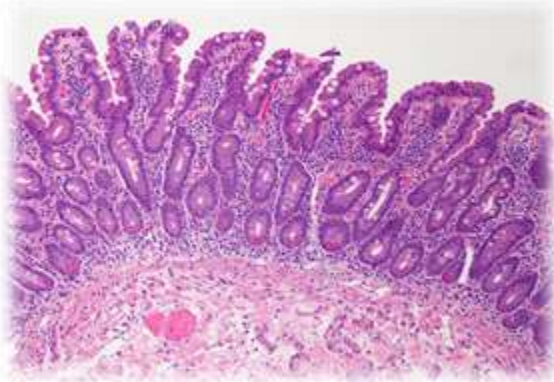




Celiac Mimickers: A Sheep in Wolf's Clothing



Amy S. Oxentenکو, MD FACP, FACG

Professor of Medicine, Mayo Clinic College of Medicine & Science

Vice Dean of Practice, Mayo Clinic

Consultant, Division of Gastroenterology/Hepatology

Oxentenکو.amy@mayo.edu



[@AmyOxentenکوMD](https://twitter.com/AmyOxentenکوMD)

DISCLOSURES

None...
other than I consume gluten!



Objectives

Detail

Detail the entities that can mimic celiac disease either clinically or histologically

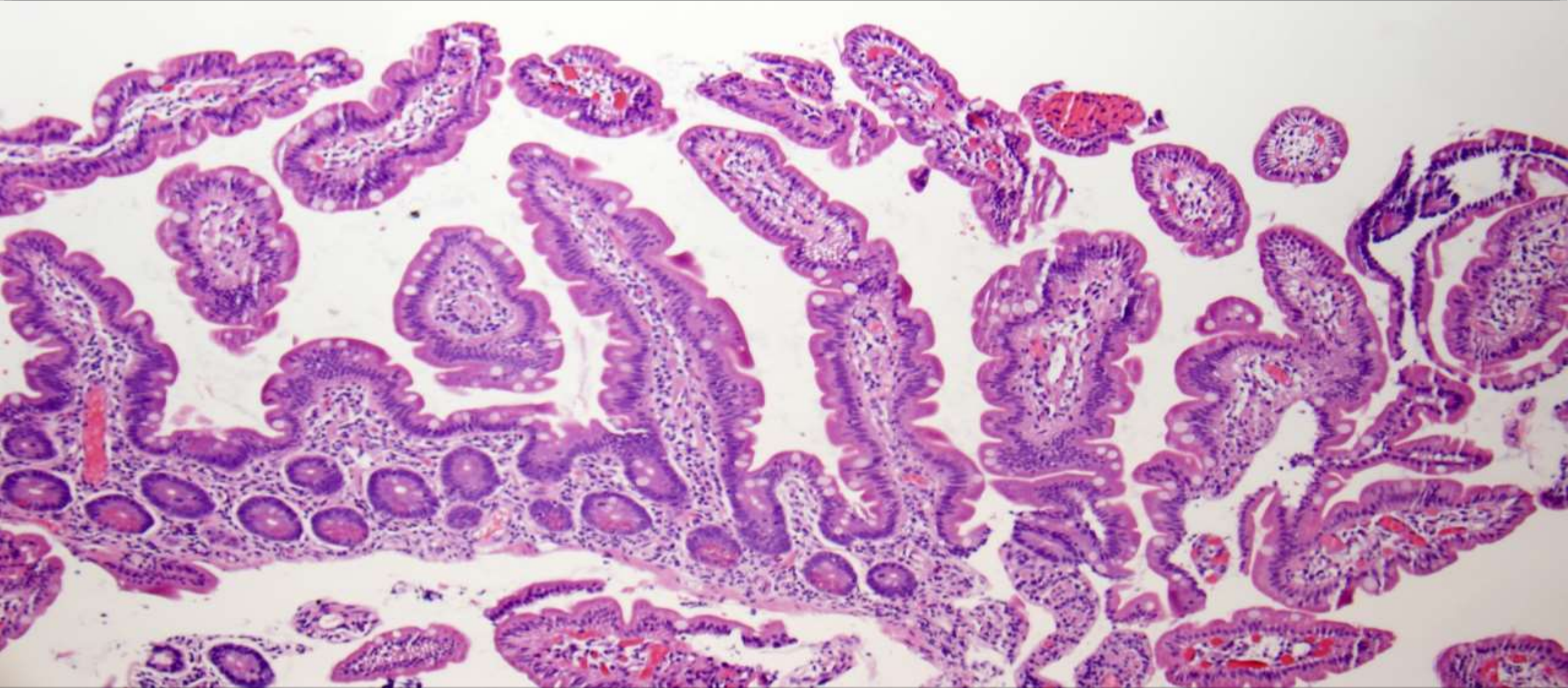
Identify

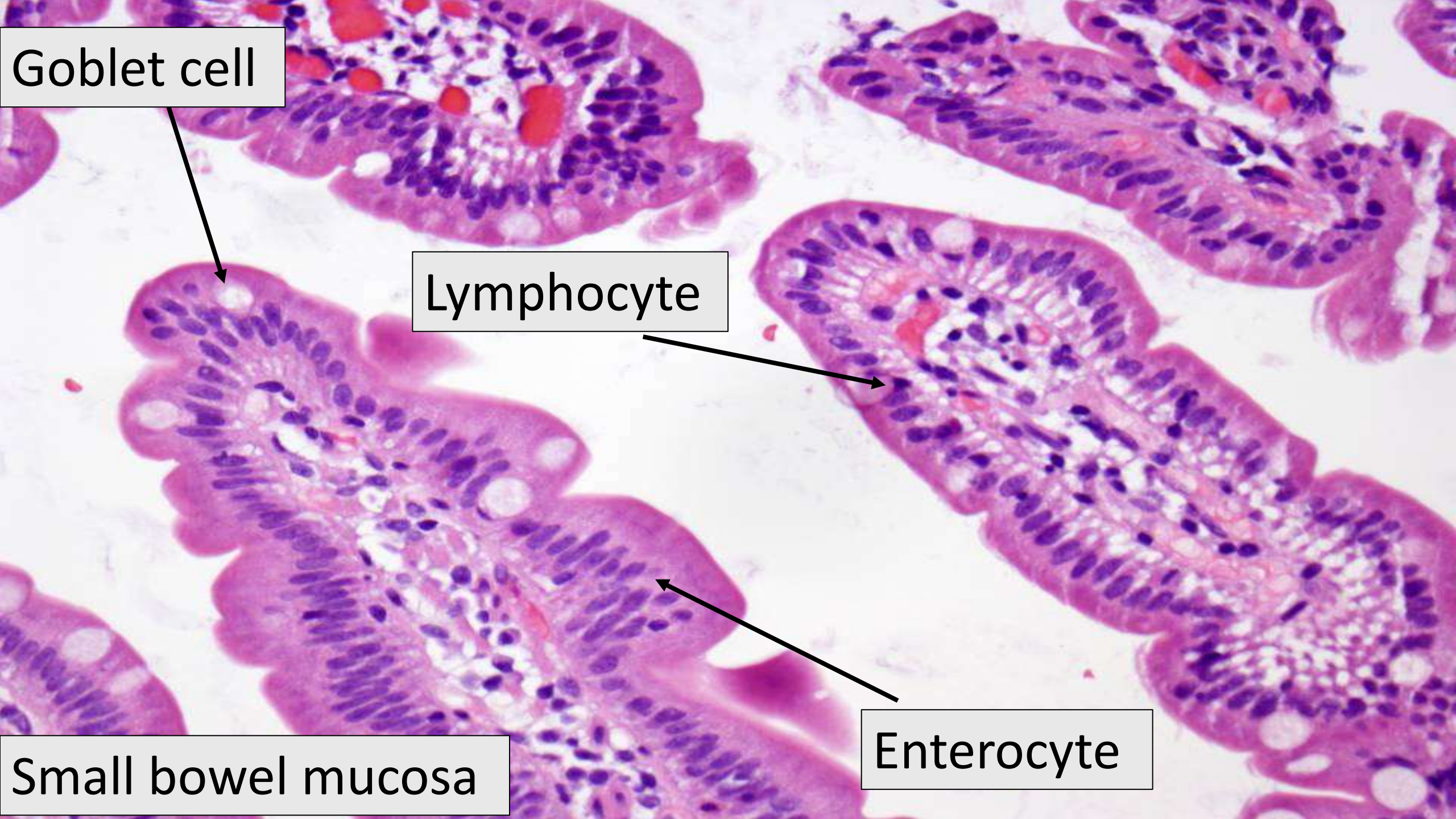
Identify the clinical and/or histologic differences to be able to distinguish between the differing disorders

