The Celiac conundrum:

a case-based approach to understand the many facets of gluten toxicity

Jean-Frédéric LeBlanc
PGY-5 Adult Gastroenterology
McGill University Health Centre
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McGill

Disclosure

I am not a dietitian and will not attempt to act as one.

Otherwise, I have no conflicts of interest.

session's objectives

1- Review the evolution of medical experts' understanding of gluten toxicity

2- Highlight typical and atypical presentations of celiac disease and non-celiac gluten sensitivity

3- Identify the challenging areas in the diagnosis and management of celiac disease

4- Apply practical tips to optimize patient adherence to suggested therapies

The Cases of M. F. Sili and ms. B. Ghet

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The Case of ms. B. Ghet

34 year-old female

She presents to the outpatient clinic for a two-month history of abdominal cramps and constipation. She has tried multiple laxatives, probiotics, antispasmodics without any benefit.

She is now worried about cancer because she has lost around 5 kilograms in the last month.

Her father passed away from colorectal cancer at age 55 and he had complained of similar symptoms.

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The Case of M. F. Sili

45 year-old male

He is referred for a one-year history of abdominal cramps and non-bloody diarrhea (from one to four liquid stools per day). He has noticed a partial improvement by avoiding certain foods.

He does not exhibit any weight loss, nor extra-GI symptoms. He has no family history of celiac disease, nor colorectal cancer.

What types of testing should we request?

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Gluten is deadly

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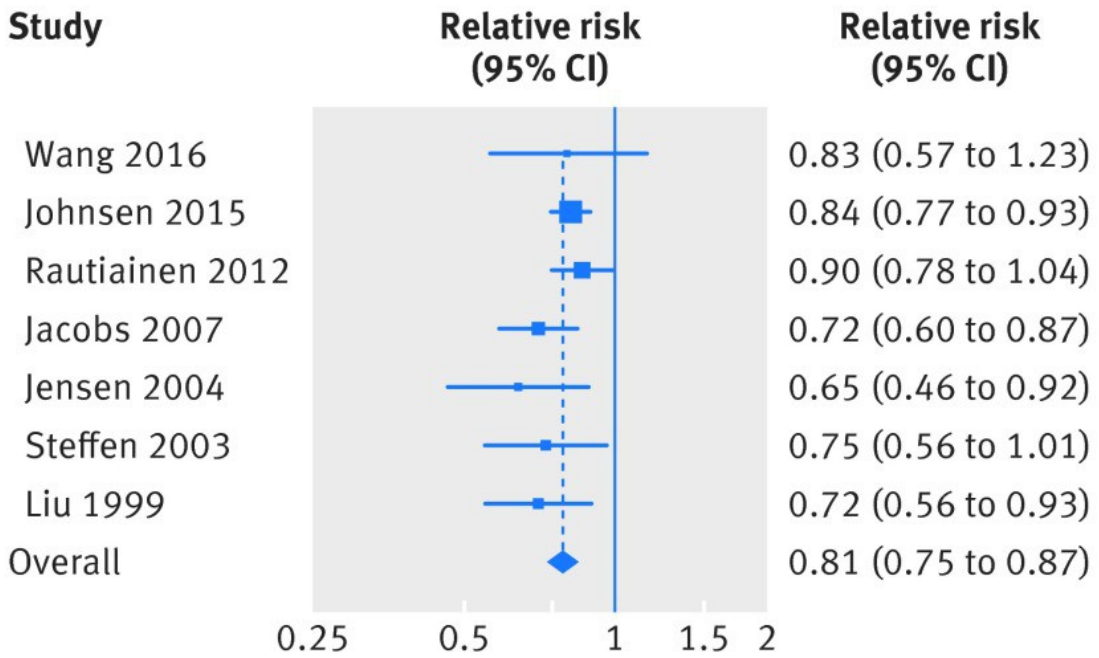
On the contrary...

Higher intake of whole grains leads to lower rates of heart disease, stroke, type 2 diabetes and death from all causes.



Gluten


Figure 1: Wheat


Figure 2: Rye


Figure 3: Barley

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1- Etymology: latin word “glue”

2- Prolamin storage proteins found in cereal grains:

- Wheat
- Barley
- Rye
- Contaminated oat

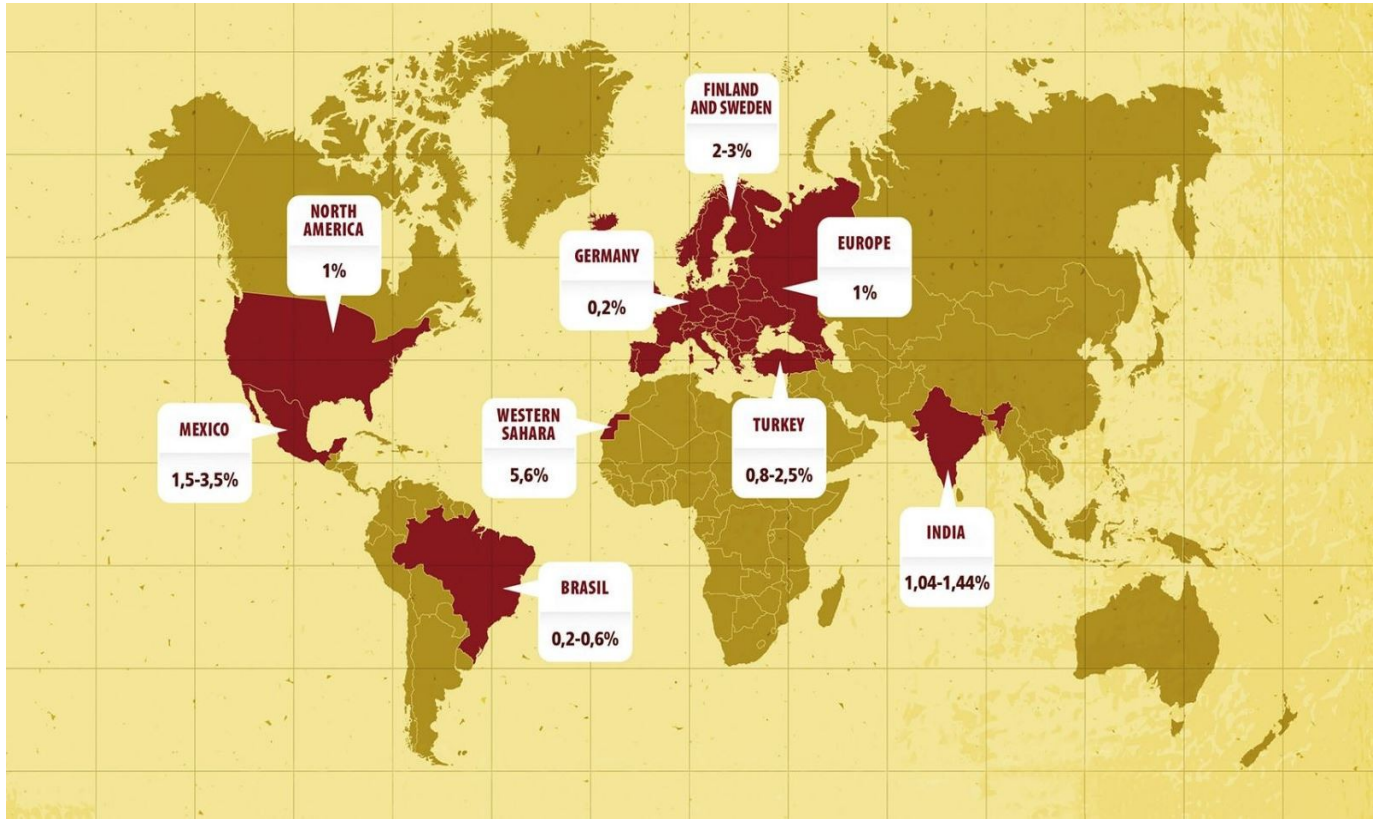
3- Enriched in glutamines and prolines, causing incomplete digestion by gastric, pancreatic and border brush peptidases

