Inflammatory bowel diseases

Dr. Balázs Varga

University of Debrecen, Faculty of Medicine,
Department of Pharmacology and Pharmacotherapy

Definition and types

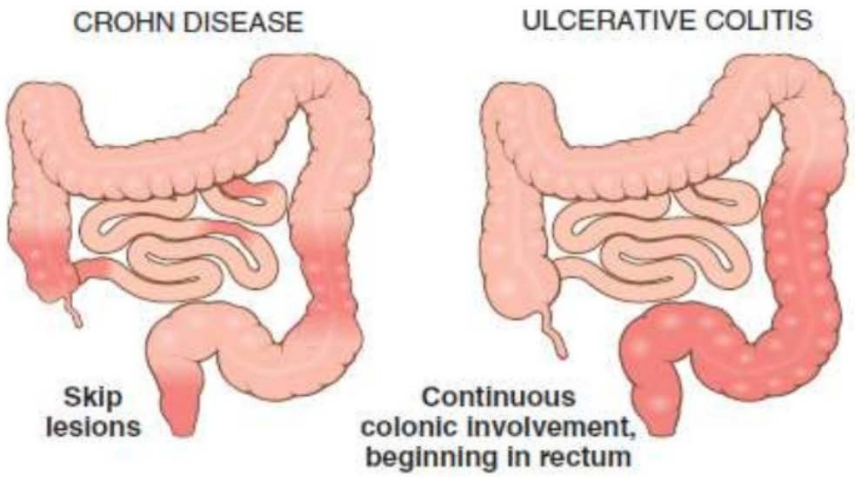
- Inflammatory bowel disease (IBD) is a spectrum of chronic, idiopathic, inflammatory intestinal conditions.

- Two major types:
  - Ulcerative colitis
  - Crohn's disease

- Two distinct pathogenetic mechanisms
- Some similarities in clinical manifestations &
- Both respond to similar drugs

Signs and symptoms I.

- Both may present:
  - Abdominal pain
  - Diarrhoea
  - Rectal bleeding
  - Sever internal cramps/muscle spasms (pelvic region)
  - Weight loss
  - Anemia



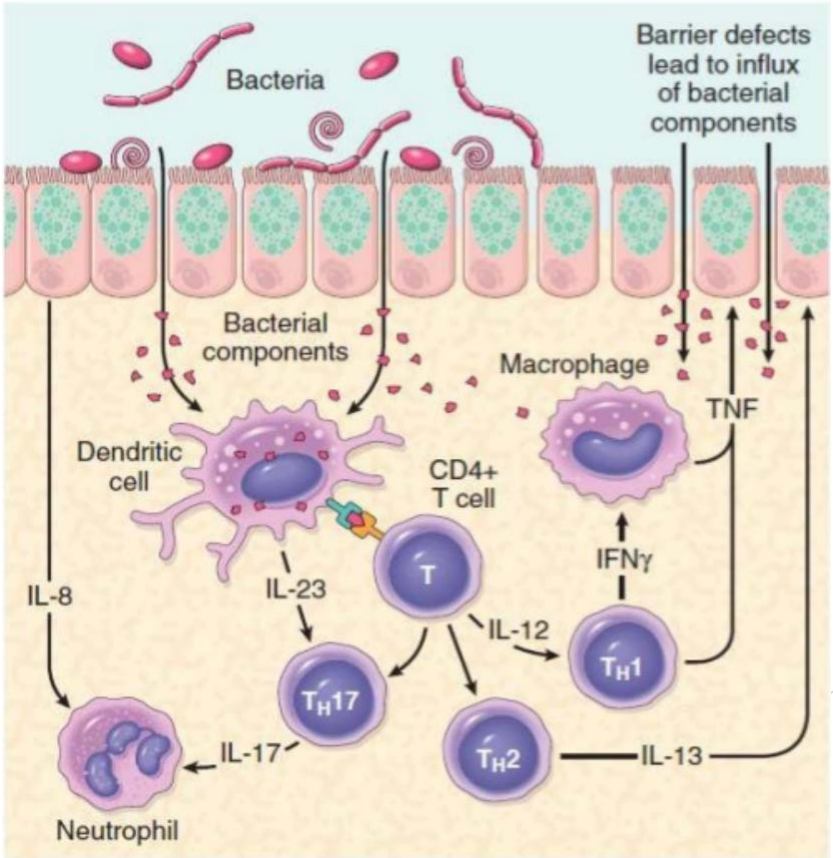
Signs and symptoms II.

