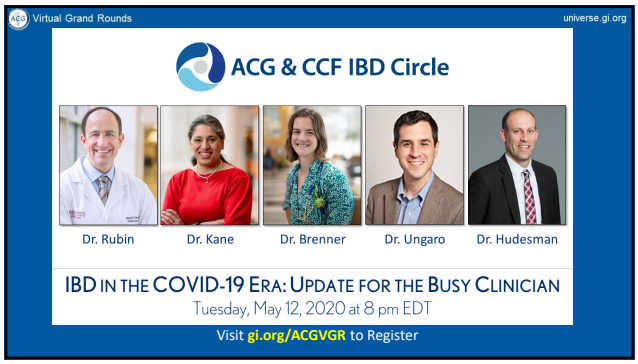
Virtual Grand Rounds
universe.gi.org
ACG & CCF IBD Circle
Dr. Rubin
Dr. Kane
Dr. Brenner
Dr. Ungaro
Dr. Hudesman
IBD IN THE COVID-19 ERA: UPDATE FOR THE BUSY CLINICIAN
Tuesday, May 12, 2020 at 8 pm EDT
Visit gi.org/ACGVGR to Register

1


Virtual Grand Rounds
ACG Virtual Grand Rounds
Join us for upcoming Virtual Grand Rounds!
Week 7: C. difficile and Fecal Microbiota Transplant: The Beginnings of Microbiome Therapy
Neil H. Stollman, MD, FACG
May 7, 2020 at Noon EDT
Week 8: Serrated Polyps and Serrated Polyposis Syndrome
Carol A. Burke, MD, FACG
May 14, 2020 at Noon EDT
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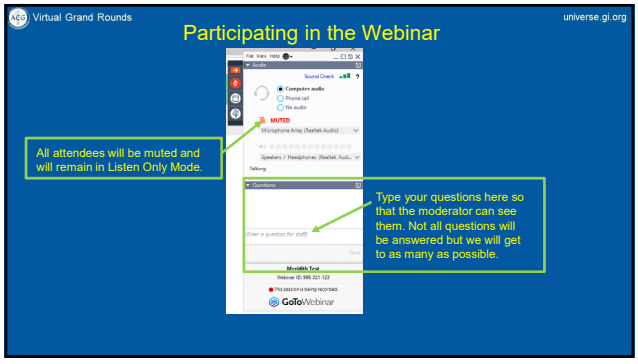
Virtual Grand Rounds
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Participating in the Webinar
All attendees will be muted and will remain in Listen Only Mode.
Type your questions here so that the moderator can see them. Not all questions will be answered but we will get to as many as possible.
GoToWebinar

3

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How to Receive CME and MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.

ACG will submit MOC points on the first of each month. Please allow 3-5 business days for your MOC credit to appear on your ABIM account.

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MOC QUESTION

If you plan to claim MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

5

Virtual Grand Rounds

ACG Virtual Grand Rounds

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Virtual Grand Rounds

Disclosures:

Moderator:
William D. Chey, MD, FACG
Board Member: American College of Gastroenterology, American Neurogastroenterology Motility Society, GI Health Foundation, GI on Demand, International Foundation of Functional GI Disorders, Rome Foundation
Consultant: Allergan, Alnylam, Bayer, Biomerica, IM Health, Ironwood, QOL Medical, Phathom, Ritter, Salix/Valeant, Takeda, Urovant
Grant/Research Support: Biomerica, Commonwealth Diagnostics International, QOL Medical, Salix, Urovant, Vibrant, Zespri
Stock/Stock Options: Ritter

Speaker:
Amy S. Oxentenko, MD, FACG
Dr. Oxentenko has indicated no relevant financial relationships.

Off Label Use:
None

7

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Celiac Disease…Or Not?:

A Guide to Celiac Mimickers

April 30, 2020

Amy S. Oxentenko, MD, FACG
Program Director and Associate Chair, IM
Professor of Medicine
Mayo Clinic, Rochester
@AmyOxentenkoMD

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Objectives

- Detail the entities that can mimic celiac disease either clinically or histologically
- Identify the clinical and/or histologic differences to be able to distinguish between the differing disorders
- Outline an approach to the patient with serologically-negative enteropathy

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Why Is This Relevant?

- Celiac disease common
  - Present in roughly 1% of population
- Often underdiagnosed due to non-classical features or lack of awareness
- A surge in those that are "gluten sensitive" and on a gluten-free diet without a substantiated diagnosis
- Although CD is diagnosed more, not all diagnosed meet the criteria for CD

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Gluten-Free Diet Not an Easy "Pill" to Swallow!

- Life-long behavioral change; not easy!
- Significantly affects:
  - Dining out
  - Social events
  - Travel
- Availability/cost of food

We need to be as sure as we can be about the diagnosis!!!

