CME: Current & Emerging Advanced Therapeutics in the IBD Landscape

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Current & Emerging Advanced Therapeutics in Inflammatory Bowel Disease

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Disclosure

The following relevant financial relationships have been disclosed by faculty, and all have been mitigated.

- **Neilanjan Nandi, MD, FACP:** Consultant for AbbVie, Boehringer-Ingelheim, BMS, Janssen, and Pfizer.

- Moderators and non-faculty contributors involved in the planning, development, editing and review of the content have disclosed no relevant financial relationships.

Off-Label/Investigational Discussion:

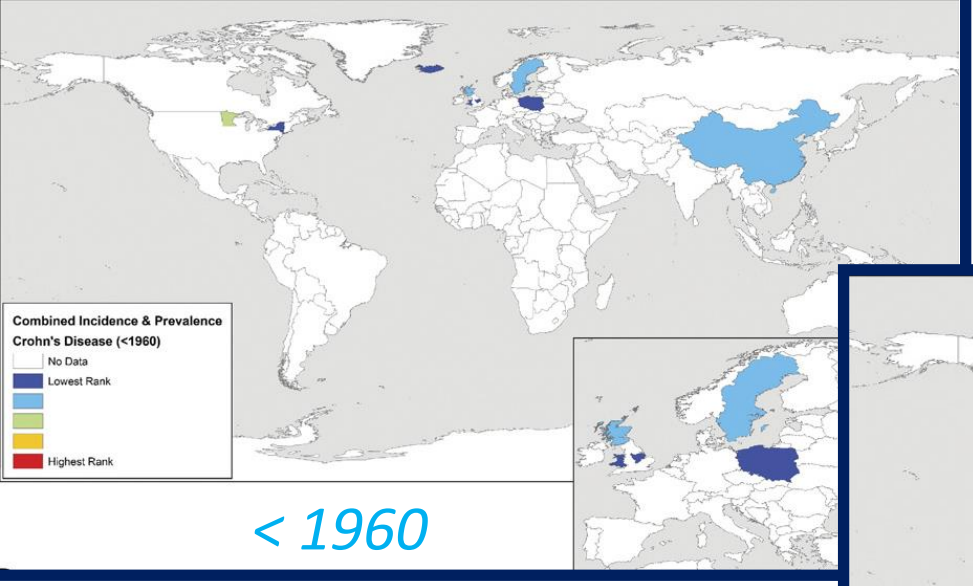
Faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices, as well as topics that are new and evolving, during the course of their presentations.

Learning Objectives

- Review the epidemiology of Inflammatory Bowel Disease (IBD)
- Highlight key differences in the clinical presentation of the two major IBD phenotypes: Crohn's disease and Ulcerative colitis
- Identify the basic mechanisms of action of different biologic and small molecule therapies in treating IBD
- Understand new research into the role of hyperbaric oxygen therapy, mesenchymal stem cell therapy and microbiota restorative therapy for different forms of IBD

