

	Epidemiology	Pathogenesis	Pathology	Clinical	Treatment
Inflammatory Bowel Disease	<ul style="list-style-type: none"> <li>• 1-2 million Americans suffer from it</li> <li>• Jews &gt; non-Jews</li> <li>-Ashkenazi &gt; Sephardic</li> <li>• smoking</li> <li>-↑incidence w/ CD</li> <li>-↓incidence w/ UC</li> <li>• freq. of IBD in 1<sup>st</sup> degree relatives is ↑ by 30-100X</li> <li>• assoc. w/ certain HLA II genes</li> </ul>	<p>Epithelial Factors</p> <ul style="list-style-type: none"> <li>• intestinal epithelium</li> <li>- has selective transport processes for ion and food-derived molecules</li> <li>-acts as a barrier to non-specific entry of other substances</li> <li>• compromised epithelium</li> <li>-↑rate of protein entry</li> <li>-immune tolerance may be overcome</li> <li>-chronic inflammation may develop</li> </ul> <p>Immune System Factors</p> <ul style="list-style-type: none"> <li>• in normal intestine</li> <li>-inflammation always present</li> <li>-greater in colon than SI</li> <li>-lymphocytes, histiocytes, plasma cells always seen</li> <li>• epithelial cells are 1<sup>st</sup>-line Ag presenting cells</li> <li>-generate MHC I and II molecules</li> <li>• lamina propria APCs also pick up free Ags which pass epithelium</li> </ul>		<ul style="list-style-type: none"> <li>•</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>
Ulcerative Colitis	<ul style="list-style-type: none"> <li>• 4X more common than CD</li> <li>• chronic relapsing inflammatory disease</li> <li>• peak incidence 20-25y.o.</li> </ul> <p>3 forms</p>	<ul style="list-style-type: none"> <li>• aberrant Th2-type response</li> <li>-NO Δ IL-12 or IFN-γ</li> <li>- NO Δ IL-4, but ↑IL-5</li> </ul>	<ul style="list-style-type: none"> <li>• <b>diffuse</b> as opposed to segmental in CD</li> <li>• pathologic changes in <b>mucosal layer</b></li> <li>• mucosal surface is red, swollen, friable, granular</li> <li>• regenerating mucosa between ulcers becomes polypoid → <b>pseudopolyps</b></li> <li>• <b>gradual transition</b> from diseased to non-diseased</li> <li>• <b>no skip areas</b></li> <li>-proximal spread is always continuous w/ distal disease</li> <li>• after many episodes, muscular contraction &amp; thickening, NOT fibrosis → shortened colon</li> <li>• mucosa diffusely infiltrated w/</li> <li>-plasma cells lymphocytes &amp; eosinophils</li> <li>-variable # of PMNs</li> <li>• <b>crypt abscesses</b>: UC &gt; CD</li> <li>-rupture and coalescence of crypt abscesses → ulcers</li> <li>-repeated episodes → atrophy or regeneration → irregularly shaped and distributed crypts</li> <li>-<b>more marked than CD</b></li> <li>• muscularis is hypertrophic and submucosa is obliterated by fibromuscular tissue, however</li> <li>-<b>no transmural inflammation</b></li> <li>-<b>no granulomas</b></li> </ul>	<ul style="list-style-type: none"> <li>• toxic megacolon</li> <li>-ulcerated bowel w/systemic toxicity</li> <li>-occurs in 2-4% of UC</li> <li>-usually in early stages</li> <li>• colon carcinoma</li> <li>-duration and extent determine risk</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>
	<ul style="list-style-type: none"> <li>• <b>ulcerative proctitis &amp; proctosigmoiditis</b></li> <li>-80%</li> </ul>		-distal large bowel	<ul style="list-style-type: none"> <li>-pain and bleeding</li> <li>-no diarrhea</li> <li>-NO additional cancer risk</li> </ul>	
	<ul style="list-style-type: none"> <li>• <b>left-sided colitis</b></li> </ul>		-mid transverse colon or less	<ul style="list-style-type: none"> <li>• colon carcinoma risk</li> <li>-minimal risk in disease of &lt; 10yr duration</li> <li>-2% after 20 yrs.</li> </ul>	
