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Current Trends in Celiac disease


Daniel Gelfond, MD
Digestive Disease and Nutrition Center,
WCHOB
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History of Celiac Disease

- **Aretaeus, the Cappadocian**
 - Second century
 - "Celiac Affection"
 - from Greek κοιλιακός <koiliakos>
 - malabsorptive syndrome with chronic diarrhoea
 - "lack of heat in the stomach necessary to digest food"
- **Samuel Gee** - British physician - London, 1887
 - Modern description of Celiac disease
 - "if the patient can be cured at all, it must be by means of diet."




Gee S. On the coeliac affection. St Bart Hosp Rep 1890; 24: 17-20




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History of Celiac disease




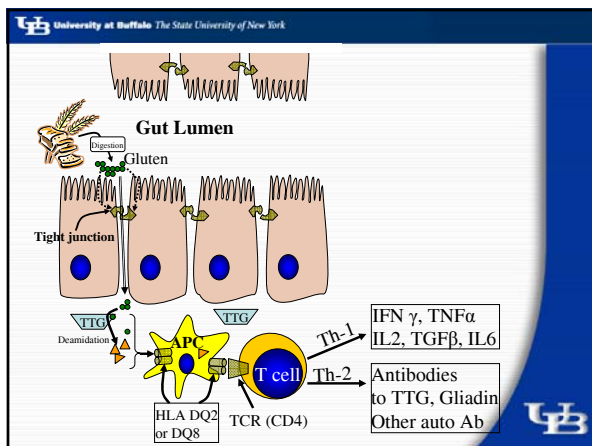
- **Christian Archibald Herter** - American physician
 - In 1908 noted growth retardation in children with celiac disease "intestinal infantilism"
 - Fat was better tolerated than carbohydrate
- **Willem Karel Dicke** Dutch Pediatrician
 - Noted that death rate of children affected by CD dropped from 35% to <1% during the shortage of bread in 1944 Dutch famine
 - With the availability of wheat mortality rate soared to previously high levels



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Celiac disease


- Immune-mediated enteropathy triggered by inappropriate and permanent sensitivity to ingested gluten and gluten like proteins found in wheat, rye and barley
- Limited to individuals with genetic susceptibility
 - Presence of HLA DQ2 or DQ8 on chromosome 6
 - Membrane receptors involved in preferential antigen presentation to CD4+ T cells

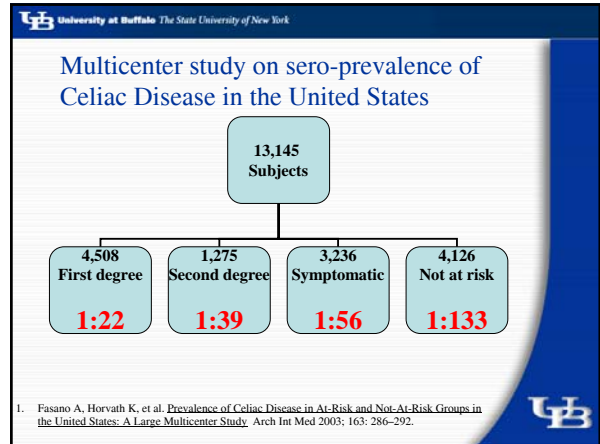
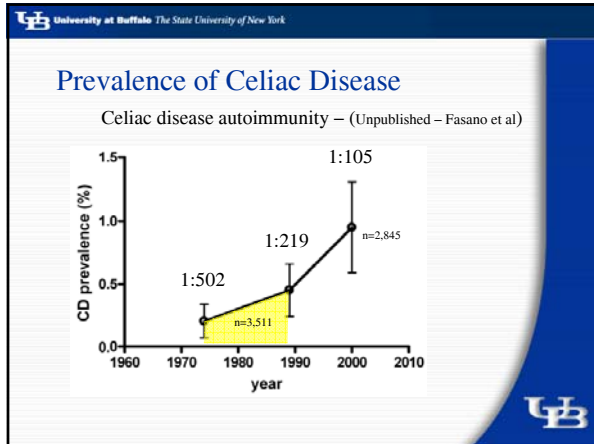



