Inflammatory Bowel Disease (IBD)

Pharmacotherapy I

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Required Reading

Hemstreet BA. Chapter 34. Inflammatory Bowel Disease. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L. eds. *Pharmacotherapy: A Pathophysiologic Approach, 10e.* New York, NY: McGraw-Hill; 2017.

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Inflammatory Bowel Disease (IBD)

IBD = Crohn's disease (CD) + ulcerative colitis (UC)

- characterized by inflammation of the GI tract

Crohn's disease – may affect any portion of GI tract

- Discontinuous "skip lesions"
- Granulomatous inflammation

Ulcerative colitis – mostly limited to colon and rectum (95%)

- Diffuse mucosal inflammation & ulceration
- symmetrical, circumferential, uninterrupted continuous pattern

IBD is a progressive disease characterized by periods of disease activity, remission, and relapses

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Risk Factors & Prevalence

IBD more common in Western countries

- More common in US and Europe
- Distribution of disease is shifting, with incidence increasing in Asia and the developing world

Age

- Peak incidence between 15 and 35 years of age
- 20% of Crohn's and 12% of Ulcerative Colitis patients present before 20 years of age

Genetics

- 10 to 30 times greater risk if close relative has disease
- 5%-20% have a 1st-degree relative who is also affected

Ethnicity

- Ashkenazi Jews incidence ↑ 4-5x

Smoking

- Active smokers are more than 2 times as likely to develop CD than nonsmokers, but less likely to develop UC

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Etiology

The exact etiology of IBD is unknown.

It is postulated that the cause of IBD is a combination of:

- Infectious factors
- Genetic factors
- Immunologic mechanisms
- Environmental causes
  - Psychological factors
  - Lifestyle, Dietary, and drug-related causes

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Etiology

Genetic predisposition

- deregulation of process for recognition / degradation of bacterial products by gut wall

Inflammatory response – "Hygiene Theory"

- inappropriate processing of antigens
  - role of T-helper type 1 (CD) and type 2 (UC)
- Directed at normal GI bacterial flora
- T-cell stimulation → excess pro-inflammatory cytokines (TNF-α)

Smoking cigarettes

- Protective in UC
- ↑ symptoms or worsening of disease in CD

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Pathophysiology: IBD

	UC	CD
Presenting signs and symptoms	Abdominal pain, chronic or nocturnal diarrhea, bloody diarrhea	Abdominal pain, chronic or nocturnal diarrhea, nausea, vomiting, weight loss; can have obstructing or perforating symptoms
Location	Large intestine only	Entire GI tract involvement possible
Distribution pattern	Continuous; rectal origination, proximal progression	Discontinuous, with skip lesions
Rectal involvement	Very common	Uncommon
Perianal disease	Uncommon	Common
Depth of inflammation	Mucosal	Transmural
Fistulas/strictures	Very uncommon	Common
Smoking	Negative association	Exacerbation of disease activity

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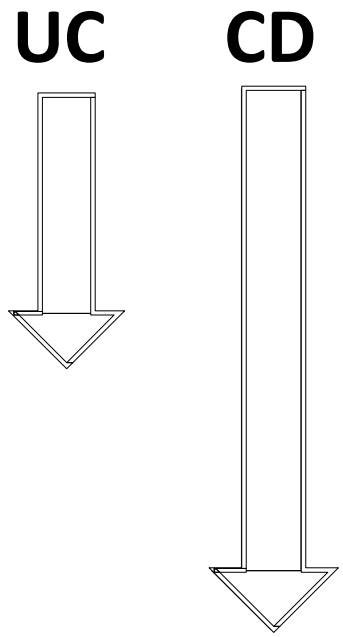
Depth of Penetration in GI Tract



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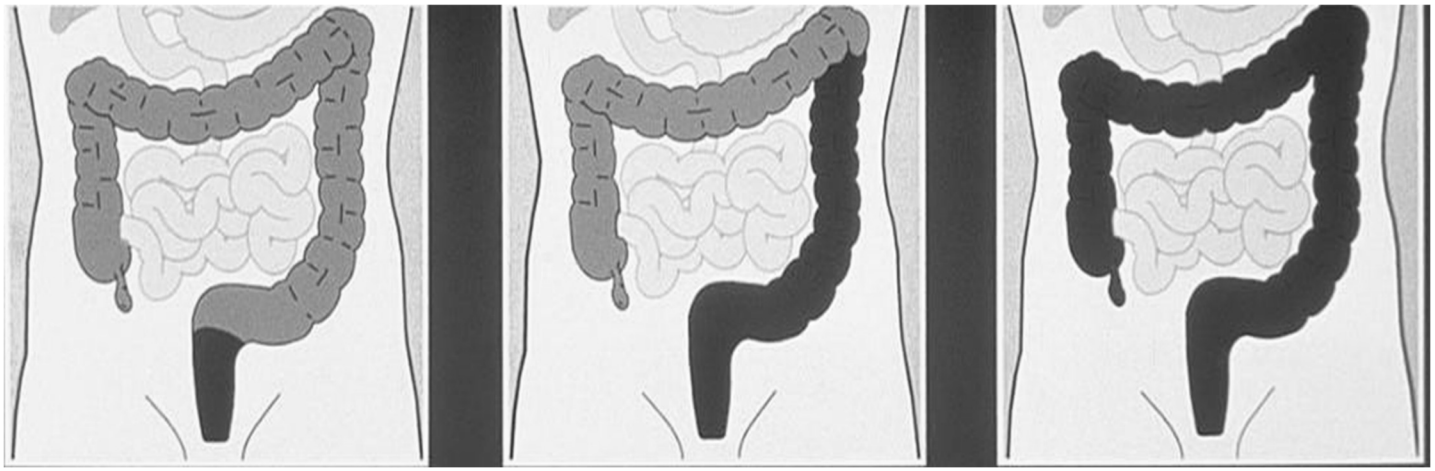
UC



Proctitis **Left-sided Colitis** **Pancolitis**

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Pathophysiology: UC

Confined to colon and rectum

- ALWAYS involves rectum, extends proximally
- Rectal = proctitis
- Rectum + sigmoid colon = proctosigmoiditis
- Entire colon = pancolitis

Inflammatory response mediated by Th2 and Th17 cells

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Pathophysiology: UC

Fistulas, perforation, and obstruction are **<u>uncommon</u>** because only involves superficial layers of mucosa

Extensive mucosal damage leads to diarrhea and bleeding

Local complications – most patients

- hemorrhoids, anal fissures, abcesses
- toxic megacolon – colonic distension and acute colitis
  - systemic toxicity – colonic perforation
  - mortality rates up to 50%
- colon cancer risk much higher in UC

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Pathophysiology: CD

Any part of GI tract may be involved

- small intestine most common site
  - terminal ileum and cecum
- ~30% have isolated colonic involvement

Inflammatory response mediated by Th1 and Th17 cells

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Pathophysiology: CD

Bowel wall injury is extensive, regardless of site of injury (transmural)

- lumen tends to be narrowed
- ulcers tend to be deep and elongated and extend along longitudinal axis of bowels

Complications

- small bowel stricture and obstruction
- fistula and abscess formation

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Hematologic, Coagulation, and Metabolic Abnormalities

Prevalence of anemia in IBD patients is up to 74%

Anemia may present at iron deficiency due to chronic blood loss, inflammation, malnutrition, hemolysis, or bone marrow suppression from drug therapy

