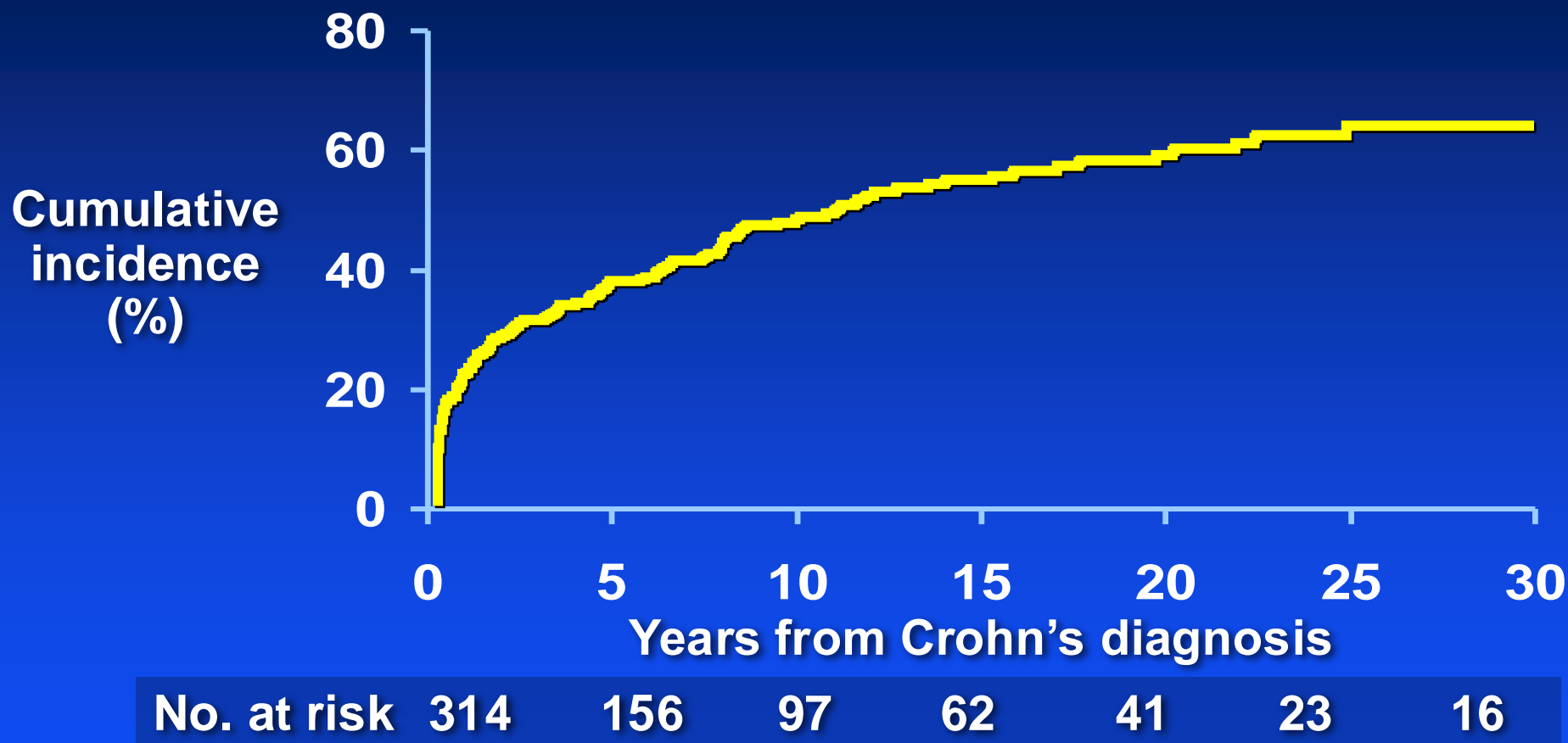


Cumulative Risk of Intestinal Resection in Crohn's Disease, 1940-2001



Dhillon S, Am J Gastroenterol, 2005

Patient Stratification:

Risk Factors for Crohn's Disease Complications

- Large or deep ulcers
- Present of fistula +/- abscess
- Intestinal resection (>40 cm of ileum)
- Presence of stoma
- Extensive disease
 - >40cm ileum or pan colitis
- 10 loose stools per day
- Strictures
- Anemia, CRP, Low albumin

Goal of therapy:

Prevent complications & disability

Extraintestinal Manifestations of IBD

Spondyloarthropathy

Ankylosing spondylitis

Sacro-ileitis

Peripheral arthritis

Dermatological

Pyoderma gangrenosum

Erythema nodosum

Ocular

Uveitis, Episcleritis, Iritis

Hepatobiliary

Primary sclerosing
cholangitis

Thromboembolism

Osteoporosis

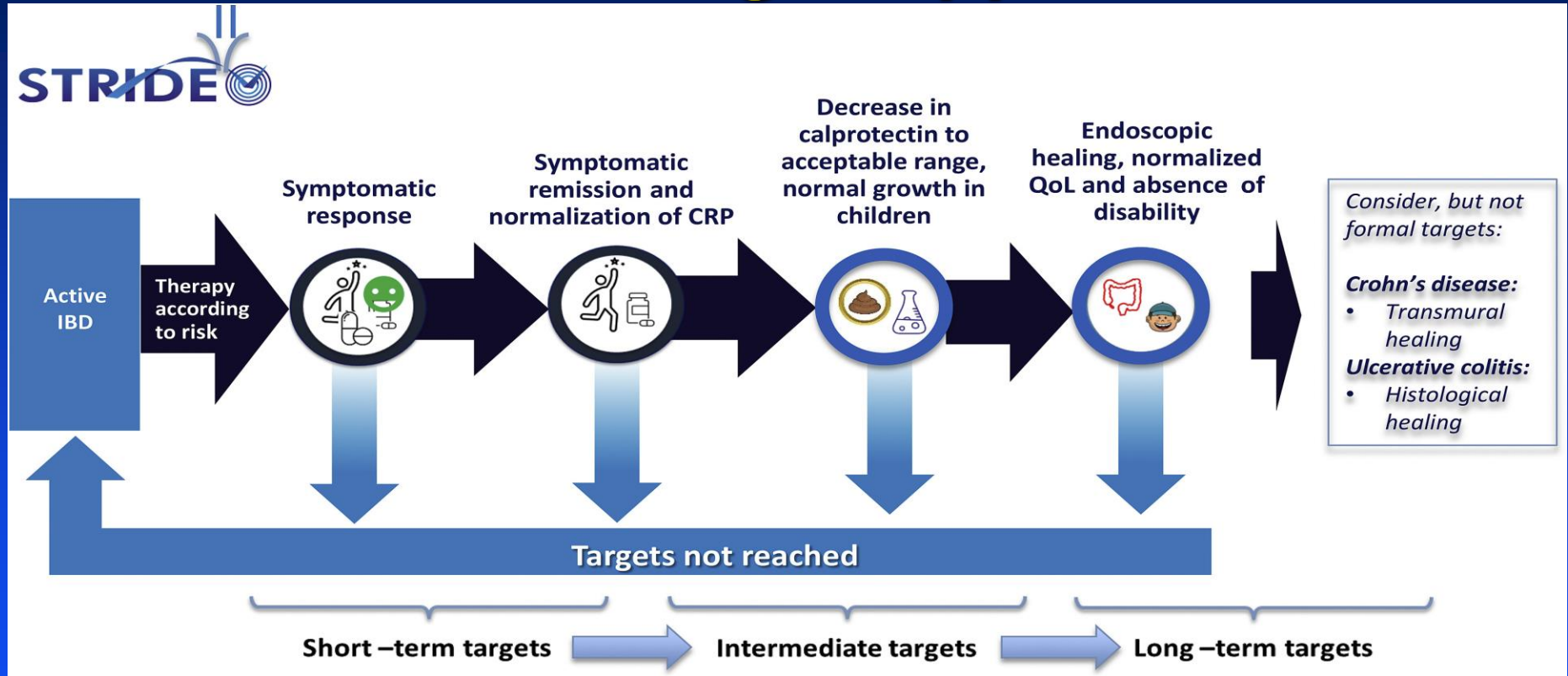
Miscellaneous

Anemia

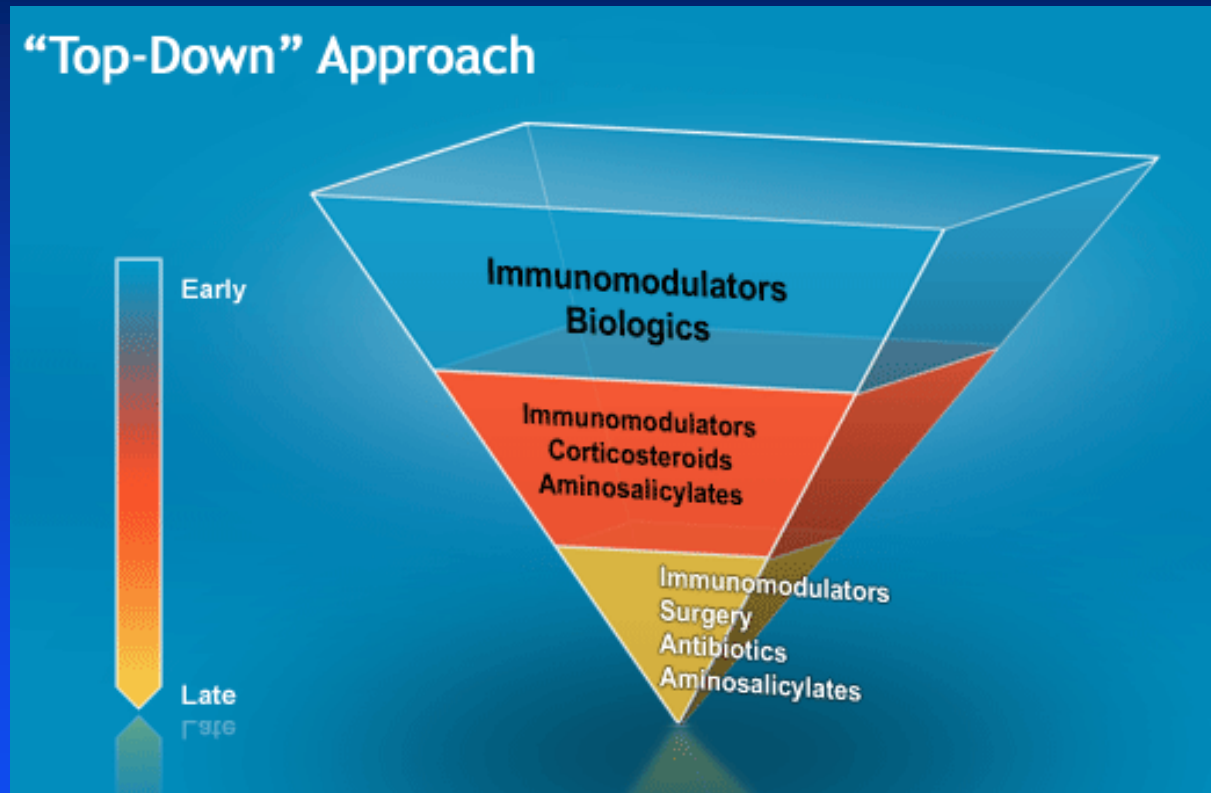
Pericarditis

Pancreatitis

Approach to Treatment in IBD: Treat-to-Target Approach



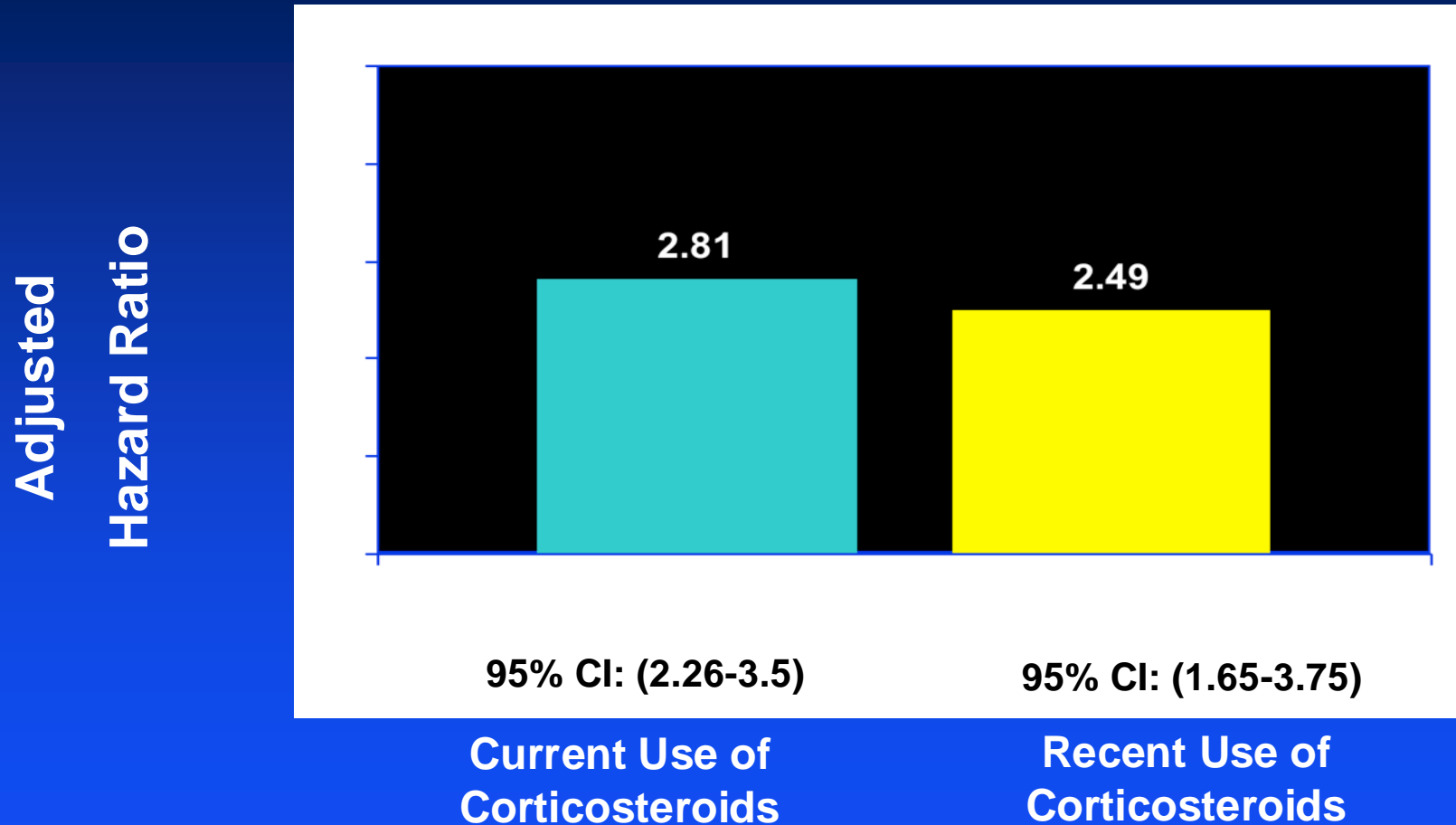
Paradigm Shift to “Top Down” Therapy in High Risk Patients



