



Inflammatory Bowel Disease (IBD)

Pharmacotherapy I

Dr. Abdallah Abukhalil

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.

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

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

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

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)

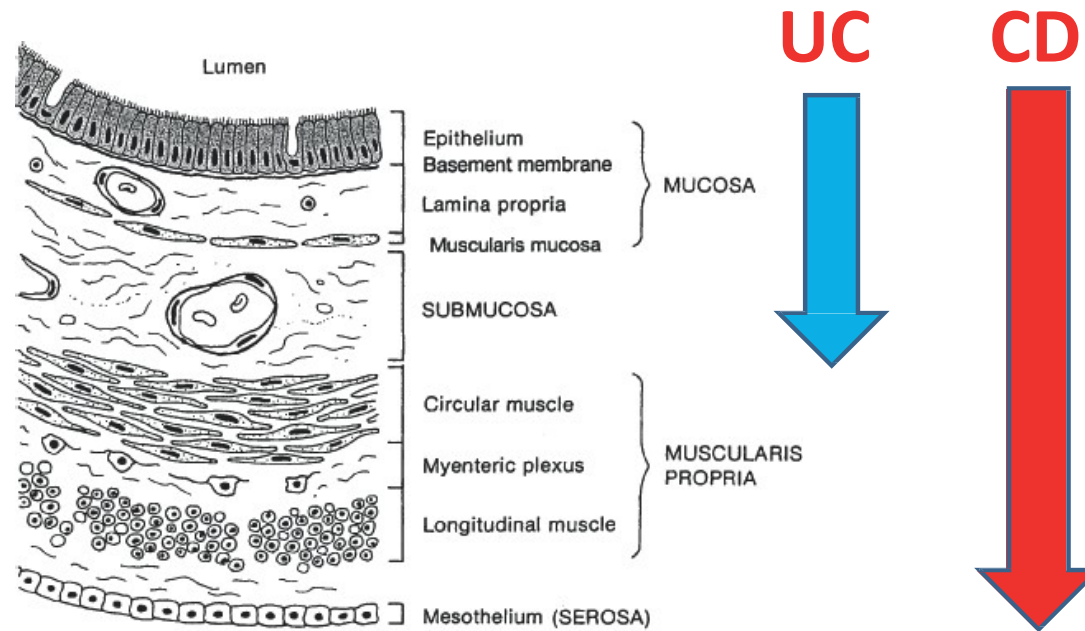
Smoking cigarettes

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

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 |

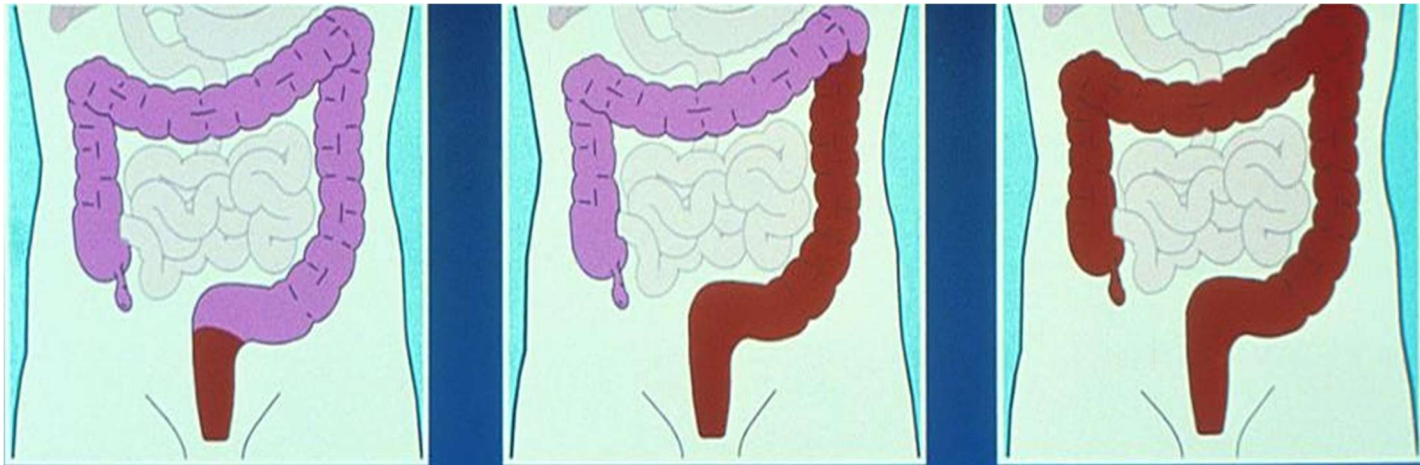
Depth of Penetration in GI Tract



Source: Barrett KE: *Gastrointestinal Physiology*:
<http://www.accessmedicine.com>

