INFLAMMATORY BOWEL DISEASE:

- IBD = chronic, relapsing inflammation of the intestinal tract
- IBD is characterized by diarrhea, abd.l pain, bleeding, anemia & weight loss
- IBD affects 1 in every 250 individuals (25% develop symptoms in childhood)
- Divided into two major subtypes: ulcerative colitis & Crohn's Disease
  - No unique abnormality has been identified in these conditions and symptoms fluctuate markedly
  - Therapy is aimed at controlling acute exacerbations of the disease, maintaining remission, and treating specific complications

ULCERATIVE COLITIS:

- Limited to mucosal inflammation of the colon confluent (all areas are joined)

CROHN'S DISEASE:

- Transmural (affecting all layers of bowel wall) inflammation of any part of the GIT
- Inflammation may lead to fibrosis and strictures or, alternatively, fistula formation
- Crohn's disease shows numerous deep ulcerations and areas of more normal appearing mucosa = not necessarily confluent, may skip areas

THEORETICAL MODEL:

- Endothelial barrier impaired
- Bacterial antigens gain access and antigen presented by APC (antigen presenting cell)
  - TH1 cells (Crohn's disease)
  - TH2 cells (Ulcerative Colitis)
- Production of inflammatory mediators (ex// TNF-apha)
- Activation of macrophages (Crohn's disease)

GENETICS:

- Propose that susceptibility to Crohn's may be in part genetically predetermined
- Example: nucleotide-binding oligomerization domain containing 2 (NOD2) is an intracellular receptor for a component of the bacterial cell wall found on intestinal epithelial cells and macrophages in GIT
  - Variations of NOD2 increased likelihood of developing ileal Crohn's disease 40-fold

TREATMENT OF INFLAMMATORY BOWEL DISEASE:

- Lifelong pharmacotherapy required for IBD management
- Surgery for treatment of refractory disease
- Pharmacotherapy is aimed at:
  1. Decreasing inflammation
  2. Restoring normal bowel function
  3. Inducing remission
  4. Ameliorating pain (~ 1/6 of IBD patients treated with opiates)
- Anti-inflammatory agents are the principal treatment

AZO COMPOUNDS:

SULFASALAZINE (PROGENITOR COMPOUND):

- 5-ASA bound to sulfapyridine
- Little absorbed from GI
- Azoreductase (bacterial enzyme) coverts 5-ASA and sulfapyridine in colon

ADVERSE EFFECTS OF SULFASALAZINE (DUE TO SULFAPYRIDINE):

- Nausea, GIT upset, headaches, arthralgias, myalgias, bone marrow suppression and malaise
  - 40% cannot tolerate drug
  - Often dose related & very common
- Slow acetylators of sulfapyridine at greatest risk for ADRs
- Other ADRs:
  - Oligospermia (reversible low sperm count)
  - Impairs folate absorption and processing (give folic acid)
  - Allergic reaction to sulfa
- To avoid the adverse effects of sulfasalazine and retain the therapeutic effects, products available that contain 5-ASA alone

OLSALAZINE:

- Two linked 5-ASA molecules linked by an azo bond
- Azoreductase converst olsalazine to two 5-ASA molecules
  - Sine this occurs in the colon, little drug effect in the small intestine (similar to sulfasalazine)

5-AMINOSALICYCLIC ACID (5-ASA): generically known as **mesalamine**

- Absorbed from the small intestine, but very low absorption from the colon, so drug reaching the colon stays in the GIT
- Topical anti-inflammatory
- Different formulations release at different points along the GIT

MECHANISM:

- Specific mechanism of action of 5-ASA has not been identified
- Blockade of cyclo-oxygenase does not seem to be mechanism
  - NSAIDs may exacerbate IBD

USES:

- First-line agents for treatment of mild to moderate active ulcerative colitis (induce & maintain remission in > 50% of pts)
- Many clinicians use as first-line therapy for mild-moderate Crohn's disease (colon or distal ileum), but doses are usually much higher and not usually as effective as in UC

ADVERSE EFFECTS OF 5-ASA:

- Generally well tolerated with much fewer side effects than sulfasalazine
- Higher serum 5-ASA levels could result in interstitial nephritis

GLUCOCORTICOIDS:

DOSAGE FORMS:

- Prednisone (& prednisolone) oral
- Hydrocortisone enemas, foam, or suppositories
- Budesonide (controlled-release oral)

MAJOR EFFECT:

- Anti-inflammatory & immunosuppressive effects: inhibit production of inflammatory cytokines ; reduce expression of inflammatory molecules
- Inhibit gene transcription

MECHANISM OF ACTION:

- Activate glucocorticoid receptors (hGR) to act on promoters of target genes to regulate their transcription

USES:

- Acute attacks of moderate to severe disease or non-responders to 5-ASA
- Rectally administered = lower systemic absorption (preferred if disease is rectum/colon)
- Not useful to maintain disease remission; most pts lose response to steroids over time