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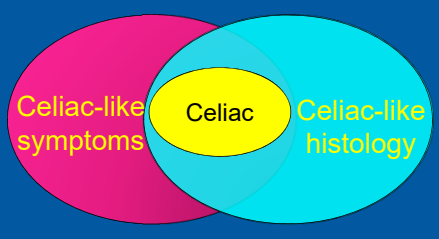
The Challenge



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Diagnosis of Celiac Disease

1. Clinical feature(s) compatible
2. Supportive serology
3. Small bowel biopsies characteristic
4. Clinical response to gluten-free diet

Testing done while on gluten-containing diet!

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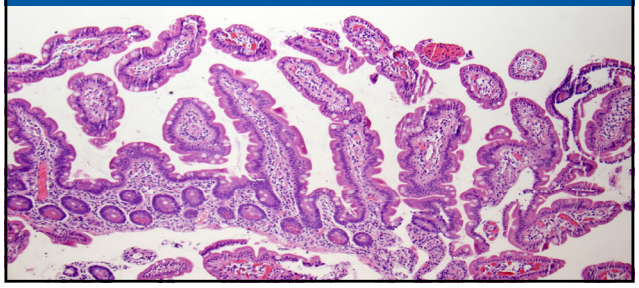
Normal Small Bowel



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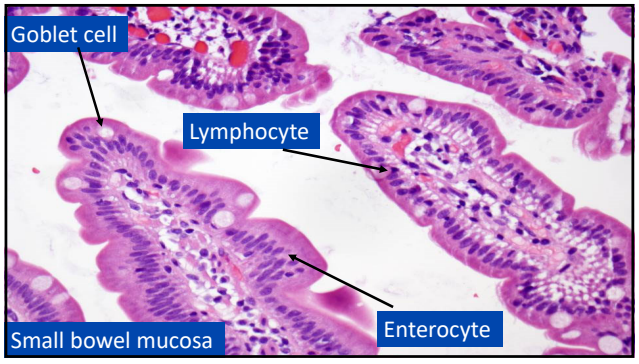

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Histologic Classification for Celiac Disease

Marsh Modified (Oberhuber)	Corazza	IELs*	Crypts	Villous blunting
0	None	Normal	Normal	None
1	Grade A	Increased	Normal	None
2		Increased	Hyperplastic	None
3a	Grade B1	Increased	Hyperplastic	Partial
3b		Increased	Hyperplastic	Subtotal
3c	Grade B2	Increased	Hyperplastic	Total

*IELs = intraepithelial lymphocytes

March MN 1992. Oberhuber G 1999. Corazza 2005.

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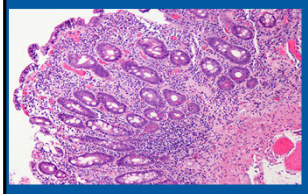
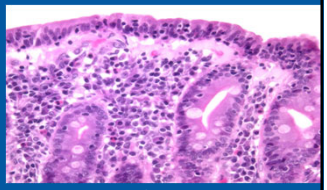
Celiac Disease





- Flattened villi (partial/total)
- Crypt hyperplasia

- Increased IELs
- Chronic inflammatory cell infiltrate in lamina propria

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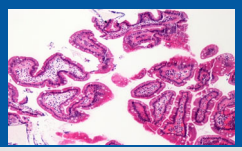
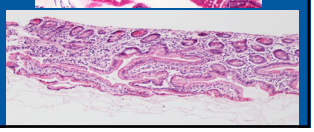
The Other Challenge: Tissue Adequacy

- Me: "Can you tell me how many biopsies were taken from the outside studies? Were the samples adequate?"



- Pathologist: "Only 2 fragments, all badly oriented and all badly stained."



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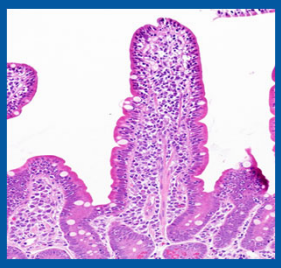
Early Histologic Mimickers

IELs, no atrophy

(Marsh 1 and 2)



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Case

- 25-year-old woman referred for "refractory sprue"
- 1 year prior:
  - Was evaluated for abdominal pain and iron-deficiency anemia:
    - IgA TTG negative (normal IgA level)
    - EGD with few scattered antral erosions
    - Small bowel biopsies show intact villi, and increased intraepithelial lymphocytes (IELs)
- Was told she had celiac disease, and put on gluten-free diet (GFD)

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Case, continued

- One year later, still has abdominal pain:
  - Claims to be strict on the GFD
  - Repeat IgA TTG negative
  - Repeat EGD with small bowel biopsies showed intact villi, and persistently increased IELs
- Comes for 2nd opinion:
  - HLA testing negative for HLA DQ2 or DQ8
  - Reports chronic headaches, menstrual pain
- *What do you need to ask her to make a diagnosis?*

NSAID use….3-4 ibuprofen daily!!!

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Intraepithelial Lymphocytes (IELs): What is "Abnormal"?

