

INFLAMMATORY BOWEL DISEASE

- Crohn's disease
- Ulcerative colitis
- Indeterminate colitis (15%)

CROHN'S DISEASE

(regional ileitis, regional enteritis, granulomatous ileocolitis)

- Involvement: alimentary tract anywhere from the mouth to the anus
- 30-40% small bowel disease alone
- 40-55% disease involving both the small and large intestines
- 15-25% colitis alone
- in 75% of patients with small intestinal disease, the terminal ileum is involved in 90%

Incidence: young adults, intermittent clinical course with mild to severe disability and frequent complications

ULCERATIVE COLITIS (UC)

- 40-50% limited to the rectum and rectosigmoid
- 30-40% extending beyond the sigmoid but not involving the whole colon
- 20% total colitis (10% backwash ileitis)

Incidence: primarily in adolescents and young adults, but onset may be in age group.

Epidemiology

Incidence (per 100,000):

- Crohn's disease: Europe: 0.3 – 12.7 North America: 0 – 20.2 (highest value in Canada) Middle East, Asia: 0.05 – 5
- Ulcerative colitis: Europe: 0.6 – 24.3 North America: 0 – 19.2 (highest value in Canada) Middle East, Asia: 0.1 – 6.3

Prevalence (per 100,000):

- Crohn's disease: Europe: 0.6 – 322 North America: 16.7 – 318.5 Middle East, Asia: 0.88 – 67.9
- Ulcerative colitis: Europe: 4.9 - 505 North America: 37.5 – 248.6 Middle East, Asia: 4.9 – 168.3

	Crohn's disease	Ulcerative colitis
Age of onset	2nd to 4th decades and 7th to 9th decades	2nd to 4th decades and 7th to 9th decades
Ethnicity	Jewish > non-Jewish white > African American > Hispanic > Asian	
Male / female ratio	0.34 – 1.65	0.51 – 1.58
Smoking	May cause disease OR: 1.76	May prevent disease (OR: 0.58)
Oral contraceptives	OR: 1.4	No increased risk
Appendectomy	Not protective	Protective (risk reduction of 13 - 26%)
Monozygotic twins	38% - 58% concordance	6% - 18% concordance
Dizygotic twins	4% concordance	0 - 2% concordance
Antibiotic use in the 1st year of life	2,9x the risk of developing childhood IBD	

A model for the syndromic nature of IBD

- Monogenic - Familial 10% - Early onset - Genetics
- Polygenic - Sporadic - Undiagnosed infections? - Environment

Etiology and pathogenesis of IBD

Interplay between

- Genetic susceptibility GWAS: 163 genes! (XBP1, NOD2, TLR4, DLG5, ECM1, ILN1, SLC22A5, DMBT1, PTGER4, CARD9, IL23R, IL12B, JAK3, STAT3, CCR6, CARD9, IRF5, ATG16L1, IRGM, LRRK2, TNFSF15, TNFRSF6B, TNFAIP3, PTPN22, NLRP3, IL18RAP, ICOSL, ARPC2, IL10)
- Immune dysregulation
- Microbial flora
- Environmental factors (enteropathogens, diet, hygiene, antibiotics, stress, NSAIDs, smoking)

Crohn's disease

Macroscopic pathology

- Thickening of the wall, with stenosis, linear serpiginous ulcers, cobblestoning of the mucosa
- Perirectal fistulas, fissures, abscesses, anal stenosis (in 1/3 of patients)

Microscopic pathology

- Earliest: aphthoid ulcerations
- Later: focal crypt abscesses, noncaseating granulomas, mixed acute and chronic inflammation, crypt atrophy, and multiple small epithelioid granulomas in the mucosa
- Marked thickening of the submucosa with lymphedema, lymphoid hyperplasia, nonspecific granulomas
- Often ulceration of the overlying mucosa
- Marked lymphadenitis in the mesenteric nodes
- Transmural inflammatory involvement

