

Protein-Losing Gastro-Enteropathy (PLGE)

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Definition of PLGE

- Syndrome due to abnormal, non-selective, plasma protein loss into the gastrointestinal tract.
- Is clinically apparent when net enteral protein loss exceeds liver synthetic capacity.
- **Clinical presentation:**
 - **hypoproteinemia, hypoalbuminemia, and edema.**
 - sometimes pleural effusion, pericardial effusion and ascites,
 - diarrhea is common but not universal,
 - hypercoagulability or recurrent infection is not a feature of the disease,
 - if lymphocytopenia is present (lymphatic obstruction), cellular immunity is frequently impaired (PPD and anergy screen are unreliable to exclude TB)

Other Clinical Features

- Laboratory:
 - Low levels of proteins with slow turnover
 - IgG, IgM, IgA, transferrin, ceruloplasmin, alpha₁ antitrypsin, some clotting factors like fibrinogen.
 - Serum IgE is normal (high turnover) or elevated (parasites or immune disorder).
 - May have low Fe, trace elements, lipids and lymphocytes, due to intestinal loss.
 - If steatorrhea is present due to lymphatic obstruction, may have fat-soluble vitamin deficiency.

Normal GI Protein Loss

- Represents less than 10% of albumin and gammaglobulin protein catabolism.
- Due mostly to sloughed enterocytes, and to pancreatic and biliary secretion.
- Most of the protein lost in the GI tract is digested and reabsorbed as aminoacids.
- In PLGE enteric protein loss increase 4-fold to 5-fold, while hepatic synthesis of albumin can increase only two-fold.

Causes of PLGE

- May be due to:
 - Protein exudation due to ulceration
 - Protein exudation without ulceration due to:
 - alteration in cell integrity,
 - extreme mucus production, or
 - increase permeability of tight junctions.
 - Impaired lymphatic venous drainage, with high intra-lymphatic hydrostatic pressure.

Ulcerative Disease

- Erosive gastritis or enteritis.
- NSAID's enteropathy
- Neoplasia:
 - Carcinoma,
 - Lymphoma,
 - Kaposi,
 - Alpha-chain disease
- Crohn's disease.
- Ulcerative colitis.
- Acute GVHD
- Post-chemotherapy
- Amyloidosis with ulcers.
- Cap polyposis
- Bacteria:
 - Pseudomembranous colitis,
 - Shigellosis,
 - Salmonellosis,
 - Staphylococcus
- Parasites:
 - Strongyloides,
 - Ancylostoma,
 - Necator,
 - Ameba,
 - Balantidium.
- Virus:
 - CMV,
 - Measles,
 - Varicella.

Non-Ulcerative Disease

- Celiac Sprue
- Tropical Sprue
- SB Bacterial overgrowth
- Menetrier's (giant hypertrophic gastritis /hypochlorhydria)
- Secretory hypertrophic gastritis
- H. pylori infection
- Lymphocytic gastritis
- Amyloidosis
- Collagenous colitis
- Henoch-Schoenlein
- Polyposis
 - Cronkhite-Canada,
 - Peutz-Jeghers S,
 - Juvenile Polyposis S,
 - Adenomatous polyposis
- Acute viral infection
- Parasitic infection
 - Malaria,
 - Giardia,
 - Cryptosporidium,
 - Schistosoma
- Whipple disease
- SLE
- Systemic Sclerosis
- RA
- MCTD
- Allergic gastroenteropathy
- Eosinophilic gastroenteritis
- Congenital Disorder of Glycosylation (Carbohydrate deficient glycoprotein S.)

Lymphatic Fluid Loss

- **Congenital Intestinal lymphangiectasia**
- Enteric-lymphatic fistula.
- Increased central venous pressure.
 - CHF
 - Constrictive pericarditis
 - Congenital heart disease
 - SVC obstruction
 - Fontan procedure for single ventricle
- Hepatic venous outflow
 - Budd-Chiari S
 - Obliterative Hepato-cavopathy
- Mesenteric lymphatic obstruction
 - Intestinal or mesenteric Tuberculosis
 - Mesenteric Sarcoidosis
 - Intestinal Lymphoma
 - Retroperitoneal Fibrosis
 - **Whipple Disease**
 - Waldenstrom macroglobulinemia
 - Endometriosis of Small bowel
 - Pancreatitis +/- pseudocyst
 - Pancreatic Cancer
 - Retroperitoneal tumor.
 - Crohn's disease
 - Intestinal malrotation

Initial Work up

- **Establish presence of non-selective protein loss:**
 - Low serum albumin, IgG, IgM, IgA, transferrin, fibrinogen, ceruloplasmin, alpha-1 antitrypsin.
 - Normal or high serum IgE
- **Establish that loss is in the bowel:**
 - A₁AT Stool clearance: 24 hour stool + same day serum sample for alpha-1 antitrypsin.
 - Normal ≤ 13 mL/d.
 - Abnormal if > 24 mL/day without diarrhea (> 56 mL/day in case of diarrhea)
 - Caution:
 - **A)** If loss is gastric and pH is acidic, result may be falsely low. Must give PPI or Cimetidine infusion, or do study by gastric analysis.
 - **B)** A1AT Stool clearance is also increased with hematochezia, or diarrhea due to lactulose, sorbitol, Na sulfate, or Phenolphthalein.

