Celiac Disease 2017: Just the Tip of the Iceberg

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What celiac disease is NOT

- IBS (or FGID → Rome IV)
- Non-immunologic food response
  - GI disorders (disaccharidase deficiency)
  - Intolerances (EtOH)
  - Poisoning (Ciguatera)
- Wheat allergy
- An "allergy" at all
  - IgE, rapid onset, systemic
- *Non-celiac gluten sensitivity*

Why me?
Great question → → →

UHealth
UNIVERSITY OF MIAMI HEALTH SYSTEM
Crohn's and Colitis Center

- Much more an "inflammatory bowel disease" than an "allergy"
  - autoimmune
  - mucosal immunology
  - microbiome, hygiene

Objectives

- Appreciate the history and epidemiology of celiac disease

- Understand the pathophysiology and diagnosis of celiac disease

- Be aware of the potential complications of the disease and the reasons for failing conventional treatment

- Know the current treatment paradigm and future therapeutic options

Celiac Disease

- condition of the small bowel in which genetically susceptible individuals develop an immune-mediated enteropathy due to a sensitivity to gluten
- this leads to mal-assimilation of both micro- and macro-nutrients
- with continued exposure to gluten, celiac disease becomes self-perpetuating and becomes harder to treat over time

History

- koiliakos → suffering in the bowels

  ◦ first described by Aretaeus of Cappadocia ~200 CE
  ◦ Francis Adams' translation to English in 1856 at the Syndenham Society described a series of patients with chronic relapsing steatorrhea, weight loss, and pallor

Adams F. On The Cœliac Affection: The extant works of Aretaeus the Cappadocian. 1856. London: Sydenham Society.

History

- In 1888, pediatrician Samuel Gee noted a likely dietary component in children in his translation of Aretaeus' work

- In 1908, American Christian Herter noted better tolerance of fats than carbohydrates in children with this syndrome→ Gee-Herter disease

Gee SJ. St Bartholomew's Hospital Report 1888;24:17-20.
Herter CA. On infantilism. 1908. New York: Macmillan & Co.

History

- Following the Dutch famine of 1944, during which flour was sparse, Dr. Willem Dicke noted improvement in children's symptoms
- In 1952, English researchers linked celiac disease to gluten insensitivity
- Later work showed the role of small bowel biopsy in making a diagnosis

Dicke WK. Celiac: an investigation into the injurious influence of different kinds of grain to the sufferer of celiac (translated). 1950. Utrecht, the Netherlands.
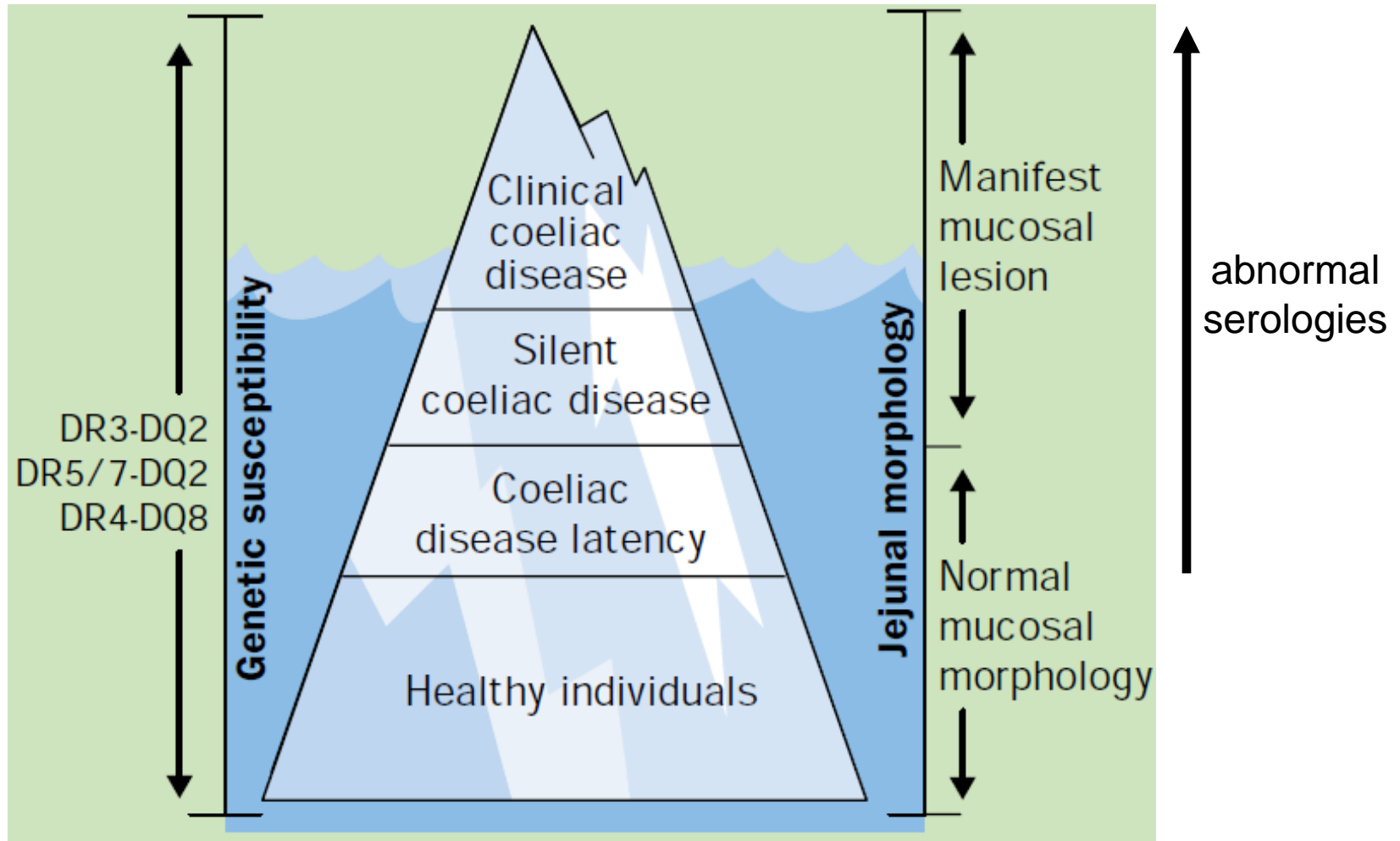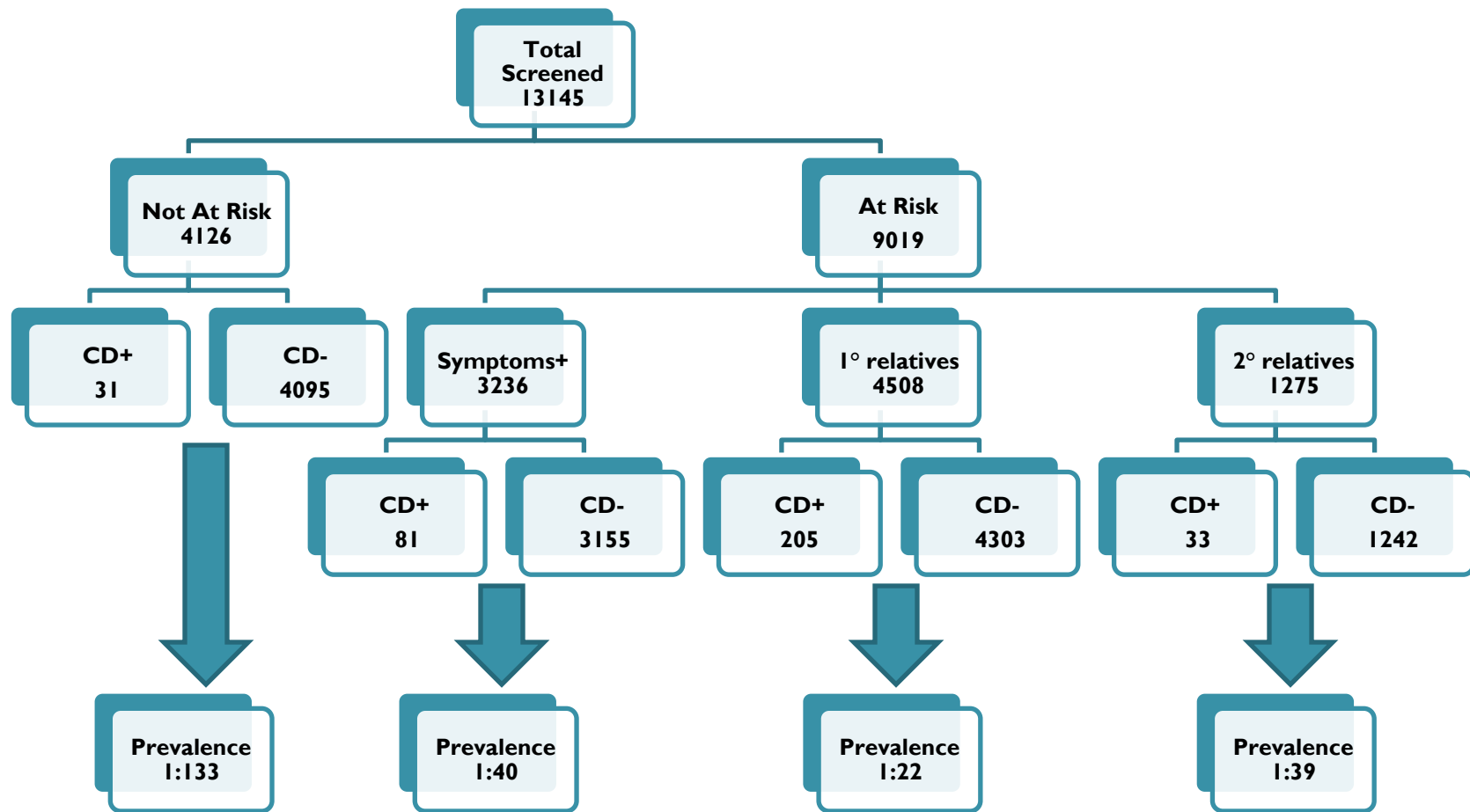van Berge-Henegouwen G. Gut 1993;34(11):1473–5.
Anderson C. Lancet 1952;1(17):836-42.

