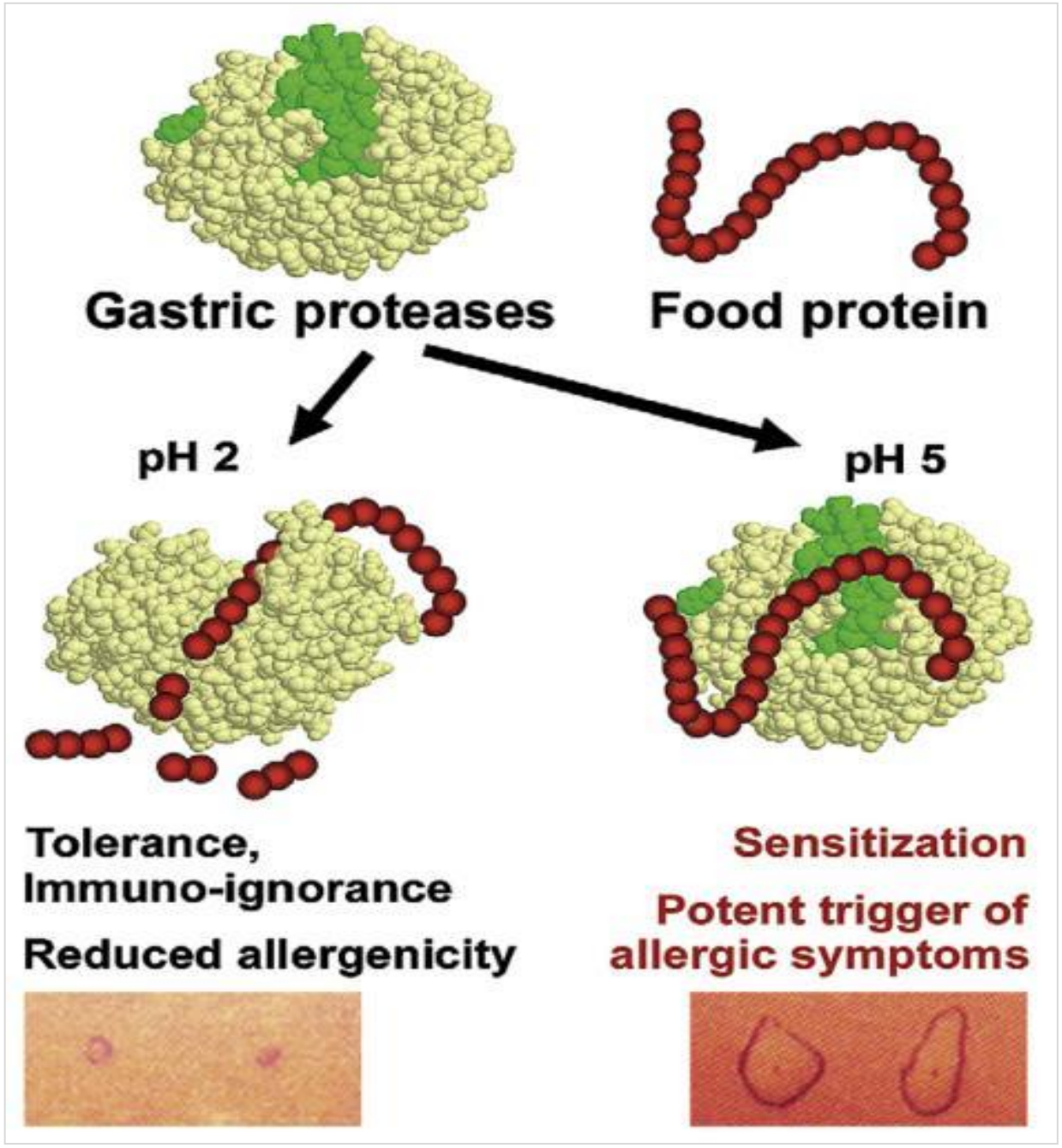
ATMs Involved in Food Allergy

Risk factors for adult anaphylaxis are agents causing increased **intestinal permeability**.

Untersmayr E et al. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J, 2005; Curr Allergy Asthma Rep. 2005 Jan;5(1):80-5.

Lower the pH and Decrease Allergic Trigger:

The Gate-Keeping Function of the Stomach in the Sensitization and Effector Phase of Food Allergy



Pali-Schöll I, Jensen-Jarolim E. Anti-acid medication as a risk factor for food allergy. Allergy. 2011;66(4):469-477. doi:10.1111/j.1398-9995.2010.02511.x

Reprinted from The Journal of allergy and clinical immunology, 121/6, Untersmayr, E., & Jensen-Jarolim, E., The role of protein digestibility and antacids on food allergy outcomes, Pages 1301-1310, Copyright 2008, with permission from American Academy of Allergy, Asthma, and Immunology.

HYPOCHLORHYDRIA HAS BEEN SHOWN TO INCREASE IgE REACTIONS > 10X

Digestion-Stable Food Antigen

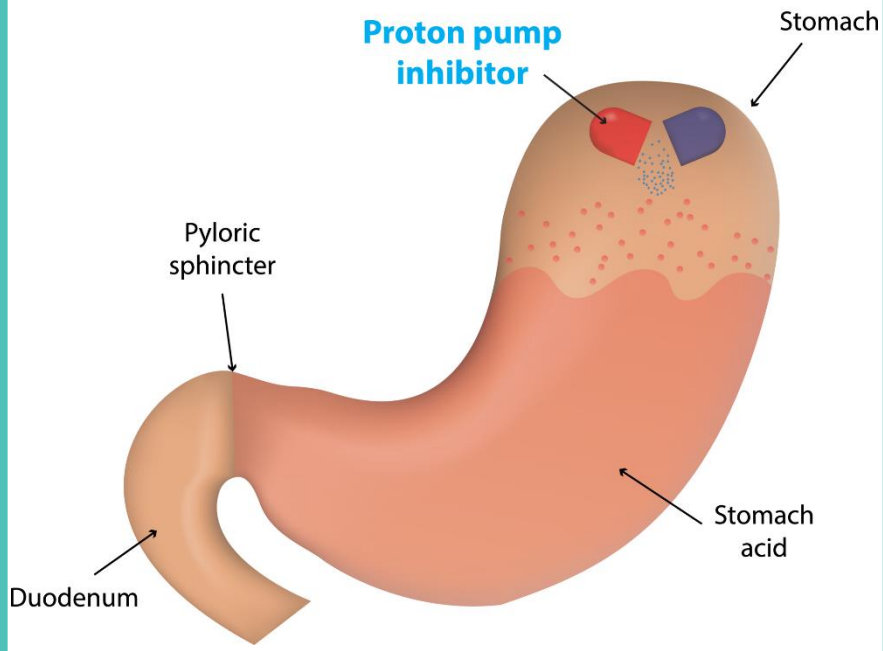
↓

Gastric Digestion

↓

Normal Immune Response

Proton Pump Inhibitor



Digestion-Labile Food Antigen

↓

Hypoacidity

↓

↑↑ Food Allergy

Untersmayr E, Bakos N, Schöll I, Kundi M, Roth-Walter F, Szalai K, Riemer AB, Ankersmit HJ, Scheiner O, Boltz-Nitulescu G, Jensen-Jarolim E. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J. 2005 Apr;19(6):656-8. doi: 10.1096/fj.04-3170fje. Epub 2005 Jan 25. PMID: 15671152.

Effects of PPIs on Allergenicity of Proteins

- Gastric digestion substantially decreases the potential of food proteins to bind IgE, which increases the threshold dose of allergens required to elicit symptoms in patients with food allergy.
- Thus, **anti-ulcer agents impeding gastric protein digestion have a major effect on the sensitization and effector phase of food allergy.**

1. Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. J Allergy Clin Immunol. 2008 Jun;121(6):1301-8; quiz 1309-10. doi: 10.1016/j.jaci.2008.04.025.
2. Pali-Schöll I, Jensen-Jarolim E. Anti-acid medication as a risk factor for food allergy. Allergy. 2011;66(4):469-477. doi:10.1111/j.1398-9995.2010.02511.x

Acid suppression in childhood can set the scene for food allergies…

- **In one study of 4724 children:**
  - Children with GERD who were treated with a gastric acid suppressor were more likely to be diagnosed with a food allergy than children who received no treatment.
- **In another study of 104 children**:
  - History of taking antacid medication was associated with an increased prevalence of food allergy.
- **In a study of health insurance records covering 97% of the Austrian population**:
  - A relationship was found between gastric acid-suppression and the development of allergic symptoms.

1. Trikha A, Baillargeon JG, Kuo YF, Tan A, Pierson K, Sharma G, Wilkinson G, Bonds RS. Development of food allergies in patients with gastroesophageal reflux disease treated with gastric acid suppressive medications. Pediatr Allergy Immunol. 2013 Sep;24(6):582-8. doi: 10.1111/pai.12103.
2. DeMuth K, Stecenko A, Sullivan K, Fitzpatrick A. Relationship between treatment with antacid medication and the prevalence of food allergy in children. Allergy Asthma Proc. 2013 May-Jun;34(3):227-32. doi: 10.2500/aap.2013.34.3657.
3. Jordakieva G, Kundi M, Untersmayr E, Pali-Schöll I, Reichardt B, Jensen-Jarolim E. Country-wide medical records infer increased allergy risk of gastric acid inhibition. Nat Commun. 2019;10(1):3298. Published 2019 Jul 30. doi:10.1038/s41467-019-10914-6

Effects of acid suppression in mothers on their babies

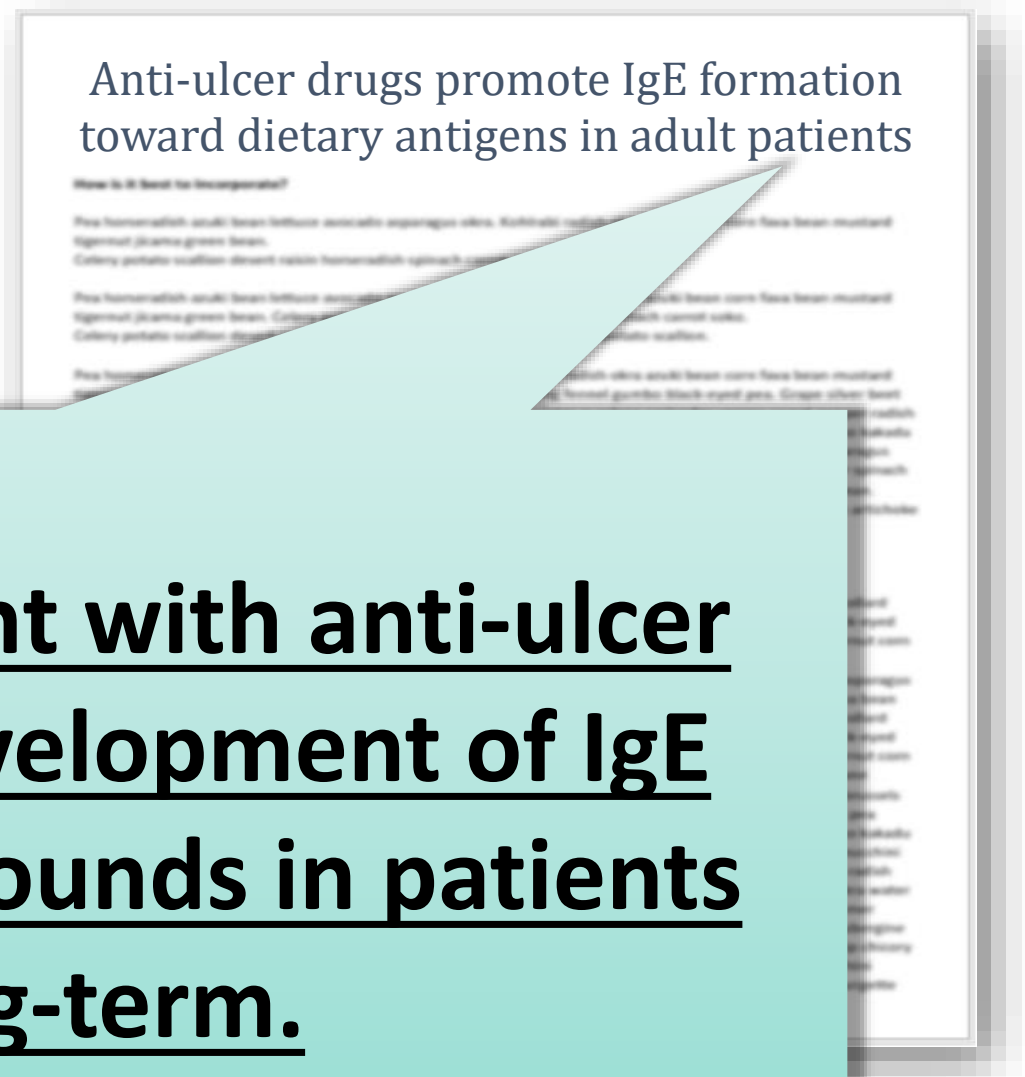
- **Maternal acid-suppressive therapy may promote allergy in the progeny** via 3 mechanisms:
  1. May interfere with digestion of labile antigens in the maternal stomach, increasing the amount of allergen the fetus is exposed to, leading to sensitization
  2. May induce a Th2 cytokine pattern in mothers, encouraging an allergy-prone state in the fetus
  3. Maternal allergen-specific immunoglobulin E could cross fetal membranes and induce sensitization of fetal immune cells to food and airborne allergens before birth.

- *A study of adults showed that **IgE sensitization was detected 5 months after discontinuation of treatment** with acid-suppressive medication.*

1. Devine RE, McCleary N, Sheikh A, Nwaru BI. Acid-suppressive medications during pregnancy and risk of asthma and allergy in children: A systematic review and meta-analysis. J Allergy Clin Immunol. 2017 Jun;139(6):1985-1988.e12. doi: 10.1016/j.jaci.2016.09.046.

2. Devine RE, Sheikh A, Nwaru BI. Acid-suppressive medications during pregnancy and risk of asthma and allergy in the offspring: protocol for a systematic review. NPJ Prim Care Respir Med. 2016;26:16001. Published 2016 Mar 3. doi:10.1038/npjpcrm.2016.1

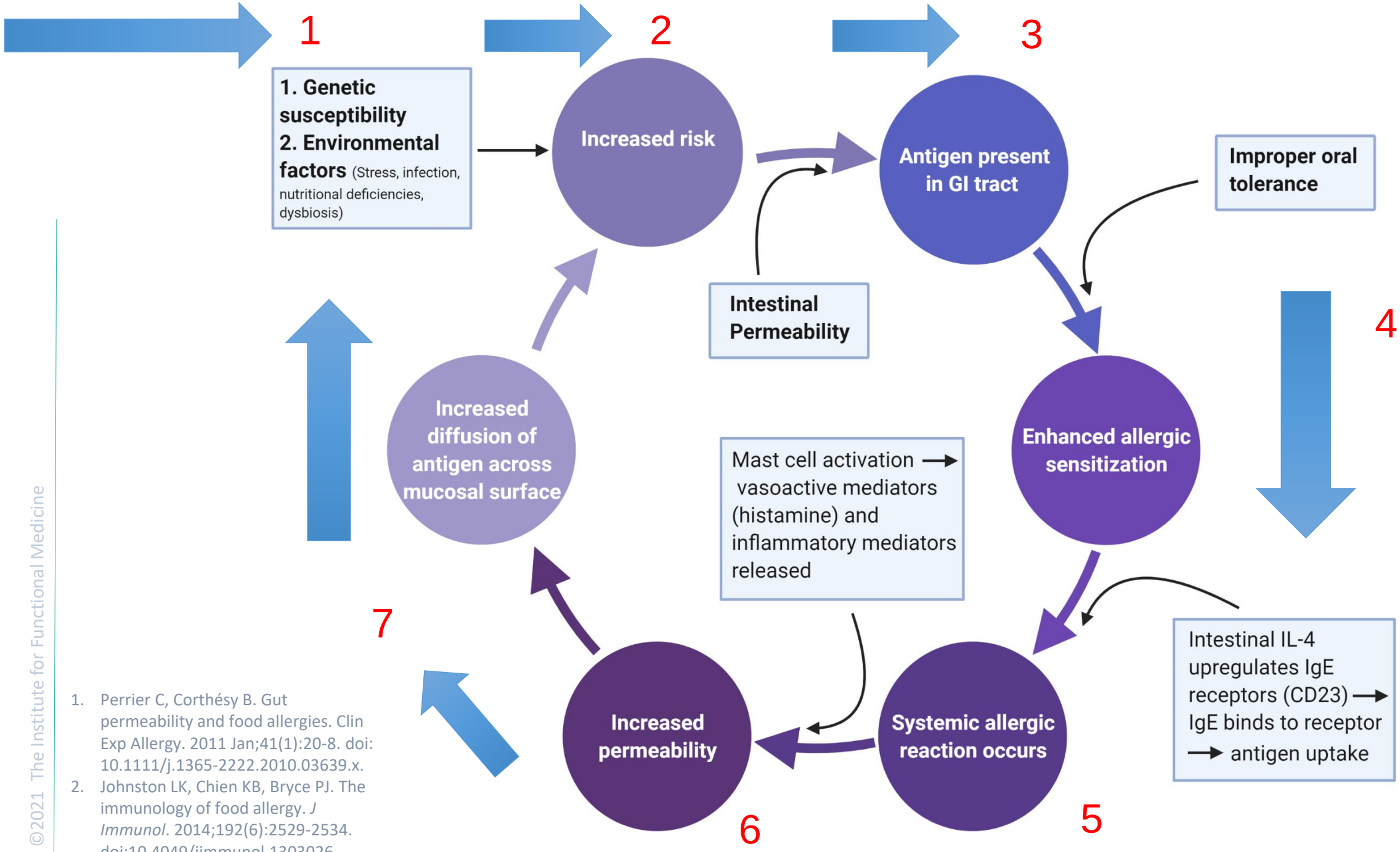
POTENTIAL CONSEQUENCES OF THE PURPLE PILL



Conclusion: Treatment with anti-ulcer drugs primes the development of IgE toward dietary compounds in patients treated long-term.

Untersmayr E, Bakos N, Schöll I, et al. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J. 2005 Apr;19(6):656-8.

Ask your doctor if medical advice from a television commercial is right for you.



1. Perrier C, Corthésy B. Gut permeability and food allergies. Clin Exp Allergy. 2011 Jan;41(1):20-8. doi: 10.1111/j.1365-2222.2010.03639.x.
2. Johnston LK, Chien KB, Bryce PJ. The immunology of food allergy. *J Immunol*. 2014;192(6):2529-2534. doi:10.4049/jimmunol.1303026

90% of all acute food allergies are:

1. **Dairy**
2. **Eggs**
3. **Peanuts**
4. **Wheat**
5. **Soy**
6. **Fish**
7. **Shellfish**
8. **Tree nuts** - walnuts, cashews, & almonds

1. Lin J, Sampson HA. The role of immunoglobulin E-binding epitopes in the characterization of food allergy. Curr Opin Allergy Clin Immunol. 2009 Aug;9(4):357-63. doi: 10.1097/ACI.0b013e32832d05ba.
2. Common Food Allergies in Infants, Children and Adults. (2012, March 6). Retrieved from http://www.niaid.nih.gov/topics/foodAllergy/understanding/Pages/foodAllergy8Allergens.aspx

Increasing Incidence of IgE Food Allergy

- Children: +18% increase last 10 years
  - Children not outgrowing at same rate
- Increase in adult food allergies and anaphylaxis
- The increase of food reactions may be, in part, due to **alterations of the Microbiome stemming from processed food**.

American adults with allergies, especially to nuts and pollen, have lower microbiome diversity and altered composition of their gut microbiome *(bacteroidales > clostridiales).*

1. Untersmayr E et al. Anti-ulcer drugs promote IgE formation toward dietary antigens in adult patients. FASEB J, 2005; Curr Allergy Asthma Rep. 2005 Jan;5(1):80-5. Adult food allergy.
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3. Hua, X., Goedert, J. J., Pu, A., Yu, G., & Shi, J. (2016). Allergy associations with the adult fecal microbiota: Analysis of the American Gut Project. *EBioMedicine*, *3*, 172-179

NIAID Guidelines on Testing

- **"Gold standard" = Elimination Diet w/ double blind oral food challenge**
  - Food challenge reaction time must occur in minutes to 2-4 hours.
- **Skin prick test**
- **IgE serum testing** *"useful but not diagnostic"*

NO other testing is considered valid by NIAID.

NIAID 2010 Guidelines J Allergy Clin Immunol. 2010 Dec;126(6 Suppl):S1-58. Medscape Food Allergy: What You Need to Know 11/2010; Medscape Food Allergy: The Definitive Guide to Clinical Practice: A Reliable Approach to Diagnosis 12/2010

IgE Evaluation

Skin prick testing:

- Good reproducibility
- But- variability with different antigen sources, preparation
- Higher sensitivity, lower specificity
- Not appropriate with: steroids, antihistamines, significant dermatitis, risk of anaphylaxis

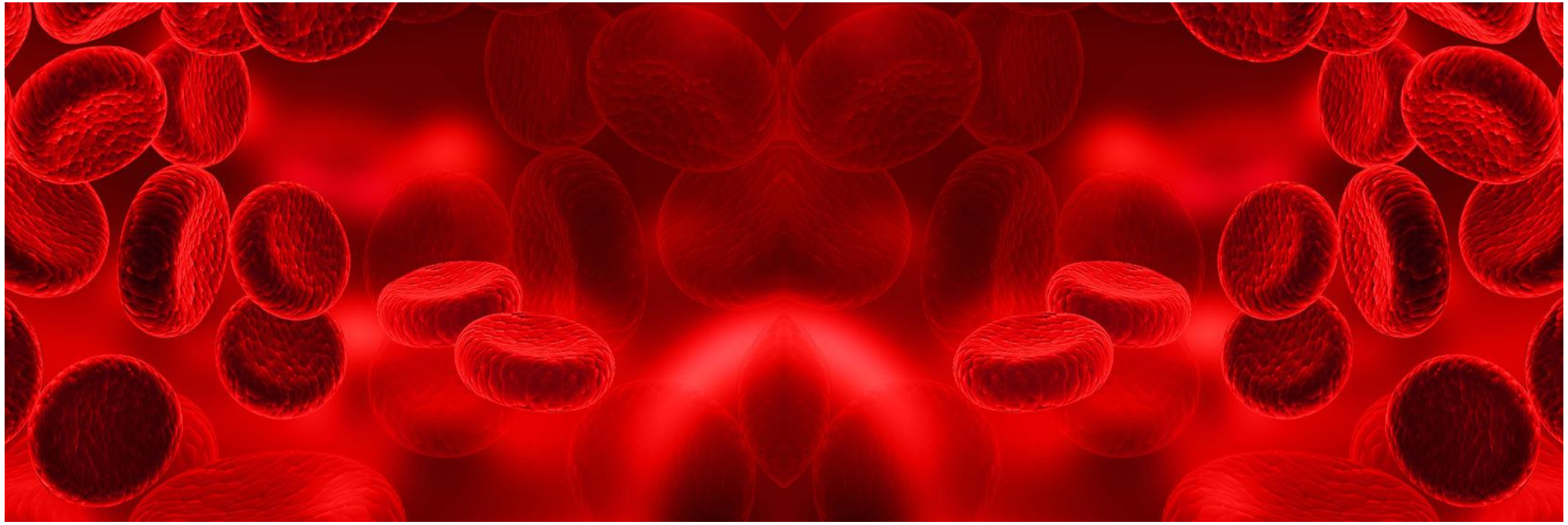
DBPC food challenge "gold standard":

- Time consuming, risky (only use in research setting). Not well-utilized.

1. Wagner, N., Rudert, M. Sensitivity and specificity of standardised allergen extracts in skin prick test for diagnoses of IgE-mediated respiratory allergies. Clin Transl Allergy. 2019; 9(8). doi:10.1186/s13601-019-0248-9.
2. Nowak-Wegrzyn A, Assa'ad AH, Bahna SL, et al. Work group report: oral food challenge testing. The Journal of Allergy and Clinical Immunology. 2009; 123(6): S365-S383. doi: 10.1016/j.jaci.2009.03.042.

IgE Blood Testing for Allergies

- Well standardized antigens and antigen preparation
- Data does not always correlate with clinical response



SERUM TESTING:
GRADE VS. CLINICAL REACTION FROM lgE

Grade	IU/mL	Approximate risk of symptoms after exposure
0	<0·35	Extremely unlikely
1	0·35-0·7	Mild, possible
2	0·70-3·5	Mild, more possible
3	3·5-17·5	Moderate, likely
4	17·5-50	Moderate, more likely
5	50-100	Very likely
6	>100	Extremely likely

Risk of allergic symptoms after allergen exposure as indicated by allergen-specific immunoglobulin E antibody grade.

Williams P, Sewell WAC, Bunn C, Pumphrey R, Read G, Jolles S. Clinical Immunology Review Series: An approach to the use of the immunology laboratory in the diagnosis of clinical allergy. *Clinical and Experimental Immunology*. 2008;153(1):10-18. doi:10.1111/j.1365-2249.2008.03695.x.