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Epidemiology

- Estimated to affect 1% of the general population in countries where population is predominantly of European descent
 - In US, prevalence between 2.5-15 years is 3-13 per 1000 (1:300 – 1:80)
 - Incidence in Europe 0.025-3.52 per 1000 live births
- An increased frequency is found in at risk groups:
 - Family members with celiac (10-20% first degree relative)
 - Autoimmune disorders (eg, Type I diabetes or autoimmune thyroiditis)
 - Down syndrome, Turners syndrome, IgA deficiency





Presence of Clinical Symptoms and Celiac Disease among first and second degree relatives

Group	No.	Symptomatic Cases			Asymptomatic Cases		
		Screened, No.	Positive, No.	Prevalence, Ratio (%)	Screened, No.	Positive, No.	Prevalence, Ratio (%)
First-degree adults	3214	1670	88	1.00 (3.3)	1030	62	1.24 (4.04)
First-degree children	1294	592	20	1.00 (3.38)	702	34	1.21 (4.84)
Second-degree adults	662	386	8	1.48 (2.07)	276	6	1.46 (2.17)
Second-degree children	613	259	9	1.20 (2.47)	254	10	1.30 (2.80)
Total	1783	2916	126	1.23 (4.32)	2687	112	1.25 (3.91)

Symptomatic Asymptomatic

- Asymptomatic cases in at risk group have similar prevalence when compared to the symptomatic cases

1. Fasano A, Horvath K, et al. Prevalence of Celiac Disease in At-Risk and Not-At-Risk Groups in the United States: A Large Multicenter Study. Arch Int Med 2003; 163: 286-292.

Common associated conditions

Celiac Disease Associated Conditions		
Autoimmune conditions	Genetic conditions	Other conditions
Type 1 Diabetes (4%-8%)	Down syndrome (5%-12%)	Neurologic
Thyroiditis (4%)	Turner Syndrome (4%-8%)	Psychologic
Arthritis (1.5%-7%)	William's syndrome (8%)	Ataxia
Primary biliary cirrhosis (6%)	Selective IgA deficiency (2%-8%)	Depression
		Epilepsy with intracranial calcifications
		IgA nephropathy
		Osteopenia/osteoporosis

- ### Associated conditions
- 90% of individuals with Type I diabetes and celiac disease are diagnosed with diabetes initially, and develop celiac disease within a few years
 - Incidence of Type II diabetes in patients with celiac disease decreased (Fasano 2003)
 - Patients with cystic fibrosis have a 5-fold risk of celiac disease compared with the general population*
- * Eleni Mihailidi, et. al. Eleni Mihailidi; Int Pediatr. 2003;18(3):141-148

Clinical presentation

- Onset of symptoms as early as 6 months

Untreated Celiac Disease in Pediatric patients	
Classic symptoms	Non-classic symptoms
Abdominal distension	Arthritis
Anorexia	Aphthous stomatitis
Chronic or recurrent diarrhea	Constipation
Failure to thrive or weight loss	Dental enamel defects
Irritability	Dermatitis herpetiformis
Muscle wasting	Hepatitis
	Iron-deficient anemia
	Short stature
	Vomiting
	Bone fractures

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Dermatitis Herpetiformis



- 1966 Dermatitis herpetiformis was linked to celiac disease
- 10% of adults with celiac disease (25-45 year)
- Uncommon in pediatric patients
- Intestinal lesions are usually less severe*

Fry, L. Dermatitis herpetiformis. *Bailliere Clin. Gastroenterol.* 9, 371-393 (1995)

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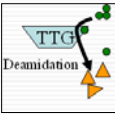
Screening - Serology

