Chronic Bowel Diseases

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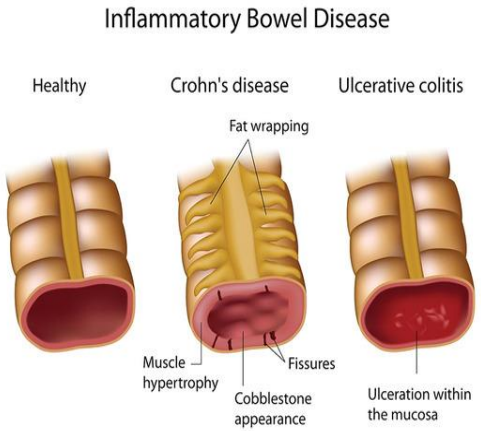
Chronic inflammatory bowel disease (IBD) includes: (ulcerative colitis & Crohn's disease).

1. **Corticosteroids:** prednisolone.
2. **Immunosuppressive agents:** azathioprine , 6mercaptopurine.
3. **Aminosalicylates.**
4. **Biological drugs**



Aminosalicylates

Up to 80% of unformulated, aqueous 5-ASA is absorbed from the small intestine & does not reach the distal small bowel or colon in appreciable quantities

- **Azo compounds**
- **Mesalamine compounds**

Mechanism of action:

- ✓ 5-ASA inhibits inflammatory mediators derived from both the cyclooxygenase &lipooxygenase pathways.
- ✓ Interferes with the production of inflammatory cytokines.
- ✓ Inhibits the activity of nuclear factor-k_B (NF-k_B), an important transcription factor for pro-inflammatory cytokines.
- ✓ Inhibits cellular functions of natural killer cells, mucosal lymphocytes, and macrophages.
- ✓ It may scavenger reactive oxygen metabolites.

Azo compounds

Prodrugs:

5-ASA bound by an azo (N=N) bond to an inert compound or to another 5- ASA molecule

Azo markedly reduces the absorption of the parent drug from the small intestine.

This bond is **stable in the upper GI tract** but is **broken by colonic bacteria (azoreductase), releasing the** active drug in the colon and terminal ileum. To act locally on target sit.

	Sulfasalazine	Olsalazine	Balsalazide
	(5-ASA+Sulfapyridine).	**(two molecules of 5-ASA).**	**(5-ASA + 4-aminobenzol-β- alanine).**
pk	10% is absorbed. After azoreductase, >85% of **sulfapyridine** is absorbed, undergoes hepatic metabolism, Metabolite is excreted by the kidney	Not absorbed in small intestine Cleaved in colon → releases 2 active 5-ASA molecules, Minimal systemic absorption → fewer systemic effects	<1% is absorbed, After azoreductase, a small amount of systemic absorption occurs
Adverse effects	>40% cannot tolerate therapeutic doses (**sulfapyridine)** 1. GIT upset, headache, arthralgia, bone marrow suppression & malaise 2. Hypersensitivity (fever, exfoliative dermatitis, pancreatitis, pneumonitis, hemolytic anemia, pericarditis, or hepatitis). 3. Reversible oligospermia 4. Impairs folate absorption	may cause secretory diarrhea (10%). Hypersensitivity (rare).	•Generally well tolerated Mild GI symptoms: Diarrhea •Abdominal pain Rare hypersensitivity Due to better tolerability its often used

Mesalamine compounds

Package of 5-ASA itself in various ways to deliver it to different segments of the small or large bowel.

Pentasa: contains timed-release microgranules that release 5-ASA throughout the small intestine.

Asacol: has 5-ASA coated in pH-sensitive resin that dissolves at pH 7 (the pH of the distal ileum & proximal colon).

Rowasa (enema formulations) &

Canasa (suppositories): delivers a high concentration of 5-ASA to the rectum & sigmoid colon.

Pk: 20-30% of 5-ASA is absorbed.

- 5-ASA undergoes N-acetylation in the liver and gut epithelium.
- Metabolite is excreted by the kidneys.