Epidemiology

- Incidence has dramatically risen with the advent of endoscopic biopsies and effective serologic markers
  - 1:130 – 1:300 in European studies (higher in Northern Europe and Scandanavia)
  - series from Africa, South America, and Asia are now showing similar incidences in parts of the world previously thought less affected

Catassi C. Lancet 1994;343(8891):200-3.
Gandolfi L. Am J Gastroenterol 2000;95(3):689-92.

Catassi C. Lancet 1999;354(9179):647-8.
Sood A. Am J Gastroenterol 2001;96(9):2804-5.

The Iceberg

Maki M. Lancet 1997;349(9067):1755-9.

So there were >2 million Americans projected with celiac disease, of which ~40K had been diagnosed → for every 1 patient with celiac disease, there were 53 undiagnosed patients[*]

Fasano A. Arch Intern Med 2003;163(3):286-92.   [*] Hamilton FA, NIH/NIDDK

Prevalence

- ~31K people <50 years old living near Mayo (MN) had blood test for celiac disease (TTG IgA) with confirmatory test (AEM IgA); none had known celiac

- Compared comorbidities between undiagnosed celiac and age/sex-matched controls (nested case-control)

- Prevalence of undiagnosed celiac 1.1%
  - not associated with diarrhea, anemia, fracture, mortality
  - increased hypothyroidism, lower cholesterol and ferritin

- 5 year cumulative incidence of celiac disease thereafter 11% compared to 0.1% in seronegative people

RS Choung. Gastroenterology 2017;152:830-9.

Pathophysiology

- In the appropriate genetic host, proteins to which those with celiac disease are intolerant induce T-cell activation and T-cell mediated inflammation of the small bowel

- HLA MHC Class II molecules DQ2 or DQ8 are necessary for phenotypic expression
  - HLA DQ2 is found in 90-95% of patients
  - HLA DQ8 is found in the other 5-10% of patients
  - new GWAS have found several other non-HLA variants in regions of immune function

Sollid LM. J Exp Med 1989;169(3):345-50.   Dubois PC. Nat Genet 2010;42(4):295-302.

Pathophysiology

- Intolerance to gluten – the protein mass left after starch is washed from dough
- Actually, it is an intolerance to the "*prolamins*;" proteins with high concentrations of proline and glutamine
  - *gluten* (of which gliadin is the alcohol-soluble portion) is the wheat protein
  - *hordein* is the protein of barley, and *secalin* is the rye protein
- Therefore, those with celiac disease are intolerant of *wheat, barley,* and *rye*

What about *oats*?

- Studies have looked at oat protein (avenin):
  - most show NO immune-mediated inflammatory response to avenin alone
  - much of the prior concern with oats was likely due to cross-contamination in mills harvesting wheat, barley, and/or rye
- Corn (zein), rice, potato, and soy proteins similarly do NOT induce an autoimmune response → less prolamin effect?

Garsed K. Scand J Gastroenterol 2007;42(2): 171–8.
Kilmartin C. Gut 2003;52(1): 47–52.
Srinivasan U. BMJ 1996;313(7068): 1300–1.
Pinto-Sanchez MI. Gastroenterology 2017;153(2):395-409.

Högberg L. Gut 2004;53(5):649-54.
Janatuinen EK. N Engl J Med 1995;333(16): 1033–7.
Hoffenberg EJ. J Pediatr 2000;137(3): 361–6.

Pathophysiology

- Lack of prolyl endopeptidases in human small bowel prevents digestion of proline-rich proteins (prolamins)
- In the presence of tissue transglutaminase (TTG), the glutamines are deamidated to negatively charged glutamic acid
- In these long polypeptides, correct spacing of prolines and glutamates can bind to HLA DQ2 and DQ8 on APCs in the lamina propria

