Gluten Related Disorders

Facts and Fallacies

Webinar

NASPGHAN FOUNDATION
For Children's Digestive Health & Nutrition

In Collaboration with

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

Faculty

Ivor Hill, MB, ChB, MD ,FAAP

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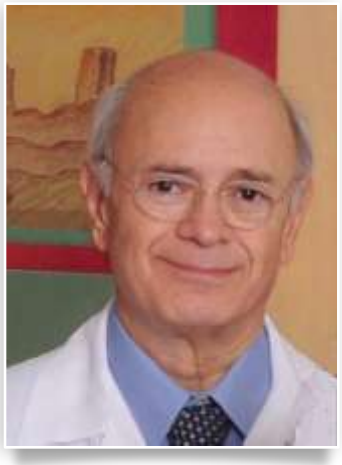

Stefano Guandalini, MD

Pam Cureton, RD ,LDN

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Objectives

- Identify clinical, epidemiological, and diagnostic characteristics of celiac disease, wheat allergy, and gluten sensitivity
- Learn the most cost effective means of testing for gluten related disorders
- List similarities and differences in implementing a gluten free diet for the three different forms of gluten-related disorders

Celiac Disease

Stefano Guandalini, MD

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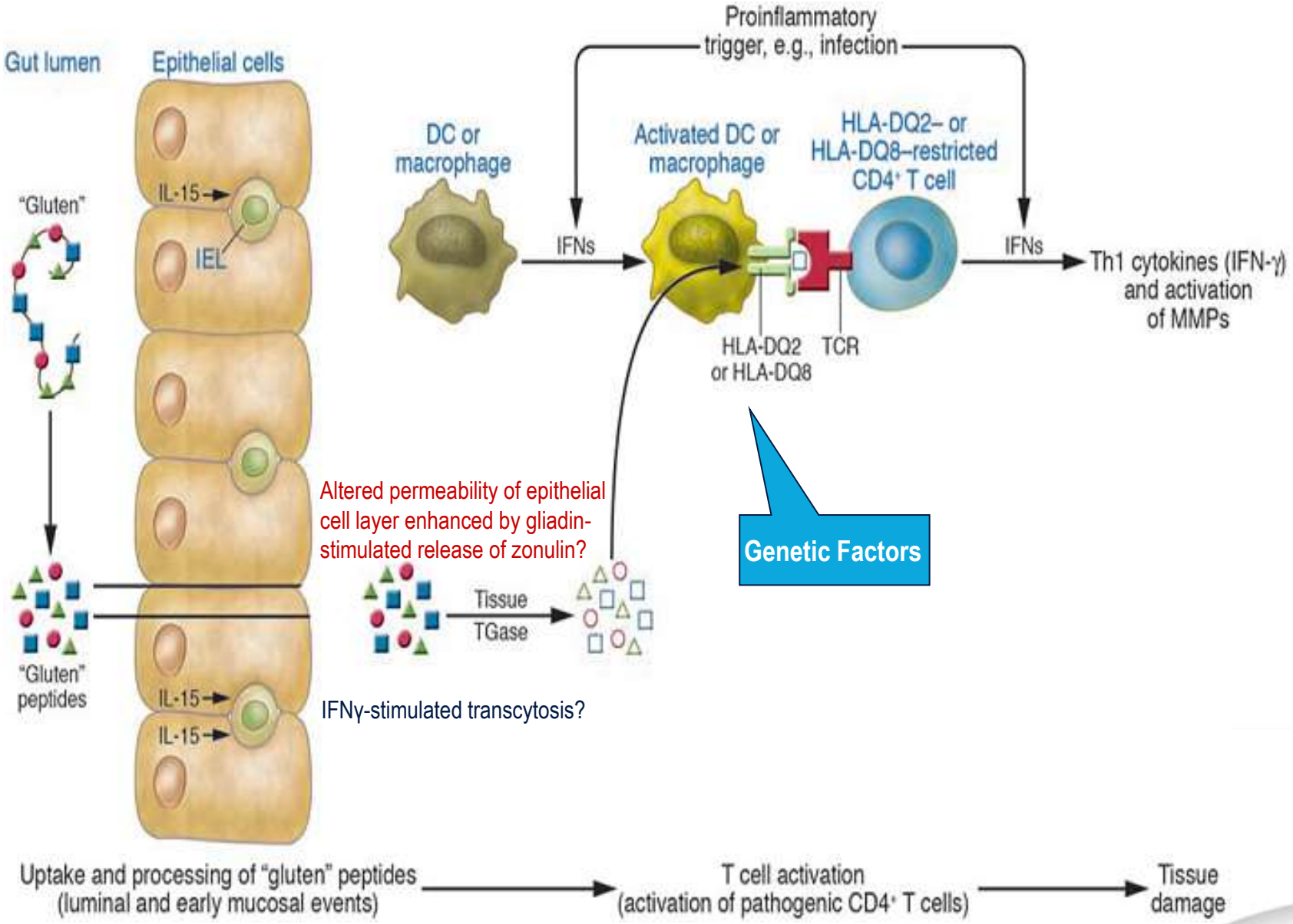
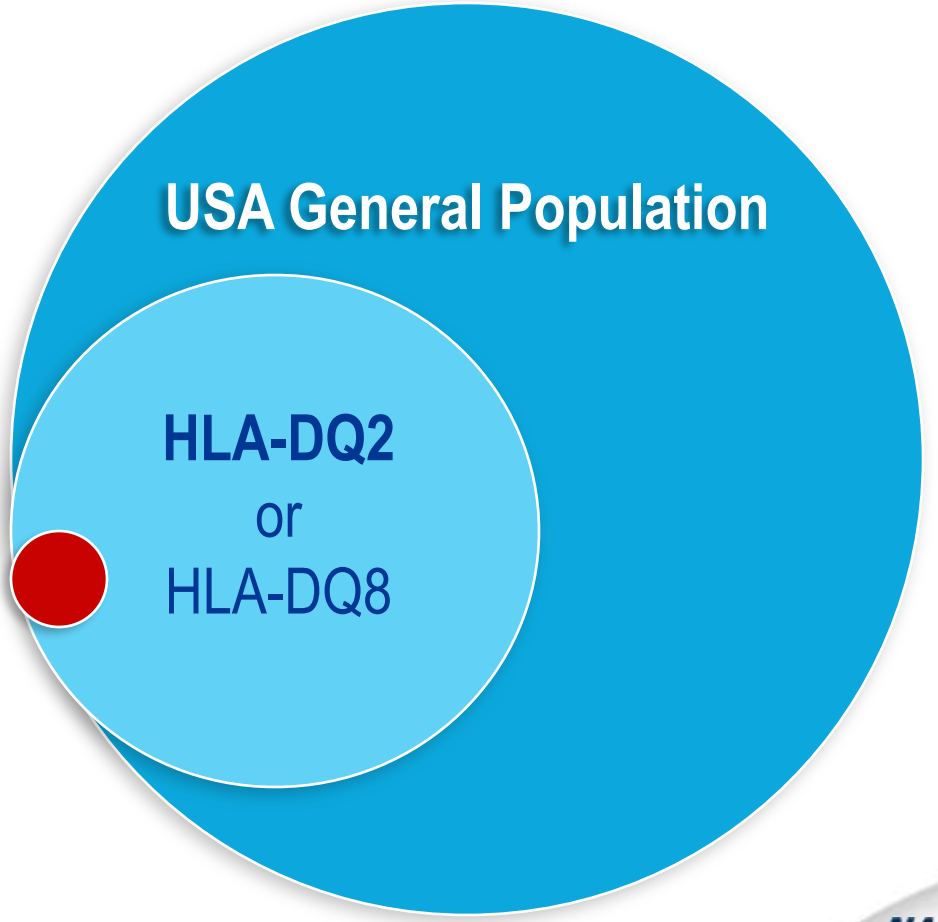
Celiac Disease

