Evaluation of Chronic Diarrhea

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Definition

- **Normal stooling frequency**:
  - 3 per day, to 3 per week.
  - Increased frequency may be diarrhea, or pseudodiarrhea.
- **Abnormal increase of stool liquidity, in excess of:**
  - 200 gm/day for US children and adults, or
  - 10 gm/kg body-weight in infants, or
  - > 85% water content in either

Classification by Duration

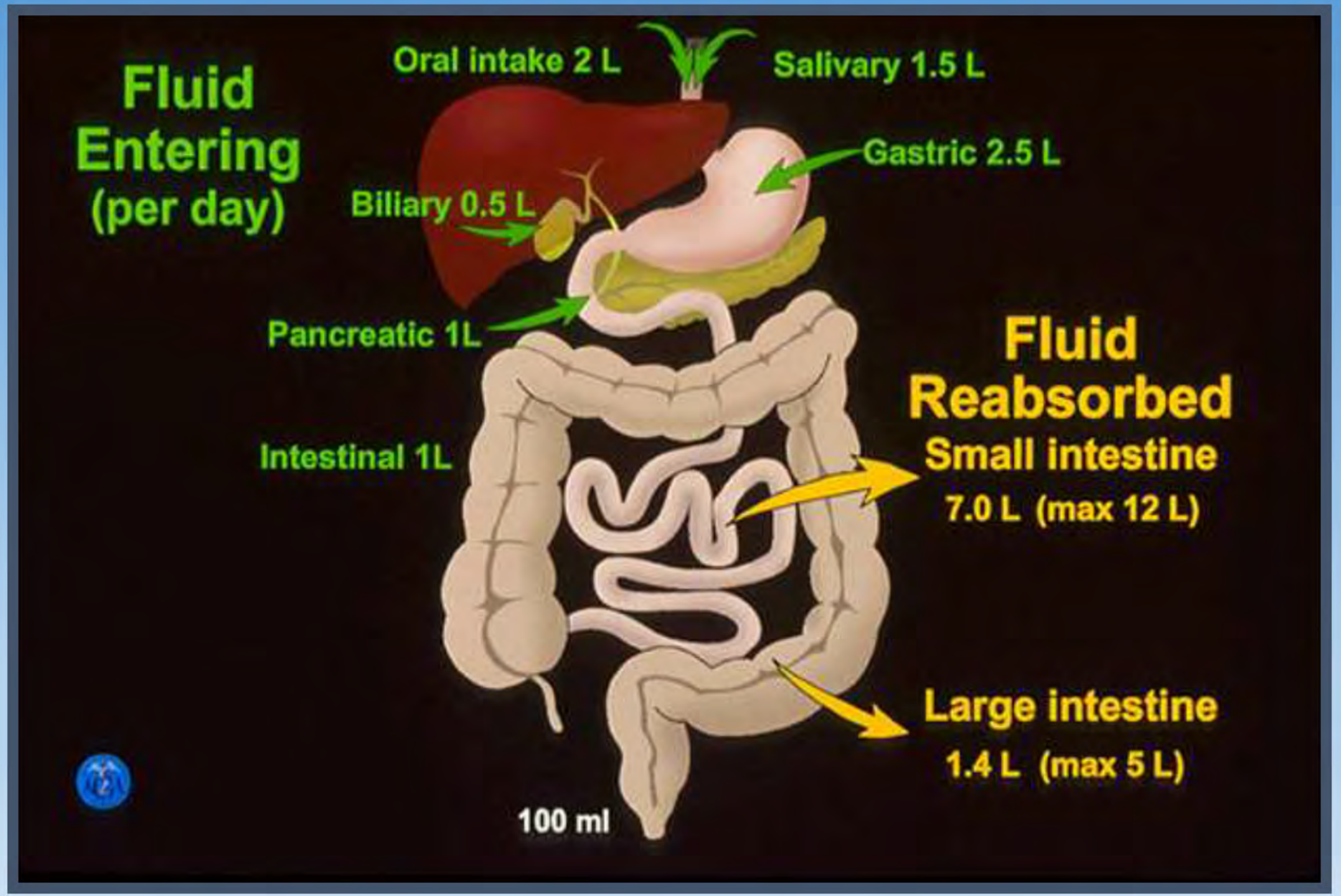
Acute: less than 3 weeks

Chronic: more than 3 weeks

Recurrent: repetitive short episodes (less than 3 weeks each) that occur for several months

Normal Volumes and Compositions

Source	Contribution mL	TOTAL IN & OUT/day mL	Na mM/L	K mM/L	Ca, Mg, NH_4 mM/L	Cl mM/L	HCO_3 mM/L	Other Anions
PO	2,000	2,000 -0	variable	variable	variable	variable	variable	variable
Saliva	1,500	3,500 -0						
Gastric	2,500	6,000 -0						
Bile	500	6,500 -0						
Pancreas	1,500	8,000 -0						
Jejunum	1,000	9,000 -5,500	130	6	variable	90	30	0
Ileum	0	3,500 -2,000	140	8	10	60	70	0
Colon	0	1,500 -1,300						
Stool		200	40	90	20	15	30	80-180


Fluid Entering (per day)
Oral intake 2 L
Salivary 1.5 L
Gastric 2.5 L
Biliary 0.5 L
Pancreatic 1L
Intestinal 1L
Fluid Reabsorbed
Small intestine
7.0 L (max 12 L)
Large intestine
1.4 L (max 5 L)
100 ml

Fluid Absorption

Absorption of water is passive; depends on the absorption of solutes.

Neurotransmitters & enteric hormones can modify net water balance.

Maximal absorptive capacity:

- **Small bowel: 12 liters**
- **Colon: 4-5 liters.**

Theoretical Maximal Continuous “Oral Rehydration Solution” rate:

- **375-400 mL/hour (9-10 L/d)**

Pathophysiologic Classification

Osmotic Diarrhea

The human bowel can not keep osmotic gradients;

- Stool osmolarity is equal to plasma osmolarity (280-310 mOsm)

If malabsorbed nutrients or non-absorbable solutes are ingested, fluid will enter the intestine to reach iso-osmolarity.

Normally, most of the stool osmolarity comes from its electrolytes (Na, K, corresponding organic anions)

Osmolar gap = 290 - 2[Na + K] ;

- Normal < 125 mOsm (usually < 50 mOsm)

Pathophysiologic Classification

Osmotic Diarrhea

- **Features of Osmotic Diarrhea:**
  - Osmolar gap > 125 mOsm
  - Stool Na < 60 mM/L
  - Fasting (food & drugs) stool output < 200 g
  - Carbohydrate related: pH<5.3 ; reducing substances (+) [does not detect lactulose, sorbitol, mannitol, nor sucrose]
- Examples:
  - **a) Osmolar load**: PEG, Mg salts, Na Phosphate, sorbitol, mannitol, lactulose, xylitol
  - **b) Malabsorption**: Mucosal damage (sprue, infections), disaccharidase deficiency, Olestra, bacterial overgrowth, pancreatic insufficiency, short bowel, IBD, lymphangiectasia, etc.

Drug Related Osmotic Diarrhea

Philip NA et al. J Clin Gastroenterol 2017;51:111–117

AGENTS	
Artificial Sweeteners (Mannitol, Sorbitol, Xylitol)	Methyldopa
Alpha glycosidase inhibitors (Acarbose, Miglitol)	Quinidine
Antibiotics (Ampicillin, Clindamycin)	Propranolol
Mg Laxatives and Antacids (Mg sulphate, Mg hydroxide, Mg Oxide)	Hydralazine
Phosphates	ACE inhibitors
Polyethylene glycol (PEG)	Procainamide
Prebiotics	Enteral Feeds
Poorly Absorbable Sugars (Fructose)	

Pathophysiologic Classification

Osmotic Diarrhea

Chloride:

- -Fecal chloride may be elevated (>35 mmol/L) in phenolphthalein- or phenolphthalein plus magnesium hydroxide-induced diarrhea.

In SO_4 or PO_4 diarrhea: they are > 10mmol/L

- Phosphorus elevation >102 mg/dL is suggestive of phosphate-induced diarrhea.

In diarrhea due to Mg salts:

- Mg concentration > 45 mM/L (usually > 100mM/L) and lower Na (30+/-5 mM/L)
- 24 hours stool Mg > 15 mmol; (7.3 g stool/ mmol Mg)
- Stool output after 24 h fasting:
  - a) Innocent < 200 g/d;
  - b) Surreptitious: > 200 g/d & gap > 100 mOsm

In diarrhea due to Na salts (Na Sulphate or Phosphate):

- Stool Na > 90 (mean 104+/-5) mM/L
- Osmotic gap < 50 mOsm
- Stool Cl^- < 20 mM/L

Unusually Measured Stool Osmolality

Time Effect	Stool Osm > 375 + Na > 150 mM/L	Stool Osm < 250	Stool [Na] + [K] > 165 mM/L
If stool is stored for hours, even in deep freeze, Osm may exceed 350 due to degradation of carbohydrates: process immediately.	• contamination with concentrated urine.	• contaminated with diluted urine, or water was added.	• concentrated urine in stool.

Pathophysiologic Classification
Secretory Diarrhea

Due to:

- Inhibition of ion (Na, K, Cl, HCO3) absorption,
- Stimulation of ion secretion, or
- Both.

May affect small bowel, colon, or both;

- in small bowel disease, the amount of fluid presented to the colon exceeds its maximal absorption capacity (5 L)

Pathophysiologic Classification

Secretory Diarrhea

- **Features of secretory diarrhea:**
  - Osmolar gap < 50 mOsm
  - Na concentration > 90 mM/L
  - 24 h fasting stool volume > 200 g
  - pH > 5.6
  - Reducing substances (-)
  - Markedly elevated fecal chloride concentration in infants (>60 mmol/L) and adults (>100 mmol/L) is associated with congenital and secondary chloridorrhea.
  - High Na concentrations (mean 104 +/- 5 mmol/L) in patients taking secretory laxatives.