	<ul style="list-style-type: none"> <li>• <b>pancolitis</b></li> <li>-10%</li> </ul>		<ul style="list-style-type: none"> <li>-entire colon</li> <li>-extensive colitis up to hepatic flexure</li> <li>-rectum involved in almost all cases</li> <li>-terminal ileus may be involved in <b>backwash ileitis</b></li> </ul>	<ul style="list-style-type: none"> <li>-bloody diarrhea</li> <li>-pain</li> <li>• colon cancer risk</li> <li>-10% at 20yrs, 15-20% at 30yrs</li> </ul>	<ul style="list-style-type: none"> <li>• rectal sparing induced by local therapy</li> </ul>

Crohn's Disease	<ul style="list-style-type: none"> <li>• affects both sexes equally</li> <li>• occurs at any age</li> <li>-preferentially at 20-30y.o.</li> </ul>	<ul style="list-style-type: none"> <li>• Th1-type response</li> <li>-↑IL-12 and ↑IFN-γ</li> <li>-↓IL-4 and ↓IL-5</li> </ul>	<ul style="list-style-type: none"> <li>• preferentially affects <b>terminal ileum</b></li> <li>• <b>granulomatous inflammation</b></li> <li>• most commonly ileitis (40%), ileocolitis (30%) or colitis (30%)</li> <li>-rectum spared</li> <li>• diseased areas sharply demarcated (<b>skip areas</b>)</li> <li>• long, serpiginous ulcers, separated by <b>cobblestone mucosa</b></li> <li>-ulcers may extend deep → fistulae</li> <li>-ulcers are <b>knife-like</b>, extending linearly → <b>fissures</b></li> <li>• <b>transmural</b> inflammation → thickened stiff bowel wall → <b>strictures</b> → obstruction</li> <li>-also transmural inflammation → extends into mesenteric fat → <b>creeping</b></li> <li>• necrosis of individual epithelial cells → small <b>aphthoid ulcers</b></li> <li>-typical for CD</li> <li>• surrounding mucosa → chronic inflammation w/<b>microgranulomas</b></li> <li>-granulomas are <b>never necrotizing</b></li> <li>-distinguishes from TB</li> <li>• ↑PMNs infiltrate crypts → <b>cryptitis</b></li> <li>-PMNs in a crypt lumen → <b>crypt abscess</b></li> <li>-typical lesion of CD</li> <li>• repeated crypt damage</li> <li>→ irregular shape and distribution of crypts</li> <li>→ appearance of cells not normally present (<b>paneth cell</b> and <b>pyloric metaplasia</b>)</li> </ul>	<ul style="list-style-type: none"> <li>• a dynamic disease</li> <li>-some areas heal, and others progress</li> <li>• spontaneous remissions in 1/3 of pts</li> <li>• <b>recurrence is the rule</b></li> <li>• complications include:</li> <li>-fistulae</li> <li>-bleeding</li> <li>-toxic dilatation and perforation</li> <li>-risk of carcinoma is ↑ 4-20X</li> <li>-25% in small intestine</li> <li>-70% colonic</li> </ul>	<ul style="list-style-type: none"> <li>• cytokine response has Tx implications</li> <li>-anti-TNFα Ab (Infliximab) used for refractory CD</li> </ul>
Infectious Enterocolitis		•	•	•	
Viral	<ul style="list-style-type: none"> <li>• Rotavirus</li> <li>-mainly children</li> <li>• Norwalk virus</li> <li>-foodborn infections</li> <li>• CMV</li> <li>• -in immunocompromised, esp. HIV</li> </ul>	•	•	•	
Bacterial	<ul style="list-style-type: none"> <li>• damage via invasion and toxin production</li> <li>-E.coli</li> <li>• damage via epithelial invasion</li> <li>-Salmonella: systemic infection → chronic infection of biliary tree, joints, bones, and meninges</li> <li>-Shigella</li> <li>-Campylobacter</li> <li>-Yersinia</li> <li>• damage via toxin production</li> <li>-C.difficile: pseudomembranous colitis</li> </ul>	•	•		
Amebiasis	<ul style="list-style-type: none"> <li>• affects approx. 500 million</li> <li>• attach to epithelium → lyse cells → invade bowel wall</li> <li>-preferentially in cecum and ascending colon</li> <li>-<b>flask-shaped ulcers</b></li> <li>-liquefactive necrosis</li> </ul>	•	•	•	
Lymphocytic	<ul style="list-style-type: none"> <li>• watery diarrhea</li> <li>• can lead to collagenous colitis</li> </ul>	•	•	•	

Malabsorption	•	•	•
Intraluminal (Digestion)	•	•	•