- The most common genetically—induced food intolerance worldwide, with a prevalence around 1% (and growing!)
- An autoimmune condition triggered and sustained by the ingestion of gluten (wheat, rye, barley) in genetically predisposed individuals
- Causes an inflammatory damage of the mucosa of the small intestine resulting in a variety of clinical presentations
- Left untreated may lead to complications and increased mortality

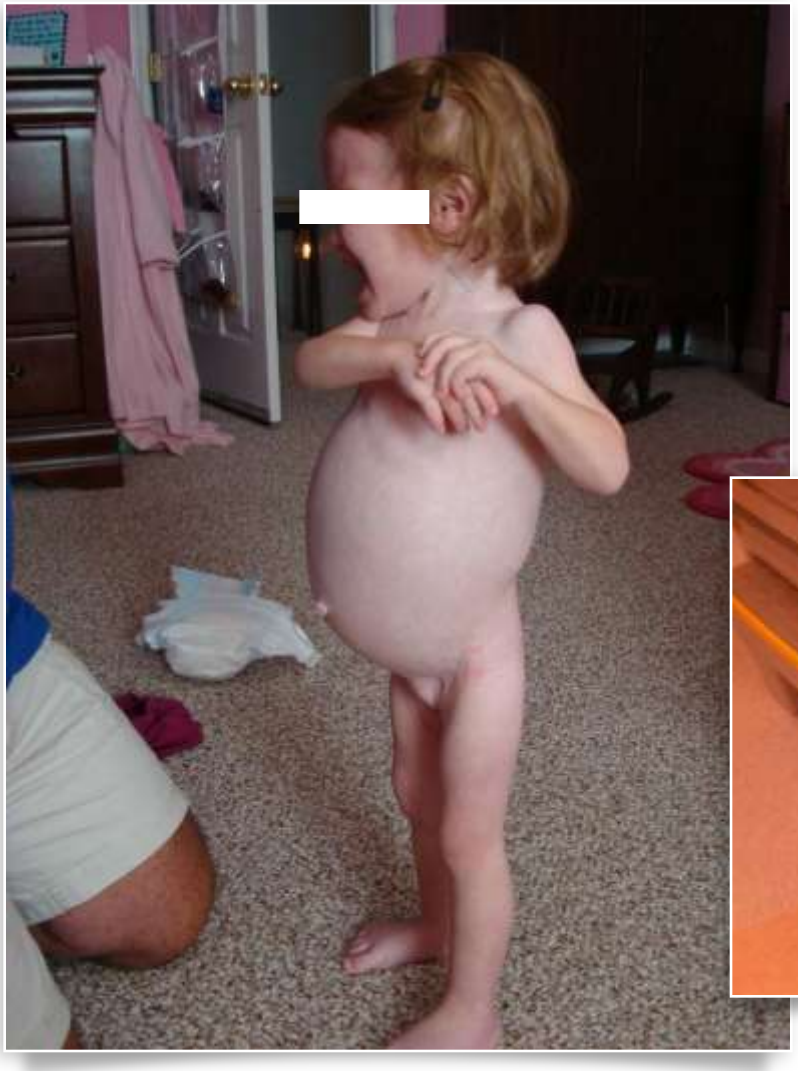


Kagnoff MF. *J Clin Invest.* 2007;117(1):41-9.