IgE Blood Testing for Allergies: Recommendations

- Useful
- Low-grade findings may be significant.
- Use same lab for baseline and follow-up.
- “Specialty labs” may have more sensitive reference ranges.
- **Positive(s) suggest intestinal permeability**
- **May miss anaphylaxis**

Therapeutic Options for Food Allergy

- **Conventional care:**
  - Avoidance
  - Allergy shots
- **SLIT- SubLingual ImmunoTherapy:**
  - Gradual increasing the number of drops of allergen that has been mixed specifically for you in response to the skin testing
  - Gradually desensitizes your immune reaction to the allergen
- **Address Intestinal Permeability**
- **Address Microbiome**

Allergen Cross-reactivity

Sensitivity	Possible cross-reaction	Risk (%)
A legume	Other legumes	5–10
A tree nut	Other tree nuts	40
A fish	Other fish	50
A shellfish	Other shellfish	50–75
A grain	Other grains	20
Egg	Chicken	5
Cow's milk	Beef	10
Cow's milk	Goat's milk	>90
Cow's milk	Mare's milk	4
Pollen	Fruits/vegetables	50
Melon	Other fruits (melon, banana, avocado)	90
Latex	Fruits	35
Fruits	Latex	10

1. Reprinted from Immunology and Allergy Clinics of North America, Vol. 25, Scurlock A. M., Lee L. A., Burks A. W., Food allergy in children, Pages 369-88, Copyright 2005, with permission from Elsevier.
2. Fireman, P: Atlas of Allergies and clinical immunology 3rd edition. P.223. Scurlock AM, AW Burks. Food Hypersensitivity.

Allergen Cross-reactivity

- **High Association:** banana, avocado, kiwi, and chestnut
- **Moderate Association:** potato, tomato, apple, carrot, apricot, celery, melon, watermelon, grape, papaya
- **Low Association:** apricot, buckwheat, castor bean, cayenne, pepper, cherry, chickpea, citrus fruits, dill, fig

1. Scurlock AM, Lee LA, Burks AW. Food allergy in children. Immunol Allergy Clin North Am. 2005 May;25(2):369-88, vii-viii. doi: 10.1016/j.iac.2005.02.005. PMID: 15878461.
2. Pollert SM, C. Warniment, T. Mori: Latex Allergy. Am Fam physicians. 2009:80(12):1413-1418.

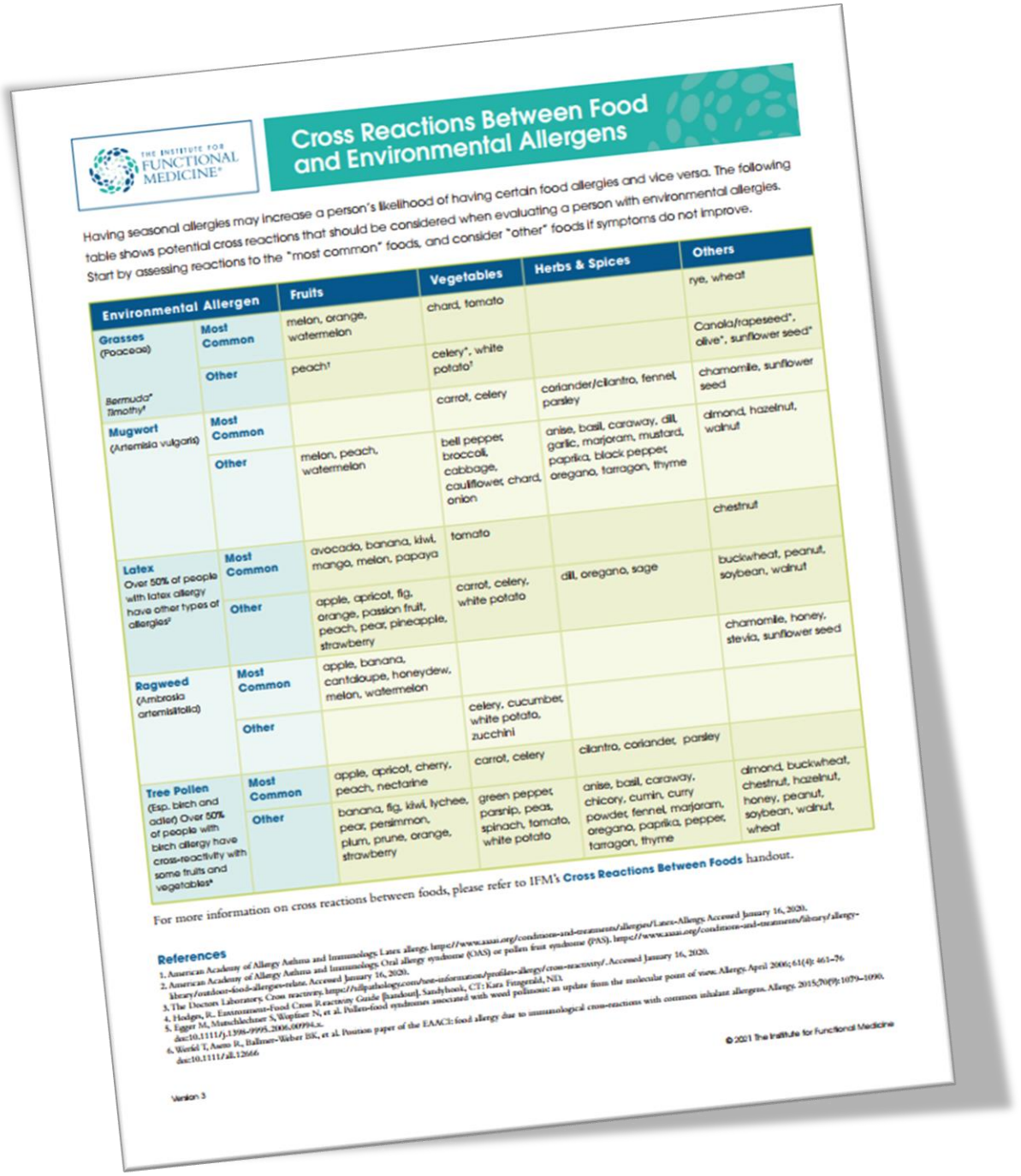
60% of IgE Food reactions are cross reactions with inhalant IgE allergens.

Worm M, Jappe U, Kleine-Tebbe J, et al. Food allergies resulting from immunological cross-reactivity with inhalant allergens: Guidelines from the German Society for Allergology and Clinical Immunology (DGAKI), the German Dermatology Society (DDG), the Association of German Allergologists (AeDA) and the Society for Pediatric Allergology and Environmental Medicine (GPA). *Allergo J Int*. 2014;23(1):1–16. doi:10.1007/s40629-014-0004-6.

Pollen/Food Syndrome Relationships

• **Ragweed**	Melons, bananas, cucumber, apples
• **Birch**	Apples, stone fruits- apricot, cherry, plum, hazelnuts, carrot
• **Mugwort**	Celery, carrot, some spices
• **Grass**	Potato, tomato, peach

The Doctors Laboratory. Cross reactivity. https://tdlpathology.com/test-information/profiles-allergy/cross-reactivity/. Accessed February 4, 2021.



Cross Reactions Between Food and Environmental Allergens

Having seasonal allergies may increase a person's likelihood of having certain food allergies and vice versa. The following table shows potential cross reactions that should be considered when evaluating a person with environmental allergies. Start by assessing reactions to the "most common" foods, and consider "other" foods if symptoms do not improve.

Environmental Allergen		Fruits	Vegetables	Herbs & Spices	Others
Grasses (Poaceae) Bermuda*, Timothy†	**Most Common**	melon, orange, watermelon	chard, tomato		rye, wheat
	Other	peach†	celery*, white potato†		Canola/rapeseed*, olive*, sunflower seed*
Mugwort (Artemisia vulgaris)	**Most Common**		carrot, celery	coriander/cilantro, fennel, parsley	chamomile, sunflower seed
	Other	melon, peach, watermelon	bell pepper, broccoli, cabbage, cauliflower, chard, onion	anise, basil, caraway, dill, garlic, marjoram, mustard, paprika, black pepper, oregano, tarragon, thyme	almond, hazelnut, walnut
Latex Over 50% of people with latex allergy have other types of allergies‡	**Most Common**	avocado, banana, kiwi, mango, melon, papaya	tomato		chestnut
	Other	apple, apricot, fig, orange, passion fruit, peach, pear, pineapple, strawberry	carrot, celery, white potato	dill, oregano, sage	buckwheat, peanut, soybean, walnut
Ragweed (Ambrosia artemisiifolia)	**Most Common**	apple, banana, cantaloupe, honeydew, melon, watermelon			chamomile, honey, stevia, sunflower seed
	Other		celery, cucumber, white potato, zucchini		
Tree Pollen (Esp. birch and alder) Over 50% of people with birch allergy have cross-reactivity with some fruits and vegetables§	**Most Common**	apple, apricot, cherry, peach, nectarine	carrot, celery	cilantro, coriander, parsley	
	Other	banana, fig, kiwi, lychee, pear, persimmon, plum, prune, orange, strawberry	green pepper, parsnip, peas, spinach, tomato, white potato	anise, basil, caraway, chicory, cumin, curry powder, fennel, marjoram, oregano, paprika, pepper, tarragon, thyme	almond, buckwheat, chestnut, hazelnut, honey, peanut, soybean, walnut, wheat

For more information on cross reactions between foods, please refer to IFM's **Cross Reactions Between Foods** handout.

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2. American Academy of Allergy Asthma and Immunology. Oral allergy syndrome (OAS) or pollen fruit syndrome (PFS). https://www.aaaai.org/conditions-and-treatments/library/allergy-library/outdoor-food-allergies-relate. Accessed January 16, 2020.
3. The Doctors Laboratory. Cross reactancy. https://tdlpathology.com/test-information/profiles-allergy/cross-reactancy/. Accessed January 16, 2020.
4. Hodges, R., Environment-Food Cross Reactancy Guide [handout]. Sandybrook, CT: Kara Fitzgerald, ND.
5. Egger M., Mutschlechner S, Wopfner N, et al. Pollen-food syndromes associated with weed pollinosis: an update from the molecular point of view. Allergy. April 2006; 61(4): 461–76. doi:10.1111/j.1398-9995.2006.00994.x.
6. Werfel T, Asero R., Ballmer-Weber BK, et al. Position paper of the EAACI: food allergy due to immunological cross-reactions with common inhalant allergens. Allergy. 2015;70(9):1079–1090. doi:10.1111/all.12666

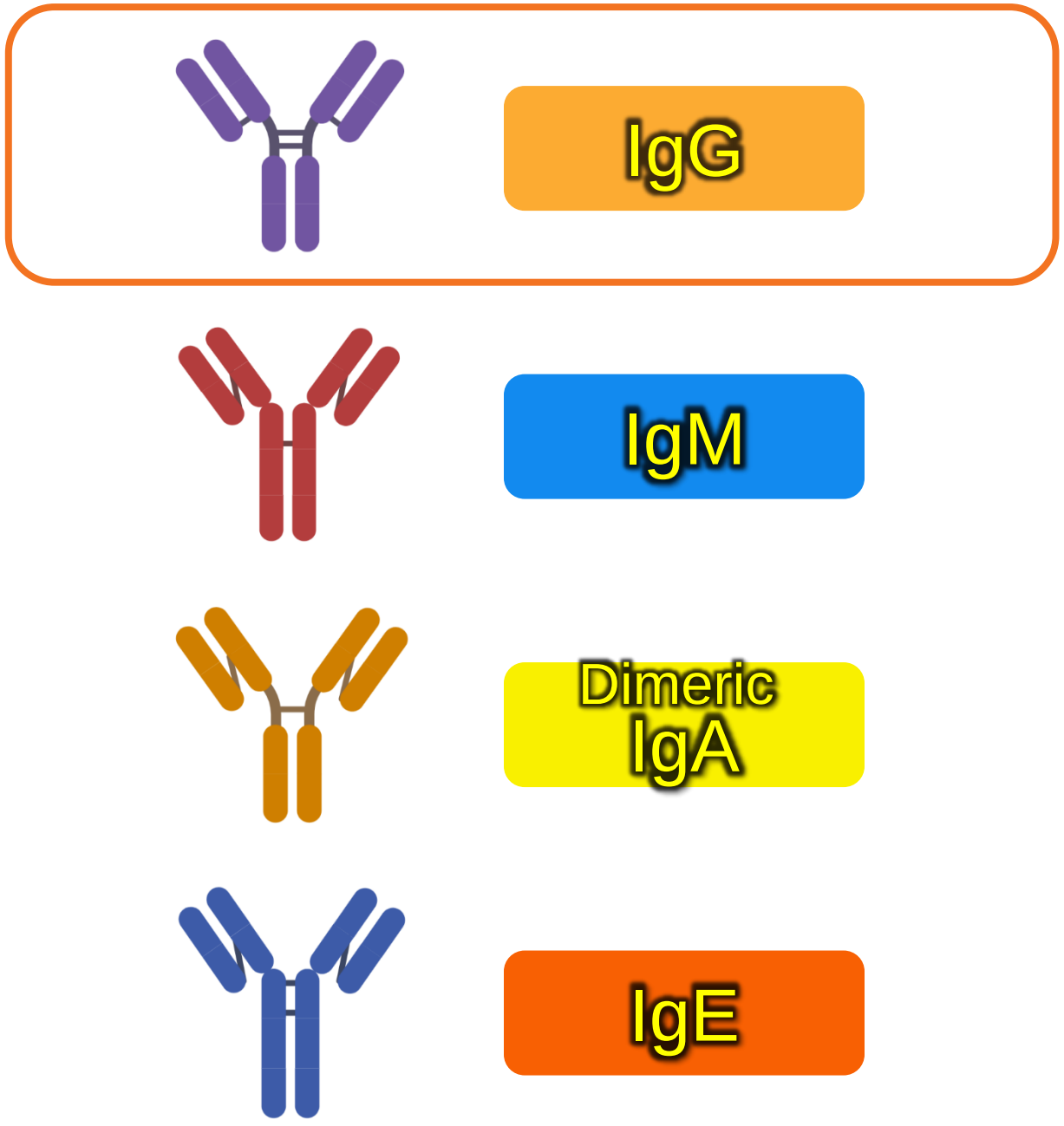
Version 3

In your Toolkit

Part 2

The Immunoglobulin Isotypes

CLASS	FEATURES	MAJOR ACTIVITY
IgE	Attaches to Mast Cells Contact with Allergen Causes Release of Histamine, etc. t1/2: **2.3 Days**	Extreme Sensitivity Gatekeeper for IgA Antiparasitic
IgG	Complement Activation Transplacental t1/2: **23 Days**	Protects Tissues
IgA	Two Forms Serum – Monomer Secretions – Dimer	Protects Mucosa Clears Absorbed Food Antigens - Biliary System



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Immunoglobulin G (IgG)

- Complex immunoglobulin class
- Crosses the placenta
- IgG makes up 75% of total immunoglobulins
- Half life of **~21-23 days**

Therefore, IgG elimination diets should be at least 3 weeks to decrease IgG by half.

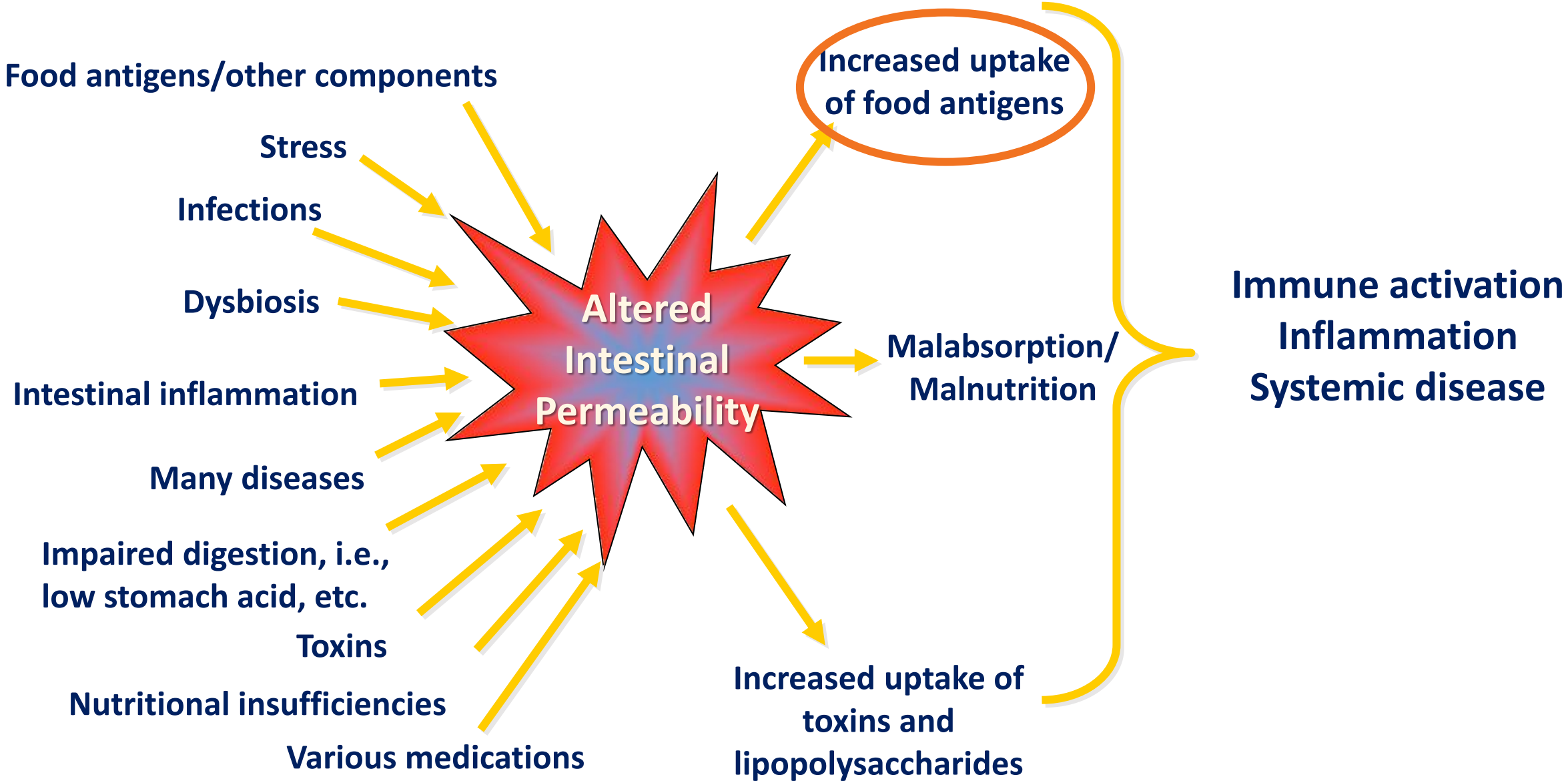
ATMs in IgG Food Sensitivity

- Genetics
- Food and/or environmental allergy
- Maldigestion
- Dysbiosis
- Nutritional insufficiencies
- Intestinal permeability

1. Shanahan F, Whorwell P,J. IgG-mediated food intolerance in irritable bowel syndrome: A real phenomenon or an epiphenomenom? Am J Gastroenterol. 2005;100:1558. http://dx.doi.org/10.1111/j.1572-0241.2005.50009.x.
2. Mullin GE, Swift KM, Lipski L, Turnbull LK, Rampertab SD. Testing for food reactions: the good, the bad, and the ugly. Nutr Clin Pract. 2010 Apr;25(2):192-8. doi: 10.1177/0884533610362696.
3. Taraghikhah N, Ashtari S, Asri N, et al. An updated overview of spectrum of gluten-related disorders: clinical and diagnostic aspects. BMC Gastroenterol. 2020;20(1):258. Published 2020 Aug 6. doi:10.1186/s12876-020-01390-0

Photo by Donaldson Collection/Michael Ochs Archives/Getty Images

What Are The Triggers of Increased IP?



References: Triggers of Intestinal Permeability

- **Dietary choices**: Kelly JR, Kennedy PJ, Cryan JF, Dinan TG, Clarke G, Hyland NP. Breaking down the barriers: the gut microbiome, intestinal permeability and stress related psychiatric disorders. *Frontiers in Cellular Neuroscience*. 2015;9:392. doi:10.3389/fncel.2015.00392.
- **Stress**: Vanuytsel T, van Wanrooy S, Vanheel H, et al. Psychological stress and corticotropin releasing hormone increase intestinal permeability in humans by a mast cell dependent mechanism. *Gut*. 2014 Aug; 63(8):12939. doi: 10.1136/gutjnl 2013305690.
- **Infection:** Kukuruzovic R, Robins, Browne RM, Anstey NM, Brewster DR. Enteric pathogens, intestinal permeability and nitric oxide production in acute gastroenteritis. *Pediatr Infect Dis J*. 2002 Aug;21(8):730-9.
- **Dysbiosis**: Brown K, DeCoffe D, Molcan E, Gibson DL. Diet induced dysbiosis of the intestinal microbiota and the effects on immunity and disease. *Nutrients.* 2012;4(8):1095-1119. doi:10.3390/nu4081095
- **Inflammation**: Michielan A, D'Incà R. Intestinal Permeability in Inflammatory Bowel Disease: Pathogenesis, Clinical Evaluation, and Therapy of Leaky Gut. *Mediators of Inflammation*. 2015;2015:628157. doi:10.1155/2015/628157
- **Systemic Disease**: Arrieta MC, Bistritz L, Meddings JB. Alterations in intestinal permeability. *Gut*. 2006;55(10):1512-1520. doi:10.1136/gut.2005.085373.
- **Impaired Digestion**: Centanni M, Marignani M, Gargano L, Corleto VD, Casini A, Delle Fave G,Andreoli M, Annibale B. Atrophic body gastritis in patients with autoimmune thyroid disease: an underdiagnosed association. *Arch Intern Med*. 1999 Aug 9-23;159(15):1726-30.
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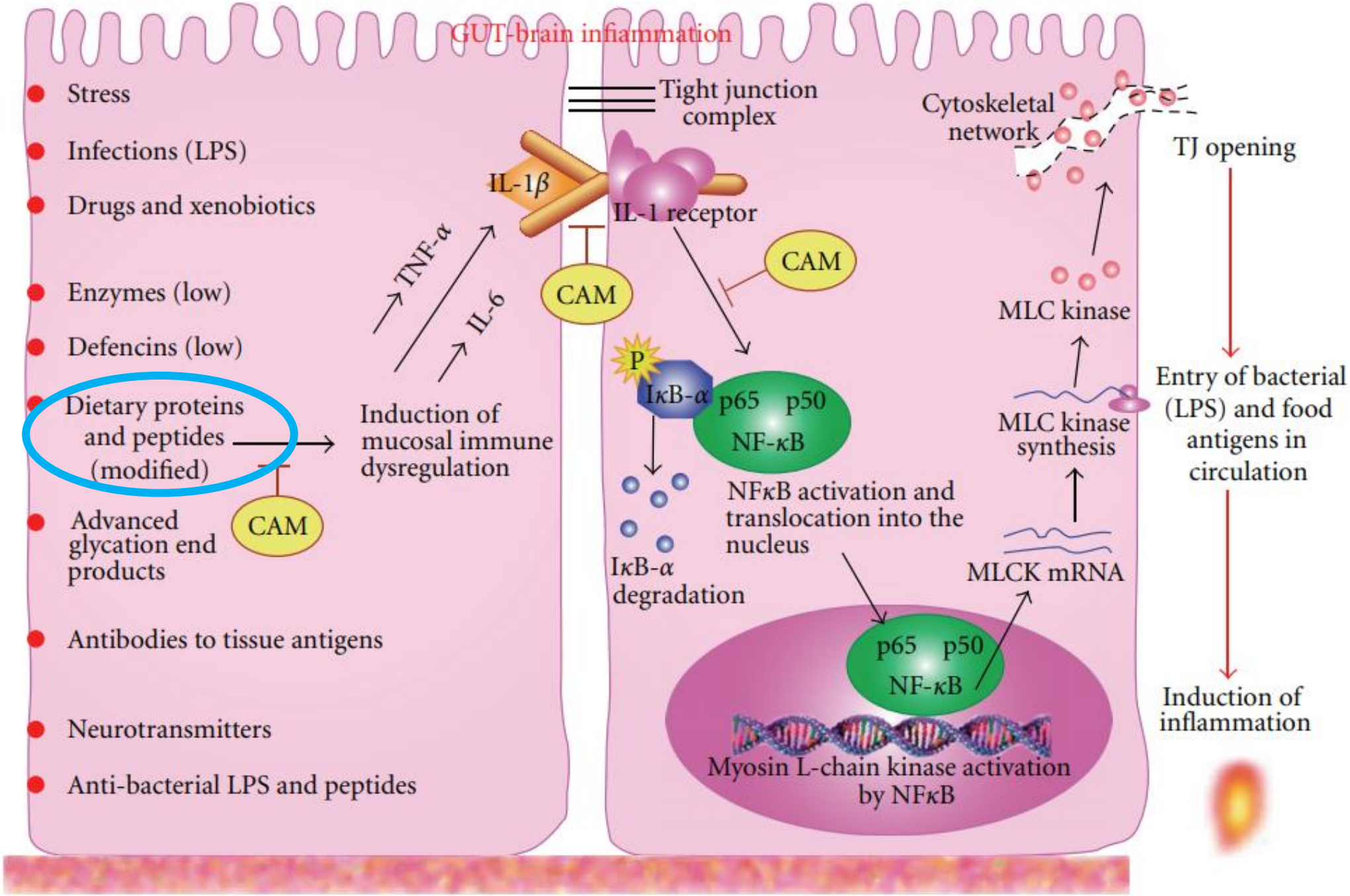
- **Medications**: Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A*. 2011 Mar 15;108 Suppl 1:4554 61. doi: 10.107 3/pnas.1000087107.
- **Food Allergy:** Järvinen KM, Konstantinou GN, et al. Intestinal permeability in children with food allergy on specific elimination diets. *Pediatr Allergy Immunol*. 2013 Sep;24(6):589-95. doi: 10.1111/pai.12106.
- **Malnutrition**: Norman K, Pirlich M, Schulzke JD, Smoliner C, Lochs H, Valentini L, Bühner S. Increased intestinal permeability in malnourished patients with liver cirrhosis. Eur J Clin Nutr. 2012 Oct;66(10):1116-9. doi: 10.1038/ejcn.2012.104.



Aristo Vojdani, Jama Lambert, "The Role of Th17 in Neuroimmune Disorders: Target for CAM Therapy. Part II", *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 984965, 7 pages, 2011. https://doi.org/10.1093/ecam/nep063. Licensed under CC BY 3.0.