Carbohydrate	<ul style="list-style-type: none"> <li>• starch digestion</li> <li>-salivary amylase</li> <li>-pancreatic amylase</li> <li>-<b>more important</b> of the two</li> <li>→ water-soluble oligosaccharides</li> <li>-secreted in great excess</li> </ul>	<ul style="list-style-type: none"> <li>• pancreatic insufficiency</li> <li>-even when severe, carbohydrate malabsorption NOT seen</li> </ul>	•
Protein	<ul style="list-style-type: none"> <li>• protein</li> <li>-begins in stomach via pepsin</li> <li>-activated by acid pH</li> <li>-accounts for small % of protein digestion</li> <li>-most digested in small intestine</li> <li>-pancreatic endo- and exopeptidases</li> <li>-hydrolases at brush border</li> <li>-amino acid transporters at brush border</li> </ul>	<ul style="list-style-type: none"> <li>• achlorhydria or total gastrectomy</li> <li>-do NOT have protein malabsorption</li> <li>• pancreatic insufficiency</li> <li>-does NOT cause clinically significant protein malabsorption</li> </ul>	•
Fat (Triglyceride)	<ul style="list-style-type: none"> <li>• absorbed w/95% efficiency</li> <li><u>Intragastric emulsification and lipolysis</u></li> <li>• motility-induced mixing → crude fat emulsion covered w/phospholipids → ↑surface area for lipolysis</li> <li>• lipolysis</li> <li>-begins in stomach</li> <li>-gastric lipase → diglycerides and fatty acids</li> <li>-released from fundic chief cells</li> <li>-active at acidic pH</li> <li>-requires no cofactors</li> <li>-inactivated by bile salts</li> <li>-gastric lipolysis products stabilize emulsion for digestion by pancreatic enzymes in the SI</li> <li><u>Small intestinal lipolysis</u></li> <li>• most (&gt;70%) fat digestion occurs in SI</li> <li>• pancreatic lipase</li> <li>-requires <ul style="list-style-type: none"> <li>-colipase</li> <li>-bile salts</li> <li>-proper pH for full activity</li> </ul> </li> <li>• colipase</li> <li>-secreted in 1:1 ratio w/lipase</li> <li>-secreted as propeptide requiring tryptic removal of N-terminal</li> <li>-anchors lipase to TGs → facilitating interaction</li> <li>• bile salts</li> <li>-stabilizes emulsion</li> <li>-removes lipolysis end-products</li> <li>• pancreatic HCO<sub>3</sub></li> <li>-alkinizes gastric chyme to pH 6-7.5</li> <li>• synchronous mixing</li> <li><u>Micellar solubilization of fat</u></li> <li>• absorption requires products are dispersed, solubilized and conveyed to brush border membrane</li> </ul>	<ul style="list-style-type: none"> <li>• congenital pancreatic lipase deficiency &amp; CF</li> <li>-gastric phase accounts for &gt; 50% of dietary fat absorption</li> <li>• chronic pancreatitis</li> <li>→ ↓↓↓ pancreatic lipase</li> <li>• Zollinger-Ellison syndrome</li> <li>→ acidification of intestinal contents → denaturation of pancreatic lipase → fat malabsorption</li> <li>→ acidification → bile salt precipitation → bile salt deficiency</li> <li>• ↓bile salt delivery</li> <li>-due to severe liver disease, common bile duct obstruction, impaired transport from liver cells</li> <li>• cholestyramine ingestion</li> <li>-binds bile salts in intestinal lumen</li> <li>• SI bacterial overgrowth (blind loop syndrome)</li> <li>-local stasis/recirculation → ↑colonic flora → bile salt deconjugation</li> <li>-bacteria use B<sub>12</sub> and produce folic acid → B<sub>12</sub> deficiency and normal or ↑folate levels</li> <li>• ileal disease or resection</li> <li>→ bile salt malabsorption</li> <li>-liver can compensate for up to 3g loss</li> <li>-directly related to length of bowel affected</li> <li>- &gt;100cm of affected bowel → fat malabsorption</li> <li>• impaired micelle formation</li> <li>-cholesterol and fat-soluble vitamins (A, D, K, E) require micelle formation</li> <li><u>stool</u></li> <li>• <b>pancreatic</b> insufficiency → unabsorbed <b>triglycerides</b> → <b>bulky, fat-laden stool</b></li> <li>• impaired <b>micelles</b> → unabsorbed <b>fatty acids</b> → <b>watery diarrhea</b></li> </ul>	•

Mucosal		•	•	•