Outline

Outline an approach to the patient with serologically-negative enteropathy

Normal Small Bowel





Goblet cell



Lymphocyte

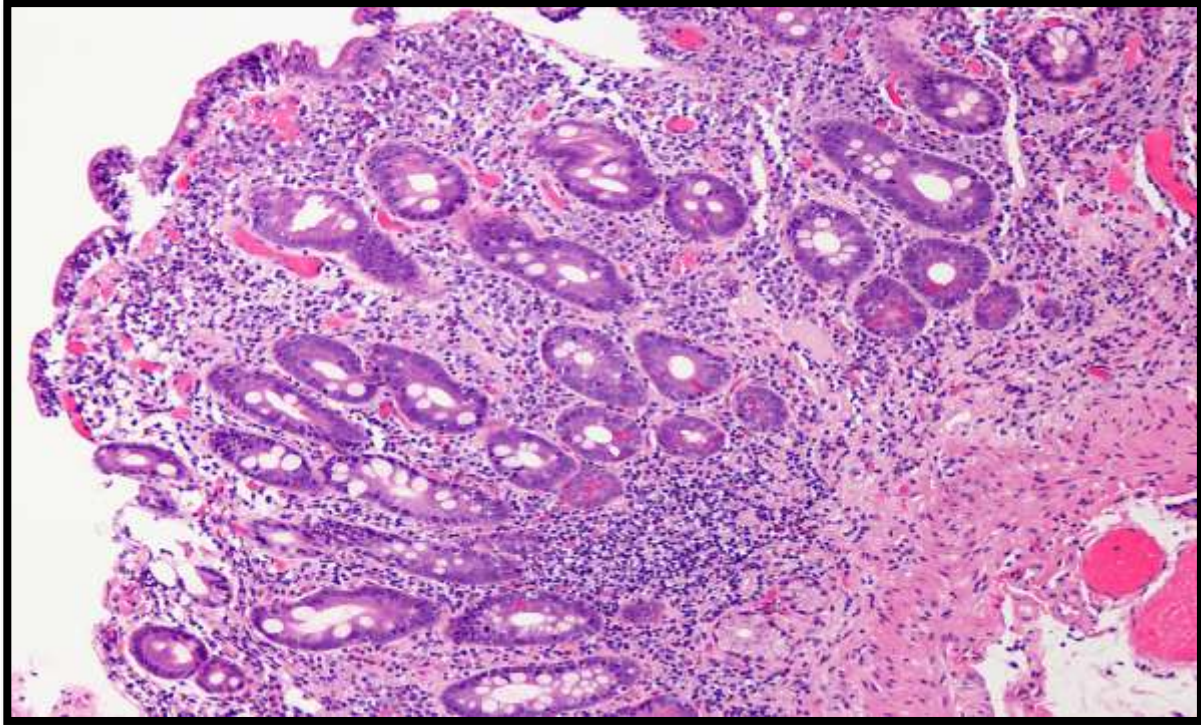


Small bowel mucosa

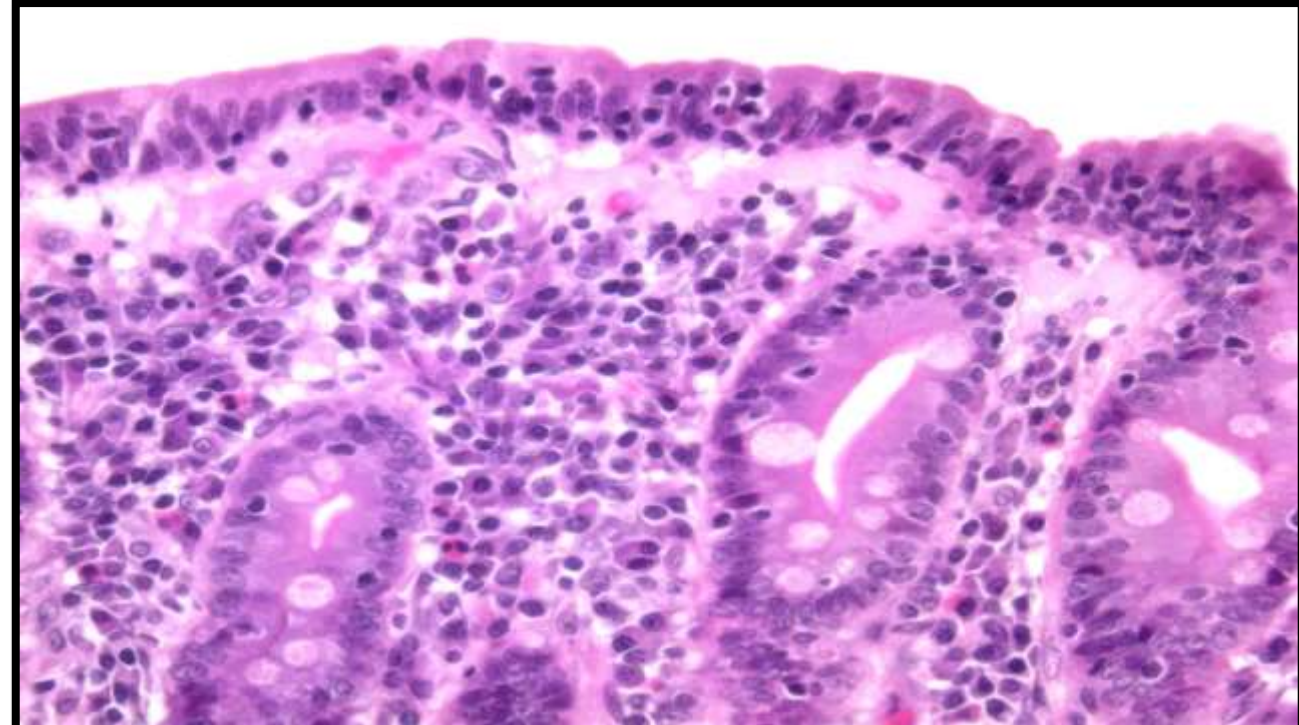
Enterocyte



Celiac Disease



- Flattened villi (partial/total)
- Crypt hyperplasia



- Increased IELs
- Chronic inflammatory cell infiltrate in lamina propria

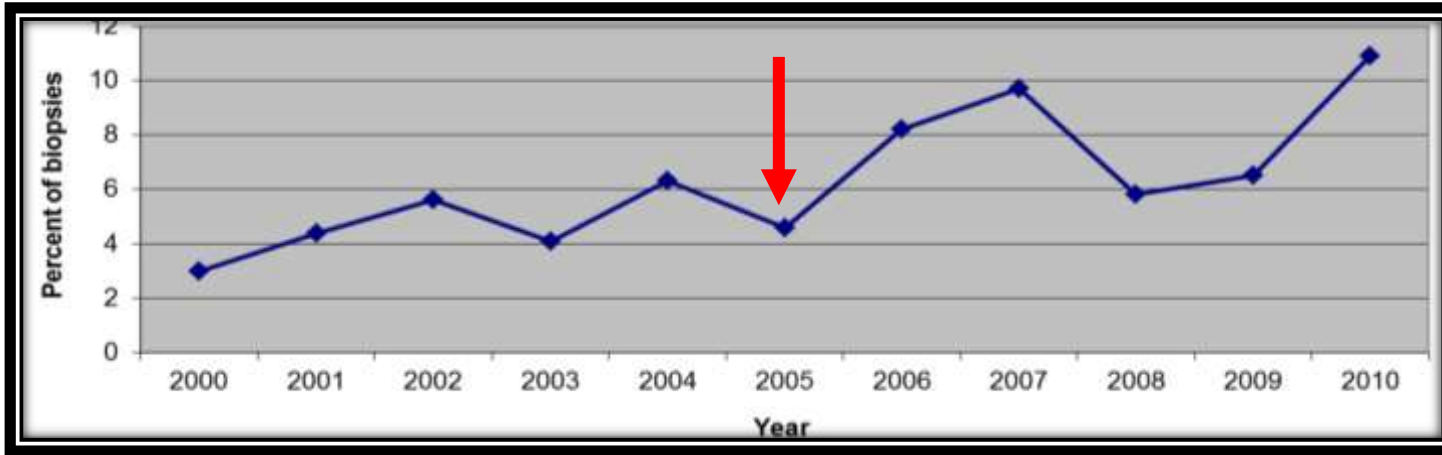
Early Histologic Mimickers

**IELs, no atrophy
(Marsh 1 and 2)**

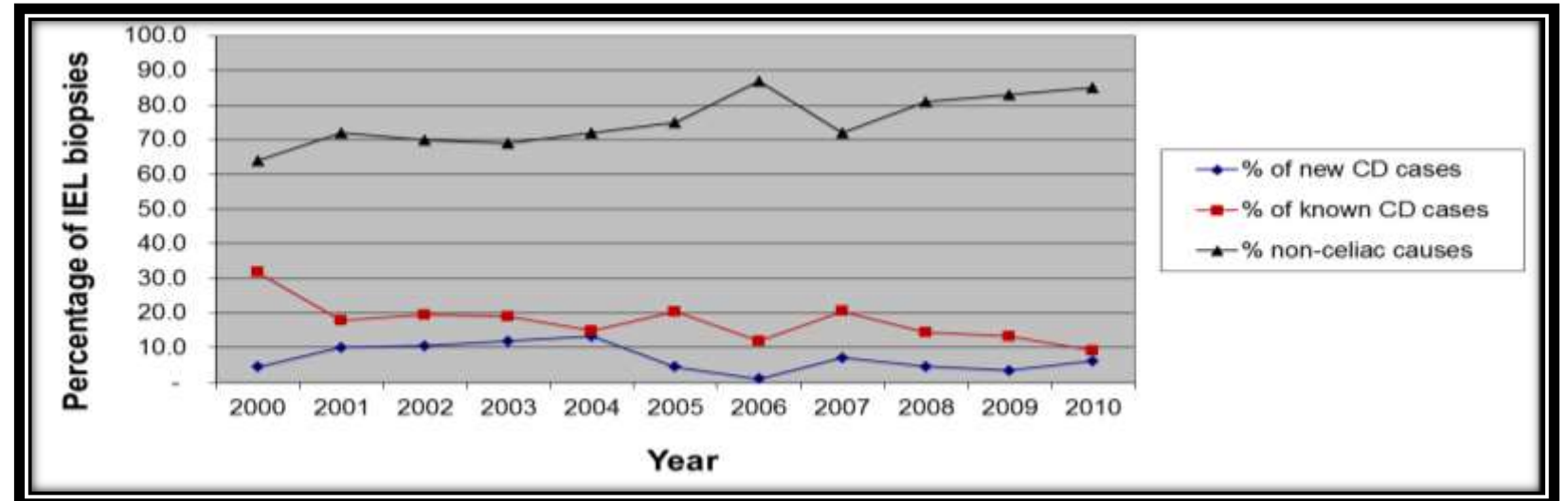


Intraepithelial Lymphocytes (IELs): What is “Abnormal”?

2005: ≥ 25 IELs/100 epithelial cells (prior 40)



Excluding known CD, only 6.8% dx with CD



Shmidt E, Smyrk TC, Boswell CL, Enders FT, Oxentenko AS, GIE 2014;80:105-11.