Pathophysiology

- This complex activates CD4+ T-cells and IFN-γ in the intestinal mucosa, initiating the inflammatory response
- The negatively charged prolamins have also been shown to induce IL-15 in enteric epithelial cells, stimulating proliferation of NK cells
- There are also large amounts of CD8+ T-cells in the intestinal epithelium
- Villous atrophy and crypt hyperplasia then lead to B cell activation and antibody production
  - including antibodies against TTG, endomysium
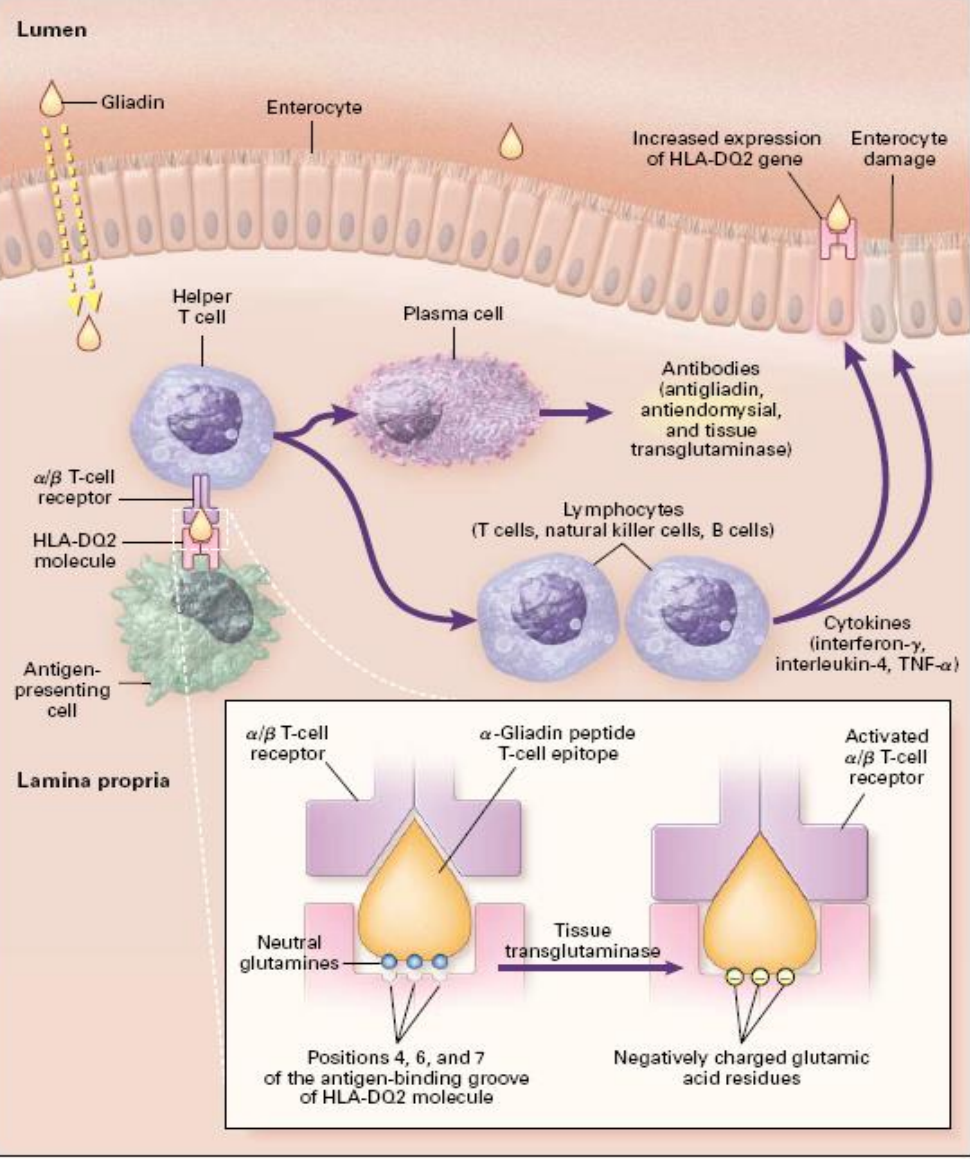
Farrell RJ. New Engl J Med 2002;346(3):180-8.
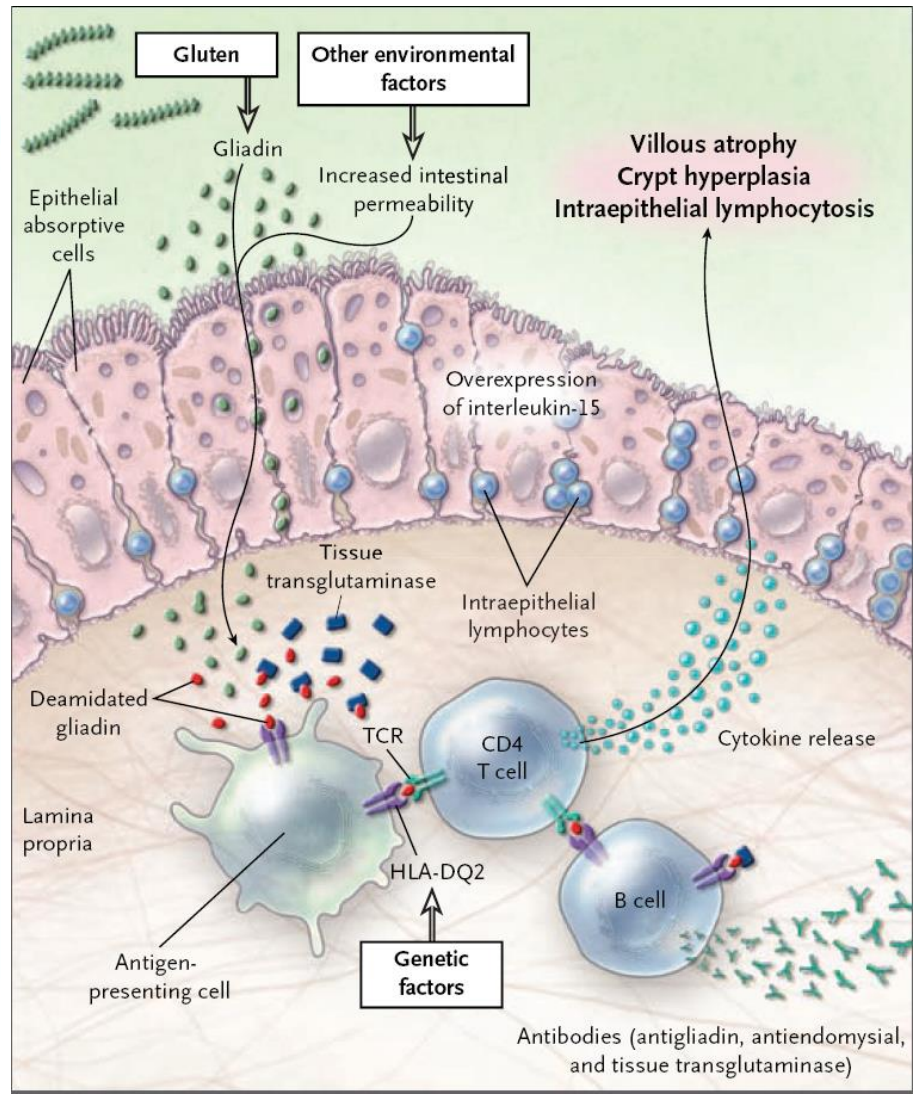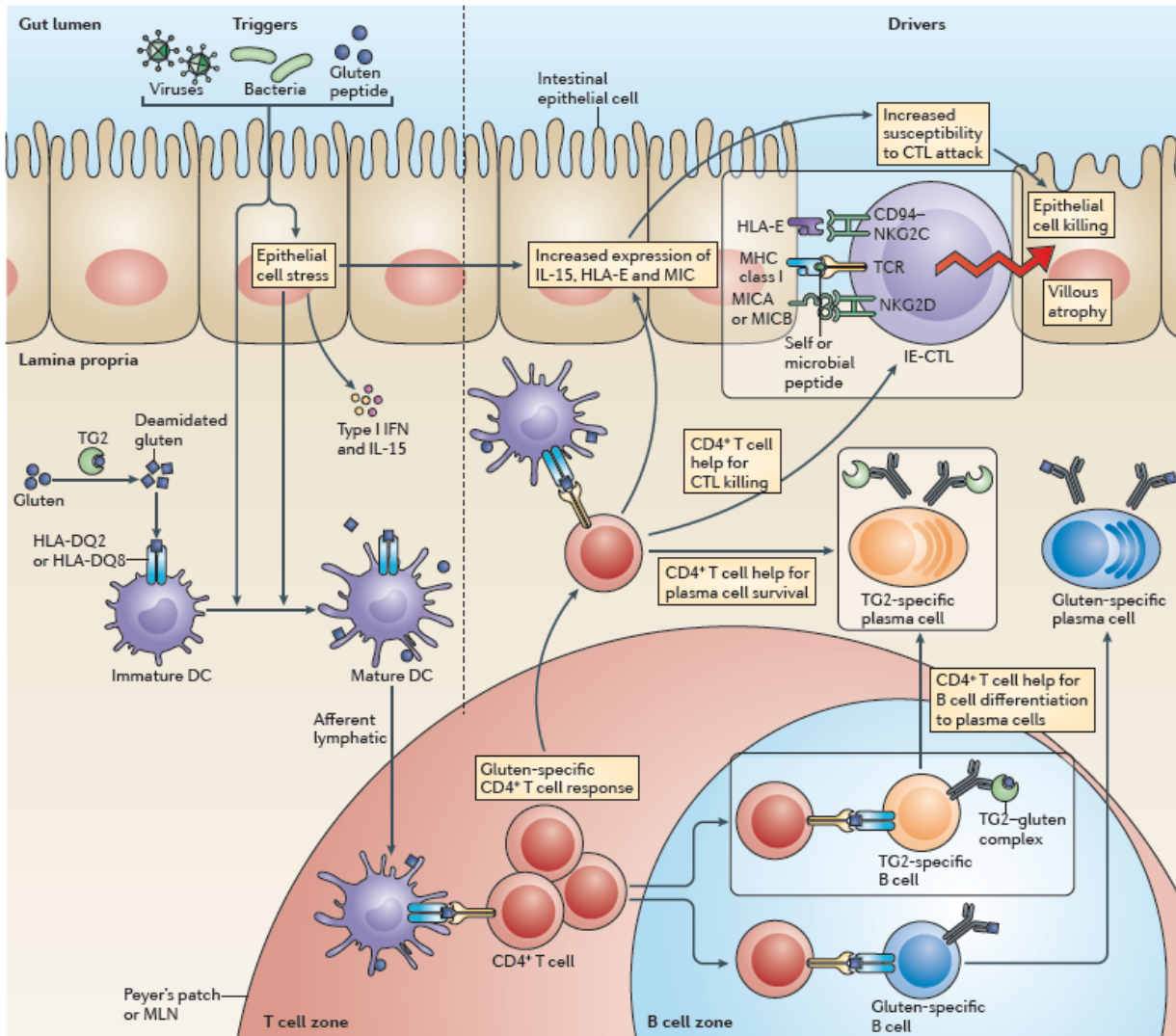
Green PH. New Engl J Med 2007;357(17):1731-43.

Figure 3 | **Dietary antigen drives autoimmune processes in coeliac disease.** Triggers such as viruses, bacteria and possibly gluten itself activate professional antigen-presenting cells, such as dendritic cells (DCs), and epithelial cells. Antigen-presenting cells mature in response to interleukin-15 (IL-15) and type I interferon (IFN) produced by stressed epithelial cells, and acquire pro-inflammatory properties; after migration to the draining Peyer's patch or mesenteric lymph node (MLN), mature DCs present gluten to induce the activation of gluten-specific HLA-DQ2- or HLA-DQ8-restricted CD4+ T cells. Transglutaminase 2 (TG2) and gluten form complexes, which TG2-specific autoreactive B cells can internalize and consequently present gluten peptides on HLA-DQ2 or HLA-DQ8 at their surface. Gluten-specific B cells can bind and present deamidated gluten peptides in a conventional manner. The gluten-specific CD4+ T cells provide help to both autoreactive TG2-specific and gluten-specific B cells, which differentiate into antibody-producing plasma cells. Whether this B cell–T cell interaction takes place in germinal centres or extrafollicularly is not known. Activated gluten-specific CD4+ T cells also provide signals (that remain to be fully defined) to pre-activated epithelial cells, which upregulate the expression of IL-15 and non-classical MHC class I molecules (such as HLA-E and MIC). Consequently, intraepithelial cytotoxic T lymphocytes (IE-CTLs) acquire lymphokine-activated killer activity and a decreased T cell receptor (TCR) activation threshold, and can kill epithelial cells on the basis of the recognition of stress signals. Whether IE-CTLs with a decreased TCR activation threshold recognize low affinity epithelial antigens and antigens of the microbiota through their TCR remains to be determined. The autoimmune phenomena are shown in boxes. MIC, MHC class I polypeptide-related sequence; NKG2D, natural killer group 2, member D.

Sollid LM. Nat Rev Immunol 2013;13(4):294-302.

Pathophysiology

- In controls, competent intercellular tight junctions in the small bowel limit prolamin passage across the intestinal epithelial barrier

- In celiac patients, however, gliadin co-localizes with CXCR3 on the apical side, recruiting receptor MyD88

- This induces release of zonulin, which increases permeability and allows further passage of prolamins

Lammers KM. Gastroenterology 2008;135(1):194-204.

