Drugs Used to Treat Inflammatory Bowel Disease

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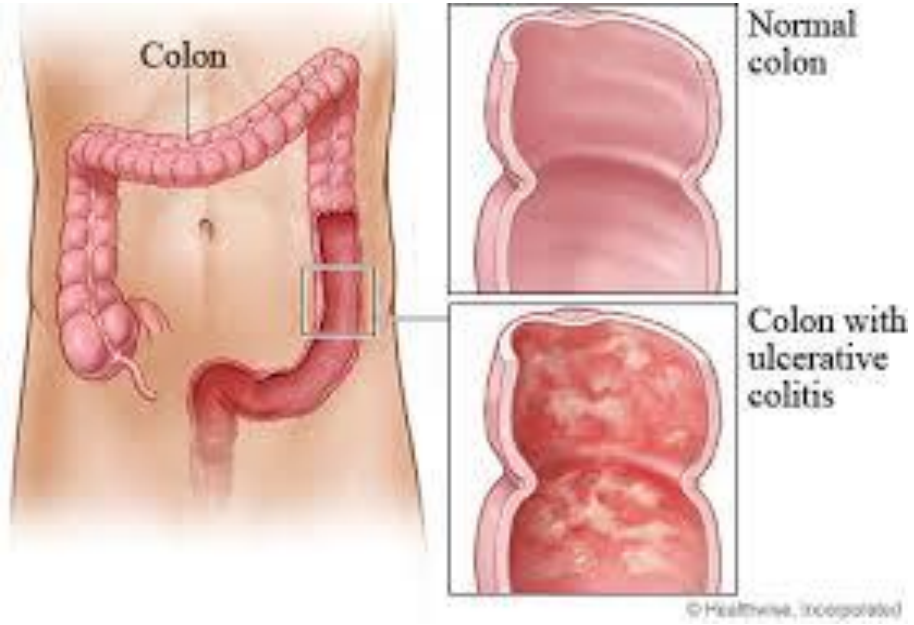
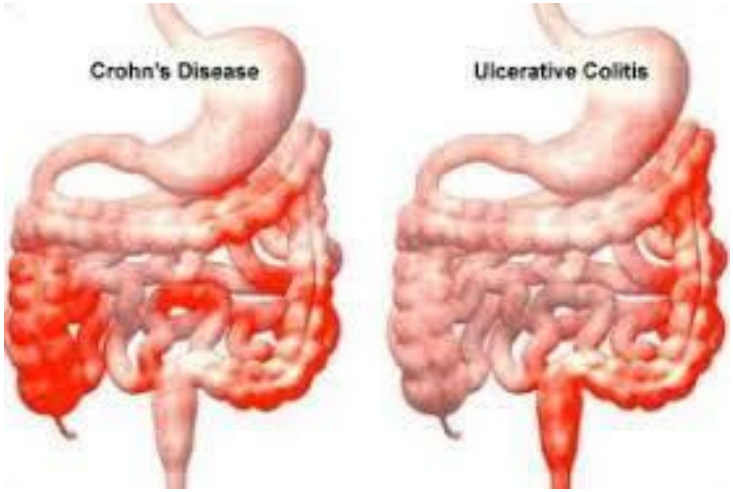
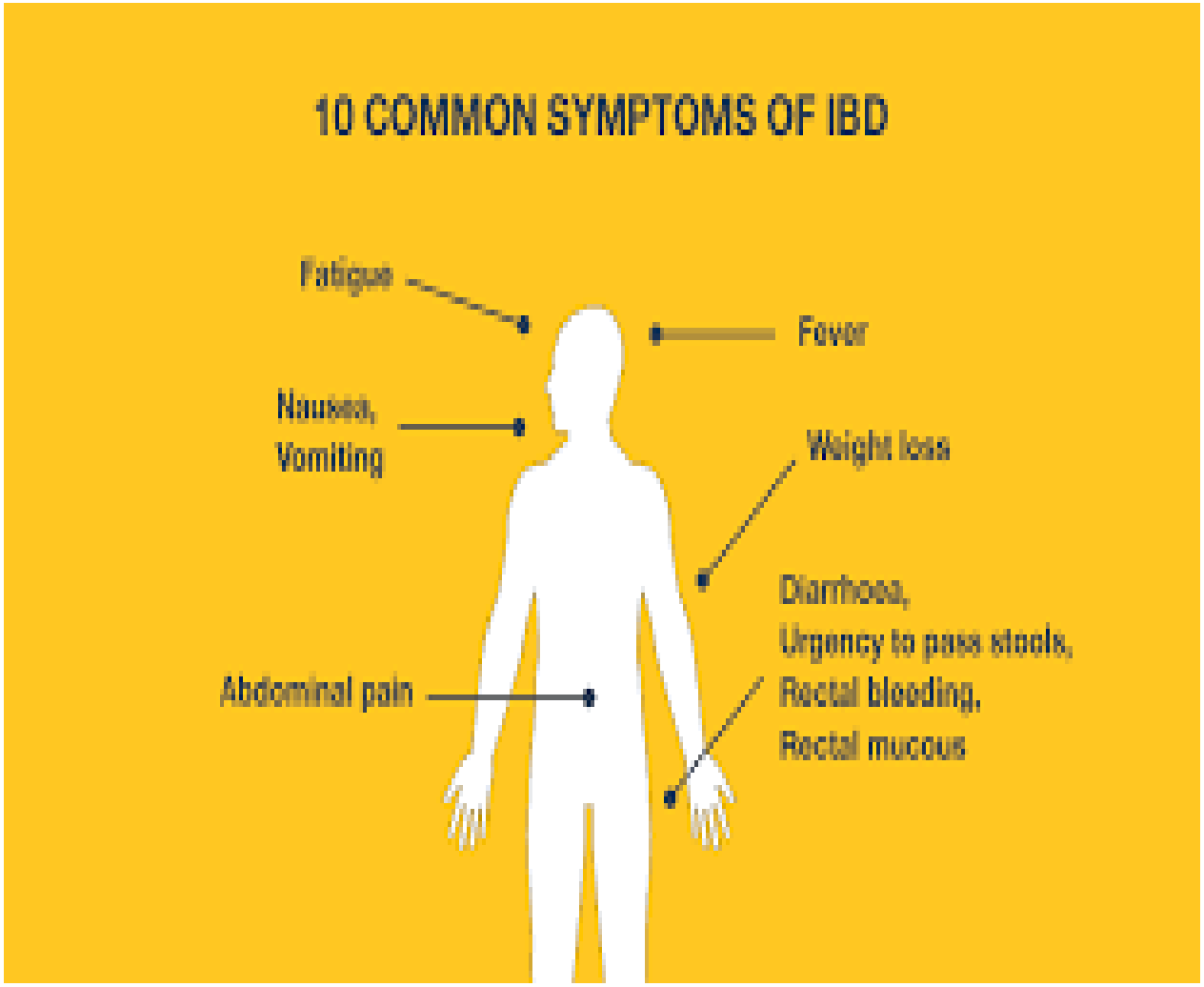