Celiac disease

A chronic, immune-mediated disease of the small bowel, triggered by exposure to dietary gluten in genetically-predisposed individuals.

Global burden

- 1% of population in North America
- Highest prevalence in Scandinavian countries, lowest in Brazil and African countries
  - Poorly understood
- Increasing prevalence due to increased physician and public awareness



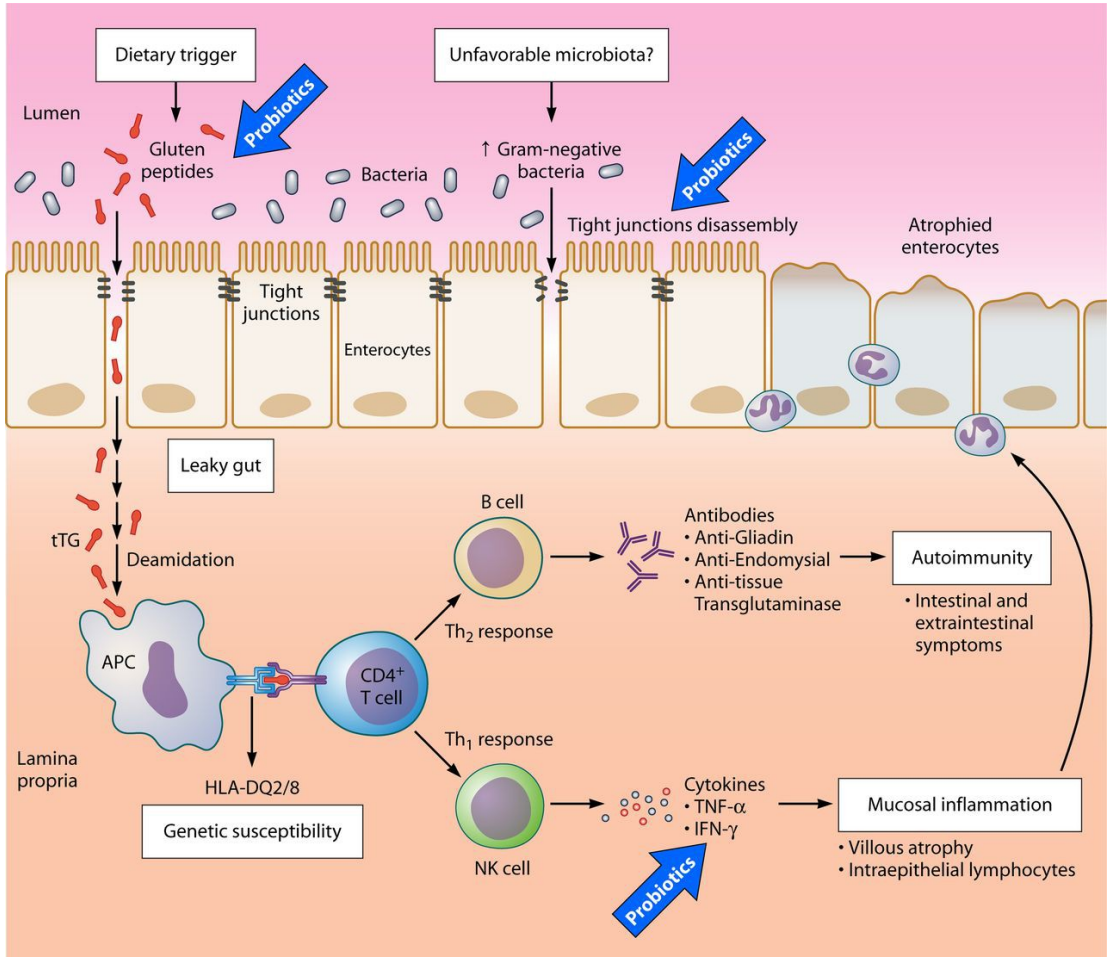
Gluten toxicity: A Simplified model

1- Absorption of gluten peptides through lamina propria

2- Deamidation of gliadin molecules by tissue transglutaminase (TTG)

3- Binding to HLA-DQ2/8 on APCs then presented to gliadin-reactive CD4+ cells

4- Activated CD4+ cells begin the inflammatory cascade (B + NK cells)



Is it all about the genes?

- Almost 100% of patients with celiac disease are HLA-DQ2/8 positive
- 40% in Americas, Europe, SE Asia are positive for HLA-DQ2/8
  - Of the 40%, only 2-3% develop celiac disease in their lifetime
- 39 non-HLA regions associated with increased risk of celiac disease

HLA predisposition and gluten ingestion is quite common. So why is only 1% of the population affected ?