- 1975 → 2005 > 40 IELs/100 epithelial cells
- 2005→ current ≥ 25 IELs/100 epithelial cells

- Early criteria of > 40 IELs based on jejunal biopsies

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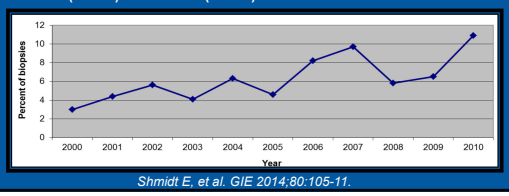
Isolated IELs on Duodenal Biopsies

- All duodenal bxs from 2000-2010 with normal villous architecture and isolated IELs, adults > 18 years
- 15,839 total duodenal bxs → 1105 (7.0%) with IELs alone
  - 3.0% (2000) → 10.9% (2010)



Shmidt E, et al. GIE 2014;80:105-11.

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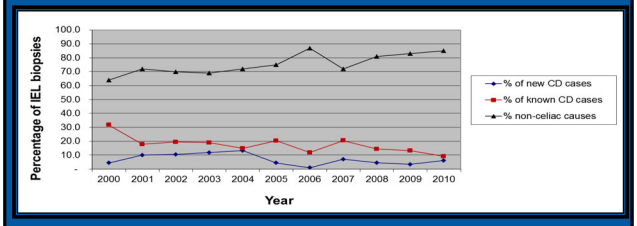
Increased IELs: Is it all CD?



- Excluding known CD, only 6.8% with increased IELs had CD

Shmidt E, et al. GIE 2014;80:105-11.

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Conditions w/Increased IELs

	Kakar (N=43)	Mahadeva (N=14)	Shmidt (N=1105)	Hammer (N=100)	Aziz (N=100)
Celiac*	9%	21%	20%	18%	16%
Tropical	1%	-----	-----	1%	-----
H. pylori	-----	-----	3%	6%	14%
SIBO	5%	-----	9%	3%	-----
NSAIDs	14%	-----	14%	8%	21%
IBD*	12%	-----	8%	8%	2%
Autoimmune	14%	-----	-----	6%	4%
Unexplained	7%	21%	33%	26%	34%
IBS	9%	14%	-----	20%	-----
Other	28%	43%	13%	4%	9%

*New and known cases

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

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Medications: NSAIDs

- Oral daily sulindac over several months can cause histopathology identical to CD
  - Healed with drug discontinuation
  - Recurred with re-administration
- Etiology?
  - Direct toxic drug or metabolite effect?
  - Hypersensitivity reaction?
  - Precipitate celiac disease?

Freeman HJ, et al. J Clin Gastroenterol 1986;8:569-71. Freeman HJ. Int J Celiac Dis 2014;2:49-53.

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Peptic Injury and IELs

- Duodenal bulb most susceptible
  - Hence why post-bulbar biopsies needed for CD
- Clues may be increased neutrophilic infiltration in lamina propria, gastric foveolar metaplasia, and Brunner gland hyperplasia
- May be seen with NSAIDs, *H. pylori*

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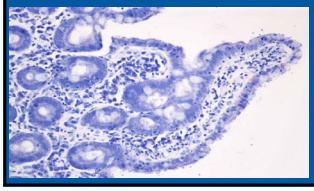
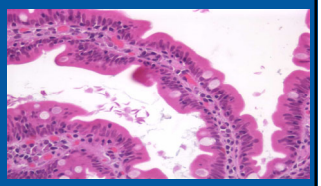
Infections

- Giardia
- Cryptosporidium
- HIV enteropathy





- Viral
- Foodborne illness
- Unidentified

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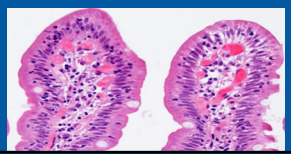
Location of the IELs Matter?

- Normally, IELs line the lateral aspects of the entire villi evenly

- In celiac disease, more IELs on the villous tips
  - > 6 IELs/20 epithelial cells at tip abnormal



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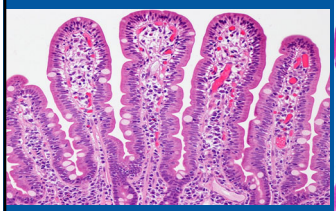
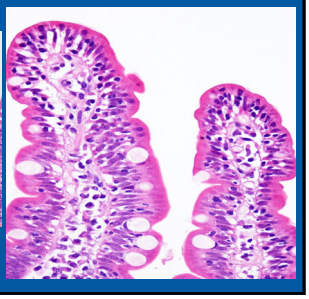
Tip-Predominant IELs in CD





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Inflammatory Bowel Disease

Characteristics	Mean Age at IEL Finding (yrs)	Mean IEL Count	IEL Distribution (even/sides/tip)
Adults			
• UC (n=13) • Crohn's (n=54) • Indeterminate (n=3)	40 39 25	45 44 35	11- 1- 1 49- 3- 2 2- 1- 0
Children			
• Crohn's (n=4)	4	55	4/0/0

➢Of the 74 with IBD and increased IELs with no villous atrophy, only 3 had a tip-predominant infiltrate IELs → All 3 negative for celiac disease

Patterson ER, et al. Am J Clin Path 2015;143:445-50.