Pathophysiology

- The resultant inflammatory cascade leads to enteritis
  - the villi atrophy, eventually manifested as scalloping of the folds
  - this leads to inadequate nutrient assimilation and resultant nutritional deficiencies
    - iron, folate, calcium, Vitamin D, magnesium, zinc
    - B12 and Vitamin K less common (ileum uncommonly involved in celiac sprue)
    - continued mucosal damage leads to mal-assimilation of fats, proteins, and carbohydrates

Pathophysiology

- >35% of white Northern Europeans are DQ2+, as opposed to 15% of black South Africans
- So what makes only certain DQ2/DQ8 people susceptible?
  - how and when prolamin sensitivity occurs is unknown
  - this seems to trigger an autoimmune response to TTG, making the intestinal barrier more susceptible to prolamins and causing a vicious cycle
  - role of early exposure to wheat?
  - ? initial enteric infection triggering differing immune response to gluten
  - ? differing ability to co-localize with CXCR3
  - different microbiota → differences in prolamin permeability of intestinal barrier and immunogenicity

Paul T. UCLA Tissue Typing Laboratory, LA:1997;427–60.   Caminero A. Gastroenterology 2016;151:60-83.
Bouziat R. Science 2017;356:44-50.   Kemppainen KM. Clin Gastroenterol Hepatol 2017;15(5):694-702.

Microbiome and Hygiene

Table 2. Risk of Celiac Disease After Cesarean Delivery

	Matched controls (%)	Celiac disease (%)	OR; 95% CI	P value	Adjusted OR,[a] 95% CI	P value
Cesarean delivery	5766/53,887 (10.7)	1299/11,749 (11.1)	1.04; 0.98–1.10	.232	1.06; 0.99–1.13	.074
Number of participants			65,636		65,493	
Emergency cesarean delivery[b]	2136/41,699 (5.1)	444/8827 (5.0)	0.99; 0.90–1.10	.857	1.02; 0.92–1.13	.749
Number of participants			50,526		50,415	
Elective cesarean delivery[b]	2125/41,688 (5.1)	508/8891 (5.7)	1.11; 1.01–1.22	.027	1.15; 1.04–1.26	.005
Number of participants			50,579		50,471	

[a]Births with complete data on infant sex, maternal age at delivery, parity, and dates of birth were included in the analysis. We adjusted for maternal age, parity, maternal diabetes, maternal celiac disease, and education level (model I). Accordingly, the number of births differs between the models: Unadjusted model (11,749 individuals with celiac disease and 53,887 controls) and adjusted model (11,738 individuals with celiac disease and 53,755 controls).

[b]Data on emergency vs elective cesarean delivery were restricted to children born between 1982 and 1989 and after 1991 because data on type of cesarean delivery were specified only during these times.

Marild K. Gastroenterol 2012;142(1): 39-45.

Pathophysiology
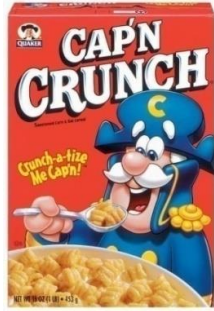
- **Trigger: is it timing of initial gluten exposure or duration of breastfeeding?**
Data conflicting:

    ◦ higher incidences of CD in those exposed to cereals at <3 months compared to those exposed to cereals at 3-6 months

    ◦ higher incidences of CD in those NOT exposed to cereals until >7 months

    ◦ higher incidences of CD in those NOT exposed to cereals until >6 months AND in those breastfed >12 months

Norris JM. JAMA 2005;293(19):2343-51.
Ivarsson A. Am J Clin Nutr 2002;75:914-21.

Auricchio S. J Pediatr Gastroenterol Nutr 1983;2:428-33.
Stordal K. Pediatrics. 2013;132(5):e1202-9.

Timing of gluten exposure – more questions than answers

- 475 kids randomized: gluten at weeks 16-24 vs placebo
  - All DQ2 or DQ8 + with one 1st degree relative with CD
  - No difference in TTG in 2 groups, and at 3 years no reduction of risk in biopsy-proven CD
- 800 newborns with 1st degree relative with CD got gluten at 6 months (A) vs 12 months (B); those with HLA risk alleles stayed in the trial
  - At 2 years more +Abs and CD in A but that went away at 5 and 10 years
  - Risk mostly driven by HLA risk rather than time of gluten exposure
- **So no clear idea of when to start gluten**

Lionetti E.   N Engl J Med 2014:371(14):1295-303.
Vriezinga SL. N Engl J Med 2014;371(14):1304-15.

TEDDY Study

- Pediatrics, January 2015
  - Multiple countries
  - **Gluten introduction <17 weeks or >26 weeks not an independent risk factor for developing celiac disease**
    - adjusted for country, HLA, gender, and FH of celiac, neither in overall nor country-level comparison

Aronsson CA. Pedatrics 2015;135(2):239-45.

Effects of Gluten Intake on Risk of Celiac Disease: A Case-Control Study on a Swedish Birth Cohort

Carin Andrén Aronsson,* Hye-Seung Lee,‡ Sibylle Koletzko,§ Ulla Uusitalo,‡ Jimin Yang,‡ Suvi M. Virtanen,‖,¶,# Edwin Liu,** Åke Lernmark,* Jill M. Norris,‡‡ Daniel Agardh,* and the TEDDY Study Group

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BACKGROUND & AIMS: Early nutrition may affect the risk of celiac disease. We investigated whether amount of gluten in diet until 2 years of age increases risk for celiac disease.

METHODS: We performed a 1-to-3 nested case-control study of 146 cases, resulting in 436 case-control pairs matched for sex, birth year, and HLA genotype generated from Swedish children at genetic risk for celiac disease. Newborns were annually screened for tissue transglutaminase autoantibodies (tTGA). If tested tTGA positive, time point of seroconversion was determined from frozen serum samples taken every 3 months. Celiac disease was confirmed by intestinal biopsies. Gluten intake was calculated from 3-day food records collected at ages 9, 12, 18 and 24 months. Odds ratios (OR) were calculated through conditional logistic regression.

RESULTS: Breastfeeding duration (median, 32 wk) and age at first introduction to gluten (median, 22 wk) did not differ between cases and tTGA-negative controls. At the visit before tTGA seroconversion, cases reported a larger intake of gluten than controls (OR, 1.28; 95% confidence interval [CI], 1.13–1.46; $P = .0002$). More cases than controls were found in the upper third tertile (ie, >5.0 g/d) before they tested positive for tTGA seroconversion than controls (OR, 2.65; 95% CI, 1.70–4.13; $P < .0001$). This finding was similar in children homozygous for DR3-DQ2 (OR, 3.19; 95% CI, 1.61–6.30; $P = .001$), heterozygous for DR3-DQ2 (OR, 2.24; 95% CI, 1.08-4.62; $P = .030$), and for children not carrying DR3-DQ2 (OR, 2.43; 95% CI, 0.90–6.54; $P = .079$).

CONCLUSIONS: The amount of gluten consumed until 2 years of age increases the risk of celiac disease at least 2-fold in genetically susceptible children. These findings may be taken into account for future infant feeding recommendations.

From TEDDY, maybe it's not when but how much: **increased intake in first 2 years of life increased risk 2 fold** (mostly intake after age 1 and CD occurred later in life)

Gluten Introduction and the Risk of Coeliac Disease: A Position Paper by the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition

March 2016

The risk of inducing CD through a gluten-containing diet exclusively applies to persons carrying at least one of the CD risk alleles. Because genetic risk alleles are generally not known in an infant at the time of solid food introduction, **the following recommendations apply to all infants**, although they are derived from studying families with first-degree relatives with CD. Although breast-feeding should be promoted for its other well-established health benefits, **neither any breast-feeding nor breast-feeding during gluten introduction has been shown to reduce the risk of CD**. Gluten may be introduced into the infant's diet **anytime between 4 and 12 completed months of age**. In children at high risk for CD, earlier introduction of gluten (4 vs 6 months or 6 vs 12 months) is associated with earlier development of CD autoimmunity (defined as positive serology) and CD, but the cumulative incidence of each in later childhood is similar. Based on observational data pointing to the association between the amount of gluten intake and risk of CD, consumption of **large quantities of gluten should be avoided during the first weeks** after gluten introduction and during infancy. **The optimal amounts of gluten to be introduced at weaning**, however, **have not been established**.