Environmental factors

- Delayed gluten introduction: only short-term effect
  - No effective prevention measures as per pediatric guidelines
  - Start between 4 and 12 months
- Infectious trigger : gastrointestinal, respiratory
  - Rotavirus vaccination : potential protective effect
- Gut microbioma:
  - Complex mechanisms, higher rates of Gram-negative bacteria and *Bifidobacterium bifidum*

Gastrointestinal symptoms

Classic symptoms (early-onset, now rare)

- Chronic diarrhea, steatorrhea, complications from malabsorption, weight loss, failure to thrive, tooth enamel defects

Non-classical symptoms (later-onset, more common)

- Abdominal pain, constipation, bloating, chronic fatigue, headache, osteoporosis complications, iron deficiency
- UK study: average 13-year delay in diagnosis

Panel 1: Terminology describing patients with coeliac disease (adapted from Ludvigsson and colleagues, 2013)[70]

Potential
Positive serological tests and normal intestinal biopsy

Asymptomatic
Absence of symptoms despite specific questioning regarding symptoms

Symptomatic
Presence of either intestinal or extra-intestinal symptoms

Classic
Diarrhoea, signs and symptoms of malabsorption, or both

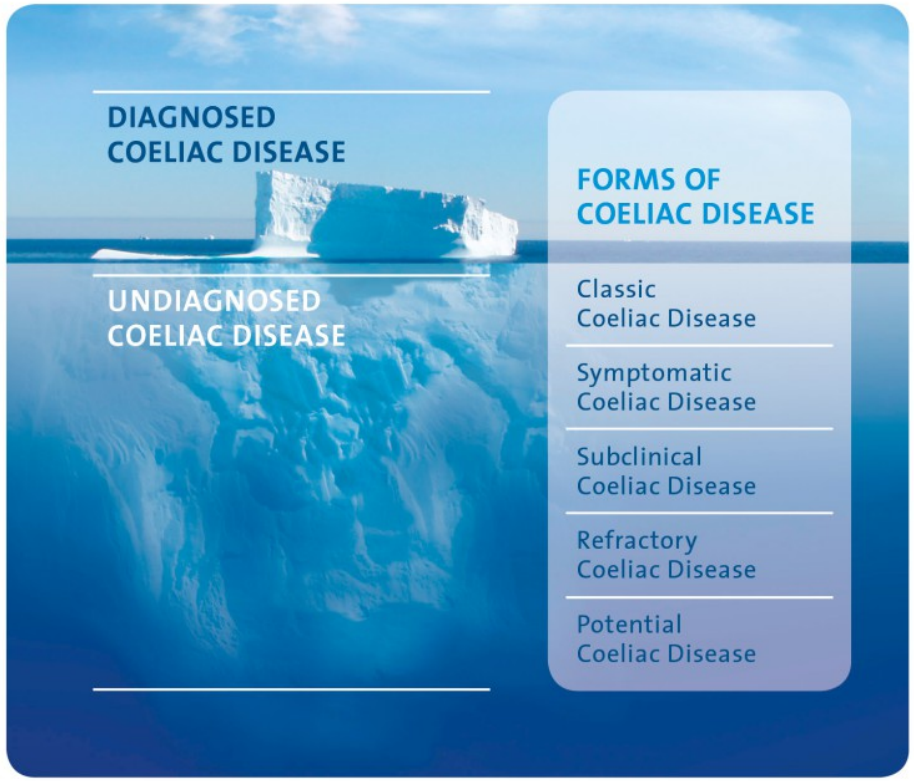
Non-classic
Lack of malabsorption symptoms, but other symptoms present (eg, anaemia, osteoporosis)

Refractory
Persistent symptoms and villous atrophy despite adherence to a gluten-free diet

THE celiac iceberg

- High number of undiagnosed cases of celiac disease, mostly due to the atypical nature of symptoms

- Estimated at 500 000 in a large UK registry



Spectrum of extra-Intestinal symptoms

- An example of what can be found on the internet within 2 minutes
- Truth lies in between:
  - Neuropsychiatric : headaches, peripheral neuropathies
  - Osteoporosis
  - Hyposplenism
  - Dermatitis herpetiformis
  - Type 1 diabetes mellitus, hypothyroidism, IBD
  - Selective IgA deficiency, IgA nephropathy
  - Transaminitis
  - Down syndrome
  - Intrauterine growth restriction, male infertility
  - Myocarditis and DCM
  - Pancreatitis

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Dermatitis herpetiformis
"celiac of the skin"

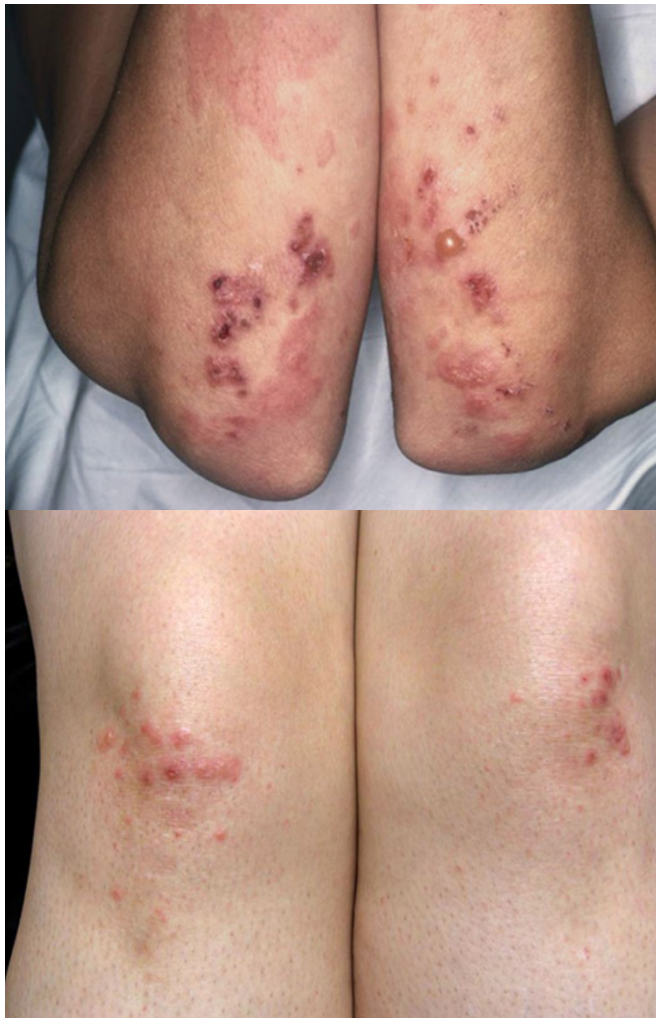
1- Multiple intensely pruritic papules and vesicles, in grouped arrangement (herpetiformis), commonly associated to celiac disease