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Clues to Duodenal IBD Compared to Celiac

- Endoscopic erosions
- Neutrophilic inflammation
- Crypt abscesses
- Granulomas (rare)
- Location of IELs (sides vs tips)

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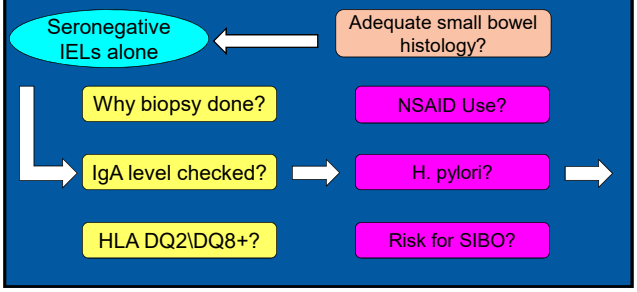
Proposed Algorithm



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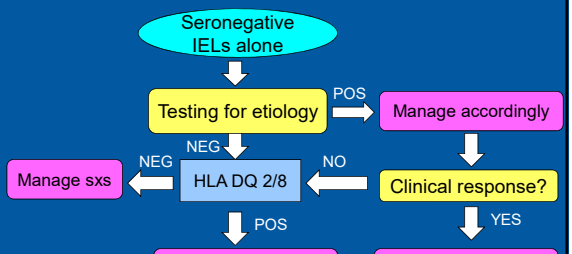
Proposed Algorithm



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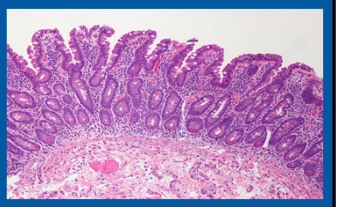
Late Histologic Mimickers

Villous atrophy, partial/total

(Marsh 3+)



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Villous Atrophy and Negative Celiac Serology

- 10-year period (2001-2011)
- Adults with - Villous atrophy in duodenum AND
  - Negative celiac serology (TTG, DGP, EMA)
- Testing done:
  - HLA haplotyping
  - Anti-enterocyte antibodies
  - Giardia stool antigen
  - HIV testing
  - Immunoglobulin levels
  - Breath testing for SIBO
  - T-cell gene rearrangement
  - Medication review

DeGaetani M, et al. Am J Gastroenterol 2013;108:647-53.

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How Seronegative CD Defined

- Negative TTG, DGP, EMA
- Positive for HLA DQ2 or DQ8
- Histology c/w celiac disease
- Response to gluten-free diet
  - Clinically and/or histologically
- Tested negative for other entities

DeGaetani M, et al. Am J Gastroenterol 2013;108:647-53.

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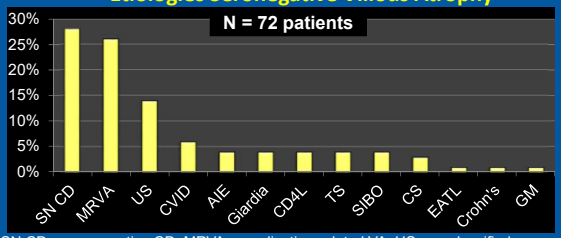
Etiologies Seronegative Villous Atrophy



SN CD = seronegative CD; MRVA = medication-related VA; US = unclassified sprue; AIE = autoimmune enteropathy; CD4L = CD4+ T-cell lymphoma; TS = tropical sprue; CS = collagenous sprue; GM = gastric metaplasia

DeGaetani M, et al. Am J Gastroenterology 2013;108;647-53.

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Next Case

- 72-year-old woman referred for "refractory sprue"
  - Severe diarrhea (8-10 stools daily) x 1 year
  - 30 pound weight loss
  - 3 hospitalizations for dehydration
    - Last admit one month ago
- Diagnosis of CD made 9 months ago
  - IgA TTG and EMA negative
  - HLA DQ2 positive
  - Biopsy: total villous atrophy, crypt hyperplasia, IELs
- No response to gluten-free diet

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Next Case

- The month before her appointment, her symptoms had started to improve
  - Now with 4-6 stools daily
  - Had regained 5 pounds of weight
- PMH: Prior hypertension, osteopenia
- Meds: Calcium and vitamin D
- *What 1 thing do you need to make a diagnosis?*

Hospital dismissal summary…olmesartan was stopped last admit due to hypotension!!!

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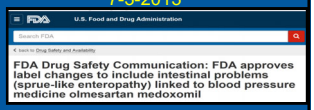
Medications: Olmesartan

- Angiotensin 2 receptor blocker (ARB)
- Approved 2002 USA (2003 Europe)
  - Indication: hypertension
- Report in 2012 from Mayo (22 pts)
  - Serologically negative
  - Referred as "refractory celiac disease"
  - All on olmesartan for hypertension

7-3-2013



Rubio-Tapia A, et al. Mayo Clin Proc 2012;87:732-38.