EPIDEMIOLOGY
&
ETIOLOGY

Cumulative Incidence & Prevalence of Crohn's



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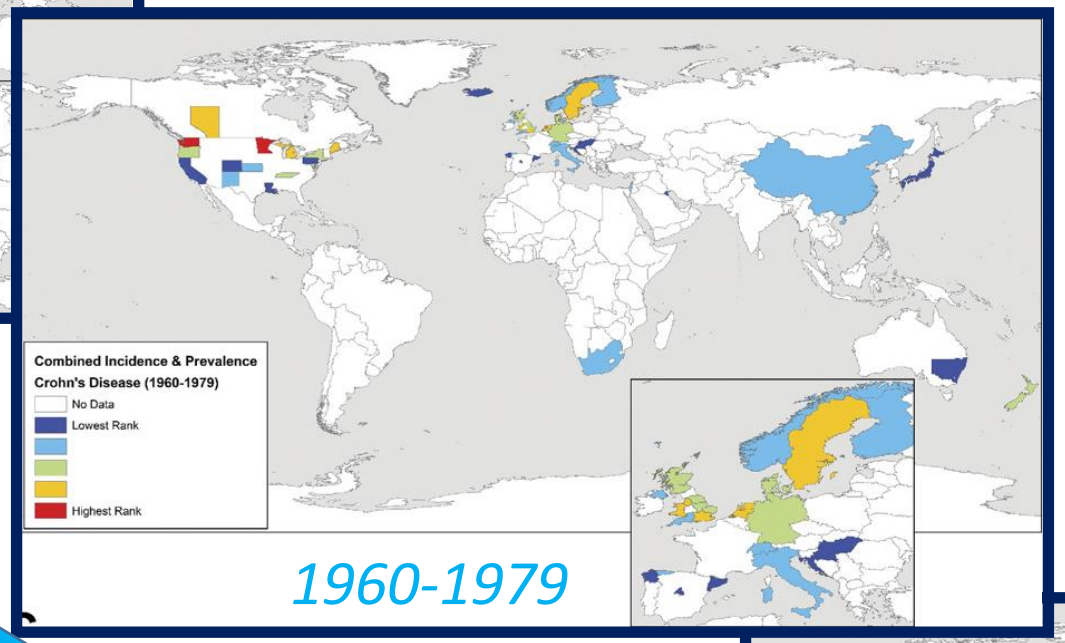
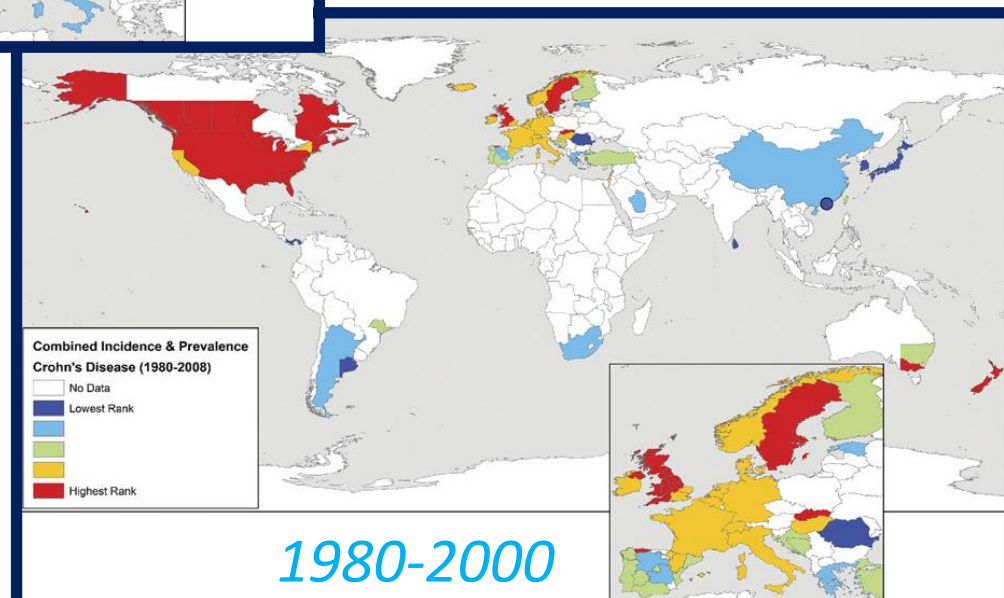


