Celiac Disease 2017: Just the Tip of the Iceberg

Amar R. Deshpande MD
Associate Professor of Medicine
Asst Dean for Medical Education
Vice Chief for Education, Division of Gastroenterology
University of Miami Miller School of Medicine
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

- 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

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.
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.
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

Sood A. Am J Gastroenterol 2001;96(9):2804-5.
The Iceberg


abnormal serologies
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*


* 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

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.
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 prolamain effect?

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

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 autoantigens, 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 MIEC). 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. MIEC, MHC class I polypeptide-related sequence; NKG2D, natural killer group 2, member D.
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

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

Microbiome and Hygiene

Table 2. Risk of Celiac Disease After Cesarean Delivery

<table>
<thead>
<tr>
<th></th>
<th>Matched controls (%)</th>
<th>Celiac disease (%)</th>
<th>OR; 95% CI</th>
<th>P value</th>
<th>Adjusted OR, a</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cesarean delivery</td>
<td>5766/53,887 (10.7)</td>
<td>1299/11,749 (11.1)</td>
<td>1.04; 0.98–1.10</td>
<td>.232</td>
<td>1.06; 0.99–1.13</td>
<td>.074</td>
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<tr>
<td>Number of participants</td>
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<tr>
<td>Emergency cesarean delivery b</td>
<td>2136/41,699 (5.1)</td>
<td>444/8827 (5.0)</td>
<td>0.99; 0.90–1.10</td>
<td>.857</td>
<td>1.02; 0.92–1.13</td>
<td>.749</td>
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<td>Number of participants</td>
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<tr>
<td>Elective cesarean delivery b</td>
<td>2125/41,688 (5.1)</td>
<td>508/8891 (5.7)</td>
<td>1.11; 1.01–1.22</td>
<td>.027</td>
<td>1.15; 1.04–1.26</td>
<td>.005</td>
<td></td>
</tr>
<tr>
<td>Number of participants</td>
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</tbody>
</table>

aBirths 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).

bData 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.

http://www.intratext.com/ixt/_EXT-REP/_P2R.HTM
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

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

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

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)
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

Please Excuse Me From Being Late. I HAVE Explosive Diarrhea.

-K
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

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

### 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

adapted from Dermatol Nursing 2004, AAD website
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)
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

**Serologies**

<table>
<thead>
<tr>
<th>Serologic Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive Predictive Value</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test for IgA antiendomysial antibody</td>
<td></td>
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<tr>
<td>Indirect immunofluorescence assay</td>
<td>85–98</td>
<td>97–100</td>
<td>98–100</td>
<td>80–95</td>
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<tr>
<td>ELISA that uses guinea pig tissue transglutaminase</td>
<td>95–98</td>
<td>94–95</td>
<td>91–95</td>
<td>96–98</td>
</tr>
<tr>
<td>Dot blot test that uses human tissue transglutaminase</td>
<td>93</td>
<td>99</td>
<td>99</td>
<td>93</td>
</tr>
<tr>
<td>Test for IgA antigliadin antibodies</td>
<td>75–90</td>
<td>82–95</td>
<td>28–100</td>
<td>65–100</td>
</tr>
<tr>
<td>Test for IgG antigliadin antibodies</td>
<td>69–85</td>
<td>73–90</td>
<td>20–95</td>
<td>41–88</td>
</tr>
</tbody>
</table>

- 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)

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

"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 small bowel folds

Scallopig of the small bowel folds

adapted from www.celiacdiseasecenter.columbia.edu
Microscopy

- <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

adapted from www.thedaveproject.com
Biopsies – Modified Marsh (Oberhuber) classification

Table 1  The modified Marsh–Oberhuber classification

<table>
<thead>
<tr>
<th></th>
<th>Marsh 0</th>
<th>Marsh 1</th>
<th>Marsh 2</th>
<th>Marsh 3</th>
<th>3a</th>
<th>3b</th>
<th>3c</th>
<th>Marsh 4†</th>
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<tbody>
<tr>
<td>IEL count*</td>
<td>&lt;30/100</td>
<td>&gt;30/100</td>
<td>&gt;30/100</td>
<td>&gt;30/100</td>
<td>&gt;30/100</td>
<td>&gt;30/100</td>
<td>&lt;30/100</td>
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</tr>
<tr>
<td>Crypt hyperplasia</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Villous atrophy</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>Pre-infiltrative</td>
<td>Infiltrative</td>
<td>Infiltrative-hyperplastic</td>
<td>Moderate</td>
</tr>
<tr>
<td>IEL, intraepithelial lymphocytes.</td>
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<td>*Number of intraepithelial lymphocytes per 100 enterocytes.</td>
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<td>†This category is principally included for historic purposes.</td>
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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

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
severe scalloping in mid-small bowel seen on capsule endoscopy
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?
  - 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
Treatment

‘Go ahead honey, it’s gluten free!’
Treatment

- Hallmark of treatment is removal of all damage-inducing prolamin 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
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
  ◦ microscopic colitis (lymphocytic > collagenous)
  ◦ ulcerative jejunitis → multiple SB ulcers
    • ? precursor to EATL
    • may respond to immunosuppression

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

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!!

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

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

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http://clinicaltrials.gov/ct2/show/NCT00620451
Konig J. DDW 2017.
No Difference Between Latiglutenate 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 latiglutenate 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, latiglutenate 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

**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

<table>
<thead>
<tr>
<th>Mode of action</th>
<th>Compound</th>
<th>Compound class</th>
<th>Company/university</th>
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<td>PHEMA-co-SS</td>
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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; PHEMA-co-SS, poly(hydroxyethyl methacrylate-co-styrene sulphonate); Approved, Approved in other diseases.

Besides QoL, do we care?

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.

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.
Lack of treatment $\rightarrow$ complications

- **Mortality**
  - large Swedish database (>45,000 cases)
  - retrospective cohort (~1:5 case:control)
  - increased all-cause mortality in:
    - Marsh 3/celiac disease: HR 1.39, 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 $\rightarrow$ increased lymphoma**

Some patient resources:
celiac.org
beyondceliac.org
csaceliacs.org
americanceliacssociety.org

THANK YOU!