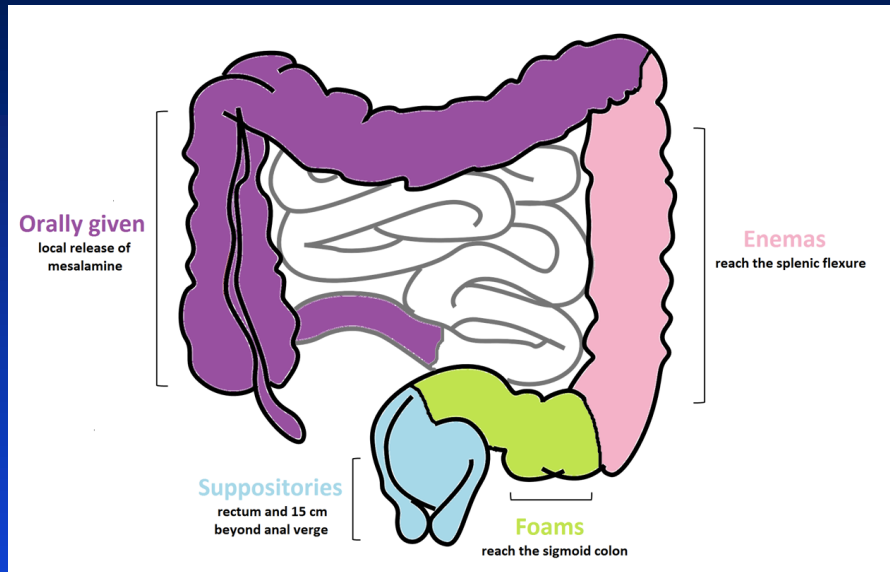
Therapies for IBD

- **Corticosteroids (short-term)**
- **Amino-salicylates (different modalities)**
Primarily effective for UC
- **Immune modulators:**
Primarily for maintenance as combination with biologics
- **Biologics (infusions/injections):**
TNF inhibitors, Leukocyte trafficking inhibitors, IL-12/23 or IL-23 inhibitors
- **New small molecules (pills):**
JAK inhibitors, S1P modulators

Mortality Associated with Corticosteroid Use



5-Aminosalicylates (5-ASA) for UC



What's New?

- Overall, not effective for CD (though frequently used)

- More Delivery systems
 - pH release
 - Local delivery
- Larger dosing units
 - Once daily dosing
- Combinations of oral and topical are more effective

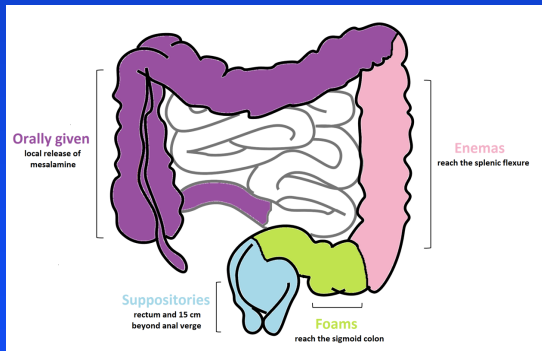
Steroids for UC & CD

Indication

- Effective for induction of response and remission in moderate to severe UC & CD

What's New?

- No long-term efficacy
- Increased risk of infection and mortality
- New formulations
 - Budesonide (ileal CD)
 - Budesonide MMX (UC)
 - Less systemic steroid exposure



Immune Modulators for IBD

Azathioprine/6MP

- MOA: inhibits purine synthesis
- Effective in maintenance of remission in UC/CD
 - Modest effect
- 4x increase in lymphoma risk (increases age >65)
 - Hepatosplenic T cell lymphoma
 - Risk of skin cancer

Methotrexate

- MOA: interferes with DNA synthesis/repair
- NOT effective as monotherapy
 - Usually in combination with biologics
- Obesity/NASH is relative contraindication