Initial Work up

- Establish if there is associated lymph loss:
 - Low serum lymphocyte count.
 - Fat in stool.
- Establish if loss is gastric versus intestinal:
 - Sometimes 99mTc-labeled albumin scan localizes the site of loss
- If Ascites or Pleural effusion is present
 - Paracentesis and thoracentesis with:
 - Cell count + diff (also Eosinophile count), protein, albumin, SAAG calculation, amylase, LDH and triglycerides (chylous). Pleural fluid pH.
 - Culture in blood culture bottles.
 - Concentrate 250 mL fluid for AFB (in Microscopic-Observation Drug-Susceptibility (MODS) Assay & Fungus culture.
 - Cytology.

Additional Studies Directed to Suspected Cause

- Serum studies:
 - If gastric folds are hypertrophic and pH is acidic:
 - check fasting serum gastrin to R/O Zollinger-Ellison S.
 - If IgA or IgM is disproportionately higher than IgG:
 - obtain SPEP + Immunofixation to R/O alpha-chain disease and Waldenstrom Macroglobulinemia, respectively.
- Stool studies:
 - most useful in diarrhea with eosinophilia, small bowel type diarrhea, dysentery, or after antibiotic or chemotherapy:
 - giardia Ag, cryptosporidium
 - Comprehensive study for O&P for strongyloides, necator, ancylostoma, ameba, schistosoma.
 - Charcot-Leyden crystals (eosinophilic or allergic gastroenteritis, parasites).
 - C. difficile toxin A&B, or Toxin B by PCR.
 - H. pylori Ag.

Additional Studies Directed to Suspected Cause or Site

- Push Enteroscopy in a.m. after fatty meal on previous night (to distend lacteals):
 - **Esophageal Bx** for eosinophiles and amyloid (Congo Red)
 - **Gastric pH**
 - Menetrier's has neutral pH;
 - "Secretory hypertrophic gastropathy" (SHG) has acid pH (may need gastric analysis to show hypersecretion),
 - **Gastric Bx** for Path, Eosinophiles & H. pylori
 - full thickness biopsy with band ligator for hypertrophic folds: Menetrier vs Lymphoma vs Secretory Hypertrophic Gastropathy
 - **Jumbo SB Bx** for Eosinophiles, Amyloid, Celiac Sprue, Tropical Sprue & Whipple.
 - **Duodenal aspirate for quant culture and O&P:**
 - dominant anaerobics and $> 10^5$ in SBBO;
 - gram(-) in Tropical Sprue: E. coli, Klebsiella, enterobacter.
 - Inform Pathologist that you saw prominent white lymphatics.
 - Consider viral culture of suspicious lesions

Additional Studies Directed to Suspected Cause or Site

- Colonoscopy + TI exam:
 - Exam for evidence of Neoplasia, IBD, Polyposis, Cap polyposis, Pseudomembranes, NSAID lesions, or viral ulcers.
 - Random Bx for Collagenous colitis, eosinophiles, schistosoma & amyloid.
 - Directed Bx for IBD, PMC, Ameba, Balantidium, Cap polyposis.
 - Exam TI for Crohn's and parasites.
- Video Capsule Enteroscopy or Balloon Assisted/Spiral Enteroscopy after fat-rich meal on previous night:
 - for enteral protein loss with negative Push-enteroscopy & Colonoscopy.

Additional Studies Directed to Suspected Cause

- Echocardiogram: for protein loss with lymphopenia
 - Evaluate for pericardial disease, heart failure, amyloid, congenital heart disease, pulmonary HTN.
 - Can give false negatives; may need Right Heart Catheterization.
- Localization of lymph obstruction: protein loss + lymphopenia
 - CT scan for retroperitoneal disease, pancreas disease, lymphoma, sarcoidosis, neoplasia, small bowel endometriosis, Budd-Chiari, obliterative hepato-cavopathy.
 - Lymphangiography
 - MR Lymphangiography

Selected Causes of PLGE

(topics rarely discussed)

- Menetrier Disease
- Hyperplastic Hypersecretory Gastropaties
- Eosinophilic Gastroenteritis
- Cap Polyposis
- Cronkhite-Canada
- Whipple Disease
- Congenital Intestinal Lymphangiectasia
- Tropical Sprue
- Allergic Enteropathy

Menetrier

- Represents only 8% of non-varicose large gastric folds: others are
 - chronic gastritis/ lymphoid hyperplasia 40%,
 - benign tumors 16%,
 - gastric Ca 12%,
 - Z-E 10%.
- Pathogenesis:
 - Acquired hyperplasia of mucus and epithelial cells of gastric fundus and body (foveolar gland hyperplasia) due to excessive stimulation of Epidermal Growth Factor Receptor by TGF-alpha.
 - TGF-alpha also inhibits acid secretion. Is usually accompanied by atrophy of oxyntic glands and hypochloridia.
 - May occur after prolonged H₂-blocker use.
 - CMV & H. pylori may be aggravating factors, and should be treated.
 - CMV may cause pediatric Menetrier; CMV Menetrier is very rare in adults.

Menetrier

- Signs & Symptoms:
 - Severe enlargement of gastric folds in body and fundus (100%),
 - enteric protein loss with hypoalbuminemia (80%),
 - epigastric pain (65%),
 - asthenia (60%),
 - anorexia (45%),
 - edema (38%),
 - vomiting (38%).
 - Acid secretion is low, and gastrin may be moderately elevated.