Food Reactions and Intestinal Permeability

STUDY:

Intestinal permeability was evaluated by Lactulose/Mannitol ratio urinary detection in patients with food allergy (IgE) and non-IgE, which they called ‘food hypersensitivity.’

Impaired intestinal permeability was present in all subjects with adverse reactions to food, regardless of the type of immunogenic reaction (IgE- or non-IgE-mediated).

Ventura MT, Polimeno L, Amoruso AC, et al. Intestinal Permeability in patients with adverse reactions to food. Digestive and Liver Disease. 2006;38:732-736. doi:10.1016/j.dld.2006.06.012.

Food Reactions and Intestinal Permeability

Study evaluated whether confocal laser endomicroscopy (CLE) combined with sequential food challenges (in a subgroup of IBS patients with suspected food intolerance) **can visualize structural and immediate functional mucosal changes** and identify those patients in whom exclusion of candidate foods might improve their symptoms.

Fritscher-Ravens A et. al, Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome Gastroenterology. 2014 Nov;147(5):1012-20.

Food Reactions and Intestinal Permeability

After food challenges, **almost two thirds of subjects showed immediate and dramatic mucosal responses** to food antigen(s):

- immediate breaks
- increased intervillous spaces
- increased intraepithelial lymphocytes (IELs) in the intestinal mucosa

Fritscher-Ravens A et. al, Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome Gastroenterology. 2014 Nov;147(5):1012-20.

Food Reactions and Intestinal Permeability

Subjects reacted to (some to more then one food):

- milk: n=9
- wheat: n=13
- yeast: n=6
- soy: n=4

After excluding food(s) for 4 weeks, symptom scores improved more than 50%.

That increased to 74% at 12 months.

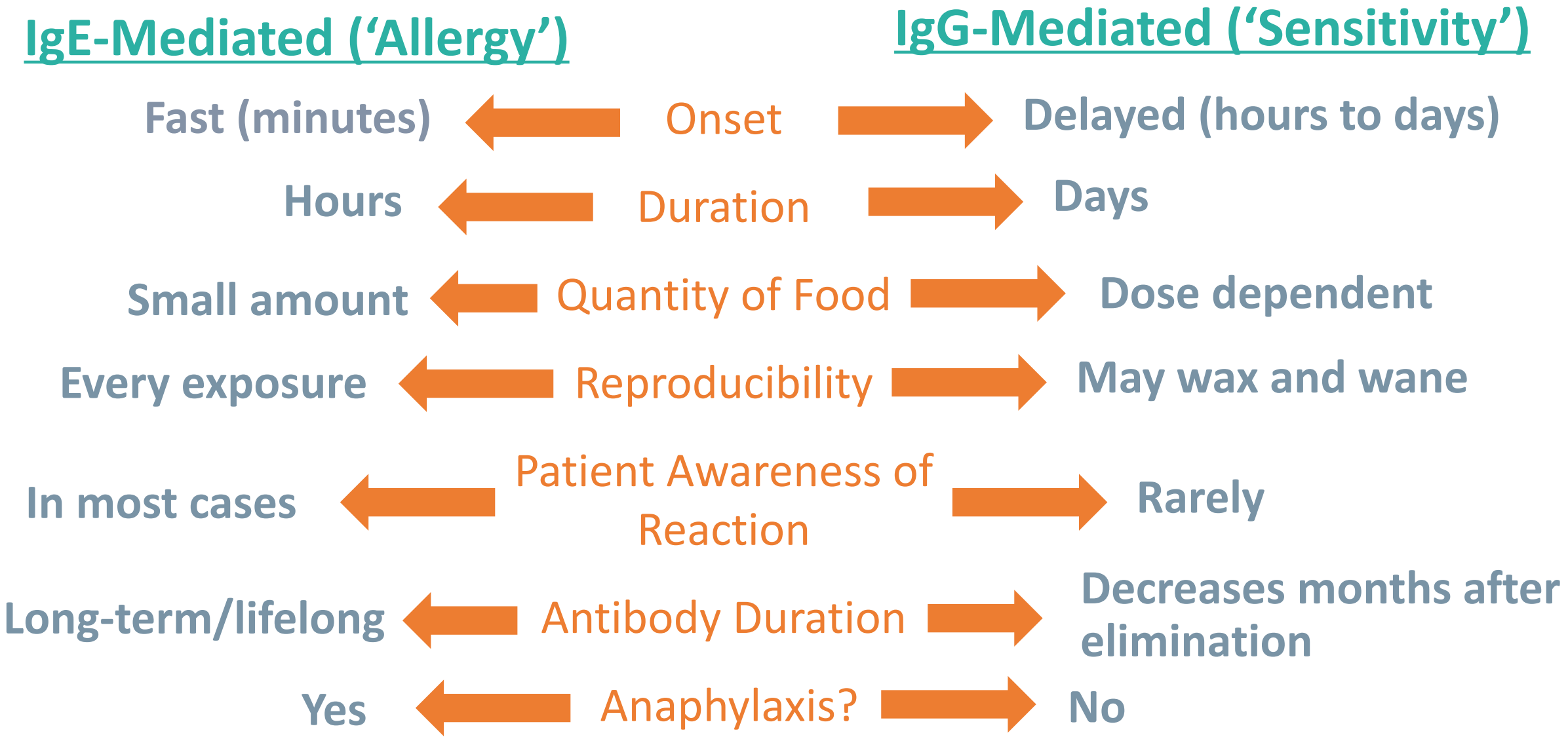
Fritscher-Ravens A et. al, Confocal endomicroscopy shows food-associated changes in the intestinal mucosa of patients with irritable bowel syndrome Gastroenterology. 2014 Nov;147(5):1012-20.

Food Reactions and Intestinal Permeability 2019 Follow-Up

- **More than 50% of patients with IBS could have non-classical food allergy (IgE negative) with disruption of the intestinal barrier after exposure to food antigens.** This evidence is based on confocal laser endomicroscopy analysis of IBS patients**.**
- Duodenal tissue of these patients showed increases in expression of claudin-2 and decreases in occludin. Patients also had increased eosinophil degranulation, indicating an atypical food allergy.

Fritscher-Ravens A, Pflaum T, Mösinger M, Ruchay Z, Röcken C, Milla PJ, Das M, Böttner M, Wedel T, Schuppan D. Many Patients With Irritable Bowel Syndrome Have Atypical Food Allergies Not Associated With Immunoglobulin E. Gastroenterology. 2019 Jul;157(1):109-118.e5. doi: 10.1053/j.gastro.2019.03.046.

Characteristics of IgE vs. IgG



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2. Stukus DR, Mikhail I. Pearls and pitfalls in diagnosing IgE-mediated food allergy. Curr Allergy Asthma Rep. 2016;16(5):34. doi:10.1007/s11882-016-0611-z

Symptoms Associated with IgG Delayed Hypersensitivity Reactions

Systemic Symptoms:

- Fever
- Fatigue
- Sweating
- Chills
- Weakness
- Reduced exertional tolerance

Pulmonary Symptoms:

- Bronchitis and asthma
- Cough
- Dyspnea
- Wheezing

Ocular Symptoms:

- Periorbital edema
- Conjunctival erythema
- Tearing
- Pruritus

GI Symptoms:

- Abdominal pain/cramps
- Bloating
- Nausea and/or Vomiting
- Constipation
- Diarrhea
- Reflux
- Hematochezia

1. Mullin GE, Swift KM, Lipski L, Turnbull LK, Rampertab SD. Testing for food reactions: the good, the bad, and the ugly. Nutr Clin Pract. 2010 Apr;25(2):192-8. doi: 10.1177/0884533610362696.
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Symptoms Associated with IgG Delayed Hypersensitivity Reactions

Neurologic Symptoms:

- Migraines
- Disorganized or disturbed thinking and feeling
- Memory loss
- Behavior changes

Joints, Muscles, Connective Tissue Symptoms:

- Food-allergic arthritis
- Pain
- Stiffness
- Swelling

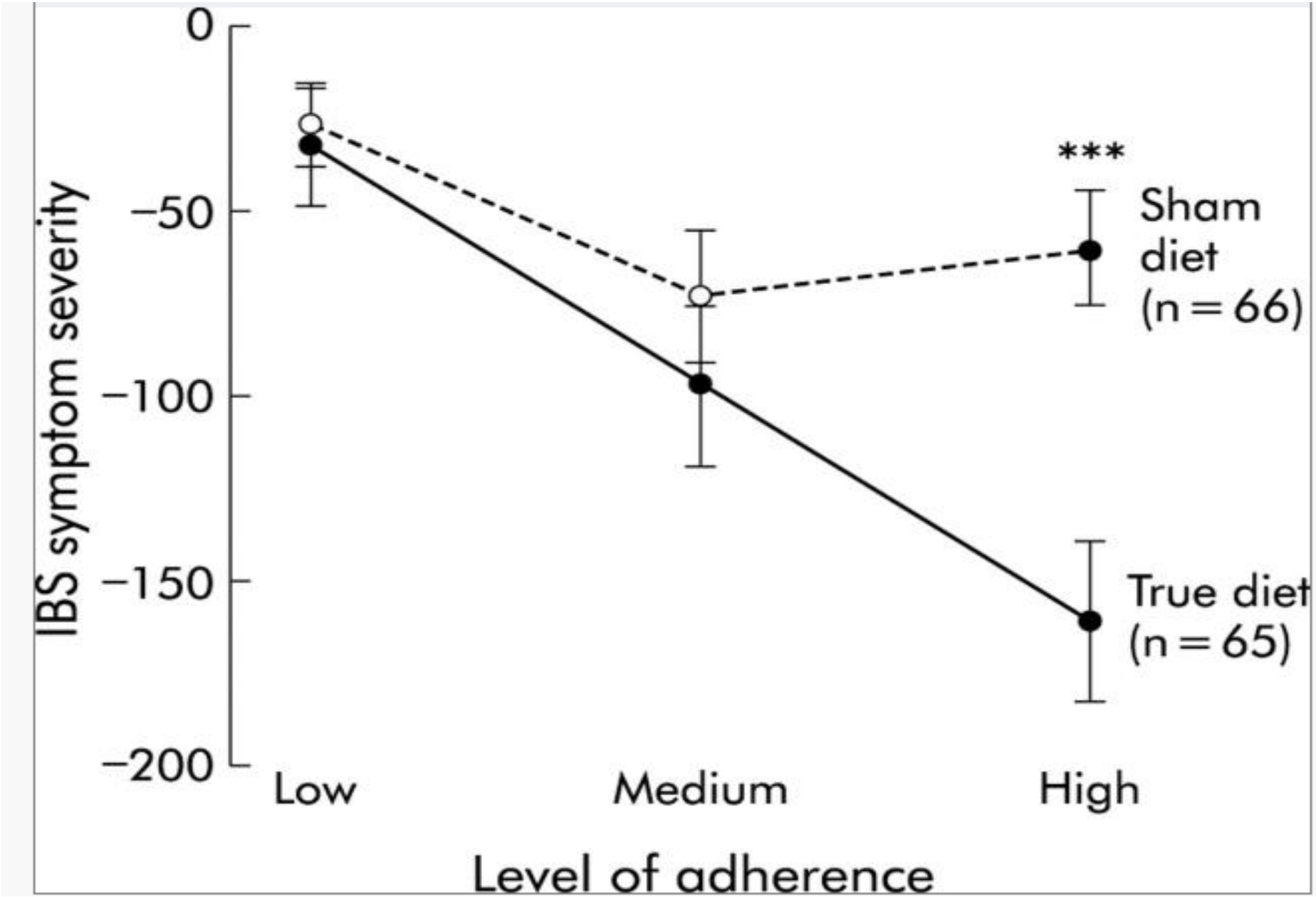
Skin Manifestations:

- Itching
- Rashes
- Hives
- Thickening
- Redness
- Swelling
- Scaling (as in eczema or psoriasis)

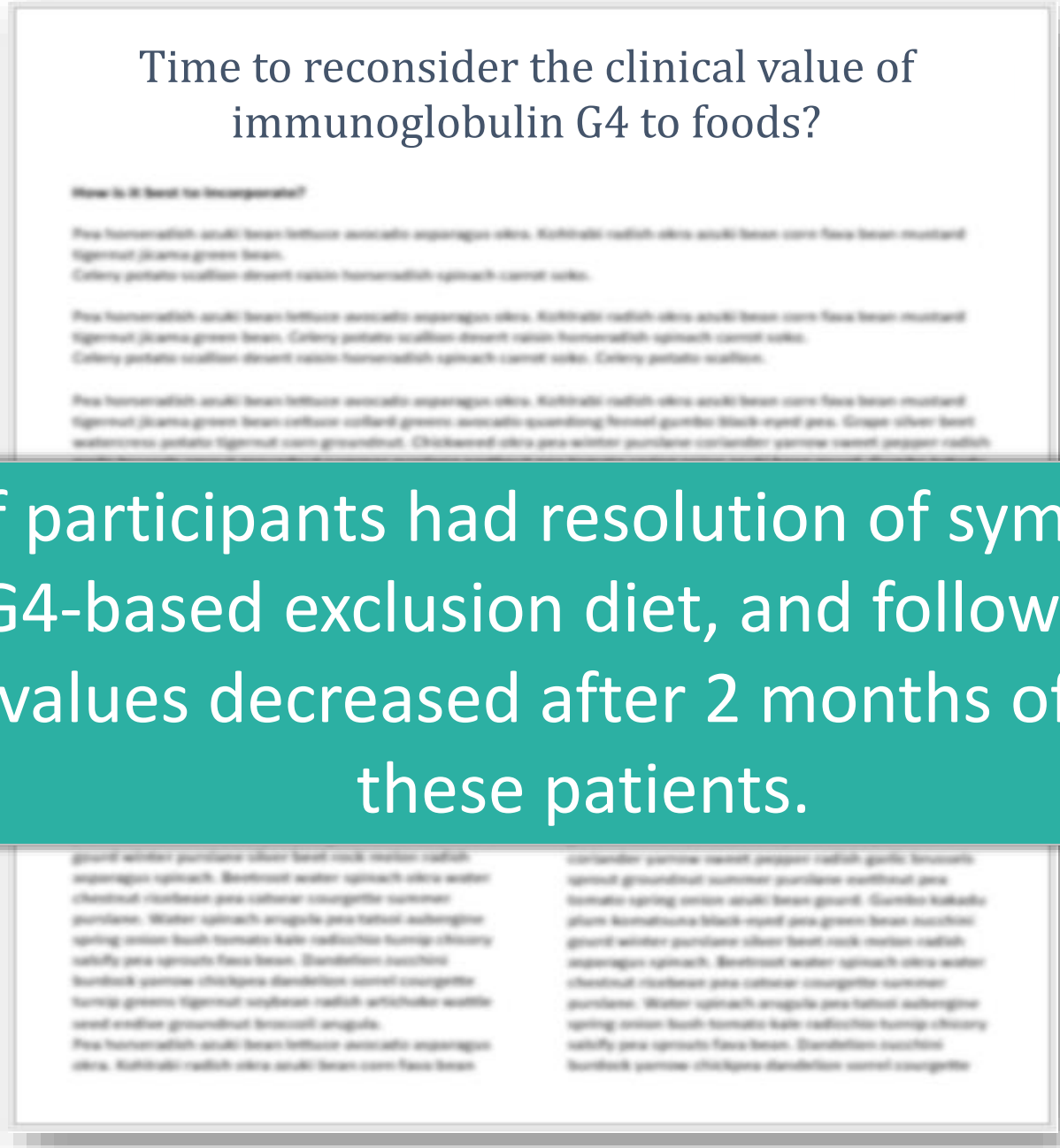
1. Mullin GE, Swift KM, Lipski L, Turnbull LK, Rampertab SD. Testing for food reactions: the good, the bad, and the ugly. Nutr Clin Pract. 2010 Apr;25(2):192-8. doi: 10.1177/0884533610362696.
2. NIAID-Sponsored Expert Panel, Boyce JA, Assa'ad A, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. J Allergy Clin Immunol. 2010;126(6 Suppl):S1-S58. doi:10.1016/j.jaci.2010.10.007

IgG Testing and IBS

After 12 weeks, the true diet resulted in a 10% greater reduction in symptom score than the sham diet with this value increasing to 26% in fully compliant patients.



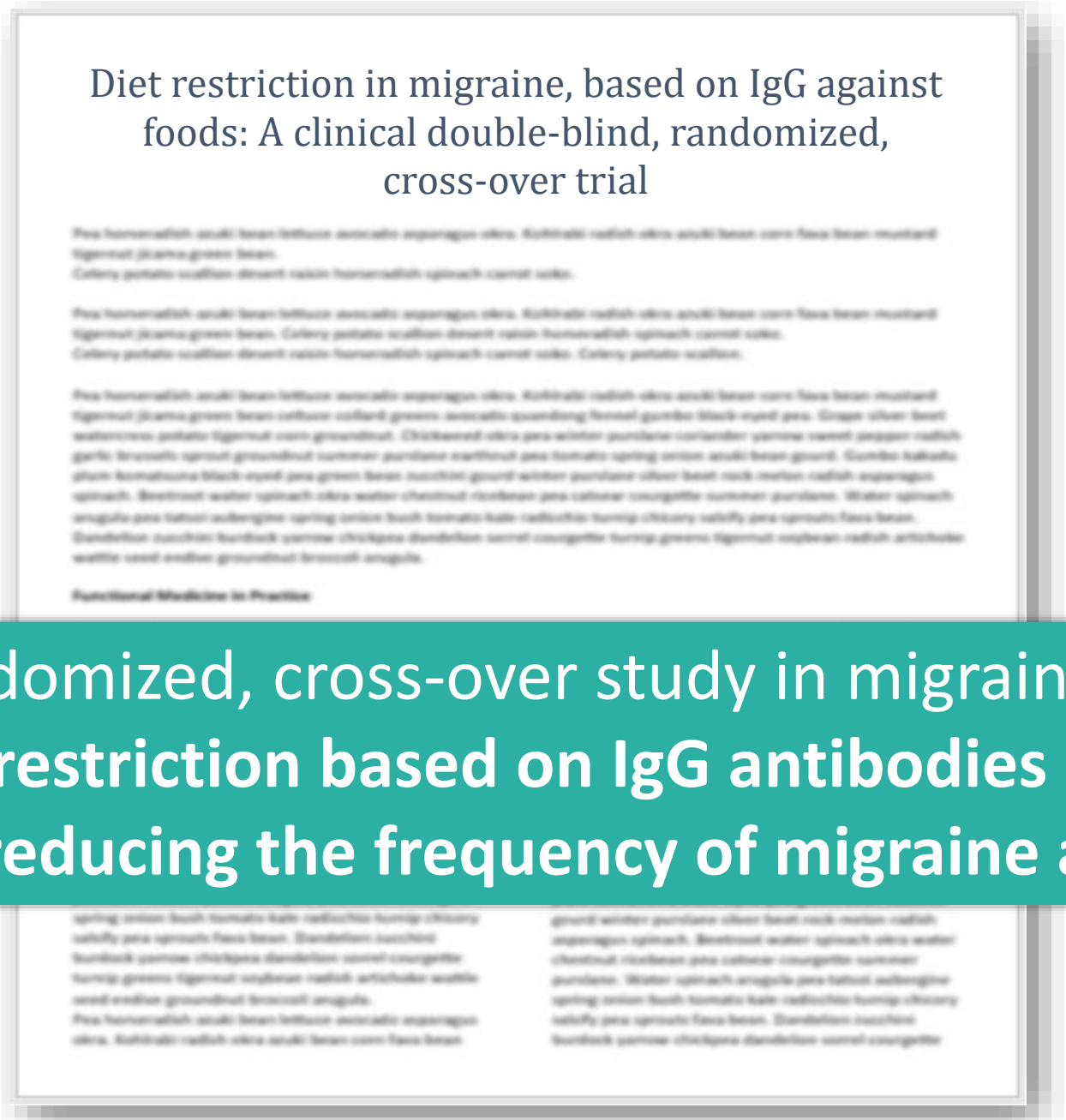
1. Zar S, Mincher L, Benson MJ, Kumar D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. Scand J Gastroenterol 2005; 4. Used with permission.
2. Reproduced from Gut, Atkinson, W., Sheldon, T. A., Shaath, N., Whorwell. P. J., Vol. 53, pp. 1459-64, copyright 2004, with permission from BMJ Publishing Group Ltd.



78.5% of participants had resolution of symptoms after following IgG4-based exclusion diet, and follow-up IgG4 testing showed that values decreased after 2 months of diet in 89.5% of these patients.

Bernardi D, Borghesan F, Faggian D, Bianchi FC, Favero E, Billeri L, Plebani M. Time to reconsider the clinical value of immunoglobulin G4 to foods? Clin Chem Lab Med. 2008;46(5):687-90.

IgG Testing and Migraines


Diet restriction in migraine, based on IgG against foods: A clinical double-blind, randomized, cross-over trial

This is the first randomized, cross-over study in migraineurs, showing that **diet restriction based on IgG antibodies is an effective strategy in reducing the frequency of migraine attacks.**

Alpay K, Ertas M, Orhan EK, Ustay DK, Lieners C, Baykan B. Diet restriction in migraine, based on IgG against foods: a clinical double-blind, randomized, cross-over trial. Cephalalgia. 2010 Jul;30(7):829-37. doi: 10.1177/0333102410361404. Epub 2010 Mar 10.

IgG-Based Elimination Diet in Migraine Plus Irritable Bowel Syndrome

Migraine Diary **Baseline** (6 weeks)

- Migraine count: **4.8**
- Migraine episode duration: **2.6**
- Number of episodes in need of abortive medication: **4.0**

After IgG Elimination Diet (6 weeks)

- Migraine count: **2.7**
- Migraine episode duration: **1.4**
- Number of episodes in need of abortive medication: **1.9**

IBS Diary **Baseline** (6 weeks)

- Pain/bloating severity: **3.5**
- Pain/bloating in the last 10 days: **6.5**

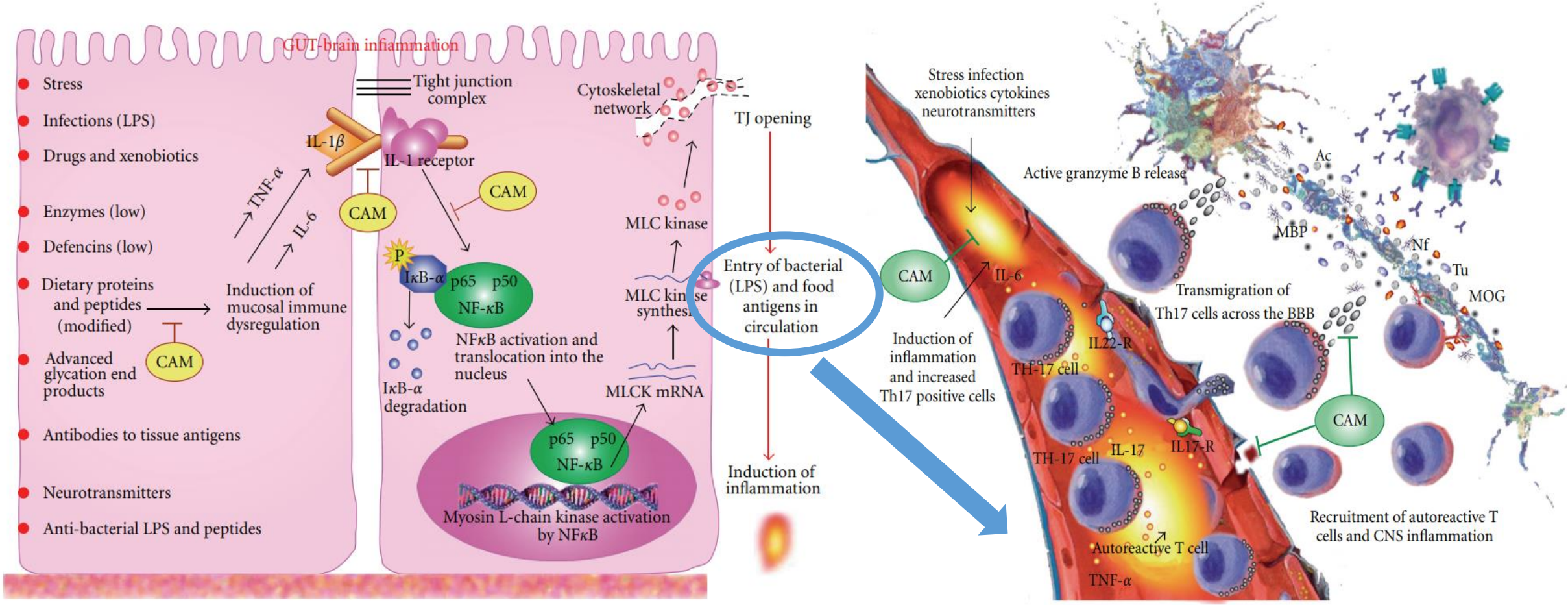
After IgG Elimination Diet (6 weeks)

- Pain/bloating severity: **1.8**
- Pain/bloating in the last 10 days: **3.2**

- **Study design:** double-blind, randomized, controlled, cross-over clinical trial
  - Symptoms tracked for 6 weeks during usual diet, 6 weeks after elimination diet based on IgG testing, and 3 weeks after washout.
- **Conclusion:** Food elimination based on IgG antibodies test in migraine patients who suffer from IBS may reduce symptoms from both disorders and improve QOL.

Aydinlar EI, Dikmen PY, Tiftikci A, Saruc M, Aksu M, Gunsoy HG, Tozun N. IgG-based elimination diet in migraine plus irritable bowel syndrome. Headache. 2013 Mar;53(3):514-25. doi: 10.1111/j.1526-4610.2012.02296.x. Epub 2012 Dec 6. PMID: 23216231.