1960-1979

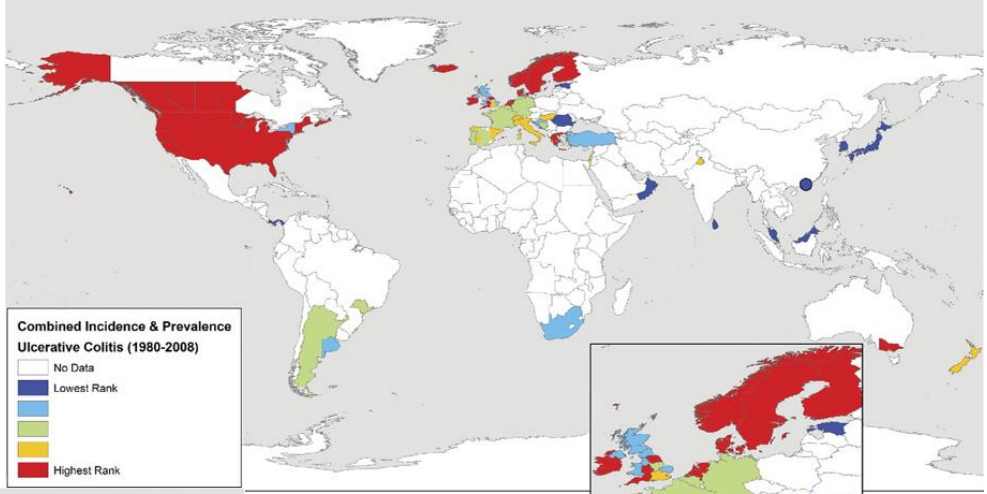


1980-2000

Increasing with time.

Molodecky NA, et al. Gastro, Jan 2012; 142(1):46-54.e42.

Cumulative Incidence & Prevalence of Ulcerative Colitis



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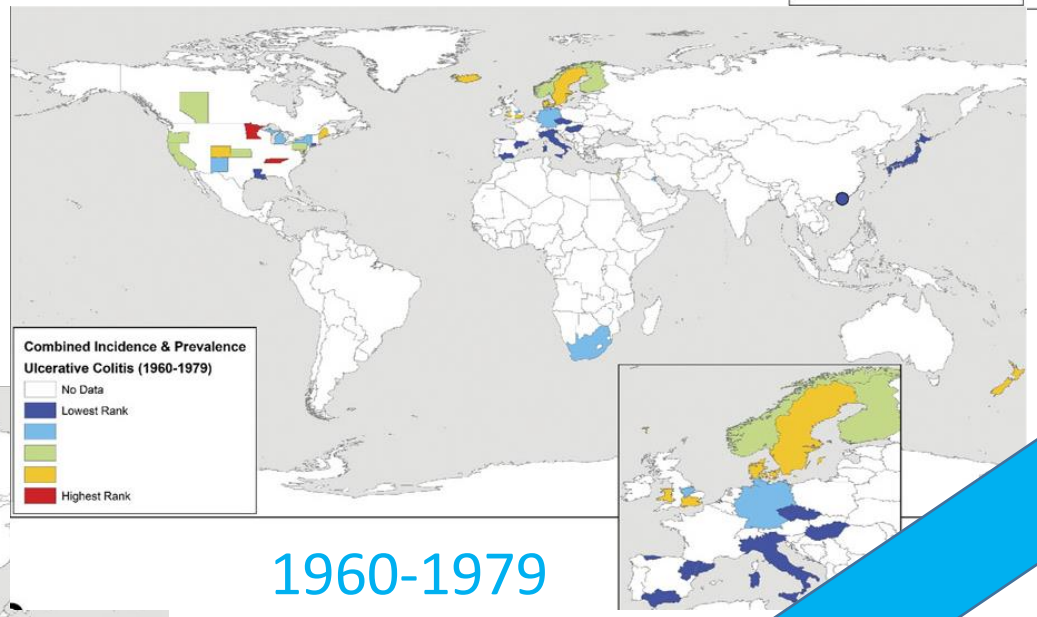
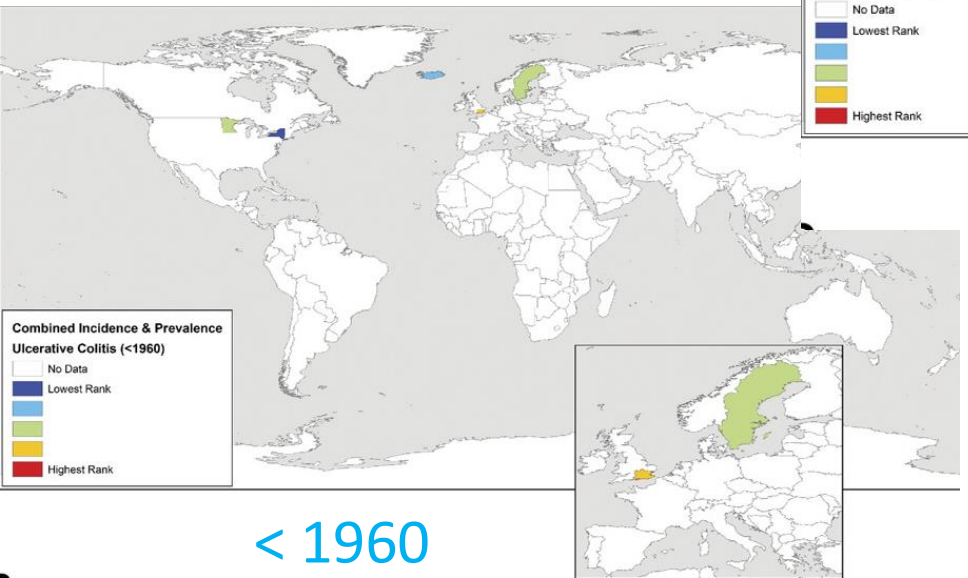