HLA-DQ2, DQ8 Are Necessary But Not Sufficient



“Typical” Celiac Children



The "Typical" (GI) Presentation

- Diarrhea
- Vomiting
- Failure to thrive or weight loss
- Abdominal bloating/pain
- Constipation

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The Main Atypical (Extra-GI) Presentations

- Dermatitis Herpetiformis
  and other skin disorders
- Short Stature
  (15% of our pts!)
- Delayed Puberty
- Dental enamel hypoplasia
- Osteopenia
- Iron-deficient anemia resistant to oral Fe
- Liver and biliary tract disease (High transaminases)
- Arthritis
- Neurological problems
  - Headaches
  - Peripheral Neuropathy
  - "Gluten Ataxia"
- Fatigue
- Behavioral changes/Psychiatric Disorders
- Reduced female fertility or pregnancy adverse events

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Polling Question

Patients with potential for Celiac Disease have:

A- a normal biopsy but positive serology
B- a damaged mucosa but have no symptoms
C- a damaged mucosa, positive serology but do not possess neither DQ2 nor DQ8
D- a normal biopsy, negative serology but are first degree relatives of celiac

Current Classification of Celiac Disease Presentations

Type	Serology *(tTG and/or EMA)*	Age affected	Symptoms	Pathology
"Typical"	Positive	Toddler, Young Child	Abdominal Pain, Distention Diarrhea Vomiting Anorexia Constipation	Marsh 2-3
"Atypical"	Positive	Older Child Adult	Mostly extra-intestinal	Marsh 1-3
Silent	Positive	All Ages	None	Marsh 2-3
Potential	Positive	Any age	None Gastrointestinal Extra-intestinal	Marsh 0-1 (may or may not develop enteropathy if left on gluten)
Latent	Positive or Negative	Mostly Adults	None Gastrointestinal Extra-intestinal	Marsh 0-1 (previously had gluten-dependent enteropathy)

Polling Question Results

Potential celiacs are subjects who:

A- have a normal biopsy but positive serology
B- have a damaged mucosa but have no symptoms
C- have a damaged mucosa, positive serology but do not possess neither DQ2 nor DQ8
D- have normal biopsy, negative serology but are first degree relatives of celiac.

Celiac Disease Is More Frequent In:

- **Autoimmune disorders**
  - Type 1 diabetes
  - Autoimmune Thyroiditis…
- **Relatives of a celiac**
- **Genetic syndromes**
  - Down
  - Turner
  - Williams

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Who Should Be Screened?

- **Subjects with suggestive GI complaints**
  - Diarrhea (±FTT)
  - Vomiting
  - Anorexia
  - Abdominal distention
  - Recurrent abdominal pain
  - Constipation
- **Subjects with extra-intestinal manifestations**
  - Dental enamel dysplasia
  - Short stature
  - High Transaminases
  - Fe-deficient anemia (unexplained)
  - Fatigue
  - Arthritis….

Who Should Be Screened?

Subjects who may be asymptomatic but are at increased risk of CD

- Autoimmune conditions
  - Type 1 Diabetes
  - Autoimmune Thyroiditis…
- First-degree relatives of celiac patients
- Down syndrome
- Turner syndrome
- William syndrome

Wheat Allergy

Joseph Levy, MD

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IgE-Mediated Wheat Allergy

- Food allergy, by definition, depends on an underlying immune-mediated process for its occurrence
- Food allergy is most common in the first year of life, decreasing in adolescence and adulthood
- Wheat is among the 10 most common allergens responsible for food allergy

Wang et al. *J Clin Invest*. 2011;121(3):827-35.

Venter et al. *Allergy.* 2008;63(3):354-9.

Inomata et al. *Curr Opin Allergy Clin Immunol.* 2009;9:238-243.

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Food Allergy

- Prevalence rates in the first 3 years of life range 3-8%
- Most common allergens are milk, egg, corn and peanuts
- Discrepancy between parent's reports of suspected allergy and objective tests
- Clinical manifestations include: abdominal pain, nausea, vomiting, diarrhea, skin rashes, rhinitis, conjunctivitis

Wang et al. *J Clin Invest*. 2011;121(3):827-35.
Venter et al. *Allergy.* 2008;63(3):354-9.
Inomata et al. *Curr Opin Allergy Clin Immunol.* 2009;9:238-243

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Eosinophilic Esophagitis

- Increasing incidence world-wide
- Symptoms overlap GERD
- Suspect in cases of feeding aversion, dysphagia, food impaction
- Diagnosis made by endoscopy, biopsies
- Treatment involves AA-based formulas, elimination diets, topical steroids
- Complications include esophageal strictures, perforation
- Instigated by several food allergens including gluten

Liacouras et al. ***J Allergy Clin Immun.*** **2011 Jul; 128(1): 3-20.**

Baker's Asthma

- One of most common asthma associated to specific occupation
- Caused by inhalation of cereal proteins (rye and wheat most common) and/or potential contaminants aerosolized during milling or baking process
- Symptoms include: cough, wheezing chronic congestion, rhinitis, conjunctivitis

Brant. *Curr Opin Allergy Clin Immunol.* 2007;7:152-155.

Polling Question

Are you aware of the clinical entity wheat-dependent, exercise-induced anaphylaxis?

- A. Yes
- B. No

Wheat-dependent, Exercise-induced Anaphylaxis

- High index of suspicion needed for diagnosis
- Ingestion of wheat is a pre-condition, but clinical picture does not manifest unless subject engages in exercise
- Intensity of exercise can be as mild as game of ping-pong or walking up hill
- Exercising within 2 hours carries high risk of unchaining immune reactions leading to anaphylaxis

Morita et al. ***J Dermatol Sci*****. 2007; 47(2):109-17.**
Shadick et al. ***J Allergy Clin Immunol.*** **1999;104(1):123-7.**

Polling Question Results

Are you aware of the clinical entity wheat-dependent, exercise-induced anaphylaxis?

- A. Yes
- B. No

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Wheat-dependent, Exercise-induced Anaphylaxis

- Multiple factors play a role in causing the severe reaction:
  - Dose of protein antigen
  - Intensity of exercise
  - Timing of the exercise
  - Individual factors: menstrual cycle, fatigue, etc
  - Aggravated by aspirin
- Caution: avoid exercise for 4-5 hrs post- prandially

Morita et al. ***J Dermatol Sci*****. 2007; 47(2):109-17.**
Shadick et al. ***J Allergy Clin Immunol.*** **1999;104(1):123-7.**