Menetrier

- Dx:
 - Done by snare or suction-band Bx of enlarged folds.
 - Extreme foveolar hyperplasia, frequently with oxyntic glandular atrophy, in a patient with striking enlargement of gastric folds.
- Treatment:
 - Eliminate H. pylori and CMV (gancyclovir)
 - PPI therapy.
 - Octreotide may regulate EGFR signaling downstream: 100-200 mcg SQ TID or Octreotide LAR 20-60 mg q 4 weeks IM.
 - Erbitux (monoclonal Ab anti-EGFR)
 - Cetuximab (monoclonal Ab anti-EGFR)
 - Consider EGD surveillance q 1-2 years for neoplasia risk (unknown degree; 2-15% adenoCa risk?)
 - Gastrectomy.

Hyperplastic Hypersecretory Gastropathies

- Pathology Types: two
 - Mixed foveolar and oxyntic gland hyperplasia:
 - Idiopathic,
 - H. pylori hypertrophic gastropathy,
 - Sarcoid,
 - Childhood CMV gastritis
 - Cronkhite-Canada,
 - Lymphocytic gastritis (associated to Celiac Sprue)
 - Oxyntic gland hyperplasia without foveolar hyperplasia
 - secondary to gastrinoma (Z-E Syndrome)
- Physiologic feature:
 - Patients have increased Basal acid secretion.
 - Stimulated gastric secretion is also elevated but response is less intense in Z-E due to pre-existing gastrin overstimulation.
- Diagnosis:
 - Snare or rubber band assisted biopsy,
 - Gastric acid analysis (basal & stimulated), and
 - Fasting serum gastrin.

Eosinophilic Gastroenteritis

- Involved areas:
 - **Organ:** may involve stomach, small bowel, bile ducts and/or colon.
 - **Layer:** may involve mucosa, muscle and/or subserosa.
 - **Path:** Bx of normal and abnormal mucosa shows > 20 Eo/HPF. May be patchy.
- Epidemiology:
 - Occurs at any age, with male predominance.
 - Most common in 3rd to 5th decade.
 - Fifty percent of patient have allergic diseases.
- Symptoms:
 - **Mucosal Disease:** abdominal pain, nausea, vomiting, diarrhea. One third have abnormal weight loss. Can cause malabsorption and protein-loss.
 - **Muscle-layer Disease:** thicken and rigid gut may cause obstruction. May cause pseudo-achalasia or GOO. Because mucosa may be normal, requires full-thickness Bx.
 - **Subserosal Disease:** causes eosinophilic ascites or eosinophilic pleural effusion.

Eosinophilic Gastroenteritis

- **Laboratory:**
 - Absolute eosinophilia (>500) in 80%.
 - Modest elevation of ESR in 25%.
 - Elevated IgE may be present.
 - Studies for parasites are negative.
 - Charcot-Leyden stool crystals.
 - Skin prick testing and patch testing to food allergens may be done to identify IgE-mediated and cell-mediated food allergies.
- **Treatment:**
 - Five-food elimination diet (soy, wheat, egg, cow-milk, and seafood). Peanuts and corn may also be responsible
 - Prednisone 20-40 mg/d x 2 weeks or until improvement, followed with taper over 2 weeks. Periodic flares are treated similarly. Rarely IV steroids are needed.
 - Entocort may help in SB disease.
 - Oral cromolyn, or montelukast have helped some patients.

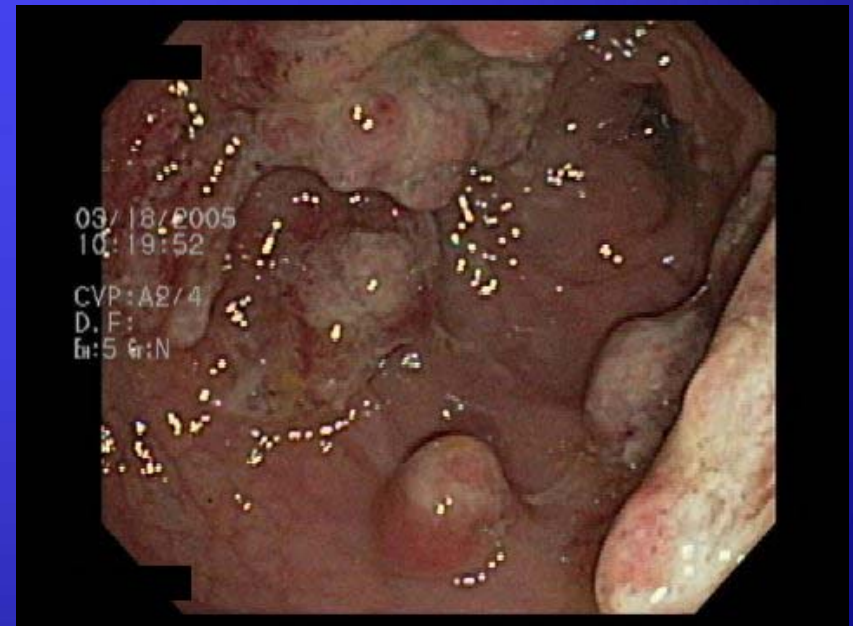
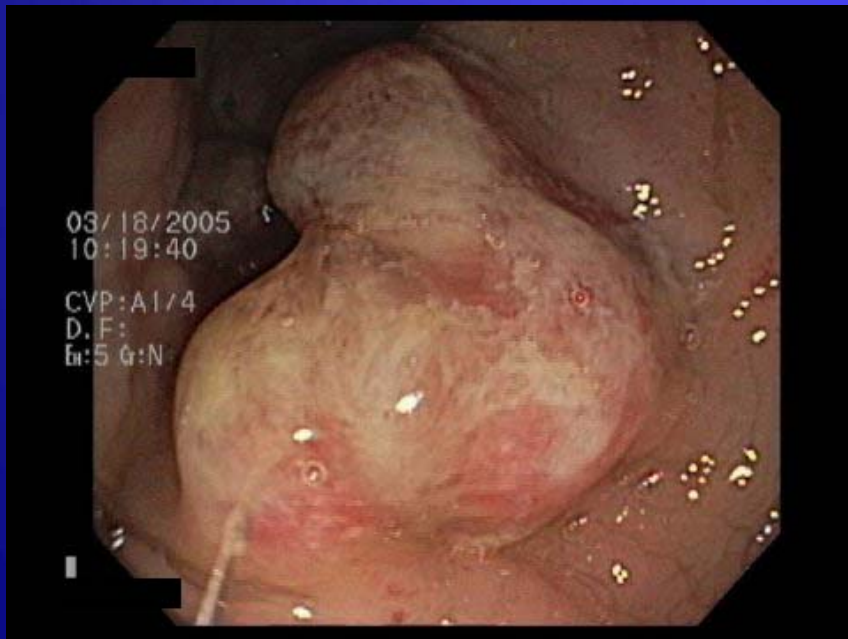
Cap Polyposis