A/E: Interstitial nephritis (rare, high doses of ***mesalamine)***

Therapeutic uses

1- **First-line** agents for treatment of mild to moderate active ulcerative colitis

2-Crohn's disease involving the small bowel **mesalamine** compounds, which release 5-ASA in the small intestine, have an advantage over azo compounds

3- Ulcerative colitis or Crohn's colitis that extends to the proximal colon, both azo & mesalamine compounds are useful.

4- Ulcerative colitis or Crohn's disease confined to the rectum or distal colon, suppositories or enema are useful.

Biological agents

class	members	MOA	pk	A/E
. Anti–TNF-α	Infliximab adalimumab	• Bind TNF-α (soluble + membrane-bound) • Prevent TNF receptor activation • ↓ NF-κB signaling → ↓ cytokines (IL-1, IL- • Induce apoptosis of activated T-cells	i.V or s.c	-infections (TB, fungal) -Infusion/injection reactions Autoantibodies (lupus-like) ↑ lymphoma risk
Anti-Integrin Agents	Vedolizumab (gut selective) Natalizumab	• Block integrins on lymphocytes • Prevent binding to endothelial adhesion molecules↓ leukocyte migration into gut mucosa	i.v	Vedolizumab: safer, mild infections Natalizumab: risk of PML (JC virus reactivation)
3. Anti–IL-12 / IL-23 Agents	Ustekinumab Risankizumab	• Block p40 subunit (IL-12 & IL-23) → (ustekinumab)or selectively block IL-23 (risankizumab) so ↓ Th1 & Th17 cell differentiation and ↓ cytokines (IL-17, IFN-γ)	i.V and s.c	Infections (less than anti-TNF) Injection site reactions Rare malignancy risk
Selective IL-23 Inhibitors	Guselkumab Mirikizumab	• Block p19 subunit of IL-23 • More selective → ↓ Th17 activation		Better safety profile Less immunosuppression
JAK Inhibitors	Tofacitinib	• Inhibit JAK-STAT pathway • Block intracellular signaling of multiple cytokines:IL-2, IL-6, IL-12, IL-23,	Oral Rapid onset	Hyperlipidemia Thrombosis risk Serious infections

Recent protocols to treat IBD

1- Advanced Therapy ("Top-Down"):

New guidelines recommend early biologics , Especially in moderate–severe disease (Anti-TNF (e.g., infliximab)Anti-integrin (vedolizumab)Anti-IL-23 (risankizumab, guselkumab)JAK inhibitors (upadacitinib)

2. Step- up protocol:

- Low-risk patients:5-ASA (mainly UC) and Short-course steroids
- Moderate–Severe: Start biologic / targeted therapy early
- High-risk features: Early biologics ± immunomodulatory Combination therapy preferred
- Acute Severe Ulcerative Colitis: IV corticosteroids (first-line)If no response →Infliximab

N.B: Before starting advanced therapy: TB screening, Hepatitis B screening, Vaccination update

Irritable bowel syndrome: IBS

Functional Idiopathic chronic relapsing disorder characterized by:

- Abdominal discomfort (pain, bloating, distention, or cramps).
- Alteration of bowel habits (diarrhea, constipation, or both).
- Common in woman before 50 years.

Diagnosis by symptoms:

started at least 6 months before diagnosis

Recurrent abdominal pain or discomfort at least 3 days/ months in the last 3 months

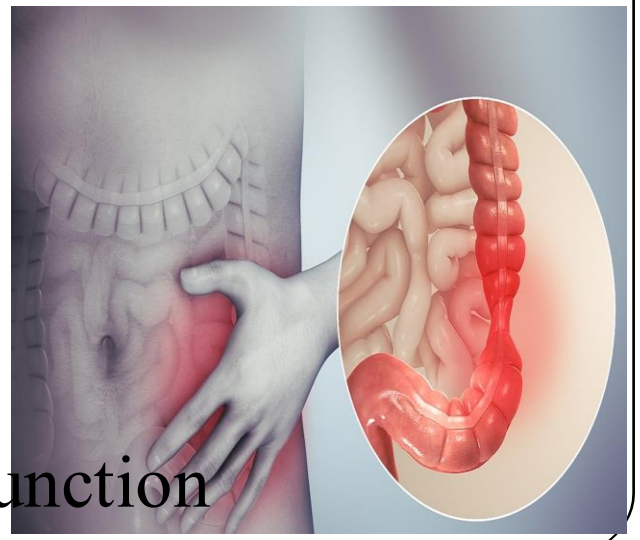
Associated with 2 or more of the following