Gluten Related Disorders Webinar

Non-Celiac Gluten Sensitivity

Alessio Fasano, MD

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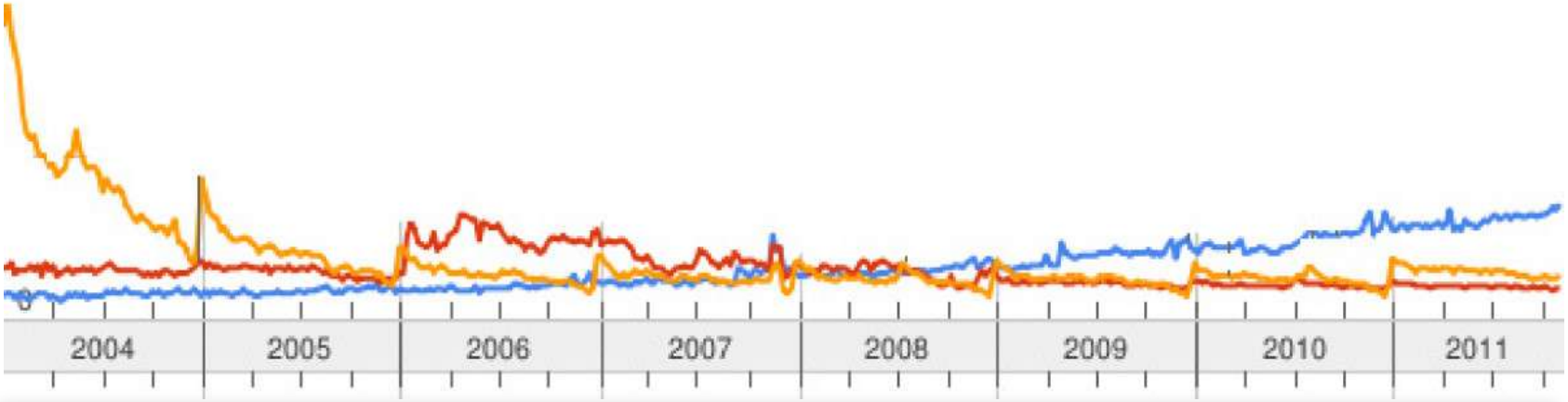
Gluten Free Market

Low Carb Diet Fat Free Diet Gluten Free Diet



For the American general population, adopting a gluten-free diet is becoming an increasingly popular solution. The market for gluten-free food and beverage products grew at a compound annual growth rate of 28% from 2004 to 2008, to finish with almost $4.2 billion in retail sales last year. By 2017 the market is expected to reach about $6.4 billion in sales.

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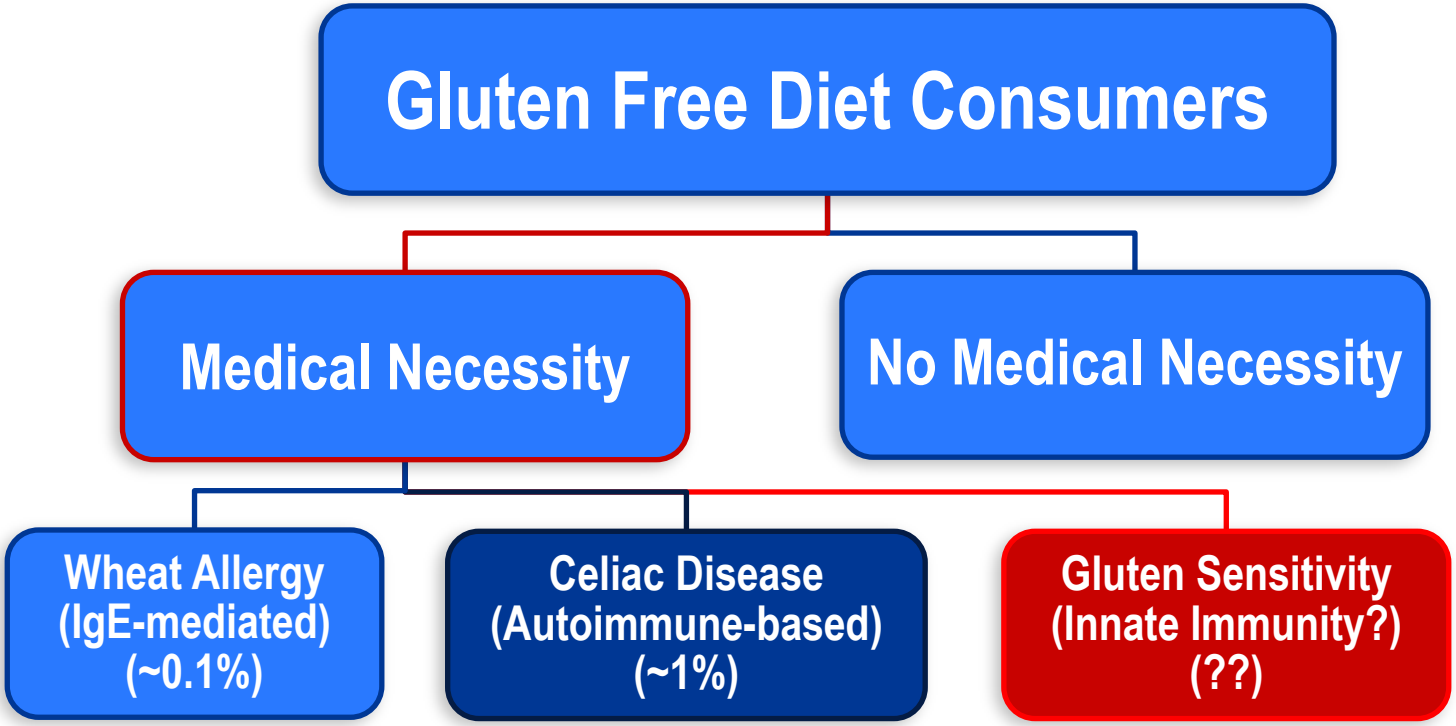
The Gluten Free Diet: Not Only Celiac Disease



Gluten Sensitivity: Definition

Cases of gluten reaction in which both allergic and autoimmune mechanisms have been ruled out (diagnosis by exclusion criteria)

- Negative immuno-allergy tests to wheat;
- Negative CD serology (EMA and/or tTG) and in which IgA deficiency has been ruled out;
- Negative duodenal histopathology;
- Presence of biomarkers of gluten immune-reaction (AGA+);
- Presence of clinical symptoms that can overlap with CD or wheat allergy symptomatology;
- Resolution of the symptoms following implementation of a GFD (double blind)

Sapone et al. *BMC Medicine* 2012, 10:13.