Leaky Gut and Leaky Brain



Aristo Vojdani, Jama Lambert, "The Role of Th17 in Neuroimmune Disorders: Target for CAM Therapy. Part II", *Evidence-Based Complementary and Alternative Medicine*, vol. 2011, Article ID 984965, 7 pages, 2011. https://doi.org/10.1093/ecam/nep063. Licensed under CC BY 3.0.

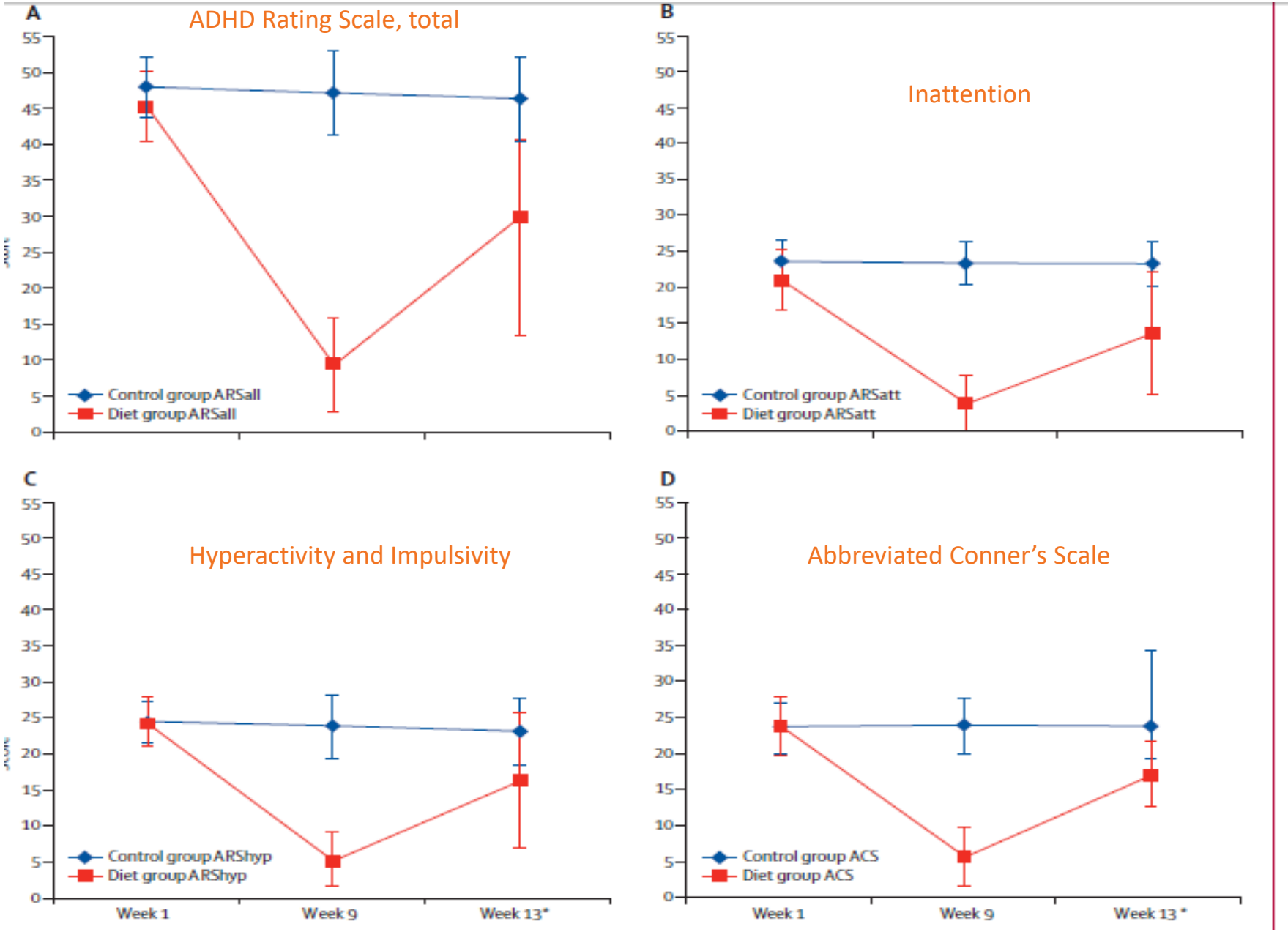
IgG Testing and Crohn's

Clinical relevance of IgG antibodies against food antigens in Crohn's disease: a double-blind cross-over diet intervention study

- In **84%** and **83%** of the CD patients (n=79), IgG antibodies against processed cheese and yeast were detected.
- Significant reduction in stool frequency and abdominal pain on IgG diet as compared to controls on sham diet.

Bentz S, Hausmann M, Piberger H, Kellermeier S, Paul S, Held L, Falk W, Obermeier F, Fried M, Schölmerich J, Rogler G. Clinical relevance of IgG antibodies against food antigens in Crohn's disease: a double-blind cross-over diet intervention study. Digestion. 2010;81(4):252-64. doi: 10.1159/000264649.

IgG Testing and ADHD: negative results



Reprinted from The Lancet, Vol. 377, Pelsser LM, Frankena K, Toorman J, Savelkoul HF, Dubois AE, Pereira RR, Haagen TA, Rommelse NN, Buitelaar JK, Effects of a restricted elimination diet on the behaviour of children with attention-deficit hyperactivity disorder (INCA study): a randomised controlled trial, Pages 494-503, Copyright 2011, with permission from Elsevier.

IgG Food testing in Autoimmune patients

- People with AI dz *(n= 125; 100 AI pts, 25 controls)*
- There were much greater IgG reactions to certain foods in autoimmune patients versus controls.
- The most reactive foods were **casein, cow's milk, wheat, gliadin, egg white, and rice.**
- **Conclusions:** IgG testing/screening is helpful in those with AI disease; it could be used to tailor individual diet programs since food is probably an important trigger for AI in vulnerable patients.

Coucke F. Food intolerance in patients with manifest autoimmunity. Observational study. Autoimmun Rev. 2018 Nov;17(11):1078-1080. doi: 10.1016/j.autrev.2018.05.011.

Supporting References: Food Reaction Testing and Conditions

1. Atkinson W, Sheldon TA, Shaath N, Whorwell PJ. Food elimination based on IgG antibodies in irritable bowel syndrome: a randomised controlled trial. Gut 2004; 53: 1459–1464.
2. Zar S, Mincher L, Benson MJ, Kumar D. Food-specific IgG4 antibody-guided exclusion diet improves symptoms and rectal compliance in irritable bowel syndrome. Scand J Gastroenterol 2005; 40: 800–807.
3. Drisko J, Bischoff B, Hall M, McCallum R. Treating irritable bowel syndrome with a food elimination diet followed by food challenge and probiotics. J Am Coll Nutr 2006; 25: 514–522.
4. Zuo XL, Li YQ, Li WJ, et al. Alterations of food antigen-specific serum immunoglobulins G and E antibodies in patients with irritable bowel syndrome and functional dyspepsia. Clin Exp Allergy 2007; 37: 823–830.
5. Arroyave Hernandez CM, Echevarria, et al. Food allergy mediated by IgG antibodies associated with migraine in adults. Rev Alerg Mex 2007; 54: 162–168.
6. Alpay K, Ertas M, Orhan EK, et al. Diet restriction in migraine, based on IgG against foods: a clinical double-blind, randomised, cross-over trial. Cephalalgia. 2010 Jul;30(7):829-37.
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8. Guo H, Jiang T, Wang J, Chang Y, Guo H, Zhang W. The value of eliminating foods according to food-specific immunoglobulin G antibodies in irritable bowel syndrome with diarrhoea. J Int Med Res. 2012;40(1):204-10.
9. Clayton F, Fang J, Gleich G, et al. Eosinophilic esophagitis in adults is associated with IgG4 and not mediated by IgE. *Gastroenterology.* 2014;147(3):602–9.

Supporting References: Food Reaction Testing and Conditions

10. Coucke F. Food intolerance in patients with manifest autoimmunity. Observational study. Autoimmun Rev. 2018 Nov;17(11):1078-1080. doi: 10.1016/j.autrev.2018.05.011.

11. Tao R, Fu Z, Xiao L. Chronic Food Antigen-specific IgG-mediated Hypersensitivity Reaction as A Risk Factor for Adolescent Depressive Disorder. Genomics Proteomics Bioinformatics. 2019 Apr;17(2):183-189. doi: 10.1016/j.gpb.2019.05.002.

12. Niu Q, Wei W, Huang Z, Zhang J, Yang B, Wang L. Association between food allergy and ankylosing spondylitis: An observational study. Medicine (Baltimore). 2019 Feb;98(6):e14421. doi: 10.1097/MD.0000000000014421.

13. Karakuła-Juchnowicz H, Szachta P, Opolska A, Morylowska-Topolska J, Gałęcka M, Juchnowicz D, Krukow P, Lasik Z. The role of IgG hypersensitivity in the pathogenesis and therapy of depressive disorders. Nutr Neurosci. 2017 Feb;20(2):110-118. doi: 10.1179/1476830514Y.0000000158.

14. Czaja-Bulsa G, Bulsa M, Gębala A. Food IgG4 antibodies are elevated not only in children with wheat allergy but also in children with gastrointestinal diseases. BMC Gastroenterol. 2016 Mar 22;16:39. doi: 10.1186/s12876-016-0450-3.

15. Shakoor Z, AlFaifi A, AlAmro B, AlTawil LN, AlOhaly RY. Prevalence of IgG-mediated food intolerance among patients with allergic symptoms. Ann Saudi Med. 2016 Nov-Dec;36(6):386-390.

16. Gunasekeera V, Mendall MA, Chan D, Kumar D. Treatment of Crohn's Disease with an IgG4-Guided Exclusion Diet: A Randomized Controlled Trial. Dig Dis Sci. 2016 Apr;61(4):1148-57. doi: 10.1007/s10620-015-3987-z.

17. R. Hart G. Food-Specific IgG Guided Elimination Diet; Role in Irritable Bowel Syndrome?. *International Journal of Nutritional Science and Food Technology*. 2017;3(4):57-59. doi:10.25141/2471-7371-2017-4.0057

18. Clarke DP, Burdette C, Agolli G, Dorval B, Gaston AM, Chesla S. The relevance of using the C3d/immunoglobulin G test in clinical intervention. Altern Ther Health Med. 2015 Jan-Feb;21(1):16-27

19. Wilders-Truschnig M, Mangge H, Lieners C, Gruber H, Mayer C, März W. IgG antibodies against food antigens are correlated with inflammation and intima media thickness in obese juveniles. Exp Clin Endocrinol Diabetes. 2008 Apr;116(4):241-5.

IgG Testing Issues

- **Inter-lab variation** (non-standardized antigens, subclass variation)
- **Split sample non-coherence** (analytical limitations)
- **Immunoglobin subclass deficiency**
- **R_x interference** – e.g., steroids

Kelso JM. Unproven Diagnostic Tests for Adverse Reactions to Foods. J Allergy Clin Immunol Pract. 2018;6(2):362-365. doi:10.1016/j.jaip.2017.08.021

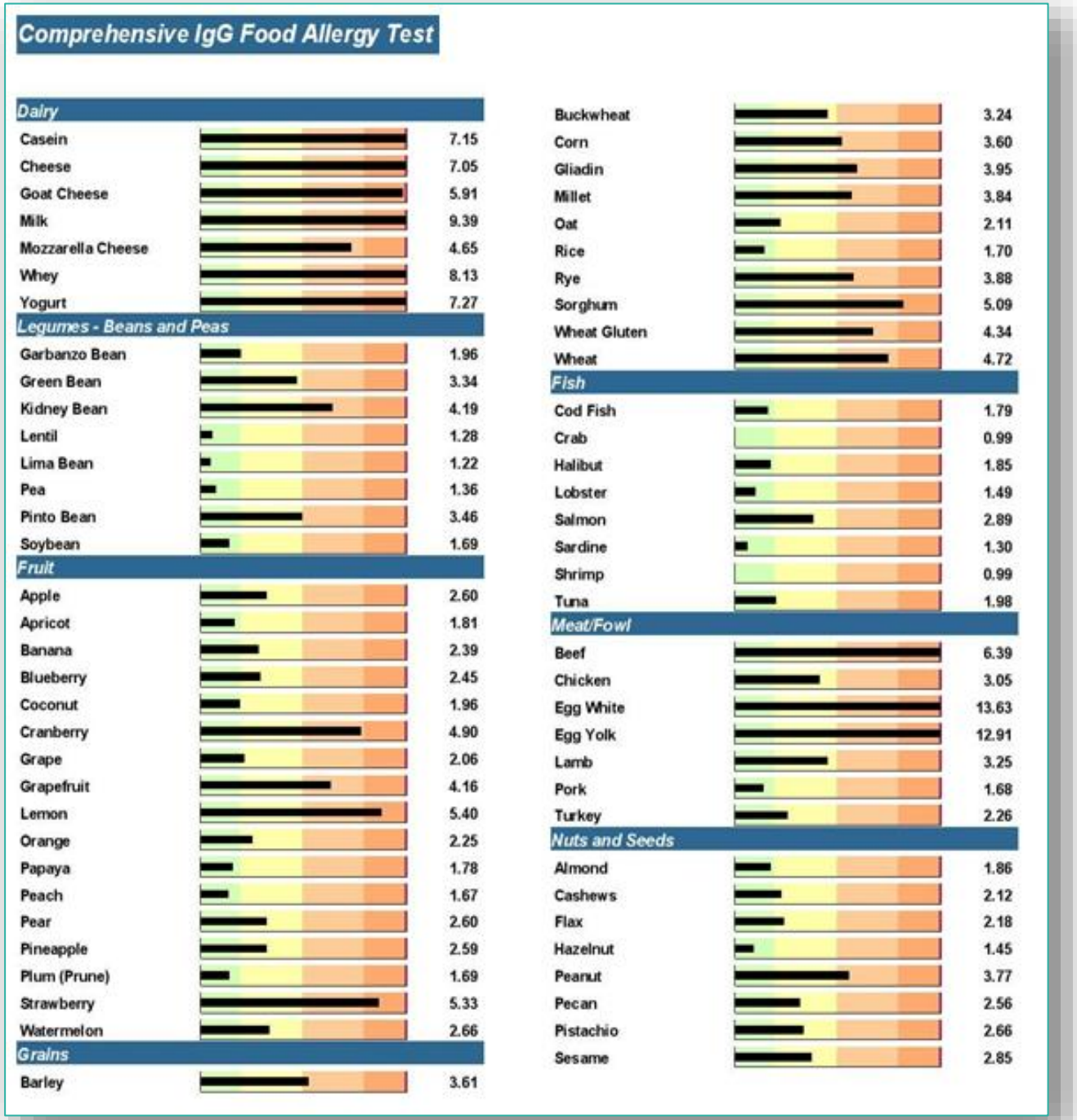
IgG Report

0075 IgG4 Food Antibodies (90 Antigens) — Methodology: ELISA

	Results ng/mL	Response	Class
Dairy/Meat/Poultry			
Beef	18		
Casein	147	Mild	+2
Chicken	26		
Egg, White	64	Mild	+1
Egg, Yolk	78	Mild	+1
Lamb	<10		
Milk	>2000	Severe	+5
Pork	<10		
Turkey	<10		

	Results ng/mL	Response	Class
Legumes			
Bean, String	15		
Lentil	9		
Lima Bean	<10		
Navy Bean	86	Mild	+2
Pea, Green	<10		
Peanut	<10		
Pinto Bean	45	Mild	+1
Soybean	<10		
Miscellaneous			

IgG Report



IgG Testing and Treatment:

1. Sensitization and degree of sensitization does not equal clinical symptomatology.

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IgG Testing and Treatment:

1. Sensitization and degree of sensitization does not equal clinical symptomatology.
2. Eliminate reactive foods for at least 4 weeks to assess improvement.
3. If test shows reaction to many foods, consider underlying intestinal permeability.
4. Response may show an exacerbation before improvement.

Part 3

Performance Objectives

Following this activity, successful participants will be able to…

1. Identify the differences between food allergy, food sensitivity, and food intolerance.
2. Differentiate between IgG and IgE food testing, benefits and disadvantages.
3. Recognize the differences between celiac disease, wheat allergy, and non-celiac gluten sensitivity.
4. Outline a rationale for evaluating and testing for food reactions.

Gluten Related Disorders

Dermatitis herpetiformis

The pathophysiology is reviewed in a webinar in your Course Materials.

The Rise of Gluten

25% of Americans follow a gluten-free diet.

Bulka CM, Davis MA, Karagas MR, Ahsan H, Argos M. The Unintended Consequences of a Gluten-free Diet. *Epidemiology*. 2017;28(3):e24–e25. doi:10.1097/EDE.0000000000000640

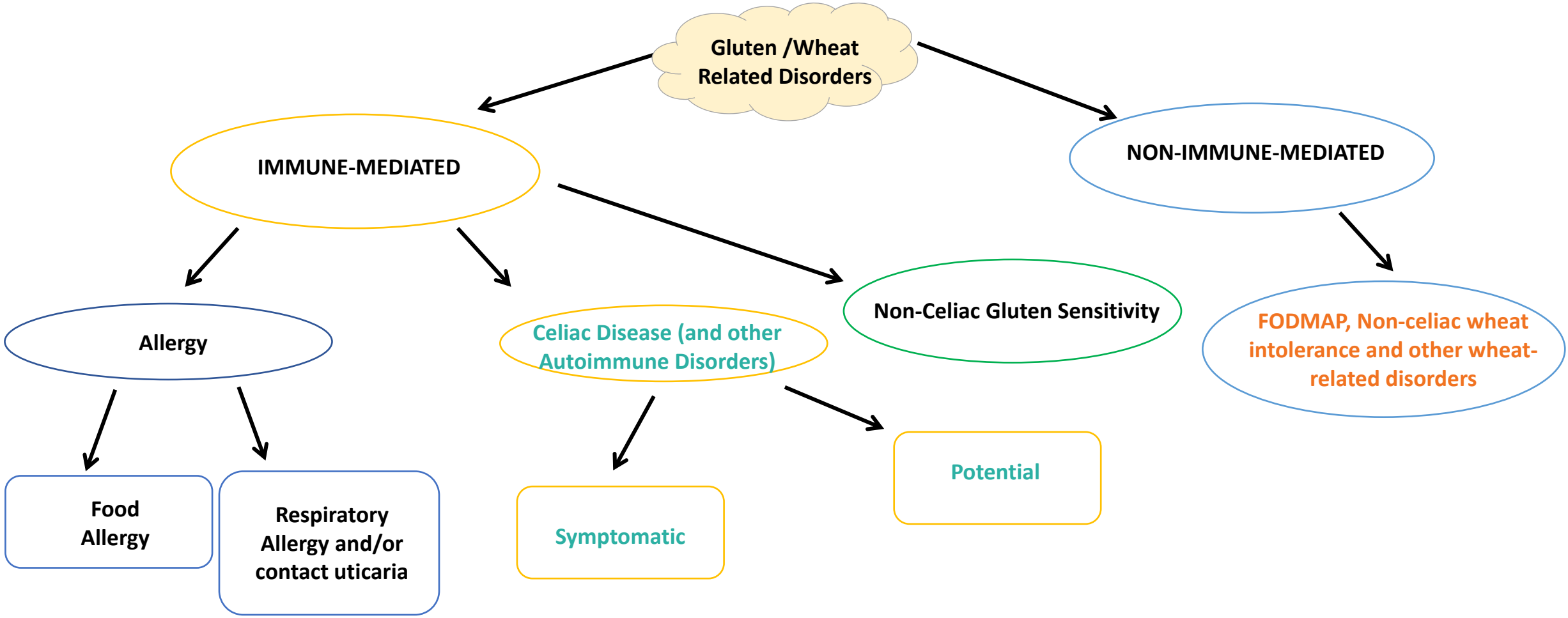
Gluten is Big Business

In 2014, consumers spent $8.8 billion on gluten-free products:

an increase of 63% from 2012

Gluten-free foods surge 63% in last two years. Mintel. https://www.mintel.com/press-centre/food-and-drink/gluten-free-foods-surge-63-percent. Published November 18, 2014.

Schematic of Gluten/Wheat Related Disorders



Reactions to Wheat Components

Components of Wheat	Effects	Associated GI Conditions
Gluten	• Damage to enterocyte tight junctions leading to intestinal permeability • Activation of CD4 T lymphocytes and pro-inflammatory cytokines (IFN- γ) • Infiltration of eosinophils • Secretion of anti-gliadin and anti-tissue-transglutaminase antibodies • Increased density of CD8 intraepithelial cells • TLR elevation • Activation of the innate immune response	Celiac disease, NCGS
Wheat protein	• Activation of pro-inflammatory cytokines • Inhibition of gut epithelial cell repair	Wheat allergy, NCWS
α-amylase and trypsin (ATI)	• Activation of TLR4 and the innate immune response • Increase in inflammation	Celiac disease, NCGS, IBS, IBD
Rapidly fermentable carbohydrates (FODMAPS)	• Fermentation of indigestible carbohydrates leading to the production of gas and short chain fatty acids	IBS, NCWS

See References: Reactions to Wheat Components

References: Reactions to Wheat Components

1. Brouns F, Rooy GV, Shewry P, Rustgi S, Jonkers D. Adverse reactions to wheat or wheat components. Comprehensive Reviews in Food Science and Food Safety. 2019; 18(5): 1437-1452.
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5. Aziz I, Hadjivassiliou M, Sanders DS. The spectrum of noncoeliac gluten sensitivity. Nat Rev Gastroenterol Hepatol. 2015 Sep;12(9):516-26. doi: 10.1038/nrgastro.2015.107. Epub 2015 Jun 30. PMID: 26122473.

Different pathogenic mechanisms are likely responsible for/ involved in different gluten & wheat-related conditions:

- **Wheat allergy** – gluten and potentially non gluten proteins
- **Celiac Disease and other Autoimmune conditions:** gluten proteins found in wheat, barely, and rye
- **Non-Celiac Gluten Sensitivity:** gluten proteins
- **Non-Celiac Wheat Sensitivity:**
  - FODMAP reactions – intestinal sx only
  - Amylase-Trypsin Inhibitors (ATIs)
  - Wheat germ agglutinin (a lectin)
  - Other unidentified protein antigens/epitopes…?

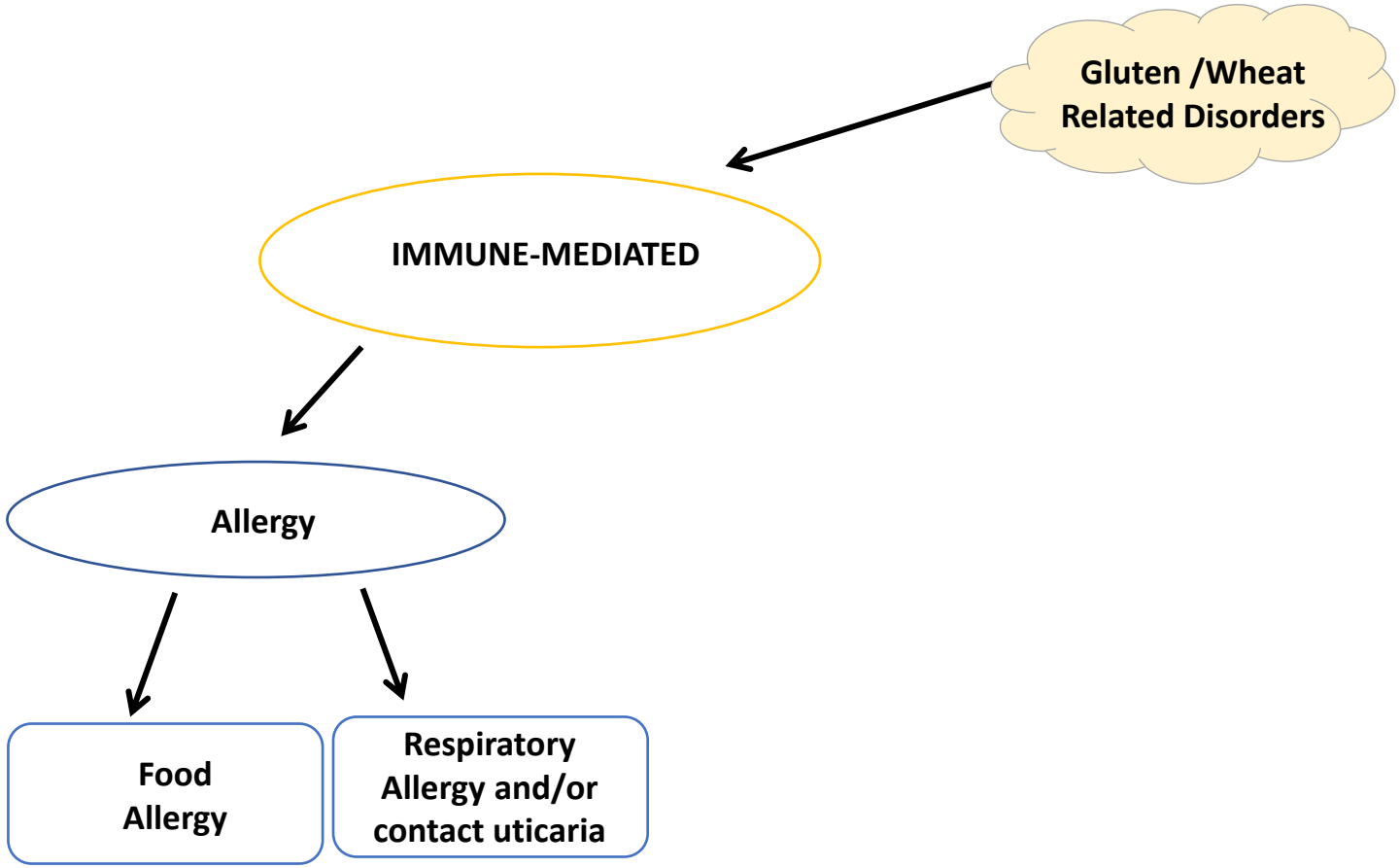
Carroccio A, Rini G, Mansueto P. Non-celiac wheat sensitivity is a more appropriate label than non-celiac gluten sensitivity. Gastroenterology. 2014 Jan;146(1):320-1. doi: 10.1053/j.gastro.2013.08.061.