	Crohn's disease	Ulcerative colitis
Defecation	Often porridge-like, sometimes steatorrhea	Often mucus-like and with blood in stool
Tenesmus	Less common	More common
Fever	Common	Indicates severe disease
Fistulae	Common	Seldom
Weight loss	Often	More seldom
Location	„mouth to anus" Commonly ileocolonic region affected; Often rectum-sparing	Colon; usually rectum is also involved
Distribution of disease	Segments/patchy areas of inflammation; „skip lesions"	Continuous area of inflammation
Endoscopy	Deep serpiginous (snake-like) ulcer; stenosis common; granulomas on biopsy	Continuous ulcer; mucosal friability & mucopurulent exudate
Depth of inflammation	May be transmural, deep into tissues	Shallow, mucosal

Causes

- Interaction of environmental & genetic factors
- Leading to immunological responses and inflammation

	Crohn's disease	Ulcerative colitis
Cytokine response	Associated with Th1 & Th17; IL-12, IFN-γ; TNF-α	Vaguely associated with Th2

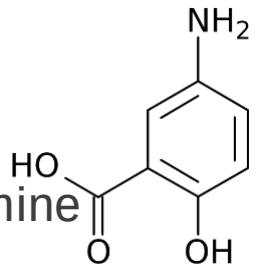


Drug Therapy for IBD

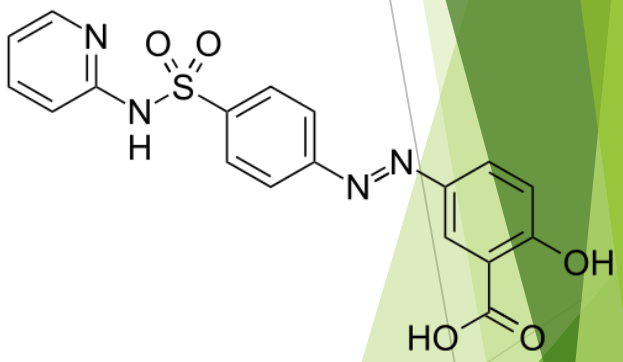
Individualised for each patient based on type, distribution, severity etc. of the disease.

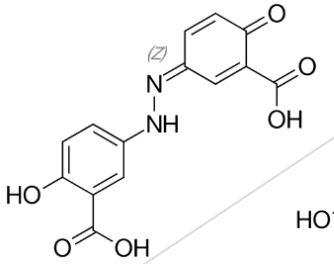
- Anti-inflammatory drugs
  - 5-ASA & derivatives
  - Corticosteroids
- Immunosupression
  - Corticosteroids
  - 6-Mercaptopurine, Azathioprine
  - Methotrexate
  - Ciclosporin
  - TNF-inhibitors