Presentation
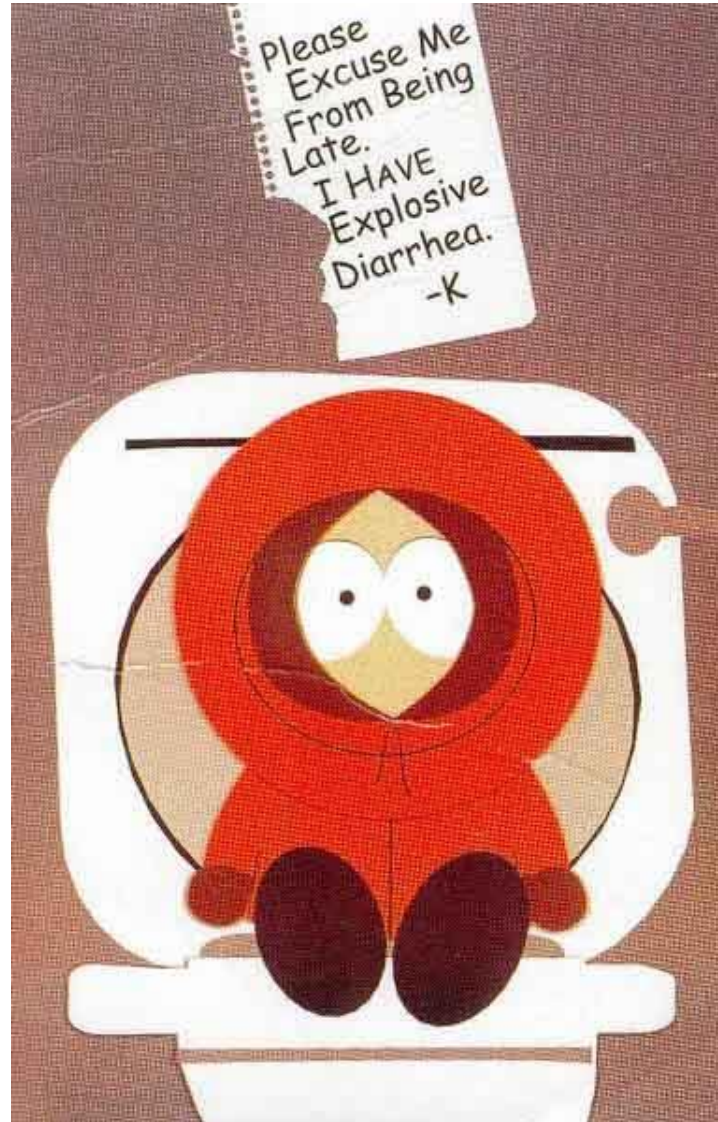
Presentation

- Typical symptoms
  - in children: diarrhea, stunted growth, anemia, failure to thrive
  - in adults: diarrhea, flatulence, IDA, weight loss, lactose intolerance, malaise, abdominal cramping
- Celiac disease can present very non-specifically, and it is critical to consider it prior to a diagnosis of "IBS"
  - 5-7% of patients with IBS/fibromyalgia actually have celiac disease
    - compared to <1% in controls
  - there also exists non-celiac gluten sensitivity
- There are myriad extraintestinal manifestations that can be the initial presentation of celiac disease
  - many of these are autoimmune in nature

Sanders DS. Lancet 2001;358(9292):1504–8.   Rodrigo L. Arthritis Res Ther 2013;15(6):R201.

Diagnosis

- In one study, 178/924 patients with CD developed another autoimmune disease (~20%)

- In another, 23/140 pediatric patients with autoimmune liver disease had CD → consider CD in cryptogenic liver disease

Cosnes J. Clin Gastroenterol Hepatol 2008;6(7):753-8.   Caprai S. Clin Gastroenterol Hepatol 2008;6(7):803-6.

Symptoms and Associated Features

COMMON FEATURES

Adults
   Iron-deficiency anemia
   Diarrhea
Children
   Diarrhea
   Failure to thrive
   Abdominal distention

LESS COMMON FEATURES

General features
   Short stature
   Delayed puberty
Gastrointestinal features
   Recurrent aphthous stomatitis
   Recurrent abdominal pain
   Steatorrhea
Extraintestinal features
   Folate-deficiency anemia
   Osteopenia or osteoporosis
   Dental-enamel hypoplasia
   Vitamin K deficiency
   Hypertransaminasemia
   Thrombocytosis (hyposplenism)
   Arthralgia or arthropathy
   Polyneuropathy
   Ataxia
   Epilepsy (with or without
     cerebral calcification)
   Infertility
   Recurrent abortions
   Anxiety and depression
   Follicular keratosis
   Alopecia

ASSOCIATED CONDITIONS

Definite associations
- Dermatitis herpetiformis
- IgA deficiency
- Type 1 diabetes
- Autoimmune thyroid disease
   Sjögren's syndrome
   Microscopic colitis
   Rheumatoid arthritis
- Down's syndrome
   IgA nephropathy
Possible associations
   Congenital heart disease
   Recurrent pericarditis
   Sarcoidosis
   Cystic fibrosis
   Fibrosing alveolitis
   Lung cavities
   Pulmonary hemosiderosis
   Inflammatory bowel disease
- Autoimmune hepatitis
- Primary biliary cirrhosis
   Addison's disease
   Systemic lupus erythematosus
   Vasculitis
   Polymyositis
   Myasthenia gravis
   Schizophrenia
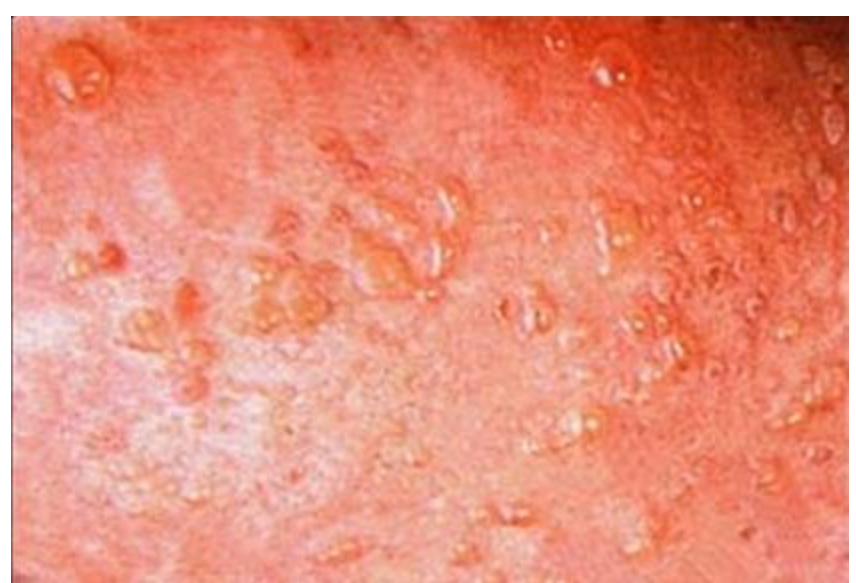
Dermatitis herpetiformis
- stains positive for IgA on skin biopsy
- treated with gluten-free diet (GFD) and dapsone

Diagnosis

- *Duodenal biopsies are the gold standard*
- Serologies have improved and are now a helpful screening tool
- If typical symptoms exist, EGD with biopsy can demonstrate enteritis with villous blunting
  - serologies can then confirm the diagnosis to rule out other causes of mal-assimilation
- If symptoms are atypical, it is more cost-effective to check serologies
  - if negative, CD is very unlikely
  - 10 EGDs are needed to diagnose 1 CD
  - if serologies are +, then EGD with duodenal biopsy can confirm the diagnosis (if needed)

Rostom A. Gastroenterology 2006;131(6):1981-2002.

Genetics

- Most celiac patients are HLA DQ2+ and the rest are HLA DQ8+

- DQ2 and DQ8 genotype testing available

- A negative genetic test essentially rules out celiac disease (NPV ~98-100%)
    - best used to definitively rule out celiac disease in those with a low pre-test probability

Lundkin KE. Hum Immunol 1994;41:285-91.

Serologies

SEROLOGIC TEST	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
		percent		
Test for IgA antiendomysial antibody				
Indirect immunofluorescence assay	85–98	97–100	98–100	80–95
ELISA that uses guinea pig tissue transglutaminase	95–98	94–95	91–95	96–98
Dot blot test that uses human tissue transglutaminase	93	99	99	93
Test for IgA antigliadin antibodies	75–90	82–95	28–100	65–100
Test for IgG antigliadin antibodies	69–85	73–90	20–95	41–88

• Antireticulin antibodies outdated
• Antigliadin antibodies also too nonspecific. These have been largely abandoned, though newer antibodies to deamidated gliadin are used
• TTG is the autoantigen for endomysial antibodies
• IgA deficiency is 10x more common in CD (1:40 vs 1:400), so *serum IgA should be checked to prevent false-negative testing* (if IgA deficiency exists, check an IgG anti-TTG)

Farrell RJ. New Engl J Med 2002;346(3):180-8.   Rostom A. Gastroenterology 2005;128(S1):S38-S46.
Sugai E. Clin Gastroenterol Hepatol 2006;4(9):1112-7.

Serologies

- The TTG antibody is the appropriate first test (or another marker like AEM or DGP)
  - only combine tests (panels) if age <2
- Antibody-negative CD increases in incidence with age
- Increasing antibody titers to TTG are statistically significantly associated with:
  - lower BMD
  - lower hemoglobin
  - lower BMI
 - lower total cholesterol
  - higher random blood glucose

West J. Clin Gastroenterol Hepatol 2007;5(1):59-62.
Rubio-Tapai A. Am J Gastroenterol 2013;108(5):656-76.

"Oh, yes...Mr. Celiac disease. I'm terrible with faces but I never forget a bowel biopsy."