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UC



Proctitis

Left-sided Colitis

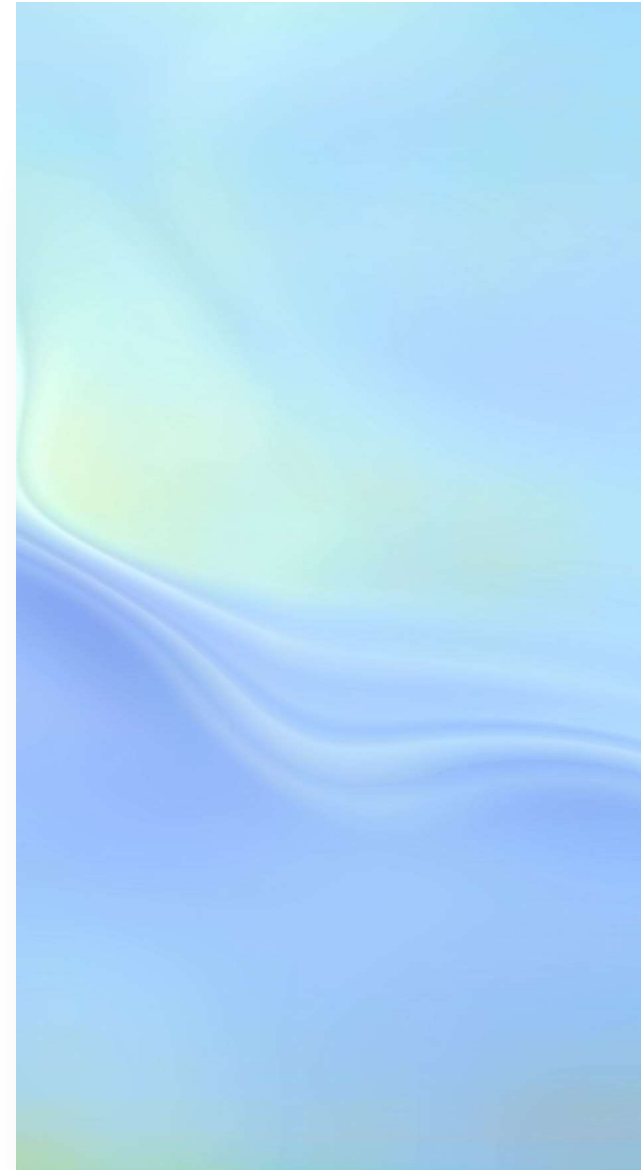
Pancolitis

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



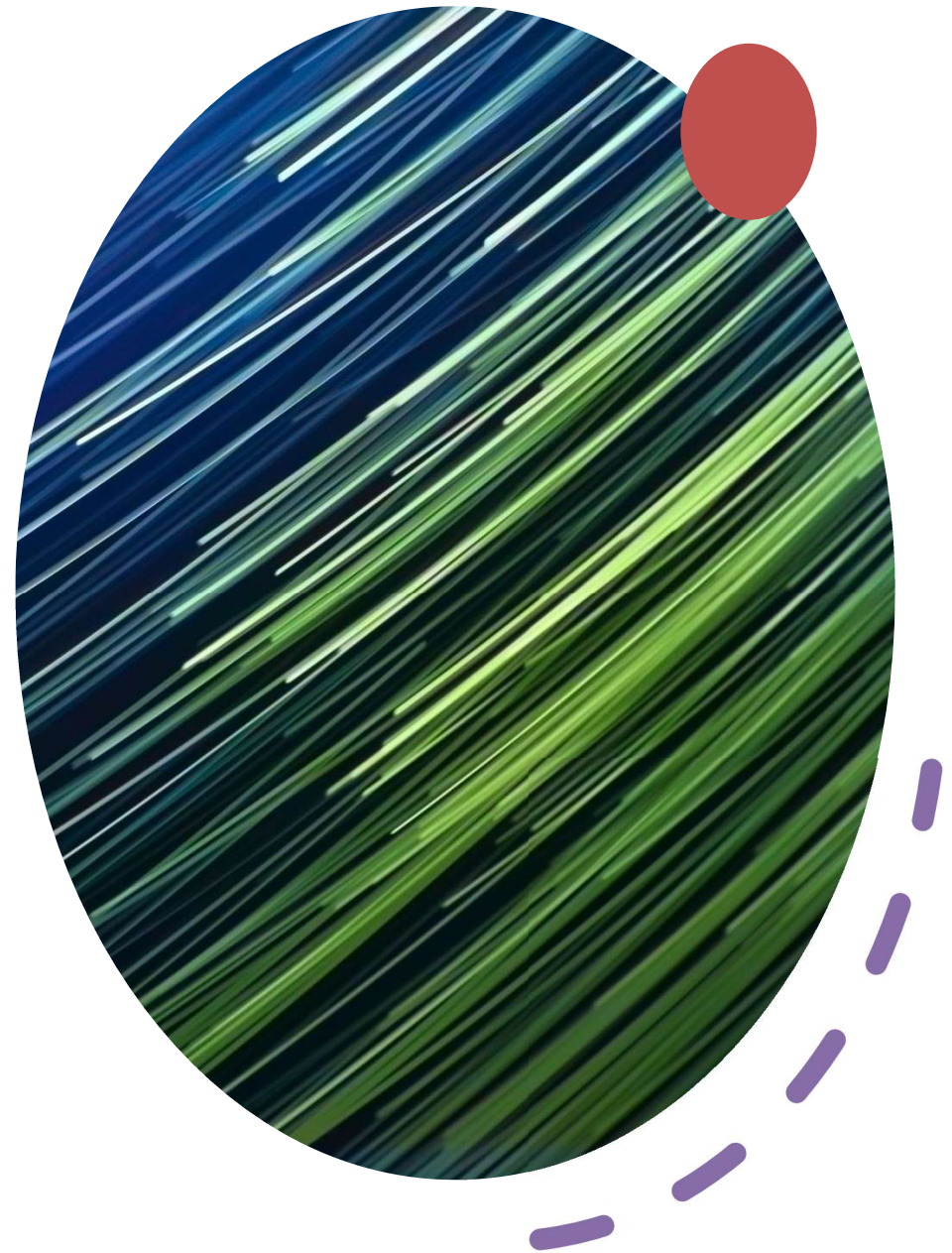
Pathophysiology: UC

Fistulas, perforation, and obstruction are **uncommon** because only involves superficial layers of mucosa

Extensive mucosal damage leads to diarrhea and bleeding

Local complications – most patients

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



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

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

Hematologic, Coagulation, and Metabolic Abnormalities

Prevalence of anemia in IBD patients is up to 74%

Anemia may present as 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

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

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

Signs and Symptoms

Ulcerative Colitis

- Bloody diarrhea (hematochezia)
- Fever and tachycardia
- Abdominal/rectal cramping (tenesmus)
- Frequent bowel movements/rectal urgency
- Weight loss
- Ocular involvement
- Arthritis