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Gluten Sensitivity: What Kind Of Symptoms?

Symptoms:

- Abdominal pain: 68%
- Eczema and/or rash: 40%
- Headache: 35%
- “Foggy mind”: 34%
- Fatigue: 33%
- Diarrhea: 33%
- Depression: 22%
- Anemia: 20%
- Numbness legs/arms/fingers: 20%
- Joint pain: 11%

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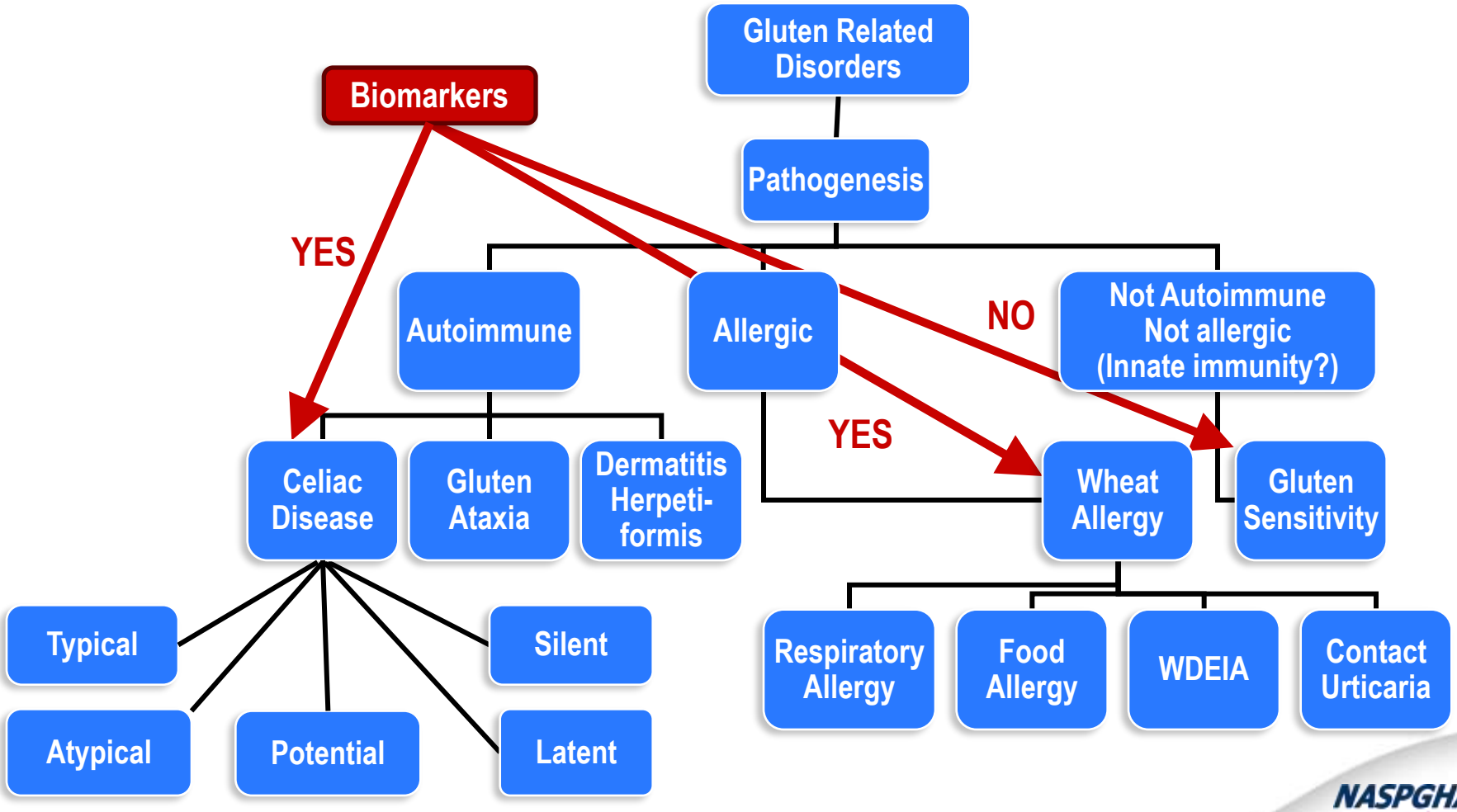
Proposed New Classification of Gluten Related Disorders



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Diagnosis of Gluten Sensitivity

Take Home Messages:

- Gluten Sensitivity is not rare;
- Gluten Sensitivity cannot be distinguished from Celiac Disease purely on the clinical basis;
- Gluten Sensitivity can present with vague, non-specific symptoms;
- A gluten free diet can be considered only when other forms of gluten reactions and other causes of pt's symptoms have been ruled out;
- Listen to your patient!!!

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Diagnosis of Celiac Disease vs. Wheat Allergy vs. Non Celiac Gluten Sensitivity