1960-1979



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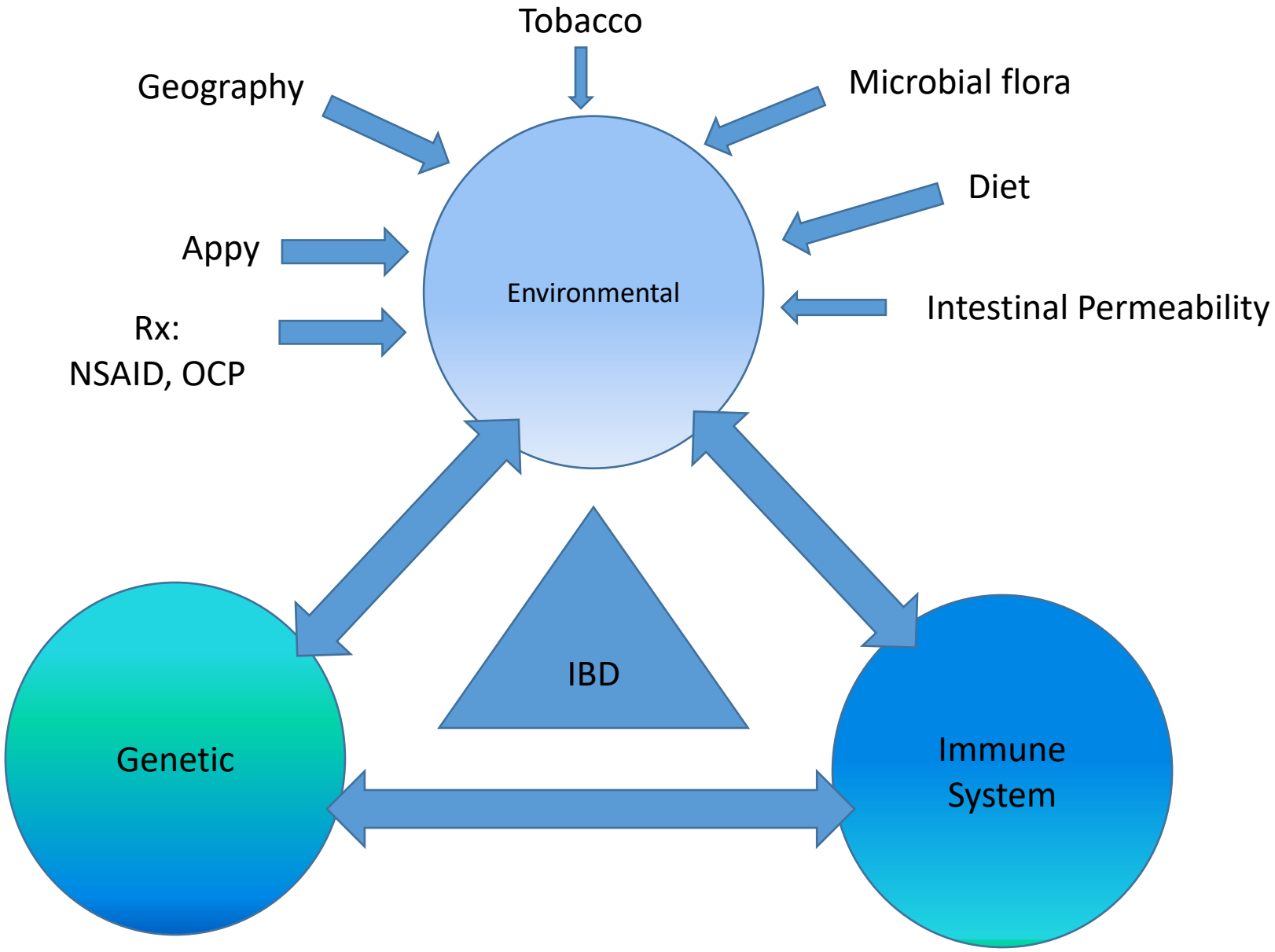
ETIOLOGY