Histologic Findings are Not Specific to CD

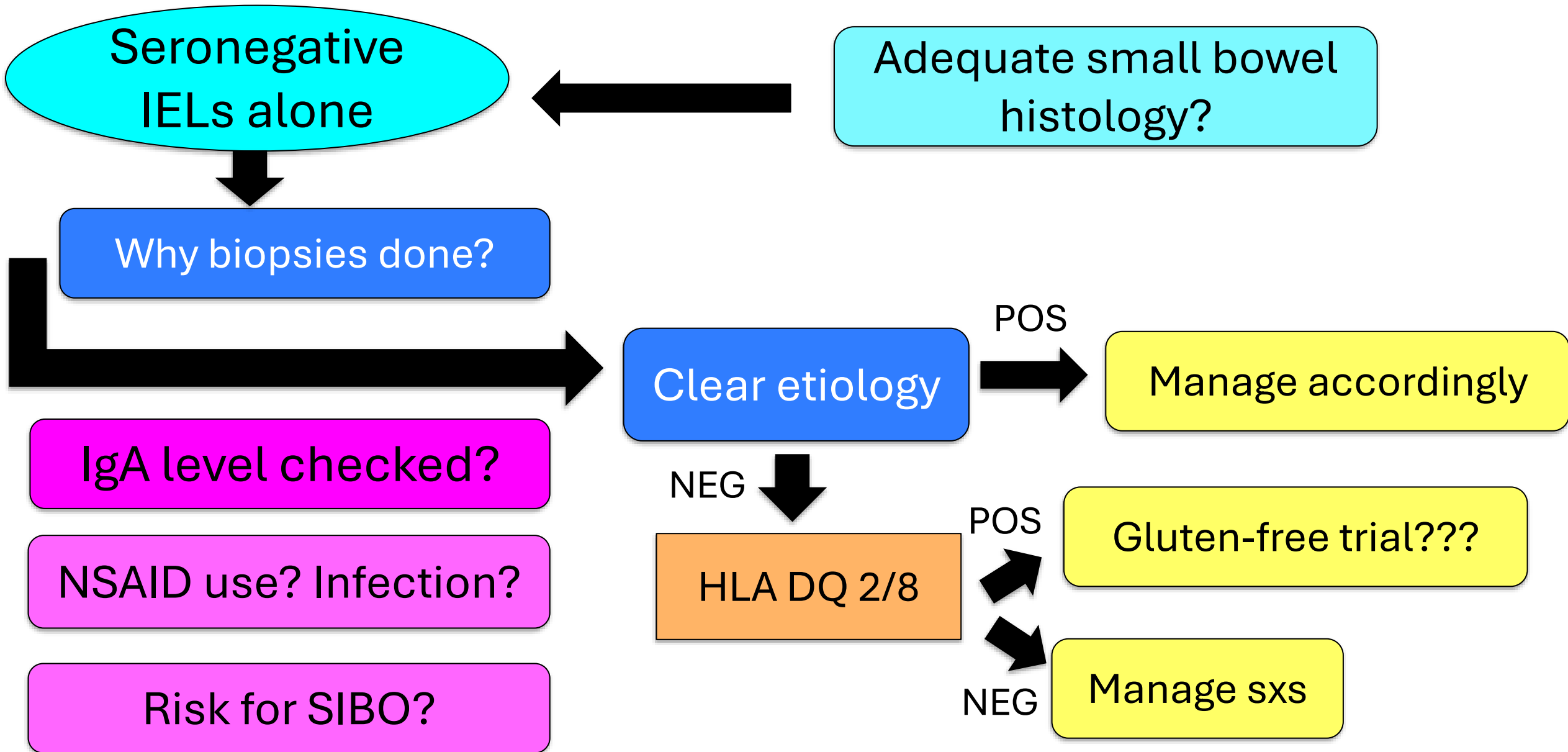
IELS:*

- NSAIDS
- H. pylori
- SIBO
- Gastroenteritis
- IBD



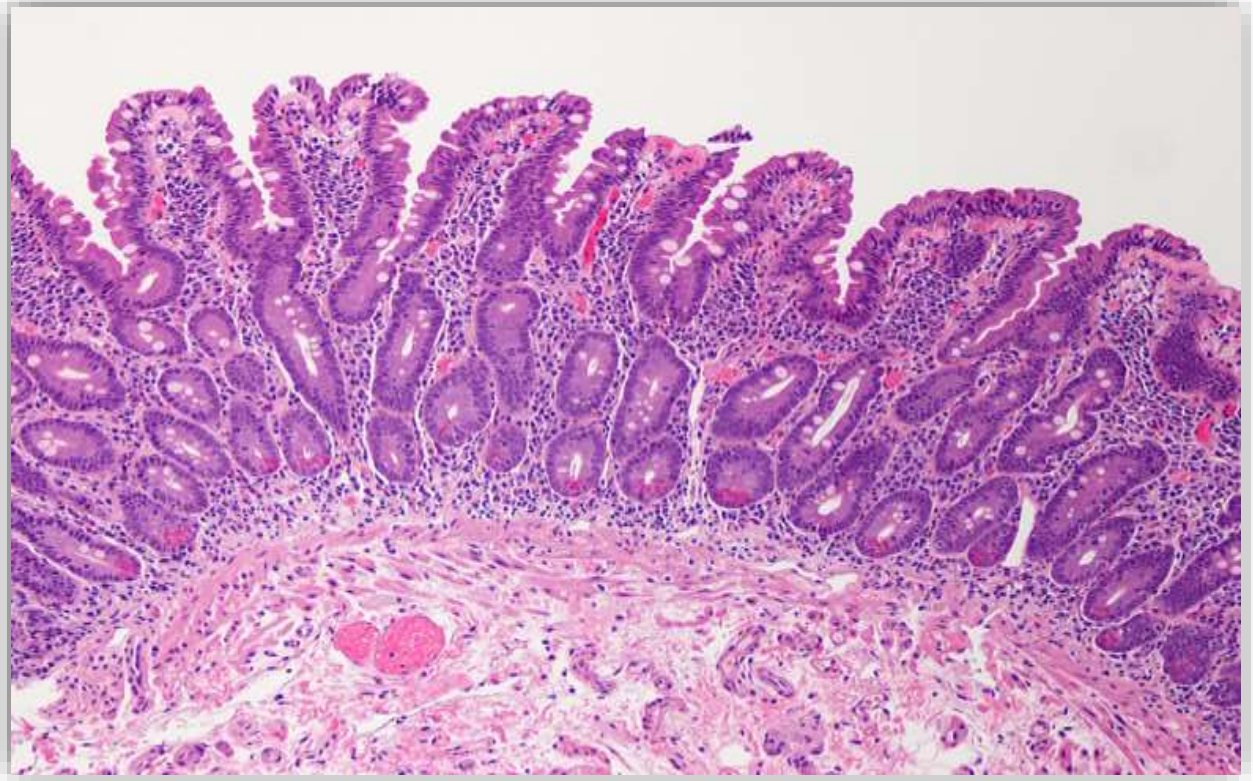
*Kakar S. AJG 2003. Mahadeva S. J Clin Path 2002.
Hammer STG 2010. Shmidt E. GIE 2014. Aziz I. APT 2010.*

Proposed Algorithm



Late Histologic Mimickers

**Villous atrophy, partial/total
(Marsh 3+)**



Autoimmune Enteropathy

Autoimmune Enteropathy

**Chronic diarrhea
(> 6 weeks)**

Malabsorption

**Enteropathy,
minimal IELs**

- May be absence of goblet and Paneth cells