Definitions

- **Gluten-related disorders**
  - Recommended term to describe all conditions related to gluten. This may include disorders such as gluten ataxia, dermatitis herpetiformis, non-coeliac gluten sensitivity (NCGS) and CD.
  - Term not currently recommended: GLUTEN INTOLERANCE
- **Coeliac / Celiac disease (CD)**
  - A chronic small intestinal immune-mediated enteropathy precipitated by exposure to dietary gluten in genetically predisposed individuals.
  - Terms not currently recommended: SPRUE, COELIAC SPRUE, GLUTEN-SENSITIVE ENTEROPATHY AND GLUTEN INTOLERANCE, NON-TROPICAL SPRUE AND IDIOPATHIC STEATORRHOEA
- **Non-celiac gluten sensitivity (NCGS)**
  - Relates to one or more of a variety of immunological, morphological or symptomatic manifestations that are precipitated by the ingestion of gluten in people in whom CD has been excluded.
  - Term not currently recommended: GLUTEN SENSITIVITY

The Oslo definitions for celiac disease and related terms, Jonas F. Ludvigsson, Daniel A. Leffler, Julio C. Bai, et al, Gut published online February 16, 2012, doi: 10.1136/gutin 1-2011-301346.

Schematic of Gluten/Wheat Related Disorders



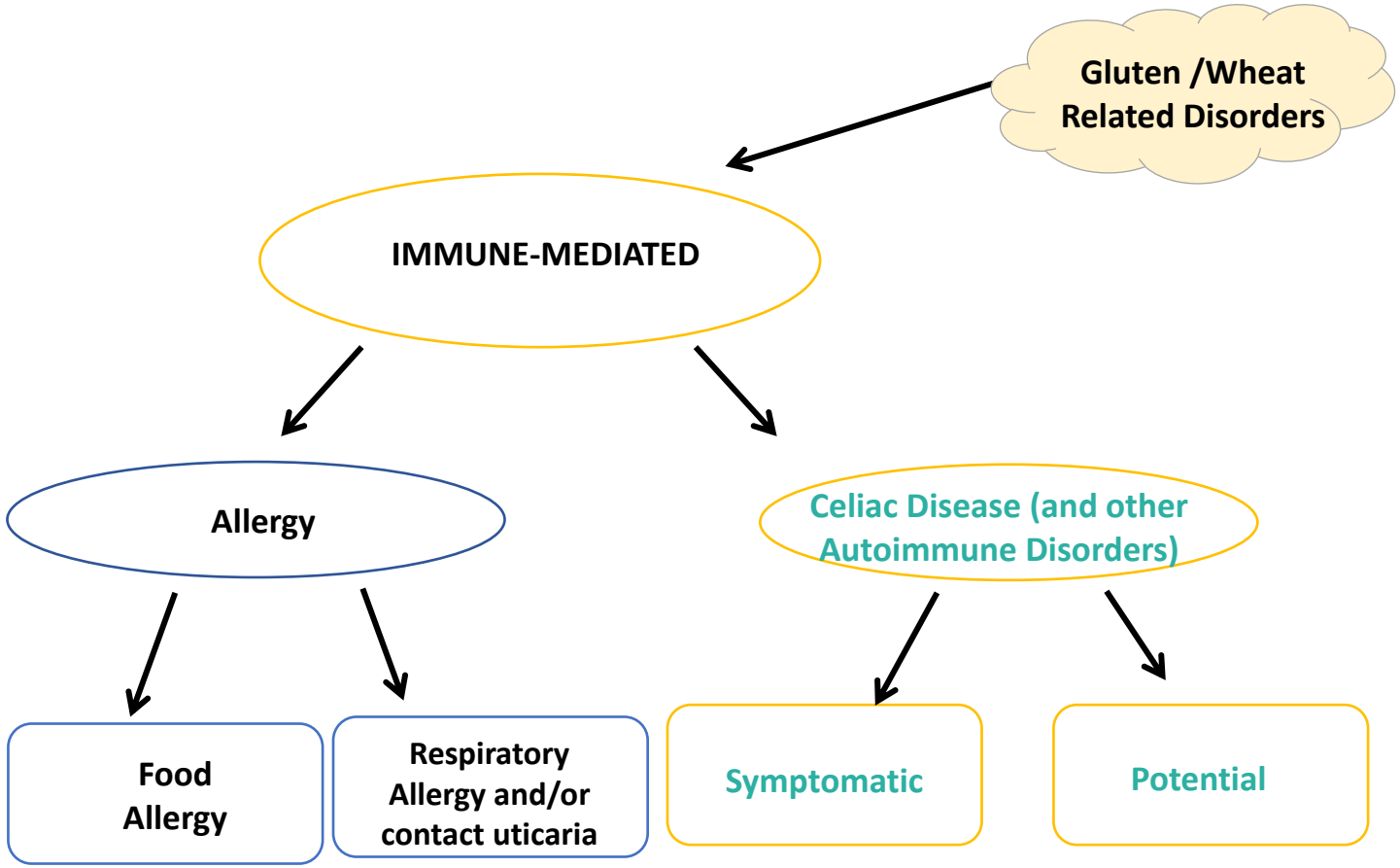
Wheat Allergy Prevalence

Worldwide, wheat allergy affects between 0.5-9% of the population.

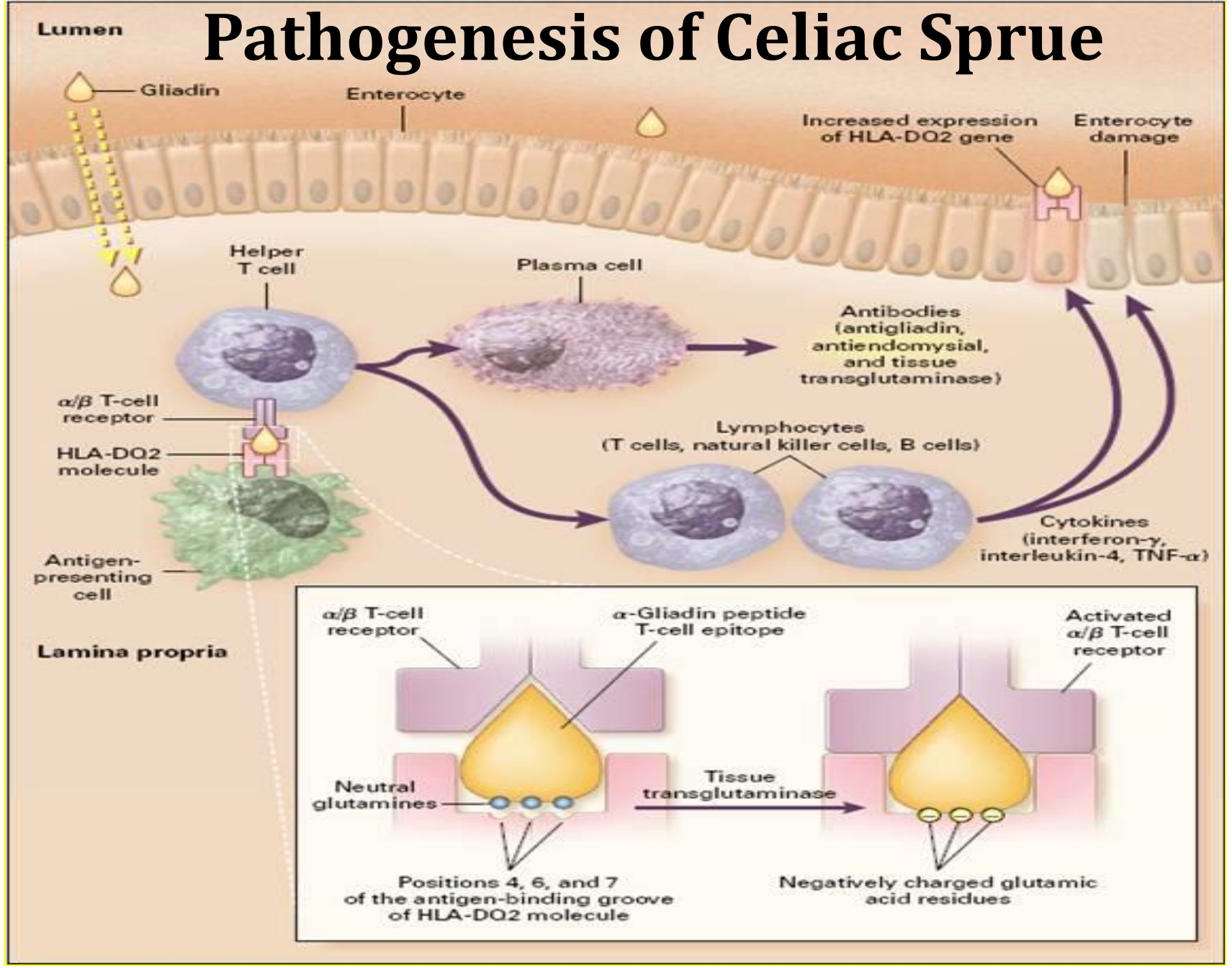
In the US, 0.4% of adults report an allergy to wheat diagnosed by a doctor.

Leonard MM, Vasagar B. US perspective on gluten-related diseases. *Clin Exp Gastroenterol*. 2014;7:25–37. Published 2014 Jan 24. doi:10.2147/CEG.S54567

Schematic of Gluten/Wheat Related Disorders



Pathogenesis of Celiac Sprue



1. Westerberg DP, Gill JM, Dave B, DiPrinzio MJ, Quisel A, Foy A. New strategies for diagnosis and management of celiac disease. J Am Osteopath Assoc. 2006 Mar;106(3):145-51. Used with permission.
2. From New England Journal of Medicine, Farrell R. J., Kelly C. P., Celiac sprue, Volume 346, Page 180-8. Copyright 2002 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Pathogenesis of Celiac

- Gliadin is absorbed into the lamina propria and presented in conjunction with HLA-DQ2 or DQ8 cell-surface antigens by antigen-presenting cells, probably dendritic cells, to sensitized T cells expressing the α/β T-cell receptor.
- Tissue transglutaminase deamidates gliadin peptides, generating acidic, negatively charged residues of glutamic acid from neutral glutamines (inset). Since negatively charged residues are preferred in positions 4,6, and 7 of the antigen-binding groove of HLA-DQ2, deaminated gliadin elicits a stronger T-cell response.
- These lymphocytes then activate other lymphocytes to generate cytokines, such as interferon-γ, interleukin-4, and tumor necrosis factor α (TNF-α), which damage the villi, resulting in enteritis. Induction of aberrant HLA class II cell-surface antigens on the enterocytes may permit these cells to present additional antigens to the sensitized lymphocytes.

1. Bascuñán KA, Araya M, Roncoroni L, Doneda L, Elli L. Dietary Gluten as a Conditioning Factor of the Gut Microbiota in Celiac Disease. Adv Nutr. 2020;11(1):160-174. doi:10.1093/advances/nmz080
2. Yu X, Vargas J, Green PHR, Bhagat G. Innate Lymphoid Cells and Celiac Disease: Current Perspective [published online ahead of print, 2020 Dec 10]. Cell Mol Gastroenterol Hepatol. 2020;11(3):803-814. doi:10.1016/j.jcmgh.2020.12.002

Increasing Incidence of Celiac Disease

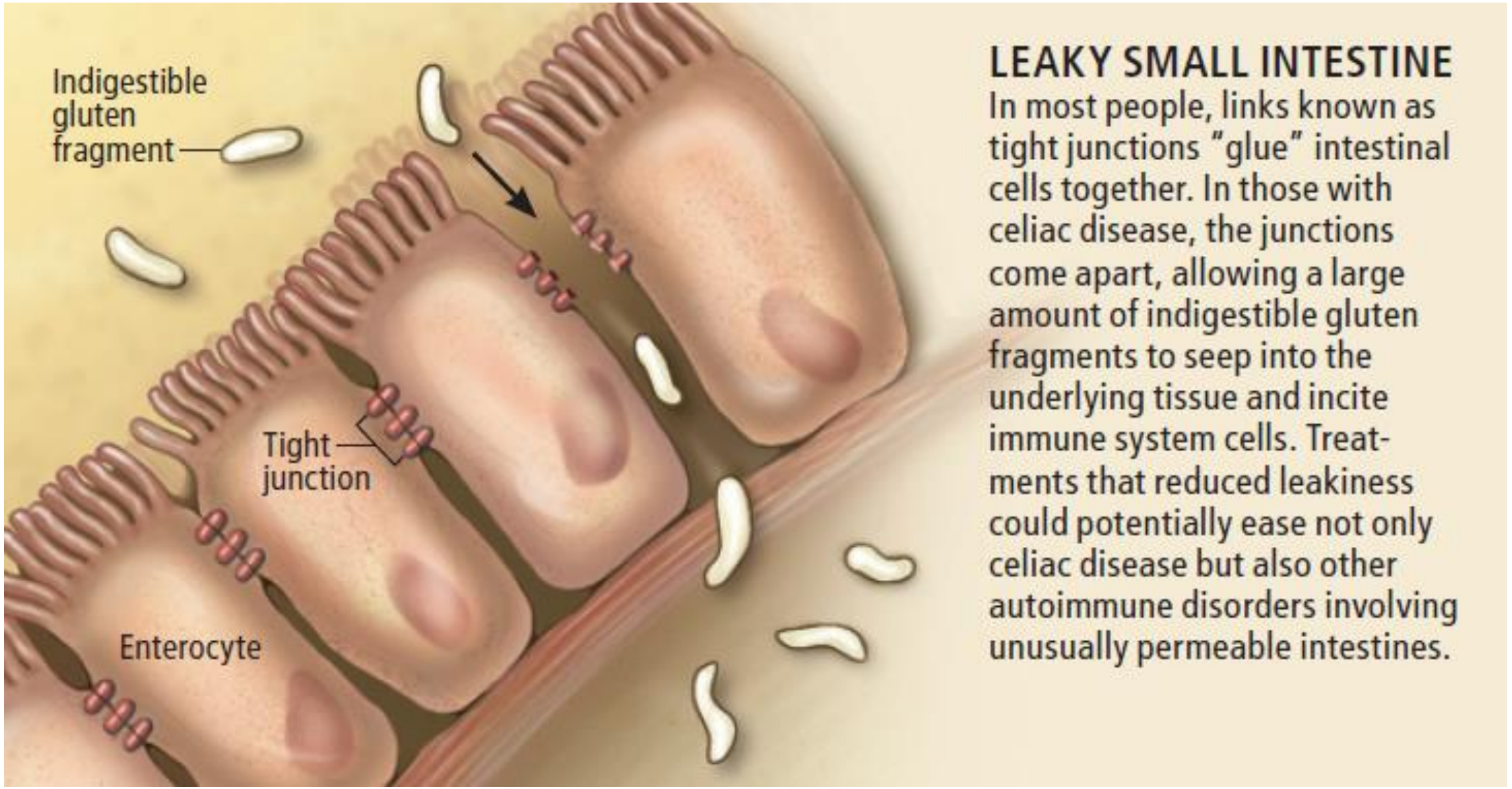
- Since 1978, **the incidence of CD has increased five-fold.**
- The incidence was 1.3 per 100,000 in 1999 and increased to **6.5 per 100,000 in 2008.**
- The highest rates of increase occurred among those over the age of 34.

1. Grainge MJ, West J, Card TR, Holmes GK. Causes of death in people with celiac disease spanning the pre- and post-serology era: a population-based cohort study from Derby, UK. Am J Gastroenterol. 2011 May;106(5):933-9. doi: 10.1038/ajg.2010.506. Epub 2011 Jan 18. PMID: 21245833.
2. Riddle MS, Murray JA, Porter CK. The Incidence and Risk of Celiac Disease in a Healthy US Adult Population. The American journal of gastroenterology. 2012;107(8):1248-1255. doi:10.1038/ajg.2012.130. Used with permission.

Surprises *from* Celiac Disease

Study of a potentially fatal food-triggered disease has uncovered a process that may contribute to many autoimmune disorders

A. Fasano



Genetic Propensity

Environmental Triggers

Altered Microbiome with Gut Inflammation

Increased Intestinal Permeability
and translocation of macromolecules (LPS, foods,…)

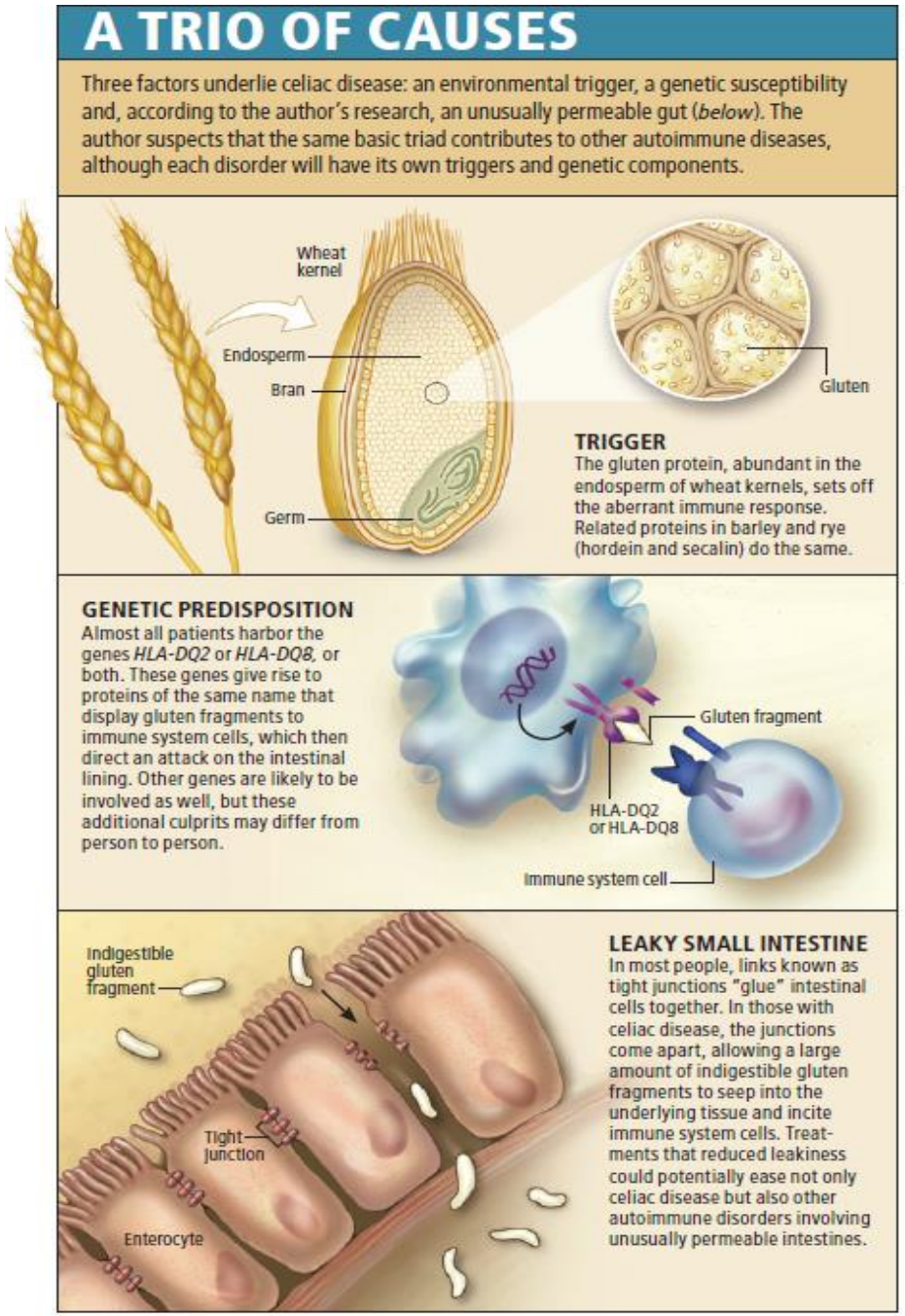
Systemic Immune Response

Initiation of the Autoimmune Spectrum

Valitutti F, Fasano A, Breaking Down Barriers: How Understanding Celiac Disease Pathogenesis Informed the Development of Novel Treatments. Dig Dis Sci. 2019 Jul;64(7):1748-1758

The Autoimmune Triad:

- Trigger
- Genetic Predisposition
- Leaky Gut



Genetics in Celiac Disease:

Celiac genes: **HLA DQ2 & DQ8**

>95% DQ2

>7% DQ8

- Estimated that 0.5% of celiac patients lack DQ2 and/or DQ8
- 30-40% of susceptible populations carry these variants

1.Pietzak MM, Schofield TC, McGinniss MJ, Nakamura RM. Stratifying risk for celiac disease in a large at-risk United States population by using HLA alleles. Clin Gastroenterol Hepatol. 2009 Sep;7(9):966-71. doi: 10.1016/j.cgh.2009.05.028.
2.Sollid LM, Lie BA. Celiac disease genetics: current concepts and practical applications. Clin Gastroenterol Hepatol. 2005;3(9):843–851.
3.U. Lindqvist, Å. Rudsander, Å. Boström, B. Nilsson, G. Michaëlsson; IgA antibodies to gliadin and coeliac disease in psoriatic arthritis, Rheumatology, Volume 41, Issue 1, 1 January 2002, Pages 31–37, https://doi.org/10.1093/rheumatology/41.1.31
4.Karell K, Louka AS, Moodie SJ, Ascher H, Clot F, Greco L, Ciclitira PJ, Sollid LM, Partanen J; European Genetics Cluster on Celiac Disease. HLA types in celiac disease patients not carrying the DQA1*05-DQB1*02 (DQ2) heterodimer: results from the European Genetics Cluster on Celiac Disease. Hum Immunol. 2003 Apr;64(4):469-77.
5. Cecilio LA, Bonatto MW. The prevalence of HLA DQ2 and DQ8 in patients with celiac disease, in family and in general population. *Arq Bras Cir Dig*. 2015;28(3):183–185. doi:10.1590/S0102-67202015000300009.

There are numerous gene variants (SNPs) that ‘predispose’ a significant percentage of the population to autoimmune development. However, only a fraction go on to develop full-blown autoimmune disorders.

Other mitigating factors (triggers & mediators) must be involved…

Why are Wheat/Gluten-related Disorders Increasing?