NOD-2/CARD-15
ATG16L1
IRGM
IL-23

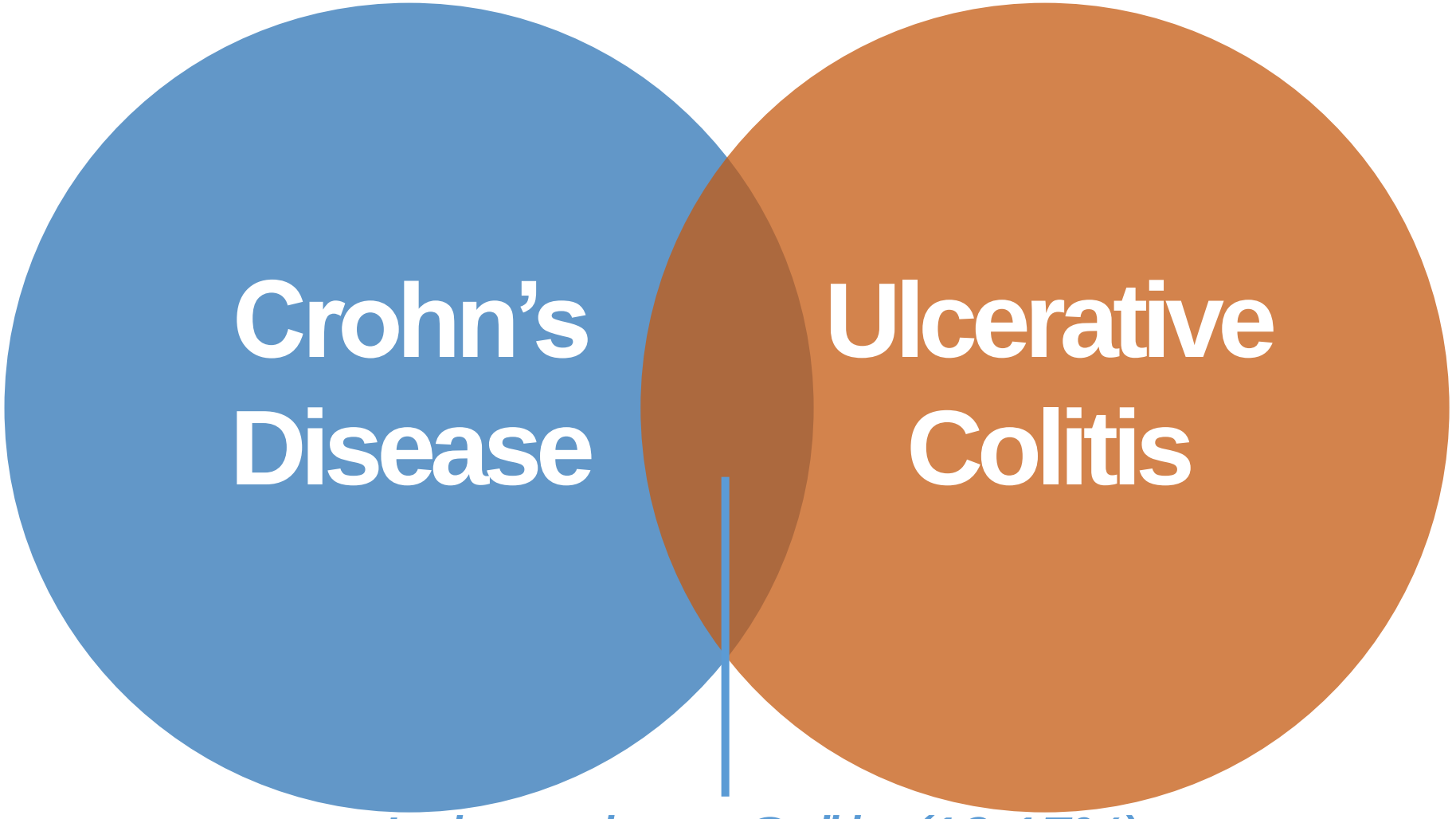
Image per Dr. Nandi

ETIOLOGY

Image per Dr. Nandi

IBD Spectrum

Chronic inflammatory conditions characterized
by *relapsing & remitting* episodes of inflammation



Yu YR, et al. Semin Pediatr Surg. 2017 Dec;26(6):349-355

Key Concepts