Drug Induced Secretory Diarrhea

Philip NA et al. J Clin Gastroenterol 2017;51:111–117

AGENTS	
Antiarrhythmics (Quinidine, Digoxin)	Flavonoid Veinotonics
Amoxicillin-Clavunate	Laxatives
Auronafin	Misoprostol
Caffeine	Metformin
Calcitonin	NSAIDs
Carbamazepine	Olsalazine
Chemotherapy (Idarubicin, Epirubicin, Pentostatin, Mitoguazone, Docetaxel, Flucytosine)	Simvastatin
Chenodeoxycholic acid	Theophylline
Cimetidine	Ticlopidine
Colchicine	Levodopa-benaserazide
Diacerein	Cholinesterase inhibitors

Pathophysiologic Classification

Secretory Diarrhea

Classification:

1) Exogenous:

- **a) Drugs**: Phenolphtalein, anthraquinones, bisacodyl, senna, aloe, ricinoleic acid, DOSS, furosemide, thiazides, theophylline, thyroid, misoprostol, 5-ASA, gold, colchicine, etc. (see PDR)
- **b) Foods**: tea, coffee, cola, ethanol, MSG, seafood toxins (ciguatera, scombroid, paralytic or neurotoxic shellfish poisoning).
- **c) Bacterial toxins**: S. aureus, C. perfringes, C. botulinum, B. cereus.
- **d) Toxins**: Arsenic, Amanita phalloides, organophosphates,

Pathophysiologic Classification

Secretory Diarrhea

- **2) Endogenous:**
  - **a) Bacterial**: V. cholerae, Toxigenic E. coli, C. jejuni, Y. enterocolitica, K. pneumonia, C. difficile.
  - **b) Endogenous laxatives**: bile acids, long-chain fatty acids.
  - **c) Hormone-producing tumors**: VIPoma, ganglioneuromas, medullary carcinoma of thyroid, gastrinoma, carcinoid, glucagonoma, mastocytosis, villous adenoma.
  - **d) Congenital**: chloridorrhea, Na diarrhea, enterocyte heparan sulphate defic., microvillous inclusion disease.
  - **e) Miscellaneous:** Microscopic Colitis, Celiac Dz, SIBO.

Pathophysiologic Classification

Inflammatory Diarrhea

Enterocyte damage or death, with minimal or severe inflammation; can cause malabsorption or secretion.

Classification:

1) Minimal to mild inflammation:

- **a) Infections**: enteroadherent or enteropathogenic E. coli, rotavirus, Norwalk, HIV, giardia, cryptosporidium, isospora, cyclospora, ascaris, trichinella, bacterial overgrowth, tropical sprue.
- **b) Cytostatics**: chemotherapy, radiation.
- **c) Hypersensitivity**: food allergy, nematodes.
- **d) Autoimmune/ idiopathic**: microscopic colitis, collagenous colitis, Canada-Cronkhite, graft-vs-host.

Pathophysiologic Classification

Inflammatory Diarrhea

- **2) Moderate to severe inflammation with or without ulceration:**
  - **a) Destruction of enterocyte**: shigella, enteroinvasive E. coli, E. histolytica, hookworm.
  - **b) Penetration of mucosa**: salmonella, C. jejuni, Y. enterocolitica, M. avium complex, Whipple dz.
  - **c) Hypersensitivity**: Celiac sprue, milk or soybean hypersensitivity, eosinophilic gastroenteritis, gold, methyldopa, nematode infestation.
  - **d) Autoimmune/ idiopathic**: Ulcerative colitis, Crohn's disease, lymphoma

Drug Induced Inflammatory Diarrhea

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AGENTS	
Antibiotics (Clindamycin, Amoxicillin, Ampicillin, Cephalosporins)	Olmesartan
Auranofin	Oral Contraceptives
Carbamazepine	Cyclosporin A
Chemotherapeutics (5-Fluorouracil, Methotrexate, Irinotecan, Cisplatin, Doxorubicin)	PPIs (Esomeprazole, Lansoprazole, Omeprazole, Pantoprazole)
Etanercept	Penicillamine
Flutamide	Rituximab
Statins (Lovastatin, Pravastatin, Simvastatin)	SSRIs (Paroxetine, Sertraline)
Ipilimumab	Sodium Phosphate
Isotretinoin	Ticlopidine
Mercaptopurine	Tyrosine Kinase Inhibitors
Mycophenolate Mofetil	Laxatives
NSAIDs	

Pathophysiologic Classification

Deranged Motility

Due to autonomic dysfunction, rapid small intestine transit, and/or colonic irritability.

Examples:

- Sandhoff disease (hexosaminidase B deficiency),
- Irritable Bowel Syndrome.

Drug Induced Pro-Motility Diarrhea

Philip NA et al. J Clin Gastroenterol 2017;51:111–117

AGENTS	
Acetylcholine Esterase Inhibitors (Tacrine, Velnacrine)	Ticlopidine
Cholinergics (Bethanechol)	Thyroid Hormones
Cisapride, Metoclopramide, Tegaserod	Colchicine
Irinotecan	Anticholinergics
Macrolides (Erythromycin, Azithromycin)	

Pathophysiologic Classification

Mixed

- Most diarrheal disorders have more than one pathophysiologic component.

Helpful Questions to the Patient with Diarrhea

- **Stool volume**:
  - a) Volume < 250 g + tenesmus, frequency, urgency, mucus or blood:
    - suggest recto-sigmoid involvement.
  - b) Volume > 400 g, watery, minimal urgency, no tenesmus, little mucus:
    - suggest SB or proximal colon origin, secretory diarrhea.
  - c) Volume > 400 g, foul smelling, greasy, minimal urgency, no tenesmus:
    - suggest SB origin with malabsorption.

Helpful Questions to the Patient with Diarrhea

Pain:

- a) Periumbilical or RUQ, crampy, with borborigmi:
  - Small bowel or asc. Colon.
- b) Hypogastric, RLQ, or LLQ, aching, with tenesmus:
  - rectosigmoid

Blood:

- mucosal invasion (salmonella, campylobacter),
- IBD,
- neoplasia,
- ischemia,
- cytotoxin (enterohemorrhagic E. coli [EHEC], C. difficile, Shigella, Klebsiella oxytoca)

Effect of fasting (48-72h):

- a) Stops: osmotic, or allergic.
- b) Continues: secretory, or exudative /inflammatory.

Nocturnal Diarrhea: suggest organicity

Diagnostic Workup

Initial Diagnostic Tests

- **Calprotectin:** Elevated fecal calprotectin indicates the migration of neutrophils to the intestinal mucosa, which occurs during intestinal inflammation (In IBD: Sensitivity 93%; Specificity 96%)
  - Calprotectin is a 24 kDa dimer of calcium binding proteins S100A8 and S100A9. The complex accounts for up to 60% of the soluble protein content of the neutrophil cytosol.
  - Increased in inflammatory bowel diseases, celiac disease, infectious colitis, necrotizing enterocolitis, intestinal cystic fibrosis, use of NASAIDs and colorectal cancer.
- **Fecal Leukocytes**: indicates inflammatory diarrhea (sensitivity=42-73%, specificity=84%); if (+); send stool culture.
  - In C. difficile colitis, has sensitivity of 30% & specificity of 75% (Reddymasu et. al: Ann Clin Microbiol Antimicrob 2006, 5:9)

Initial Diagnostic Tests

- **Fecal Lactoferrin**: indicates inflammatory diarrhea (sensitivity=90%, specificity=95%); if (+); send stool culture.
  - C. difficile colitis, 64-77% are FL(+) @ titer >1:50. (Steiner et al. Clin Diag Lab Immun 1997,719-722)
  - Cryptosporidium: 7% adults & 70-83% malnourished children are LF(+) (Alcantara et al. Am J Trop Med Hyg 2003; 68:325-328)
  - Shigella, 95% are FL(+) @ titer > 1:200. (Guerrant et al. J Clin Microbiol, 1992; 30:1238-42)

Detection of C. difficile

Toxin Assays

Test	Pro	Con
Cytotoxicity (Gold Standard; tests cytopathic effect)	Very sensitive (10 pg Toxin B) Very specific	Expensive Takes 2 days
EIA toxin A&B	Very specific (>95%) Cheap Takes < 24 h	Low sensitivity (60-90%) (100-1000 pg toxin B)
PCR (tests gene for toxin B)	Rapid (< 4h) Very sensitive Very specific (80-99%)	Expensive Does not differentiate colonization from infection

Bacteria Detection

Test	Pro	Con
GDH (common antigen testing for glutamate dehydrogenase)	High sensitivity Rapid Cheap	Intermediate specificity Does not differentiate colonization from infection
Stool culture (anaerobic stool culture)	Extremely sensitive	Turn over: 3 days Does not differentiate colonization from infection

Initial Diagnostic Tests

Stool for Ova & Parasites:

- Routine O&P ***does not include*** studies for cryptosporidium, isospora, cyclospora, nor microsporidium; giardia Ag is done in some labs. You should order the test by name.
- O&P is not helpful in hospital acquired diarrhea.
- Because of intermittent shedding, O&P studies should be done in stools of 3 different days.

Molecular Panel for GI Pathogens:

- GI Panel (Film array) or GPP (xTAG)

Second Line Diagnostic Tests

- **Flexible sigmoidoscopy or Colonoscopy**: Indicated in:
  - Dysentery with negative stool studies.
  - History of rectal intercourse.
  - Suspect IBD
  - Immunocompromised patient when CMV, C. difficile, or opportunistic infections are suspected but stool studies are negative.
  - When ischemic colitis is suspected but radiology is equivocal.
  - Suspected pseudomembranous colitis with negative stool studies.
  - Persistent diarrhea with (-) stool studies

Second Line Diagnostic Tests

- **EGD with SB Bx & Aspirate**:
  - Excellent for SB mucosal disease but can have false (-) in patchy disease.
  - Fairly good for detection of giardia, cryptosporidium, isospora, cyclospora, microspora & strongyloides (patchy); aspirate & Bx.
  - Quantitative culture of > 10^5 colonies/mL is indicative of bacterial overgrowth.

Second Line Diagnostic Tests

EGD with Small Bowel Bx & Aspirate

- **Diagnostic Histology & Diffuse distribution**
  - Whipple disease
  - M. avium complex
  - Abetalipoproteinemia
  - Agammaglobulinemia
- **Diagnostic Histology but Patchy distribution**
  - Lymphoma
  - Lymphangiectasia
  - Eosinophilic enteritis
  - Mastocytosis
  - Amyloidosis
  - Crohn disease
  - Giardia, coccidiosis, strongyloidasis

Second Line Diagnostic Tests

EGD with Small Bowel Bx & Aspirate

- **Abnormal Non-Diagnostic Histology & Diffuse distribution**

- Celiac & tropical sprue
- Viral enteritis
- Bacterial overgrowth
- Severe folate & B_{12} deficiency

- **Abnormal Non-Diagnostic Histology & Patchy distribution**

- Acute radiation enteritis
- Enteropathy of dermatitis herpetiformis

Second Line Diagnostic Tests

Stool Electrolytes:

- Na, K, Cl
- Phosphorus, Magnesium, Sulphate, PEG.
- pH and Reducing Substances.

Laxative analysis in stool & urine.

- Stool water can be tested for phenolphtalein, emetine (ipecac syrup), & bisacodyl.
- Urine can be tested for anthraquinone.