Crohn's Disease

- Chronic/nocturnal diarrhea
- Abdominal pain
- Malaise, fever, night sweats
- Frequent bowel movements
- Hematochezia (less common)
- Weight loss
- Ocular involvement
- Arthritis

Quality of Life

Significant functional impairment

Social and emotional support

Financial stress

Increased risk of anxiety and major depressive disorder

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

Physical Examination and Gross Pathology

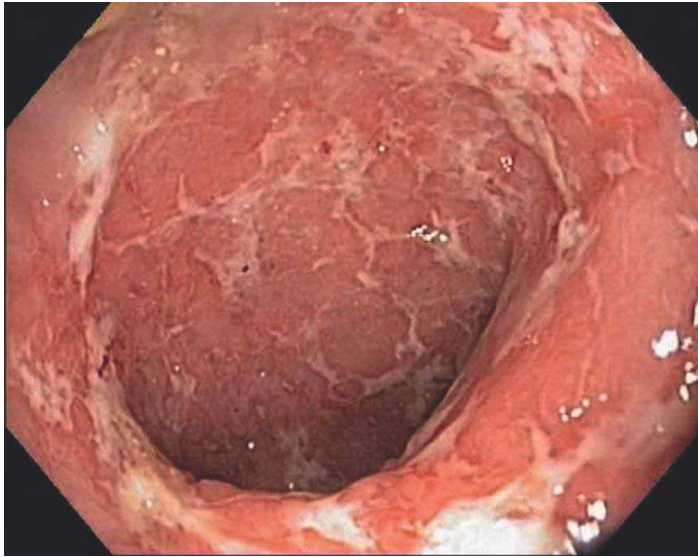
| Ulcerative Colitis | Crohn's Disease |
|--|---|
| Rectal disease (almost always), not perianal | Entire gastrointestinal tract affected; may spare the rectum; anal fissures and perirectal abscesses are common |
| Diarrhea; gross bleeding is more common | Diarrhea |
| Colicky abdominal pain | Abdominal 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

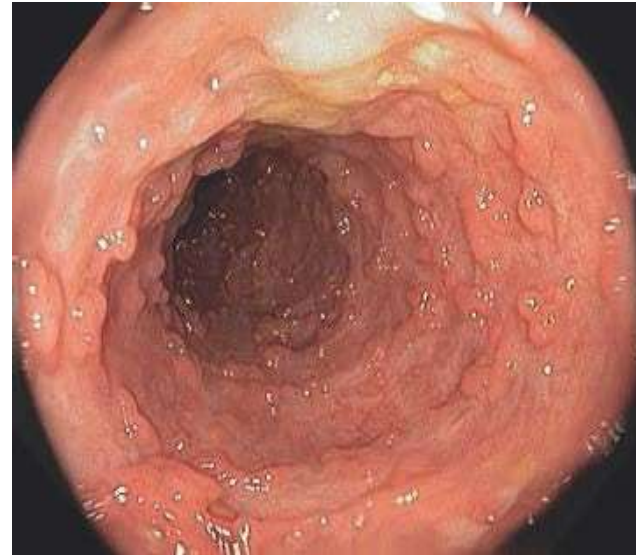
In some patients, the disease cannot be differentiated

Gross Pathology: Bowel Wall Appearance

Ulcerative Colitis

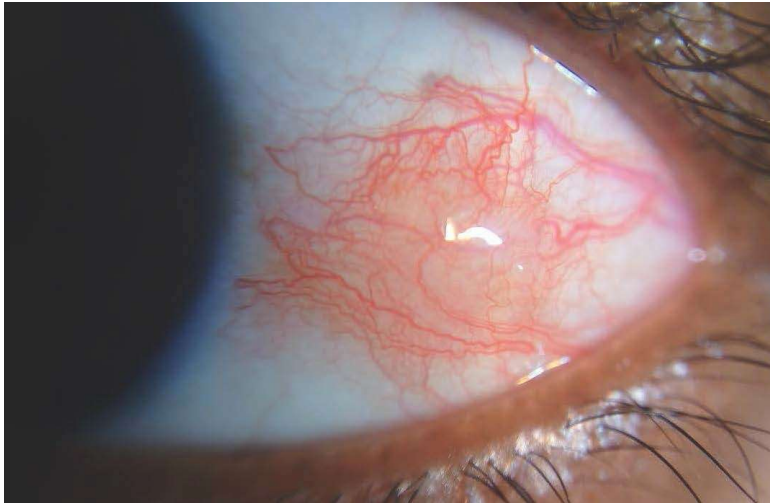


Crohn's Disease

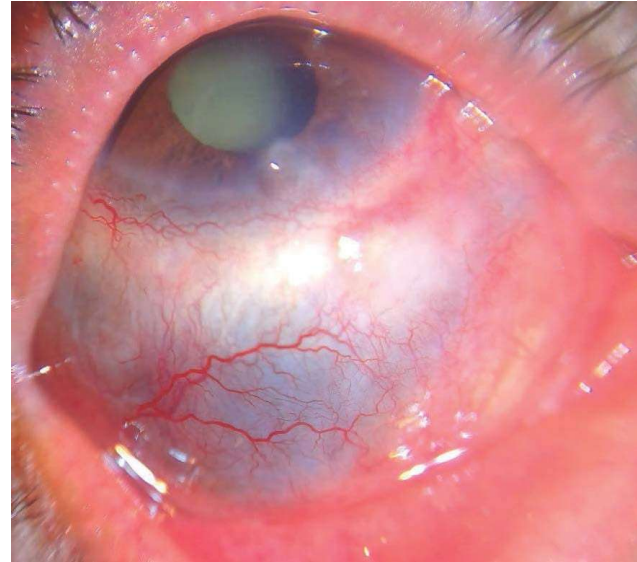


Ocular Involvement

Episcleritis



Scleritis



Dermatologic Involvement



Pyoderma Gangrenosum

Source: Goldsmith LA, Katz SI, Gilchrist BA, Paller AS, Leffell DJ, Wolff K: *Fitzpatrick's Dermatology in General Medicine, 8th Edition*: www.accessmedicine.com