Anemia may present as anemia of chronic disease secondary to chronic inflammation and overproduction of cytokines

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Hematologic, Coagulation, and Metabolic Abnormalities

Patients with IBD are at 1.5 to 3.6 times higher risk of venous thromboembolism (VTE) compared with the general population

- This is secondary to activation of the clotting cascade and platelet activation due to inflammation

Patients with IBD are at increased risk of metabolic bone disease and the development of osteoporosis

- Most likely due to a combination of nutritional deficiencies (e.g. calcium and vitamin D), chronic cytokine-related inflammatory response on bone, disease-associated hypogonadism, and use of corticosteroids

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Clinical Presentation

Highly variable

- Some patients experience one acute attack and never have recurrence
- More frequently, patients experience acute exacerbations with periods of remission
- In more severe types of disease there may be prolonged illness

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Signs and Symptoms

Ulcerative Colitis	Crohn's Disease
• Bloody diarrhea (hematochezia) • Fever and tachycardia • Abdominal/rectal cramping (tenesmus) • Frequent bowel movements/rectal urgency • Weight loss • Ocular involvement • Arthritis	• Chronic/nocturnal diarrhea • Abdominal pain • Malaise, fever, night sweats • Frequent bowel movements • Hematochezia (less common) • Weight loss • Ocular involvement • Arthritis

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Quality of Life

- Significant functional impairment
- Social and emotional support
- Financial stress
- Increased risk of anxiety and major depressive disorder

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Clinical Presentation

It can often be difficult to distinguish between Ulcerative Colitis and Crohn's disease

- – Approximately 10% of cases cannot be distinguished

Can sometimes see the extraintestinal manifestations before the GI symptoms

Extraintestinal manifestations may or may not mirror disease control

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Physical Examination and Gross Pathology

Ulcerative Colitis	Crohn's Disease
Rectal disease (almost always), not perianal	Entire gastrointestinal tract affected; may spare the rectum; anal fissures and perirectal abscesses are common
Diarrhea; gross bleeding is more common	Diarrhea
Colicky abdominal pain	Abdominal tenderness, cramping
Loss of colonic vascular markings, erythema	Fistulae and microperforations
Ulceration; may develop pseudopolyps	Cobblestone appearance of bowel wall
Mucosal lesions	Transmural lesions
Continuous disease	Non-contiguous, with skip areas

–**Common to both**: constitutional symptoms (fever, weight loss, fatigue), toxic megacolon, pseudopolyps, peripheral arthritis, dermatopathy, oculopathy, thromboembolism, hepatobiliary complications

In some patients, the disease cannot be differentiated

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Gross Pathology: Bowel Wall Appearance

Ulcerative Colitis

Crohn's Disease

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Ocular Involvement

Episcleritis **Scleritis**

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Dermatologic Involvement

Erythema Nodosum

Pyoderma Gangrenosum

Aphthous Ulcers
(with cobblestoning)

Muhvić-Urek M et al. *World J Gastroenterol*. 2016 Jul 7;22(25):5655-67.

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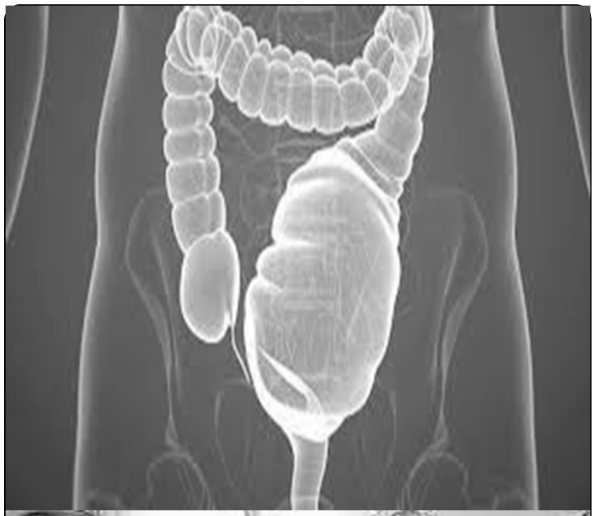

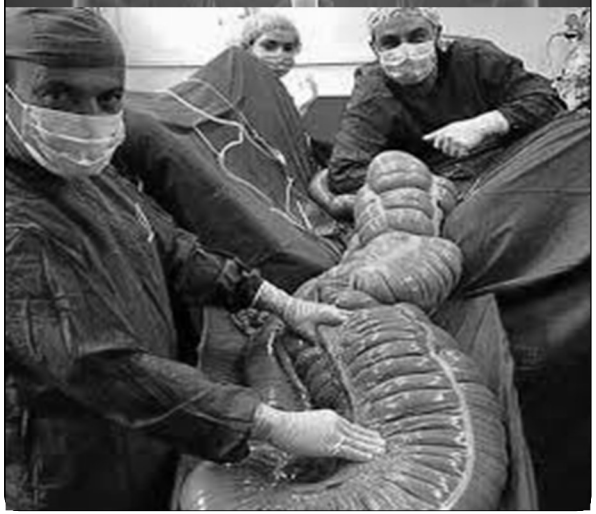

Selected Complications

Toxic Megacolon

- IBD patients are at increased risk of developing toxic megacolon, which is a segmental or total colonic distension of greater than 6cm with acute colitis and signs of systemic toxicity

Colon Cancer

- IBD patients are at higher risk of colorectal carcinoma (CRC)
- Risk factors for CRC include: young age at IBD onset (<50 years old), severe inflammation, positive family history of CRC, presence of primary sclerosing cholangitis, or inflammatory polyps
- Screening colonoscopy should be performed at 8 years after onset of IBD symptoms with subsequent screenings every 1 to 2 year if negative

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Laboratory Tests

Ulcerative Colitis

- Complete Blood Count
  - Increased WBC
  - Decreased Hgb/Hct
  - Increased ESR or CRP
- Hypoalbuminemia
- (+) perinuclear antineutrophil cytoplasmic antibodies (pANCA) (?)

Crohn's Disease

- Complete Blood Count
- Increased WBC
- Increased ESR or CRP
- (+) anti–Saccharomyces cerevisiae antibodies (ASCA) (?)

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Disease classification

Class	Ulcerative Colitis	Crohn's Disease	Class
Mild	• <4 stools/day • no systemic involvement • normal ESR	• ambulatory • tolerating po intake • well-hydrated • no systemic involvement • <10% weight loss	Mild to Moderate CD AI 150-220
Moderate	• >4 stools/day • minimal systemic involvement	• systemic involvement (including fever, significant weight loss) • abdominal tenderness • nausea/vomiting • anemia	Moderate to Severe CD AI 220-450
Severe	• >6 stools/day with blood • significant systemic involvement (fever, tachycardia, anemia) • elevated ESR	• persistent symptoms despite steroids or biologics • high fevers • persistent vomiting • intestinal obstruction • peritoneal signs of involuntary guarding or rebound tenderness • cachexia • abscess	Severe to Fulminant CDAI >450
Fulminant	• >10 stools/day with continuous bleeding • toxic symptoms • abdominal tenderness • anemia requiring transfusion • colonic dilation (toxic megacolon)		

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Disease Classification

Ulcerative Colitis

- Distal disease
  - Limited to areas distal to the splenic flexure
- Extensive disease
  - Disease extended proximal to the splenic flexure
- Proctitis
- Proctosigmoiditis
- Pancolitis