Second Line Diagnostic Tests

- **Serologic studies**:
  - Quantitative serum IgG, IgA, & IgM: to evaluate for “combined variable immunodeficiency” & IgA deficiency; also for proper interpretation of Celiac Sprue serology
  - Anti-tissue transglutaminase (IgA & IgG) and Anti-Deamidated Gliadin Peptide (DGP) (IgA and IgG) for Celiac Sprue.
  - Ameba serology
  - Anti-HIV serology

Second Line Diagnostic Tests

Tests suggestive of Malabsorption

- **Decreased**:
  - Hemoglobin,
  - RBC folate,
  - Vitamin B_{12},
  - Transferrin saturation,
  - Ferritin,
  - carotene,
  - albumin,
  - cholesterol,
  - Mg,
  - Ca

- **Elevated**:
  - Urine oxalate,
  - Prothrombin time

Second Line Diagnostic Tests

- **Qualitative fecal fat** (while in >/= 100 gm/d fat diet):
  - 90% sensitive & 90% specific.
  - Neutral fat (dietary triglycerides) detected with alcohol + sudan stain.
  - Fatty acids (endogenous phospholipids & cholesterol) detected with glacial acetic acid + sudan.
  - False (+) with suppositories & mineral oil use.

Second Line Diagnostic Tests

- **72 hours stool fat**: (with food intake diary)
  - Start 100 gm/d fat diet at least 2 days before stool collection.
  - Evaluate both: Absolute and Relative Values.
  - Absolute Values of 7-14 g/24 h can be seen in secretory, malabsorption, or osmotic diarrhea.
  - Absolute Values > 14 g/24 h, indicate malabsorption or maldigestion.
  - Relative Values =/> 9.5 g fat/100g of stool suggest pancreatic insuficiency, or biliary steatorrhea.
  - Relative Values < 9.5 g fat/100 g of stool suggest mucosal disease.

Second Line Diagnostic Tests

- **Bile Acid Malabsorption assay:**
  - 7α-hydroxy-4-cholesten-3-one (7C4) in serum (Prometheus Lab or Mayo)
  - Fibroblast growth factor 19 serum level
- **D-Xylose absorption test**:
  - Useful for patchy mucosal disease.
  - Overnight fast, then give 25 g of D-xylose and 1 liter of water; immediately after collect 5 hour-urine; obtain blood sample 1 hour after D-xylose ingestion.
  - **Normal:** >/= 5g D-xylose in 5-hour urine & >/= 20 mg/dl D-Xylose in serum (1.3 mmol/L/1.73m^2)
  - False (+) & false (-) in 30%.
  - False (+) in: portal HNT, ascites, decreased GFR, use of NSAID's
- **Alpha-1-antitrypsin stool clearance**:
  - Serum sample + random stool sample from 24 h stool
  - Excellent test for protein-losing enteropathy; false (-) in Menetrier's disease.

Second Line Diagnostic Tests

Peptides & Hormones

- **24 hour urine collection for**:
  - 5-HIAA (usually > 99 mg/day or > 520 micromol/day in carcinoid),
  - Fractionated metanephrines and catecholamines (pheochromocytoma),
  - Histamine.
- **Serum for**:
  - Cortisol, TSH, Free T3 and T4
  - VIP (if secretory diarrhea > 700 mL/d) and 2 VIP levels > 75 pg/mL,
  - Fasting Gastrin > 1000 pg/mL with gastric pH < / =2 (Z-E syndrome); if 110-1000: Gastrin- Secretin Stim Test; test 5 days off PPI.
  - Calcitonin > 8.8 pg/mL (males), > 5.8 pg/mL (females) (medullary Ca. of thyroid) (many drugs and disorders cause elevation, including PPIs, beta-blockers and corticosteroids).
  - Glucagon > 500 pg/mL (diagnostic if > 1000 pg/mL) (glucagonoma),
  - Chromogranin A > 31 U/L (carcinoid & neuroendocrine tumors); test 5 days off-PPI,
  - Tryptase > 20 ng/mL in Baseline state, or Increase greater than [1.2 x Baseline value + 2 ng/mL] within 3 to 4 hours after symptoms (mast cell disease & foregut carcinoids).
  - Plasma fractionated Metanephrines (Pheochromocytoma)
- **Imaging**: Octreotide scan or DOTA Scan (PET CT Scan)

24 hours 5-HIAA

(Normal: 2-8 mg/day)

(Most Carcinoids > 50 mg/d)

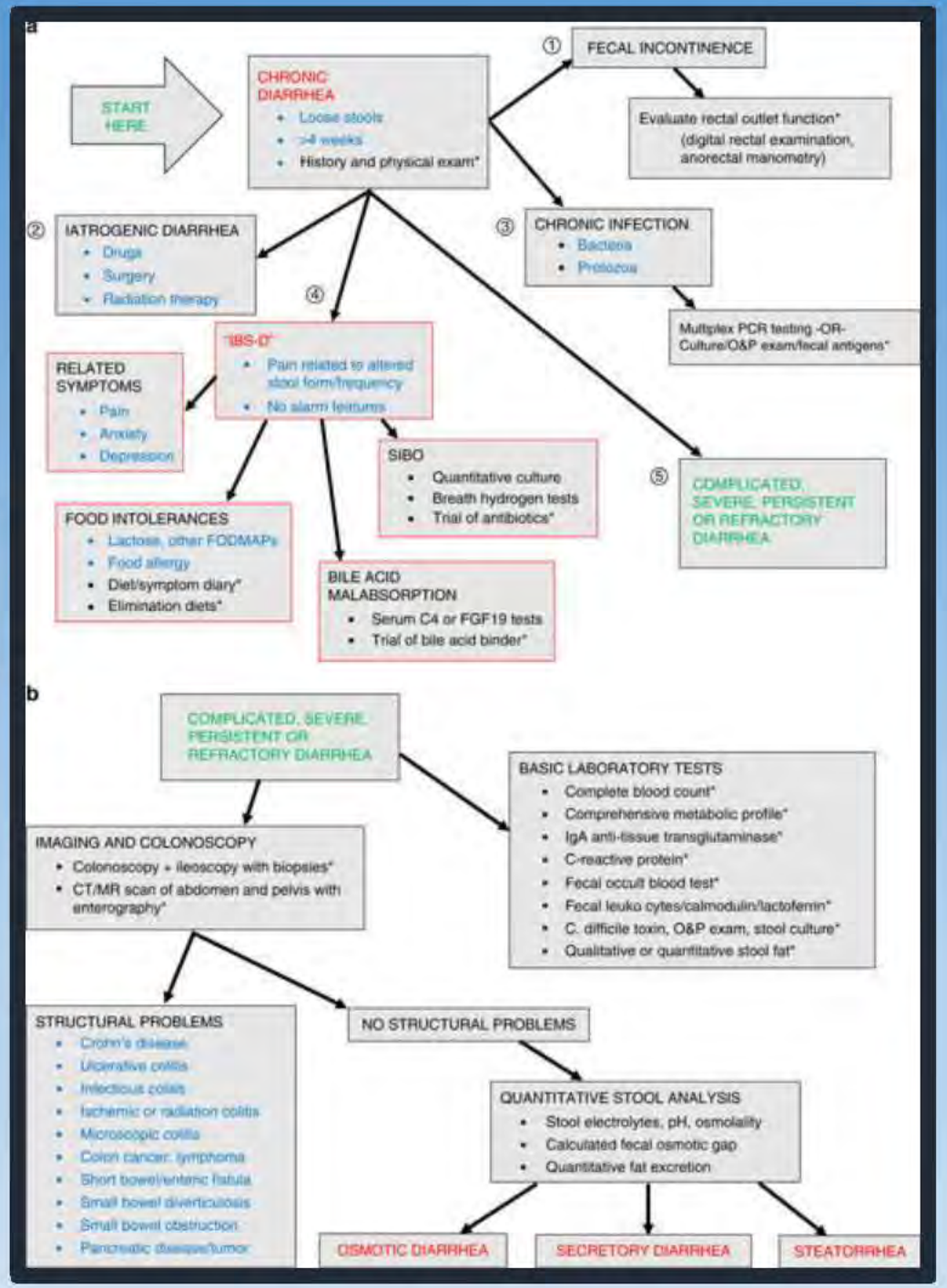
- **Falsely high values (up to 30 mg/day):**
  - **Tryptophan-rich foods:** avocados, pineapples, bananas, kiwi fruit, plums, eggplants, walnuts, hickory nuts, pecans, tomatoes, plantains
  - **Drugs:** acetaminophen, coumaric acid, guaifenisin, mephenisin, phenobarbital, reserpine, acetanilid, ephedrine, methamphetamine, nicotine, phentolamine, phenmetrazine, caffeine, flourouracil, melphalan, methocarbamol, phenacetin, mesalamine*
- **Falsely low values:**
  - **Drugs:** corticotrophin, ethanol, imiprimine, levodopa, MAO inhibitors, phenothiazines, aspirin, isoniazid, gentisic acid, methenamine, streptozotocin, heparin, methyldopa