Advanced Therapies for IBD

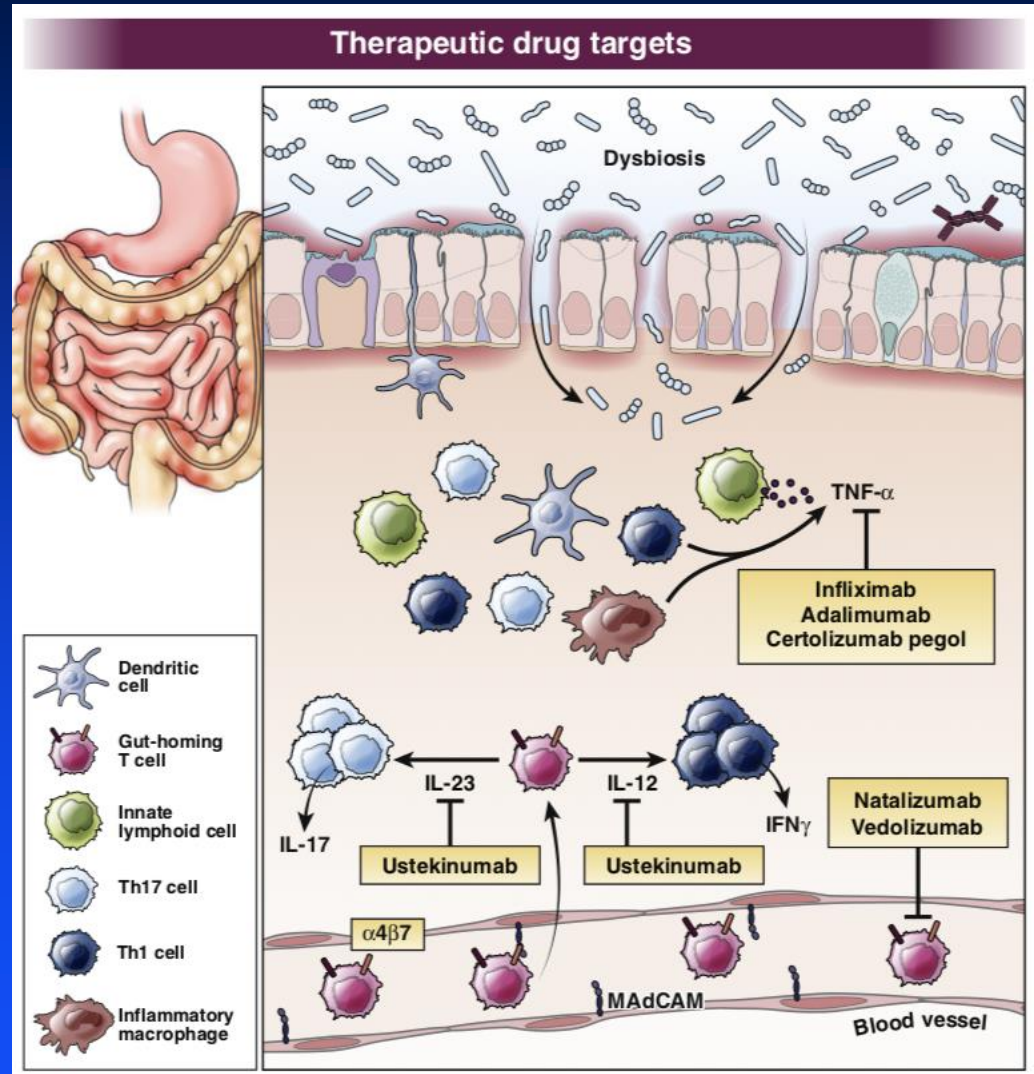
Biologics:

3 main pathways

- anti-TNF
- anti-integrin
- anti-IL-12/23

Small molecules:

- JAK inhibitors
- S1P modulators



Tumor Necrosis Factor (TNF) Antibodies

Indication

- Induces and maintains remission for UC and CD
- Risk of immunogenicity
- Combination therapy:
More effective, less immunogenicity

Potential Risks

- Lymphoma
- Serious infections
- Opportunistic infections:
TB, hep B
- Relative Contraindications
May exacerbate CHF (esp severe)
Demyelinating disease