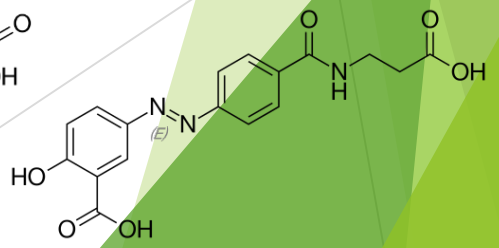
5-ASA and derivatives



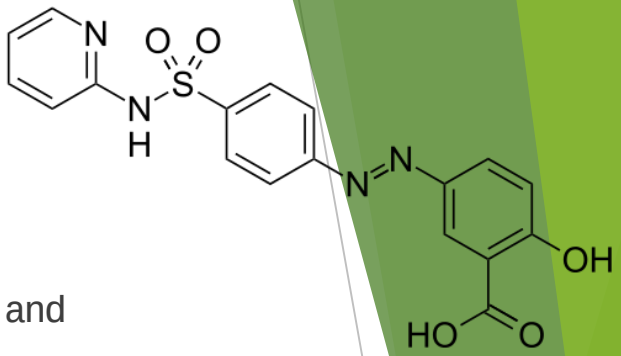
- Names: 5-aminosalicylic acid, Mesalazine, Mesalamine
  - May be absorbed from small intestine ➔ retard tablets, rectal suppos., rectal susp. OR ➔
- Sulfasalazine = 5-ASA + supfapyridine
  - linkage = azo-bond
    - Prevents absorption in stomach & small intestine
    - Colon bacteria cleave bond (azo-reductases) ➔
  - Sulfapyridine is absorbed and metabolised
  - Mesalazin remains in colon
- Similar agents: Olsalazine, Balsalazide
- Indications:
  - in mild to moderate ulcerative colitis and Crohn's Disease
  - For inducing remission in both
  - For maintaining remission in UC
  - Sulfasalazine also first line treatment in Rheumatoid Arthritis (DMARD)



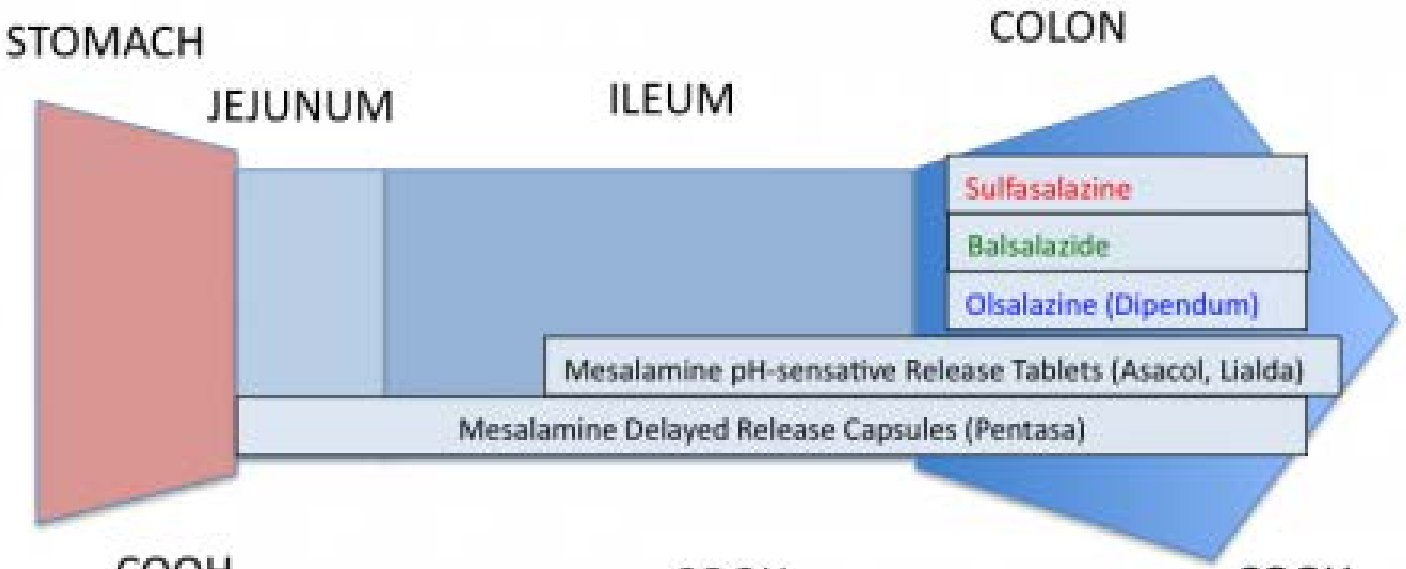


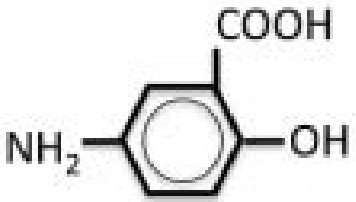


Sulfasalazine



- Mechanism of action:
  - 5-ASA:
    - COX-inhibitor (inhibits synthesis of interleukins and prostaglandins),
    - LOX-inhibitor (inhibits synthesis of leukotrienes), and
    - trapping of free radicals
    - decreases T-cell function
    - decreases release of inflammatory citokines (IL-1, IL-6, IL-12, TNF-α)
- clinical use
  - 2-3g/day maintaining dose
  - 3-8g/day in active stage
- Adverse effects (mainly due to sulfapyridine)
  - agranulocytosis
  - hypospermia
- Contraindicated:
  - Aspirin or sulfonamide allergy