2- Areas affected: elbows, forearms, knees, scalp, back and buttocks

3- Biopsy shows granular IgA deposits along the basement membrane

4- Treatment:

- Combination of gluten-free diet (GFD) and dapsone



Liver injury

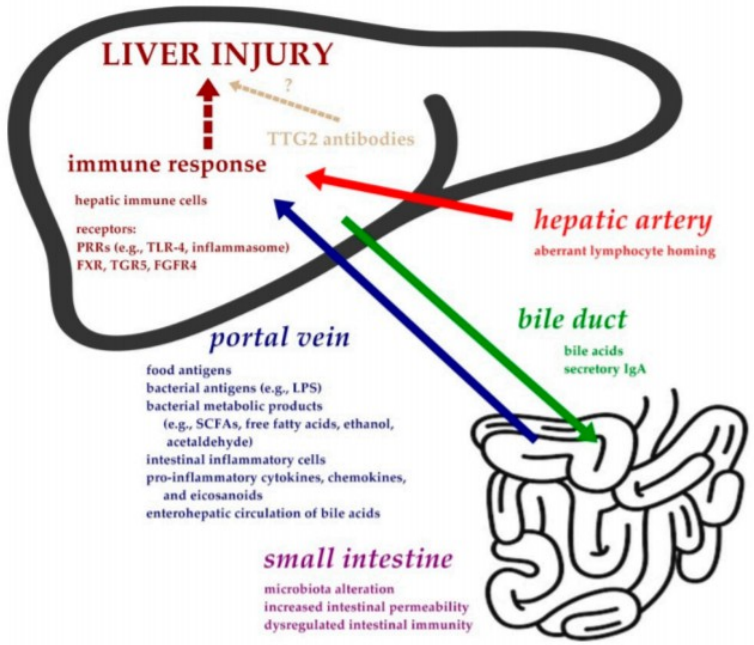
1- Liver-gut axis: complex interactions between disrupted intestinal barrier and liver's immune capacity

2- Prevalence of high serum transaminases in active celiac disease: 10-50%

3- Most commonly, mild chronic elevation in AST (30-80) and ALT (60-130).

- Responsive to GFD in a majority of cases within 1 year

4- Associated with advanced liver disease, likely related to the underlying etiology (autoimmune liver diseases)



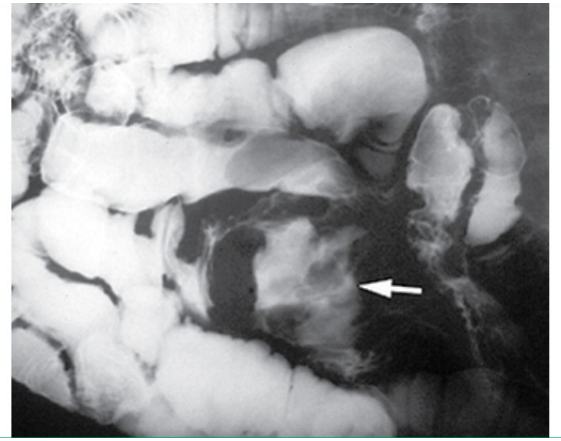
Malignancy and mortality risk

1- Gastrointestinal malignancy

- Two-fold increased risk compared to controls
- Anywhere in the GI tract, mostly liver and small intestine

2- Small bowel non-Hodgkin lymphoma

- Six-fold increased risk compared to controls
- Associated to refractory celiac disease



3- Gluten-free diet:

- Uncertain benefit in preventing malignancies

4- Increased overall mortality, especially closer to time of diagnosis

- Related to cardiovascular, respiratory disease and malignancy

Who should be tested?

Coeliac testing recommended

- Persistent unexplained abdominal or gastrointestinal symptoms
- Faltering growth
- Prolonged fatigue
- Unexpected weight loss
- Severe or persistent mouth ulcers
- Unexplained iron, vitamin B12, or folate deficiency
- Type 1 diabetes
- Autoimmune thyroid disease
- Irritable bowel syndrome
- First degree relatives of people with coeliac disease

Coeliac testing should be considered

- Metabolic bone disorders (reduced bone mineral density or osteomalacia)
- Unexplained neurological symptoms (particularly peripheral neuropathy or ataxia)
- Unexplained subfertility or recurrent miscarriage
- Persistently increased concentrations of liver enzymes with unknown cause
- Dental enamel defects
- Down's syndrome
- Turner syndrome

Diagnostic methods

1- Serology testing*

2- Genetic factors

3- Endoscopy and biopsy*

* A gluten-containing diet is required to optimize diagnostic reliability. Gluten Challenge: Traditionnally, 10g of daily gluten for 6 weeks. Recent data opt for shorter, lower dose of gluten (example 3g daily for 2-4 weeks).

serologies

1- IgA-based anti-transglutaminase (TTG)

- High sensitivity (90%), low cost. Measure IgA levels.