Selective Carbohydrate Malabsorption	<u>Normal</u>	<ul style="list-style-type: none"> <li>• only sugar monomers can be taken up into villus</li> <li>• monomers transported into cells via specific proteins</li> <li>-glucose &amp; galactose via SGLT</li> <li>-fructose by GLUT</li> </ul>	<ul style="list-style-type: none"> <li>• in these disorders</li> <li>-villous architecture is normal</li> <li>-protein and fat absorption are normal</li> <li>• malabsorbed sugar is osmotically active → drawing water and electrolytes into gut lumen</li> <li>→ watery diarrhea if fluid is &gt; than colon's reabsorptive capacity</li> <li>• bacteria metabolize unabsorbed sugars →</li> <li>-short chain FAs → absorption w/some fluid</li> <li>-CO<sub>2</sub> and H<sub>2</sub> → gas, bloating and cramps</li> </ul>	•
	<u>Acquired lactase deficiency</u>	<ul style="list-style-type: none"> <li>• most common cause</li> <li>• most lose lactase activity by 5y.o.</li> <li>• prevalence highest in Asians, AAs, and Native Americans</li> </ul>	<ul style="list-style-type: none"> <li>• most cases due to ↓enzyme synthesis</li> <li>• some have defective intracellular transport</li> </ul>	
	<u>Congenital deficiencies</u>	<ul style="list-style-type: none"> <li>• includes: lactase, sucrase-isomaltase, glucose-galactose malabsorption</li> <li>• rare</li> </ul>	<ul style="list-style-type: none"> <li>• watery diarrhea at birth</li> <li>-low pH</li> <li>-reducing sugars</li> </ul>	
Selective Protein Malabsorption	<ul style="list-style-type: none"> <li>• NO deficiencies of individual pancreatic protease found</li> <li>• congenital enterpeptidase deficiency</li> <li>-rare</li> <li>• defects of amino acid uptake</li> <li>-cystinuria</li> <li>-Hartnup disease</li> <li>-do NOT cause protein malabsorption in the intestine</li> </ul>	<ul style="list-style-type: none"> <li>• enterokinase deficiency → ↓activation of trypsinogen to trypsin</li> <li>-diarrhea</li> <li>-growth retardation</li> <li>-hypoproteinemic edema</li> </ul>	•	•
Mucosal Defect in Lipid Absorption	<ul style="list-style-type: none"> <li>• Abetalipoproteinemia</li> </ul>	•	<ul style="list-style-type: none"> <li>• low fat diet w/ medium chain triglycerides</li> </ul>	•

Intestinal Mucosal Diseases	•	•	•	•	•
Celiac	<ul style="list-style-type: none"> <li>• ↑prevalence in N. Ireland, Europe and US</li> <li>• type 1 diabetics and autoimmune thyroid disease have ↑risk</li> </ul>	<ul style="list-style-type: none"> <li>• environmental factors <ul style="list-style-type: none"> <li>-gliadins are most toxic <ul style="list-style-type: none"> <li>-rich in glutamine and proline</li> </ul> </li> </ul> </li> <li>• genetic factors <ul style="list-style-type: none"> <li>-70% of monozygotic twins will both have the disorder</li> <li>-assoc. certain HLA class II (HLA-D) <ul style="list-style-type: none"> <li>- &gt;95% inherit alleles in DQ subregion</li> </ul> </li> <li>• DQ binds peptide → presentation to CD4 → inflammatory reaction</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• significant # of T-cells in the gut</li> <li>• <b>Abs to gliadin</b> <ul style="list-style-type: none"> <li>-unknown whether they play a role</li> <li>-provide a useful screening test</li> </ul> </li> <li>• <b>anti-EMA</b> (smooth muscle component) Abs <ul style="list-style-type: none"> <li>-most sensitive and specific</li> <li>-recognizes <b>tissue transglutaminase</b></li> <li>• <b>distal duodenum</b> (proximal SI) <ul style="list-style-type: none"> <li>-absence of villi</li> <li>-lengthened crypts w/↑mitotic activity</li> </ul> </li> <li>• surface epithelium <ul style="list-style-type: none"> <li>-↑<b>intraepithelial T-lymphocytes</b></li> <li>-cuboidal (rather than columnar) shape</li> </ul> </li> <li>• microvilli <ul style="list-style-type: none"> <li>-sparse and damaged</li> </ul> </li> <li>• ↓enzyme activity assoc. w/nutrient