Ivor Hill MD

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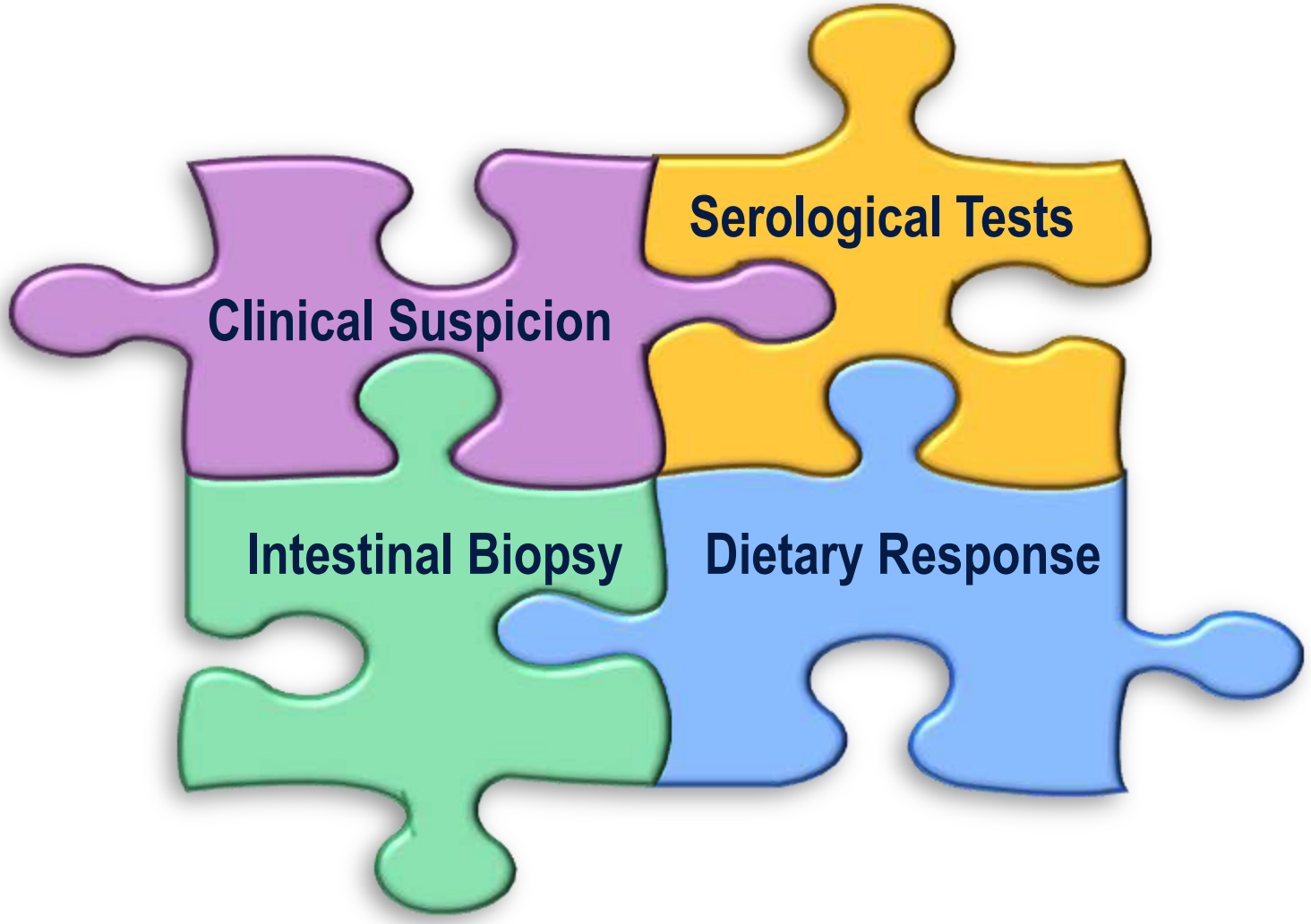
Celiac Diagnosis



Rubio-Tapia et al. *J Gastroenterol*. 2013; 108:656–676; doi:10.1038/ajg.2013.79; published online 23 April 2013. Hill et al. *J Pediatr Gastroenterol Nutr.* 2005;40:1-19. Husby et al. *J Pediatr Gastroenterol Nutr.* 2012;54:136-160.AGA Institute. *Gastroenterology.* 2006;131:1977-1980.

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Serological Tests

- Antigliadin –IgA & IgG
- Endomysium – IgA (IgG)
- Tissue Transglutaminase – IgA (IgG)
- Deamidated Gliadin Peptides –IgA & IgG

Rubio-Tapia et al. *J Gastroenterol*. 2013; 108:656–676; doi:10.1038/ajg.2013.79; published online 23 April 2013. Hill et al. J *Pediatr Gastroenterol Nutr*. 2005;40:1-19. Husby et al. *J Pediatr Gastroenterol Nutr.* 2012;54:136-160.AGA Institute. *Gastroenterology.* 2006;131:1977-1980.

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Polling Question

When testing for celiac disease, do you request

- A. Celiac panel
- B. Specific serological test

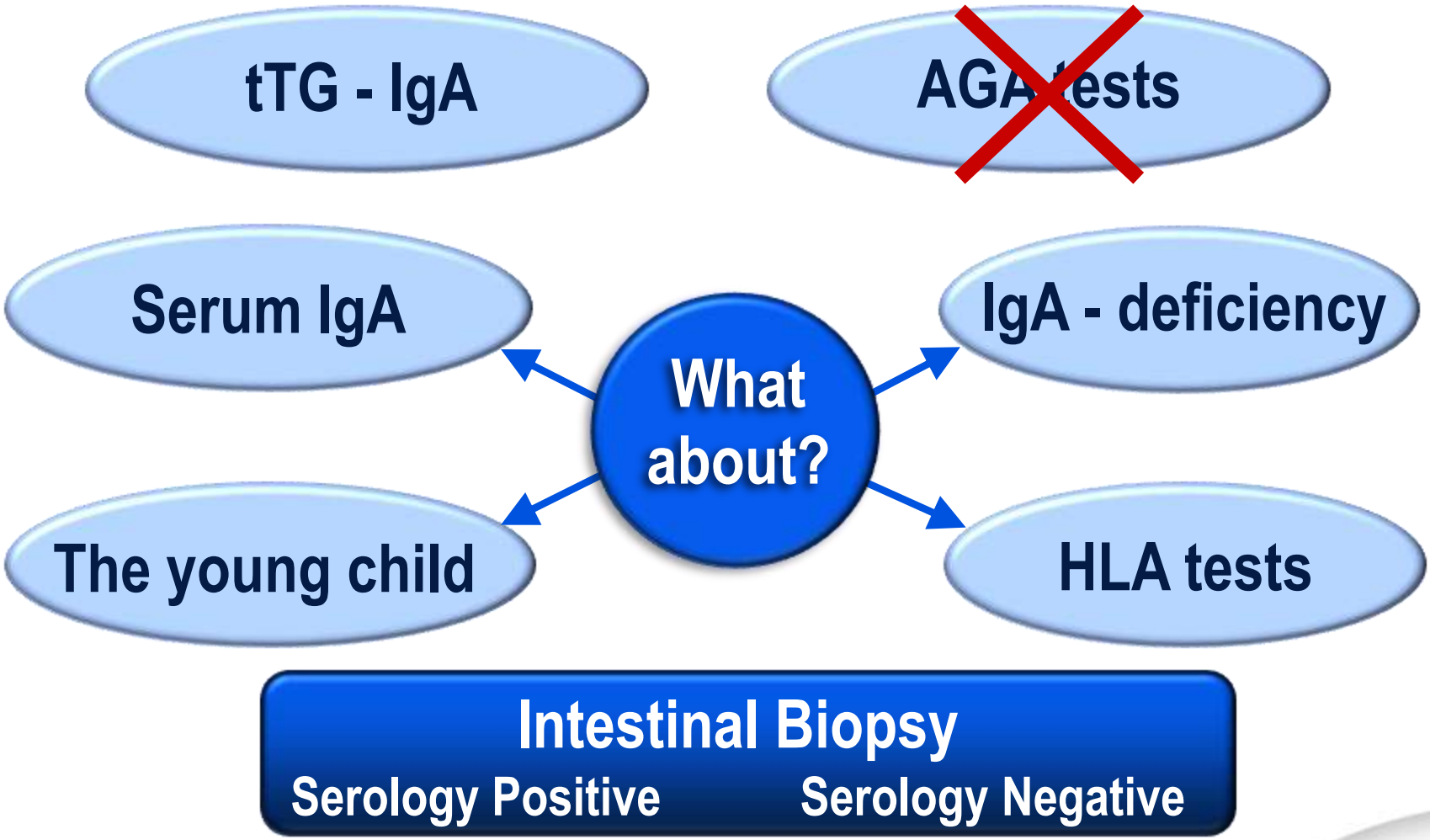
How to Test?