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Olmesartan and Case Finding

- Pathologist: "Here is a great case of collagenous gastritis and enteritis sent by a GI doc that I previously worked with. I called him and told him that I suspect he needs to do a medication review and he will see that the patient is taking olmesartan….he called back today absolutely AMAZED at my brilliance. ☺"
- ("p.s. Guess he's never been to any of your talks.")

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Olmesartan-Induced Enteropathy

	Mayo[1]	French[2]	Spain[3]
Patients (#)	22	36	11
Median age (years)	69.5	70	72
Median dose (mg)	40	40	40
Mean time on drug (years)	3.1	2.3	36 (median)
HLA DQ2 or 8 positivity	81% of tested	61% of tested	100%
Symptoms • Diarrhea • Abdominal pain • Weight loss	 • 100% • 50% • 18 kg	 • 100% • 75% • 18% wt loss	 • 100% • 45% • 73% lost wt
Villous atrophy (#)	22	32	?
Collagenous deposition (#)	7	2	?
Acute inflammation (#)	15	?	?

[1]Rubio-Tapia A. Mayo Clin Proc 2012; [2]Marthey L. APT 2014; [3]Marco-Marques A. AJG 2015.

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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%

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

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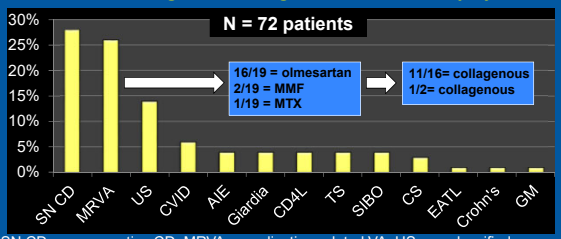
Etiologies Seronegative Villous Atrophy



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DeGaetani M, et al. Am J Gastroenterology 2013;108;647-53.

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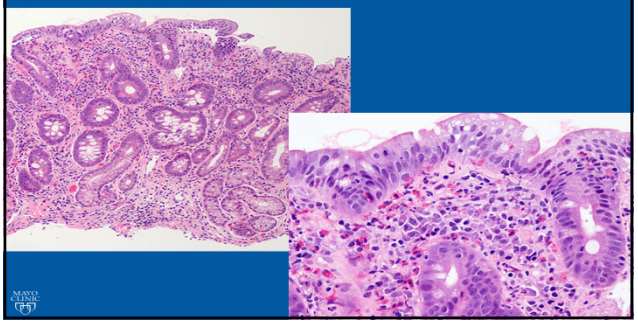
Olmesartan



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Bottom Line: Olmesartan-Associated Enteropathy

- Consider in the patient with serologically-negative enteropathy
  - Especially if ~age 70 (HLA DQ2/8 at risk?)
  - Careful review of medication list (prior/current)
- Histology with villous atrophy and inflammation
  - May have acute and chronic inflammation
  - May have collagen deposition
- Most started months to years earlier, often leading to a delay in diagnosis
- Stopping the medication results in improvement

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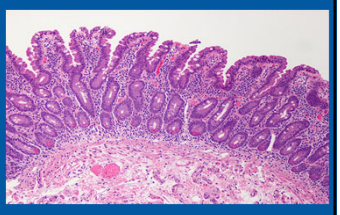
Collagenous Sprue

- All the usual histologic features of CD
- Irregularly thickened layer of type 1 collagen adjacent to the surface epithelium
- May have some surface epithelial damage and detachment



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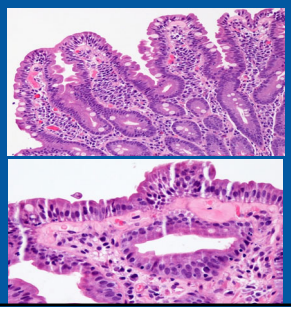
Collagenous Sprue

- Normal collagen < 5 microns
  - Half of a lymphocyte
- Management:
  - Review medications
  - Initiate a gluten-free diet
  - Frequently need immunosuppression
- Histology may persist



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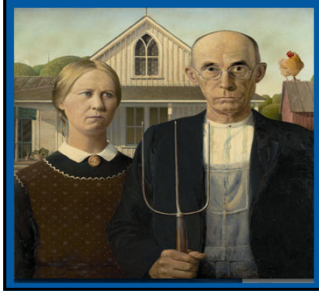
American Gothic



What is there that shouldn't be?

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American Gothic

It is easier to see what does not belong!