2- IgG-based anti-transglutaminase (TTG)

- Variable sensitivity, slightly increased cost

3- IgA-based Endomysial antibodies (EMA)

- Slightly lower sensitivity, higher specificity (95%)
- Difficult access (from monkey esophagus or human umbilicus)

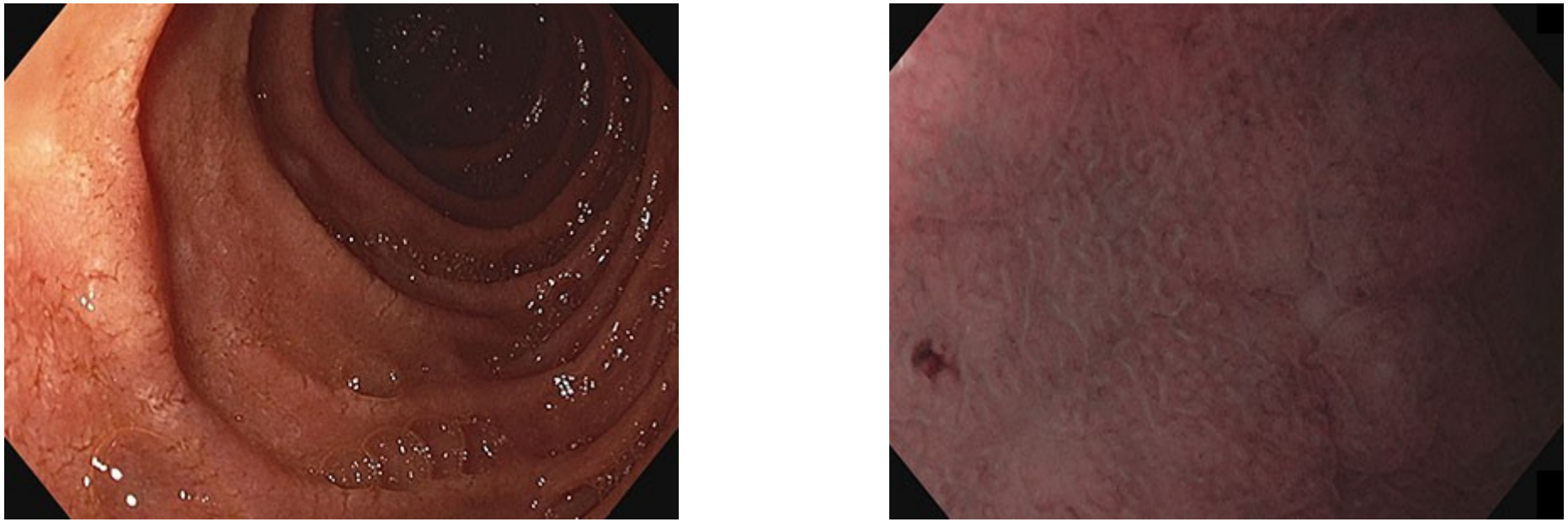
4- Anti-gliadin deamidated peptide (GDP)

5- Anti-gliadin antibodies – to avoid

Table 3. Range of Sensitivity and Specificity and Use of Current Serologic Tests for Celiac Disease[a]

Serologic Study	% Sensitivity	% Specificity	Application in Clinical Practice
IgA tTG	73.9-100	77.8-100	First-line testing to screen for celiac disease[b]
IgG DGP	80.1-96.9	86.0-96.9	First-line testing for celiac disease in patients with IgA deficiency
IgA EMA	82.6-100	94.7-100	Second-line confirmatory test to screen for celiac disease
IgG tTG	12.6-99.3	86.3-100	Not recommended for routine use because of poor sensitivity compared with IgG DGP
IgA DGP	80.7-95.1	86.3-93.1	Not recommended for routine use because of poor sensitivity and specificity compared with IgA tTG and IgA EMA

Ms. B. Ghet's Gastroscopy results...



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Four biopsies of the second part of the duodenum and one biopsy of the duodenal bulb are taken. She is curious about the results: villous atrophy, crypt hyperplasia and marked intraepithelial lymphocytosis.

Role of Endoscopy

1- Findings:

- Atrophic duodenal mucosa, absent villi
- Visible fissures
- Scalloped or nodular folds
- Normal duodenal mucosa

2- Biopsies required: minimum 4 in D2 and 1 in duodenal bulb (ideally separate into 2 specimen jars)

3- Perform biopsies even in cases of high anti-TTG levels:

- Serologies' sensitivity often decrease in real-world setting
- Impact of a lifelong gluten-free diet
- Avoids diagnostic uncertainty in patient who do not respond to GFD
- Provides a baseline histologic reference

Potential findings - Endoscopy

Endoscopy in pediatric population

1- Higher risk of morbidity (general anesthesia)

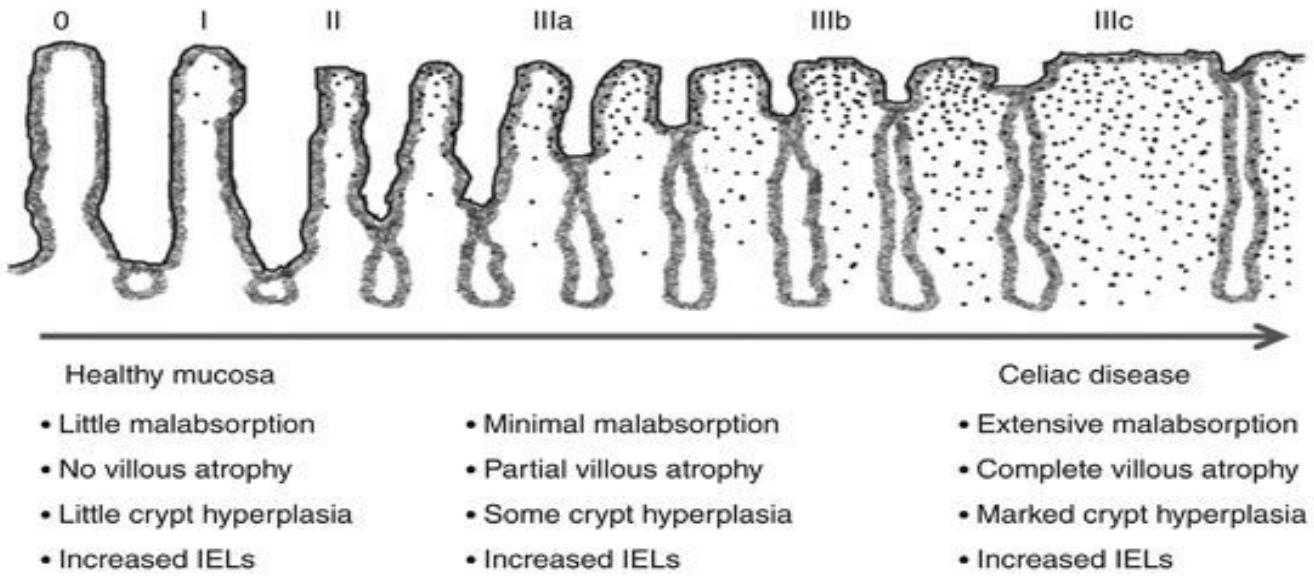
2- Diagnosis can be done without endoscopy in carefully selected symptomatic patients (ESPGHAN, 2012):