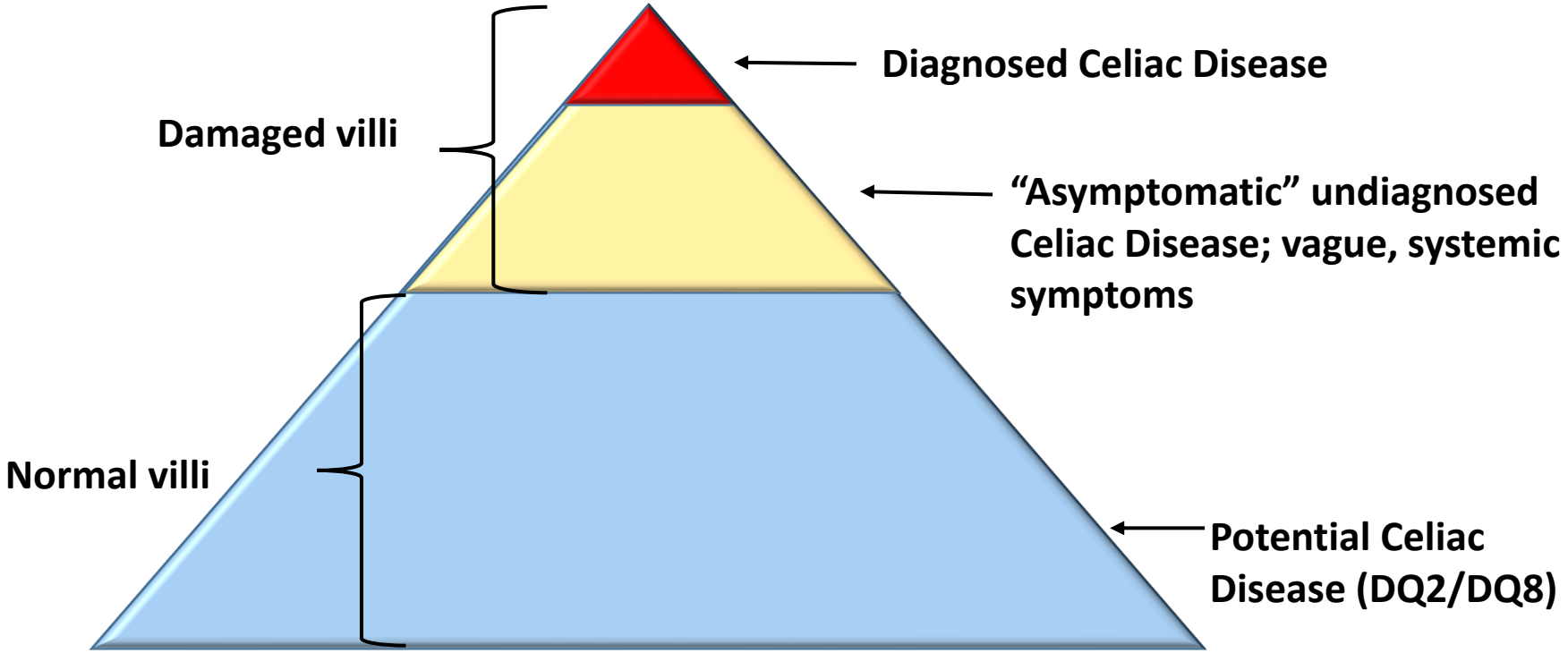
Possible reasons:

- **Modern hybridized wheat**[1,5,6] – higher levels of 33-mer gliadin peptide and higher ATI activity
- Significantly **increased consumption of wheat**[1,3,7,8] *(wheat and wheat isolates that contain deamidated gluten proteins and/or microbial tTG are pervasive in Westernized diets)*
- **Increased use of chemicals/pesticides** such as glyphosate[9]? *(may change gliadin immunogenicity, also alter microbiome)*
- **Gut microbiome** changes[4]?
- **Early introduction/high consumption**?[8]
- **Increased environmental allostatic load** leading to increase in intestinal permeability/vulnerability?
- **Hygiene Hypothesis**[10]

See References: Increasing gluten related disorders

References: Increasing gluten related disorders

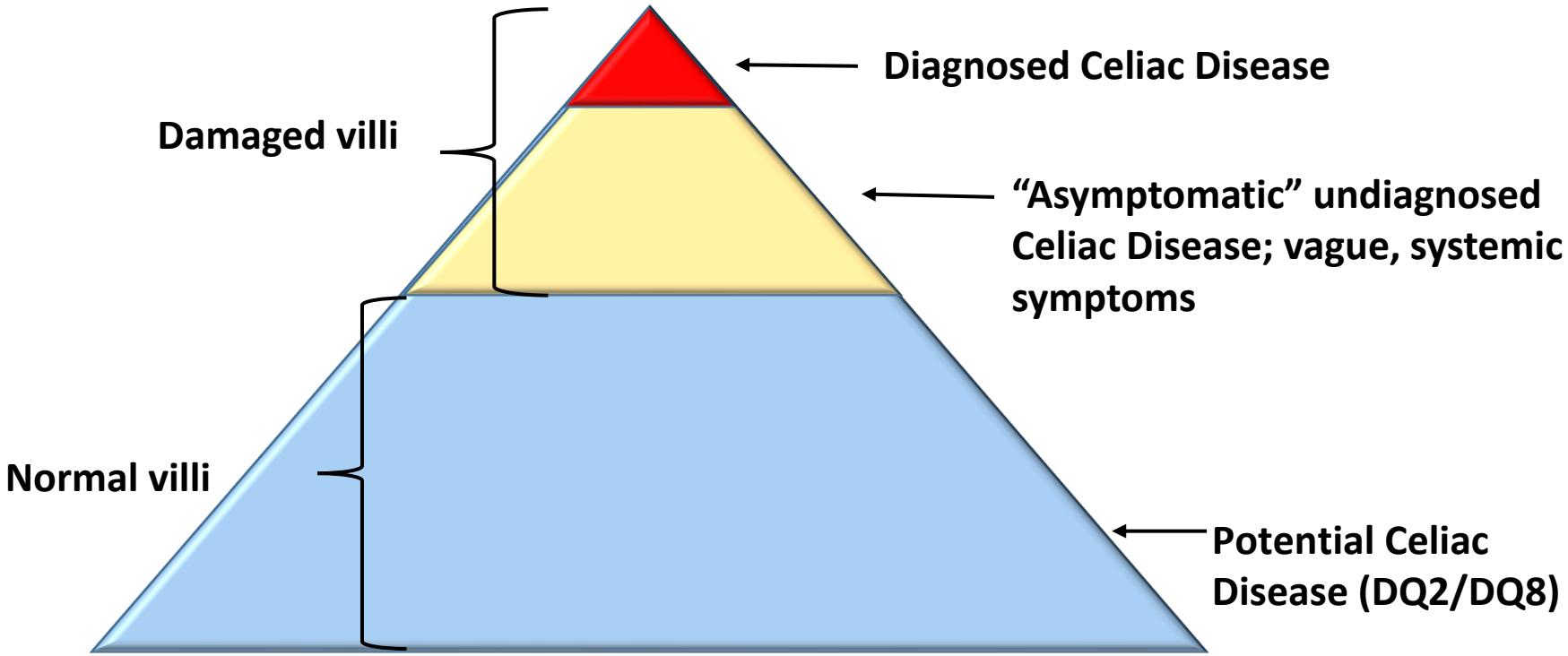
1. Fasano, A. et al. (2015). Nonceliac Gluten Sensitivity. *Gastroenterology*, Mar. 2015, 1-10.
2. Samsel, A., & Seneff, S. (2013). Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. *Interdisciplinary Toxicology*, *6*(4), 159–184. http://doi.org/10.2478/intox-2013-0026.
3. Khamsi, R. (2014). The Trouble with Gluten. *Scientific American*, Feb. 2014.
4. Fasano, A. (2015). Celiac Disease and Gluten-Related Disorders: A Clinical Conversation. *Alternative and Complementary Therapies*, 2015 Feb, Vol. 21:1, 18-21.
5. Sapone, A. et al. (2012). Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Medicine* 2012, 10:13.
6. Kasarda DD. Can an Increase in Celiac Disease Be Attributed to an Increase in the Gluten Content of Wheat as a Consequence of Wheat Breeding? Journal of Agricultural and Food Chemistry. 2013;61(6):1155-1159. doi:10.1021/jf305122s.
7. Koning F. Celiac disease: quantity matters. Seminars in Immunopathology. 2012;34(4):541-549. doi:10.1007/s00281-012-0321-0.
8. Andrén Aronsson C, Lee HS, Hård Af Segerstad EM, Uusitalo U, Yang J, Koletzko S, Liu E, Kurppa K, Bingley PJ, Toppari J, Ziegler AG, She JX, Hagopian WA, Rewers M, Akolkar B, Krischer JP, Virtanen SM, Norris JM, Agardh D; TEDDY Study Group. Association of Gluten Intake During the First 5 Years of Life With Incidence of Celiac Disease Autoimmunity and Celiac Disease Among Children at Increased Risk. JAMA. 2019 Aug 13;322(6):514-523. doi: 10.1001/jama.2019.10329.
9. Samsel A, Seneff S. Glyphosate, pathways to modern diseases II: Celiac sprue and gluten intolerance. Interdisciplinary Toxicology. 2013;6(4):159-184. doi:10.2478/intox-2013-0026.
10. Riddle MS, Murray JA, Porter CK. The Incidence and Risk of Celiac Disease in a Healthy US Adult Population. The American journal of gastroenterology. 2012;107(8):1248-1255. doi:10.1038/ajg.2012.130.



The celiac iceberg represents all persons genetically susceptible to celiac disease. The majority of such persons will not develop celiac disease. The “tip of the iceberg” represents the minority of persons who have been diagnosed with celiac disease.

Epidemiological studies suggest 1:105 have CD.

1. Fasano A, Berti I, Gerarduzzi T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: A large multicenter study. Arch Intern Med.2003;163:286–292.
2. Adapted from Gastroenterology, Vol. 128, Fasano, A., Clinical presentation of celiac disease in the pediatric population, Pages S68-73, Copyright 2005, with permission from American Gastroenterological Association.



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2. Adapted from Gastroenterology, Vol. 128, Fasano, A., Clinical presentation of celiac disease in the pediatric population, Pages S68-73, Copyright 2005, with permission from American Gastroenterological Association.

GLUTEN FREEDOM

BY
ALESSIO FASANO, MD

The Trouble with Gluten

"The presence of these undigested gluten peptides in the upper small intestine is perceived by our gut immune surveillance system as the presence of a potential enemy…

I am now convinced that our immune system mistakenly interprets gluten as a component of a dangerous bacterium or bacteria. When this happens, it unleashes an immune response similar to that triggered by bacteria to rid the body of the attackers. This response is elicited in everyone. It is not exclusive to people affected by gluten-related disorders."

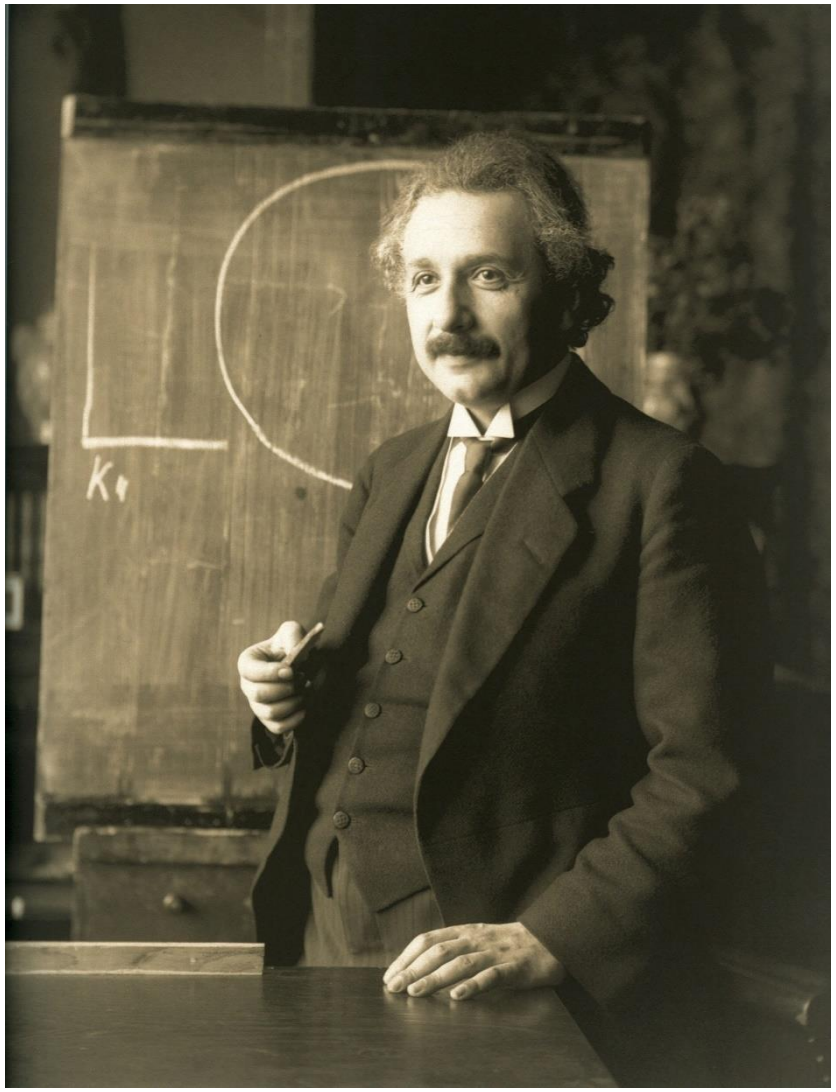
Fasano A, Flaherty S. *Gluten Freedom: the Nations Leading Expert Offers the Essential Guide to a Healthy, Gluten-Free Lifestyle*. Nashville, TN: Wiley General Trade, an imprint of Turner Publishing Company; 2014.

The Trouble with Gluten?

"Consequently, I have colleagues who support the notion that gluten is toxic for humankind and, therefore, everybody should embrace a gluten-free diet. ***Although I have contributed to the discoveries of some of these inappropriate immune responses elicited by gluten in humans, I do not share the position of the proponents of a gluten-free world,*** *who often cite my work to support their position.*

We engage daily in a war with many dangerous bacteria, but rarely do we lose this battle, which is an event that leads to infection. We are also engaged in a daily confrontation with gluten, but only a minority of us will lose this battle. These are the genetically susceptible individuals who will develop gluten-related disorders."

Fasano A, Flaherty S. *Gluten Freedom: the Nations Leading Expert Offers the Essential Guide to a Healthy, Gluten-Free Lifestyle*. Nashville, TN: Wiley General Trade, an imprint of Turner Publishing Company; 2014.



"Make everything as simple as possible, but not simpler."

Albert Einstein

1. Photograph of Albert Einstein by Ferdinand Schmutzer.
2. Quote: Sessions R. How a 'Difficult' Composer Gets That Way. New York Times. Published January 8, 1950. (Paraphrasing of Albert Einstein from a lecture delivered at Oxford, June 10, 1933: 'On the Method of Theoretical Physics').

SENSITIVITY AND SPECIFICITY OF SEROLOGIC TESTS FOR CELIAC DISEASE

Test	Sensitivity	Specificity
IgA anti-tissue transglutaminase	95-98	94-95
IgA anti-endomysial antibody	85-98	97-100
IgA anti-gliadin	75-90	82-95
IgG anti-gliadin	69-85	73-90

Derived from Rashtak, S., Ettore, M. W., Homburger, H. A., & Murray, J. A. (2008). Comparative usefulness of deamidated gliadin antibodies in the diagnosis of celiac disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, *6*(4), 426–370. https://doi.org/10.1016/j.cgh.2007.12.030

Comparative Usefulness of Deamidated Gliadin Antibodies in the Diagnosis of Celiac Disease

N = 216: 92 bx + celiac (untreated) vs 124 bx- controls

Antibody	Sensitivity	Specificity	Accuracy
Deamidated gliadin-IgA	74%	95%	86%
Deamidated gliadin-IgG	65%	98%	84%
Deamidated gliadin-IgA+G	75%	94%	86%
Gliadin-IgA	63%	90%	79%
Gliadin-IgG	42%	90%	69%

Derived from Rashtak, S., Ettore, M. W., Homburger, H. A., & Murray, J. A. (2008). Comparative usefulness of deamidated gliadin antibodies in the diagnosis of celiac disease. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*, *6*(4), 426–370. https://doi.org/10.1016/j.cgh.2007.12.030

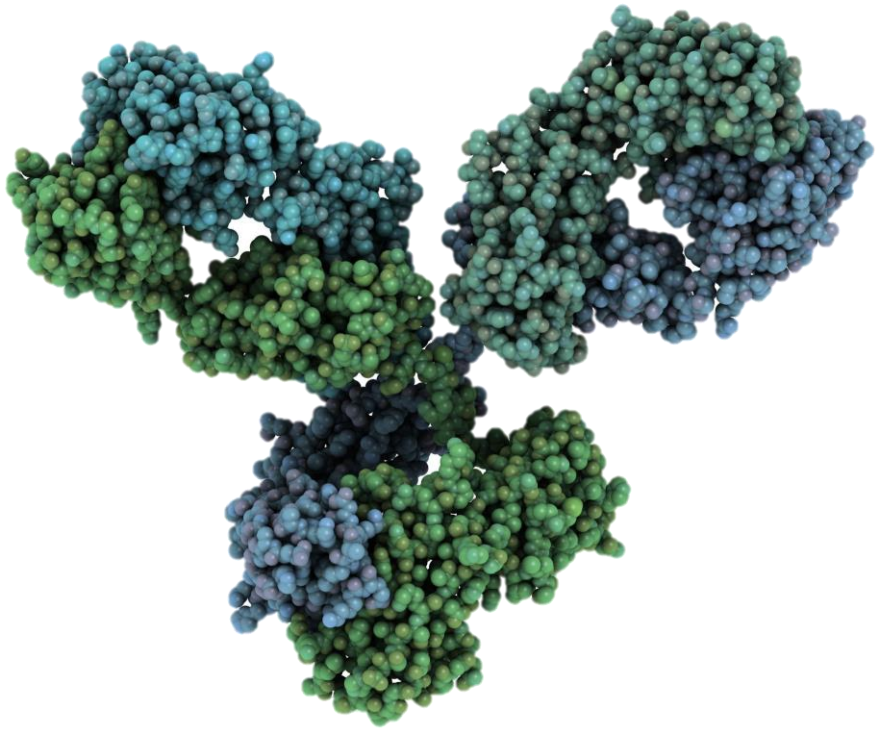
Clinical Significance of **Anti-gliadin IgG**

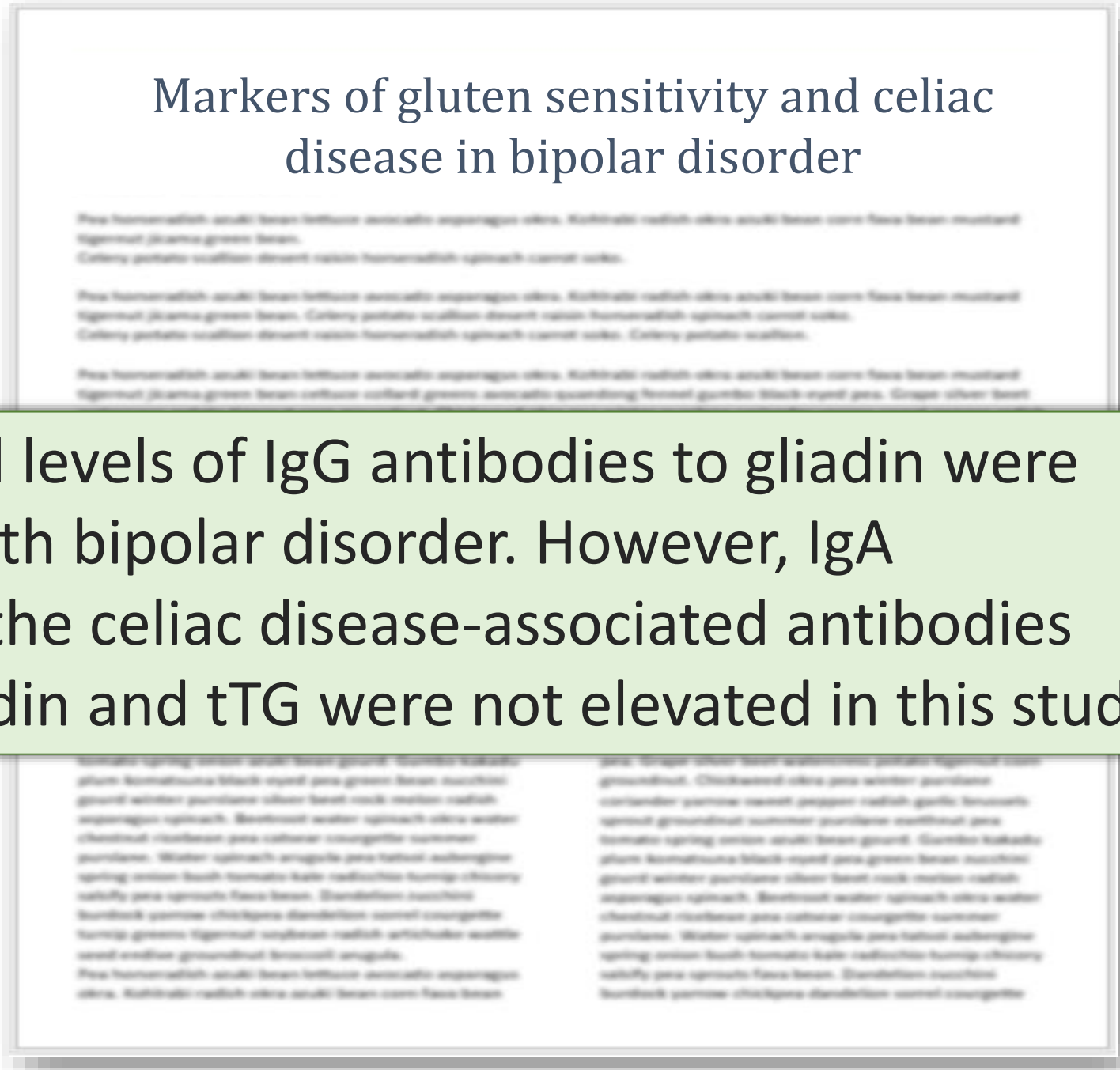
Elevated anti-gliadin IgG only associated with increased all-cause mortality

Current Opinion in Gastroenterology 2008. 4:687-691;

Nat Genet. 2008 Apr;40(4):395-402.

World J Gastroenterol. 2007 Jan 7;13(1):146-51.





CONCLUSION: Increased levels of IgG antibodies to gliadin were present in individuals with bipolar disorder. However, IgA antibodies to gliadin or the celiac disease-associated antibodies against deamidated gliadin and tTG were not elevated in this study.

Dickerson F, Stallings C, Origoni A, et al. Markers of gluten sensitivity and celiac disease in bipolar disorder. Bipolar Disord. 2011 Feb;13(1):52-8. doi: 10.1111/j.1399-5618.2011.00894.x.

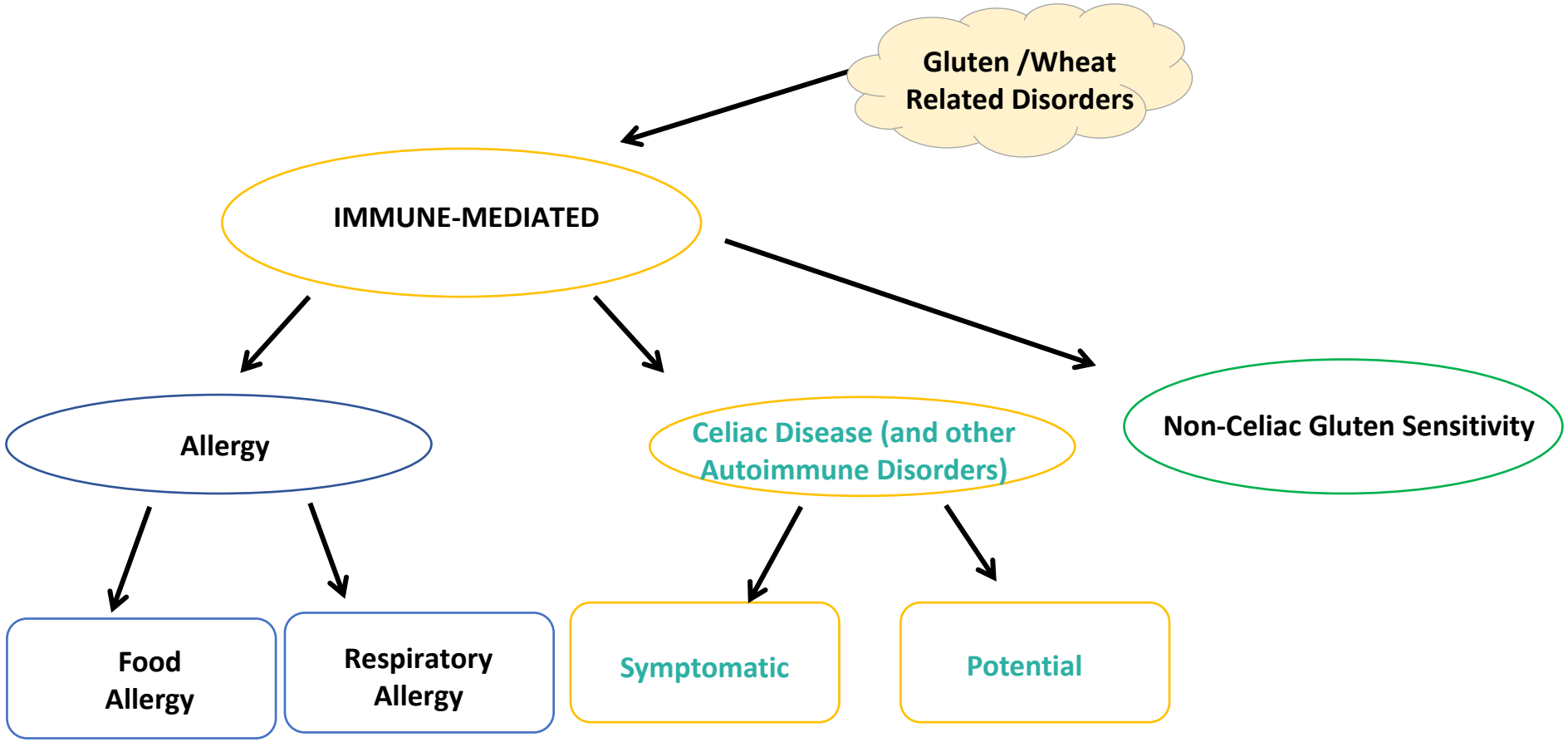
Testing Summary for Diagnosis of Celiac Disease

- **Serum Testing:**
  - Total IgA
  - IgA/ IgG tissue transglutaminase (tTG) antibody
  - IgG/ IgA Deaminated antigliadin (DGP) antibody
  - IgA anti-endomysial antibodies (EMA)
    - – REFLEX if DGP IgG or tTG IgA positive
- **Consider Confirmatory Small Bowel Biopsy**
- **Consider DQ2/DQ8** to rule out risk of CD In patients who are currently gluten-free or first degree relatives
- **Consider Antigliadin IgG** to expand beyond Celiac Disease

Conventional Clinical Guidelines for Diagnosis of Celiac Disease

- Mayo Clinic Lab Algorithm: https://www.mayocliniclabs.com/it-mmfiles/Celiac_Disease_Comprehensive_Cascade.pdf
- American College of Gastroenterology (ACG) clinical guideline on diagnosis and management of celiac disease: Am J Gastroenterol 2013 May;108(5):656
- American Gastroenterological Association Institute (AGA) statement: Gastroenterology 2006 Dec;131(6):1977
- United States Preventive Services Task Force (USPSTF) recommendations on screening for celiac disease: JAMA 2017 Mar 28;317(12):1252

Schematic of Gluten/Wheat Related Disorders



Non-Celiac Gluten Sensitivity (NCGS)

Gluten can cause GI and systemic symptoms in the absence of celiac disease.

- DBPCRT with symptomatic IBS patients in whom celiac disease was excluded
- Placed on Gluten or GF diet x 6 weeks. (N = 34)
- Those in the gluten group had significantly worse symptoms within 1 week, including: pain, bloating, satisfaction with stool consistency, and tiredness.
- HLADQ2 or DQ8 status did not affect outcome.