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Diagnosis

Endoscopy

- Have to determine the distribution of disease
- Looking for the pattern and depth of the inflammation
- Want to obtain a biopsy

Stool cultures

- Mostly to rule out other etiologies of the symptoms

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IBD Diagnosis

The diagnosis of IBD is made on clinical suspicion confirmed by a thorough medical evaluation using:

Sigmoidoscopy or colonoscopy	Biopsy	Stool examinations	Barium radiographic contrast studies	Laboratory testing

The presence of extraintestinal manifestations may also aid in establishing a diagnosis

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Complications & Prognosis of IBD

UC

Severe hemorrhage

Toxic megacolon

CD

Abscess

Fistulae

Obstruction

Malabsorption

UC & CD

Perforation

Colorectal cancer (CRC)

Nonmelanoma skin cancer (r/t thiopurines)

Lymphoma (r/t thioprunes, age > 65, EBV infection

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Treatment Approach

Major treatment goals:

Acute (induce remission):

- Alleviation of symptoms and suppression of inflammation during acute episodes

Long-term:

- Maintenance of remission / prevention of relapse
- Improve quality of life
- Prevention of hospitalization or surgical intervention
- Management of extraintestinal manifestations
- Prevention of malnutrition
- Reduce exposure to corticosteroids
- Prevention of treatment-associated adverse effects

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Treatment Considerations

About 20% of patients with acute colitis will experience spontaneous improvement

Some patients with acute and mild disease may progress to more serious or severe disease over a short time

When remission is achieved, with proper therapy, we should expect it to last about a year

- – Without therapy relapse is likely to occur within 9 months in 50-67% of patients

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Treatment Considerations

In severe disease, remission cannot be expected without treatment

The chance of sustained remission is highly impacted by the response to treatment

Maintaining remission is vital for adequate treatment of IBD	Patients who remain in remission for 1 year have 80% chance of remaining in remission during the following year

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Approach to Treatment

Nonpharmacologic Therapy

- Surgery
- Nutrition
- Medications to avoid

Pharmacologic Therapy

- Target the inflammatory process
- Antimicrobials
- Iron supplementation

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Nonpharmacologic Therapy
Nutritional Support

- Important due to the potential for malnourishment
- Eliminate foods that tend to exacerbate symptoms
- Milk, high residue foods
- Vitamin and mineral supplementation
- B12, Vit. A,D,E,K, iron, Ca
- Enteral or parenteral nutrition may be necessary in severe disease

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Nonpharmacologic Therapy
Surgery

Resection of affected areas of the intestines and colon

- Complete bowel resection (colectomy) is curative for ulcerative colitis
  - – This is NOT the case for Crohn's disease

Drainage of abscesses

Correction of fistulas

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Pharmacologic Therapy

Medications to Avoid

- NSAIDs
- Anti-diarrheal medications
  - Particularly those that decrease motility
    - Loperamide, diphenoxylate/atropine, codeine
  - Can risk precipitation of toxic megacolon, especially during active disease
- Anticholinergic medications
- Narcotic analgesics

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Pharmacologic Therapy

Aminosalicylates	• Sulfasalazine, mesalamine, balsalazide, olsalazine
Corticosteroids	• Topical, oral, or IV hydrocortisone, oral budesonide, oral or IV prednisone, and methylprednisolone
Immunosuppressants	• Thiopurines: azathioprine, 6-mercaptopurine • Misc: cyclosporine, methotrexate
Antimicrobials	• Metronidazole, ciprofloxacin
Anti-TNF-α antibodies	• Infliximab, adalimumab, certolizumab, golimumab
Other biologics	• Natalizumab, ustekinumab, tofacitinib

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Treatment Approach

Acute disease / Induction of remission

- continue therapy until symptom remission
  - usually some improvement within 2-4 weeks
  - maximal improvement within 12-16 weeks
- failure to respond (continued symptoms)
  - offer alternative treatments

Maintain response / remission

- if respond to induction therapy

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Pharmacologic Therapy

Factors to consider:	Patient symptoms	Medical history
Current medications	previous IBD therapies	Drug allergies
	Extent, location and severity of disease	

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Aminosalicylates

All formulations deliver 5-aminosalicylate (5-ASA, mesalamine) to the inflamed GI tract

5-ASAs are appropriate for induction and maintenance

MOA – unknown…anti-inflammatory

↓ prostaglandin and leukotriene production	inhibit bacteria-induced chemotaxis - ↓TNF, ↓IL-1	free radical scavenger

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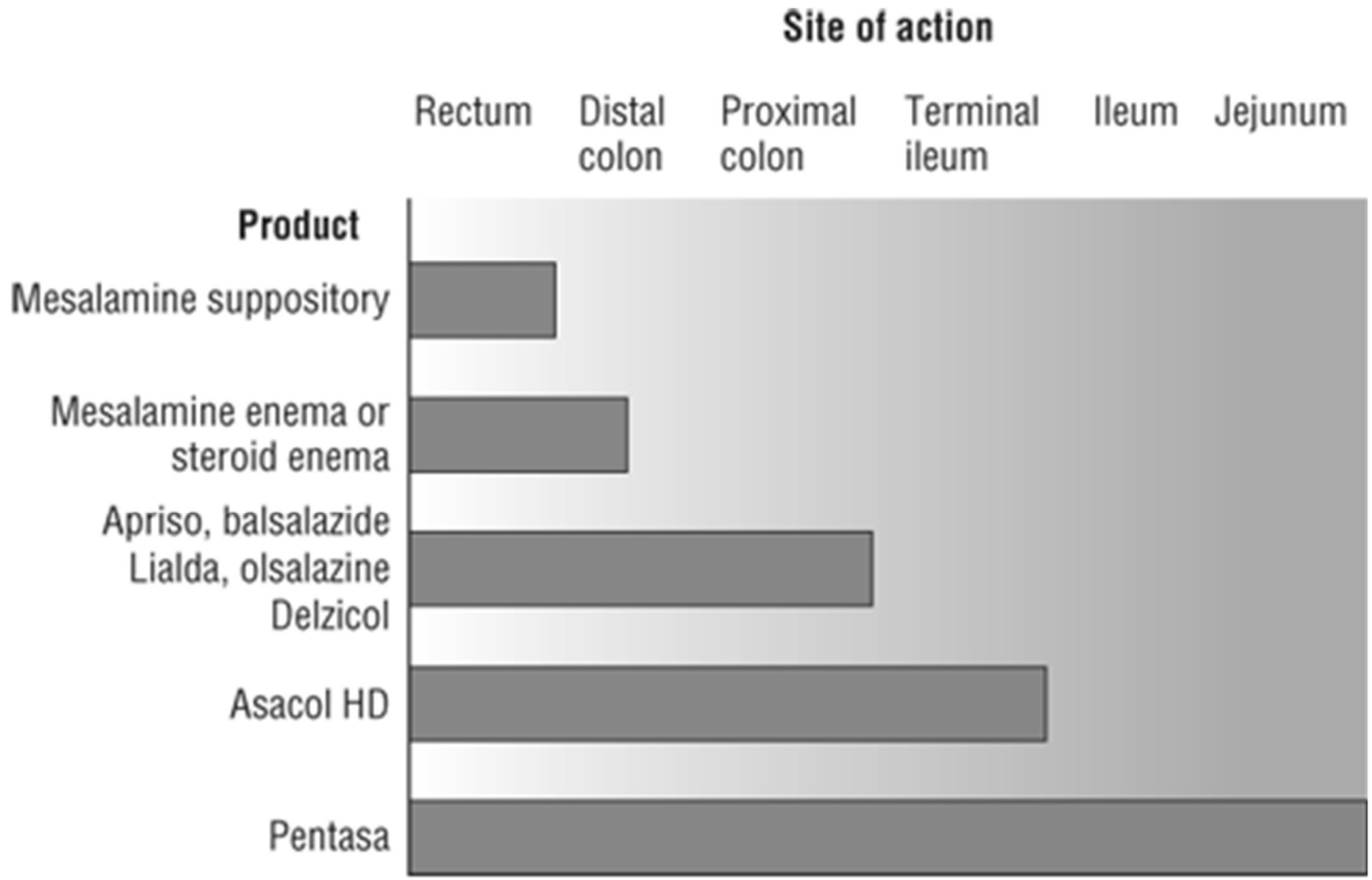