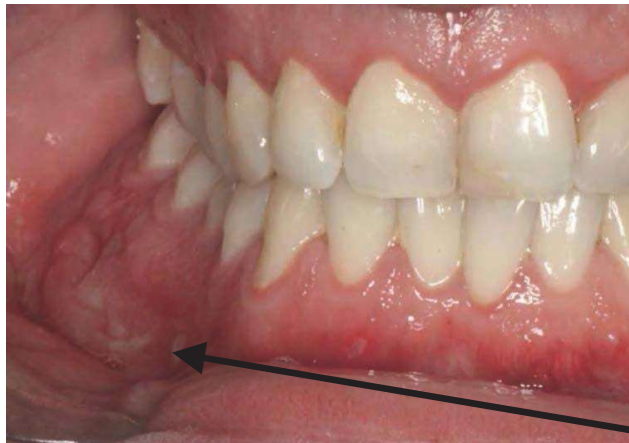
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Erythema Nodosum



Source: Wolff K, Johnson RA: *Fitzpatrick's Color Atlas and Synopsis of Clinical Dermatology, 6th Edition*: <http://www.accessmedicine.com>

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**Aphthous Ulcers
(with cobblestoning)**

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



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

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) (?)

Disease classification

| Class | Ulcerative Colitis | Crohn's Disease | Class |
|-----------|--|---|--|
| Mild | <ul style="list-style-type: none"> • <4 stools/day • no systemic involvement • normal ESR | <ul style="list-style-type: none"> • ambulatory • tolerating po intake • well-hydrated • no systemic involvement • <10% weight loss | <p>Mild to Moderate</p> <p>CD AI 150-220</p> |
| Moderate | <ul style="list-style-type: none"> • >4 stools/day • minimal systemic involvement | <ul style="list-style-type: none"> • systemic involvement (including fever, significant weight loss) • abdominal tenderness • nausea/vomiting • anemia | <p>Moderate to Severe</p> <p>CD AI 220-450</p> |
| Severe | <ul style="list-style-type: none"> • >6 stools/day with blood • significant systemic involvement (fever, tachycardia, anemia) • elevated ESR | <ul style="list-style-type: none"> • persistent symptoms despite steroids or biologics • high fevers • persistent vomiting • intestinal obstruction • peritoneal signs of involuntary guarding or rebound tenderness | <p>Severe to Fulminant</p> <p>CDAI >450</p> |
| Fulminant | <ul style="list-style-type: none"> • >10 stools/day with continuous bleeding • toxic symptoms • abdominal tenderness • anemia requiring transfusion • colonic dilation (toxic megacolon) | <ul style="list-style-type: none"> • cachexia • abscess | |

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

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

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

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 thiopurines, age > 65, EBV infection)

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

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

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

Approach to Treatment

Nonpharmacologic Therapy

- Surgery
- Nutrition
- Medications to avoid

Pharmacologic Therapy

- Target the inflammatory process
- Antimicrobials
- Iron supplementation

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

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

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

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

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

Pharmacologic Therapy

Factors to consider:

Patient symptoms

Medical history

Current medications

previous IBD therapies

Drug allergies

Extent, location and severity of disease

Aminosalicylates

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



5-ASAs are appropriate for induction and maintenance

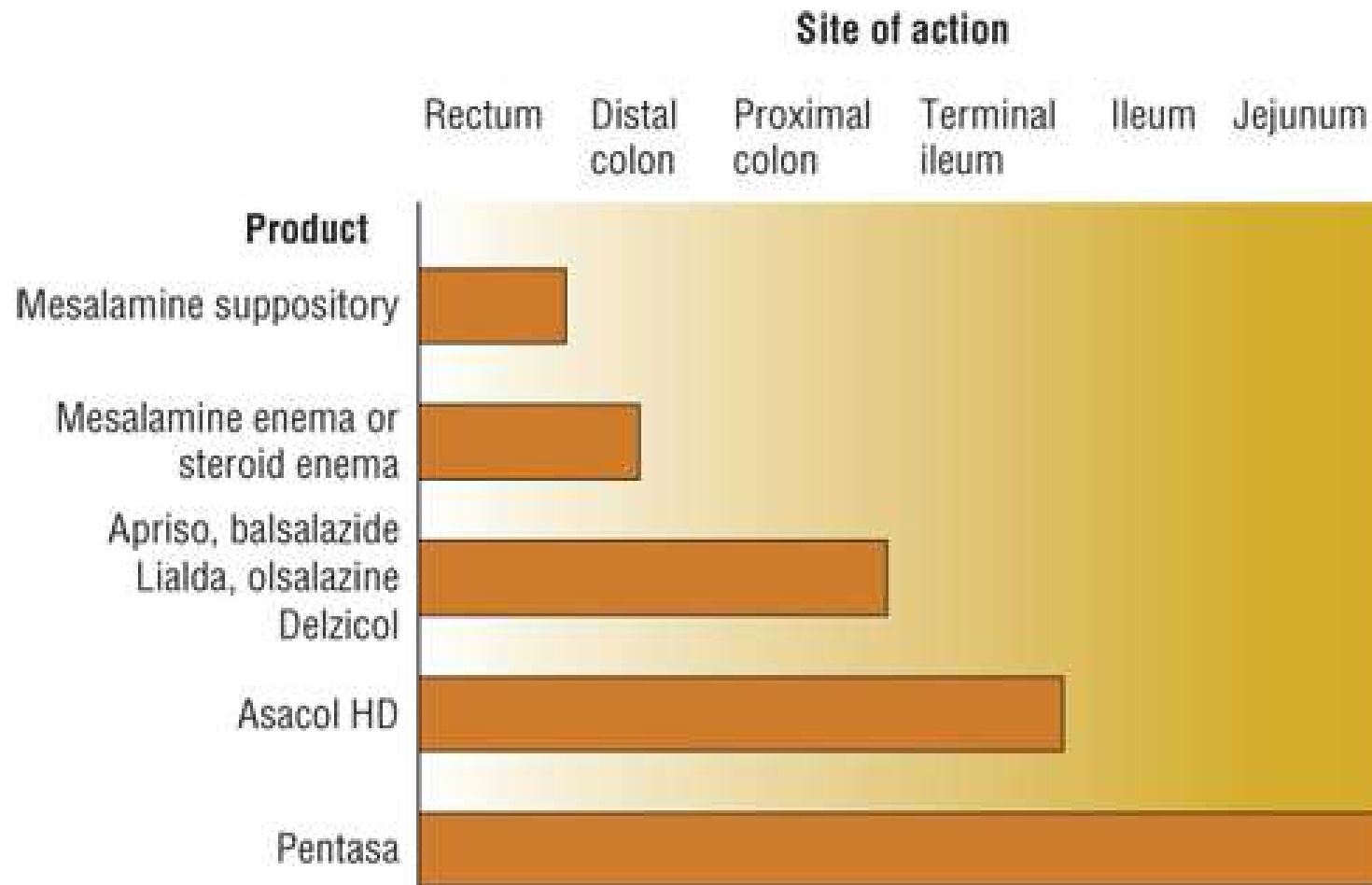


MOA – unknown...anti-inflammatory

↓ prostaglandin and leukotriene production

inhibit bacteria-induced chemotaxis - ↓TNF, ↓IL-1

free radical scavenger



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.

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.



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)

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 |

Balsalazide and Olsalazine

Balsalazide (Colazal[®], Giazol[®])

- 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

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

Administration Technique

Enemas

- 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)

Suppositories

- 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

Administration Technique

Side Position

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

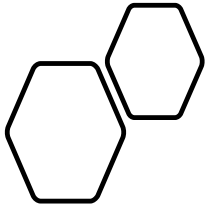


Knee-to-chest Position

- Position patient on knees, leaning down



sfRowasa[®] package insert. Alaven Pharmaceutical LLC.



Aminosalicylates: Place in therapy

Most common drugs used
for inducing and
maintaining remission



Effectiveness in UC >>>
CD



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

limit to short-term use



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: | <ul style="list-style-type: none"> Moon face Hypertension Infection Osteoporosis Cataracts Adrenal suppression | <ul style="list-style-type: none"> Acne Diabetes Osteonecrosis Myopathy Glaucoma Psychosis |
| Corticosteroids are appropriate for induction of remission ONLY | | |

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

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

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

Immunosuppressants

| Drug | Trade Names | Dose | Uses |
|--|----------------------|---|--|
| Cyclosporine | Sandimmune® | 4 mg/kg/day IV cont. infusion | CD, UC (steroid failure, induction ONLY) |
| Methotrexate (MTX) <i>Off-label use</i> | 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

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

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)

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

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%

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

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

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)

| | |
|------------------------------------|---|
| | |
| 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 |

CSA-induced hypertrichosis



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

Immunosuppressants: Role in Therapy

AZA/6-MP:

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

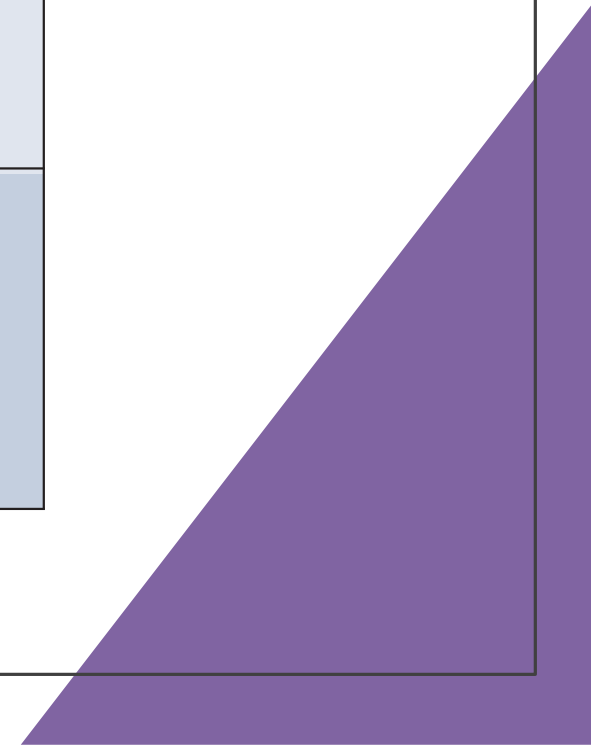
Cyclosporine (CSA):

- 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

| Drug | Counseling/Monitoring |
|------------------------------------|--|
| Azathioprine / 6-Mercaptopurine | <ul style="list-style-type: none">- May take >4 months at target dose for max effect- Avoid prolonged sun exposure- Baseline LFTs, weekly CBC |
| Cyclosporine (CSA) | <ul style="list-style-type: none">- Renal function (SCr, BUN)- BP- 4th dose trough levels (goal: 200-300 ng/mL) |
| Methotrexate (MTX) | <ul style="list-style-type: none">- Periodic CBC- LFTs (liver enzymes, albumin) ±liver biopsy- Baseline CXR- Replace folic acid |



Antibiotics

Metronidazole and Ciprofloxacin

- more effective in CD in treating mild disease

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

Probiotics?