**Exclusion of other
causes of villous
atrophy**

**Anti-
enterocyte/anti-
goblet cell
antibodies**

Autoimmune Enteropathy

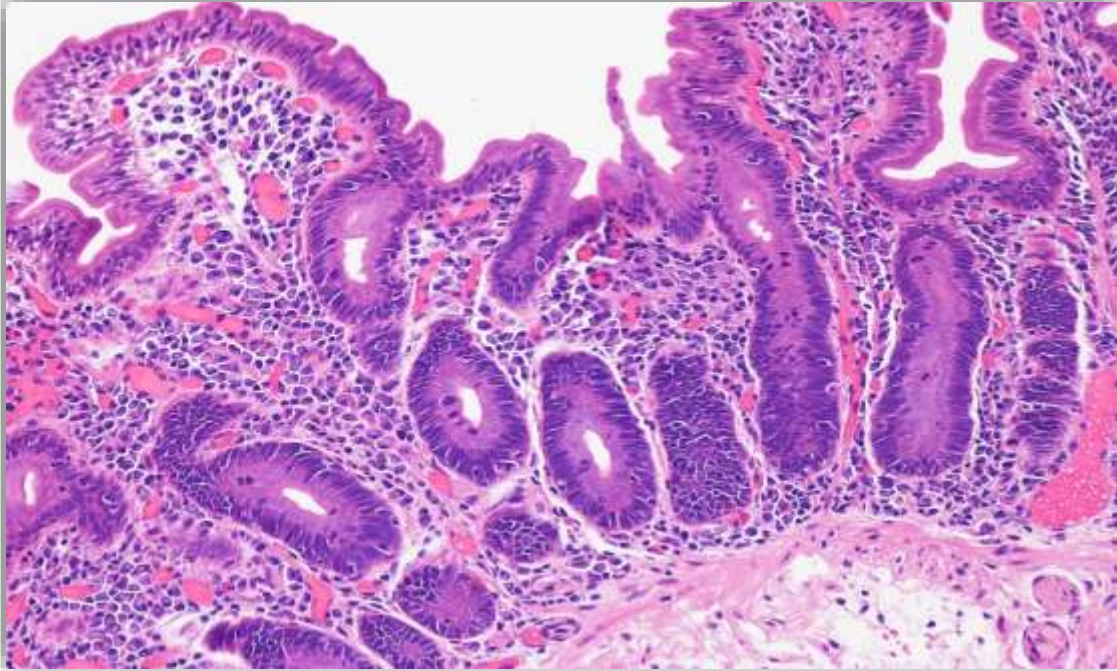
- Increased recognition
 - Equal M:F
 - Age mean 44-55 years
 - Delay in dx median 1.5 years
- Refractory diarrhea and nutritional issues
- No response to diets

Anti-goblet cell antibodies are common and non-specific.
30-40% prevalence in population of healthy + disease.



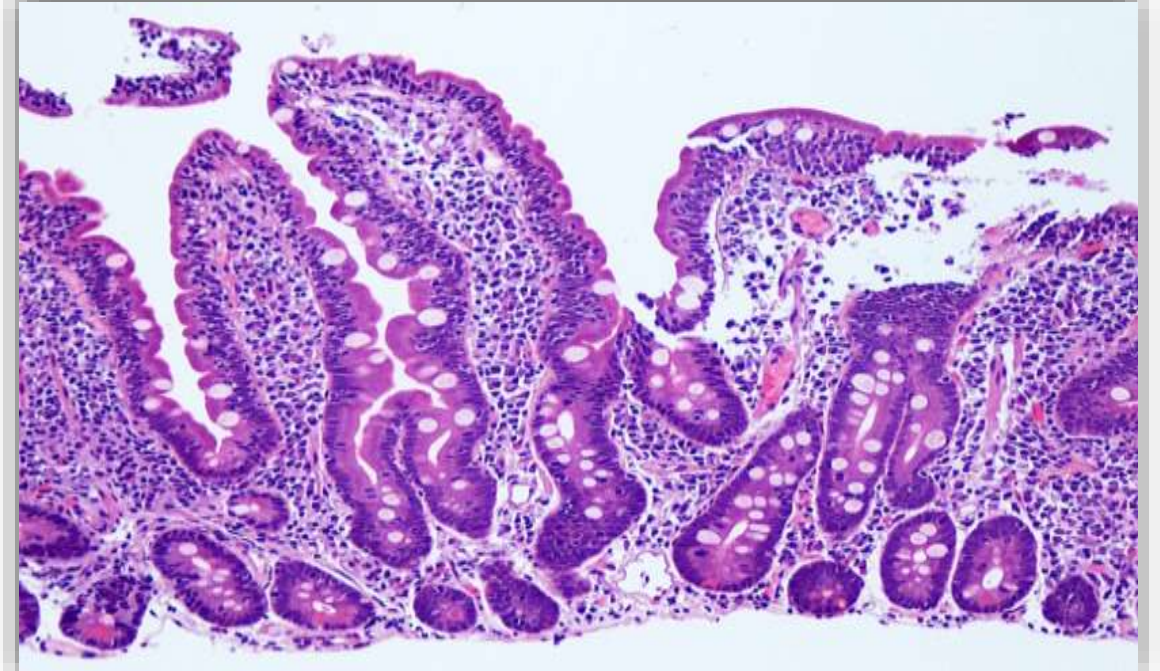
*Akram S, et al. CGH 2007;5:1282-90.
Sharma A, et al. CGH 2018;16:887-83.*