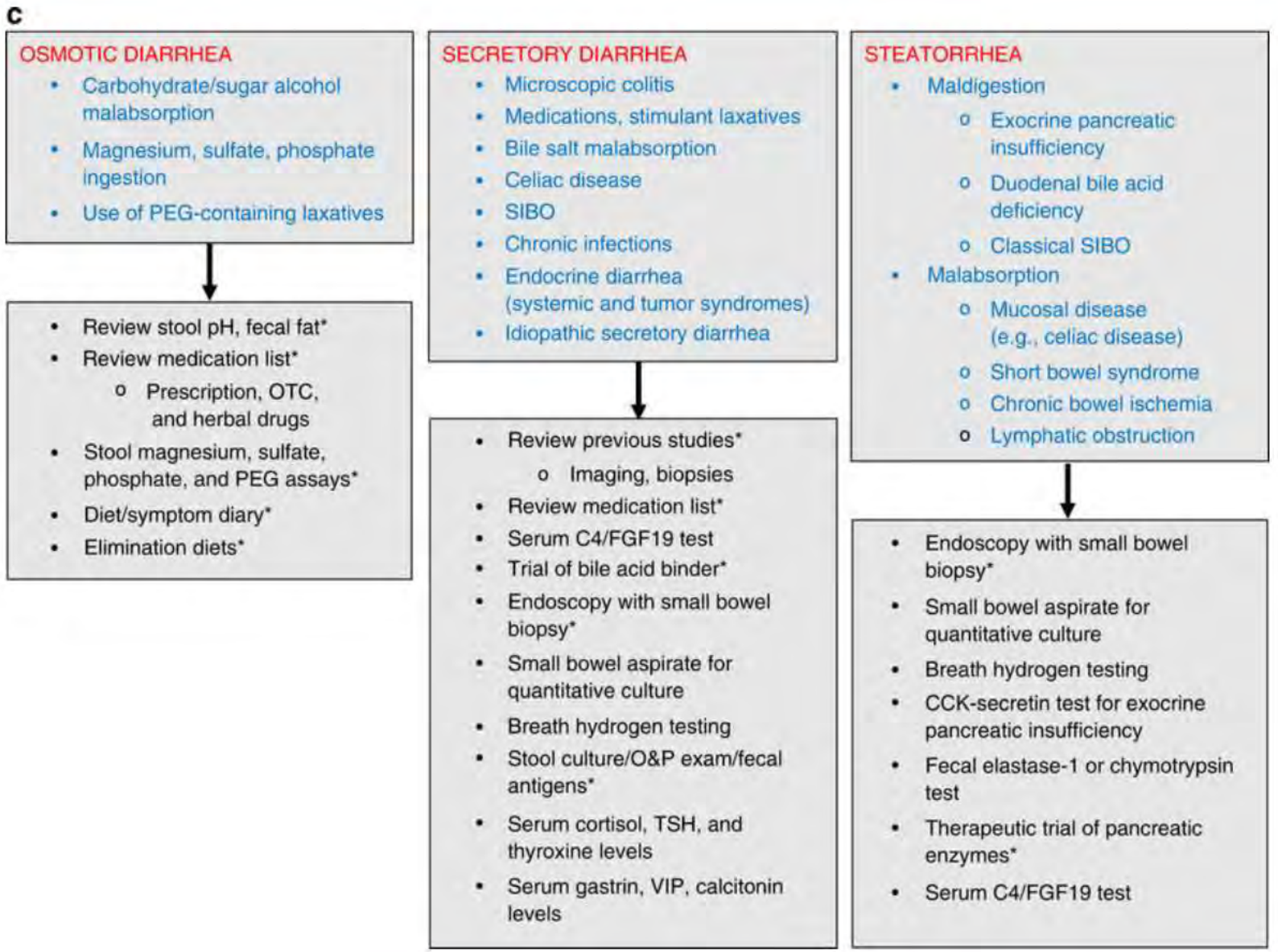
Second Line Diagnostic Tests

- **Test used less often**:
  - **Lactose Breath Test** (25 g) vs. milk removal test, for milk intolerance.
  - **Glucose Breath Test** (50-100 g) vs. quantitative SB fluid culture, for bacterial overgrowth.
  - **Schilling-II Test** (radiolabeled B_{12} + IF) vs. Bx of terminal ileum, for TI disease.
  - **Radiolabeled bile acid Test** (75Se-HCAT) vs. Cholestiramine trial, for bile malabsorption
  - **Pancreatic enzyme/bicarbonate Secretin Test** vs. pancreas CT scan or EUS + pancreas enzyme trial
  - **Fecal Elastase 1:** low in pancreatic insufficiency causing steatorrhea.

EVALUATION OF CHRONIC DIARRHEA

LR Schiller
AJG May 2018

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OSMOTIC DIARRHEA
Carbohydrate/sugar alcohol malabsorption
Magnesium, sulfate, phosphate ingestion
Use of PEG-containing laxatives
Review stool pH, fecal fat*
Review medication list*
Prescription, OTC, and herbal drugs
Stool magnesium, sulfate, phosphate, and PEG assays*
Diet/symptom diary*
Elimination diets*
SECRETORY DIARRHEA
Microscopic colitis
Medications, stimulant laxatives
Bile salt malabsorption
Celiac disease
SIBO
Chronic infections
Endocrine diarrhea (systemic and tumor syndromes)
Idiopathic secretory diarrhea
Review previous studies*
Imaging, biopsies
Review medication list*
Serum C4/FGF19 test
Trial of bile acid binder*
Endoscopy with small bowel biopsy*
Small bowel aspirate for quantitative culture
Breath hydrogen testing
Stool culture/O&P exam/fecal antigens*
Serum cortisol, TSH, and thyroxine levels
Serum gastrin, VIP, calcitonin levels
STEATORRHEA
Maldigestion
Exocrine pancreatic insufficiency
Duodenal bile acid deficiency
Classical SIBO
Malabsorption
Mucosal disease (e.g., celiac disease)
Short bowel syndrome
Chronic bowel ischemia
Lymphatic obstruction
Endoscopy with small bowel biopsy*
Small bowel aspirate for quantitative culture
Breath hydrogen testing
CCK-secretin test for exocrine pancreatic insufficiency
Fecal elastase-1 or chymotrypsin test
Therapeutic trial of pancreatic enzymes*
Serum C4/FGF19 test

Physical Finding Clues in Chronic Diarrhea

Findings	Potential implications
Orthostasis, hypotension	Dehydration, neuropathy
Muscle wasting, edema	Malnutrition
Urticaria pigmentosa, dermatographism	Mast cell disease (mastocytosis)
Pinch purpura, macroglossia	Amyloidosis
Hyperpigmentation	Addison's disease
Migratory necrotizing erythema	Glucagonoma
Flushing	Carcinoid syndrome
Malignant atrophic papulosis	Kohlmeier–Degos disease
Dermatitis herpetiformis	Celiac disease
Thyroid nodule, lymphadenopathy	Medullary carcinoma of the thyroid
Tremor, lid lag	Hyperthyroidism
Right-sided heart murmur, wheezing	Carcinoid syndrome
Hepatomegaly	Endocrine tumor, amyloidosis
Arthritis	Inflammatory bowel disease, yersinosis
Lymphadenopathy	HIV, lymphoma, cancer
Abdominal bruit	Chronic mesenteric ischemia
Anal sphincter weakness, perianal dermatitis	Fecal incontinence

Patterns of stool composition in chronic diarrhea

Stool Weight < 200 g/day

Features	Possible Diagnosis
No objective evidence of diarrhea	Change in stool frequency, intermittent diarrhea, fecal incontinence, treatment with antidiarrheal drugs during collection
Hyperdefecation (increased frequency without excess volume)	Possible IBS, proctitis, abnormal rectal reservoir function
Abnormal consistency (unformed-runny stools)	Possible IBS
Elevated fecal osmotic gap	Presumed mild carbohydrate malabsorption or excess Mg intake from supplements
Steatorrhea	Malabsorption or maldigestion

Stool Weight > 200 g/day

Features	Possible Diagnosis
Secretory diarrhea without steatorrhea	Microscopic colitis or other cause of secretory diarrhea Carbohydrate malabsorption without steatorrhea
High fecal osmotic gap	Ingestion of poorly absorbed carbohydrates, malabsorption
Steatorrhea with or without carbohydrate malabsorption	Small bowel mucosal disease, small intestinal bacterial overgrowth, bile acid deficiency, pancreatic exocrine insufficiency
Osmotic diarrhea	Ingestion of poorly absorbed ions (e.g., magnesium, phosphate, sulfate) or osmotically active polymers (e.g., polyethylene glycol)
Unclassified	Blood or pus suggests inflammatory causes of diarrhea

Differential diagnosis of Chronic Watery Diarrhea

Osmotic

Cause	Examples
Medications	Osmotic laxatives (Mg, SO_4, PO_4)
Unabsorbed sugars/sugar alcohols	Diet foods/drinks/gum (sorbitol, mannitol, others)
	Enzyme dysfunction (e.g., lactase, sucrase)

Secretory

Cause	Examples
Medications	Stimulant laxatives, antibiotics, many others
Small intestinal bacterial overgrowth	
Microscopic colitis	
Endocrine	
Tumors	Carcinoid, gastrinoma, medullary thyroid cancer, VIPoma
Systemic	Adrenal insufficiency, hyperthyroidism
Bile salt malabsorption	Ileal resection, postcholecystectomy, idiopathic
Non-invasive infections	Giardiasis, cryptosporidiosis

Differential Diagnosis of Chronic Fatty and Inflammatory Diarrhea

Fatty Diarrhea

Cause	Examples
Maldigestion	Decreased duodenal bile salt concentration (cirrhosis, bile duct obstruction, ileal resection)
	Pancreatic dysfunction (chronic pancreatitis, cystic fibrosis, duct obstruction)
Malabsorption	Mucosal disease (celiac sprue, tropical sprue, giardiasis, Whipple's disease, chronic mesenteric ischemia)
	Short bowel syndrome
	Small intestinal bacterial overgrowth (diabetes mellitus, scleroderma, prior bowel surgery)
	Lymphatic obstruction

Inflammatory Diarrhea

Cause	Examples
Inflammatory bowel disease	Ulcerative colitis, Crohn's disease
Malignancy	Colon cancer, lymphoma
Radiation colitis/enteritis	
Mastocytosis	
Invasive or inflammatory infections	*Clostridium difficile*, cytomegalovirus, *Entamoeba histolytica*, tuberculosis
Ischemia	

Differential diagnosis of IBS-D and diagnostic strategies

Diagnosis	Estimated prevalence in IBS-D	Diagnostic strategy
Food intolerances	20–67%	Diet and symptom diary → exclusion diet
Bile acid malabsorption	10–40%	SeCHAT retention, Serum 7C4 or Fibroblast Growth Factor-19 assay; trial of bile acid sequestrant
Small intestinal bacterial overgrowth	23–45%	Quantitative culture of small intestinal aspirate, breath hydrogen testing; trial of antibiotic therapy
Post-infectious IBS	28–58%	Anti-cytolethal distending toxin B and anti-vinculin antibody assays (IBS-Smart)
Microscopic colitis	5–10%	Colon biopsies (from above rectum)
Celiac disease	0.4–4%	IgA anti-tissue transglutaminase antibody and total IgA assays; duodenal biopsy
Pancreatic exocrine insufficiency	unknown	Fecal elastase-1 concentration; trial of pancreatic enzyme replacement
Rapid or slow intestinal transit	unknown	Scintigraphic or capsule-based transit study

Initial Treatment

- **Oral Rehydration Solution (ORS)**:
  - Best way to treat fluid loss from diarrhea (unless vomiting)
  - WHO: 1 L water + 3.5 g NaCl (3/4 tsp)+ 2.5 g Na bicarbonate (1/2 tsp) + 1.5 g KCl (20 mEq) + [40 g sucrose (3 tbsp), or 20 g glucose, or 50-80 gm rice powder cooked x 3 minutes]. [Na=90 mEq, K=20 mEq, Cl=80 mEq, HCO_3=30 mEq, glucose=111 mMol]
  - WHO: Water 1 liter + ¾ tsp salt + ½ tsp baking soda + 1 cup orange juice + 4 Tbs of sugar.
  - Ceralyte-70 1 liter + ¼ tsp salt or 11 Zesta crackers
  - Pedialyte 1 liter + 1 Tbs sugar + ½ tsp salt, or 22 Zesta crackers
  - Gatorade 3 glasses + 1 glass orange juice + {[½ tsp salt + ½ tsp baking soda], or [37 Zesta crackers]}

½ tsp salt = 22 Zesta crackers

½ tsp baking soda = 15 Zesta crackers

Initial Treatment

Racecadotril: reduces output & duration of diarrhea in children and adults; is taken in addition to ORS

Zn supplements: Decrease duration & need of antibiotics; taken in addition to ORS.

Crofelemer (Fulyzaq): 125 mg BID. For non-infectious diarrhea in HIV/AIDS.