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[®])

Tumor Necrosis Factor (TNF) Inhibitors

MOA

- Inhibits endogenous TNF α . Elevated levels of TNF α have been found in involved tissues of various disease states including CD and UC. Biological activities of TNF α 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.

| | 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 |

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

Safety Considerations & Challenges of Biologics

Heart Failure (HF)- use all anti-TNF α 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

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

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

Infliximab (Remicade[®])

Murine-human IgG₁ 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

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

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

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.

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

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

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 year^{1,2} (Secondary Non-Response)

Pharmacotherapy for IBD

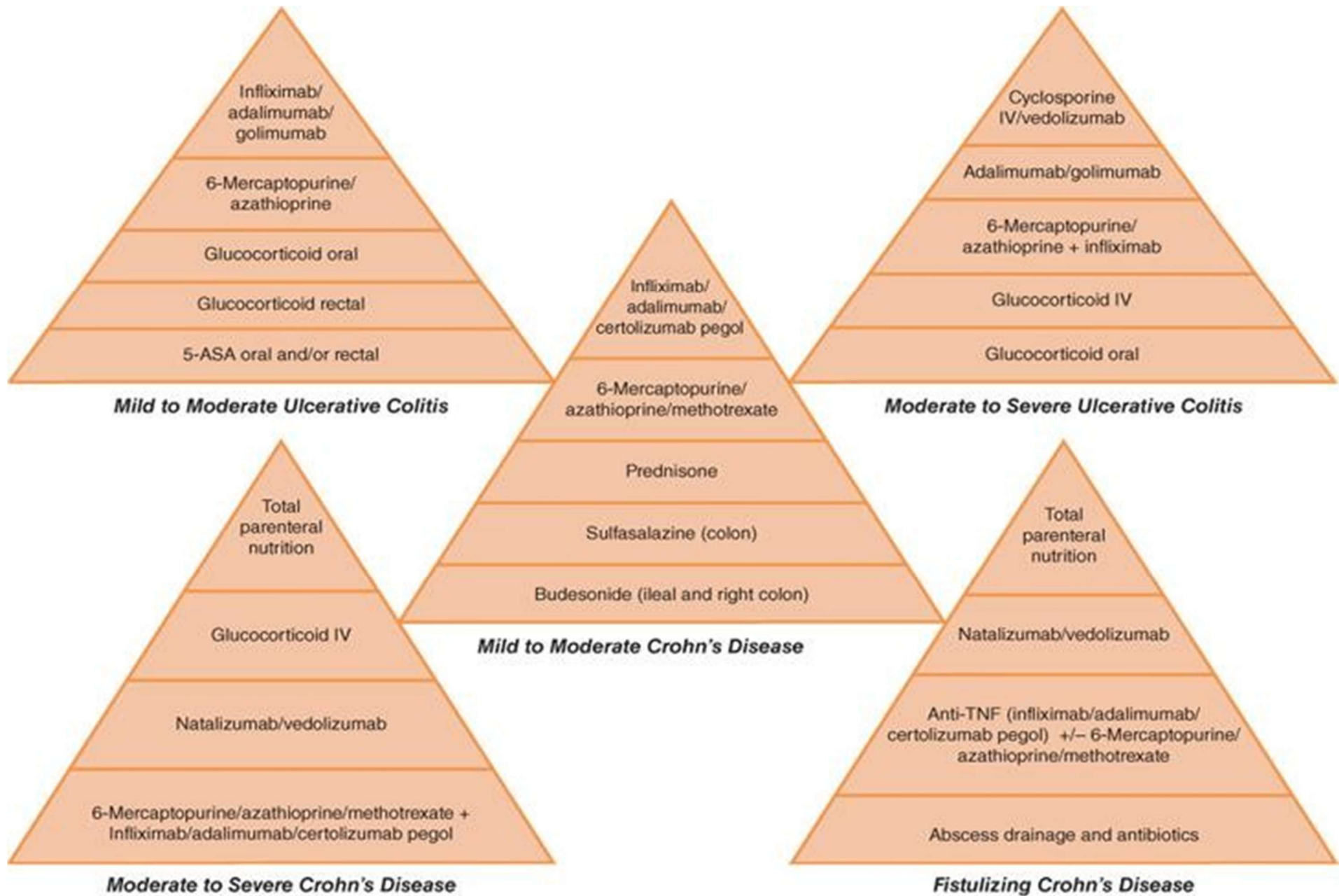
Treatment selection is dependent on the

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



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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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)