Autoimmune Enteropathy vs Others



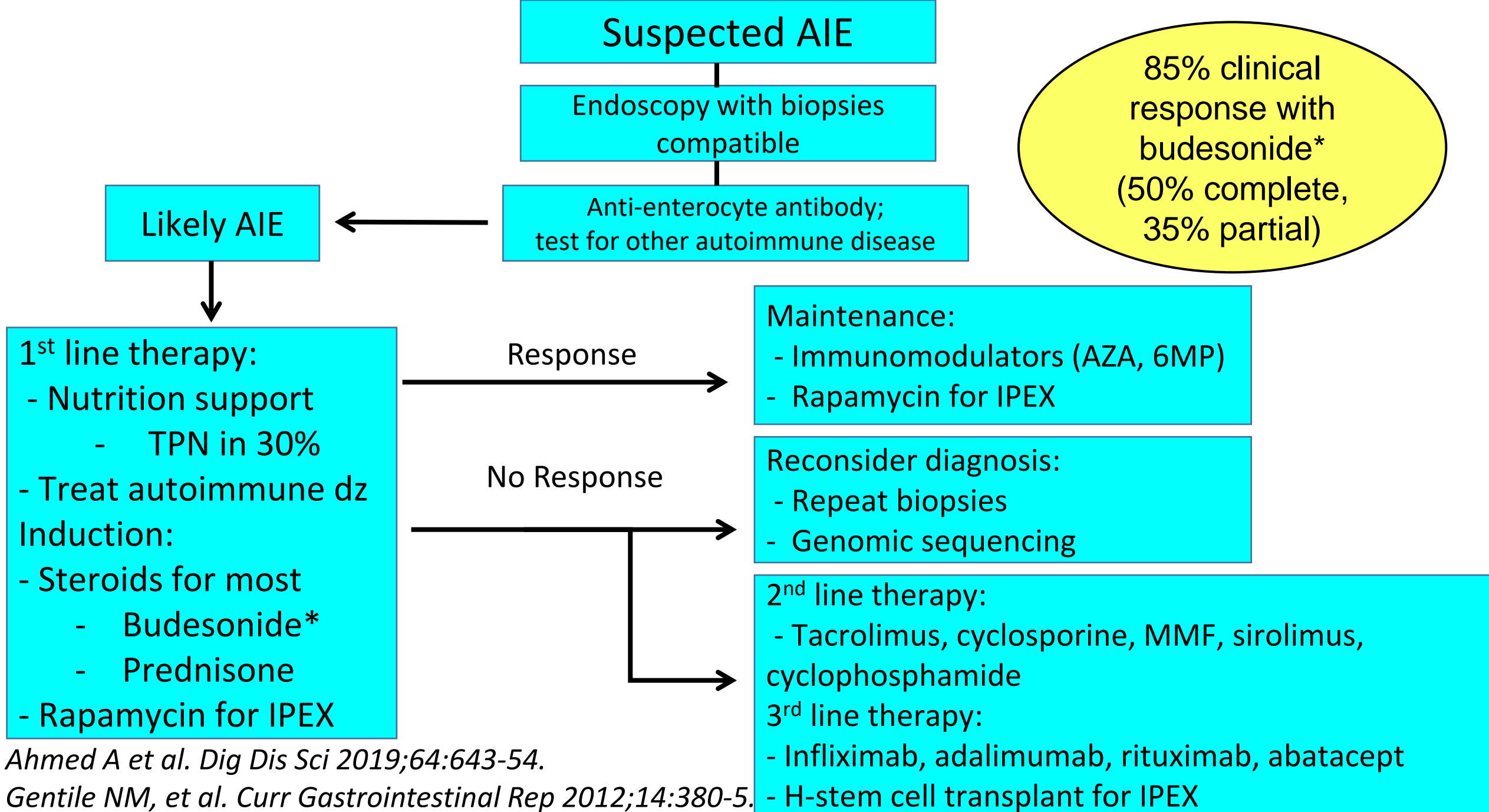
Autoimmune

- No goblet cells; no Paneth cells
- Surface IELs less prominent
- Lymphoplasmacytic infiltrate



Other Enteropathies

- Goblet and Paneth cells present
- Surface IELs more prominent



Ahmed A et al. *Dig Dis Sci* 2019;64:643-54.

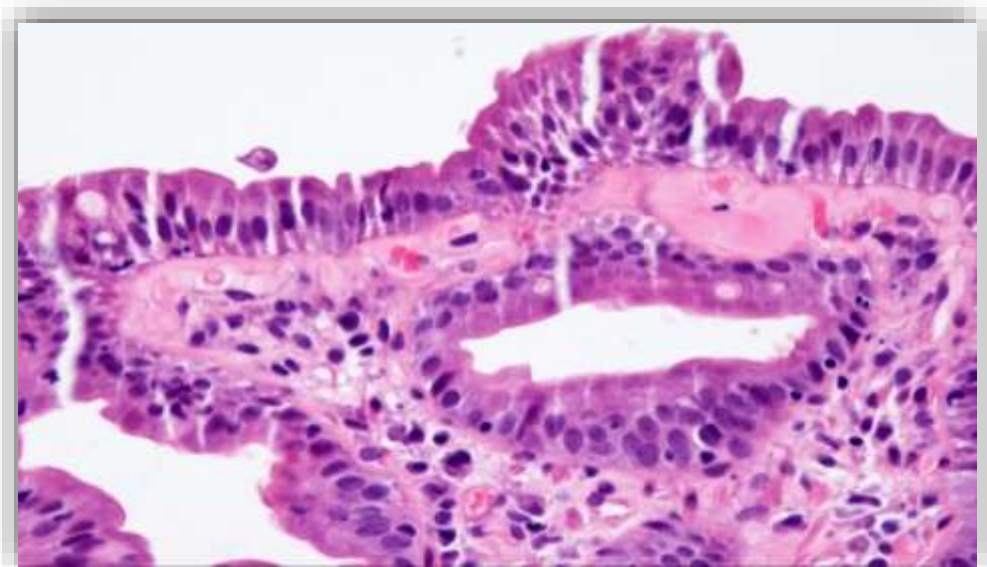
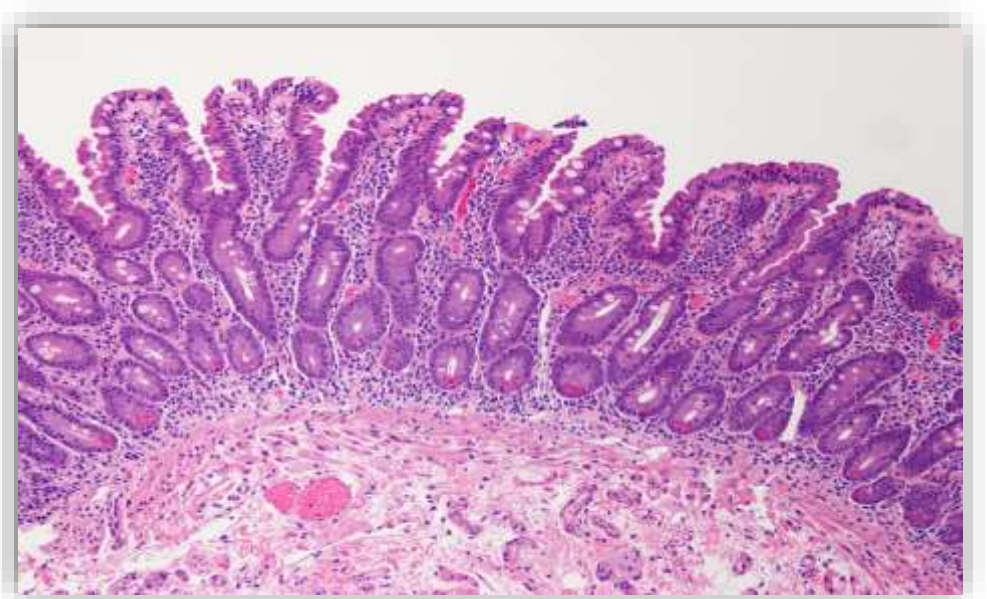
Gentile NM, et al. *Curr Gastrointestinal Rep* 2012;14:380-5.

*Sharma A, et al. *CGH* 2018;16:877-883.