IBD is an immune mediated, chronic, inflammatory condition with relapsing & remitting course

Two Major IBD Phenotypes - Crohn's & Ulcerative Colitis

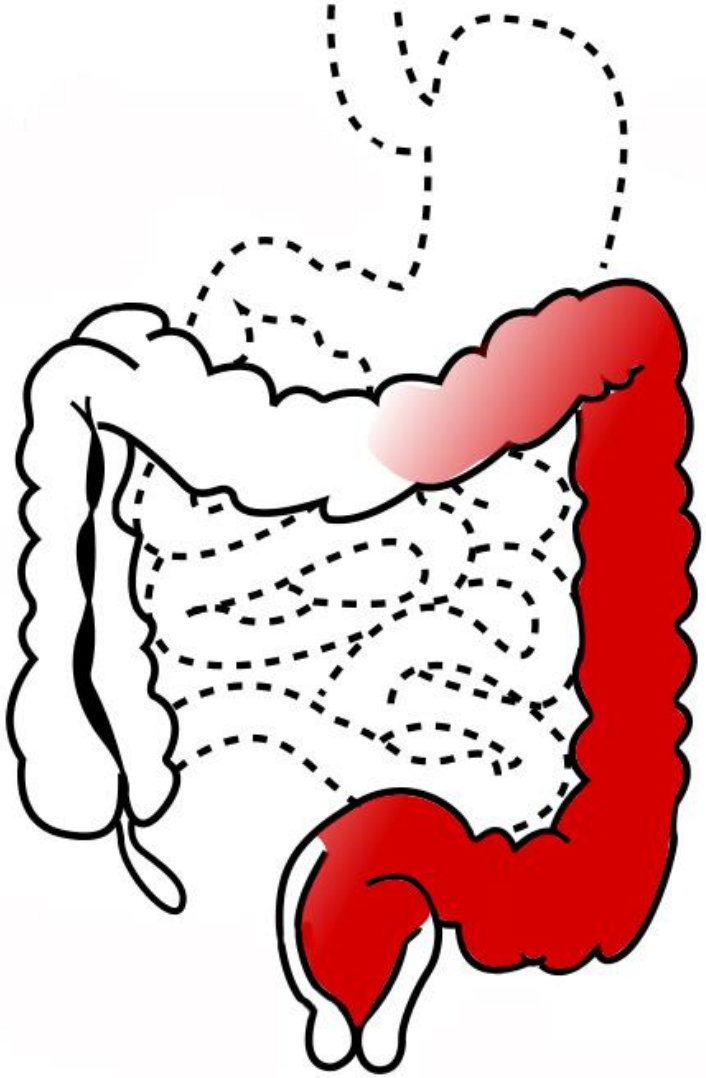
10-15% w/Overlapping features: Indeterminate Colitis

Increasing global incidence & prevalence, esp in developing countries

Etiology Multi-factorial : Genetic, Immune, Microbiota, Diet, Environmental & *MORE* !