- Antigliadin antibody (AGA) IgA and IgG has a low sensitivity and has **not** been recommended in testing for Celiac disease by NASPGHAN and NIH
- Present in 80-90% of untreated Celiac
- False positive: esophagitis, gastritis, gastroenteritis, IBD, cystic fibrosis, cow's milk protein intolerance, liver disease and neurological conditions

"Serologic testing for celiac disease in children less than 5 years of age may be less reliable and requires further study" NIH consensus on Celiac disease

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Screening - Serology



- Deamidated AGA antibody recognizes gliadin after TTG deamidation process (DGP more specific than AGA) IgG
- Tissue transglutaminase antibody (TTG IgA and IgG)
- Anti-endomysium IgA (EMA)

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Screening - Serology

Efficacy of serology assays in diagnosing CD		
	Sensitivity	Specificity
AGA IgA	0.5 - 1.0	0.92 - 0.97
AGA IgG	0.5 - 1.0	0.5
EMA*	0.88 - 1.0	0.91 - 1.0
TTG IgA	0.92 - 1.0	0.91 - 1.0

- 157 samples previously tested for TTG / EMA
- Increased concordance of DGP
 - with Positive TTG and EMA (97%)
 - With Negative TTG and EMA (96%)

Harry E. Prince Evaluation of the INOVA Diagnostics Enzyme-Linked Immunosorbent Assay Kits for Measuring Serum Immunoglobulin G (IgG) and IgA to Deamidated Gliadin Peptides. *Clin. Vaccine Immunol.* 2006 13: 150-151

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Efficacy of serology testing in children less than 3 years

- 116 children with clinical signs of celiac disease and positive family history
- All underwent endoscopy with biopsies and serological testing

Parizade M, Bujanover Y, Weiss B, Nachmias V, Shainberg B Performance of Serological Assays for Diagnosing Celiac in a Clinical Setting. *Clin Vaccine Immunol.* 2009 Sep 23

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Median concentration of CD specific antibodies in biopsy positive children

	≤3 years	>3 years	p value
No. of children	26	59	
IgA (mg/dL)	86.8	121.0	0.045
TTG-IgA Celikey (IU/ml)	119.1	29.9	0.017
EMA (reciprocal of end point titer)	160	160	0.102
TTG-IgG Celikey (IU/ml)	28.0	8.5	0.007
DGP (IgG+IgA) Screen (U)	95.9	68.1	0.007
TTG-IgA Immulite 2000 (IU/ml)	71.6	42.5	0.398

Performance of Serology Assays for Diagnosing Celiac in a Clinical Setting. Parizade M, Bujanover Y, Weiss B, Nachmias V, Shainberg B. *Clin Vaccine Immunol.* 2009 Sep 23

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HLA testing

- HLA DQ – 9 serotypes on chromosome 6p21
 - HLA DQ2 - HLA-DQA1*0501 and DQB1*02 alleles
 - HLA DQ8 -HLA-DQA1*0301-DQB1*0302 alleles
- 90-99% of Celiac have DQ2 or DQ8
 - 90-95% with DQ2 and 5-10% with DQ8
- 35-45% of US population have DQ2 or DQ8
 - At most 1% of population suspected of having celiac
 - Other genetic factors

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Screening ↔ Diagnosis

- Endoscopy with biopsy is required to confirm serological diagnosis of Celiac disease
 - 6 to 8 random biopsy specimens from the duodenum or further
 - Except in biopsy proven dermatitis herpetiformis
- Patchiness in 73%
- At least one normal appearing fragment - 36%
 - Emphasis on obtaining biopsies from the duodenal bulb in addition to other random small bowel sites

Am J Gastroenterol advance online publication, 6 October 2009

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Endoscopic biopsies in the evaluation of celiac disease