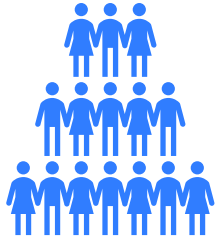
Collagenous Sprue

Collagenous Sprue

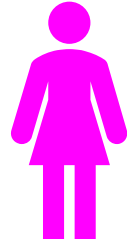
- **Clinical/histologic features of CD**
 - **Diarrhea, malabsorption**
- **Thick type 1 collagen**
 - **>10-20 um (reports of 260 um!)**
 - **Normal collagen < 5 microns**
 - **Half of a lymphocyte**



15 Year History of Collagenous Sprue (CS)



74 patients
Mean age 66
92% white



76% women



Diarrhea 81%
Wt loss 77%



60% HLA DQ2/8
44% + serology



30% on ARB
83% olmesartan



TVA 72%
Concurrent:
LG 10% CC 18% LC 12%



GFD 86%
Budesonide 74% **Thiopurine 15%**
Infliximab 3%

Management of Collagenous Sprue (CS)



- Review medications
 - Stop offenders
- Initiate gluten-free diet
 - If HLA permissive
- Immunosuppression
 - Budesonide, prednisone, AZA, infliximab, others

If you find collagenous sprue, you are not done.

Review the meds!!!

*Gastroenterology 2016;150:S307-8;
BMJ Open Gastroenterol 2016;
JGH 2017;32:120-7.*

Drug-Induced Enteropathy

ARB-Induced Enteropathy

Systematic review: 82 case reports/series + 5 comparative studies

Patients (#)	248
Type of ARB used	Olmesartan (223; 94%) Telmisartan (5; 2.0%) Irbesartan (4; 1.6%) Valsartan (3; 1.2%) Losartan (2; 0.8%) Eprosartan (1; 0.4%)
Age range(years)	45-89
Range of time on drug	2 weeks – 13 years (mean/median 3 years other studies)
HLA DQ2 or 8 positivity	71.4% (checked in 59% of patients)
Negative celiac serology	98.8% (checked in 68% of patients)
Failure of response to GFD	97.7%
Complete symptom remission	97.4%

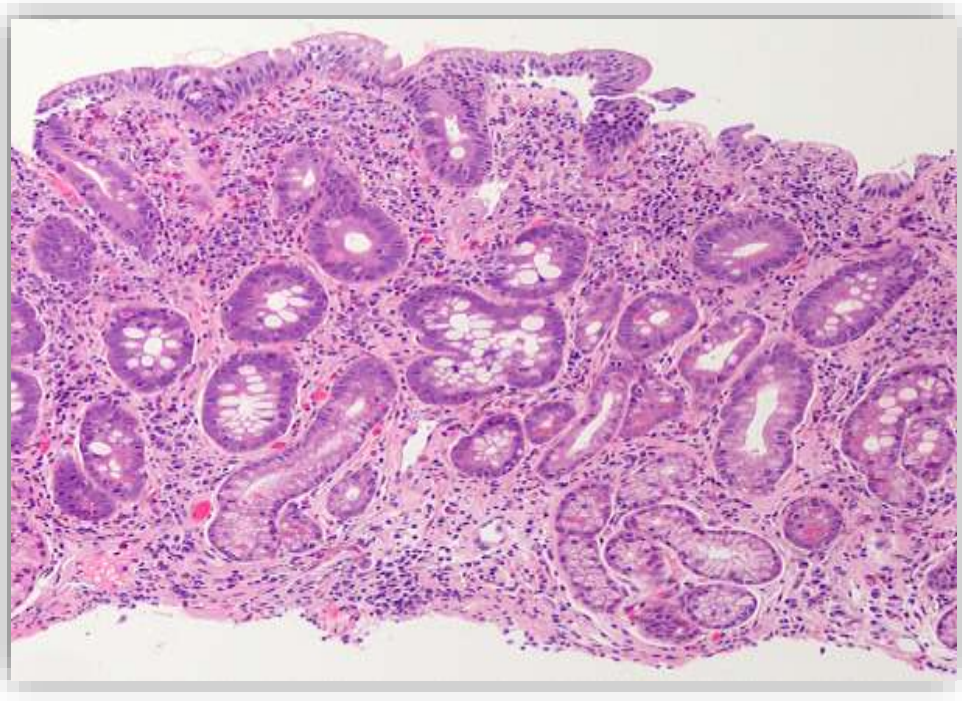
Other meds causing enteropathy:

- Checkpoint inhibitors
- Mycophenylate mofetil
- Methotrexate

Kamal A, et al. Gastroenterol Rep 2019;7:162-7.

Gentile NM. Mayo Clin Proc 2013; Ziegler TR. Gastroenterology 2003.

Drug-Induced Enteropathy Management



- Consider in the patient with:
 - Serologically-negative enteropathy
 - Collagenous deposition a clue
- Olmesartan started months to years earlier, leading to a delay in diagnosis
- Treatment:
 - Stop the medication if able
 - For immunosuppression, reduce dose if able

***Combined Variable
Immunodeficiency***

Combined Variable Immunodeficiency (CVID)

Impaired B cell differentiation, abnormal Ig production

Any age (most 20-45 at dx), M:F equal

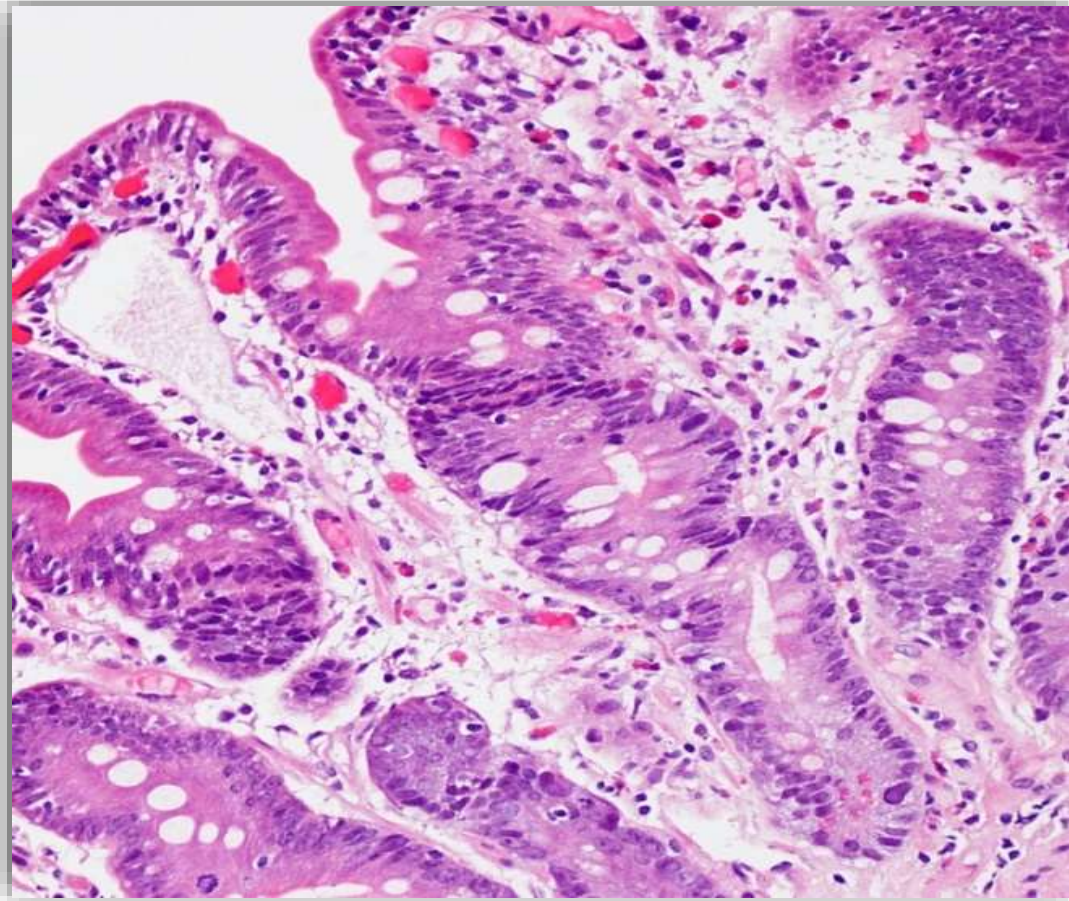
+/-Respiratory and GI infections; delayed dx

Other features: autoimmunity, liver, lymphoma

CVID Criteria:

- IgG 2 SD below normal AND
- One other low Ig level (IgA or IgM) AND
- Failure to mount vaccine reaction
- Absence of other immunodeficiency