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Next Case

- 28-year-old man referred for "refractory sprue"
- Diagnosed 2 years ago when he presented with diarrhea and weight loss
- IgA and IgG TTG negative, HLA DQ2 positive
- Duodenal biopsies (outside):
  - "Total villous atrophy, crypt hyperplasia, consistent with celiac disease"
- Put on a gluten-free diet, with no clinical response

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Case, continued

- Follow-up in 2 years:
  - IgA/IgG TTG negative, biopsies no change
- Referred for ongoing complaints
- Initial step was pathology review of outside small bowel histology:
  - "Total villous atrophy, crypt hyperplasia, increased intraepithelial lymphocytes and lamina propria lymphocytes, but reduced plasma cells visualized."
- *What needs to be checked next?*

Immunoglobulin levels…he had undiagnosed CVID!

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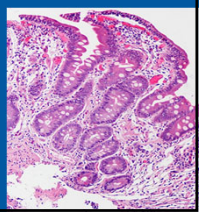
Immunodeficiency

- Common variable immunodeficiency (CVID)
  - Can cause increased IELs; villous atrophy
- CVID Criteria:
  - IgG 2 SD below normal AND
  - One other low Ig level AND
  - Failure to mount vaccine reaction
- Any age (most < 30), M:F equal
- Respiratory and GI infections



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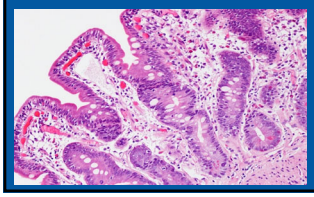
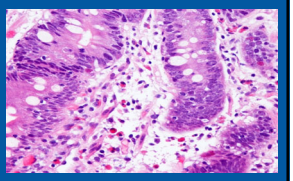
CVID

- Histologic clues:
  - Reduced/absent plasma cells
    - 30% w/ normal numbers*
  - Glandular apoptosis





- May have neutrophils, lymphoid aggregates
- Secondary infections

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

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What is missing?

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It is harder to recognize what is absent!

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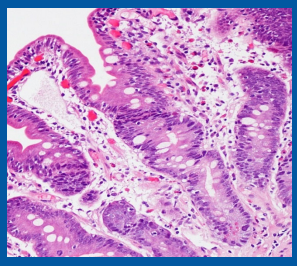
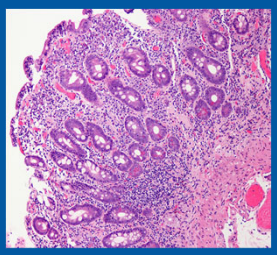
CVID



Celiac Disease



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Small Intestinal Bacterial Overgrowth

- 52 subjects with no risk for SIBO
- Duodenal aspirates and biopsies taken
- 26/52 (50%) had SIBO
- No difference in those with vs w/o SIBO
  - Villous height, crypt depth, ratios, lamina propria cell count
- Was a difference in:
  - IEL counts with colonic type bacteria (higher in SIBO)
    - Yet within normal range

Riordan SM, et al. Am J Gastroenterol 2001;96:494-500.

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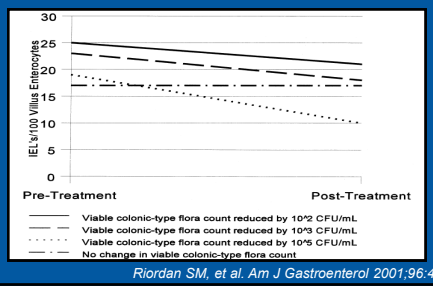
Small Intestinal Bacterial Overgrowth



Riordan SM, et al. Am J Gastroenterol 2001;96:494-500.

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Another Study: SIBO and Small Bowel Histology

- 67 pts with SIBO; 55 control
  - SIBO pts older (60 vs 52, *p* 0.02)
  - SIBO pts more likely to have risk factor (66 vs 36%, *p* 0.002)

Finding	SIBO (n=67) No. (%)	Controls (n=55) No. (%)	P-value
Villous:crypt <3:1	16 (24)	4 (7)	0.01
Increased IELs			
Villi	15 (22)	8 (15)	0.35
Crypts	3 (4)	1 (2)	0.63
Basal plasmacytosis	5 (7)	2 (4)	0.46
Crypt apoptosis	3 (4)	2 (4)	>0.99
ANY abnormality	32 (48)	20 (36)	0.27

Lappinga PJ, et al. Arch Pathol Lab Med:2010;134:264-70.

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Tropical Sprue

- Areas of risk:
  - Asia, India, Caribbean, Central/South America
- Symptoms: Identical to CD
- Tests:
  - None specific
  - Negative CD serologies
- Treatment: folate, B12, tetracycline

TRAVEL HISTORY IMPORTANT!!!

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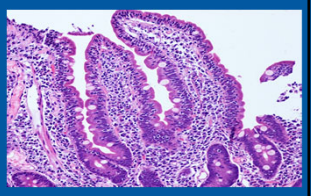
Tropical Sprue: The Challenges of Making the Diagnosis

- Pathologist: "Here is a new case of tropical sprue. You couldn't make up a better story for it. In fact, the story almost SOUNDS made up!"
- Me: "Let me guess…traveled to a tropical region and later got diarrhea?"
- Pathologist: "No. Lives in a tropical region and fell into a septic tank, then got diarrhea."