Source: JT DiPiro, GC Yee, LM Posey, ST Haines, TD Nolin, VL Ellingrod. Pharmacotherapy: A Pathophysiologic Approach. 11th Edition.
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Site of activity of various agents used to treat inflammatory bowel disease.

Citation: Inflammatory Bowel Disease, DiPiro JT, Yee GC, Posey L, Haines ST, Nolin TD, Ellingrod V. *Pharmacotherapy: A Pathophysiologic Approach, 11e;* 2020. Available at: https://accesspharmacy.mhmedical.com/content.aspx?bookid=2577&sectionid=219309811 Accessed: May 08, 2020
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Sulfasalazine (Azulfidine, Sulfazine)

Administration route: orally

- immediate release, enteric coated
- 500mg tabs

Site of action: colon

- How? Bacterial degradation of diazo- bond delivers mesalamine and sulfapyridine
- Where? Mesalamine works locally,
- What else? Sulfapyridine is absorbed and excreted renally and is responsible for most side effects.

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Sulfasalazine (Azulfidine, Sulfazine)

Contraindications – sulfonamide allergy, salicylate allergy, G6PD deficiency

ADRs: HA, dyspepsia, nausea, vomiting, fatigue

- up to 45% of patients (dose related)
- Decrease by administering with food

Idiosyncratic reactions

- hepatitis, interstitial nephritis, interstitial pneumonia
- Bone marrow suppression, blood dyscrasias (monitor CBC)

crystalluria risk: counsel to increase fluid intake

Important ADR: impairs folate absorption

- Supplement folate (1 mg/day)

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Mesalamine

Brand Name	Formulation	Strength	Site of Action
Apriso®	Enteric coated polymer matrix tablet	375mg	Colon
Asacol®	Delayed release resin tablet	400mg	Distal ileum and colon
Canasa®	Suppository	1000mg	Rectum
Lialda®	pH dependent polymer film coated tablet (MMX)	1.2gm	Terminal ileum and colon
Pentasa®	Controlled-release capsule	250mg, 500mg	Small bowel
Rowasa®	Enema	4gm/60mL	Distal colon and rectum

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Balsalazide and Olsalazine

Balsalazide (Colazal®, Giazo®)

- mesalamine linked to inert carrier by diazo bond
- delayed-release capsule – 750mg
- Site of action: colon

Olsalazine (Dipentum®)

- 2 mesalamine molecules linked by diazo bond
- delayed-release capsule – 250mg
- Site of action: colon

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Mesalamine Considerations

- Contraindications – salicylates allergy, G6PD deficiency
- ADRs: similar to sulfasalazine
  - overall lower incidence (no sulfa-allergy issues)
  - Olsalazine – secretory diarrhea up to 17%
- Onset of effect – 2-4 weeks
- Patient adherence
- Cost of therapy
  - newer formulations

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Administration Technique

Enemas	Suppositories
• Remove from foil, shake • Remove the protective cover from the applicator • Assume the position • Insert the rectal tip, tilt the nozzle and squeeze slowly • Withdraw and discard the bottle • Remain position at least half hour (ideally, all night)	• Empty your bladder/bowel if possible • Wash your hands • Remove from foil • Apply water soluble lubricant prn • Insert suppository (pointed end first) into rectum with gentle pressure. • Retain 1-3 hours or longer, avoiding voiding

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Administration Technique

Side Position

- Position patient on side, with right knee pulled forward for balance

Knee-to-chest Position

- Position patient on knees, leaning down

sfRowasa® package insert. Alaven Pharmaceutical LLC.

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Aminosalicylates: Place in therapy

Most common drugs used for inducing and maintaining remission

Effectiveness in UC >>> CD

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Corticosteroids

Used for potent anti-inflammatory properties

MOA:

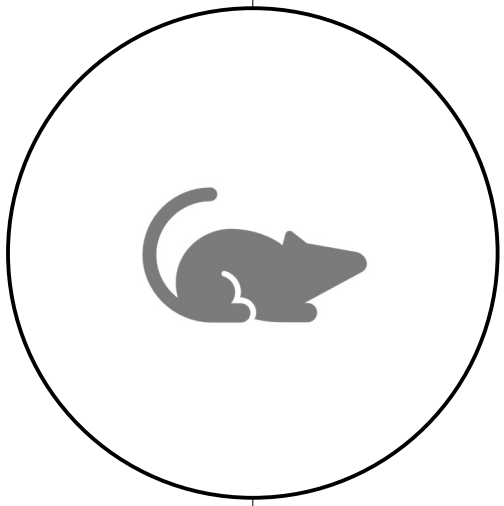
↓T lymphocytes - ↓IL-1, IL-2, IL-6

↓ production of prostaglandins and leukotrienes

70-80% full or partial clinical response

In 5days - 40% full, 30-40% partial

limit to short-term use



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Pharmacologic Options: Corticosteroids

Corticosteroids	**Uses**	
Budesonide EC (Entocort)	CD (proximal)	
Budesonide MMX (Ucerise)	UC (any disease extent)	
Budesonide rectal foam (Uceris®)	UC (left-sided disease)	
Hydrocortisone rectal	UC (left-sided)	
Systemic Hydrocortisone Prednisone Methylprednisolone	CD,UC	
Adverse Effects:	Moon face Hypertension Infection Osteoporosis Cataracts Adrenal suppression	Acne Diabetes Osteonecrosis Myopathy Glaucoma Psychosis
Corticosteroids are appropriate for induction of remission ONLY		

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Corticosteroids

ADRs

- Short-term
- Long-term

Additional monitoring prolong therapy

- Annual ophthalmologic exams
- Hypothalamic-pituitary-adrenal (HPA) axis suppression tests
- Urinalysis, blood glucose, blood pressure, weight, chest X-ray at regular intervals

Place in Therapy

- Short-term use to treat active disease
- most common drugs for acute flares
- NO role in long-term maintenance

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Corticosteroids

Patient Counseling

Advise to take with food or milk to minimize GI upset

Patient should report signs and symptoms of infection and adrenocortical insufficiency

Advise diabetes patients to report problems with glycemic control

Consult health care provider prior to receiving vaccines

- Corticosteroid therapy beyond 2 weeks may cause immunosuppression, which is a concern with live vaccines