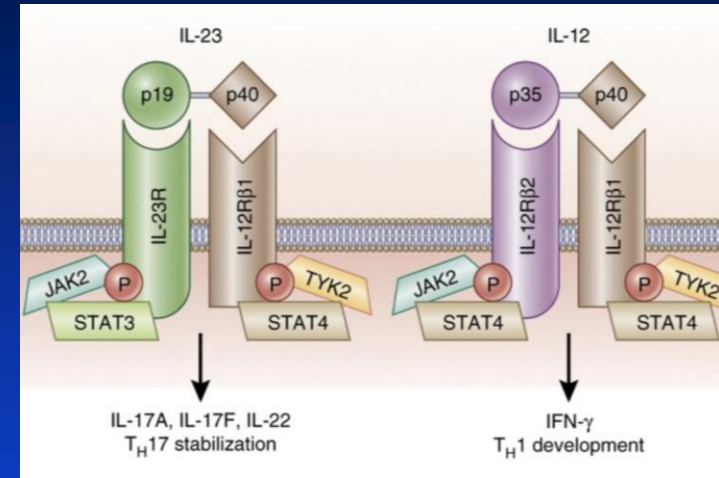
Vedolizumab for IBD

- **Humanized antibody against $\alpha 4\beta 7$**
 $\alpha 4\beta 7$ = Homing receptor for the GI tract
Blocks lymphocyte trafficking to the gut
- **No increase in opportunistic infections**
- **Slower onset of action, esp in CD**
No cases of Progressive Multifocal Leukoencephalopathy (PML)*



Anti-IL12/23 and Anti-IL23 in IBD

- Humanized antibody to IL-12/23 or IL23
 - Ustekinumab
 - Anti IL-12/23 for UC & CD
 - Risankizumab
 - Anti-IL23 for CD*
 - Mirikizumab
 - Anti IL-23 for UC
- Lower infection risk v. TNFinh
 - Good safety profile
 - Effective against psoriasis
- Lower rates of immunogenicity



New Therapies for IBD

OZANIMOD (UC)

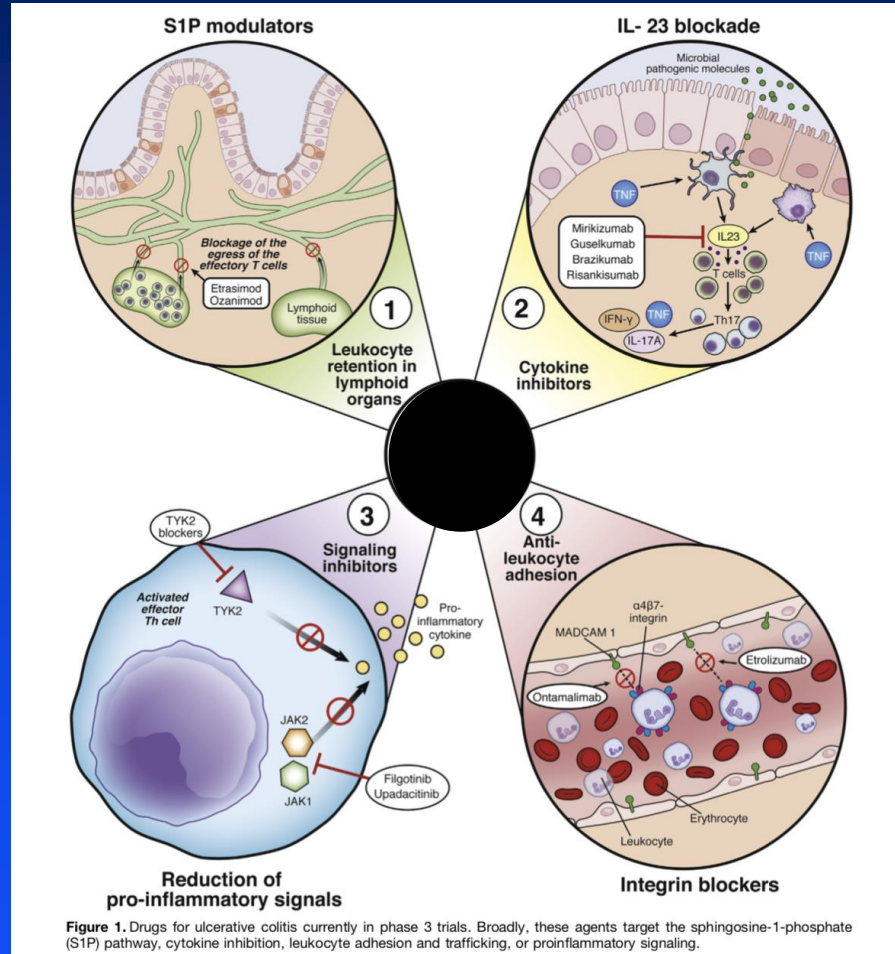
ETRASIMOD (UC)