Biopsies

- Despite improvements in serologic testing, *small bowel biopsies are still the gold standard* and recommended for diagnosis
- As celiac disease affects the small bowel in a proximal → distal pattern, EGD is the best modality to acquire tissue
- The nature of mucosal damage is often patchy
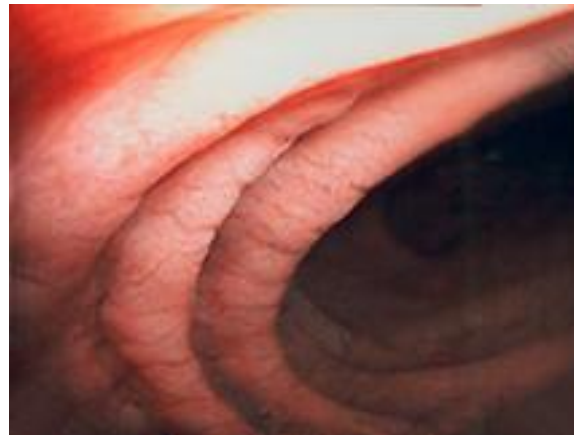 - sometimes enteroscopy is needed to obtain diagnostic specimens
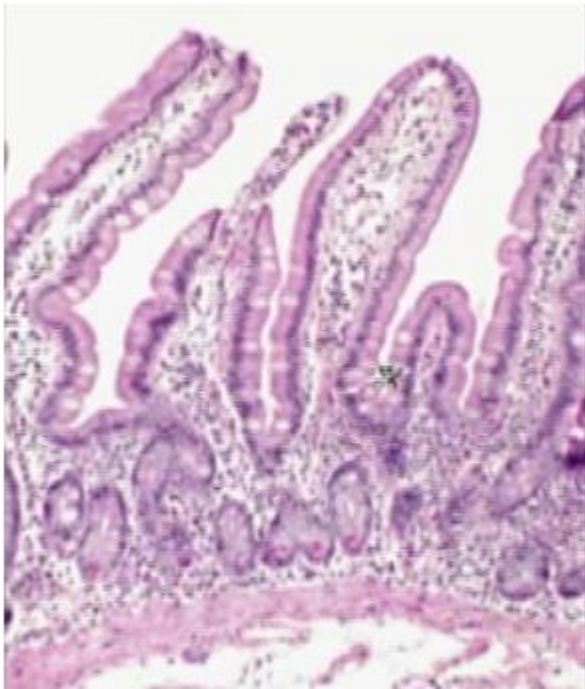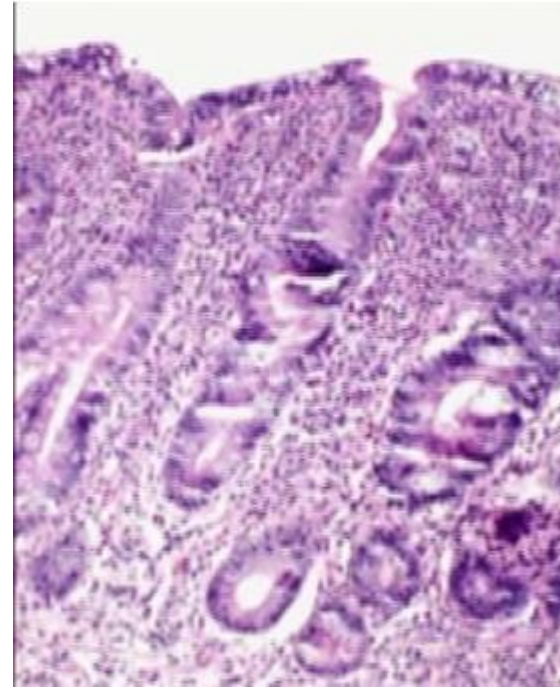
Small bowel endoscopy
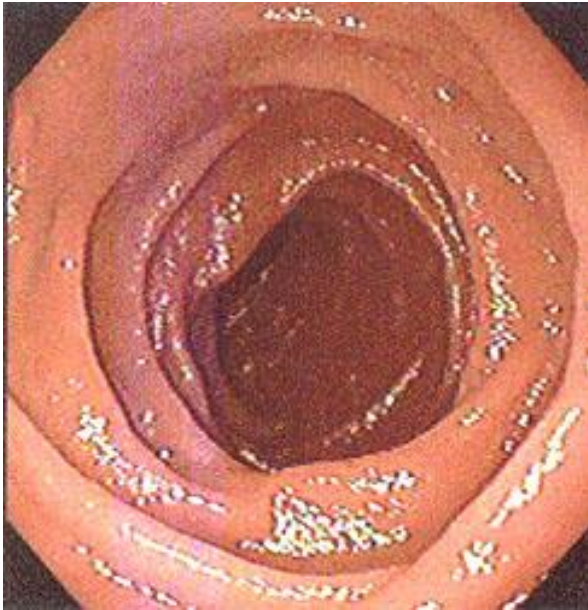
normal
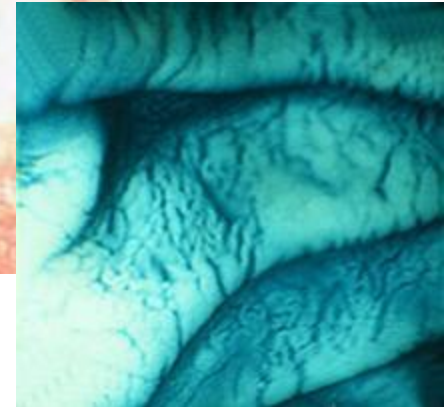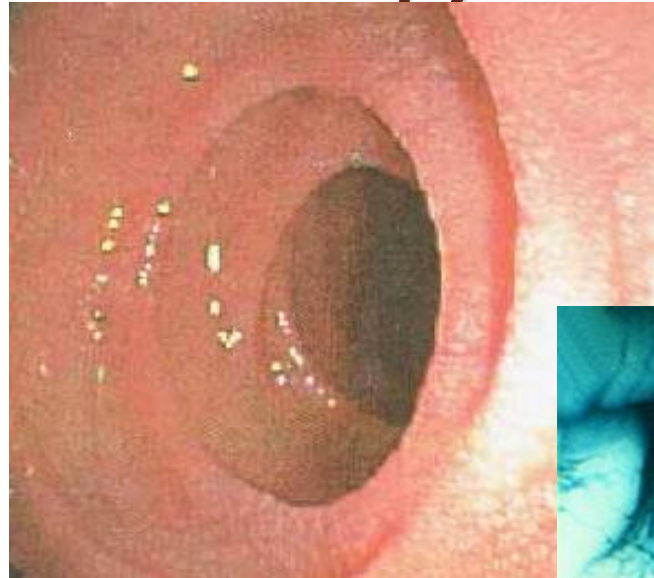
scalloping of the small bowel folds

Microscopy

normal

celiac disease

- <30-40 intraepithelial lymphocytes (IELs) per 100 enterocytes versus increased number
- bland lamina propria (normal) versus dense lymphocytic infiltrate (CD)
- 1:3 crypt to villous ratio versus 1:1
- normal villous height versus blunted

Biopsies – Modified Marsh (Oberhuber) classification

Table 1 The modified Marsh–Oberhuber classification

	Marsh 0	Marsh 1	Marsh 2	Marsh 3 3a	3b	3c	Marsh 4†
IEL count*	<30/100	>30/100	>30/100	>30/100	>30/100	>30/100	<30/100
Crypt hyperplasia	–	–	+	+	+	+	–
Villous atrophy	–	–	–	Mild	Moderate	Total	Total
	Pre-infiltrative	Infiltrative	Infiltrative-hyperplastic	Flat destructive			Atrophic-hypoplastic

IEL, intraepithelial lymphocytes.
*Number of intraepithelial lymphocytes per 100 enterocytes.
†This category is principally included for historic purposes.

Marsh MN. Gut 1990;31:111-4
Dickson BC. J Clin Pathol 2006;59:1008-16.

Biopsies

- What are the limitations in biopsy?
  - in a large multicenter study, ~10% of biopsy specimens were inadequate for diagnosis, mainly due to suboptimal **orientation** of the small duodenal specimens
  - **availability** of GI pathologists who know the different criteria and stages of disease
  - known **patchiness** of the disease
- So how many biopsies are needed?
  - 4 is best: 2 biopsies confirms diagnosis in 90%, 3 confirms in 95%, and 4 confirms in 100%
  - at least 1 in the bulb: sometimes villous atrophy only there

Collin P. Eur J Gastroenterol Hepatol 2005;17(1):85-91.   Pais WP. Gastrointest Endosc 2008;67(7):1082-7.
Evans KE. Am J Gastroenterol 2011;106(10):1837-42.

Enteritis

- In those with villous blunting, do not forget other etiologies
  - Giardia, Whipple disease, tropical sprue, CVID/HIV enteropathy, IL, eosinophilic disease, Crohn disease, ZES, SIBO, food allergies
  - most of these do NOT have ↑IELs
- Wireless capsule endoscopy has an emerging role in small bowel visualization in biopsy/serology negative CD → no controlled studies of balloon enteroscopy in this area yet

Spada C. World J Gastroenterol 2008;14(26):4146-51.

severe scalloping in mid-small bowel seen on capsule endoscopy

Dickey W. Clin Prac Gastroenterol Hepatol 2006;3(10):546-51.

What about NCGS?