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Immunosuppressants

Agents target the excessive immune response or cytokines involved in IBD

steroid “sparing” effects

slow onset of action 3-12 months

- cyclosporine IV onset 7 days

all agents have serious side effects

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Immunosuppressants

Drug	**Trade Names**	**Dose**	Uses
Cyclosporine	Sandimmune®	4 mg/kg/day IV cont. infusion	CD, UC (steroid failure, induction ONLY)
Methotrexate (MTX) *Off-label use*	Otrexup®, Rasuvo®	Induction: 25 mg/week IM/SubQ Maintenance: 15 mg/week IM	CD
Thiopurines			
Azathioprine (AZA)	Imuran®	1.5-2.5 mg/kg/day orally	CD UC
6-mercaptopurine (6-MP)	Purinethol®	1.5-2.5 mg/kg/day orally	CD, UC

Thiopurines and MTX are appropriate for maintenance of remission ONLY

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Thiopurines: azathioprine (AZA) and 6-mercaptopurine (6-MP)

AZA is converted to 6-MP non-enzymatically and through GST (glutathione S-transferase)

Thiopurine methyltransferase (TPMT) inactivates an intermediary metabolite of 6-MP

Xanthine oxidase (XO) inactivates 6-MP

MOA: 6-MP is metabolized to a 6-thioguanine metabolite, inhibiting *de novo* purine synthesis, DNA replication, and cellular proliferation

- suppresses cytotoxic T cell proliferation and function
- inhibits NK cell activity

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Azathioprine (AZA) and Mercaptopurine (6-MP)

Are effectively used in long-term treatment of both UC and CD

Generally reserved for patients who fail 5-ASA therapy or are refractory to or dependent on corticosteroids

May be used in conjunction with 5-ASAs, corticosteroids, and TNF-inhibitors

TPMT (thiopurine methyltransferase) is partially responsible for the metabolism of AZA and 6-MP.

- Genotype/phenotype prior to initiation in order to determine enzyme activity and properly dose (especially concerned with bone marrow, hepatic, and renal toxicity)

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Azathioprine (AZA) and Mercaptopurine (6-MP)

Are indicated for IBD maintenance therapy due to a long onset of action

- Onset of action can range from a few weeks to up to 12 months before benefits are seen

Adverse reactions: pancreatitis, bone marrow suppression, anemia, thrombocytopenia, hepatotoxicity, renal toxicity, nausea, diarrhea, rash

Monitoring: CBC w/diff and platelets weekly for 1 month, biweekly for 1 month, then every 1 to 2 months; LFTs and renal function every 1 – 2 weeks for 1st month then every 3 months thereafter

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Cyclosporine (CSA)

Formulations:

- Modified ("microemulsion"): Gengraf®, Neoral®
- Non-modified: SandIMMUNE®

MOA: calcineurin inhibitor; blocks T-cell intracellular signaling pathways to

↓expression/synthesis of IL-2 and IFN-gamma

- preferential for cell-mediated T-cell proliferation
  - ↓ by about 50%

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Cyclosporine

Used in severe flares of IBD not responding to IV corticosteroids

Poses a risk of nephrotoxicity and neurotoxicity

Adverse reactions: hypertension, headache, renal dysfunction, GI adverse effects, hepatotoxicity, leukopenia, anemia, thrombocytopenia, infection

Monitoring: Blood pressure, renal function, liver function, and CBC with differential

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Methotrexate (MTX)

MOA: folate antimetabolite – in Crohn's, the MOA is not clearly known, but is suspected to modulate immune response and have anti- inflammatory effects

Off label use, but recommended in Crohn's clinical practice guidelines

Used in steroid dependent and steroid-refractory

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Methotrexate (MTX)

Useful for the treatment and maintenance of CD; data supporting use in UC is lacking

Adverse reactions: reddening of skin, hyperuricemia, GI adverse effects, leukopenia, myelosuppression, thrombocytopenia, renal failure, nephropathy, immunosuppression, cirrhosis

Monitoring: CBC w/ diff and platelets, Scr, LFTs (baseline then every 2 to 4 weeks for first 3 months then every 8-12 weeks for 3-6 months of therapy, then every 12 weeks after 6 months of therapy); chest x-ray (baseline); PFTs (if MTX induced lung disease suspected); hepatitis B and C testing (baseline)

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Drug	Major Side Effects
Azathioprine / 6-Mercaptopurine	N/V, bone marrow suppression (10%), pancreatitis (5%), hypersensitivity (5%), rash, fever, hepatitis
Cyclosporine (CSA)	Nephrotoxicity, seizures, hypertension, hepatitis, infection, hypertrichosis, gingival hyperplasia - Many significant drug-drug interactions
Methotrexate (MTX)	Increased liver enzymes and hepatic fibrosis, GI effects (N/V/D), bone marrow suppression, hypersensitivity pneumonitis

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CSA-induced hypertrichosis

Miwa et al. *Ann. Pharmacother*. 1990;24:365-8.

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Immunosuppressants: Role in Therapy

AZA/6-MP:

- long-term maintenance of remission
- reduce need for corticosteroids

Cyclosporine (CSA):

- reserved for acute treatment of severe/fulminant or refractory IBD

Methotrexate (MTX):

- reserved for steroid dependent and steroid- refractory Crohn's disease
- caution/avoid if high hepatotoxicity risk

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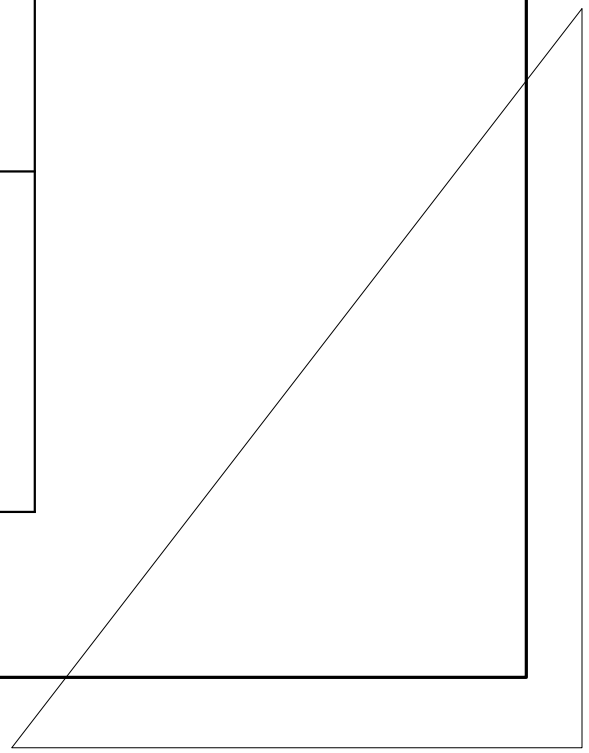
Drug	Counseling/Monitoring
Azathioprine / 6-Mercaptopurine	- May take >4 months at target dose for max effect - Avoid prolonged sun exposure - Baseline LFTs, weekly CBC
Cyclosporine (CSA)	- Renal function (SCr, BUN) - BP - 4th dose trough levels (goal: 200-300 ng/mL)
Methotrexate (MTX)	- Periodic CBC - LFTs (liver enzymes, albumin) ±liver biopsy - Baseline CXR - Replace folic acid



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Antibiotics

Metronidazole and Ciprofloxacin

- more effective in CD in treating mild disease

MOA: may interrupt the inflammatory process directed against endogenous bacterial flora

Probiotics?