Concurrent biopsies of the duodenum and duodenal bulb	n=101
Marsh 3 histology	
At both sites	77 (76%)
In the duodenum only	12 (12%)
Normal in duodenal bulb	3 (3%)
Peptic duodenitis in duodenal bulb	6 (6%)
Marsh 2 histology in duodenal bulb	2 (2%)
Marsh 1 histology in duodenal bulb	1 (1%)
In the duodenal bulb only	12 (12%)
Normal in the duodenum	6 (6%)
Peptic duodenitis in duodenum	1 (1%)
Marsh 2 histology in duodenum	2 (2%)
Marsh 1 histology in duodenum	3 (3%)

Am J Gastroenterol, 6 October 2009

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Pathology scores

Marsh 0	Marsh 1	Marsh 2	Marsh 3	Marsh 4
pre-infiltrative, normal	infiltrative Normal mucosa and villous architecture, IELs	hyperplastic; +enlarged crypts , increased turnover normal villi, IELs	Destructive lesion with IELs: A. partial VA B. sub-total VA C. total VA	Hypoplastic: total VA, IELs

Rostami Am.J.Gastro. 1989; 94: 888

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Capsule endoscopy

- Features suggestive of celiac disease:
 - villous atrophy
 - Scalloping
 - Fissuring
 - Mosaic patterns
- **No tissue samples**

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Treatment

GFD (Gluten Free Diet)

- Avoid wheat, rye, barley and their derivatives
Malt is also harmful - partial hydrolysate of barley prolamins
- Oats – High incidence of cross contamination
- FDA definitions of FGD <20ppm (<20mg/kg)
- Improved carbohydrate intolerance

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Gluten containing grains

- Barley
- Barley malt/extract
- Bran
- Bulgur
- Couscous
- Bromated or Durum Flour
- Einkorn
- Emmer
- Enriched or Self Rising Flour
- Farina
- Faro
- Graham Flour
- Kamut
- Matzo Flour/meal
- Orzo
- Panko
- Phosphated Flour
- Rye
- Seltan
- Semolina
- Spelt
- Triticale (cross between wheat/rye)
- Udon
- Wheat
- Wheat Bran
- Wheat germ
- Wheat starch

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Gluten free grains and starches

- Amaranth
- Arrowroot
- Buckwheat
- Corn
- Flax
- Millet
- Montina
- Potato Starch
- Potato Flour
- Flours made from nuts, beans and seeds
- Quinoa
- Rice
- Rice Bran
- Sago
- Sorghum
- Soy (soya)
- Tapioca
- Teff

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Benefits of strict dietary compliance

- Eliminate immunological damage
- Improve nutrition, vitamin absorption
 - Growth, bone mineralization
 - Physical and psychosocial well being
- No consensus on the minimal amount of gluten in food
- Patient reported adherence to GFD – 45-81%
 - Serological monitoring every 6-12months
- No increase in mortality compared to general population

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Consequence of Non Compliance

- Increased chance of developing other immune mediated conditions (Autoimmune diseases)
- Increased lifelong incidence of malignancy
 - If diagnosed and treated in childhood, lifelong risk of gastrointestinal lymphoma is not higher than general population
- Mortality rate*
 - Double in patients suspected on non compliance
 - X6 in patients not on diet

*Biagi, F. & Corazza, G. R. *Nat. Rev. Gastroenterol. Hepatol.* 7, 158–162 (2010)
 *Corrao, G. et al. Mortality in patients with coeliac disease and their relatives: a cohort study. *Lancet* 358, 356–361 (2001)

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Mortality

- Early diagnosis in pediatric patients associated with decreased mortality
- Increased gluten consumption
- Lymphoma

Biagi, F. & Corazza, G. R. *Nat. Rev. Gastroenterol. Hepatol.* 7, 158–162 (2010)