Various clinical patterns

- Fibrostenotic obstructive pattern
- Penetrating fistulous pattern
- Indolent and symptomatology mild
- Toxic: fever, toxic erythema, arthralgia, anemia.
- Complicated: stricture or perforations of the bowel, suppurative complications of intra-abdominal perforation.
- Exacerbations and remissions
- Colicky, steady abdominal pain: right lower quadrant or periumbilical area; at some time during the course of the disease; mild to severe.
- Diarrhea: usually with intervening periods of normal bowel function or constipation.
- Milk products, chemically or mechanically irritating food aggravate symptoms.
- Abdominal tenderness: especially in the right lower quadrant, with signs of peritoneal irritation;
- Abdominal and pelvic mass in the same area. Mass: sausage like thickened intestine to matted loops of intestine.
- Fever: low-grade or rarely, spiking with chills.
- Anorexia, flatulence, malaise, weight loss
- Loss of adsorptive surface: malabsorption syndrome:
- Anemia (Fe↓, vit. B12↓), albumin↓, Mg↓, Ca↓ vit K↓, hyperoxaluria

Imaging

- Small bowel x-ray: mucosal irregularity, ulceration, stiffening of the bowel wall, luminal narrowing.
- Barium enema: fissuras, ulcers. Eccentric involvement, skipped areas of involvement, strictures → Crohn's disease of the colon is suggested.
- CT: Marked thickening of the colonic wall (CT is good at detecting fistulas), dilation of small-bowel loops, segmental mucosal hyperenhancement, mesenteric fat stranding.

Endoscopic examination

- Down to the deep duodenum, edematous hyperemic mucosa; when colon is involved - discrete ulcers.
- Wireless capsule endoscopy

Complications

- Ischiorectal, perianal fistulas: frequent. Fistulas to the bladder, vagina, even to the skin in the area of a previous scar.
- Mechanical intestinal obstruction.
- Malabsorption, maldigestion (decreased bile salt pool) → sprue-like syndrome.
- Generalized peritonitis: rare. Perforation occurs slowly, is locally contained, or results in internal fistula formation.
- Migratory peripheral synovitis, axial arthropathy: indistinguishable from ankylosing spondylitis.
- The incidence of colorectal or small bowel cancer: normal population < Crohn's disease < ulcerative colitis

Ulcerative colitis

Macroscopic pathology

- Acute nonspecific inflammation of the colonic mucosa, particularly the rectosigmoid area, multiple ulcerations.
- Repeated episodes → thickening of the wall tissue with scar formation
- Proliferative changes in epithelium → polypoid structure; pseudopolyps → severe ulceration
- Diffuse (nonsegmental) mucosal disease, with broad areas of ulceration.
- The bowel wall is not thickened, and there is no cobblestoning

Microscopic pathology

Diffuse chronic inflammation of the lamina propria with crypt distortion, crypt abscess, basal lymphoplasmacytosis, crypt atrophy, irregularity, and dysplasia, superficial erosion

Clinical symptoms

- Variations: from mild cases with relatively minimal symptoms to acute and fulminating cases with severe diarrhea and prostration.
- Remissions - exacerbations.
- Diarrhea: characteristic. Up to 10-25 discharges daily, with blood and mucus in the stools. Blood or mucus may occur without feces. Nocturnal diarrhea is usually present when daytime diarrhea is prominent.
- Blood in the stool is the cardinal manifestation.
- The small intestine is very rarely involved.
- Rectal tenesmus, anal incontinence.
- Cramping lower abdominal pain: mild
- Anorexia, malaise, weakness, fatigability.
- Fever, weight loss, evidence of toxemia: vary with the severity of the disease.
- Abdominal tenderness: mild; without signs of peritoneal irritations.
- Abdominal distension: in the fulminating form; poor prognosis.
- Rectal examination: perianal irritation, fissure, hemorrhoids. Uncommonly, fistulas, abscesses.

Imaging

- Barium enema in a patient with acute ulcerative colitis: inflammation of the entire colon

Endoscopy

- Sigmoidoscopy: Discloses rectal involvement in over 95 % of cases. In mild cases: mucosal hyperemia, petechiae, minimal granularity. In severe cases: polypoid changes. The mucosa may appear grossly normal, it is friable when wiped with a cotton sponge.

