

**Navigating The Spectrum of Gluten Related Disorders:
Examining 3 Cases: Celiac Disease,
Gluten Sensitivity, Wheat Allergy**

Presented by Alessio Fasano, MD,
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Complimentary 1-Credit Continuing Education Webinar

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Disclosures

Both presenters have certified that no conflict of interest exists for this program.



Alessio Fasano, MD
 Alessio Fasano reports the following relevant disclosure: he is a stock shareholder of Alba Therapeutics.



Pam Cureton, RD, LDN
 Pam Cureton reports the following relevant disclosure: she is a brand ambassador for Dr. Schär.



Learning Objectives

Suggested CDR Learning Codes:

1. Identify clinical, epidemiological, and diagnostic characteristics of celiac disease, wheat allergy, and gluten sensitivity.
2. Identify and treat non-responsive celiac disease (NRCD).
3. List similarities and differences in implementing a gluten free diet for the three different forms of gluten-related disorders.



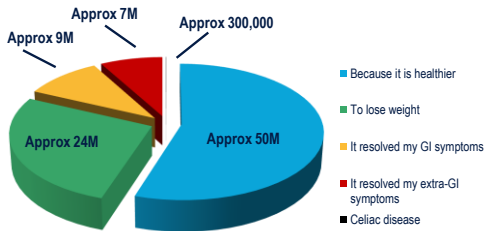
Gluten Free Market



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 percent from 2004 to 2008, to finish with almost \$2.6 billion in retail sales last year. By 2017 the market is expected to reach about \$ 6.1 billion in sales.



Why People in the US Embrace a GFD



Based on internet interview users age 18y+ who eats GF food



Celiac Disease



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.



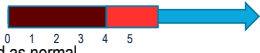
Celiac Disease as a Unique Model of Autoimmunity

- The only autoimmune disease in which specific MHC class II HLA (DQ2 and/or DQ8) are present in >95% of patients;
- The auto-antigen (tissue Transglutaminase) is known;
- The environmental trigger (gluten) is known;
- Elimination of the environmental trigger leads to a complete resolution of the autoimmune process that can be re-ignited following re-exposure to gluten.



Description of the Case

- Pt was referred to a GI doctor who performed a colonoscopy that was reported as normal.
- The following year she experienced a 30 pound weight loss and was referred back to GI doctor who performed an upper endoscopy that revealed typical features of celiac disease. The diagnosis was confirmed by serology tests. She was placed on a GFD.
- Following implementation of the GFD, her symptoms improved but did not resolve. CD serology test remained positive and an endoscopy repeated after 12 months showed improvement but not resolution of the enteropathy.
- She was referred to a dietician that confirmed that the Pt was compliant with the diet.



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Poll Question #1

Celiac disease patients that do not respond to the gluten free diet despite good compliance to the GFD are always affected by refractory celiac disease.

- True
- False



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Poll Question #1 Results

Celiac disease patients that do not respond to the gluten free diet despite good compliance to the GFD is always affected by refractory celiac disease.

- True
- False



Treatment



“Non-responsive” Celiac Disease

Persistent or recurrent signs/symptoms despite confirmed & treated CD occurs in ~10% of patients (range 10 – 30%).

- **Gluten Exposure 36 – 51%**
- IBS 18%
- Refractory 2%
 - Type 1 benign prognosis , more common
 - Type 2 refractory very rare, associated with T-cell lymphoma
- Di/monosaccharidase Deficiency 9%
- Microscopic Colitis 7%
- Small Intestinal Bacterial Overgrowth 6%
- Eating Disorder 6%
- Other 8% Peptic ulcer disease, Crohn’s disease, Food allergy, Gastroparesis

Leffler et al. *Clin Gastroenterol Hepatol.* 2007;5:445–450.



Gluten Exposure

- Recheck labels of favorite everyday foods as ingredients can change. Check label of foods not labeled gluten free for ingredients.
- Look for sources of contamination at home and away from home.
 - Toaster, condiment containers, colanders
 - Meal prep: making gluten free along side gluten containing foods
 - Eating at restaurants, school, daycare or social events



Approach to our patient with Non-Responsive CD

- Assessment of adherence to the diet
- Repeat biopsy and serum testing
- Marsh 3
 - IEL population shown to be polyclonal
- Continued to be symptomatic
- Placed on the Gluten Contamination Elimination Diet (GCED or Fasano Diet)



Gluten Contamination Elimination Diet "Fasano Diet"

- Modified gluten free diet of whole unprocessed foods.
- Typically 3-6 month duration.
- Aims to eliminate any source of gluten contamination in an already strict diet.