- TTG 10 times higher than upper limit of normal
- Positive EMA in a different blood sample
- Presence of HLA-DQ2/8

3- Not yet applicable to the adult population

Pathology

Marsh Type	IEL / 100 enterocytes - duodenum	Crypt hyperplasia	Villi
0	<30	Normal	Normal
1	>30	Normal	Normal
2	>30	Increased	Normal
3a	>30	Increased	Mild atrophy
3b	>30	Increased	Marked atrophy
3c	>30	Increased	Complete atrophy

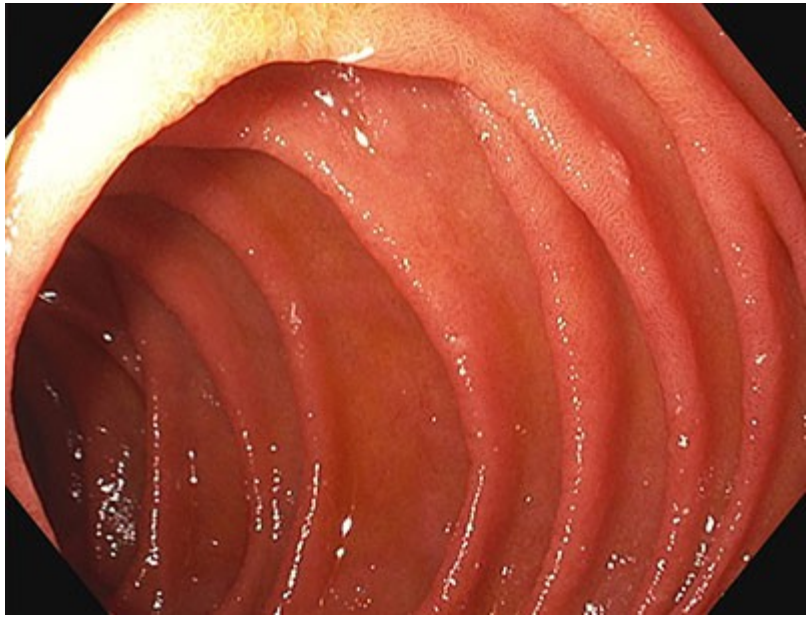


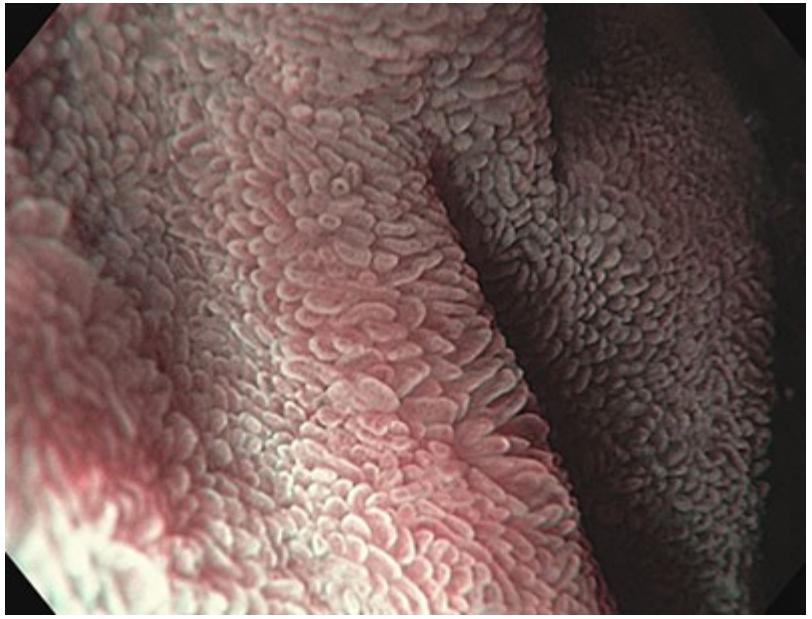
Villous atrophy: Not only celiac disease...

Causes of small intestinal villous atrophy other than celiac disease

Small intestinal bacterial overgrowth
Crohn disease
Cow's milk or soy protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Intestinal lymphoma
Peptic duodenitis
Post-gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically, eg, AIDS enteropathy, hypogammaglobulinemic sprue)
Medications (eg, olmesartan)
Whipple disease
Malnutrition
Intestinal tuberculosis
Graft-versus-host disease

M. F. SILI insists for a Gastroscopy...





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Similar biopsy protocol for celiac disease: normal duodenal mucosa in all specimens

Negative tests, persisting symptoms

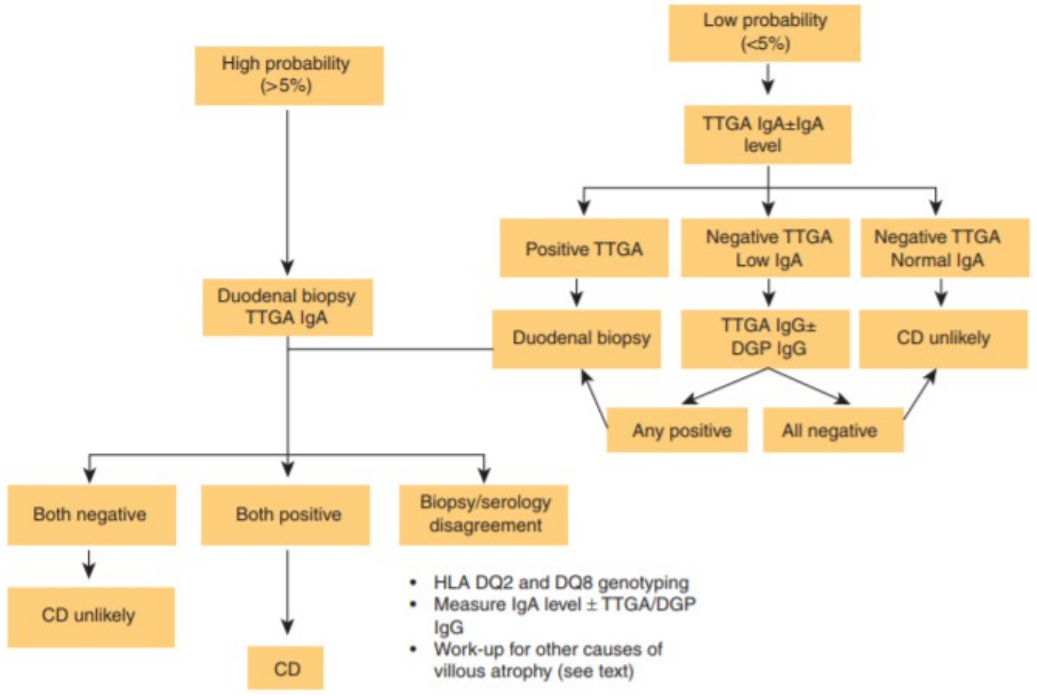
Non-celiac gluten sensitivity (gluten intolerance):