Conclusion: gluten-free trial warranted in all IBS patients

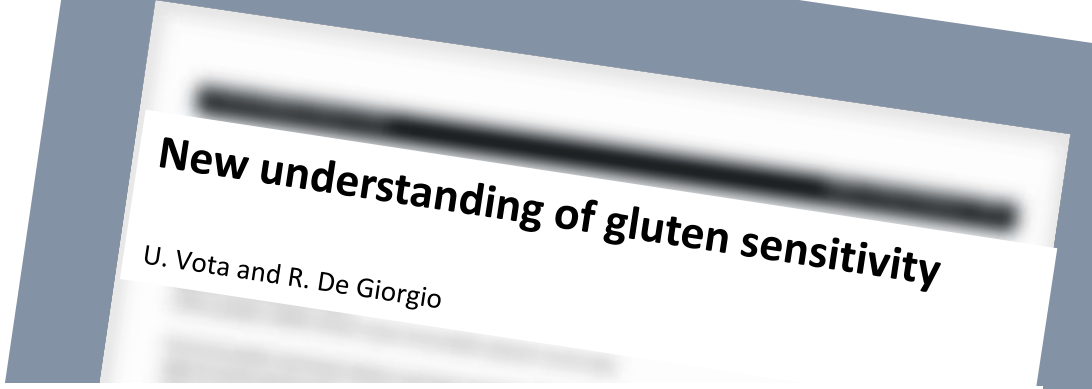
Biesiekierski, et al. Gluten causes gastrointestinal symptoms in subjects without celiac disease: a double-blind randomized placebo-controlled trial.Am J Gastroenterol. 2011 Mar;106(3):508-14;

Celiac Disease and Non-Celiac Gluten Sensitivity

Based on the results, CD and NCGS are caused by different intestinal mucosal responses to gluten and, therefore, should be considered distinct clinical entities.

Sapone, et al. BMC Medicine 2011,9:23 Divergence of gut permeability and mucosal immune gene expression in two gluten- associated conditions: celiac disease and gluten sensitivity.

Symptoms reported by 78 patients with gluten sensitivity; **most patients complained of two or more symptoms.**



Gastrointestinal Symptoms:

- Abdominal pain: 37%
- Bloating: 35%
- Diarrhea: 19%
- Constipation: 9%

Extraintestinal Symptoms:

- Brain fog: 19%
- Fatigue: 16%
- Skin rash: 15%
- Headache: 15%
- Joint/muscle pain: 13%
- Leg/arm numbness: 8%
- Depression: 7%
- Anemia: 7%

Volta U, De Giorgio R. New understanding of gluten sensitivity. Nat Rev Gastroenterol Hepatol. 2012 Feb 28;9(5):295-9. doi: 10.1038/nrgastro.2012.15. PMID: 22371218.

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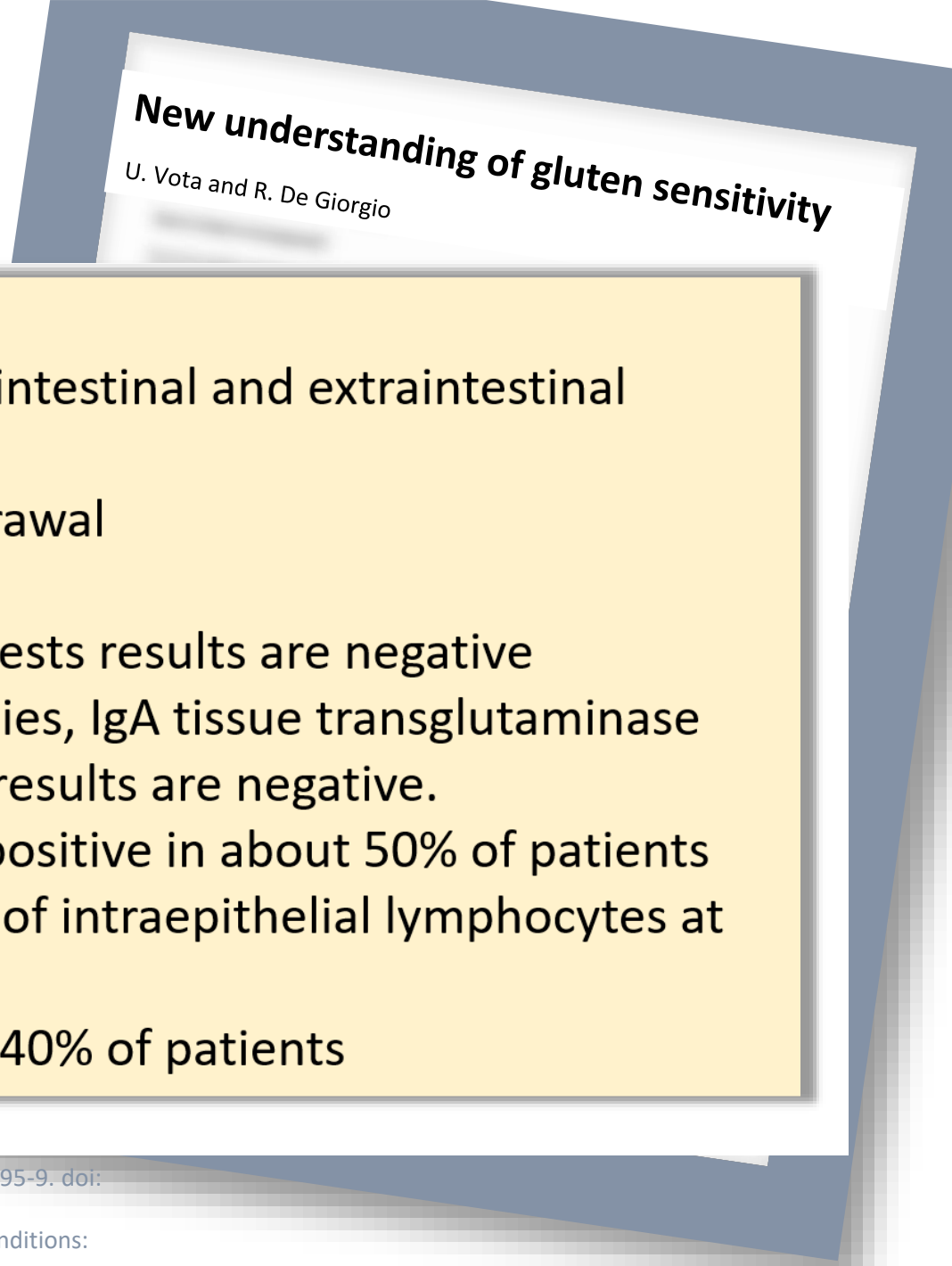


Diagnostic criteria for gluten sensitivity

- Gluten ingestion elicits the rapid occurrence of intestinal and extraintestinal symptoms
- Symptoms disappear rapidly after gluten withdrawal
- Reintroduction of gluten causes symptoms
- Specific IgE to gluten and wheat and skin prick tests results are negative
- Celiac disease serology (IgA endomysial antibodies, IgA tissue transglutaminase antibodies, IgG deamidated gliadin antibodies) results are negative.
- Antigliadin antibodies (mainly of IgG class) are positive in about 50% of patients
- Normal mucosa or mild increase in the number of intraepithelial lymphocytes at histopathology
- HLA-DQ2 and/or HLA-DQ8 possibly positive in ~40% of patients

Volta U, De Giorgio R. New understanding of gluten sensitivity. Nat Rev Gastroenterol Hepatol. 2012 Feb 28;9(5):295-9. doi: 10.1038/nrgastro.2012.15.
Sapone A, et al. Divergence of gut permeability and mucosal immune gene expression in two gluten-associated conditions: celiac disease and gluten sensitivity. BMC Med. 2011 Mar 9;9:23. doi: 10.1186/1741-7015-9-23.

Extra-intestinal Symptoms

Gluten Sensitivity

- Bone and joint pain
- Osteoporosis
- Leg numbness
- Muscle cramps
- Unexplained anemia
- Glossitis

Celiac Disease

- Bone and joint pain
- Osteoporosis
- Tingling leg numbness
- Muscle cramps
- Behavioral changes
- Missed menstruation
- Infertility
- Recurrent miscarriage
- Delayed growth
- Thyroiditis
- Tooth discoloration
- Unexplained anemia
- Seizures
- Dementia
- Hepatitis

Intestinal Symptoms

Gluten Sensitivity

- Diarrhea
- Abdominal pain
- Gas

Celiac Disease

- Chronic diarrhea
- Abdominal pain
- Smelly, fatty stools

Overlap Between Gluten Sensitivity and Celiac Disease

Gluten Sensitivity

- Epithelial barrier function **increased**

Both

- Enhanced recruitment of neutrophils
- Inflammation in the GI tract
- Immune response to gliadin (AGA)

Celiac Disease

- Epithelial barrier function **decreased**
- Damage to the intestinal mucosa
- Autoimmune (tTGA)

Volta U, De Giorgio R. New understanding of gluten sensitivity. Nat Rev Gastroenterol Hepatol. 2012 Feb 28;9(5):295-9. doi: 10.1038/nrgastro.2012.15. PMID: 22371218.

Lab Comparisons

Test	Gluten Sensitivity	Celiac Disease	Healthy Population
Endomysial Ab IgA	Negative	90-100% [illegible]sitive	Negative
tTG-IgA	Negative	[illegible]ve	Negative
AGA IgA/IgG	50% [illegible]	[illegible]itive	Negative
MHC Profile	[illegible] DQ8	90% positive	-
Wheat IgE	[illegible]egative	Negative	2.5% positive

No perfect test for 'Gluten Sensitivity'

See References: Lac Comparison

References: Lab Comparison

1. Sapone A et al: Divergence of gut permeability and mucosal immune gene expression in Two gluten associated conditions: celiac disease and gluten sensitivity. BMC Medicine 2011,9:23.
2. Volta U, Tovoli F, Cicola R, Parisi C, Fabbri A, Piscaglia M, Fiorini E, Caio G. Serological tests in gluten sensitivity (nonceliac gluten intolerance). J Clin Gastroenterol. 2012 Sep;46(8):680-5. doi: 10.1097/MCG.0b013e3182372541. PMID: 22138844.
3. Porcelli B, Ferretti F, Vindigni C, Terzuoli L. Assessment of a test for the screening and diagnosis of celiac disease. J Clin Lab Anal. 2016;30(1):65-70. doi:10.1002/jcla.21816
4. Gujral N, Freeman HJ, Thomson AB. Celiac disease: prevalence, diagnosis, pathogenesis and treatment. World J Gastroenterol. 2012;18(42):6036-6059. doi:10.3748/wjg.v18.i42.6036
5. Watanabe C, Komoto S, Hokari R, et al. Prevalence of serum celiac antibody in patients with IBD in Japan. J Gastroenterol. 2014;49(5):825-834. doi:10.1007/s00535-013-0838-6
6. Terryberry J, Tuomi J, Perampalam S, Peloquin R, Brouwer E, Schuppan D, Guandalini S. Diagnostic accuracy of a fully automated multiplex celiac disease antibody panel for serum and plasma. Clinical Chemistry and Laboratory Medicine (CCLM). 2019 Jul 26;57(8):1207-17. DOI: https://doi.org/10.1515/cclm-2019-0088

Laboratory Analysis (at this point) is not able to ID Non-Celiac Gluten Sensitivity.

The Gold Standard is an Elimination Diet.

How many people do in fact have Non-Celiac Gluten Sensitivity?

Most studies suggest

between 1-6% of the population

1. Sapone A, et. al Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012, 10:13-25
2. Volta U, et, al. :An Italian prospective multicentre survey on patients suspected of having non-gluten sensitivity. *BMC Med* 12:85.
3. DiGiacomo DV, et al. Prevalence of gluten-free diet adherence among individuals without celiac disease in the USA: results from the Continuous National Health and Nutrition Examination Survey 2009–2010. *Scandinavian Journal of Gastroenterology*. 2013 Aug;48(8):921–5. PMID

What about other research that showed NCGS doesn't really exist?

- **Subjects with NCGS were fed a low FODMAP diet for two weeks.**
  - Nearly all subjects experienced a decrease in GI symptoms
  - Then randomized and crossed over onto a high gluten, low gluten or placebo (whey protein) diet.

- **Results**: No gluten-specific gastrointestinal symptoms were evident.

Biesoeloerski, J. R., & Gibson, P. (2013). No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates. Retrieved from http://dx.doi.org/10.1053/j.gastro.2013.04.051

Conclusions (and Controversy)

- Essentially asserted that NCGS is really a problem with FODMAPs
- This study has now been repeatedly cited in other review articles and the popular press.

Biesoeloerski, J. R., & Gibson, P. (2013). No Effects of Gluten in Patients With Self-Reported Non-Celiac Gluten Sensitivity After Dietary Reduction of Fermentable, Poorly Absorbed, Short-Chain Carbohydrates. Retrieved from http://dx.doi.org/10.1053/j.gastro.2013.04.051

Holes in the Study

- Participant Selection
- Statistical Power
- Self Selection
- Placebo confounder
- Primary focus was on GI symptoms; however, NCGS is purported to have a variety of non-GI symptoms

Could NCGS/NCWS be a FODMAP issue?

- GI symptoms including bloating, abdominal pain, or diarrhea are frequently self-reported by patients.
- These patients often suspect a "gluten sensitivity" and find that their symptoms resolve on a gluten-free diet.[1]

- **NCGS may be related to FODMAPs in some patients reporting IBS symptoms.**
- People with NCGS can have IBS-like sx, but also extra-intestinal sx that cannot be explained with FODMAPs.

1. Capili, B., Chang, M., & Anastasi, J. K. (2014). A clinical update: Nonceliac gluten sensitivity--is it really the gluten? The Journal for Nurse Practitioners, 10(9), 666-673. doi:http://dx.doi.org/10.1016/j.nurpra.2014.07.036
2. Fasano, A. et al. (2015). Nonceliac Gluten Sensitivity. *Gastroenterology*, Mar. 2015, 1-10.
3. Fasano, A. (2015). Celiac Disease and Gluten-Related Disorders: A Clinical Conversation. *Alternative and Complementary Therapies*, 2015 Feb, Vol. 21:1, 18-21.

Perhaps a more nuanced view is in order…

Conclusion: Patient populations reporting an intolerance to a diet containing gluten is a mixed population of NCGS and FODMAPs - sensitive patients.

Zanini B, Basche R, Ferraresi A, Lanzarotto F, Marullo M, Ricci C, Lanzini A. PTH-111 "Non celiac gluten sensitivity" (ncgs) is uncommon in patients spontaneously adhering to gluten free diet (gfd), and is outnumbered by "fodmaps sensitivity". *Gut.* 2014; 63: A260. doi:10.1136/gutjnl-2014-307263.557.

Experimental Laboratory Tests of Gluten Sensitivity

- Current testing for Gluten Sensitivity and Celiac disease includes IgG and IgA against gliadin and tissue transglutaminase.
- These antibodies are measured against a single component of wheat protein called alpha-gliadin.
- However, wheat proteins consist of alpha-gliadin, omega-gliadin, glutenin, gluteomorphin, prodynorphin and agglutinins, each of which has a capacity to challenge the immune system.

Experimental Laboratory Tests of Gluten Sensitivity

Technologies have been developed to measure IgA and IgG against various wheat components including:

- Wheat
- Wheat Germ Agglutinin
- Deamidated Gliadin 15 Mer
- Deamidated Gliadin 17 Mer
- Deamidated Gliadin 33 Mer
- Omega Gliadin
- Glutenin
- Pro-dynorphin
- Gluteo-morphin
- Gliadin bound to tTg
- Transglu-taminase
- GAD-65

References: Experimental Laboratory Tests

- Interview with Aristo Vodjani, PhD. Enhanced Testing for Gluten and Food Sensitivity (Jan 2013) Townsend Letter for Doctors & Patients. Townsendlettercom. 2017. Available at: http://www.townsendletter.com/Jan2013/enhancetest0113.html. Accessed October 6, 2017.
- Vader W, et al. The gluten response in children with celiac disease is directed toward multiple gliadin and glutenin peptides. Gastroenterology. 2002 Jun;122(7):1729-37.
- Camarca A, et al. Intestinal T cell responses to gluten peptides are largely heterogeneous: implications for a peptide-based therapy in celiac disease. J Immunol. 2009 Apr 1;182(7):4158-66. doi: 10.4049/jimmunol.0803181.
- Vojdani A. The characterization of the repertoire of wheat antigens and peptides involved in the humoral immune responses in patients with gluten sensitivity and Crohn's disease. ISRN Allergy. 2011;2011:950104. Published 2011 Oct 27. doi:10.5402/2011/950104.
- Vallejo-Diez S, et al. (2013) Detection of Specific IgA Antibodies against a Novel Deamidated 8-Mer Gliadin Peptide in Blood Plasma Samples from Celiac Patients. PLoS ONE 8(11): e80982. https://doi.org/10.1371/journal.pone.0080982.
- Stamnaes J, Dorum S, Fleckenstein B, Aeschlimann D, Sollid LM. Gluten T cell epitope targeting by TG3 and TG6; implications for dermatitis herpetiformis and gluten ataxia. Amino Acids. 2010 Nov;39(5):1183-91. doi: 10.1007/s00726-010-0554-y.

Experimental Laboratory Tests

Fecal anti-gliadin Ab

Kappler et al. (2006)

- Negative in most cases of Celiac Disease
- Not a reliable screening test

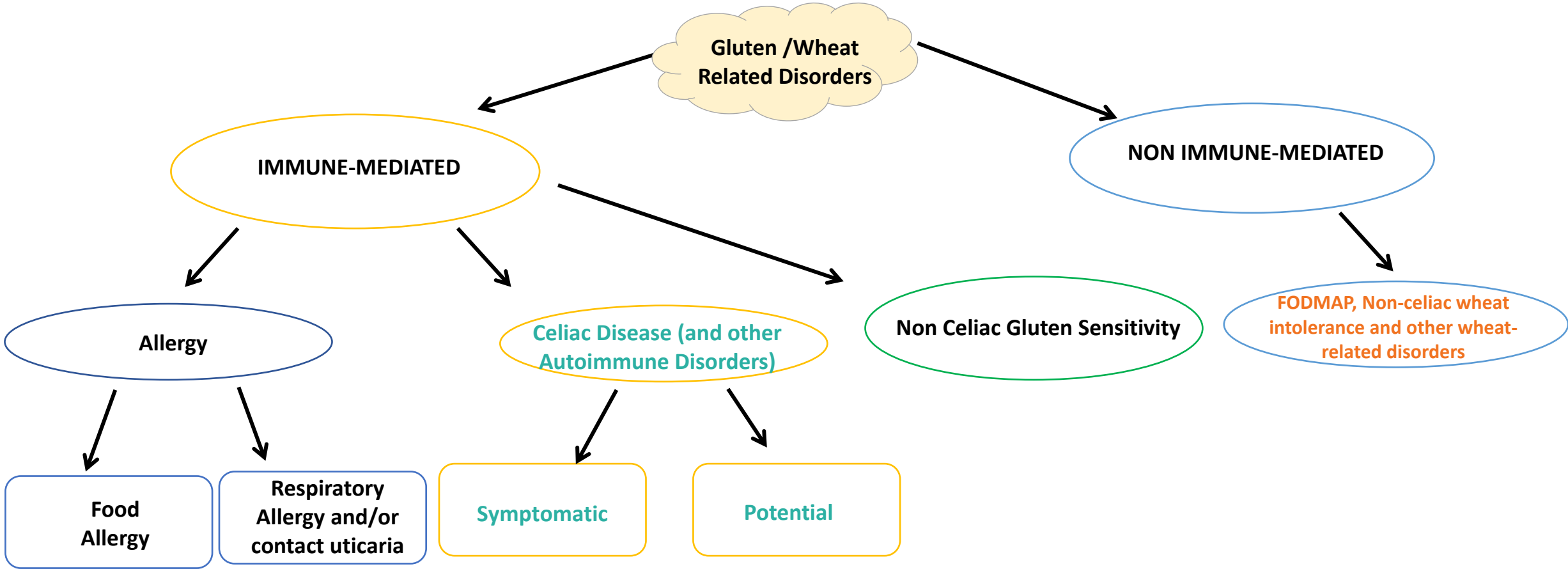
Halblaub et al. (2004)

- The results in this study were obtained by fecal scIgA AGA and a combined determination of fecal IgA AGA, IgG AGA and IgM AGA.

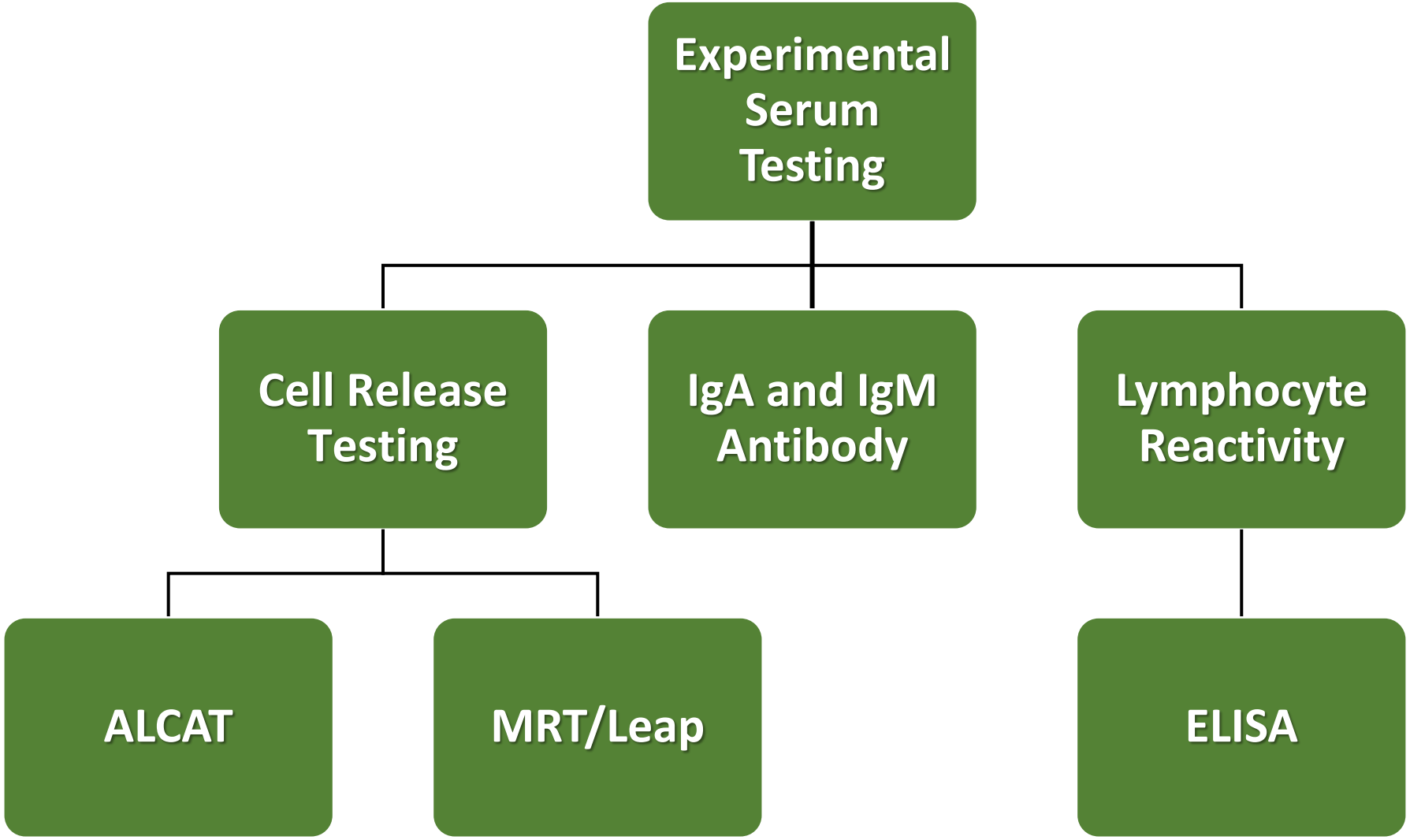
Kappler M, Krauss-Etschmann S, Diehl V, Zeilhofer H, Koletzko S. Detection of secretory IgA antibodies against gliadin and human tissue transglutaminase in stool to screen for coeliac disease in children: validation study. BMJ. 2006 Jan 28;332(7535):213-4.

Halblaub JM, Renno J, Kempf A, Bartel J, Schmidt-Gayk H. Comparison of different salivary and fecal antibodies for the diagnosis of celiac disease. ClinLab. 2004;50(9-10):551-7.

Schematic of Gluten/Wheat Related Disorders



Experimental Testing for Food Sensitivity



Leukocyte Variability Testing

- WBC size changes after in vitro food exposure demonstrating release of immune mediators.
- Does it correlative with in vivo behavior?
- Minimal research on the method in recognized journals.
- A successful, small weight loss trial with diet based on results.
- Significant intra-individual variability has been demonstrated.

Middle East Journal of Family Medicine April 2009 - Volume 7, Issue 3

Hodsdon W, Zwickey H. Reproducibility and Reliability of Two Food Allergy Testing Methods. Natural Medicine Journal. 2010 March;2(3):8-13.

IgA and IgM Food Antibody Testing?