- Clinical Features:
 - Mucoïd, and/or bloody stool associated with erythematous, inflammatory colonic polyps covered by a cap of fibrinopurulent mucous.
 - Most common in women, during the fifth decade. However, it has been described in men and women ranging from 12 to 76 years of age.
 - Weeks to months of mucoïd and bloody stool; 82% have rectal bleeding, 64% chronic straining and constipation, 46% mucus diarrhea.
 - May also have abdominal pain, tenesmus, weight loss, constipation, and hypoproteinemia due to protein loss.
- Pathogenesis: *unknown*;
 - form of IBD, vs
 - infectious origin such as *Helicobacter pylori* or *Escherichia coli* 018, vs
 - abnormal colonic motility resulting in mucosal prolapse at redundant transverse folds causing local ischemia, recurrent mucosal trauma, constipation, and the development of cap polyposis.

Cap Polyposis



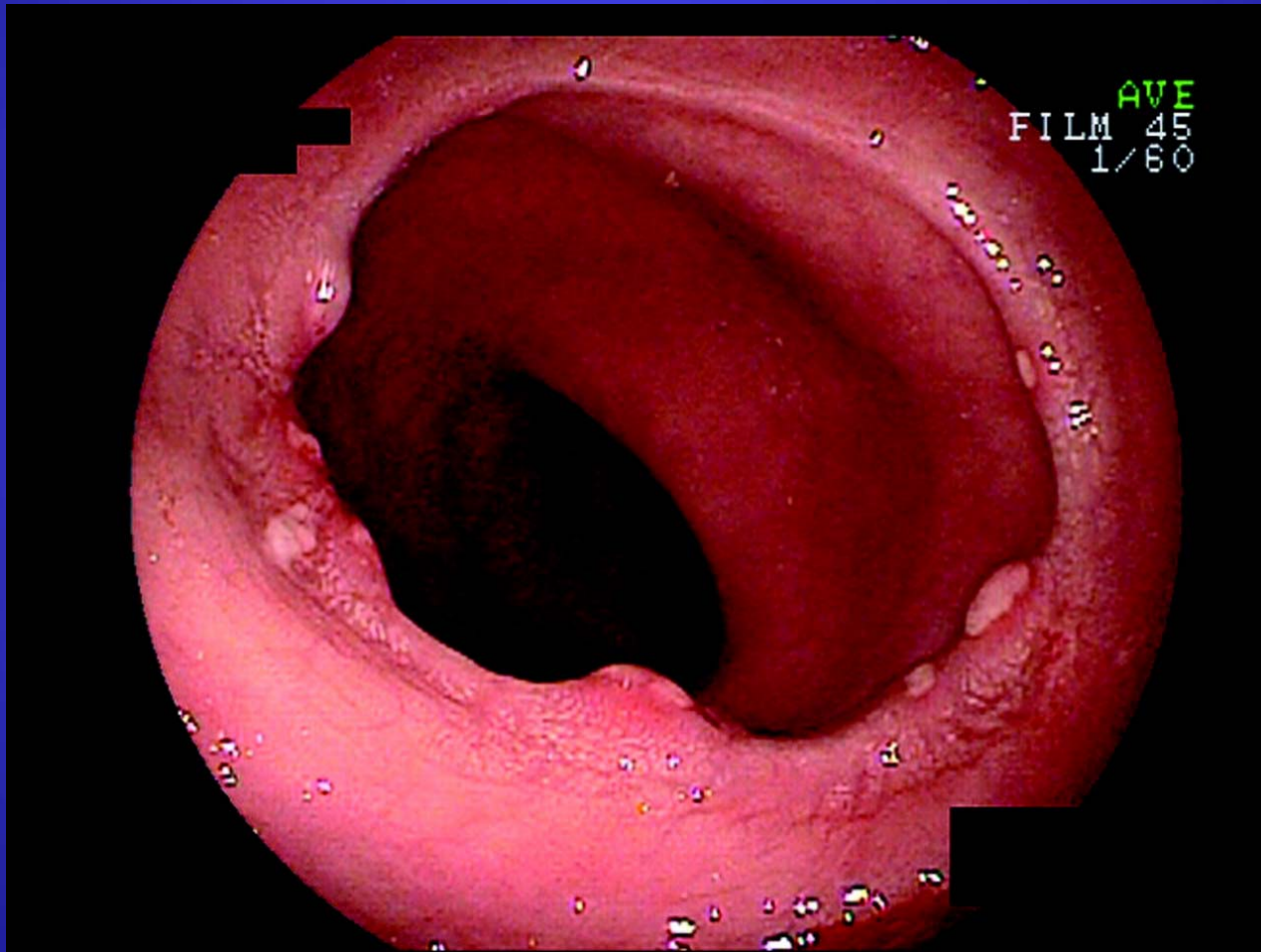
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Cap Polyposis