Products Allowed/Not Allowed in the GCED

	Allowed	No Allowed
Grains	Plain, unflavored, brown and white rice	Millet, sorghum, buckwheat or other inherently gluten-free grains, seeds, or flours
Fruits/Vegetables	All fresh fruits/vegetables	Frozen, canned or dried
Proteins	Fresh Meats Eggs Dried Beans Unseasoned Nuts in the shell	Frozen, canned or dried Lunch meals Ham, bacon Other processed, self-basted or cured meat products
Dairy	Butter, Yogurt (unflavored), milk (unflavored) aged cheeses	Seasoned or flavored dairy products Processed cheeses Flavored and malt vinegars
Condiments	Oils, vinegar, honey, salt	
Beverages	100% fruit/vegetable Gluten-free supplemental formulas Gatorade milk, water	

Hollon et al. BMC Gastroenterology. 2013;13:(1)1-9.



Guide to GCED

- Handbook
- G-free multivitamin
- Prescription medication is continued.
- Provided w/ sample menus
- Food diary
- Contact information for the dietitian is provided
- RTC in 3 months for repeat celiac serology and symptom re-evaluation



GCED Success

Response to the GCED is defined as being

- Asymptomatic after the diet, with normal villous architecture (Marsh 0-2) on repeat biopsy, if performed.
- Presence or absence of celiac auto-antibodies is not used in the definition for NRCD or RCD. Nor is normalization of celiac serology, used as a criterion for response to the GCED.

Hollon et al. BMC Gastroenterology. 2013;13(1):1-9.



Re-Introduction to GFD

- Slow introduction of gluten free items from trusted brands and grains.
- Pt developed joint pains but no abdominal symptoms.
- Underwent repeat endoscopy to ensure tolerance to GFD.



RESEARCH ARTICLE Open Access

Trace gluten contamination may play a role in mucosal and clinical recovery in a subgroup of diet-adherent non-responsive celiac disease patients

Justin B Holbro^{1,2}, Pamela A Cuentos³, Margaret L Martin⁴, Elaine L Leonard Pappas⁵ and Alessio Fasano⁶

Abstract
 Background: Patients with persistent symptoms and/or villous atrophy despite strict adherence to a gluten-free diet (GFD) have non-responsive celiac disease (NRCD). A subset of these patients has refractory celiac disease (RCD), yet some NRCD patients may simply be reacting to gluten cross-contamination. Here we describe the effects of a 3-6 month diet of whole, unprocessed foods, termed the Gluten Contamination Elimination Diet (GCEd), on NRCD. We aim to demonstrate that this diet includes the majority of patients thought to have RCD (type 1 NRCD).
 Methods: We reviewed the results of all GFD-adherent NRCD patients listed for in-person celiac disease from 2005-2011 who were documented to have started the GCEd. Response to the GCEd was defined as being asymptomatic after the diet with normal villous architecture on repeat biopsy if performed.
 Results: Prior to the GCEd, all patients were interviewed by an experienced dietitian and six sources of hidden gluten ingestion were identified. 17 patients completed the GCEd. 15 were female (88%). Median age at start of the GCEd was 42 years (range 6-73). Fourteen patients (82%) responded to the GCEd. Six patients met criteria for RCD (type 1) and 8 (48%) were asymptomatic after the GCEd and no longer require RCD status. Of the 14 patients who responded to the GCEd, 11 (79%) had biopsy-proven a histological or serologic remission of celiac disease. Combining the GCEd may be an effective therapeutic option for GFD-adherent NRCD patients. Response to this diet identifies a subgroup of patients previously classified as RCD, that is not truly refractory to dietary treatment. Preparing an accurate diagnosis of RCD avoids immunotherapy. Most patients are able to return to a traditional GFD without return of symptoms.
 Keywords: Celiac disease, Refractory celiac disease, Refractory sprue, Non-responsive celiac disease, Gluten-free diet