Improvement with defecation

Change in frequency or form of stool

Goal of therapy:

Relieving abdominal pain, discomfort and improving bowel function



A-Predominant diarrhea (Diarrhea-predominant IBS)

B-Predominant constipation (Constipation- predominant IBS)

C- Chronic abdominal pain:

D. Spasmolytics (Antispasmodics)

Non pharmacological treatment:

1- Cognitive behavioral therapy

2- Dietary modification: such as gases forming food, low **FODMAP** diet, fiber supplementations

A-Predominant diarrhea (Diarrhea-predominant IBS):

- Anti-diarrheal agents, diphenoxylate and loperamide.
- **Alosetron**

5-HT3 antagonist.

- Binds with higher affinity and dissociates more slowly from 5-HT3 R than other 5-HT3 antagonists (long duration).
- Uses: Women with severe irritable bowel syndrome with diarrhea.
- Dose: 1mg once or twice daily.

A/E:

- Rare but serious G.I.T. toxicity may occur:
- Constipation (↑30%).
- Episodes of ischemic colitis (3 per 1000).
- Restricted to women withsevere diarrhea- predominant IBS.

B-Predominant constipation (Constipation- predominant IBS)

- Fiber supplements (however, ↑gas production may exacerbate bloating and abdominal discomfort).
- Laxative: psyllium, PEG- based laxative, Osmotic laxatives, ***milk of magnesia*.**
- **Avoid stimulant laxative as it worsen abdominal pain**
- **Lubiprostone (cl channel activator), linaclotide mosapride, (5HT4 partial agonist)**
- ***Tegaserod* (partial 5-HT_4 agonist).**

Used in restricted cases of irritable bowel syndrome with constipation (IBS-C)

Chronic idiopathic constipation (selected cases)

Adverse Effects: Diarrhea, Abdominal pain, Headache.

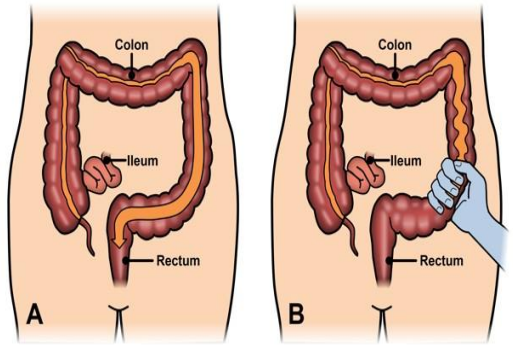
Serious: Myocardial infarction, Stroke, Unstable angina

Contraindications: Ischemic heart disease, Stroke or TIA, Severe renal/hepatic impairment, Bowel obstruction.

C- Chronic abdominal pain:

- **TCAs: Low doses** of Tricyclic antidepressants (amitriptyline or desipramine, 10-15mg/d).
- At these doses, these agents have no effect on mood but may alter central processing of visceral afferent information.
- Anti-cholinergic effects → reduce stool frequency & liquidity of stool.
- Alter receptors for enteric neurotransmitters such as serotonin, affecting visceral afferent sensation.
- **SSRIs** as fluoxetine, citalopram,

D. Spasmolytics (Antispasmodics):



Short term relief of abdominal pain

1- **Anticholinergic**

Hyoscine

Dicyclomine, dicycloverine

Clidinium (+ chlordiazepoxide =librax)

N.B: BZ WITH MORPHIN CAUSE C.N.S DEPRESSON

2- Direct spasmolytics

- Volatiles oils (peppermint oil) .
- Khellin.
- Papaverine.
- Aminophylline.
- Nitrites.


THANK YOU