Inflammatory bowel disease (IBD) is a group of idiopathic chronic intestinal conditions characterized by immune mediated GI tract inflammation in response to bacterial antigens in the intestinal lumen. The most common subtypes of IBD **are Crohn's disease** (CD) and **ulcerative colitis (UC)**. CD can **affect any portion of the GI tract from the mouth to the anus in a noncontinuous fashion and is characterized by transmural inflammation**. UC usually affects the **rectum**. It may extend continuously to affect other parts of the colon, and is characterized by inflammation limited to **the mucosal layer**

Remission of IBD can be induced with the use of rectal and oral 5-aminosalicylates (5-ASAs), corticosteroids (rectal, oral locally delivered and systemic), and biologic agents (TNF-α inhibitors, α-4 integrin inhibitors, and the IL-12/23 inhibitor. Drugs used to maintain remission are the same as those immunomodulators used for induction. The (*azathioprine*,*6mercaptopurine*, and *methotrexate*) are **maintenance of remission in** additional agents used in the IBD.




10 COMMON SYMPTOMS OF IBD
Fatigue
Fever
Nausea,
Vomiting
Weight loss
Diarrhoea,
Urgency to pass stools,
Rectal bleeding,
Rectal mucous
Abdominal pain

A. 5-Aminosalicylates

Two types of 5-ASA compounds exist, the azo compounds and the mesalamine compounds. The azo compounds are prodrugs that consist of a 5-ASA molecule bound via an azo (N=N) bond to another molecule. These include balsalazide , olsalazine, and sulfasalazine . The oral **mesalamine** compounds consist of single 5-ASA molecules enclosed within an enteric coat or a semipermeable membrane. The first 5-ASA agent used in the treatment of IBD, **sulfasalazin**e, is a prodrug consisting of 5-ASA linked to sulfapyridine. Colonic bacteria cleave sulfasalazine to produce 5-ASA (mesalamine) and sulfapyridine . When it became known that 5-ASA was responsible for the efficacy of sulfasalazine while sulfapyridine was mainly responsible for its adverse effects

unlinked 5-ASA is rapidly absorbed, with only 20% reaching the site of action in the terminal ileum and colon. Therefore, other azo bonded compounds and various formulations of *mesalamine* were developed to limit absorption of 5-ASA in the proximal GI tract and allow increased drug delivery to the colon

DRUG	BRAND(S)	ROUTE	DOSING FREQUENCY	FORMULATION	SITE OF DELIVERY
Balsalazide	Colazal	PO	Three times daily	5-ASA azo bonded to inert carrier molecule; release dependent on cleavage by colonic bacteria	Colon
Mesalamine	Apriso	PO	Once daily	pH-dependent (≥ 6) delayed release with extended-release matrix core	Colon
	Asacol, Asacol HD	PO	Three times daily	pH-dependent (≥ 7) delayed release	Distal ileum, colon
	Canasa	Rectal	Once daily	Suppository	Rectum
	Lialda	PO	Once daily	pH-dependent (≥ 7) delayed-release multimatrix system	Distal ileum, colon
	Pentasa	PO	Four times daily	Ethyl cellulose membrane controlled-release micropellets	Entire small intestine, colon
	Rowasa	Rectal	Once daily	Liquid enema	Rectum, sigmoid colon
Olsalazine	Dipentum	PO	Twice daily	5-ASA azo bonded to another 5-ASA molecule; release dependent on cleavage by colonic bacteria	Colon

Actions:

The 5-ASAs exhibit anti-inflammatory and immunosuppressive properties that are the main determinants of their efficacy in IBD. The exact mechanism of action of 5-ASA is unknown but is thought to be due in part to 1) inhibition of cytokine synthesis, 2) inhibition of leukotriene and prostaglandin synthesis, 3) scavenging of free radicals, 4) inhibition of T-cell proliferation, activation, and differentiation, and 5) impairment of leukocyte adhesion and function.

Therapeutic uses

The 5-ASA drugs are the mainstay of treatment in UC. All 5-ASA formulations and *sulfasalazine* are indicated in UC for induction and maintenance of remission. Current guidelines recommend these agents as first line for mild– moderate disease. Use of 5-ASA drugs in CD is limited due to a general lack of efficacy.