- Colonoscopic examination: Not in actively symptomatic patients! Useful in defining the extent ulcerative colitis. Highly recommended: annually after the 10th year of disease colonoscopy with multiple biopsies - looking for dysplasia and cancer. Colonoscopy with acute ulcerative colitis: Severe colon inflammation with erythema, friability, and exudates

Complications

- Colonic perforation
- Massive hemorrhage
- Toxic dilatation of colon
- Carcinoma. The incidence of carcinoma is significantly greater in patients with ulcerative colitis. Involvement: the entire colon - greater risk than minimal disease. Disease confined to the rectum is unassociated with higher risk of cancer. Duration: The risk rises from approximately 0.2% at 1 year to 2.8% at 15 years , 4.5% at 20 years and 13.5% at 30 years.

Extra-intestinal manifestations (both in Crohn’s disease and ulcerative colitis)

- Dermatologic: erythema nodosum (10-15%), pyoderma gangrenosum (UC: 1-2%, CD: less frequent)
- Rheumatologic: polyarthritis, ankylosing spondylitis, sacroileitis
- Oral ulcers
- Urologic: nephrolithiasis (oxalate stones)
- Ocular (1-10%): episcleritis, iritis, uveitis
- Liver disease: sclerosing cholangitis (pANCA pos.), pericholangitis (small duct PSC)
- Cardiovascular: pleuropericarditis, endocarditis, thrombophlebitis
- Metabolic bone disorders: osteoporosis (OR: 1,59 - 1,72), osteonecrosis
- Amyloidosis
- Impaired growth in children

Laboratory findings (both in Crohn’s disease and ulcerative colitis)

- ESR ↑, leukocytosis with shift to the left, CRP ↑
- Occult blood in the stool.
- Hypochromic anemia: macrocytic due to vitamin B12 malabsorption.
- Hypoproteinemia (in UC)
- Fecal lactoferrin and calprotectin - specific for IBD
- Specific autoantibodies – limited specificity
 - Anti-saccharomyces cerevisiae (ASCA): CD: 60-70% pos., UC: 10-15% pos.
 - p(perinuclear) or x(atypical) ANCA: UC: 60-70% pos., CD: 5-10% pos.
 - E. coli outer membrane porin protein C (OmpC): 55% pos. in CD
 - Anti-I2: CD: 50-54% pos.
 - Anti-flagellin (anti-CBir1): CD: 50% pos.

Different features of Crohn’s disease and ulcerative colitis

	Crohn’s Disease	Ulcerative Colitis
Gross blood in stool	Occasionally	Yes
Mucus	Occasionally	Yes
Systemic symptoms	Frequently	Occasionally
Pain	Frequently	Occasionally
Abdominal mass	Yes	Rarely
Significant perineal disease	Frequently	No
Fistulas	Yes	No
Perforation	Frequently	Rarely
Small intestinal obstruction	Frequently	No
Colonic obstruction	Frequently	Rarely

Response to antibiotics	Yes	No
Recurrence after surgery	Yes	No
Endoscopic		
Rectal sparing	Frequently	Rarely
Continuous disease	Occasionally	Yes
„Cobblestoning“	Yes	No
Granuloma on biopsy	Occasionally	No
Radiographic		
Small bowel sign. abnormal	Yes	No
Mucosa	Fissures to deep ulcers	Serrated
Abnormal terminal ileum	Yes	No
Segmental colitis	Yes	No
Asymmetric colitis	Yes	No
Stricture	Frequently	Occasionally
Pathology		
	Transmural involvement, granulomas	Mucosal microabscesses

Differential diagnosis of IBD

Infectious

- Bacterial: Salmonella, Shigella, Toxygenic, E. coli, Yersinia, Campylobacter, Cl. difficile, Gonorrhoea, Cl. trachomatis, M. tbc, M. avium-intracellulare
- Parasitic: Amebiasis, Isospora, Trichuriasis, Hookworm, Strongyloides
- Viral: CMV, HSV, HIV
- Fungal: Histoplasmosis, Candida, Aspergillus