- Similar gastrointestinal symptoms, relieved by a GFD without evidence of celiac disease (negative serologies, genetic studies and normal histology)
- Treatment: symptomatic relief by a GFD
- Not associated with:
  - Genetic predisposition
  - Nutritional deficiencies, nor increased risk for intestinal malignancy

Wheat allergy:

- Typical allergic symptoms of nasopharyngeal pruritus and edema, maculopapular rash, wheezing and/or anaphylaxis within minutes to hours of wheat ingestion
- Diagnosed by symptoms and positive skin-prick and grain-specific IgE
- Most often resolves by 5 years of age

Diagnostic algorithm



ACG Guidelines, 2013

Treatment

#1 Strict gluten-free diet

- Symptoms improve within days or weeks (80%), usually before normalization of anti-TTG and histology

- Caveats:
  - Controls the disease, not a cure
  - Increased cost of GFD
  - Erroneous online resources about gluten-containing food
  - Contamination in restaurants
  - Social pressures (teenage years)
  - Trace amounts in Rx or supplements

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Valuable tidbits

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1- Refer to a dietitian as soon as the diagnosis is confirmed

- Important to keep adequate nutrients and fiber intake
- Help in pure oat reintroduction in small amounts if desired

2- Refer to the Canadian Celiac Association:

- Gouvernment funding for incremental costs of GFD products
- Involve celiac patients in support groups
- Reliable source for the do's and dont's of celiac disease:
  - Gluten Awareness: avoid sharing toaster, butter dish, cutting board, and wear a mask (gluten-containing flour)

3- Celiac disease app:

- On-the-go app to look into gluten-free products and restaurants

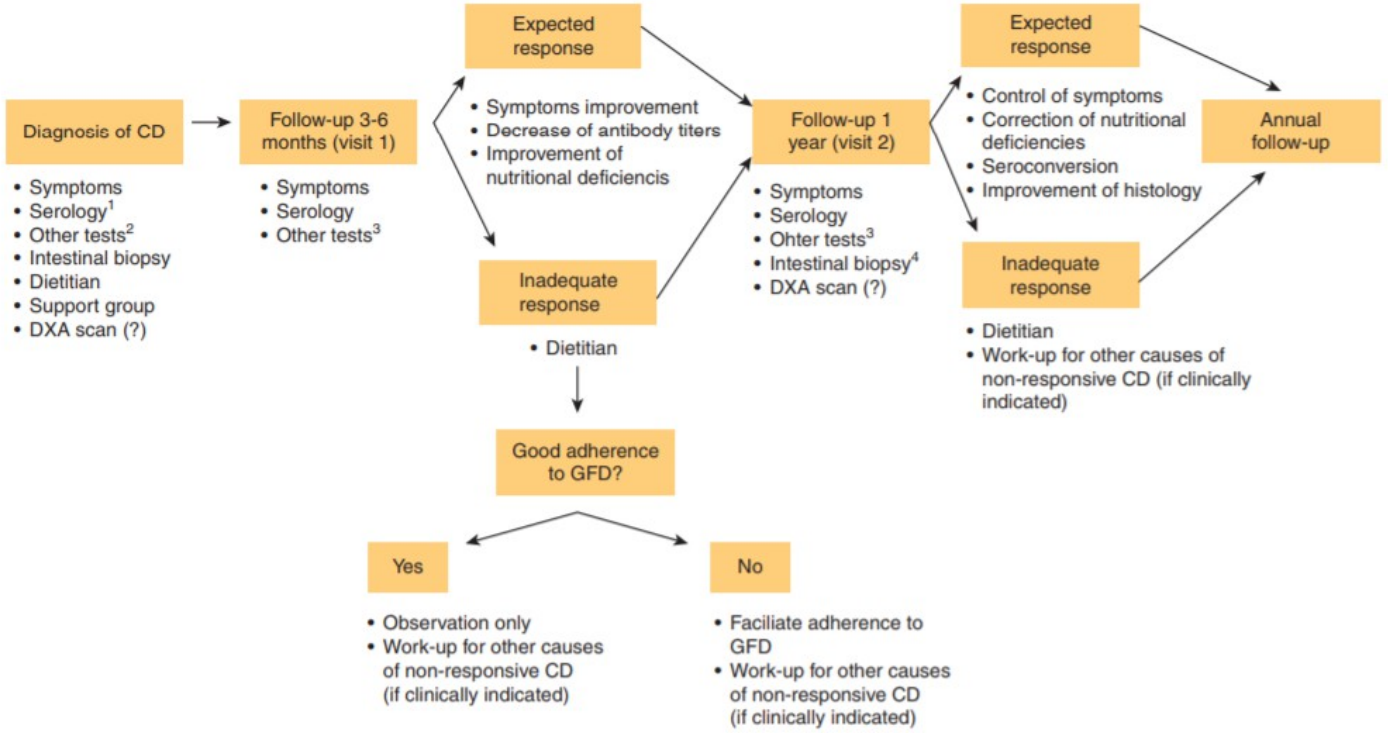
Valuable tidbits

4- Measure iron, vitamin D, B12, folic acid in all patients and replete PRN

5- Consider pneumococcal vaccination (hyposplenism)

6- In patients 55 years or older or at high risk of osteoporosis, refer for bone mineral density testing 1 year after GFD

Monitoring algorithm



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Non-dietary approach

Therapeutic advances:

1- Vaccine consisting of epitopes for gluten-specific CD4+ cells (phase 1)

2- Larazotide acetate : peptide which prevents passage of gliadin peptides through epithelial barrier (combined with GFD, phase 2)

3- Latiglutenase: enzyme preparation which prevents pathological damage caused by gluten (combined with GFD, phase 2)

Let us recall the objectives

1- Review the evolution of medical experts' understanding of gluten toxicity

2- Highlight typical and atypical presentations of celiac disease and non-celiac gluten sensitivity

3- Identify the challenging areas in the diagnosis and management of celiac disease

4- Apply practical tips to optimize patient adherence to suggested therapies

References

1- West J, Fleming KM, Tata LJ et al. *Incidence & prevalence of coeliac disease and dermatitis herpetiformis in the UK over two decades: Population-based study.* Amer J Gastroenterol 2014; 109:757-768

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3- Lebwohl et al, *Coeliac disease*, Lancet Seminar, 2017 July 28; vol 91; 70-81

4- Leonard et al, *Celiac Disease and Nonceliac Gluten Sensitivity: A Review*, JAMA. 2017; 318(7):647-656.