absorption <ul style="list-style-type: none"> <li>→ 2° milk intolerance</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• most often present in early childhood</li> <li>• in <b>severe</b> disease <ul style="list-style-type: none"> <li>-<b>diarrhea</b></li> <li>-weight loss</li> <li>-nutrient deficiency</li> </ul> </li> <li>• in <b>mild</b> disease affecting only proximal SI <ul style="list-style-type: none"> <li>-selective vitamin or mineral deficiencies</li> <li>-<b>NO diarrhea</b></li> <li>• malabsorption <ul style="list-style-type: none"> <li>-<b>primarily due to 2° loss of absorptive surface area</b></li> <li>-however, <b>usually NOT present</b> b/c only limited length involved</li> </ul> </li> <li>• protein loss → hypoalbuminemic <b>edema</b></li> <li>• assoc. w/ <b>dermatitis herpetiformis</b></li> <li>-presence of <b>asymptomatic flat mucosa</b></li> <li>-pruritic skin disorder</li> <li>-papules infiltrated w/eosinophils</li> <li>-<b>IgA</b> deposition</li> <li>• long term complication <ul style="list-style-type: none"> <li>-intestinal <b>lymphoma</b> <ul style="list-style-type: none"> <li>-<b>T-cell type</b>, in contrast majority (95%) of GI lymphomas <ul style="list-style-type: none"> <li>-aggressive w/ poor prognosis</li> <li>-GI and extraintestinal carcinoma</li> </ul> </li> </ul> </li> </ul> </li> </ul> </li></ul>	<ul style="list-style-type: none"> <li>• gluten free diet</li> </ul>
Tropical Sprue	<ul style="list-style-type: none"> <li>• residents of the tropics</li> <li>-native born and visitors</li> </ul>	<ul style="list-style-type: none"> <li>• disease may be an <b>infection</b> <ul style="list-style-type: none"> <li>-no causal agent found</li> </ul> </li> <li>• jejunal bacterial overgrowth found in most pts.</li> <li>-some bacteria produce enterotoxins</li> <li>• 2° effects of folate and B<sub>12</sub> deficit</li> </ul>	<ul style="list-style-type: none"> <li>• mucosa less severely affected than in celiac disease</li> <li>• changes in <b>both distal &amp; proximal SI</b></li> <li>• <b>B<sub>12</sub></b> often malabsorbed</li> <li>-normally absorbed in <b>ileum</b></li> </ul>	<ul style="list-style-type: none"> <li>• classic presentation is megaloblastic anemia assoc. w/diarrhea</li> </ul>	<ul style="list-style-type: none"> <li>• anti-biotics</li> <li>• folate and B<sub>12</sub></li> <li>-corrects anemia and often other symptoms as well</li> </ul>
Whipple's Disease	<ul style="list-style-type: none"> <li>• rare cause of malabsorption</li> </ul>	<ul style="list-style-type: none"> <li>• linked to infection w/gram pos. actinomycete</li> <li>-Tropheryma whippleii</li> <li>-not been cultured</li> </ul>	<ul style="list-style-type: none"> <li>• may involve any organ, but 1° affects <ul style="list-style-type: none"> <li>-intestines</li> <li>-CNS</li> <li>-joints</li> </ul> </li> <li>• SI mucosa <ul style="list-style-type: none"> <li>-infiltrated w/ distended MΦs</li> <li>-finely granular cytoplasm</li> <li>-stains w/ PAS</li> </ul> </li> <li>• MΦs expand lamina propria → villous blunting → flattening of the surface</li> <li>-<b>important to distinguish from MΦs in MAI infections</b></li> </ul>		<ul style="list-style-type: none"> <li>• responds to antibiotics</li> <li>-MAI does NOT</li> </ul>
Lymph-angiectasia	<ul style="list-style-type: none"> <li>• 1° congenital</li> <li>• 2°</li> </ul>	<ul style="list-style-type: none"> <li>• defective formation of lymphatics</li> <li>• heart disease complication</li> <li>• any lesion interfering w/lymph circ.</li> </ul>	<ul style="list-style-type: none"> <li>• dilated lymph vessels</li> <li>• lamina propria packed w/chylomicrons</li> <li>• lympho-enteric fistulas form</li> </ul>	<ul style="list-style-type: none"> <li>• hypoproteinemic edema</li> </ul>	<ul style="list-style-type: none"> <li>•</li> </ul>