Combined Variable Immunodeficiency (CVID)

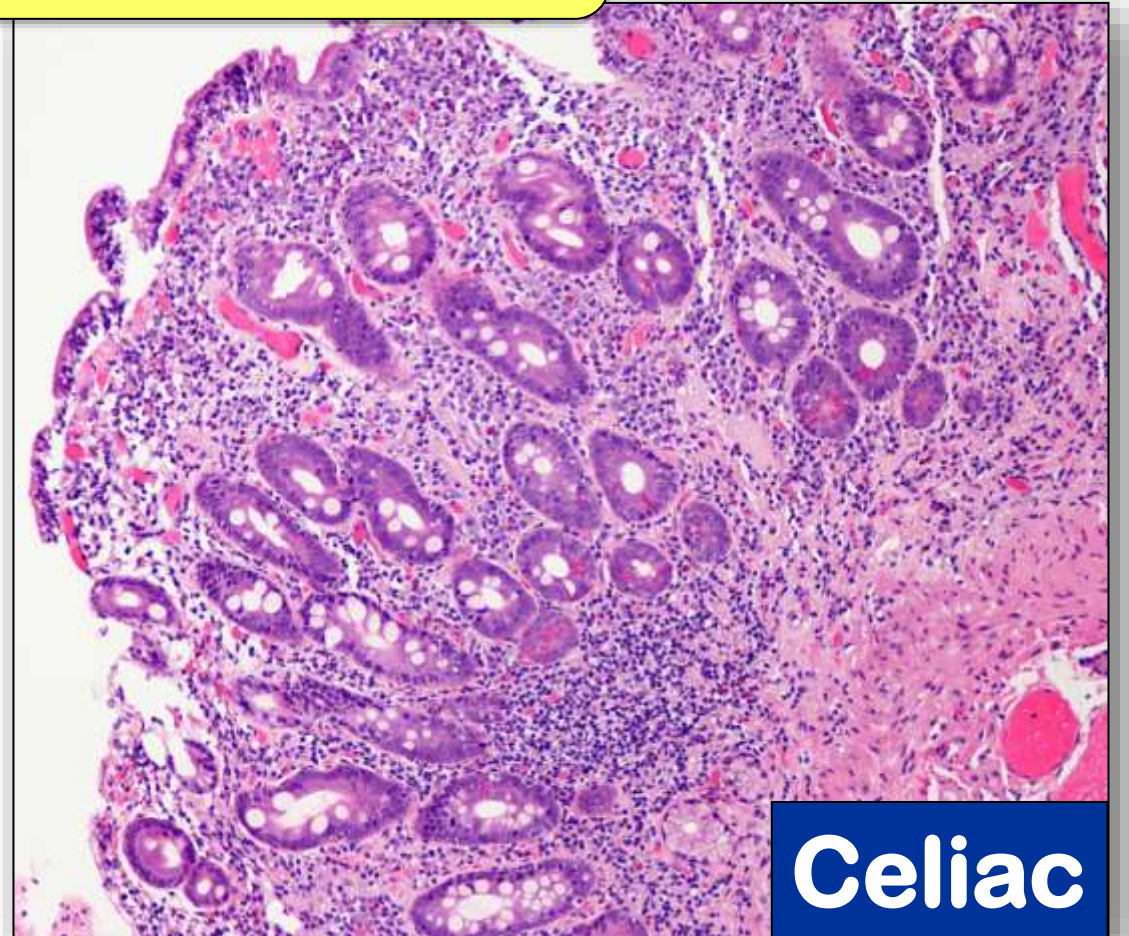
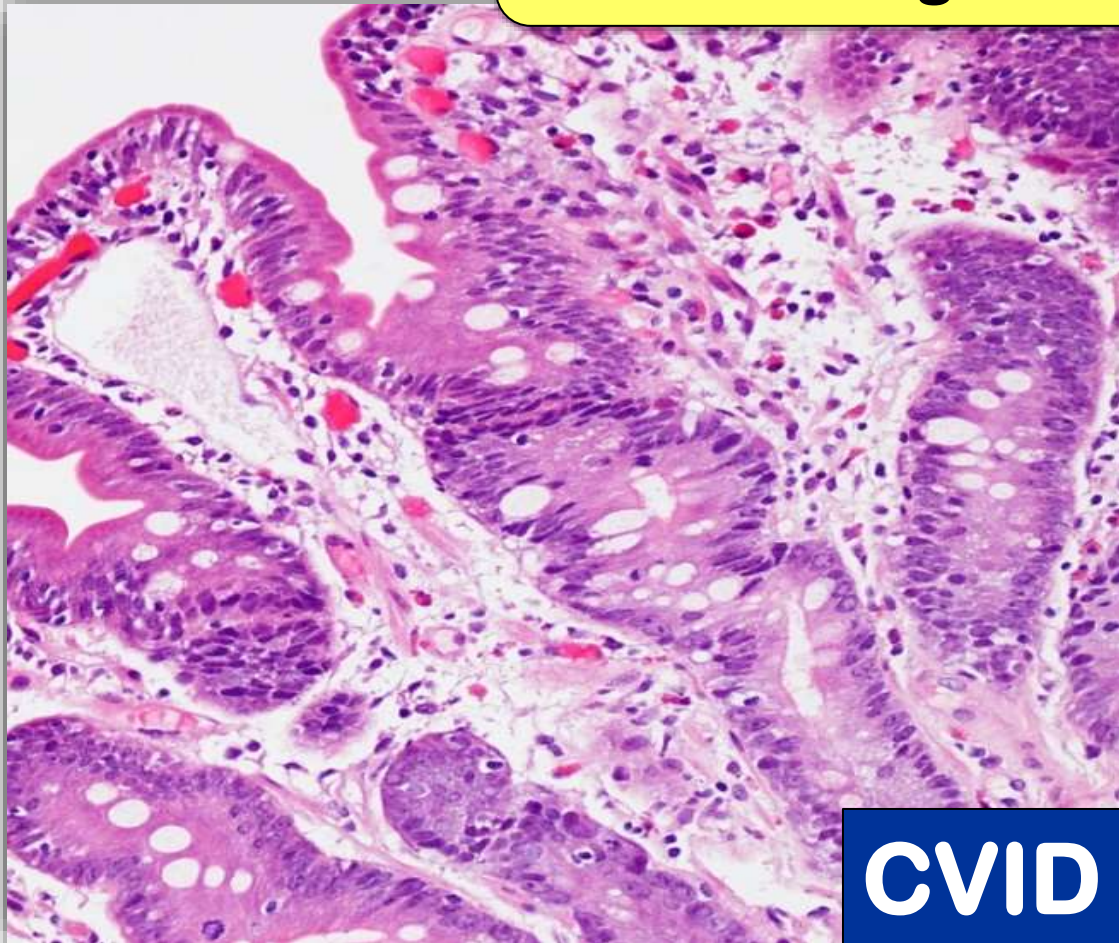


Histologic clues:

- Reduced plasma cells
 - 30% w/normal #
- IELs, villous atrophy
- Apoptosis, neutrophils
- “Empty” lamina propria

**Daniels, et al. Am J Surg Pathol 2007;31:1800-12.*

People can have CVID and celiac disease!
Hard to diagnosis – serologies negative!