tTG - IgA

~~AGA tests~~

Rubio-Tapia et al. *J Gastroenterol*. 2013; 108:656–676; doi:10.1038/ajg.2013.79; published online 23 April 2013. Hill et al. J *Pediatr Gastroenterol Nutr*. 2005;40:1-19. Husby et al. *J Pediatr Gastroenterol Nutr.* 2012;54:136-160.AGA Institute. *Gastroenterology.* 2006;131:1977-1980.

How to Test?



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Polling Question Results

When testing for celiac disease, do you request

- A. Celiac panel
- B. Specific serological test

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Who to Test?

- Symptomatic
  - Typical (gastrointestinal) symptoms
  - Atypical (non gastrointestinal) symptoms
- Asymptomatic at-risk
  - Relatives
  - Autoimmune Disorders
  - Non Autoimmune Disorders

Rubio-Tapia et al. *J Gastroenterol*. 2013; 108:656–676; doi:10.1038/ajg.2013.79; published online 23 April 2013. Hill et al. J *Pediatr Gastroenterol Nutr*. 2005;40:1-19. Husby et al. *J Pediatr Gastroenterol Nutr.* 2012;54:136-160.AGA Institute. *Gastroenterology.* 2006;131:1977-1980.

Polling Question

In a patient with symptoms of celiac disease but negative serological tests, would you advise a trial of a gluten free diet?

- A. Yes
- B. No

Gluten Related Disorders

- Wheat Allergy
  - skin prick tests
  - allergen specific IgE antibodies
  - oral wheat challenge
- Non Celiac Gluten sensitivity
  - negative tests for celiac disease
  - negative tests for wheat allergy
  - DBPCFC

Rubio-Tapia et al. *J Gastroenterol*. 2013; 108:656–676; doi:10.1038/ajg.2013.79; published online 23 April 2013. Hill et al. J *Pediatr Gastroenterol Nutr*. 2005;40:1-19. Husby et al. *J Pediatr Gastroenterol Nutr.* 2012;54:136-160.AGA Institute. *Gastroenterology.* 2006;131:1977-1980.

Polling Question Results

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- A. Yes
- B. No

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Differential Diagnosis Between CD, GS, & WA

	Celiac Disease	Gluten Sensitivity	Wheat Allergy
Time interval between gluten exposure and onset of symptoms	Weeks-Years	Hours-Days	Minutes-Hours
Pathogenesis	Autoimmunity (Innate+ Adaptive Immunity)	Immunity? (Innate Immunity?)	Allergic Immune Response
HLA	HLA DQ2/8 restricted (~97% positive cases)	Not-HLA DQ2/8 restricted (50% DQ2/8 positive cases)	Not-HLA DQ2/8 restricted (35-40% positive cases as in the general population)
Auto-antibodies	Almost always present	Always absent	Always absent
Enteropathy	Almost always present	Always absent (slight increase in IEL)	Always absent (eosinophils in the lamina propria)
Symptoms	Both intestinal and extra-intestinal (not distinguishable from GS and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and WA with GI symptoms)	Both intestinal and extra-intestinal (not distinguishable from CD and GS when presenting with GI symptoms)
Complications	Co-morbidities Long term complications	Absence of co-morbidities and long term complications (long follow up studies needed to confirm it)	Absence of co-morbidities. Short-term complications (including anaphylaxis)

Fasano et al. *N Engl J Med*. 2012;367:2419-26.

Diagnosis - Summary

Celiac Disease
- Clinical indication
- Serological test
- Intestinal biopsy
- Response to GFD

Wheat Allergy
- Clinical indication
- Skin prick tests
- Allergen specific IgE
- Oral food challenge

Non CD Gluten Sensitivity
- Clinical indication
- Negative CD serology
- Negative allergy testing
- DBPCFC

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Treatment

Pam Cureton, RD,LDN

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Gluten Free Diet: Overview

- Celiac Disease
  - Only treatment: avoid gluten containing grains, wheat, rye, barley and cross contaminated oats
  - Strict adherence
  - Life long
- Non Celiac Gluten Sensitivity
  - Only treatment
  - Strict adherence ?
  - Life long ?