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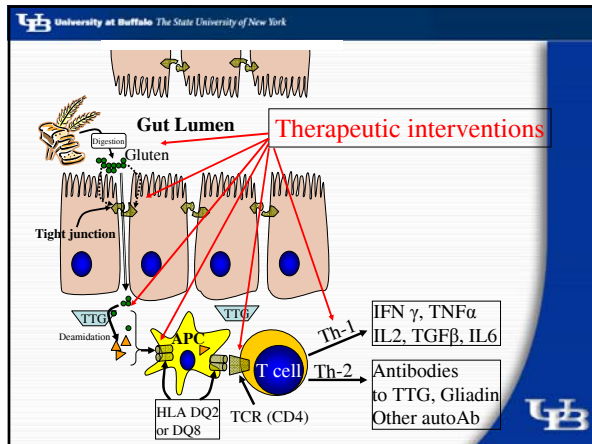
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Can bacterial or viral infection trigger the onset of celiac disease?

- The association of celiac disease with adenovirus (serotype 12) *
 - Viral protein- E1b demonstrates similar antigenic sequencing of amino acids to that of gluten peptides
 - Infection with adenovirus and subsequent exposure to gliadin could trigger the development of cross-reacting immune response
- Welander et al. (2/2010)** looked at nearly 10,000 children in Sweden and showed no increased incidence of future celiac disease development in children exposed to gluten during the time of infectious illness

*M.F. Kagnoff, Kagnoff MF, et. al. Evidence for the role of a human intestinal adenovirus in the pathogenesis of coeliac disease *Gut* 1987;28:995-1001
 **Adina Welander et al. Infectious Disease and Risk of Later Celiac Disease in Childhood *Pediatrics* 2010;125:e530-e536

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New Therapeutic Strategies

- Genetic alterations to remove or modify immunogenic sequences
 - Interferes with the main structural role in maintaining protein matrix in the grain
 - Interferes with the dough strength
- Selection of grains with low or absent immunogenic sequences
- Polymeric binders to reverse gliadin effect on the intestinal barrier

Lerner, A New Therapeutic strategies for Celiac disease Autoimmunity Reviews 9 (2010) 144-147

New Therapeutic Strategies

- Enzymatic degradation of gluten prior to ingestion
 - Enzymes used during food preparation and storage
 - Probiotics to degrade gluten into less immunogenic form
 - VSL3 was shown to hydrolyze gliadin peptide responsible for mucosal immune response
- Inhibition of intestinal permeability
 - AT1001 (1002) blockage of tight junction relaxation leading to paracellular permeability

Lerner, A New Therapeutic strategies for Celiac disease Autoimmunity Reviews 9 (2010) 144-147

New Therapeutic Strategies

- Blocking TTG
 - Interferes with deamidation of gluten by TTG
 - Decrease immune response
 - Potentially harmful since TTG has a role in apoptosis, cell adhesion, signal transduction, collagen assembly and would repair
- Blocking HLA DQ groove
 - Single amino acid substitution of a gliadin can abolish immunogenicity of a T cell response
- Shifting from Th1 to Th2 response
 - Inhibiting inflammation
 - Nematode infection (Australia)

Lerner, A New Therapeutic strategies for Celiac disease Autoimmunity Reviews 9 (2010) 144-147

New Therapeutic Strategies

- Anti-inflammatory cytokines
 - Human recombinant - IL10 suppresses gluten dependent T activation in cultured cells
- Gluten peptide vaccine
 - peptide that combines two immunodominant α and ω -gliadin 17-mer peptides is currently under investigation
- Inhibition by dietary Antigen specific T regulatory cells (Type 1)
 - Shown to inhibit pathogenic T cells

Lerner, A New Therapeutic strategies for Celiac disease Autoimmunity Reviews 9 (2010) 144-147

New Therapeutic Strategies

- Gluten tolerance induction in high risk infants
 - Currently under investigation in Europe in children 4-7 months of age
 - Promising results in DQ8 transgenic mice
- Anti adhesion therapy
 - Selective inhibition of leukocyte adhesion
- Intestinal trophic mitogens
 - Stimulation of intestinal growth and regeneration (R-spondin 1, KFG)

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And the Winner is:

GFD

With COMPLIANCE



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Questions?