Non-infectious

- Inflammatory: appendicitis, diverticulitis, collagenous/ lymphocytic colitis, ischemic colitis, eosinophilic gastroenteritis, neutropenic colitis, Behçet's syndr., GVHD
- Neoplastic: cc, lymphoma, metastatic, carcinoid, familial polyposis
- Drugs and chemicals: NSAIDs, phosphosoda, cathartics, oral contraceptives, cocaine, ipilimumab, mycophenolate-mofetil

Treatment of IBD

Remission induction and maintenance

- Glucocorticoids: prednisone, prednisolone, methylprednisolon IV, PO or rectally (40-60 mg/d)
- Oral 5-ASA preparations: sulfasalazine (sulfapyridine + 5-aminosalicylic acid), mesalamine (1.6-4.8 g/d), others: ofsalazine, balsalazide
- Azathioprin (2-3 mg/kg/d)
- 6-mercaptopurine (6-MP) (1-1.5 mg/kg/d)
- Methotrexate (MTX) (15 mg/kg/wk)
- Cyclosporine (CyA) (2-4 mg/kg/d)
- Tacrolimus

Biological (anti-cytokine) therapy

- Anti-TNF α agents: infliximab, adalimumab, certolizumab, golimumab
- Anti-integrins: natalizumab (against α 4 integrin, ly trafficking), vedolizumab (against α 4 β 7 integrin, specific gut-selective immunosuppression)

General Measures

- Bowel rest and total parenteral nutrition in active CD
- Diet: high in calories and vitamins and adequate protein. Nonresidue, well balanced diet: to maintain nutrition until obstructive symptoms subside. Raw fruits and vegetables: avoid in patients with obstructive symptoms.
- Anemia, dehydration, diarrhea, avitaminosis: treatment as indicated
- When terminal ileal disease is present: vitamin B12, calcium supplementation

Antimicrobial agents - only for specific infectious problems

- abscess, fistulas: ampicillin, clindamycin or metronidazole (15-20 mg/kg/d in 3 doses), ciprofloxacin (2*500 mg/d) and aminoglycosides.
- bacterial overgrowth: tetracycline + correction of absorptive malfunction.

Surgical measures (resection, stricturoplasty)

- Crohn’s disease: stricture, obstruction, perianal disease unresponsive to medical therapy, intractable, fulminant colonic disease, massive hemorrhage, refractory fistula, abscess, colonic obstruction, cancer prophylaxis, colon dysplasia or cancer
- Ulcerative colitis: intractable disease, fulminant disease, toxic megacolon, colonic perforation, massive colonic hemorrhage, extracolonic disease, colonic obstruction, colon cancer prophylaxis, colon dysplasia or cancer

	Mild to moderate CD		Moderate to severe CD		Fistulizing CD
↓	• Budesonide	↓	• 6-MP • azathioprine • MTX + • Infliximab • Adalimumab • Certolizumab pegol	↓	• Abscess drainage + • antibiotics
↓	• Sulfasalazine	↓	• Natalizumab • vedolizumab	↓	• Anti-TNF (infliximab, adalimumab, certolizumab pegol, golimumab) +/- • 6-MP/ • azathioprine • MTX
↓	• Prednisone	↓	• Glucocorticoid IV	↓	• Natalizumab • vedolizumab
↓	• 6-MP • Azathioprine • MTX		• Total parenteral nutrition		• Total parenteral nutrition
	• Infliximab • Adalimumab • Certolizumab pegol • Golimumab				

	Mild to moderate UC		Moderate to severe UC
↓	• 5-ASA oral and/or rectal	↓	• Glucocorticoid oral
↓	• Glucocorticoid rectal	↓	• Glucocorticoid IV
↓	• Glucocorticoid oral	↓	• 6-MP/ • azathioprine

			+
↓	<ul style="list-style-type: none"> • 6-MP • azathioprine 	↓	<ul style="list-style-type: none"> • Infliximab • adalimumab • golimumab
	<ul style="list-style-type: none"> • Infliximab • adalimumab • golimumab 		<ul style="list-style-type: none"> • CyA IV • vedolizumab

Source: Harrison's Principles of Internal Medicine 19th Edition (ed. KasperDL, Fauci A, Hauser SL, Longo DL, Jameson JL, Loscalzo JL), McGrawHill, (2015)