Background
 Celiac disease (CD) is an immune-mediated small intestinal enteropathy triggered by the ingestion of gluten in the genetically susceptible, with prevalence in the United States of nearly 1% (1). While the histopathologic disease entity classically only CD symptoms, including diarrhea, malabsorption and weight loss, more contemporary patients are asymptomatic or present with extraintestinal manifestations to include iron-deficiency anemia, osteoporosis, osteopenia, depression and autoimmune disease (osteosarcoma, (2)). The prevalence of Refractory CD (RCD) is low (3) but the GCEd, with the vast majority of patients demonstrating histologic improvement within the first few weeks to months after diet initiation (4). However, there is a subset of patients who have no clinical response to the diet (NRCD) (5) that may either not be responsive to the GFD or have a recurrence/relapse of symptoms despite being on a GFD.
 By the most common cause of non-response to failure to adhere to the prescribed GFD, either inadvertent or intentional, they highlighting the importance of a full list of other attention is available at the end of the article.
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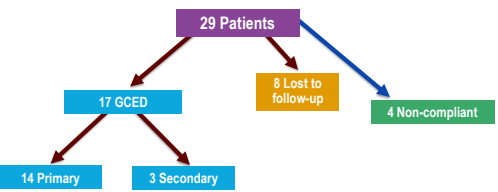


Methods

- Retrospective chart review:2005-2011.
- Of the 1288 patients seen 29 (2.3%) met criteria for NRCD.
- NRCD: Biopsy proven CD with persistence or relapse of symptoms and/or villous atrophy despite a GFD>12 months.



Methods



Results

- Response rate to the GCED was 82%.
 - Success: Asymptomatic after the diet, with normal villous architecture (Marsh 0-2) on repeat biopsy, if performed.
- 5 of 6 meeting criteria for RCD had full resolution after the dietary modification.

Hollon et al. *BMC Gastroenterology*. 2013;13:(1)1-9.



Results

- 11/14 of those who responded to the GCED were able to return to a typical GFD without return of symptoms.
- Those that relapsed returned to GCED for extended time but have since returned to a typical GFD.

Hollon et al. *BMC Gastroenterology*. 2013;13:(1)1-9.



Conclusion

- The GCED may be an effective option for NRCD patients that are failing a strict GFD.
- It differentiates patients responding to a miniscule amount of gluten from those who truly have RCD1.
- By avoiding an inaccurate diagnosis patients are able to avoid corticosteroids or immunotherapy.
- Most patients who respond to the GCED may return to a typical GFD after 3-6 months.

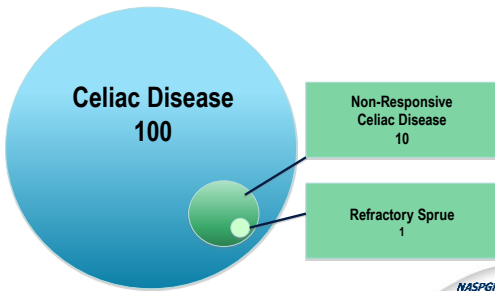


Description of the Case

- Pt was placed on the "Fasano" Diet and her symptoms resolved within three months.
- Serology was repeated a month later and was finally within normal limits.
- The following month she underwent to an upper endoscopy that showed normal mucosa (Marsh I).
- Gradually she was transitioned back to a typical GFD with no relapse of her symptoms.



CD Clinical Outcomes Following Implementation of the GFD





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Non-Celiac Gluten Sensitivity



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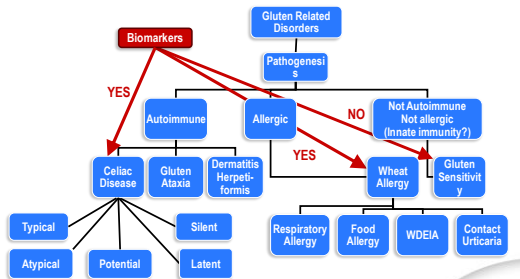
Poll Question #2

Non celiac gluten sensitivity:

- Is a condition that causes exclusively GI symptoms (IBS-like symptoms)
- Is a food intolerance
- Causes intestinal damage
- Occurs within a few hours/days the ingestion of gluten containing grains



Proposed New Classification of Gluten Related Disorders



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Poll Question #2 Results

Non celiac gluten sensitivity:

- Is a condition that causes exclusively GI symptoms (IBS-like symptoms)
- Is a food intolerance
- Causes intestinal damage
- Occurs within a few hours/days the ingestion of gluten containing grains



Gluten Sensitivity (NCGS): Facts Definition

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

- Triggered by the ingestion of gluten-containing grains;
- 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;
- Possible 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 and relapse after re-exposure to gluten-containing grains (double blind).