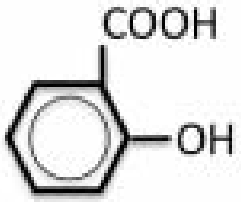




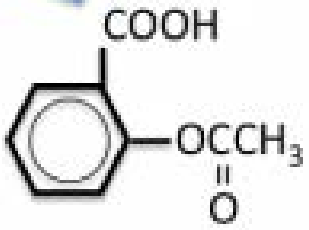
5-ASA

(5-Aminosalicylic acid)

Mesalamine



Salicylate



Aspirin

Glucocorticoids

- Prednisolone, hydrocortisone, prednisone, betamethasone, budesonide, beclometasone, tixocortol
- Indications:
  - Effective in acute exacerbations
  - in moderate to severe IBD only

- Three types of patients based on response to steroids exist:
  - Steroid-responsive (~40%): improve clinically within 1-2 week & remain in remission as steroids tapered and discontinued
  - Steroid-dependent (30-40%): also respond but experience relapse of symptoms as dose tapered
  - Steroid-unresponsive (15-20%): do not improve even with prolonged high-dose

Glucocorticoids

- Mechanism of action
  - anti-inflammatory
    - Phospholipase A2 (PLA2)-inhibition (mediated by lipocortin/annexin 1 protein) ➔ inhibits formation of arachidonic acid ➔ inhibits formation of inflammatory eicosanoids

      transactivation
    - inhibits inflammatory cytokine-synthesis
  - immunoregulatory activity
    - decrease number of inflammatory cells

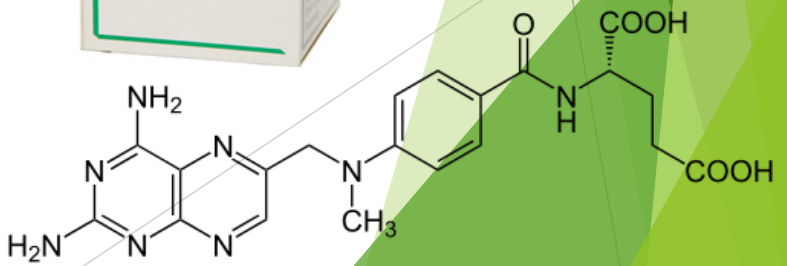
  transrepression
- Doses:
  - Prednisolone, methylprednisolone 40-60mg/day per os (or in severe cases i.v.)
  - Hydrocortisone 300mg/day per os; 100mg/per night rectally
  - Higher doses generally are no more effective
  - Minimize duration of steroid therapy: tapered -5mg/week
- Side effects:
  - fluid retention (due to mineralocorticoid –effect)
  - Fat redistribution
  - Hyperglycemia
  - Cataract, glaucoma
  - Myopathy
  - Osteoporosis
  - Increased risk of infection etc

Immunosuppressants - Thiopurine derivatives

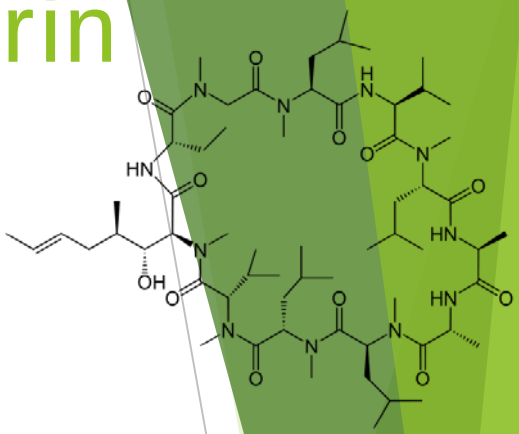
- 6-Mercaptopurine (6-MP); Azathioprine (6-MP analogue, converted to 6-MP)
- Mechanism of action: purin-analogue ➔ metabolised to 6-thioguanine (active form)
  - suppresses inosinic acid synthesis (purine synthesis)
  - ↓T-cell, B-cell function
  - ↓IG production
  - ↓IL-2 secretion
- Indications: 2mg/kg/day
  - Severe IBD or
  - Steroid-resistant/steroid-dependent patients for maintaining remission
  - Rheumatoid arthritis
  - As cancer chemotherapy
- Adverse effects:
  - bone marrow supression
  - Nausea & vomiting
  - Increased risk of infection