- Pathology:
 - Erythematous, pedunculated or sessile polyps, with adherent mucus or a white mucoid cap.
 - Typically in the rectosigmoid colon but may involve the entire colon.
 - They are located at the apices of enlarged transverse mucosal folds and can number from few to many. Often mistaken for inflammatory pseudopolyps.
 - The intervening mucosa is normal.
 - On microscopic exam:
 - elongated hyperplastic appearing glands with a mixed inflammatory infiltrate in the lamina propria and fibromuscular obliteration of the lamina propria.
 - The cap overlying the polyps is formed by mucus, fibrin, and leukocytes.
 - No evidence of malignant potential.

Cap Polyposis



Cap Polyposis

- Natural history:
 - usually with chronic and recurrent symptoms.
- Treatment: unsatisfactory. Several options:
 - Eradicate *H. pylori* + laxatives
 - Polypectomy + APC eradication + laxatives to prevent constipation & straining.
 - Metronidazole 250 TID for 2-4 weeks + laxatives.
 - Infliximab + laxatives.
 - Proctocolectomy.

Cronkhite-Canada

- Rare, nonfamilial disorder of unknown etiology associated with alopecia, cutaneous hyperpigmentation, gastrointestinal hamartomatous polyposis, onychodystrophy, diarrhea, weight loss, and abdominal pain.
- Clinical features:
 - Patients are middle-aged or older (average, 62 years) with acute rapidly progressive illness consisting of chronic diarrhea and protein-losing enteropathy with the associated integumentary abnormalities.
 - Gastrointestinal polyps are found in 52% to 96% of patients and range in location from the stomach to the rectum.

Cronkhite-Canada

- Integumentary Abnormalities:
 - Hyperpigmentation
 - Hyperpigmented light-to-dark brownish macules and plaques are diffusely distributed. Most commonly on hands and arms, they are also found on the legs, face, palms, soles, neck, trunk, and elsewhere.
 - They may coalesce and range from a few millimeters to 10 cm in diameter.
 - Patchy vitiligo is relatively common.
 - Alopecia
 - The alopecia is initially patchy; however, it rapidly progresses and leads to complete hair loss.
 - Hair loss typically involves the scalp, eyebrows, face, axillae, pubic areas, and extremities; however, loss of only scalp hair has also been described.
 - Regrowth is noted after treatment, during spontaneous remissions, and despite ongoing active disease.
 - Onychodystrophy (nail changes)
 - Nail changes involve thinning, splitting, and color changes in all fingernails and toenails.
 - Onycholysis (partial separation of the nail from its bed) leads to a unique pattern of an inverted triangle of normal nail bordered by a dystrophic nail.
 - Onychomadesis (the loss of all finger and toenails) occurs over several weeks.
 - Partial or total regeneration of nails occurs spontaneously in spite of active disease or remission.

Cronkhite-Canada

- Pathophysiology:
 - The diarrhea is primarily due to diffuse small intestinal mucosal injury, but bacterial overgrowth may be contributory.
- Pathology:
 - The polyps are hamartomas, but may have adenomatous foci.
 - Characteristic features include myxoid expansion of the lamina propria and increased eosinophils in the polyps.
 - Mucosa between polyps is histologically abnormal, with edema, congestion, and inflammation.
 - A recent report described the infiltration of immunoglobulin G4 (IgG4)–producing plasma cells in half of the Cronkhite-Canada syndrome polyps studied in 7 affected individuals. This histochemical finding is the criteria for IgG4–related autoimmune disease (IRAD)

Cronkhite-Canada

- Complications:
 - The risk of colon cancer is approximately 9%, and the risk of adenomas or adenomatous change is 40%.
 - Gastric cancer risk is also increased.
 - Five-year mortality rates as high as 55 percent have been reported with most deaths due to gastrointestinal bleeding, sepsis, and congestive heart failure.
- Treatment has included:
 - aggressive enteral (+/- parenteral) nutritional support,
 - replacement of vitamins and minerals (including Zn), and
 - antibiotics to control bacterial overgrowth.
 - no specific treatment has proven to be consistently effective
 - screening of the colon and stomach should be considered.

Whipple Disease

- Organism:
 - Tropheryma whipplei, a gram-positive bacillus related to Actinomycetes.
 - The organism is detectable in the saliva in up to 35 percent of healthy individuals and in the dental plaque and feces of healthy hosts.
 - PAS(+) bacillus found best by PCR in lymphatic tissue, vitreous fluid in Whipple's uveitis, peripheral blood, cardiac valves, cerebrospinal fluid (CSF), and synovial fluid and tissue.
- Incidence:
 - 30 cases per year;
 - has a predilection for white males of European ancestry, suggesting an underlying genetic predisposition that leads to colonization of T. whipplei throughout the intestinal tract, lymphoreticular system, and central nervous system upon exposure to soil microbes.