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Biologic Agents

Anti-TNF monoclonal antibodies

- Infliximab (Remicade®)
- Certolizumab pegol (Cimzia®)
- Adalimumab (Humira®)
- Golimumab (Simponi®)

Anti-IL-12 and IL-23 monoclonal antibody

- Ustekinumab (Stelara®)

Anti α-4 integrin monoclonal antibody

- Natalizumab (Tysabri®)

Anti α-4 β-7 integrin monoclonal antibody

- Vedolizumab (Entyvio®)

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Tumor Necrosis Factor (TNF) Inhibitors

MOA

- Inhibits endogenous TNFα. Elevated levels of TNFα have been found in involved tissues of various disease states including CD and UC. Biological activities of TNFα include the induction of proinflammatory cytokines, enhancement of leukocyte migration, activation of neutrophils and eosinophils, and the induction of acute phase reactants and disease degrading enzymes.

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	Infliximab	**Adalimumab**	**Certolizumab**
Class	Monoclonal antibody	Monoclonal antibody	Monoclonal antibody
Route of administration	**Intravenous**	**Subcutaneous**	**Subcutaneous**
Half-life	8–10 days	10–20 days	14 days
Approved Indication	CD (*including fistulizing) UC	CD UC	CD
Maintenance Dosing Interval	8	2	**4**
Induction dose	5 mg/kg at 0, 2, and 6 weeks	160 mg, 80 mg, and 40 mg at 0, 2, and 4 weeks	400 mg at 0, 2, and 4 weeks
Maintenance dose	5 mg/kg every 8 weeks	40 mg every 2 weeks	400 mg every 4 weeks

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Safety Considerations & Challenges of Biologics

Immunogenicity

- Infusion reactions (anaphylactoid): slow 2-hour infusion, pre-medicate with acetaminophen and/or antihistamine
- Loss of response to therapy
- Methods to reduce immunogenicity
  - Concomitant thiopurine or methotrexate decreases infusion reactions and increases efficacy

Infection

- Increased risk of bacterial pneumonia, fungal Infections and opportunistic infections
- Tuberculosis- test and treat latent tuberculosis (TB) prior to initiation
- Hepatitis B Virus (HBV) – Risk for reactivation; obtain HBV serology prior to treatment. Risk category based on HBsAg & anti-HBc status

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Safety Considerations & Challenges of Biologics

Heart Failure (HF)- use all anti-TNFα with caution in patients with HFrEF

- Infliximab is contraindicated at doses > 5 mg/kg in patients with NYHA class III/IV HF

Neutropenia – usually mild

Liver Injury – rare, monitor AST/ALT q3-6 months; d/c if increase > 5 x upper limit of normal

Malignancy risk?

- Rare, usually fatal, case reports of hepatosplenic T- cell lymphoma in patients treated with TNF blockers. Almost all patients had received concomitant azathioprine or 6-MP and occurred in adolescent and young adult males.
- Non-melanoma skin cancer (risk increased with thiopurine combination)

Very expensive

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TNF Blockers

Disadvantages

- All injectable preparations
- Extreme $$$$$$
- Serious adverse drug effects
  - hypersensitivity, pancytopenia, hepatitis
  - heart failure

FDA Black Box Warnings

- Fatal infections
- Malignancy – lymphomas
- Tuberculosis evaluation

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TNF Blockers: Prior to Initiating Therapy

- Tuberculin skin test (TST) (PPD) for TB
- Warning: IBD patients are often anergic
- Hepatitis B screening
- Immunizations: patients should be brought up to date with all immunizations before initiating therapy
- Live vaccines should not be given concurrently

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Infliximab (Remicade®)

Murine-human IgG_1 antibody

Route: IV ONLY

Biosimilar: Inflectra®

Dose: 5 mg/kg IV infusion over 2 hours

Median time to response 2 weeks

ADRs: infusion reactions (fever, chest pain, hypotension, dyspnea)

- May be acute or delayed

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Adalimumab (Humira®), Certolizumab (Cimiza®), & Golimumab (Simponi®)

- Available for SQ injection
  - – administer every 2 weeks to start
- Common ADRs: headache, nausea, rash, injection site reactions
  - –SQ; avoids infusion reaction risk of infliximab
- Certolizumab – combined with polyethylene glycol to extend duration

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Ustekinumab (Stelara®)

MOA: human IgG monoclonal antibody blocks IL-12 and IL-23 receptors on T cells

Use: moderate to severe CD when:

- Failed or intolerant to immunomodulatory or corticosteroid therapy but never failed anti-TNF therapy
- OR, failed/intolerant to anti-TNF therapy

Dosing

- Induction: weight based, one-time IV dose
- Maintenance: start 8 weeks after IV induction dose
  - 90mg q8wk subcutaneously

ADRs: infection, headache, fatigue, dizziness

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Natalizumab (Tysabri®)

MOA: monoclonal Ab against alpha-4 subunit of integrin molecule

- prevents leukocyte adhesion and migration across endothelium

Use: restricted to patients who have failed other therapies Of CD refractory to conventional therapy and TNF inhibitors

Dosing: 300mg IV infusion over 1 hour Q4 weeks

ADEs: infusion reactions up to 24%, hepatitis, infections

- **Black Box Warning: progressive multifocal leukoencephalopathy (PML)**

CD-TOUCH program –enroll and renew Q6 months

Do not use concurrently with immunosuppressants or TNF antagonists

Black Box Warning

- • Natalizumab increases the risk of progressive multifocal leukoencephalopathy (PML), which may lead to death or severe disability. Risk factors for PML include therapy duration, prior immunosuppressant use, and presence of anti-JC virus antibodies.

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Natalizumab

Monitoring

Baseline brain MRI

Monitor patients for any new sign or symptom that may be suggestive of PML and interrupt therapy at the first sign or symptom suggestive of PML. For diagnosis, a gadolinium-enhanced MRI scan of the brain and, if indicated, cerebrospinal fluid analysis for JC viral DNA are recommended

Signs and symptoms of infection

LFTs and signs and symptoms of liver injury

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Vedolizumab (Entyvio®)

MOA: human monoclonal antibody which blocks $\alpha_4\beta_7$ integrin to selectively block gut lymphocyte trafficking

Use in active CD and UC – failed previous therapy

Dosing: 300mg IV at 0, 2, 6 weeks then every 8 weeks

- Discontinue therapy by week 14 if there is no evidence of therapeutic benefit
- Infuse over 30 minutes

ADEs: headache, arthralgia, nasopharyngitis, fatigue, antibody development

Monitoring:

- Hypersensitivity reactions and infusion reactions
- TB screening
- Sign and symptoms of PML

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Response Rates

Aminosalicylates

- Induction failure rates in patients with UC are 19%-54% for rectal aminosalicylates and 71%-91% for oral aminosalicylates
- 40%-63% of patients with UC fail to maintain remission with aminosalicylates over a 6-month or longer period.

Corticosteroids

- Rates of failure to achieve remission with systemic steroids are ~54% for patients with UC and 17%-53% for patients with CD3

Immunomodulators

- Maintenance failure rates with immunomodulators are 18%-58% for patients with UC and 5%-44% for patients with CD, over a 6-month to 2-year period

Biologics

- 20%-30% of patients with refractory CD, and roughly 40% of patients with refractory UC, do not have an initial response1 (Primary Non-Response)
- Up to 40% of patients may lose response to anti-TNFs within a year1,2 (Secondary Non-Response)

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Pharmacotherapy for IBD

Treatment selection is dependent on the

Type (UC or CD)

Severity (mild, moderate, severe, fulminant)

Site of disease (proctitis, distal disease, extensive disease, small intestine involvement, etc.)