Immunosuppressants - Methotrexate

- Mechanism of action:
  - inhibition of dihydrofolate reductase (DHFR) → ↓FH4 →
    TS ↓ (= ↓ dUMP → dTMP) → ↓DNA synthesis ➔ cell death (cancer chemotherapy)
  - Inhibition of T-cell activation; down-regulation of B-cells
  - Decrease IL-1 production and binding to its receptor
- clinical use
  - Steroid-resistant/dependent IBD (15-25mg/week); limited studies in ulcerative colitis
  - Mostly for Crohn's: For induction & maintenance of remission
    - More rapid than 6-MP
  - RA (first choice) (low doses)
  - cancer chemotherapy (AML) (high doses)
- Adverse effects:
  - mucosal ulcers
  - hepatotoxicity
  - bone marrow suppression
  - Leukopenia
  - teratogenic
- Antidote: leucovorin

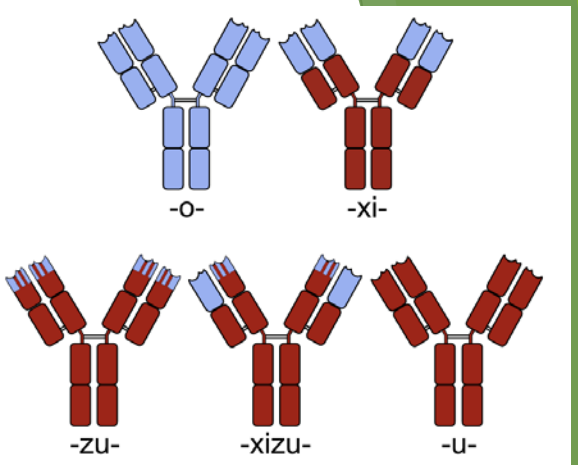


Immunosuppressants - Ciclosporin



- Cyclic peptide of 11 aminoacids
  - Synthetised by a fungi
  - Contains a D-Alanine (which is rarely encountered in nature)
- Mechanism of action:
  - Inhibits Calcineurin ➔ thus regulates gene transcription ➔
  - decreases IL-1, IL-2 production
  - decreases T-cell activity,
  - decreases Macrophage responsiveness
- Indications: 2-5 mg/kg/day
  - Ulcerative colitis (steroid-unresponsive)
  - Rheumatoid arthritis
  - Psoriasis
  - Organ transplantation
- Adverse effects:
  - Nephrotoxicity (metabolites)
  - Gingival hyperplasia
  - GIT disturbances
  - Carcinogenic
  - Opportunistic infections (*Pneumocystis carinii* pneumonia)

Anti-TNF Therapy



- Monoclonal antibodies:
  - Infliximab (chimera)
  - Adalimumab (human)
  - Certolizumab pegol (humanized)
  - Golimumab (human)
  - Etanercept (fusion protein)
- Tumor Necrosis Factor Alpha (TNF-α)
  - Cytokine (protein) involved in inflammation
  - Mediate Th1 immune response (characteristic of Crohn's Disease)
- Mechanism of action of anti-TNF therapy:
  - Lysis of TNF- α-producing macrophages & T-cells
    - (through complement fixation & antibody-dependent citotoxicity)
- Indications:
  - Steroid-refracter severe Crohn's disease (mostly infliximab & adalimumab) **5mg/kg**
  - Rheumatoid arthritis
  - Cancer chemotherapy (renal, breast, ovarian cancer)
- Adverse effects:
  - Hepatosplenic T-cell lymphoma
  - Opportunistic infections (TBC, fungal)