Antisecretory Drugs

- **BSS** will reduce the stools passed by ~40%.
- **Crofelemer (Fulyzaq)**:
  - cystic fibrosis transmembrane regulator chloride-channel blocker
  - Effective in some forms of diarrhea including TD and AIDS-associated diarrhea.
- **Zaldaride**:
  - calmodulin-inhibiting drug that has antisecretory properties related to intracellular concentrations of calcium.

Antisecretory Drugs

- **Racecadotril**,
  - Specific enkephalinase inhibitor that prevents degradation of the endogenous antisecretory peptide neurotransmitter enkephalins that inhibit cyclic nucleotide secretory pathways
  - No effect on gut motility
  - Used successfully in pediatric diarrhea and in adults.

- **Loperamide** works through two mechanisms:
  - Primary effect is production of segmental contraction of the gut, which slows the intraluminal movement of fluids and allows greater absorption. A
  - Secondary effect appears to be inhibition of calmodulin leading to reduced mucosal secretion

Other Drugs to Treat Chronic Diarrhea

- **Eluxadoline (Viberzi):** mu-opioid receptor agonist and delta-opioid receptor antagonist. Dose: 100 mg BID. Contraindications: history of biliary disorders, pancreatitis, severe liver impairment (Child-Pugh C) and heavy alcohol use.
- **Alosetron (Lotronex):** 5-hydroxytryptamine-3 receptor (5HT-3) antagonist. Approved for the treatment of severe diarrhea-predominant IBS in female patients. Dose: Start at 4 mg/day.
- **Octreotide:** Dose 100-500 mcg SQ TID
- **Clonidine:** decreases intestinal transit and small intestinal secretion, but its use is limited by adverse effects
- **Paregoric:** Paregoric oral liquid contains morphine 2 mg/5 mL (0.4 mg/mL) Diarrhea dose: Oral: 5 to 10 mL 1 to 4 times daily.

Autoimmune Enteropathy

Chronic diarrhea (> 6 weeks)

Malabsorption

Enteropathy, minimal IELs

- May be absence of goblet and Paneth cells

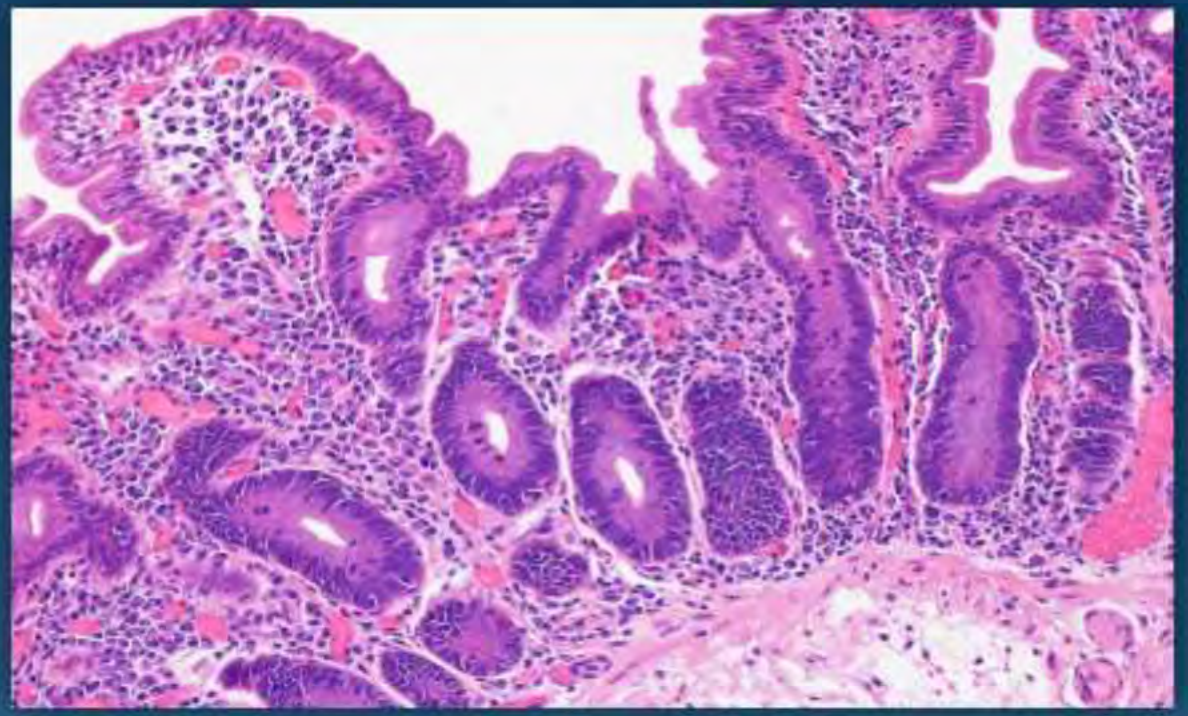
Exclusion of other causes of villous atrophy

Anti-enterocyte/anti-goblet cell antibodies

Patey-Mariuad DE, et al. Mod Pathol 2009;22:95-102.
Akram S, et al. CGH 2007;5:1282-90.

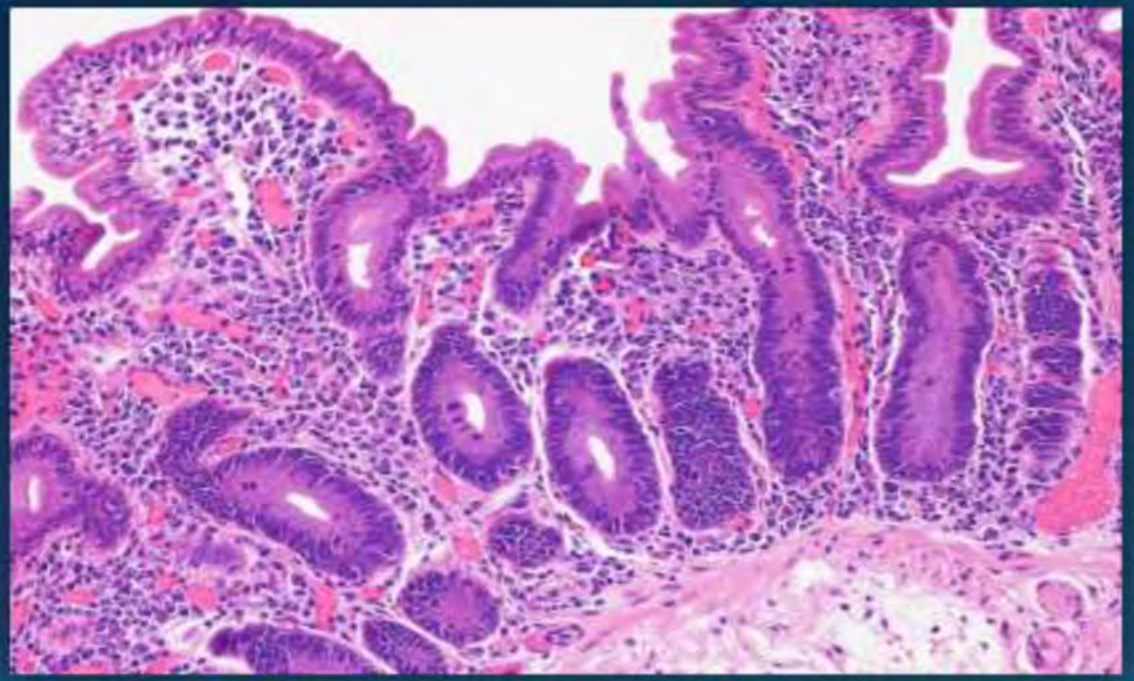
Autoimmune Enteropathy

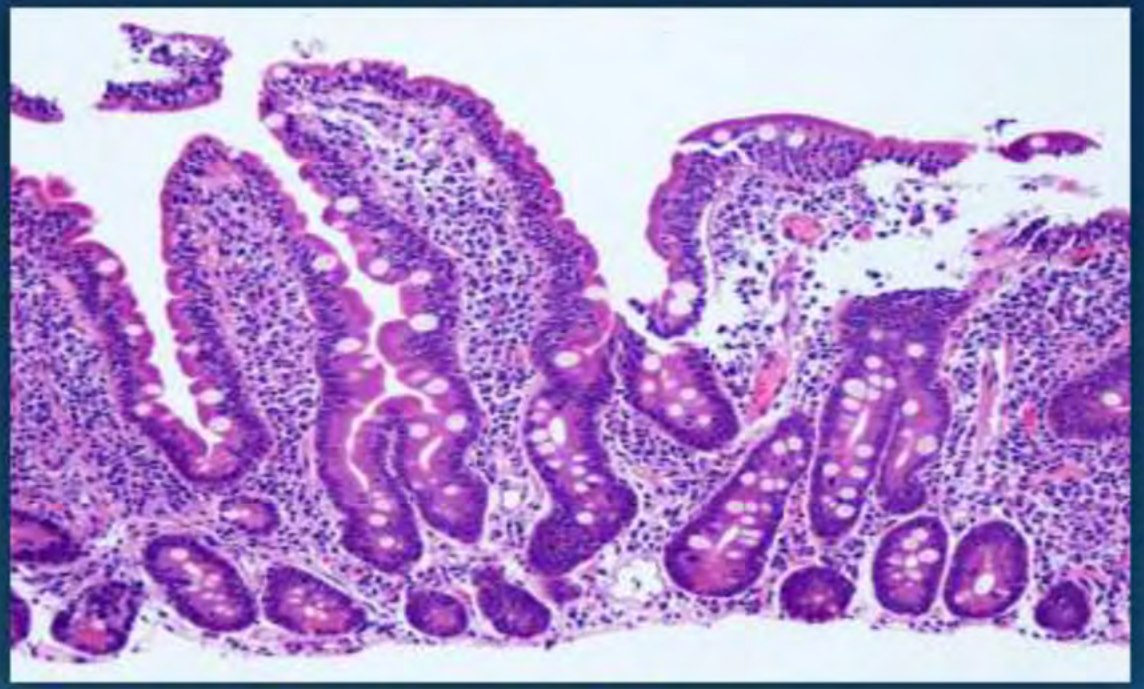
- Increased adult recognition
  - Equal M:F
  - Age mean 44-55 years
  - Delay in dx median 1.5 years
- Refractory diarrhea and nutritional issues
  - Large volume, non-bloody
  - Weight loss
  - Enteropathy
- No response to dietary trials



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

Anti-Enterocyte Antibody (IgG)