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

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

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-TNF α +/- thiopurine

Evaluate anti-TNF α +/- thiopurine response in 8-12 weeks

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

Moderate-Severe & Severe- Fulminant UC

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

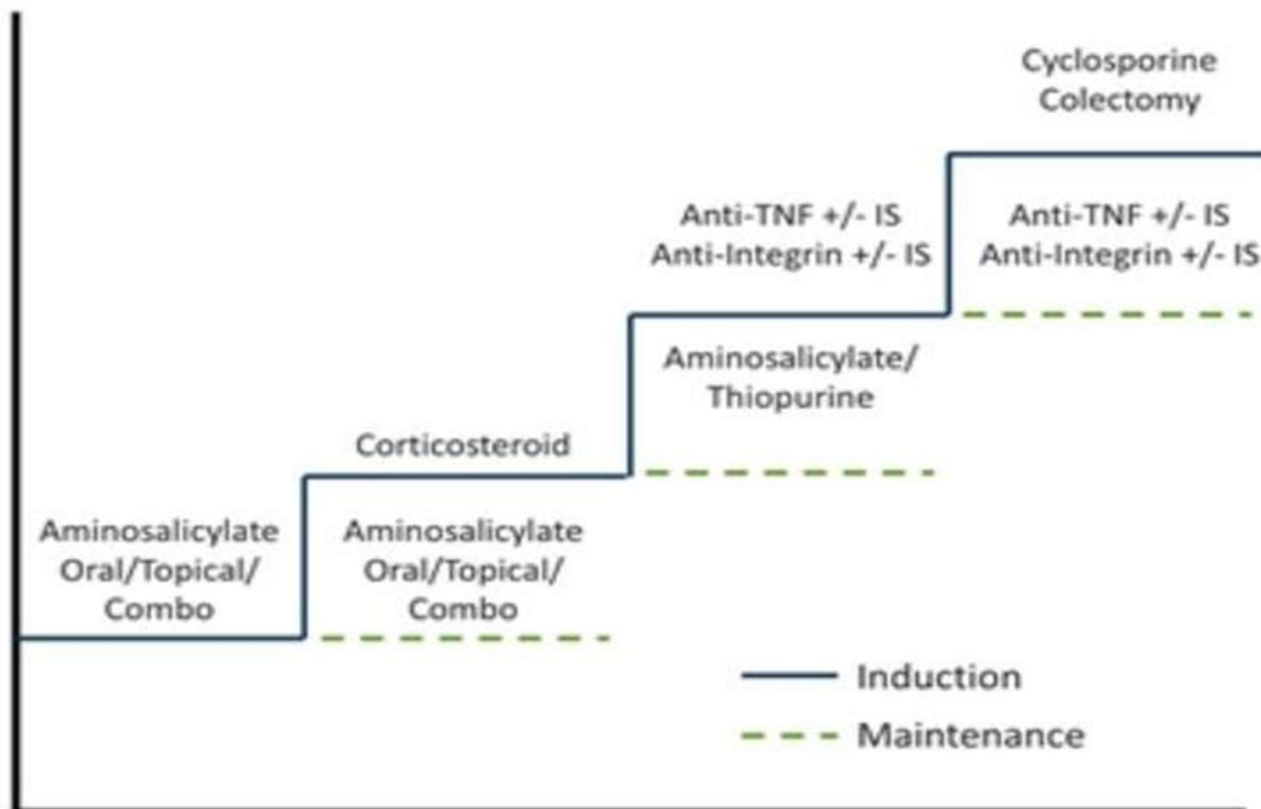
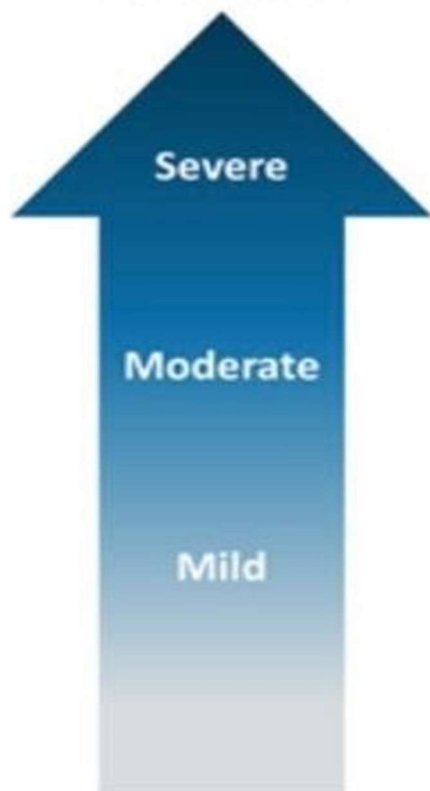
- IV corticosteroids
- Hydrocortisone 100mg IV q8h (or equivalent) x 7-10 days; conversion to PO prednisone when appropriate
- If no response after 3-5 days- Cyclosporine continuous IV 4mg/kg/day
- If no response – Infliximab, colectomy

Maintenance

- Same as 2nd line mild-moderate UC management

Crohns Disease

Disease Severity at Presentation



Therapy is stepped up according to severity at presentation or failure at prior step.