It is usually not this easy!

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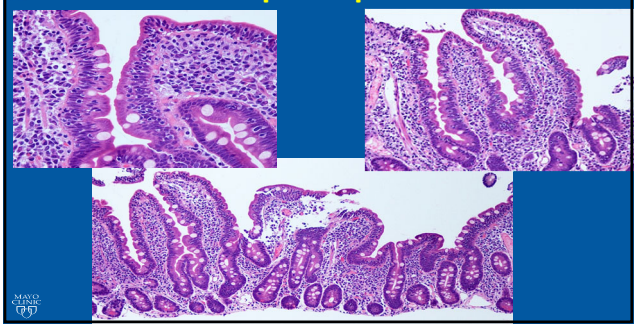
Tropical Sprue



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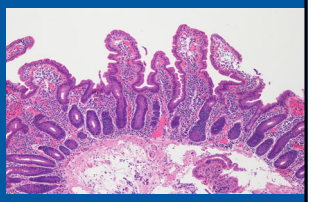
Autoimmune Enteropathy

- Increased adult recognition
  - Equal M:F, age 55 yrs
- May be a/w IPEX or APECED
  - FOXP3 mutation that controls regulatory T cells*
- Refractory diarrhea and nutritional issues



*Patey-Mariuad DE, et al. Mod Pathol 2009;22:95-102.

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Criteria for Diagnosis: Autoimmune Enteropathy

1. Chronic diarrhea (> 6 weeks)
2. Malabsorption
3. Partial/total villous blunting, deep crypt lymphocytosis, increased apoptotic bodies, minimal IELs (< 40/100 cells)
   - May be absence of goblet and Paneth cells
4. Exclusion of other causes of villous atrophy
5. Anti-enterocyte or anti-goblet cell antibodies supportive
   - Sensitivity 85-87%; non-specific

Akram S, et al. CGH 2007;5:1282-90.

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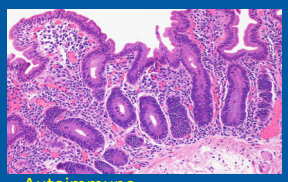
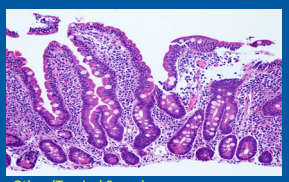
Autoimmune Enteropathy vs Others



Autoimmune

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



Other (Tropical Sprue)

- Goblet and Paneth cells present
- Surface IELs more prominent

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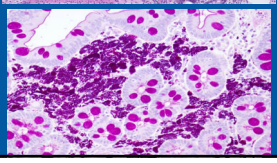
Whipple's

- Very rare to see
- Clinical features can help:
  - White men, 30s-40s
  - Multi-system:
    - Diarrhea, weight loss
    - Arthralgias
    - Fever, adenopathy
    - Cardiac, neuro
- Villi are broad, lamina propria expanded with macrophages, dilated lacteals, lipid deposits



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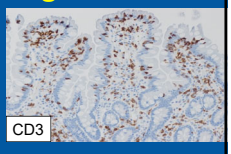
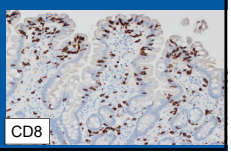
T-cell Receptor Testing

- Two stains are most important:
  - CD3 (all T cells)
  - CD8 (T suppressor cells)



- Should be equal in the surface epithelium
- Loss of CD8 → abnormal clone



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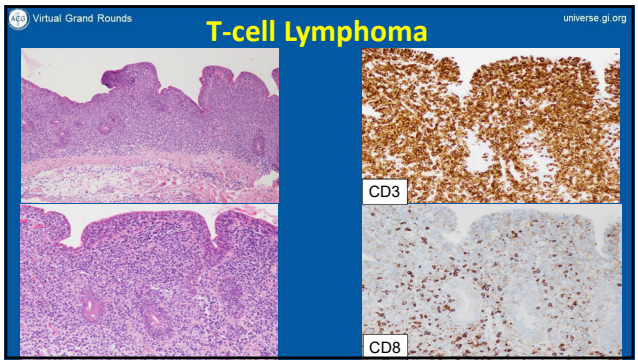
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T-cell Lymphoma
CD3
CD8