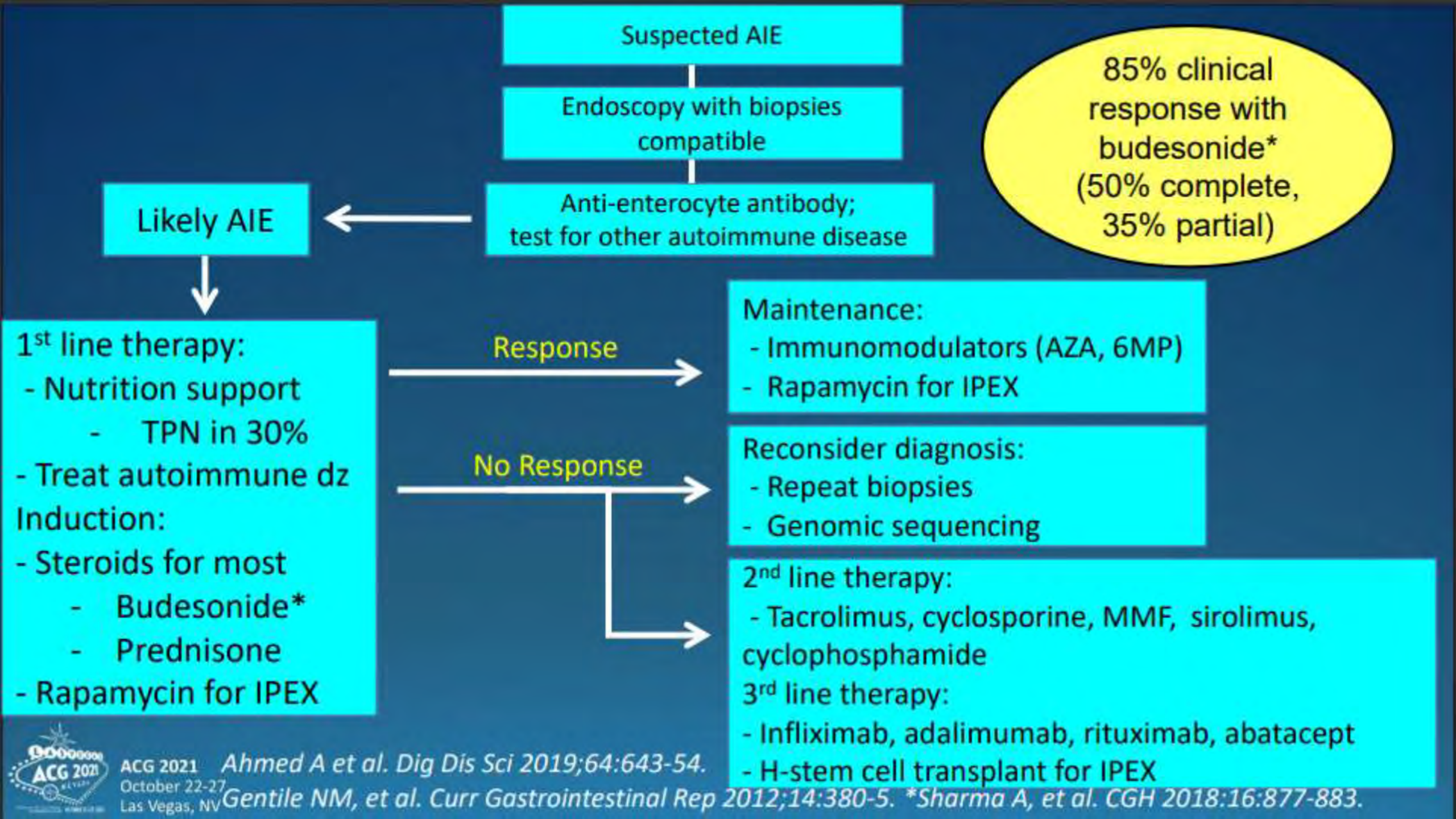
- Sensitivity 85-87%
- Non-specific
- Titer does not correlate w/severity
- Secondary epiphenomena?
  - Appear after onset
  - May normalize before restorative

Anti-Goblet Cell Antibody (IgG)

Anti-goblet cell antibodies are common and non-specific.

30-40% prevalence in population of healthy + disease.

CGH 2007;5:1282-90.;Scand J Gastro 2009;44:1029-36;
Nature Gen 2000;26:51-5.;Am J Gastroenterol 2009;104:3112.


Suspected AIE
Endoscopy with biopsies compatible
Anti-enterocyte antibody; test for other autoimmune disease
Likely AIE
85% clinical response with budesonide* (50% complete, 35% partial)
1st line therapy:
- Nutrition support
- TPN in 30%
- Treat autoimmune dz
Induction:
- Steroids for most
- Budesonide*
- Prednisone
- Rapamycin for IPEX
Response
No Response
Maintenance:
- Immunomodulators (AZA, 6MP)
- Rapamycin for IPEX
Reconsider diagnosis:
- Repeat biopsies
- Genomic sequencing
2nd line therapy:
- Tacrolimus, cyclosporine, MMF, sirolimus, cyclophosphamide
3rd line therapy:
- Infliximab, adalimumab, rituximab, abatacept
- H-stem cell transplant for IPEX
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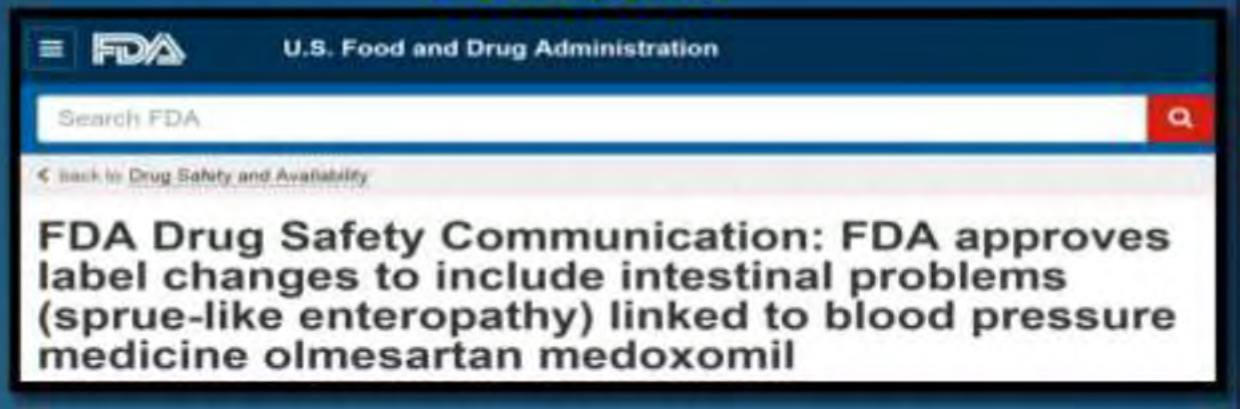
Ahmed A et al. Dig Dis Sci 2019;64:643-54.
Gentile NM, et al. Curr Gastrointestinal Rep 2012;14:380-5. *Sharma A, et al. CGH 2018:16:877-883.

Drug-Induced Enteropathy

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.

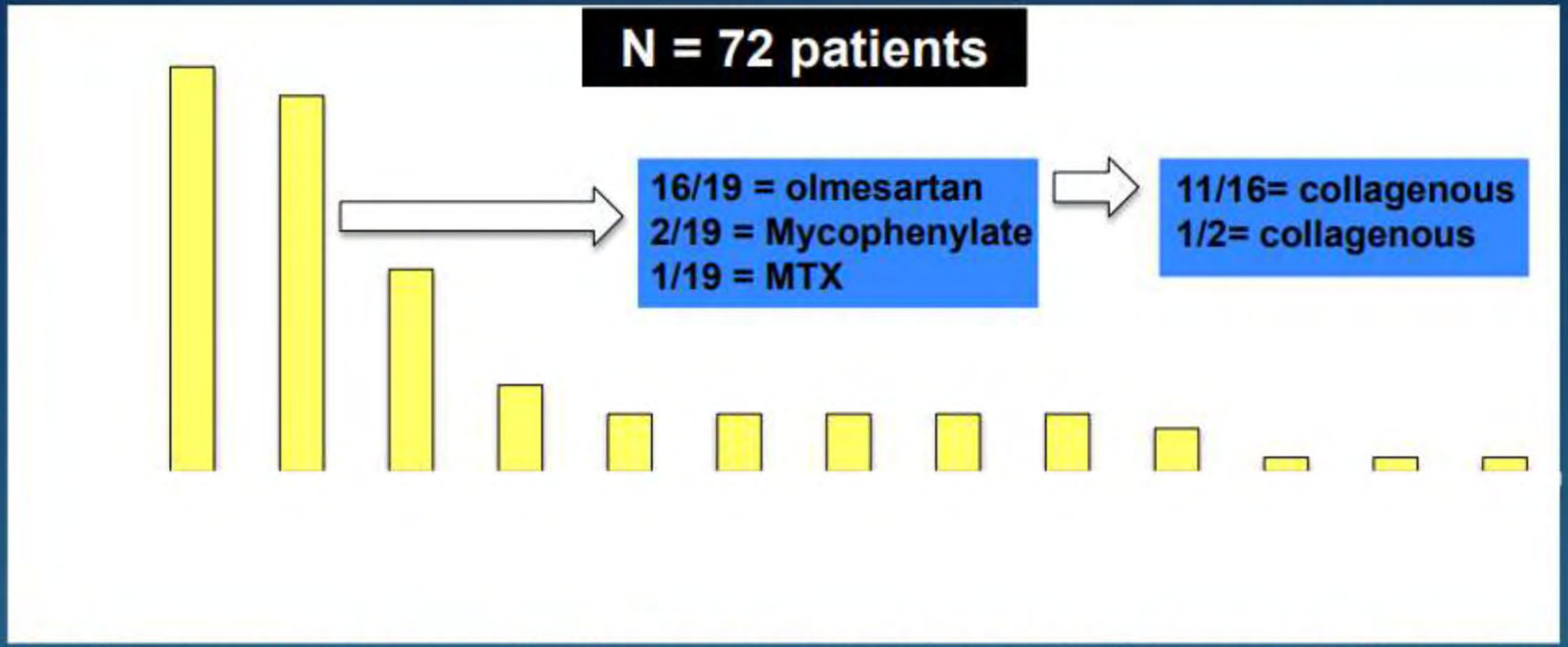
ARB-Induced Enteropathy

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

Rachal A, et al. Gastroenterol Rep 2019;7:162-7.
Gentile NM. Mayo Clin Proc 2013; Ziegler TR. Gastroenterology 2003.