IMMUNOMODULATORS:

AZATHIOPURINE, 6-MERCAPTOPURINE, METHOTREXATE:
- Induction and maintenance of remission of ulcerative colitis and Crohn's disease
- 3-6 months of treatment, 50-60% of patients with active disease achieve remission
- Can allow dose reduction or elimination of steroids

METHOTREXATE:
- Inhibits dihydrofolate reductase, important for the production of purines and thymidine
- Used at low dose, it may interfere with inflammatory cytokines
- It may increase the release of adenosine, which has anti-inflammatory effects in the GIT
- It may cause cell death of activated T lymphocytes

AZATHIPURINE & 6-MERCAPTOPURINE:
- Purine biosynthesis inhibitors = antiproliferative agents
- Liver converts drug to 6-mercaptopurine by a non-enzymatic process → enters the cell to form 6-MP ribonuceotide
  - Resembles inosine monophosphate (important precursor in nucleic acid synthesis)
- Feedback inhibition of the early enzymes, catalyzing the cellular synthesis of DNA, RNA, and other cofactors
- Early during the proliferative cycle of effector T- and B-cell clones

ADVERSE EFFECTS:
- Potent myelosuppression (suppresses bone marrow functions) = leukopenia, thrombocytopenia, anemia
- Hepatotoxicity
  - Eliminated by enzyme xanthine oxidase (potential for drug interactions with XO inhibitors (allopurinol))
- Pancreatitis, nausea/diarrhea, alopecia

CYCLOSPORINE (CALCINEURIN INHIBITOR):
- Effective but frequent relapses so usually used to treat specific problems over the short-term only
- Significant adverse effects: nephrotoxicity, neurotoxicity, tremor/headache, seizures, HTN, hypercholesteremia, gingival hyperplasia, hirsutism

ANTI-TUMOR NECROSIS ALPHA (TNF-α) THERAPY:

INFLIXIMAB (ADALIMUMAB, GOLIMUMAB, USTEKINUMAB):
- Chimeric mouse-human monoclonal antibody to human TNF-α
- Binds to soluble and membrane bound TNF-α and makes it impossible for it to bind to its receptor
- Intravenous infusion antibodies stay in plasma 8-12 weeks

USES:
- Moderate to severe Crohn's disease and ulcerative colitis
  - 2/3rd respond, 1/3rd go into disease remission
- ~ 1/3 of responders eventually lose response
  - Antibodies to infliximab?
- Response takes ~ 2 weeks
- Responders may be treated with repeat IV infusions every 8 weeks

ADVERSE EFFECTS OF INFLIXIMAB:
- Infection or reactivation of a chronic infection (ex// TB or other respiratory infection)
  - Suppresses TH1 inflammatory response
- 1/3rd of patients develop antibodies against the mouse portion of the molecule
- Infusion reactions include: fever, headache, dizziness, urticaria, mild cardiopulmonary sx (chest pain, dyspnea, hemodynamic instability)
  - Severe infusion reactions: hypotension, SOB, muscle spasms, and chest discomfort may require treatment
- Serum sickness-like infusion reaction (1-2 weeks after infusion)
  - Myalgia, arthralgia, jaw tightness, fever, rash, urticaria, edema

VEDOLIZUMAB:
- Humanized monoclonal antibody against $\alpha_4\beta_7$ integrin
  - **$\alpha_4\beta_7$ integrin** expressed on circulating B & T lymphocytes
- It interacts with a mucosal addressin cell adhesion molecule (MAdCAM-1) on intestinal vasculature, to facilitate movement of leukocytes out of the blood
  - This antibody blocks lymphocyte movement into areas of inflammation in the gut

USES:
- Given by IV infusion, initially at weeks 0, 2 and 6, followed by every 8 weeks (if no benefit, stop at 14 weeks)
- Effective in both ulcerative colitis and Crohn's disease for both induction and maintenance of remission
- Approved for moderate to severe Crohn's Disease, after failure on TNF-α sequestering antibodies and other treatments

ADVERSE EFFECTS:
- Side effects are generally low
- Most common reported effect worsening of disease sx of inflammatory bowel disease, and nasopharyngitis
- Serious infections and cancer have been associated with the use of this antibody

ETRANERACEPT:
- A dimeric P75 (TNF-α) receptor is ineffective in Crohn's disease

ANTIBIOTICS/PROBIOTICS – CROHN'S DISEASE:

BACKGROUND:
- Colonic bacteria may either initiate or perpetuate the inflammation
- Specific bacterial antigens may be involved
- Certain bacterial strains are pro- (ex// bacteroides) or anti- (ex// lactobacillus) inflammatory

MANIPULATION OF THE COLONIC FLORA:
- Antibiotics: metronidazole, ciprofloxacin, and clarithromycin
  - Significant side effects of prolonged systemic antibiotic use must be balanced against their potential benefits
- Probiotics: mixture of putatively beneficial lyophilized bacteria given orally
  - Role in treatment unclear at present