Gluten Free Food Labeling

- In 2006, the Food Allergen Labeling and Consumer Protection Act (FALCPA) requires that companies identify in “plain English” the eight most prevalent food allergens: egg, fish, milk, peanuts, shell fish, soybean, tree nuts and WHEAT
- Identified by listing in ( ) next to ingredient i.e.: Ingredients: Enriched flour (wheat flour), or listed in the “Contains” statement i.e.: Contains Wheat, Milk, Egg, and Soy
- FALCPA does not include:
  - Barley (malt), rye or oat (but not “hidden” ingredients)
  - Meat products covered by USDA (although 90% of manufactures follow FALCPA guidelines)
  - FALCPA covers ingredients not the contamination of the product
  - Over the counter or prescription medications (www.glutenfreedrugs.com)
  - Alcoholic beverages (Distilled beverages are gluten free)

http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/default.htm.

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FDA Proposed GF Labeling Rule

A product may be defined as "Gluten Free" if all of the following conditions are met:

1. Will not contain a prohibited grain, (i.e. wheat, barley, rye, and crosses).
2. Will not contain an ingredient derived from a prohibited grain that has not been processed to remove gluten, (i.e. hydrolyzed wheat protein, and barley malt).
3. If the food contains an ingredient derived from a prohibited grain that has been processed to remove gluten, such as wheat starch or modified food starch, use of that ingredient in the food product may not result in the food product containing 20 parts per million or more gluten.
4. The food product contains less than 20 parts per million gluten

The Food and Drug Administration at the end of February 2013 sent the rules to the White House Office of Management and Budget.

http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Allergens/default.htm.

Nutritional Aspects of the GFD

- The GFD can be missing important nutrients needed for optimal health and wellness
  - Lacks fiber
  - Lacks iron
  - Lacks B vitamins- folate, niacin, B12
  - Lacks calcium
  - Phosphorous
  - Zinc
- Nutrition deficiencies lead to:
  - Iron deficiency anemia
  - Reduced bone mineral density
  - Constipation
- Many gluten free foods are not enriched or fortified as their wheat counterpart
- Weight gain on GFD due to high fat, sugar and calorie content

http://www.adaevidencelibrary.com. Saturni et al. *Nutrients.* 2010; 2(1): 16–34.

Nutritional Counseling

- Nutritional assessment
- Physical findings
- Patient's history
  - Personal, medical and health history
  - Family medical health history
  - Social history

http://www.adaevidencelibrary.com. Saturni et al. *Nutrients.* 2010; 2(1): 16–34.

Quality of Life on the GFD

- Social and economic aspect
- Availability of GF foods
- Religious considerations
- Meals away for home
  - Restaurants
  - School
  - hospitals
- Barriers to compliance
  - Diet too restrictive
  - Uncomfortable in social setting
  - Too difficult
  - Tasteless
  - Too expensive

Green et al. *Am J Gastroenterol. 2001;96:126-131.*

Summary

- Gluten can trigger celiac and other immune-mediated disorders (wheat allergy and non-celiac gluten sensitivity)
- The three forms of gluten related disorders can clinically overlap and cannot be distinguished on the basis of their clinical presentation;
- The prevalence of wheat allergy/celiac disease is well established, but the magnitude of non-celiac gluten sensitivity remains un-established. (lack of validated biomarkers)

Summary *Cont'd*

- The diagnosis of wheat allergy and celiac disease is based on specific screening tests, while the diagnosis of non-celiac gluten sensitivity is currently based on exclusion criteria.
- A gluten free diet is the cornerstone of treatment of the three gluten related disorders, but the way the diet is implemented differs greatly from one form to another.
- It is imperative to establish which form of gluten reaction affects the patient before implementing a gluten free diet.

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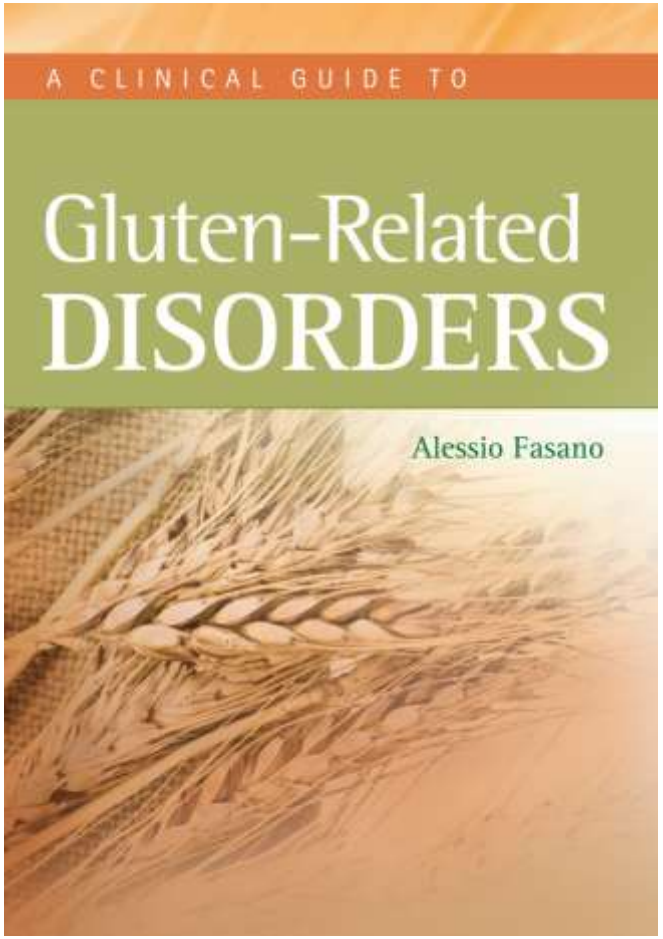
2013
CHICAGO
Attend the
15th International
Celiac Disease
Symposium
September 22–25, 2013
ICDS2013.ORG
THE UNIVERSITY OF CHICAGO
CELIAC
DISEASE CENTER

Clinical Guide to Gluten Related Disorders
published by Wolters Kluwer



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Questions and Answers

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Gluten Related Disorders

Facts and Fallacies

Webinar

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