5- *UpToDate* – online medical resource, Diagnosis and management of celiac disease

Any questions?

Thank you to Mildred Clément and to the Canadian Society of Gastroenterology Nurses & Associates for the invitation !

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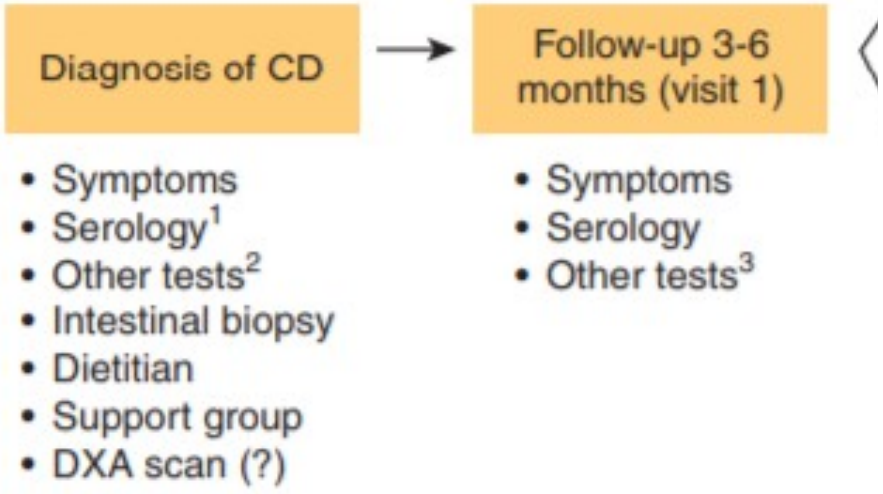
Additional slides

Monitoring algorithm



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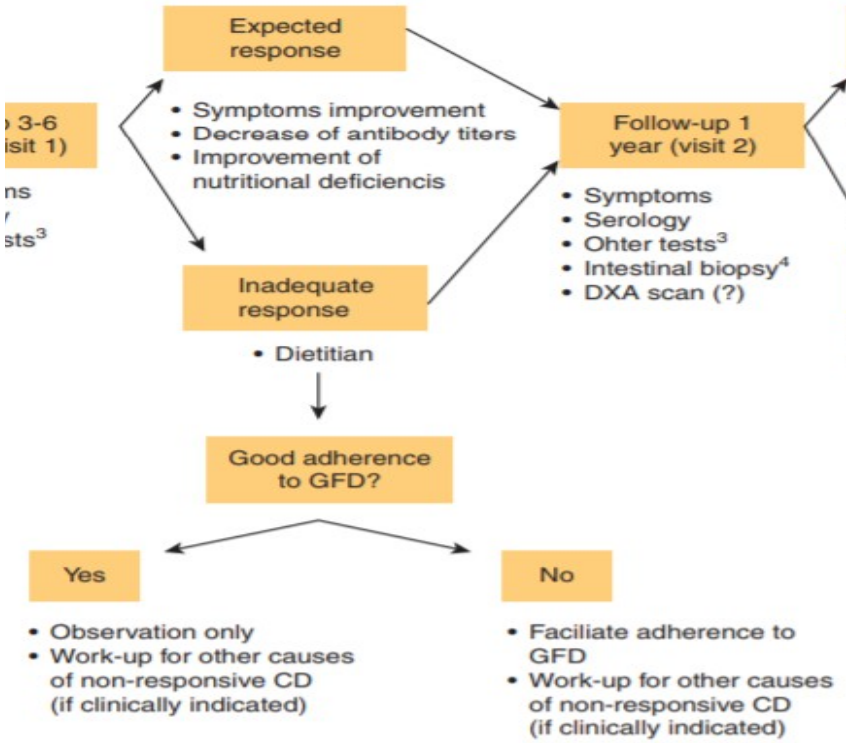

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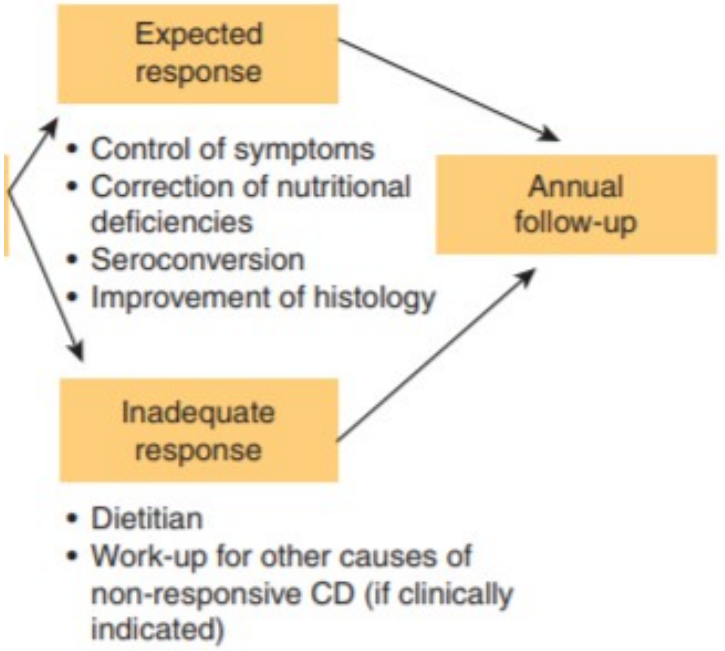

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Refractory

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Type I

- No aberrant

- Better prognc

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