Sapone et al. *BMC Medicine*. 2012;10:1.
 Ludvigsson et al. *Gut*. 2013;62(1):43-52.
 Catassi et al. *Nutrients*. 2013 Sep 26;5(10):3839-53.



Non Celiac Gluten Sensitivity: Facts Definition of Food Reactions

Food intolerance occurs when the body lacks a particular enzyme to digest nutrients, nutrients are too abundant to be completely digested, or a particular nutrient cannot be properly digested. Common examples are lactose intolerance, FODPAM intolerance, or lactulose intolerance (side effect of laxatives).

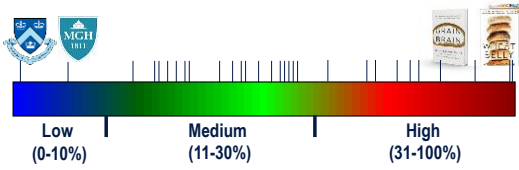
Food sensitivity, an understudied area, are immune-mediated reaction to some nutrients and these reactions do not always occur in the same way when eating that particular nutrient.

Food allergy is a very specific immune system response involving either the immunoglobulin E (IgE) antibody or T-cells. Both are immune system cells that react to a particular food protein, such as milk protein.

(Consensus NIAID 2011)



Estimated Prevalence of NCGS:





Gluten Sensitivity:

*What is the Magnitude of the Problem?
The CFCR Experience (2004-2010)*

- Nr. of the patients seen at the CFCR clinic: **5,896**
- Nr. of patients fulfilling criteria for GS: **347**
- Prevalence in our cohort: **1:17 (6%)**
- 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%



Case Presentation 2:
Gluten Sensitivity



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Description of the Case

MJM 40 y old F



- 6 months history of:
 - Recurrent abdominal pain (mainly epigastric)
 - Heartburn
- Suspecting GERD, pt was placed on PPI, but no resolution of symptoms.
- One month after the onset of GERD symptoms pt developed headaches, dizziness, numbness of fingers, paresthesia.



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Description of the Case

Suspecting multiple sclerosis patient underwent to:



- MRI
- Evoked potentials

Both resulted negative

Other diagnoses that were considered include:

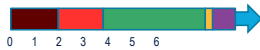
- Lyme disease;
- Epstein Barr Virus
- Pernicious Anemia
- Lupus

All were ruled out



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Description of the Case



Because of the persistence of GERD symptoms pt underwent to an EGD reported as normal (including duodenal biopsy that showed only increased IEL).

She was also screened for CD and tested negative.



Description of the Case

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Despite negative results, pt decided to embrace a GFD.

- Within a week most of her neurological symptoms resolved (only occasional tingling);
- Within 3 weeks also her GI symptoms resolved.



Gluten Free Diet: Overview

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	Celiac Disease	Gluten Sensitive
Treatment: GFD	Yes	Yes
Strict adherence to GFD	<10 mg / day	?
Life Long	Yes	?
Improvement of symptoms on GFD	Yes	Yes
Consequence of non-compliance:		
Physical symptoms	Yes	Yes
Intestinal damage	Yes	No
Monitored by bio marker	Yes	No
Co morbidities	Yes	?



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Wheat Allergy



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Poll Question #3

Wheat allergy:

- Can cause extra-intestinal symptoms like asthma
- Occurs only in children
- Causes intestinal damage
- Affects 20% of the general population



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
- 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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Poll Question #3 Results

Wheat allergy:

- Can cause extra-intestinal symptoms like asthma
- Occurs only in children
- Causes intestinal damage
- Affects 20% of the general population



Case Presentation 3: Wheat Allergy



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Description of the Case

AF 27 y old M



After 6 months working in a bakery, he started experiencing shortness of breath, fatigue and, finally an asthma attack.

He was referred to an allergist who performed a series of tests, including prick and RAST tests that tested positive for cow's milk, strawberries, and wheat.

He was placed on an elimination diet with no major improvement of his symptoms.



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Description of the Case



He was again referred to the allergist who performed additional tests and trigger tests that led to the diagnosis of bakers asthma.

He was recommended to wear a mask while working in the bakery with resolution of his asthma.