Need for acute treatment or maintenance therapy

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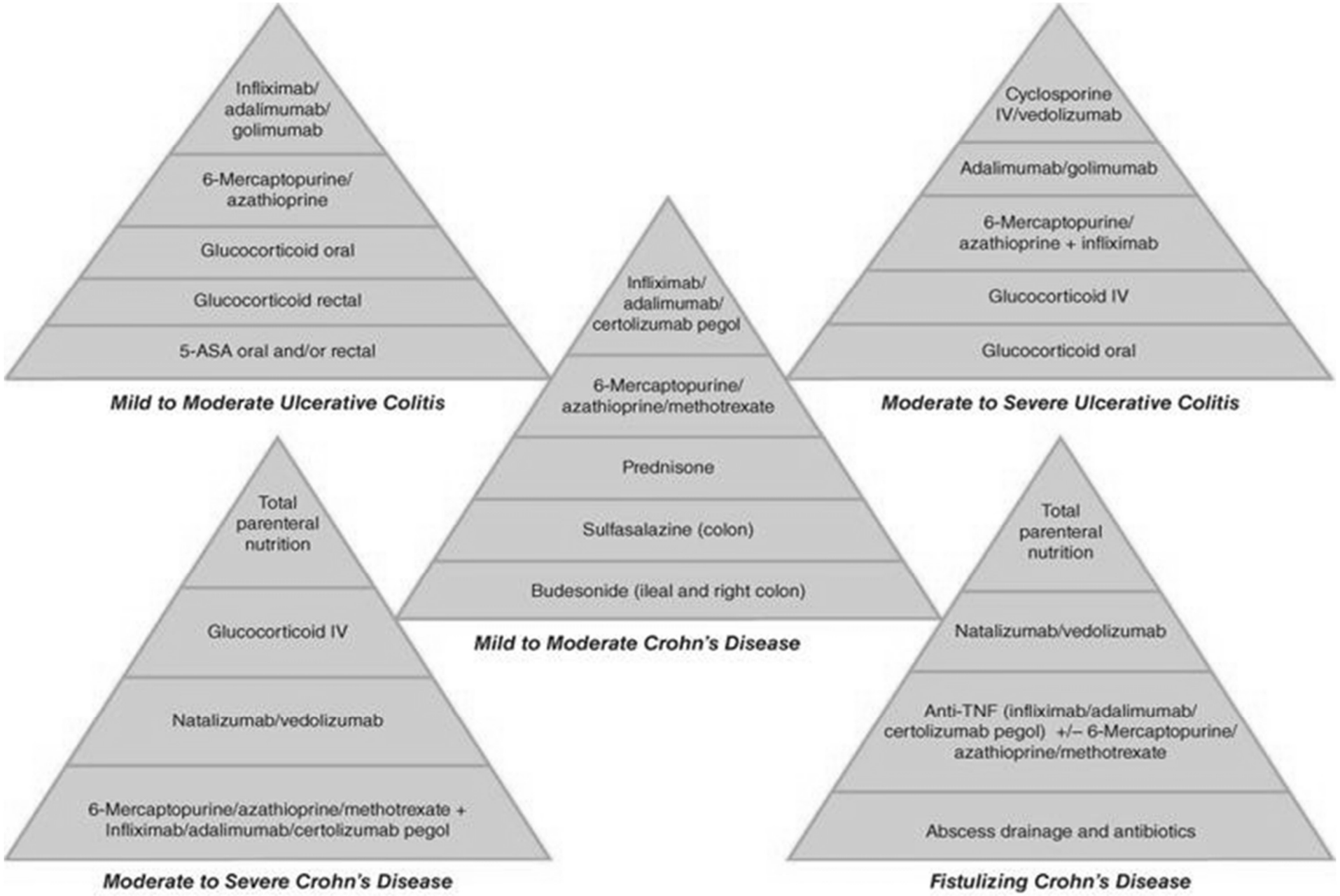

Source: D.L. Kasper, A.S. Fauci, S.L. Hauser, D.L. Longo, J.L. Jameson, J. Loscalzo: Harrison's Manual of Medicine, 19th Edition, www.accessmedicine.com

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Mild-Moderate UC: 1st Line Induction

Proctitis – inflammation confined to the rectum

- Topical therapy used most often
- Mesalamine suppository 1 gm PR qhs

Distal disease (AKA left-sided disease) – inflammation limited to areas distal to the splenic flexure

- May use either systemic or topical therapy or a combination
- Mesalamine enema 4 gm PR qhs + Mesalamine oral 2.0-4.8 gm/day or sulfasalazine 2.0-6.0 gm/day

Extensive colitis – inflammation extending proximal to the splenic flexure

- Must use systemic therapy. May add topical therapy to systemic therapy if needed/appropriate
- Mesalamine oral 2.0-4.8 gm/day or sulfasalazine 2.0-6.0 gm/day + Mesalamine enema 4gm PR qhs

Alternative 1st line for mild-moderate UC of any disease extent

- Budesonide MMX oral 9 mg/day

Evaluate symptomatic response in 2-4 weeks, expect remission by 12 weeks

If ineffective, do NOT switch to other 5-ASA (see 2nd Line Induction slide)

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- Budesonide MMX oral 9 mg/day

Evaluate symptomatic response in 2-4 weeks, expect remission by 12 weeks

If ineffective, do NOT switch to other 5-ASA (see 2nd Line Induction slide)

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Mild-Moderate UC: 1st Line Maintenance of Remission

If 5-ASAs are effective, continue same regimen with possible less aggressive dosing

Proctitis

- Mesalamine suppository 500mg BID has a lower relapse rate than 500mg once daily (10% v. 36% at 1 year)

Left Sided and extensive colitis

- Mesalamine enema 2-4g/day have similar relapse rates when dose daily (22%), every other day (28%) or even every third day (35%)
- Oral 5ASA doses ≥ 2.0 g/day
  - Combination with topical preferred over oral monotherapy

Efficacy of budesonide MMX for maintenance is uncertain

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Mild-Moderate UC: 2nd Line Induction

5-ASA intolerance (rare)

- Proctitis- Hydrocortisone suppository 25-30mg PR bid
- Left-sided- Hydrocortisone enema 100mg PR qhs
- Extensive colitis- Budesonide MMX 9mg PO daily

5-ASA or topical steroid failure (any disease extent)

- Budesonide MMX 9mg PO daily up to 8 weeks
- Prednisone 40-60mg/day until improvement (up to 8 weeks)
  - Taper by 5–10mg/week to 20mg/day then taper by 2.5 mg/week
- Evaluate for response within 2 weeks

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Mild-Moderate UC: 2nd Line Maintenance of Remission

If oral steroid responsive

- Initiate thiopurine monotherapy during steroid taper

If oral steroid unresponsive/dependent

- Initiate anti-TNFα +/- thiopurine

Evaluate anti-TNFα +/- thiopurine response in 8-12 weeks

- If response, continue anti-TNFα +/- thiopurine for maintenance
- If no response, switch to vedolizumab over another anti-TNFα
- If suboptimal response, increase dose and/or decrease dosing interval of anti-TNFα