- Non-celiac gluten sensitivity, ?etiology
  - better with gluten avoidance but NOT celiac disease (genetics, serologies, biopsies)
- What else does a gluten-free diet change?
  - fewer FODMAPs? fewer preservatives? "healthier" diet?
  - perhaps some immunologic basis
- Gluten-free diet may be most popular diet ever, but not without ?risk
  - more coronary artery disease?

  Lebwohl B.. BMJ 2017;357:j1892.
  - trace metal imbalance?

Whom to screen

- concomitant autoimmune disease
- 1st degree relatives of those with CD
- unexplained IDA
- unexplained osteoporosis
- any of the high-risk groups (one or more of the associated conditions/features)

- **NOT** in the general population as per March 2017 USPSTF recommendation

USPSTF. JAMA 2017;317(12):1252-7.
Chou R. JAMA 2017;317(12):1258-68.

Treatment

'Go ahead honey, it's gluten free!'

Treatment

- Hallmark of treatment is removal of all damage-inducing prolamins from diet (wheat, barley, rye)
- Congress passed the FDA's Food Allergen Labeling and Consumer Protection Act (FALCPA) in 2004, requiring food manufacturers to clearly state if a product contains any of the eight major food allergens
  - milk, eggs, peanuts, tree nuts, fish, shellfish, wheat, and soy
  - it also made more stringent guidelines on what constitutes "gluten-free"
- FINALLY, in August 2013 FDA mandated that "gluten-free" can only be used if <20 ppm
  - but some may get symptoms at >1 ppm

www.fda.gov
Forbes GM. Clin Gastroenterol Hepatol 2015;13(3):614-5.

Treatment

- Time to symptomatic improvement
  - days to weeks
- Time to serologic conversion
  - weeks to months
  - only relevant if pre-GFD serology was +
  - a non-invasive way of monitoring improvement/adherence
- Time to histologic improvement
  - months

The National Institutes of Health suggests these points to keep in mind as you care for your celiac disease:

C - **Consultation with a skilled registered dietitian (RD)**
- Ask your GI doctor for a recommendation.
- Perform a Google search for registered dieticians in your area who specialize in celiac disease.

E – **Education about celiac disease**
- Get and stay informed! Trusted websites, like government sites, can give you great information.

L – **Lifelong adherence to a GFD**
- Even a little bit of gluten can go a long way in terms of harming your gut. Learn the best ways to eat gluten-free while still keeping up your daily routines.

I – **Identification and treatment of nutritional deficiencies**
- This means having routine health exams so you doctor can check blood levels of certain vitamins, minerals and nutrients.

A – **Access to a support group**
- There are plenty of community groups that focus on celiac disease. Reach out and get connected!

C – **Continuous long-term follow-up by a multidisciplinary team**
- Since celiac disease stays with you your whole life, you need to create a good, long-term relationship with you doctor and dietitian. Be open with them about symptoms, questions or concerns.

Treatment

- In those not responding to a gluten-free diet (GFD), consider:
    - noncompliance → very difficult diet
    - inadvertent nonadherence
        - hordein in beer, gliadin in meds and the sticky part of envelopes/stamps, etc

        MOST COMMON
    - microscopic colitis (lymphocytic > collagenous)
    - ulcerative jejunitis → multiple SB ulcers
        - ? precursor to EATL
        - may respond to immunosuppression

Sussman DA. Am J Gastroenterol 2007;102(8):1833-4.   Parra J. Dig Dis Sci 2007;52(3):698-701.

ulcerations/erosions in the jejunum seen on capsule endoscopy (ulcerative jejunitis in a patient with celiac sprue not responding to a GFD)

Dickey W. Nat Clin Prac Gastroenterol Hepatol 2006;3(10):546-51.

Poor response to GFD

- concomitant food allergy/IBD
- small intestinal bacterial overgrowth
- malignancy
  - enteropathy-associated T-cell lymphoma (EATL) → high mortality
  - NHL (usually diffuse large B-cell)
  - small bowel adenocarcinoma
  - SCC of esophagus and oropharynx are increased in CD

Refractory sprue

- ~5% of patients, two types (RCD 1 and 2)
- Lose CD8 positivity, clonal expansion of aberrant IELs
  - ↑risk of lymphoma
  - usually responds to steroids
    - open-capsule budesonide
  - immunosuppressives and biologics may be needed long-term
  - cases of autologous hematopoietic SCT have been reported

Mauriño E. Am J Gastroenterol 2002;97(10):2595-602.
Al-toma A. Blood 2007;109(5):2243-9.
Gillett HR. Gastroenterology 2002;122(3):800-5.
Mukewar SS. Am J Gastroenterol epub online 03/21/17

How are we doing?

- US diagnosis rates so low in 2004 that NIH convened a Consensus Development Conference

- One CORI database study showed that in patients undergoing EGD for the following reasons, only:
  - 10% with anemia
  - 7% with iron deficiency
  - 6% with weight loss
  - 19% with diarrhea

  underwent a duodenal biopsy

- We continue to underdiagnose this common disease!!

James SP. Gastroenterology 2005;128(4):S1-9.   Harewood GC. Am J Gastroenterol 2004;99(9):1790-4.

Future Therapies

- Zonulin inhibition
  - Multicenter, randomized, double-blind, placebo-controlled study
  - Larazotide acetate 0.5, 1, or 2 mg 3 times daily
    - 342 adults with celiac disease on a GFD for ≥12 months
    - 4-week placebo run-in, 12 weeks treatment, 4-week placebo run-out
    - Primary endpoint: difference in symptoms (Celiac Disease Gastrointestinal Symptom Rating Scale score)
      - met with the 0.5-mg dose by mITT with decrease in non-GI symptoms too
      - 1- and 2-mg doses no different than placebo, safety comparable to placebo

Leffler DA. Gastroenterology 2015;148:1311-9.

Future Therapies

- Chemokine trafficking antagonism
  - CCR9 oral inhibitor CCX282-B (Traficet-EN, ChemoCentryx) originally studied for Crohn disease, now being evaluated for celiac disease
- Providing prolyl endopeptidases with food
  - no difference in symptoms, ↓fecal fat
  - perhaps as on-demand therapy for inadvertent consumption
  - see next slide
- Peptide immunotherapy?
  - there are 3 major peptides in prolamins that elicit the majority of the immunogenic T-cell response

http://clinicaltrials.gov/ct2/show/NCT00620451   Tye-Din JA. Sci Transl Med 2010;2(41):41ra51.
Salden BN. Aliment Pharmacol Ther 2015;42(3):273-85.   Konig J. DDW 2017.

No Difference Between Latiglutenase and Placebo in Reducing Villous Atrophy or Improving Symptoms in Patients With Symptomatic Celiac Disease

oral combination of two recombinant gluten-targeting proteases (glutenases)

RESULTS: In a modified intent-to-treat population, there were no differences between latiglutenase and placebo groups in change from baseline in villous height:crypt depth ratio, numbers of intraepithelial lymphocytes, or serologic markers of celiac disease. All groups had significant improvements in histologic and symptom scores. **CONCLUSIONS:** In a phase 2 study of patients with symptomatic celiac disease and histologic evidence of significant duodenal mucosal injury, latiglutenase did not improve histologic and symptom scores when compared with placebo. There were no significant differences in change from baseline between groups. ClinicalTrials.gov no: NCT01917630.

But symptoms do improve in some

- In a post-hoc analysis, patients with celiac disease who were seropositive despite adhering to a GFD had significant improvement in symptoms with latiglutenase

Syage JA. Dig Dis Sci, epub ahead of print 07/28/17.
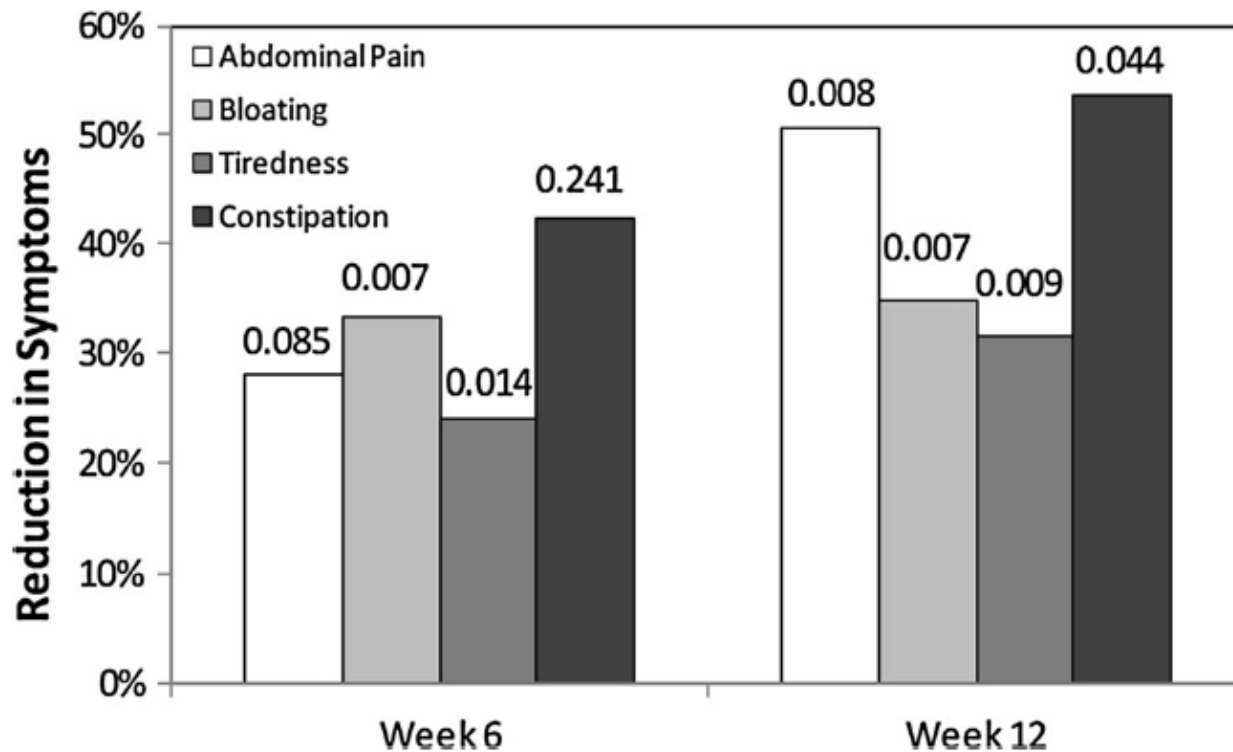
Vaccine?