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

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

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

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

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

Remission/Maintenance Therapy for Crohn's Disease

No role for long-term corticosteroid use



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graph TD; A[No role for long-term corticosteroid use] --> B[First Line: Azathioprine or 6-mercaptopurine plus or minus oral aminosalicylate]; B --> C[Second Line: TNF-inhibitor plus or minus azathioprine or 6-mercaptopurine or methotrexate (if intolerant of AZA or 6-MP)]; C --> D[Alternative: Vedolizumab];
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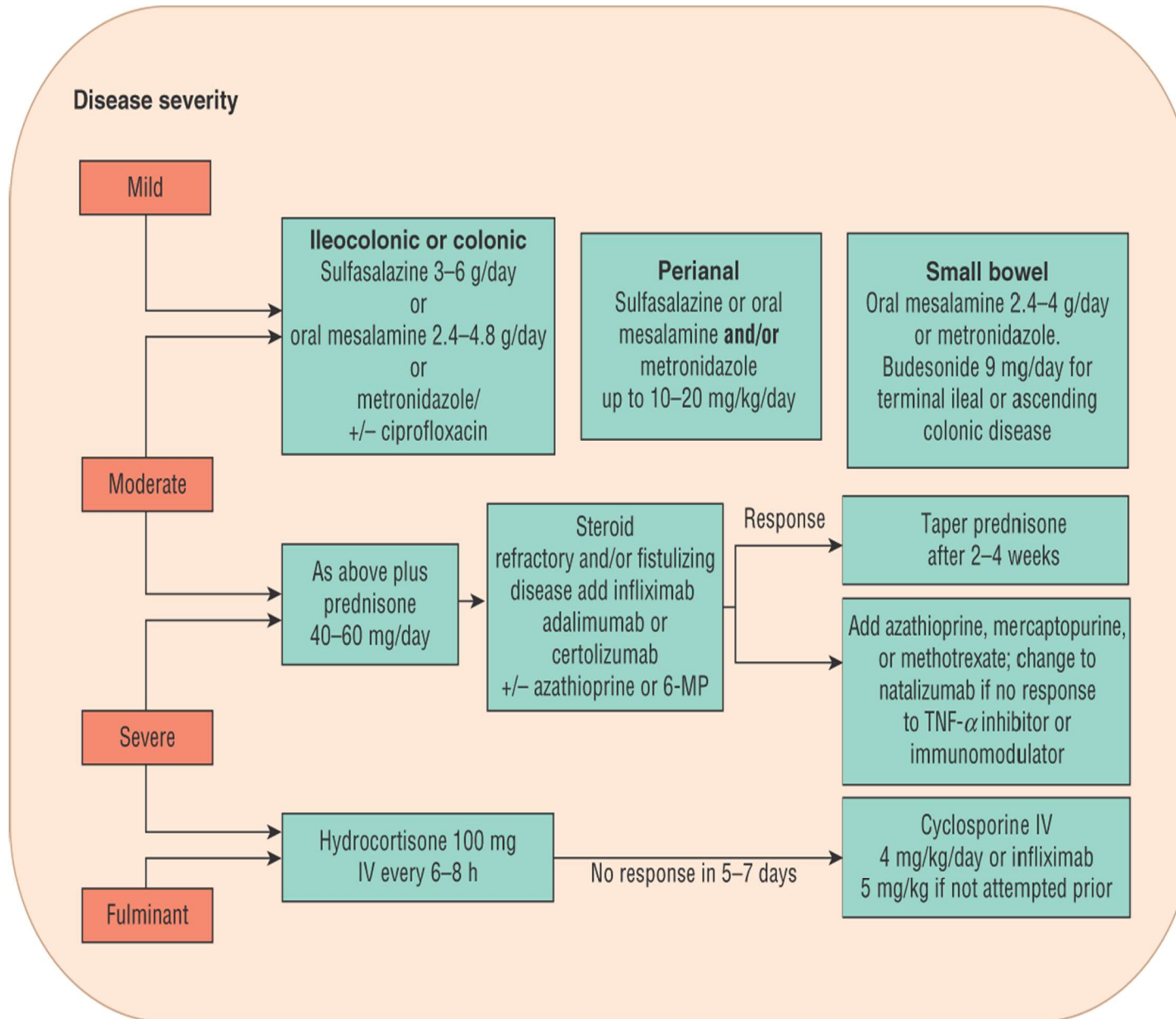
First Line: Azathioprine or 6-mercaptopurine plus or minus oral aminosalicylate

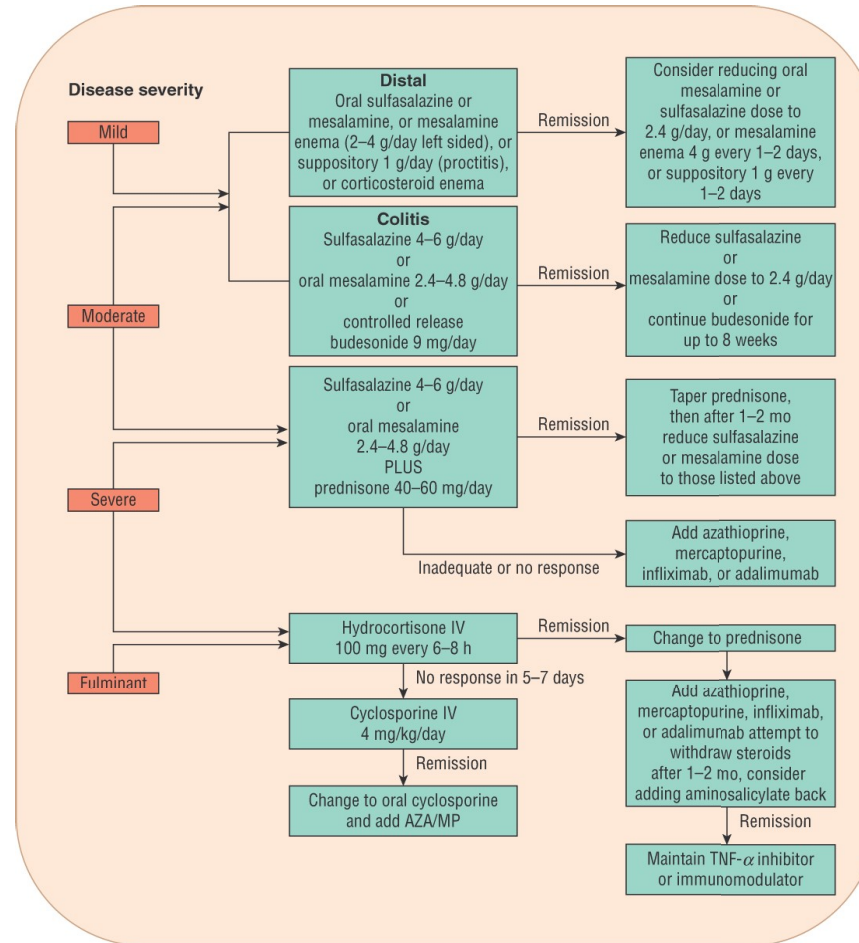
- If intolerant to AZA or 6-MP, then try methotrexate

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

Alternative: Vedolizumab

Crohn's Disease





Source: D'Inca JT, Talbert RL, Yee GC, Matzke GR, Wells SG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition*; www.accesspharmacy.com; Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Ulcerative Colitis