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Moderate-Severe & Severe- FulminantUC

Moderate-severe (Non-hospitalized)

- Induction and maintenance similar to 2nd line mild-moderate UC management

Severe-fulminant (Hospitalized)

- Immediate hospitalization
- If evidence of toxic megacolon, colonic perforation, systemic inflammatory response
- Investigations for causative organisms (e.g. C.diff, CMV) and give appropriate antimicrobials
- Bowel decompression and surgery consult for toxic megacolon

Induction

- IV corticosteroids
- Hydrocortisone 100mg IV q8h (or equivalent) x 7-10 days; conversion to PO prednisone when appropriate
- If no response after 3-5 days- Cyclosporine continuous IV 4mg/kg/day
- If no response – Infliximab, colectomy

Maintenance

- Same as 2nd line mild-moderate UC management

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Crohns Disease

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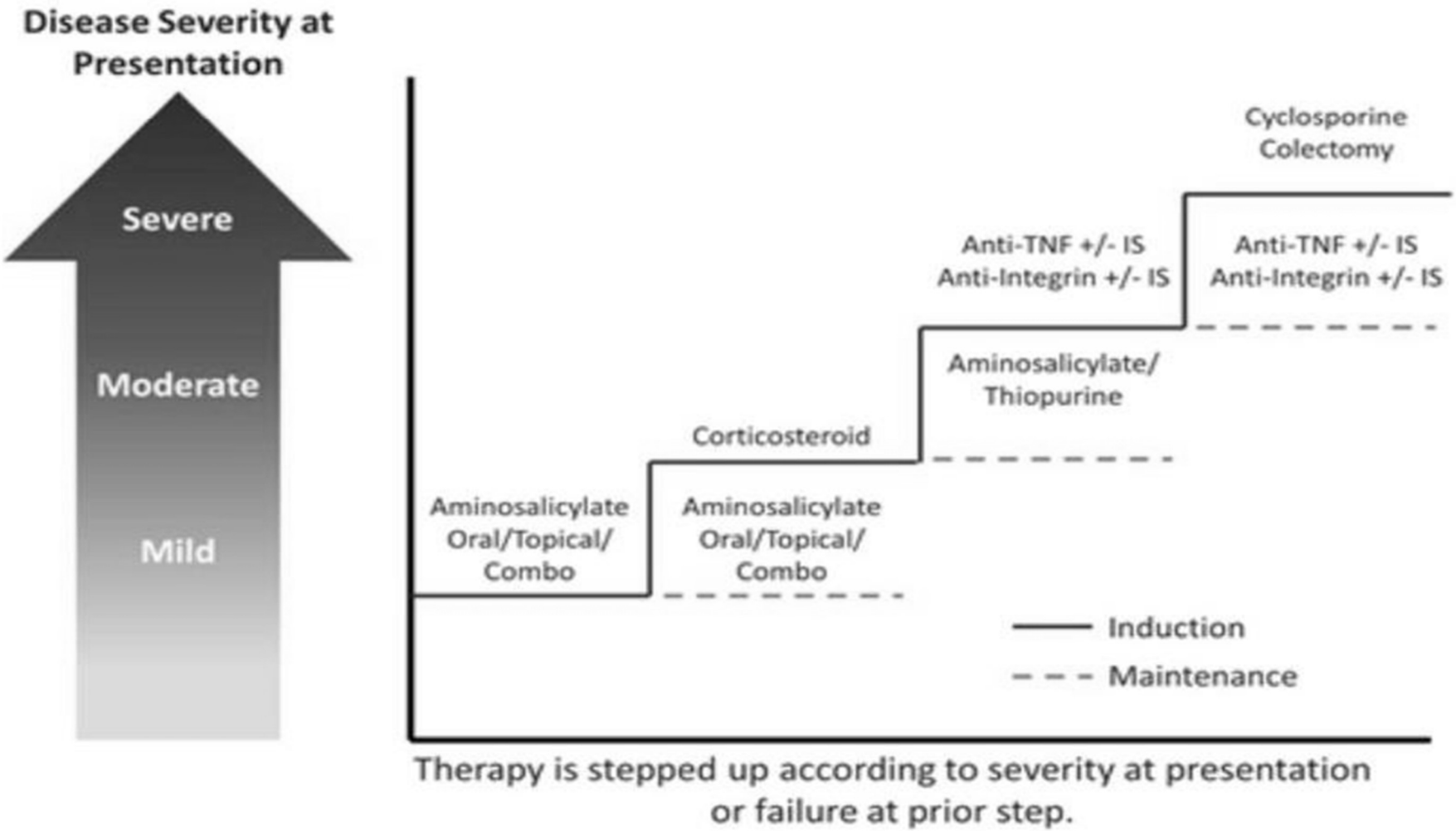

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5-ASAs in CD

Use of 5-ASAs in CD is controversial

- Inconsistent efficacy even in mild disease

2011 Meta-Analysis1

- Sulfasalazine superior to placebo but inferior to corticosteroids
- Mesalamine NOT superior to placebo
- Some experts will use in mild colonic CD

Major guidelines recommend AGAINST use of 5ASAs in CD

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Mild-Moderate CD Low-Risk Induction of Remission

Ileitis and/or proximal colitis

- Budesonide EC 9mg/day +/- AZA
  - OR
- Tapering course of prednisone +/- AZA

Diffuse and/or distal colon

- Tapering course of prednisone +/- AZA

Initiate prednisone 40-60mg/day x 10-14 days then taper

- Suggested taper: 5-10mg/week to 20 mg/day then
- taper by 2.5 mg/week

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Mild-Moderate CD Low-Risk After Induction

Stop therapy and observe

- High chance of relapse over 1 year

Budesonide EC 6mg/day

- Prolongs time to relapse by ~4 months
- No difference in remission at 1 year
- Consider bone mineral density monitoring

Begin (or continue) AZA, 6-MP or MTX to maintain remission

If failure to achieve remission, then treat as moderately severe

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Moderately Severe CD
Induction of Remission

First-line: Aminosalicylate OR metronidazole +/- ciprofloxacin PLUS prednisone at a dose of 40-60mg/day until resolution of symptoms or resumption of weight gain (7-28 days)

If steroid refractory and/or fistulizing disease

- Add infliximab, adalimumab, or certolizumab +/- azathioprine, mercaptopurine, or methotrexate

If no response to TNF-inhibitor and/or immunomodulator, change to natalizumab or vedolizumab

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Moderately Severe CD
Induction of Remission

Treatment of ACTIVE disease

May need surgical intervention (mass, obstruction, abscess, etc.)

Administer IV hydrocortisone 100mg every 6 to 8 hours

If no response to hydrocortisone in 5 to 7 days, then IV cyclosporine 4mg/kg/day OR infliximab is not attempted before

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Remission/Maintenance Therapy for Crohn's Disease

No role for long-term corticosteroid use

First Line: Azathioprine or 6-mercaptopurine plus or minus oral aminosalicylate

- If intolerant to AZA or 6-MP, then try methotrexate

Second Line: TNF-inhibitor plus or minus azathioprine or 6-mercaptopurine or methotrexate (if intolerant of AZA or 6-MP)

Alternative: Vedolizumab

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Crohn’s Disease

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Ulcerative Colitis

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