Whipple Disease

- Population:
 - 86% male (mean age at diagnosis of 49),
 - 97.5% of European ancestry, 1.5% of African descent, 0.5% Indian, 0.1% American Indian, and 0.1% Japanese.
 - Thirty-five percent are farmers, and 66 percent had occupational exposure to soil or animals
- Clinical Manifestations:
 - migratory arthralgias of the large joints, weight loss, diarrhea, and abdominal pain. CNS manifestations are common.
 - In late stage has severe wasting syndrome, with abdominal distention due to ascites or massive adenopathy, as well as dementia and other central nervous system findings (such as supranuclear ophthalmoplegia, nystagmus, and myoclonus).
 - CNS findings pathognomonic for Whipple's disease are oculomasticatory myorhythmia (continuous rhythmic movements of eye convergence with concurrent contractions of the masticatory muscles), and oculo-facial-skeletal myorhythmia.

Whipple Disease

- Other Clinical Manifestations:
 - Less common symptoms include fever, skin hyperpigmentation, and cardio-pulmonary disease.
 - Hyperpigmentation may be due to:
 - Vitamin D malabsorption, with compensatory secondary hyperparathyroidism leading to enhanced MSH and ACTH production.
 - *T. whipplei* may cause hypothalamic dysfunction and adrenal gland insufficiency.
 - Malabsorption of vitamin B12 may contribute to hyperpigmentation.
 - Cardiac disease is manifested by dyspnea, pericarditis, culture-negative endocarditis, or pleuropulmonary involvement with pleural effusion,
- Diagnosis:
 - Upper gastrointestinal endoscopy with SB bx is the test of choice
 - Bx shows extensive PAS-positive material in the lamina propria and villous atrophy.
 - PCR in intestinal tissue is not needed, and can give false (+) test due to comensal *T. whipplei* or a closely related bacteria.
 - Since neurologic manifestations of Whipple's disease have the most fatal consequences, CSF should be investigated by PCR.

Whipple Disease

- Differential Diagnosis:
 - HIV-associated mycobacterial infections have a similar biopsy appearance but Whipple's disease is extremely rare in HIV-infected patients and in HIV the offending mycobacterium can be readily identified in stool samples.
 - Confirmatory electron microscopy to demonstrate *T. whipplei* should be performed if the diagnosis is in doubt.
- Treatment:
 - Ceftriaxone (2 g IV once daily) or penicillin (2 MU IV every 4 hours) for two weeks, followed by TMP-SMX (one double-strength tablet twice a day) for one year.
 - Sulfa allergic: doxycycline (100 mg PO twice daily) in combination with hydroxychloroquine (200 mg PO thrice daily).
 - Ceftriaxone and penicillin allergic patients: TMP-SMX (one double-strength tablet three times daily) plus streptomycin (1 g IM daily) for two to four weeks, followed by TMP-SMX (one double-strength tablet twice a day) for one year.

Whipple Disease

- Treatment:
 - For endocarditis: penicillin G (2 MU IV q 4 hours) or ceftriaxone (2 g IV daily) for 4 wks, followed by TMP-SMX (one double-strength (D-S) tablet BID) for one year. Surgical resection of the infected valve is usually needed.
 - For CNS disease: ceftriaxone (2 g IV daily) or penicillin G (4 MU IV q 4 hours) for 4 wks, followed by TMP-SMX (one D-S tablet BID) for one year.
 - For patients who relapse: penicillin G (4 MU IV q 4 hours) or ceftriaxone (2 g IV daily) for 4 wks followed by oral doxycycline (100 mg BID) in combination with hydroxychloroquine (200 mg PO TID) OR TMP-SMX (one D-S tablet BID) for 1 y.
- Immune reconstitution:
 - In the first few weeks after initiation of treatment may develop relapse or disease progression manifested by high fever. Those at risk for immune reconstitution inflammatory syndrome (IRIS) are:
 - Patients treated with immunosuppressive therapy for presumed rheumatic disease for an extended period prior to the diagnosis of Whipple's disease, whose immunosuppressive therapy is discontinued at the start of antibiotic treatment.
 - Patients with CNS involvement of Whipple's disease
 - In these circumstances, corticosteroid therapy may be beneficial.

Congenital Intestinal Lymphangiectasia

- Described in children and young adults. Often associated with lymphatic abnormalities elsewhere in the body, as occur with Turner, Noonan, and Klippel-Trenaunay-Weber syndromes.
- Clinical Presentation:
 - chronic diarrhea (not always present), abdominal distension, hypoalbuminemia and lymphopenia due to protein-losing enteropathy caused by lymphatic block.
 - may develop ascites, failure to thrive, generalized edema, and limb edema which may be asymmetrical.
- Diagnosis:
 - confirmed by biopsy of the duodenum, jejunum or ileum (after fatty meal).
 - gross dilatation of the lymphatics of the lamina propria of the small bowel, with distortion and enlargement of villi without villous atrophy.
 - The involvement of the small intestine may be patchy.
 - Lymphangiography: with contrast, by MRI, or by technetium labeled albumin (nuclear medicine) may localize site of lymphangiectasia.