- Adjuvant-free mix of 3 peptides that include immunodominant epitopes for gluten-specific CD4-positive T cells
- Intended to engage and render these T-cells unresponsive to further antigenic stimulation
- 2 Phase 1 studies with apparent safety and ?efficacy, further studies to follow

Goel G. Lancet Gastroenterol Hepatol 2017;2(7):479-93.

Table 1 *Overview over nondietary therapies for coeliac disease*

Mode of action	Compound	Compound class	Company/university	Status
Topical steroid	Budesonide	Small molecule	Generic drug	Approved
Rho kinase inhibition	Fasudil	Small molecule	Generic drug	Approved
Glutenase	ALV003	Enzyme	Alvine, USA	Phase II
Glutenase	AN-PEP	Enzyme	DSM, Netherlands	Phase I + II
Glutenase	STAN 1 (enzyme supplements)	Enzyme	Heim Pal Childrens Hospital, Hungary	Phase I + II
Zonulin antagonist	AT-1001	Peptide	Alba, USA	Phase II
CCR9 antagonist	CCX282-B	Small molecule	ChemoCentryx, USA	Phase II
Immune modulation	*Necator americanus*	Parasite	Princess Alexandra Hospital, Australia	Phase II
Peptide vaccination	Nexvax2	Peptide	Nexpep, Australia	Phase I
Anti-interleukin-15	AMG 714	Monoclonal antibody	Amgen, USA	Phase II in RA, psoriasis
Anti-IFN-γ	Fontolizumab	Monoclonal antibody	PDL and Biogen Idec, USA	Phase II in IBD, (discont.)
Anti-CD3	Visilizumab	Monoclonal antibody	Facet, USA	Phase II in UC, GvHD
Anti-CD3	Teplizumab	Monoclonal antibody	MacroGenics, USA	Phase II in T1D
Anti-CD3	Otelixizumab	Monoclonal antibody	Tolerx, USA	Phase III in T1D
Anti-CD20	Rituximab	Monoclonal antibody	Biogen Idec, USA	Approved
Anti-CD20	Tositumab	Monoclonal antibody	GlaxoSmithKline, USA	Approved
Anti-CD20	Ibritumomab	Monoclonal antibody	Spectrum, USA	Approved
RhoA inhibition	BA-210	Recombinant protein	Alseres, USA	Phase II in spinal cord injury
TG2 inhibitor	Dihydroisoxazoles	Small molecule	Stanford University, USA	Discovery
TG2 inhibitor	ZED-101	Small molecule	Zedira, Germany	Discovery
TG2 inhibitor	Cinnamoyl triazoles	Small molecule	University of Montreal, Canada	Discovery
HLA-DQ2 blocker	Dimeric analogue of gluten peptide	Peptide	Stanford University, USA & University of Oslo, Norway	Discovery
HLA-DQ2 blocker	Azidoproline analogue of gluten peptide	Peptide	Leiden University, Netherlands	Discovery
Gluten tolerisation	Genetically modified *Lactococcus lactis*	Bacteria	ActoGeniX, Belgium	Discovery
Gluten-sequestering polymers	P(HEMA-co-SS)	Polymer resin	University of Montreal, Canada	Discovery

RA, rheumatoid arthritis; HLA, human leucocyte antigen; IBD, inflammatory bowel disease; UC, ulcerative colitis; GvHD, graft versus host disease; TG2, transglutaminase 2; T1D, type 1 diabetes; P(HEMA-co-SS), poly(hydroxyethyl methacrylate-co-styrene sulphonate); Approved, Approved in other diseases.

Sollid LM. J Intern Med 2011;269(6):604-13.

Besides QoL, do we care?
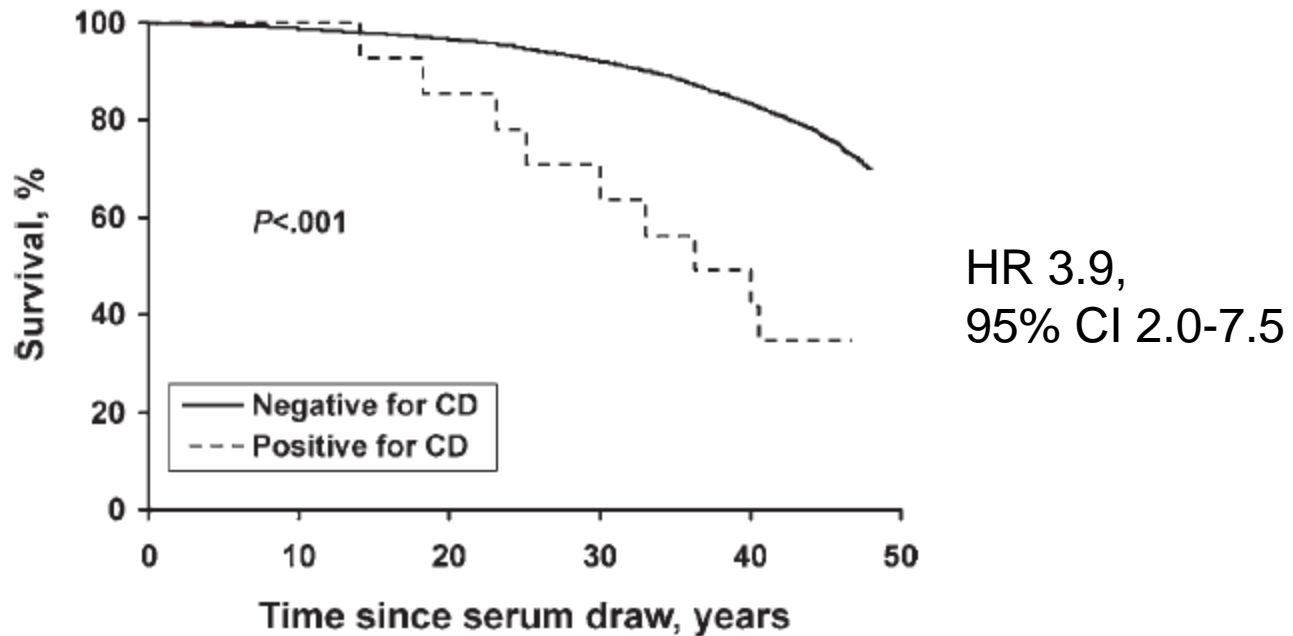

HR 3.9,
95% CI 2.0-7.5

Figure 1. Survival during 45 years of follow-up in 14 subjects with undiagnosed celiac disease (CD) and 9,076 seronegative persons in the WAFB cohort.

Sera from >9000 healthy adults at an Air Force base (1948-1954) had serology testing: 0.2% had celiac disease. 2 recent matched cohorts had 0.8% and 0.9% prevalence for undiagnosed celiac disease, a >4-fold increase.

Rubio-Tapia. Gastroenterology 2009;137(1):88-93.

Lack of treatment → complications

- Mortality
    - large Swedish database (>45,000 cases)
    - retrospective cohort (~1:5 case:control)
    - increased all-cause mortality in:
        - Marsh 3/celiac disease: HR1.39, 95% CI 1.33-1.45
        - Marsh 1-2/inflammation: HR 1.72, 95% CI 1.64-1.79
        - Marsh 0/latent celiac disease: HR 1.35, 95% CI 1.14-1.58
    - caveat: absolute mortality risk small
- If persistent villous atrophy → increased lymphoma

Ludvigsson JF. JAMA 2009;302(11):1171-8.   Lebwohl B. Ann Intern Med 2013;159:169-75.

Recent Review

Leonard MM. Celiac Disease and Nonceliac Gluten Sensitivity: A Review. JAMA 2017;318(7):647-56.

Some patient resources

celiac.org
beyondceliac.org
csaceliacs.org
americanceliacsociety.org

BifSniff.com

While he couldn't be sure this was the killer, Inspector Lynch knew now that he was dealing with a very complex carbohydrate.

THANK YOU!