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

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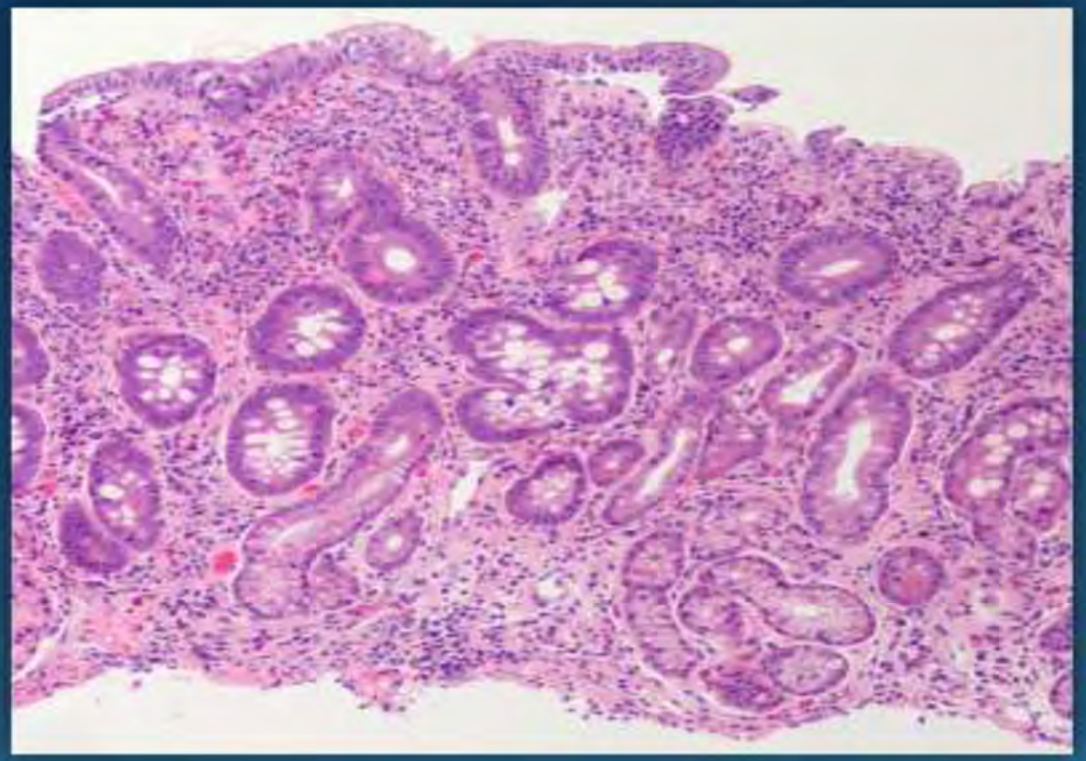
DeGaetani M, et al. Am J Gastroenterology: 2013;108;647-53.

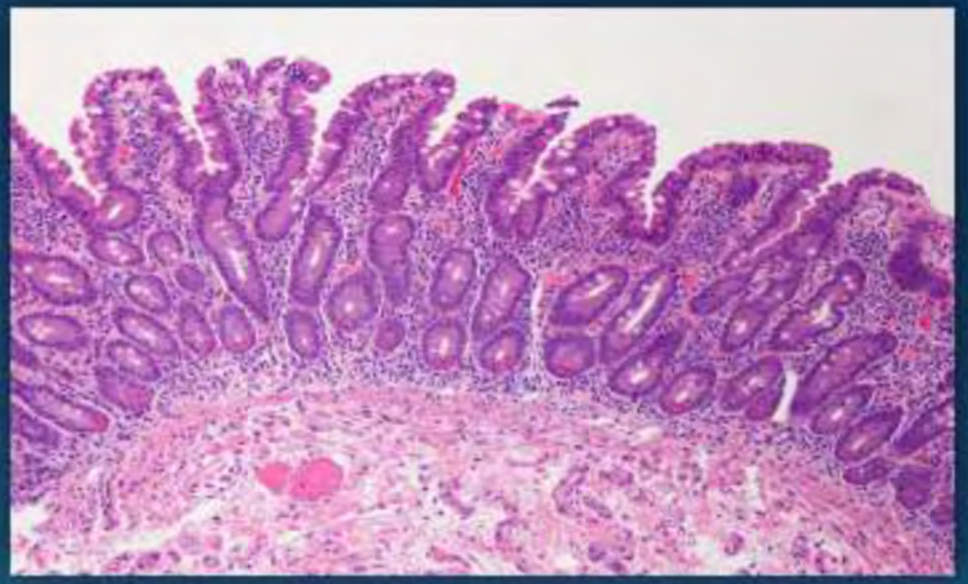
Drug-Induced Enteropathy Management

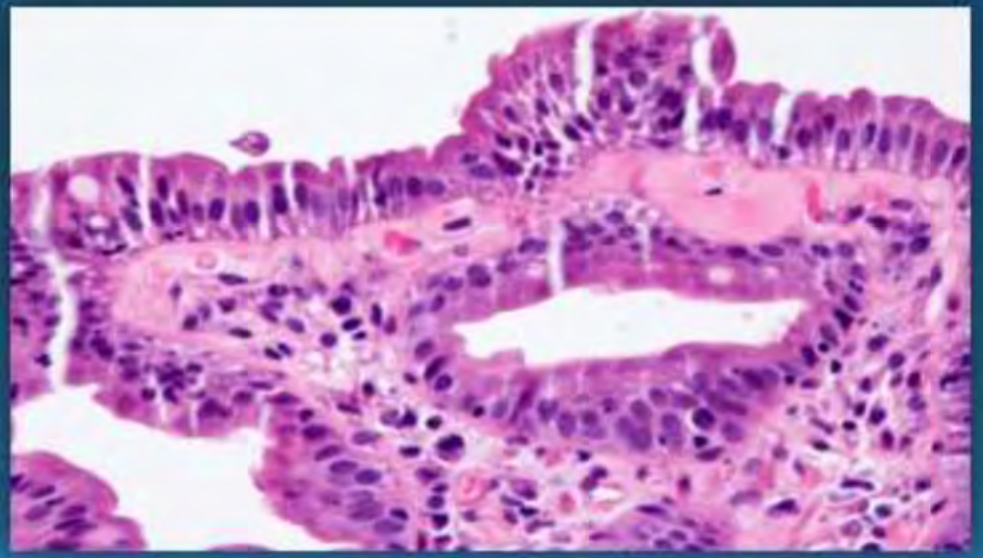


- Consider in the patient with:
  - Serologically-negative enteropathy
  - Collagenous deposition a clue
- Olmesartan started months to years earlier, leading to a delay in diagnosis
- Treatment:
  - Stop the medication if able
  - For immunosuppression, reduce dose?

Collagenous Sprue

- First described in 1947
- Clinical and histologic features of CD
  - Diarrhea, malabsorption, weight loss
- Thick type 1 collagen
  - >10-20 microns; reports of 260 um
  - Normal collagen < 5 microns
  - Half of a lymphocyte





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

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% Thiopurine15%
Infliximab 3%

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B Al-Bawardy, et al.Gastroenterology, 150 (4) (2016), pp. S307-S308

Management of Collagenous Sprue (CS)

- Review medications
  - Stop offenders
- Initiate gluten-free diet
- Immunosuppression *(typical!)*
  - Budesonide, prednisone, AZA, budesonide + AZA, infliximab

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

Combined Variable Immunodeficiency (CVID)

Impaired B cell differentiation, abnormal Ig production

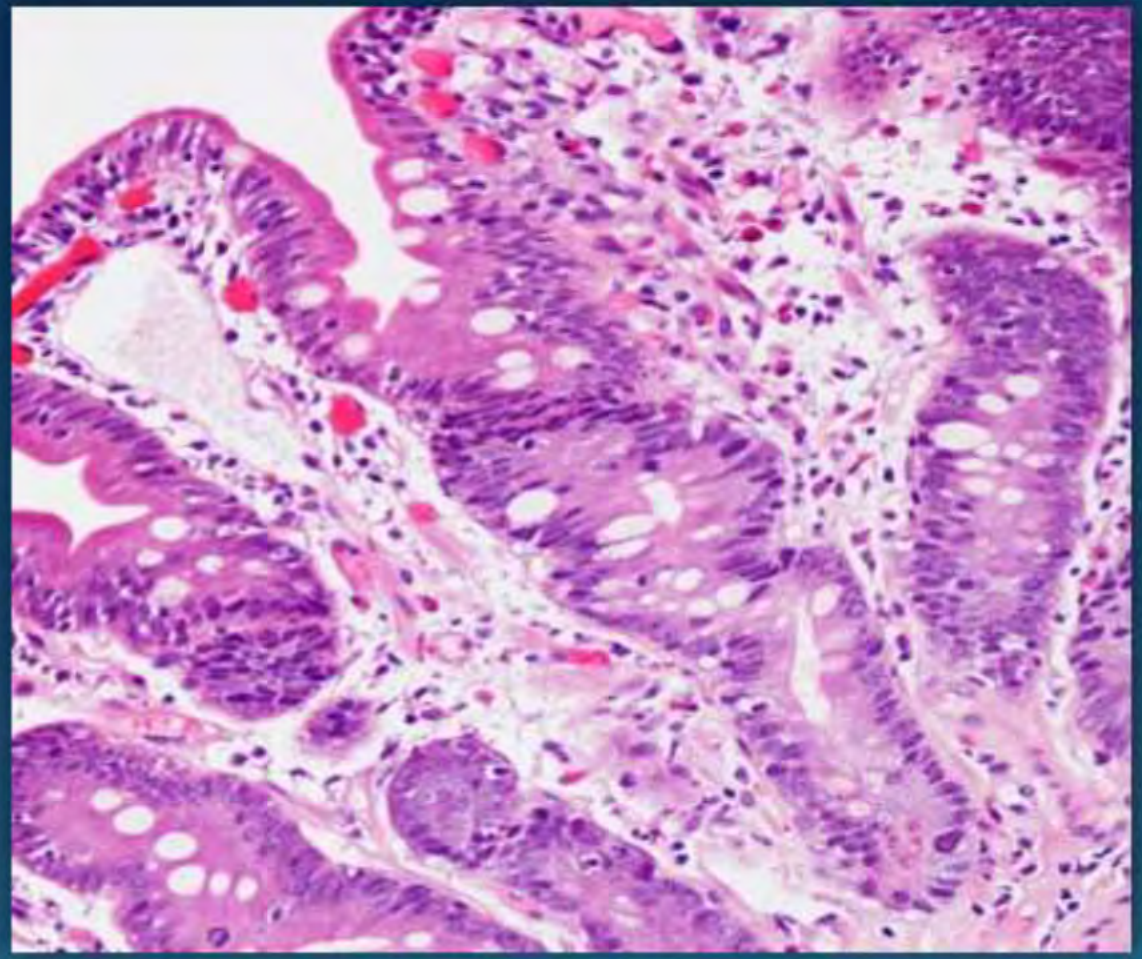
Any age (most 20-45 at dx), M:F equal

+/-Respiratory and GI infections; delayed dx

Other features: autoimmunity, liver, lymphoma

CVID Criteria:

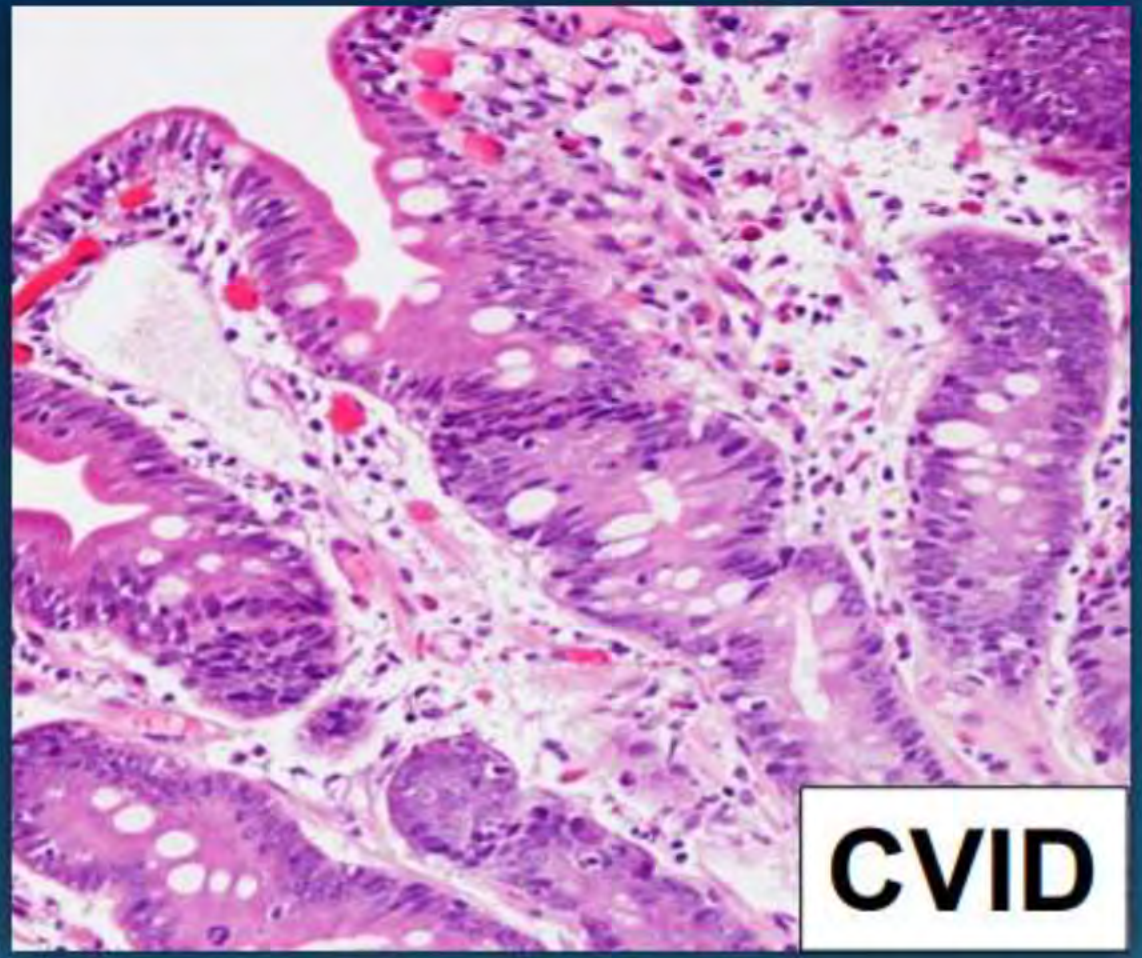
- IgG 2 SD below normal AND
- One other low Ig level (IgA or IgM) AND
- Failure to mount vaccine reaction
- Absence of other immunodeficiency



Histologic clues:

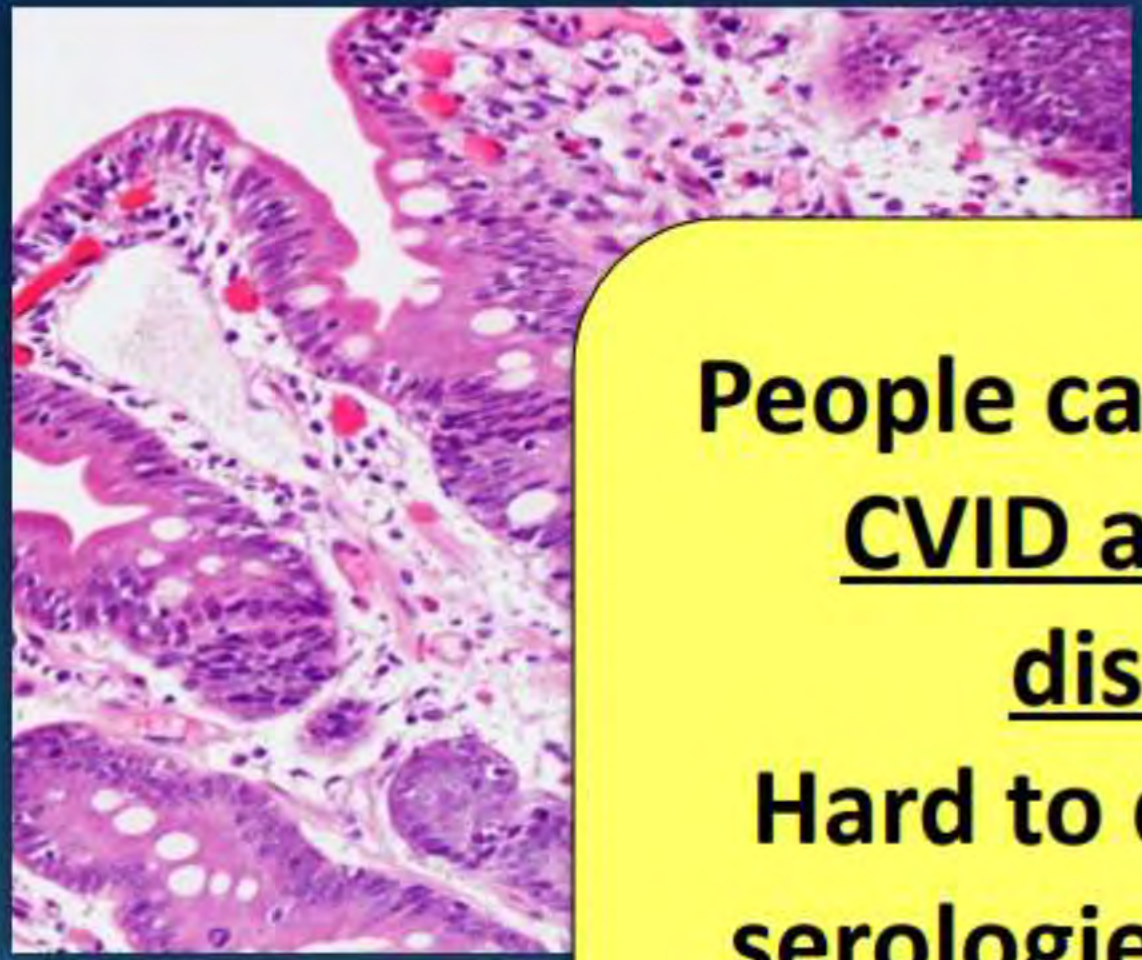
- Reduced plasma cells
  - 30% w/normal #
- IELs, villous atrophy
- Apoptosis, neutrophils
- "Empty" lamina propria

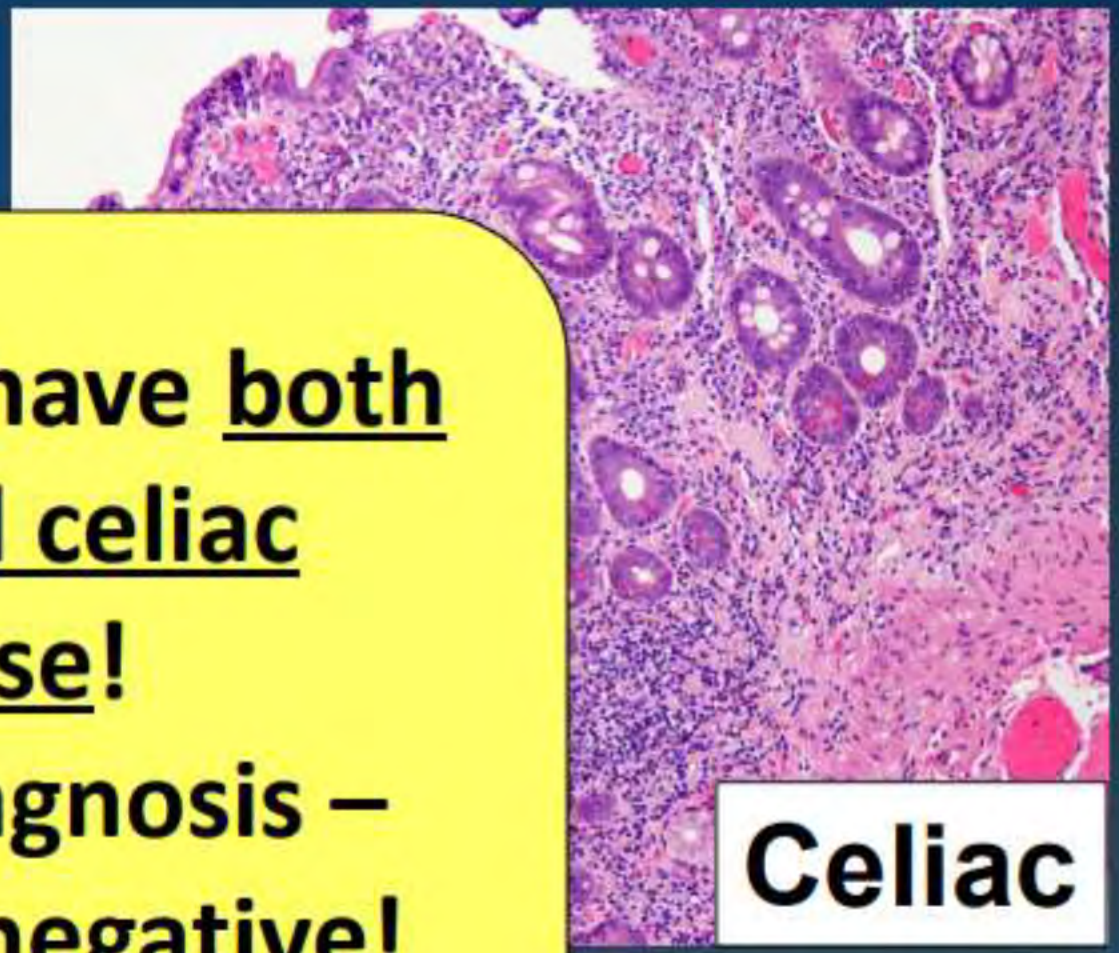
*Daniels, et al. Am J Surg Pathol 2007;31:1800-12.



Cornerstone of CVID Management:

- Immune globulin replacement
- Infection prevention





Celiac

People can have <u>both CVID and celiac disease</u>!

Hard to diagnosis – serologies negative!

- Immune globulin replacement
- Infection prevention

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