- Orally administered
- Slower acting
- Approved for MS
- Monitor EKG/macular edema in diabetics

Tofacitinib (UC)

Upadacitinib

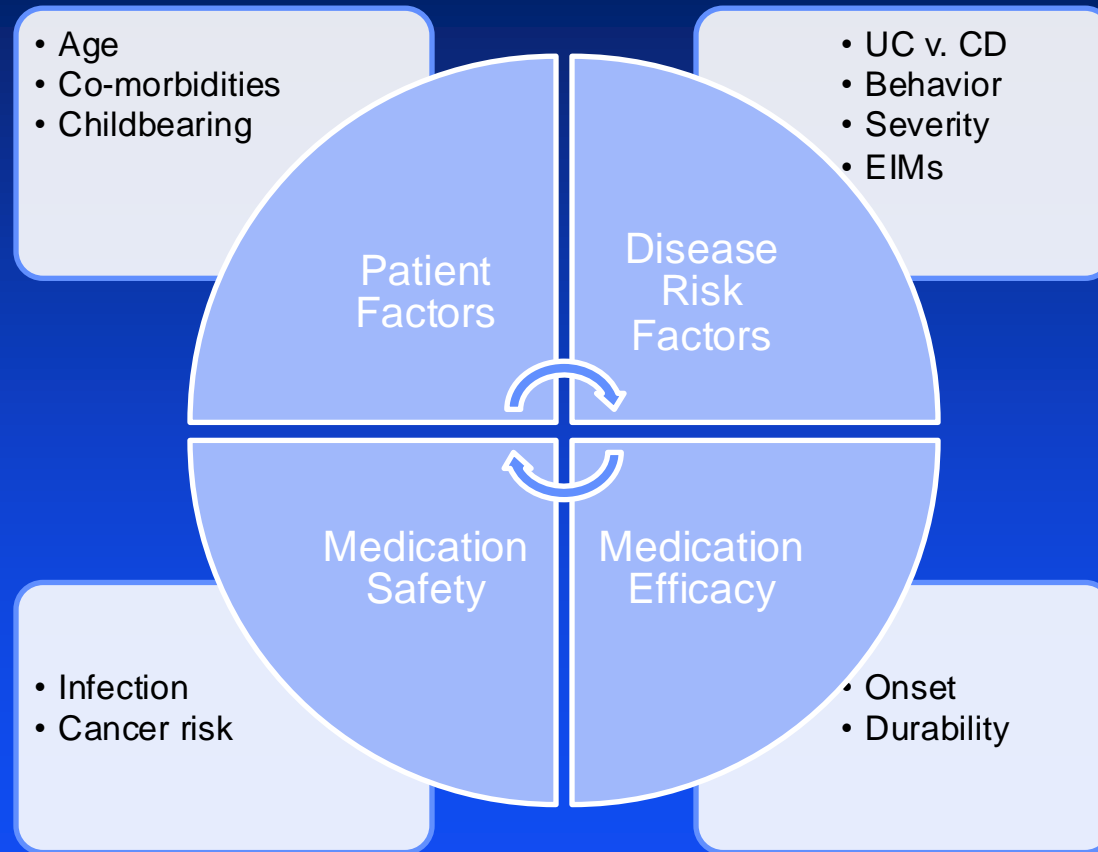
- Orally administered
- **Fast acting**
- Black Box Warning
- Only TNFi failures



Risks:

- Lymphopenia
- Shingles

Personalized Treatment Decisions



New Concepts in IBD

- **Head-to-head trials of biologics**
 - VARSLTY: adalimumab v. vedolizumab in UC**
 - SEAVUE: adalimumab v. UST in Crohn's**
- **Personalized medicine: predictive testing in clinical trials**
- **Combination therapy: multiple biologics**

Conclusions

- **IBD pathogenesis is complex**
Genetics, aberrant immune response, microbial, environmental factors
- **Shift towards early aggressive therapy to attempt to modify natural history**
- **Significant advances in medical therapy**
Shift towards personalized treatment decisions