Congenital Intestinal Lymphangiectasia

- EGD after fatty meal the night before procedure:
 - may show bleb-like white pebbly nodules or cystic nodules which are cavities of dilated lymphatics filled with chylomicrons and precipitated lymph proteins.
- UGI+SBFT:
 - thickened mucosal folds, distal dilution of barium, dilatation of the lumen and smooth nodular protrusions into intestinal lumen.
- Immunological abnormalities:
 - Deficiency in cell-mediated immunity and hypogammaglobulinemia with low immunoglobulins IgG, IgA, and IgM and lymphopenia.
 - Others include skin anergy, impaired homograft rejection and poor *in vitro* lymphocyte proliferative responses.
 - Lymphopenia is due to the loss of recirculating, long-lived CD4+ T helper cells into the lumen of the intestine resulting in a marked reduction of the percentage and absolute numbers of CD4+ T helper but normal CD8+ T suppressor cells.
 - May have recurrent bacterial infections and infections with atypical mycobacteria, warts and cellulitis.

Congenital Intestinal Lymphangiectasia

- Treatment:
- Surgery:
 - if localized (rare), segment can be resected.
 - surgical anastomosis between dilated lymphatics and a vein has been reported
- Medical:
 - Treatment is life-long.
 - Fat intake should be restricted, and the diet supplemented with medium chain triglycerides and lipid soluble vitamins.
 - MCT (C6:0 to C12:0) is given to bypass the intestinal lymphatic system and thoracic duct allowing fat to enter the portal venous system directly.
 - Supplementation with MCT improves general well-being, with sustained improvement in edema, cessation of diarrhea and improvement in growth
 - Chylous ascites may be controlled with LeVeen shunt.
 - Orlistat, which inhibits gastric and pancreatic lipase, can be given to reduce absorption of fats naturally present in some foods.
 - Octreotide 200 mcg SQ TID may help. Sometimes temporary TPN is needed.

Tropical Sprue

- Chronic diarrheal disease, possibly of infectious origin, that involves the small intestine and is characterized by malabsorption of nutrients, especially folic acid and vitamin B12.
- Occurs in the tropics in a narrow band north and south of the equator to 30° latitude, but does not occur in all countries within this band. Occurs only in people who has been \geq 1 month in the area.
 - In America is particularly prevalent in Haiti, the Dominican Republic, Puerto Rico, and Cuba.
 - In Asia is common in India and to a lesser degree in Pakistan, Burma, Indonesia, Borneo, Malaysia, Singapore and Vietnam.
 - It is virtually absent in Africa.
- Pathology:
 - Involves the entire small bowel; More severe in proximal SB. In some patients, there is mild colonic involvement.
 - Histology: blunting of villi with infiltration of chronic inflammatory cells including lymphocytes, plasma cells, and eosinophils.

Tropical Sprue

- Pathogenesis:
 - Likely infectious
 - post-gastroenteritis,
 - family clusters,
 - overgrowth of toxin-producing and ethanol-producing klebsiella, E. coli, and enterobacter in proximal SB, and
 - response to antibiotics.
 - Villous blunting and enterocyte immaturity causes:
 - deficiency of lactase, sucrase, and maltase with carbohydrate malabsorption
 - decreased fat absorption with steatorrhea and fat soluble vitamin deficiency.
 - Folate & B12 deficiency.
 - Folate deficiency is due to proximal SB disease and ethanol production and is more common in Asia;
 - B12 deficiency is from distal SB involvement as is more common in America.
 - Hypoalbuminemia is due to protein-losing enteropathy.
 - Cyclospora can cause a syndrome identical to Tropical Sprue.

Tropical Sprue

- Clinical Manifestations:
 - chronic diarrhea often with cramps, gas, fatigue and, later, progressive weight loss.
 - Signs of malabsorption including glossitis and cheilitis, protuberant abdomen, pallor, and pedal edema.
 - Auscultation of the abdomen with hyperactive borborygmi is common.
 - Steatorrhea of 10 to 40 g of stool fat per day (N < 5 g/day). The D-xylose absorption test is often abnormal.
 - Megaloblastic anemia due to folate deficiency is maximal 3-4 months after disease onset. Hematocrit < 30 and an high MCV.
 - In vitamin B12 deficiency, pancytopenia may be present.
 - Other laboratory abnormalities, including hypoalbuminemia, are present in chronic, severe disease (due to malnutrition and/or protein-losing enteropathy), mild hypocalcemia, and vitamin D deficiency.
 - Tetany and carpopedal spasm are rare.

Tropical Sprue

- Radiology:
 - small intestine reveal nonspecific changes of dilatation, thickening and edema of mucosal folds, and retention or secretion of fluid in the lumen which dilutes the barium column.
 - These changes are also described in gluten-sensitive enteropathy, scleroderma, and hypoalbuminemia and anasarca of any etiology.
- Endoscopy with Jumbo Bx, and aspirate for quantitative culture + O&P:
 - Endoscopy may show scalloping of the folds.
 - Duodenal aspirate for O&P and quantitative culture may show bacterial overgrowth in 2/3rds with dominant klebsiella, E. coli, and enterobacter (in SBBO are dominant anaerobics).
- Treatment:
 - Folic acid 5 mg/day + Tetracycline 250 mg QID, both for 3-6 months.
 - If B12 deficiency is present, must give Vit B12 1000 mcg/week, to prevent neuropathy.

Allergic Enteropathy

- Clinical Features:
 - Protracted diarrhea (not infrequently steatorrhea), vomiting, malabsorption, and failure to thrive.
 - Additional features may include abdominal distention, early satiety, occult blood in stools, anemia, protein-losing enteropathy, hypoalbuminemia and edema.
 - Symptoms usually begin in the first few months of life, but can occur at any age through adolescence.
 - More common in infants taking formula than in breast-fed.
- The immune Injury:
 - mediated by a mixture of T cell responses and eosinophilic infiltration.