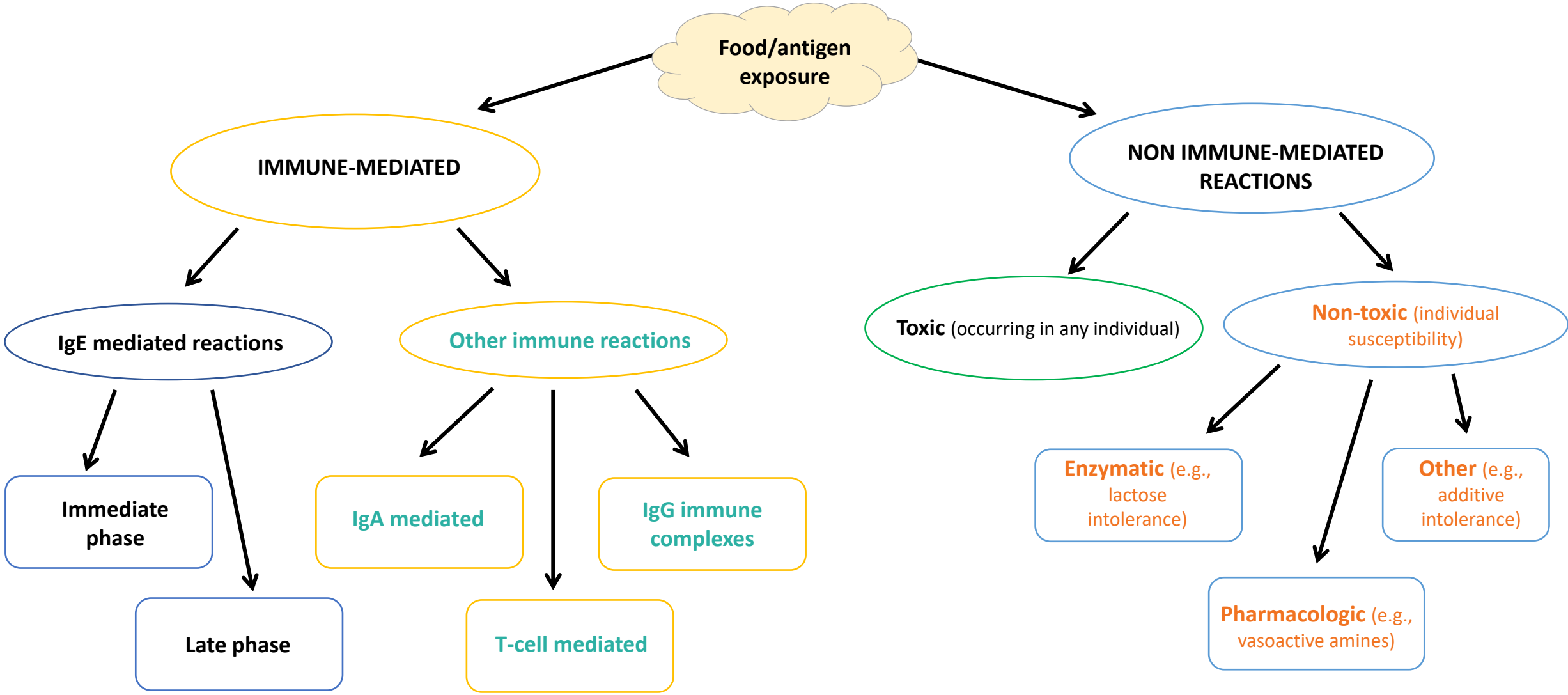
- High IgA beef-specific serum antibodies and associated symptoms were reduced in response to a cow meat exclusion diet.
- High IgM antibodies against food antigens in IgA deficient individuals who presented with recurrent infections (Clinical relevance?).
- Diabetic children had significantly higher serum levels of IgG and IgM to the proteins found in cow's milk than healthy controls ($p<0.001$).

1. Calderon TE, Ferrero M, Marino GM, Cordoba A, Beltramo D, Muino JC, Rabinovich GA, Romero MD. Meat-specific IgG and IgA antibodies coexist with IgE antibodies in sera from allergic patients: clinical association and modulation by exclusion diet. J Biol Regul Homeost Agents. 2010 Jul-Sep;24(3):261-71.
2. Cardinale F, Friman V, Carlsson B, Björkander J, Armenio L, Hanson LA. Aberrations in titre and avidity of serum IgM and IgG antibodies to microbial and food antigens in IgA deficiency. Scand J Immunol. 1992 Aug;36(2):279-83.
3. Neyestani TR, Djalali M, Pezeshki M, Siassi F, Eshraghian MR, Rajab A, Keshavarz A. Serum antibodies to the major proteins found in cow's milk of Iranian patients with Type 1 diabetes mellitus. Diabetes Nutr Metab. 2004 Apr;17(2):76-83.

IgA and IgM Food Antibody Testing?

- IgA/food complexes-normal physiology
- Minimal research on utility of IgA/food complexes EXCEPT IgA/Gliadin
- Even less research on IgM/food complexes

MECHANISMS OF IMMUNE AND NON-IMMUNE MEDIATED REACTIONS TO FOOD



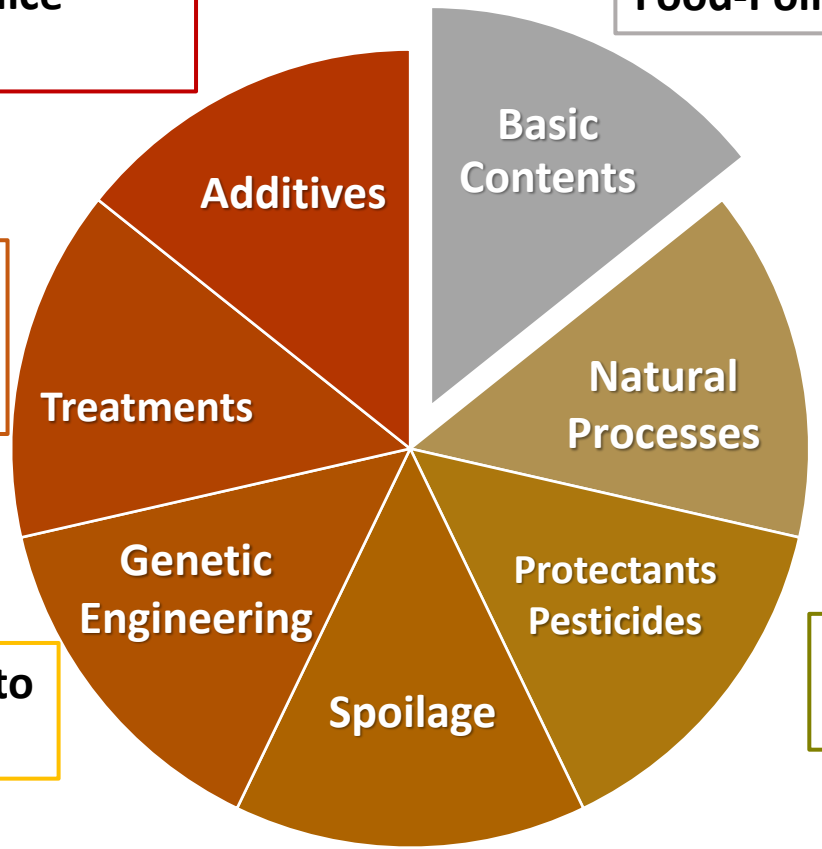
Part 4

Food Intolerances:
non-immune mediated reactions to foods

Contents/Reactants in Foods

Many, Preservatives (citric acid), Antibiotics, Hormones, Enzymes (lactase, bread-amylase, Fruit juice-cellulase…), Colorings…

Protein, Carbohydrate, Lectins, Food-Pollen Homology…



Canning, Freezing, Heating, Salting, Smoking, Marinating, Microwave

Aging, Insects, Worms, Fungi (grapes, tomato) Fermentation (chocolate, tea, malt)

Soy, Coffee, Squash, Tomato Sugar Beet, Salmon…

Pesticides, Fungicides, Antibiotics…

Bacterial, Fungal, Toxins, Histamine, Pathogens, Heavy Metals…

See References: Contents/Reactants in Foods

References: Contents/Reactants in Foods

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Food Intolerances

- **Lectins (indirect immune stimulation)**
  - Mucosal inflammation is antecedent
  - Paleolithic diet is low in lectins
- **Tyramine, histamine (monoamines)**
  - Consider for refractory migraineurs
- **MSG, aspartame, food additives**
- **Salicylates**
  - Ask: aspirin-associated asthma, tinnitus w/ foods?
  - Refractory GI pain
- **Lactose intolerance (lactase deficiency)**
  - Readily measured through breath test
    - 90% Asian Americans, 75% African Americans

See References: Food Intolerances

References: Food Intolerances

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Skypala IJ, Williams M, Reeves L, Meyer R, Venter C. Sensitivity to food additives, vaso-active amines and salicylates: a review of the evidence. Clin Transl Allergy. 2015;5. doi:10.1186/s13601-015-0078-3

Food Intolerances, Carbohydrates and FODMAPs

Think of lactose intolerance as the model…

- Poorly absorbed FODMAPs exert osmotic force in the intestinal lumen causing net increased fluid secretion into the lumen, leading to symptoms such as distention and diarrhea.
- Poorly absorbed FODMAPs are fermented by gut microbiota producing gas and bloating with associated pain.

Nanayakkara, W. S., Skidmore, P. M., O'Brien, L., Wilkinson, T. J., & Gearry, R. B. (2016). Efficacy of the low FODMAP diet for treating irritable bowel syndrome: the evidence to date. *Clinical and Experimental Gastroenterology*,*9*, 131.

FODMAPs

Fermentable, **O**ligo-, **D**i-, **M**ono-saccharides and **P**olyol

Fermentable	**The process through which gut bacteria degrade undigested carbohydrate to produce gases (hydrogen, methane and carbon dioxide)**
Oligosaccharides	Fructo-oligosaccharides (FOS) found in; wheat, rye, onions and garlic Galacto-oligosacchardies (GOS) found in; legumes and pulses
Disaccharides	Lactose found in; milk, soft cheese, yoghurts
Monosaccharides	Fructose (in excess of glucose) found in honey, apples, high fructose corn syrups
Polyols	Sugar polyols (eg. sorbitol, mannitol) found in some fruit and vegetables and used as artificial sweeteners

FODMAP Resources

- FODMAP APP/Monash University: https://www.monashfodmap.com/ibs-central/i-have-/get-the-app/
- Sue Shepherd MS, RD at Shepherd Works: http://shepherdworks.com.au/
- Taste.com.au: www.taste.com.au/recipes/collections/low+fodmap+diet+recipes
- Kate Scarlata, RDN: www.katescarlata.com
- Patsy Castos MS, RD, LD: www.ibsfree.net

FODMAP Resources:
Low-FODMAP Food Plan

In your Toolkit

How many people have some kind of food intolerance?

Literature review suggests food intolerance affects 15-20% of the population.

Lomer MC Review article: the etiology, diagnosis, mechanisms and clinical evidence for food intolerance. Aliment Pharmacol 2015 Feb;41(3):262-75.

Clinical Factors

- Commensal Flora
- Mucus layer
- Intraepithelial Cells
- Dendritic Cells
- Micronutrients (e.g. Vit D & Vit A)
- Macronutrients
- Medications
- CNS/Hormones/Stress

Performance Objectives

Following this activity, successful participants will be able to…

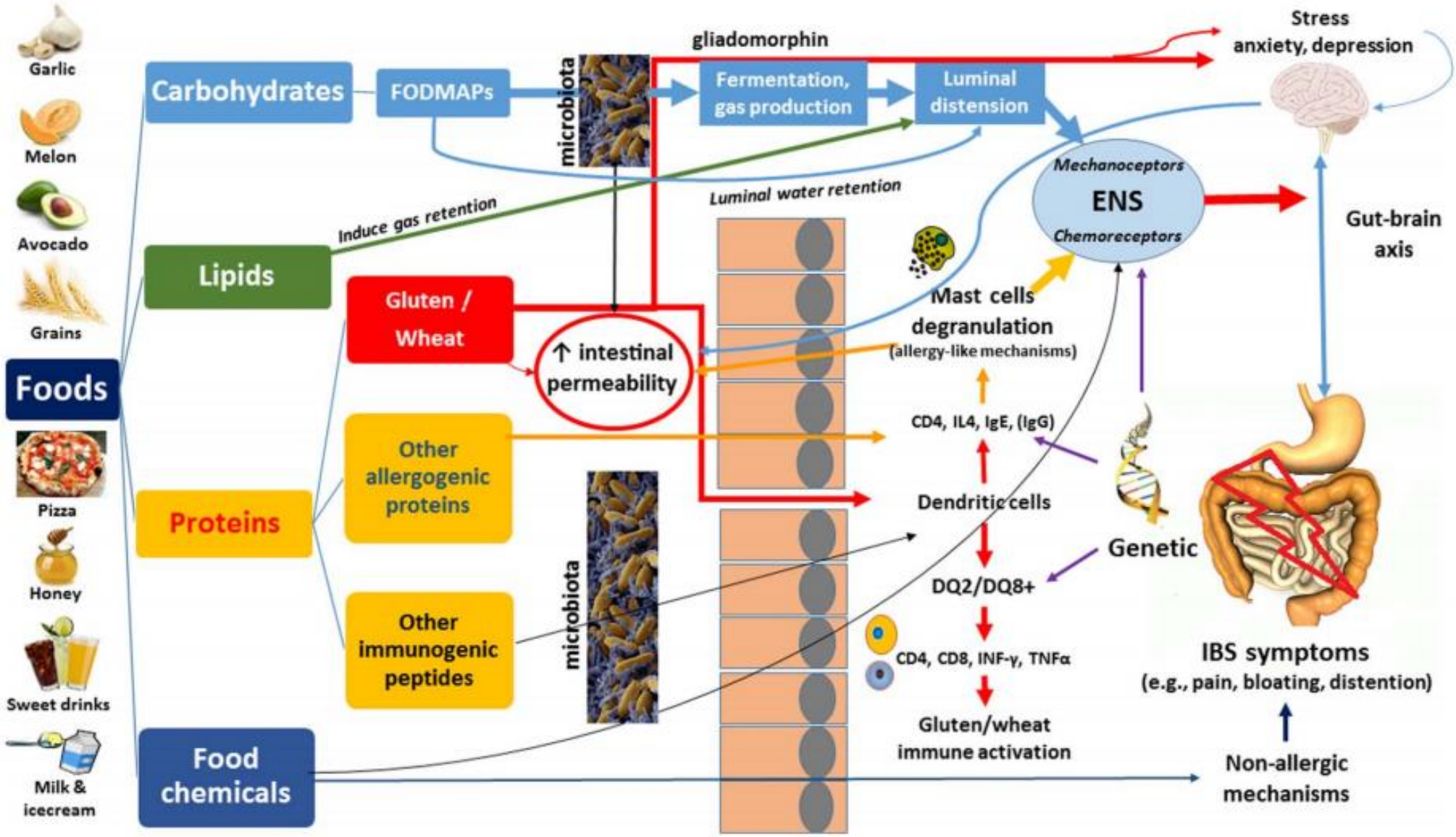
1. Identify the differences between food allergy, food sensitivity, and food intolerance.
2. Differentiate between IgG and IgE food testing, benefits and disadvantages.
3. Recognize the differences between celiac disease, wheat allergy, and non-celiac gluten sensitivity.
4. Outline a rationale for evaluating and testing for food reactions.

What to do on Monday morning?

First, Ask the Question

"Could something in your patients' diet or environment be causing symptoms?"

Could foods be causing a problem?



Reproduced from Gut, De Giorgio, R., Volta, U., Gibson, P.R., Vol. 65, 169-78, copyright 2016, with permission from BMJ Publishing Group Ltd.

The Top Two Problem Foods

Gluten/Wheat

- ✓ Celiac Disease
- ✓ Non Celiac Gluten Sensitivity
- ✓ Wheat allergy

Dairy

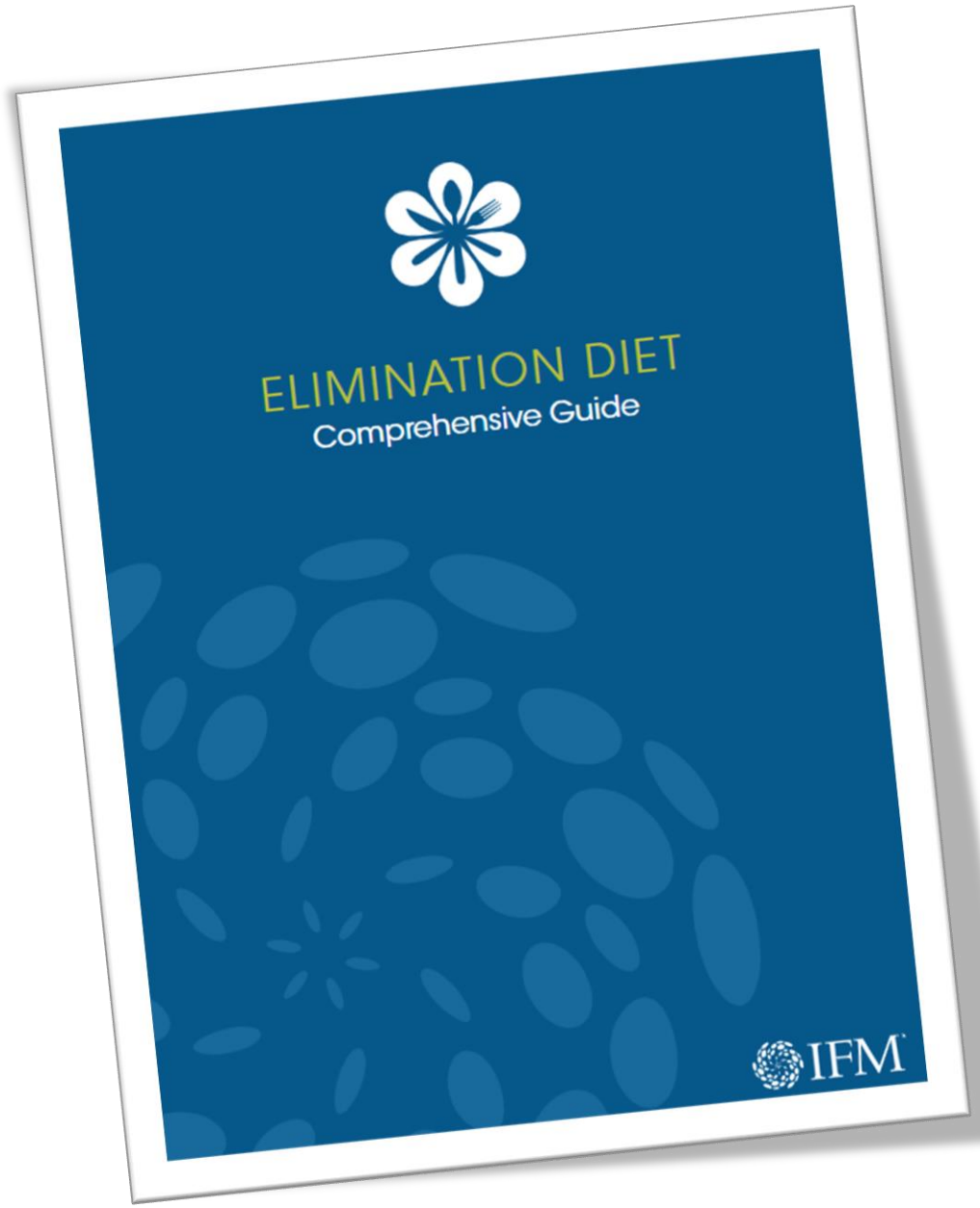
- ✓ Lactose intolerant
- ✓ Casein sensitive
- ✓ Milk allergy

Second, Look for Clues

- Careful history to answer the question…
  - *Do chronic symptoms relate to anything your patient is eating, or anything in the environment?*
- Family history-maternal/paternal
- Pet, travel, or occupational exposure history

Third, Consider Testing or a Dietary Trial

- Elimination diet or specific food avoidance (discussed later)
- Skin testing
- Serum testing
- Other testing important to support healing
- Other testing suggesting immune reaction



A Guide to Eating Gluten-Free

Cutting gluten out of your diet may seem difficult and restrictive. Fortunately, there are many healthy and delicious foods that are naturally gluten-free. These include fruits, vegetables, meat and poultry, fish and seafood, dairy products, beans, legumes, and nuts.

Grains, Flours, and Starches

Many grains and starches are naturally gluten-free, and products made with them (breads, pasta, crackers, etc.) can be incorporated into a gluten-free diet. However, some grains and starches contain gluten and must be avoided by individuals with certain health conditions. Use the following table to help guide your eating and shopping choices while following a gluten-free food plan.

Gluten-Free Grains, Flours Starches	Gluten-Containing Grains, Flours, and Starches
▪ Amaranth ▪ Arrowroot ▪ Bean flours (garbanza, fava, Romano, etc.) ▪ Buckwheat, buckwheat groats (kasha) ▪ Cassava flour ▪ Chia seeds ▪ Corn (maize), cornmeal ▪ Flax, flax meal ▪ Hominy ▪ Manioc flour ▪ Mesquite flour ▪ Millet ▪ Montina flour ▪ Nut flours and meals (almond, coconut, hazelnut, etc.) ▪ Oats (gluten-free)* ▪ Pea flour ▪ Potato flour, potato starch ▪ Quinoa ▪ Rice (all), rice bran ▪ Sago ▪ Sorghum flour ▪ Soy flour ▪ Tapioca flour ▪ Teff ▪ Yucca	▪ Barley ▪ Bulgar (bulgur) ▪ Cereal binding ▪ Chapatti flour (atta) ▪ Couscous ▪ Kinkel ▪ Durum ▪ Einkorn ▪ Emmer ▪ Farina ▪ Farrow ▪ Fu ▪ Gluten, gluten flour ▪ Graham flour ▪ Kamut ▪ Malt (malt beverages, extract, flavoring, syrup, vinegar, etc.) ▪ Matzoh meal ▪ Oats (oat bran, oat syrup)* ▪ Orzo ▪ Rye ▪ Seitan ("wheat meat") ▪ Semolina ▪ Spelt ▪ Textured vegetable protein (typically contains gluten) ▪ Triticale ▪ Wheat, all varieties (bran, germ, starch)

*Gluten-free oats have a similar structure to gluten-containing grains. Also, they may be contaminated with gluten-containing grains during processing. Because of these factors, gluten-free oats may cause negative symptoms in some patients. Those with celiac disease and gluten intolerance should use caution when consuming oats.

Gluten-Free Substitutes

Gluten-free alternatives to typical gluten-containing foods are now widely available in most grocery stores. This makes eating a gluten-free diet less of a hassle. But keep in mind that many products made with gluten-free alternatives include additives and fillers that help mimic the texture of gluten-containing products you're used to eating. Rather than relying on gluten-free convenience foods, it is important to base your diet around naturally gluten-free foods like fruits, vegetables, and other foods listed above.

Fourth, Consider Evaluation and Treatment using the “5R” Framework

- **R**emove
- **R**eplace
- **R**einoculate
- **R**epair
- **R**ebalance

Fifth, Look at Specific Symptom Control

- **Pharmaceutical Bronchodilators:** albuterol, ipratropium
- **Anti-histamines:** Benadryl, Sudafed Zyrtec/Allegra/Claritin
- **Anti-leukotriene:** Singular
- **Anti-inflammatories:** nasal or inhaled steroids
- **Mast Cell Stabilizers:** cromolyn sulfate; ketotifen

Botanical and Nutritional Symptom Control

Natural

- **Bronchodilation:** Magnesium chelate, caffeine
- **Anti-histamine:** Stinging nettles
- **Anti-leukotriene:** Quercetin
- **Prostaglandin Balancing:** Essential fatty acids
- **Anti-inflammatory:** Essential fatty acids, Vitamin D, Aloe vera, Deglycinized licorice, Pycnogenol

Acute-Emergent MUSTs

- **If IgE reaction dominant with positive history**: **Epi-Pen** (at least two)
  - ✓one for home
  - ✓one for car
  - ✓a third if active (one for backpack)
- **If reactive airways: rescue inhaler**
- **If systemic reactions: antihistamine**
- Aggressively utilize allergy specialists if you are at all uncertain or uncomfortable.

Sixth, Consider Reintroduction as Indicated

- **Timing**
  - **IgG-positive foods** – reintroduce 4/6 weeks to three months out, depending on assessment of gut restoration
  - **IgE-positive foods** – reintroduction dependent on reaction age and interventions of immune modulation
- There is 'potential' harm of undernutrition in prolonged dietary modified elimination diets.

The Bottom Line

- Do you think something in your patient's diet or environment is causing their symptoms?
- Decide if you need to test: IgE, IgG, Celiac panel
- Decide if you need to do a therapeutic trial.

Food Reactions: Clinical Takeaways

- Consider if dietary changes for your patient are warranted.
- Look for clinical clues.
- Consider testing (IgE, IgG, celiac panel) or dietary trial.
- Consider evaluation and treatment using 5R.
- Consider specific symptom control with bronchodilators, anti-histamines, anti-leukotrienes, anti-inflammatories and/or mast cell stabilizers.
- Consider careful reintroduction.

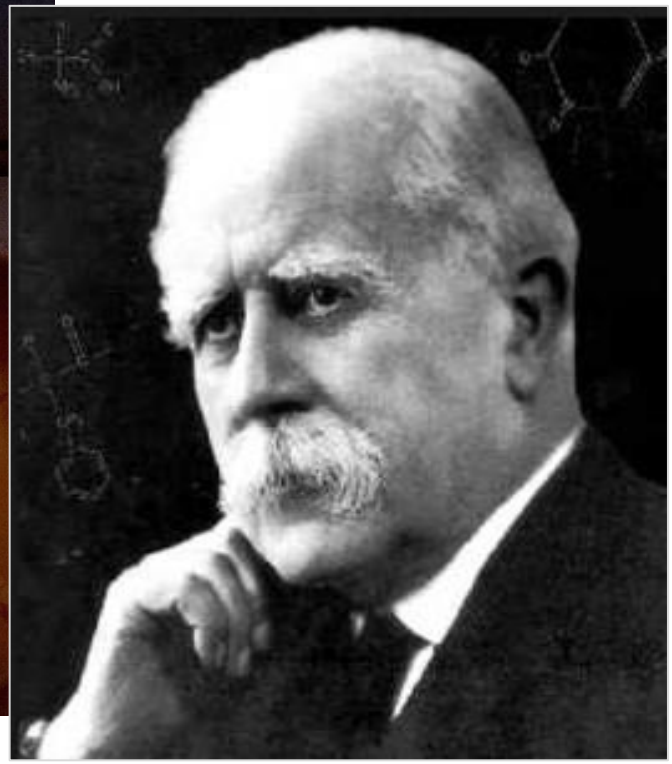
Dr. Sidney Baker's Tack Rules

Rule #1: If you are sitting on a tack, it takes a lot of aspirin to make the pain go away.

Rule #2: If you are sitting on 2 tacks, removing one does not necessarily result in a 50% improvement in symptoms.

"In every case of every malady there are two sets of factors at work in the formation of the morbid picture, namely, internal or constitutional factors inherent in the sufferer and usually inherited from his forebears, and external ones which fire the train."

- Archibald Garrod



1. Photo: Archibald Edward Garrod (from Inborn errors of Metabolism)
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