Adverse effects

Adverse effects of *sulfasalazine* occur in up to 45% of patients, with the majority due to the sulfapyridine component. Headache, nausea, and fatigue are most common and are dose related. Serious reactions include hemolytic anemia, myelosuppression, hepatitis, pneumonitis, nephrotoxicity, fever, rash, and Stevens-Johnson syndrome. Treatment should be discontinued at the first sign of skin rash or hypersensitivity. *Sulfasalazine* reversibly impairs male fertility. *Sulfasalazine* also inhibits intestinal folate absorption, and folate supplementation is recommended with chronic use

Watery diarrhea occurs in up to 20% of patients treated with *olsalazine*.

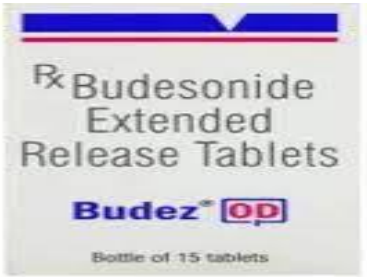
Some formulations of *mesalamine* depend on pH for their release and coadministration of drugs

that increase pH (for example, PPIs, H2 receptor antagonists, and antacids) may result in increased systemic absorption and premature release of 5-ASA before reaching the site of action. Concomitant use should be avoided or another formulation of 5-ASA that is non-pH dependent should be used (for example, *olsalazine*, *balsalazide*).

B. Corticosteroids

Corticosteroids are used in IBD for their anti-inflammatory effects as they are in other inflammatory conditions . Although very effective at inducing remission in IBD, long-term maintenance with corticosteroids should be avoided due to the deleterious effects of chronic use. Rectal formulations (for example, *hydrocortisone*

enema and *budesonide* foam) have fewer adverse effects than systemic steroids but use is limited to left-sided disease in UC.



Biologic agents

The TNF-α inhibitors, α-4 integrin inhibitors, and the IL-12/23 inhibitor are biologic agents used in the management of IBD Use of these agents is associated with an increased risk for infection. Patients should be evaluated for tuberculosis and treatment for latent TB should be considered prior to use of these drugs. Many of these agents have other therapeutic indications such as rheumatoid arthritis or psoriasis.

TNF-α inhibitors:

TNF-α inhibitors are parenteral agents that are effective for both induction and maintenance of remission in IBD.

***Infliximab* and *adalimumab* are indicated in both moderate–severe CD and UC**. The TNF-α inhibitors are generally reserved as second-line agents in patients with UC who have failed 5-ASAs, are unresponsive to or dependent on corticosteroids, or who present with more severe disease. In CD, the TNF-α inhibitors have a first-line role in patients with moderate–severe disease and those at higher risk of progression and worse outcomes

Immunomodulators:

The immunomodulator drugs most often used in IBD are *methotrexate* and the thiopurines *azathioprine* and *6- mercaptopurine* (*6-MP*). *Methotrexate* (*MTX*) also has therapeutic applications in cancer, rheumatoid arthritis, and psoriasis and *azathioprine* is sometimes used in kidney transplant

1. Methotrexate

MTX is a structural analogue of folic acid that inhibits the production of folinic acid.Only intramuscular or subcutaneous administration of *MTX* has efficacy in CD. *MTX* is a recommended monotherapy option for maintenance of remission in CD, but is not recommended in maintenance for UC. Common adverse effects of *MTX* are headache, nausea, vomiting, abdominal discomfort, serum aminotransferase elevations, and rash. Daily administration of folic acid is effective at reducing the incidence of GI adverse effects and is recommended in patients receiving *MTX*.

2. Thiopurines

The thiopurines *azathioprine* and *6-mercaptopurine* (*6-MP*) are **oral medications that have corticosteroid-sparing effects in patients with UC and CD. They are considered first line as monotherapy for maintenance of remission**.

Use of thiopurines in IBD is limited by concerns of toxicity, including bone marrow suppression and hepatotoxicity.

Monitoring of complete blood counts and liver function tests is recommended in all patients treated with a thiopurine.

Thanks


"لا يليق بالعلاقات المسمومة إلا البتر
مُجاملة الأفاعي جريمة."
- دوستويفسكي