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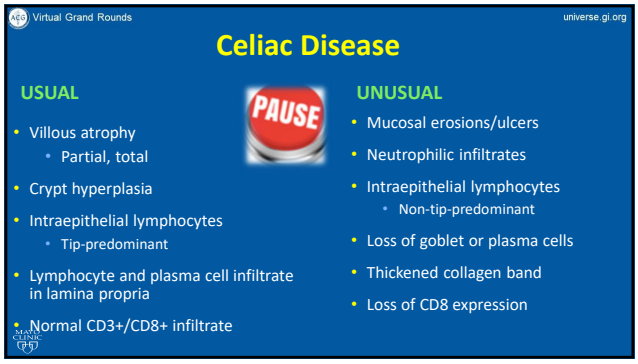
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Celiac Disease
USUAL
Villous atrophy
Partial, total
Crypt hyperplasia
Intraepithelial lymphocytes
Tip-predominant
Lymphocyte and plasma cell infiltrate in lamina propria
Normal CD3+/CD8+ infiltrate
PAUSE
UNUSUAL
Mucosal erosions/ulcers
Neutrophilic infiltrates
Intraepithelial lymphocytes
Non-tip-predominant
Loss of goblet or plasma cells
Thickened collagen band
Loss of CD8 expression

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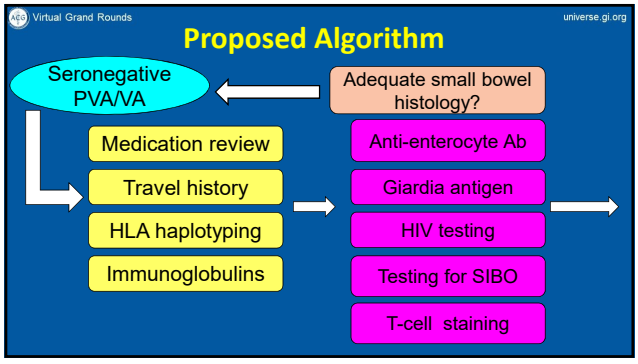
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Proposed Algorithm
Seronegative PVA/VA
Adequate small bowel histology?
Medication review
Travel history
HLA haplotyping
Immunoglobulins
Anti-enterocyte Ab
Giardia antigen
HIV testing
Testing for SIBO
T-cell staining

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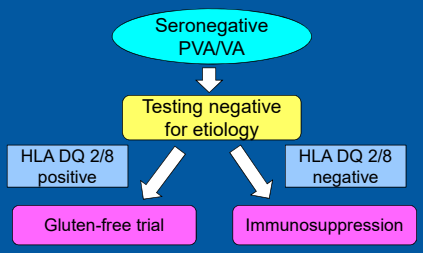
Proposed Algorithm



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Summary

- The most important things in evaluating a patient with serologically-negative enteropathy are:
  - 1) a careful history
  - 2) good communication with a GI pathologist
- Increased IELs are being seen with more frequency and are due to many things besides celiac disease
- Many mimickers of celiac disease have clues to the diagnosis and a targeted therapy; patients will prefer a correct diagnosis over a lifetime of an unnecessary gluten-free diet

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MAYO CLINIC

Thank you!

Email: Oxentenko.amy@mayo.edu

Twitter: @AmyOxentenkoMD

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How to Receive CME and ABIM MOC Points

LIVE VIRTUAL GRAND ROUNDS WEBINAR

ACG will send a link to a CME & ABIM MOC evaluation to all attendees on the live webinar.

ABIM Board Certified physicians need to complete their MOC activities by December 31, 2020 in order for the MOC points to count toward any MOC requirements that are due by the end of the year. No MOC credit may be awarded after March 1, 2021 for this activity.

ACG will submit MOC points on the first of each month. Please allow 3-5 business days for your MOC credit to appear on your ABIM account.

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ABIM MOC QUESTION

If you plan to claim ABIM MOC Points for this activity, you will be asked to: Please list specific changes you will make in your practice as a result of the information you received from this activity.

Include specific strategies or changes that you plan to implement.
THESE ANSWERS WILL BE REVIEWED.

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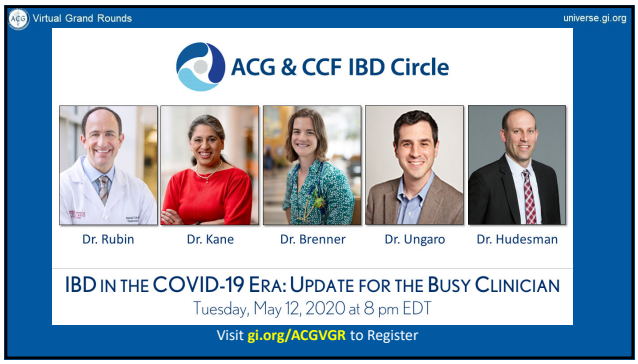
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ACG & CCF IBD Circle
Dr. Rubin
Dr. Kane
Dr. Brenner
Dr. Ungaro
Dr. Hudesman
IBD IN THE COVID-19 ERA: UPDATE FOR THE BUSY CLINICIAN
Tuesday, May 12, 2020 at 8 pm EDT
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Week 7: C. difficile and Fecal Microbiota Transplant: The Beginnings of Microbiome Therapy
Neil H. Stollman, MD, FACG
May 7, 2020 at Noon EDT
Week 8: Serrated Polyps and Serrated Polyposis Syndrome
Carol A. Burke, MD, FACG
May 14, 2020 at Noon EDT
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