Allergic Enteropathy

- Causative agents:
 - most commonly caused by an immune response to cow's milk protein, but
 - soy, cereal grains, egg, and seafood have all been implicated.
- Diagnosis:
 - Endoscopy and biopsy of the small bowel.
 - Biopsy reveals patchy small bowel villous injury, increased crypt length, intraepithelial lymphocytes, and few eosinophils.

Allergic Enteropathy

- Management:
 - Eliminate the food allergen. This leads to the clearing of gastrointestinal symptoms within 3 to 21 days.
 - A graded home food challenge can be tried following discussion with the patient. If still sensitized, symptoms may recur within days or up to several weeks.
 - Most patients outgrow their hypersensitivity at between the ages of 1-3 years.
- Natural History:
 - Resolves in 1-3 years.
 - Unlike gluten sensitive enteropathy (Celiac disease), there is no increased threat of future malignancy

Questions?

Allergic Enteritis

- **Non-IgE Mediated Food Hypersensitivity:**
 - Allergic enteropathy
 - Food protein-induced enterocolitis syndrome
 - Allergic proctocolitis
 - Celiac disease

Food Protein-Induced Enterocolitis Syndrome

- Uncommon, pediatric non-IgE-mediated disorder triggered by ingestion of certain food proteins.
- Mediated by T-cell elaboration of TNF-alpha.
- Clinical Features:
 - Most children present during the first 6 weeks of life.
 - Two hours after ingesting the food protein, develop profuse vomiting and/or diarrhea. Other associated features include pallor, lethargy, cyanosis, metabolic acidosis and neutrophilia.
 - Most children show rapid recovery within a few hours but up to 20% of children require fluid resuscitation for hypovolemic shock.
 - There is no sex predilection and may be associated with atopic disease or IgE-mediated food allergy.

Food Protein-Induced Enterocolitis Syndrome

- Causative foods are:
 - Very young Infants: cow's milk and soy, and
 - After weaning to semisolids (anytime): rice, oats, sweet potato, banana, fish, chicken and lamb at anytime.
- Diagnosis: by Sicherer criteria:
 - 1) repeated exposure to the incriminated food elicited repetitive vomiting and/or diarrhea within 24 hours without any other cause for the symptoms.
 - 2) symptoms were limited to the gastrointestinal tract.
 - 3) removal of the offending protein from the diet resulted in resolution of symptoms and/or food challenge elicited vomiting and/or diarrhea within 24 hours after administration.
- Investigations: Skin prick test and serum food-IgE levels to R/O concomitant IgE-mediated food allergy.

Food Protein-Induced Enterocolitis Syndrome

- Treatment:
 - food allergen elimination.
 - In patients with reactions to cow's milk and/or soy milk formulas, which often coexist, an extensively hydrolysed milk formula is recommended.
 - In those who do not tolerate hydrolysates, an amino acid-based formula is recommended.
 - Tolerance of the allergen is usually attained by 3 years of age.
 - Food challenges should be conducted under medical practitioner supervision in a hospital setting with resuscitation medications available.

Allergic Proctocolitis

- Disorder of infancy characterized by:
 - the presence of mucous, bloody stools in an otherwise well-appearing infant,
 - caused by an immune response directed, most commonly, against cow's milk protein.
 - absence of markers of atopy such as atopic dermatitis or positive family history for atopy, which are not significantly increased compared with general population.
- Clinical Presentation:
 - Typically presents in the first few weeks to 6 months of life.
 - Parents typically note a gradual onset of bloody stools which increases in frequency unless the casual allergen is removed.
 - Occasionally there is associated colic or increased frequency of bowel movements, but failure to thrive is absent.
 - Examination of the abdomen is benign.

Allergic Proctocolitis

- Laboratory:
 - In a minority of infants include anemia.
 - Peripheral blood eosinophilia, and mild hypoalbuminemia rarely occur.
- Cause:
 - Usually occurs in breast-fed infants (up to 60%), where the immune response results from maternal ingestion of the food allergen, usually cow's milk, which is passed in immunologically recognizable form into the breast milk.
 - Cow's milk and soy milk are the causative foods in the majority of the remaining formula fed infants.
 - Allergic proctocolitis has rarely been described in infants fed protein hydrolysate formulas.

Allergic Proctocolitis

- Diagnosis:
 - usually made through clinical history and response to an elimination diet.
 - The bleeding is often mistakenly attributed to perianal fissures, but other differentials include infection, necrotizing enterocolitis, or intussusception.
 - If symptoms fail to respond to elimination of the suspected food allergen (cow's milk in most cases), then endoscopic examination with histological diagnosis is recommended.

Allergic Proctocolitis

- Treatment:
 - Elimination of the food allergen is indicated if significant blood loss is present.
 - Mild cases can resolve spontaneously.
 - Eliminate cow's milk from the mother's diet if the mother is breastfeeding.
 - For cow's milk formula or soy milk fed infants, an extensively hydrolysed milk formula is recommended, due to the high rates (up to 30%) of concomitant cow's milk protein and soy protein allergy. Only in rare instances is an amino-acid based formula required.
 - Clearance of symptoms typically occurs within 48-72 hours.
 - gradual food introduction can be attempted after the age of 1 year as tolerance of the allergen is usually attained by that age