Cornerstone of CVID Management:

- Immune globulin replacement; Infection prevention

Tropical Sprue

Tropical Sprue

Where

- Asia, India, Caribbean, Central/South America

Who

- Indigenous groups; travelers > 1 month

What

- Steatorrhea, oral lesions, edema

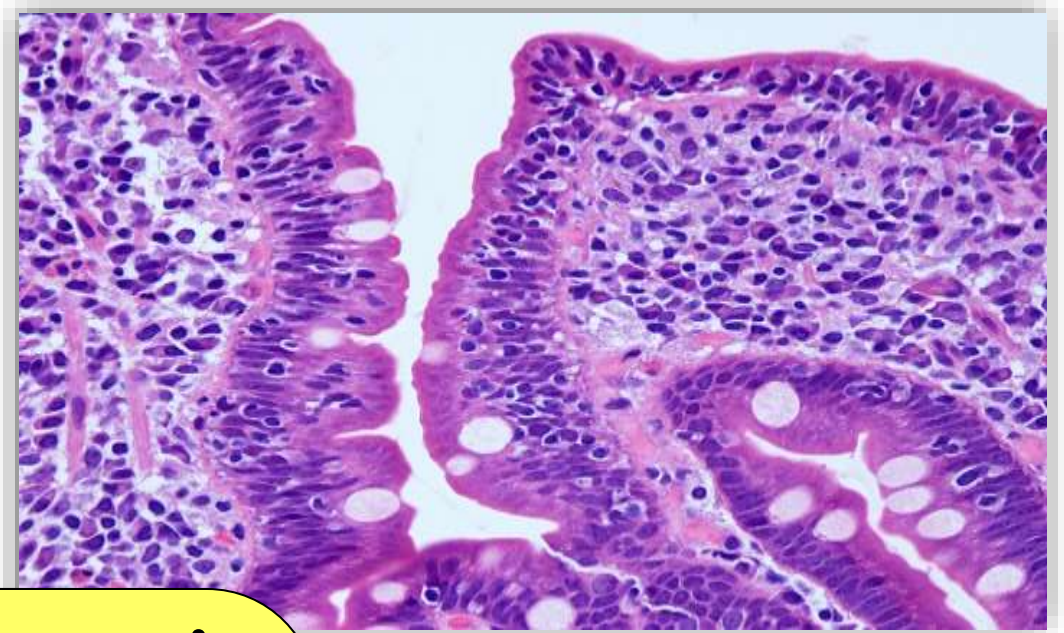
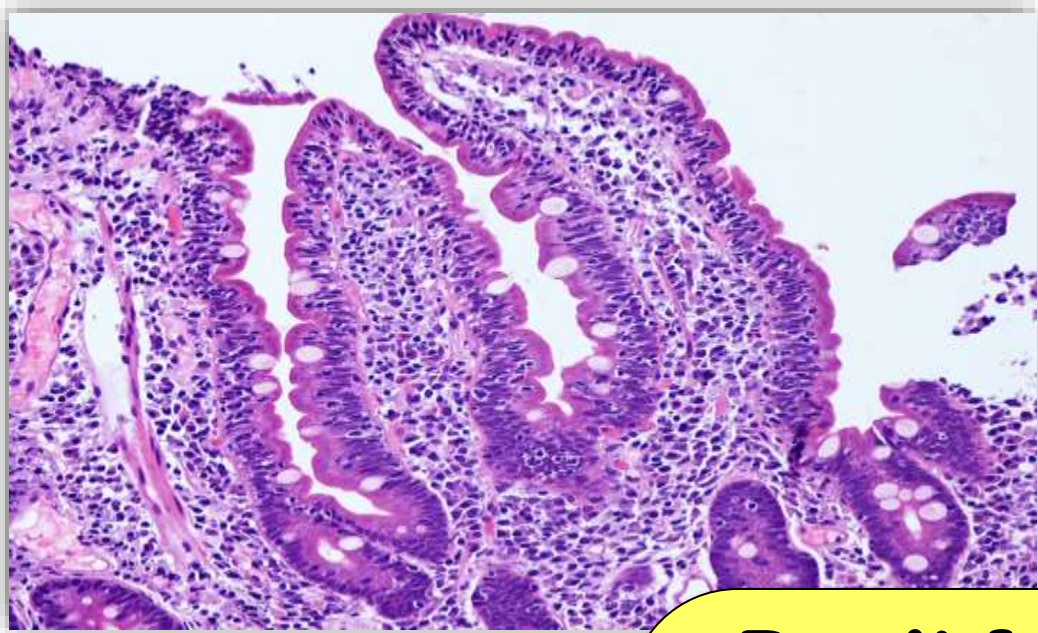
Testing

- None specific; rule out others (celiac)
- Megaloblastic anemia, low vit/min, low albumin

Management

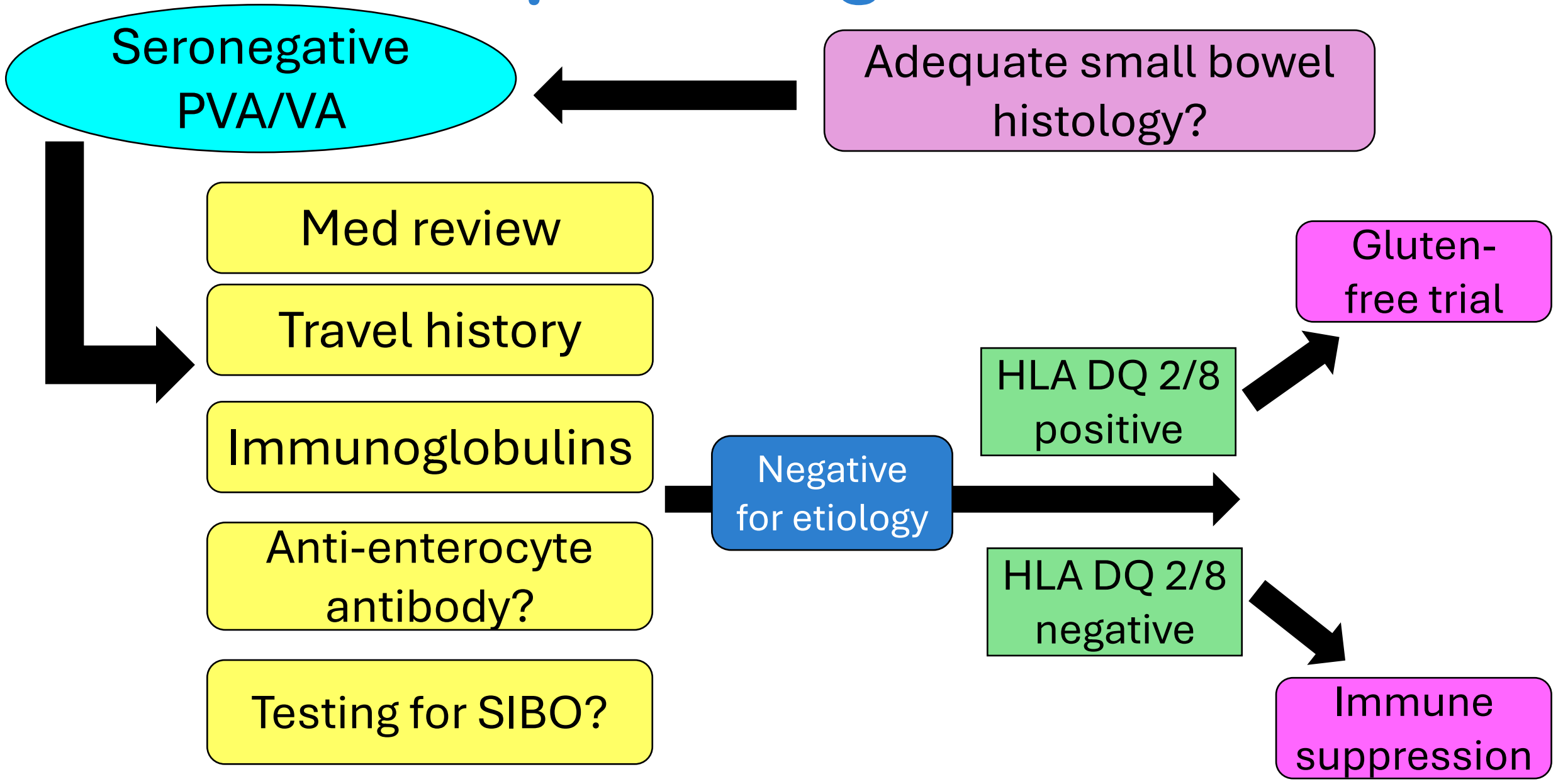
- Tetra 250 QID or doxy 100 BID x3-6 months
- Folate 5 mg QD for 3-6 months; replace others

Tropical Sprue



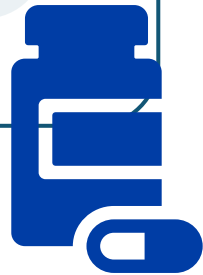
Don't forget travel history in the evaluation of serologically-negative enteropathy!

Proposed Algorithm



Take-Home Points

All enteropathy is not celiac disease, even though it is most common



Look for other clinical, laboratory or histologic clues in the case of a serologically-negative enteropathy, and include careful med review and travel history



THANK YOU!!!

EMAIL:

OXENTENKO.AMY@MAYO.EDU



@AMYOXENTENKOMD