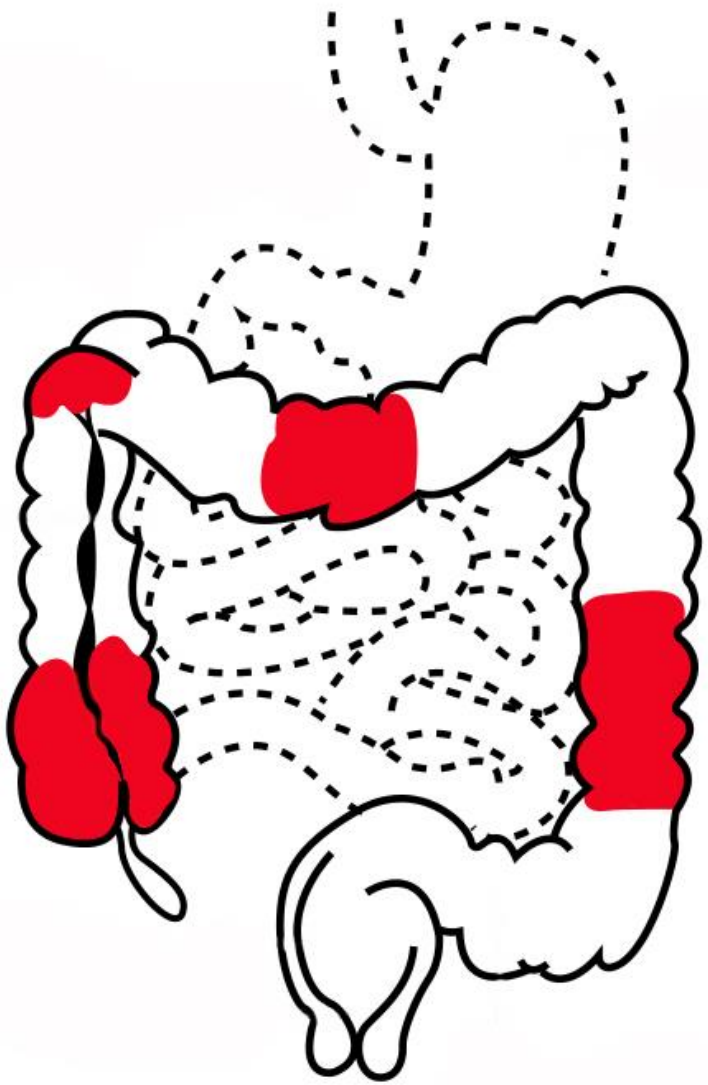
CLINICAL MANIFESTATIONS

Ulcerative Colitis

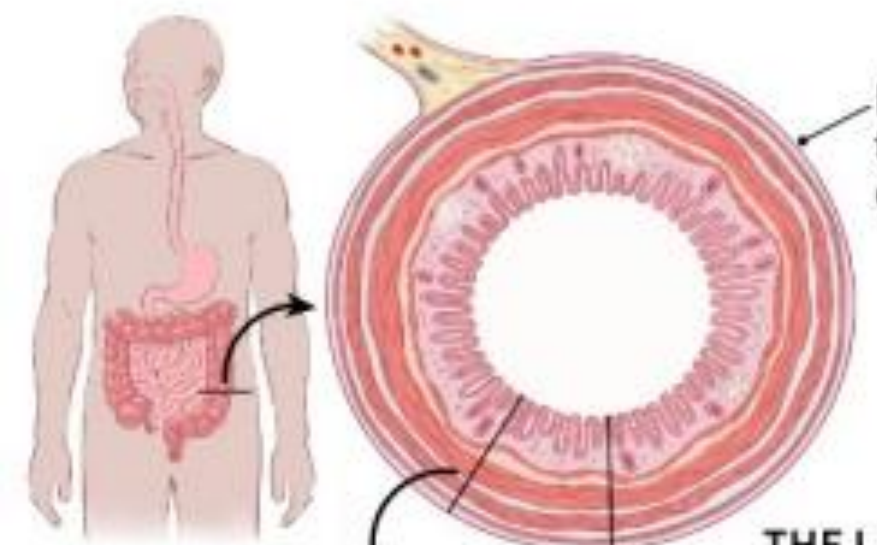


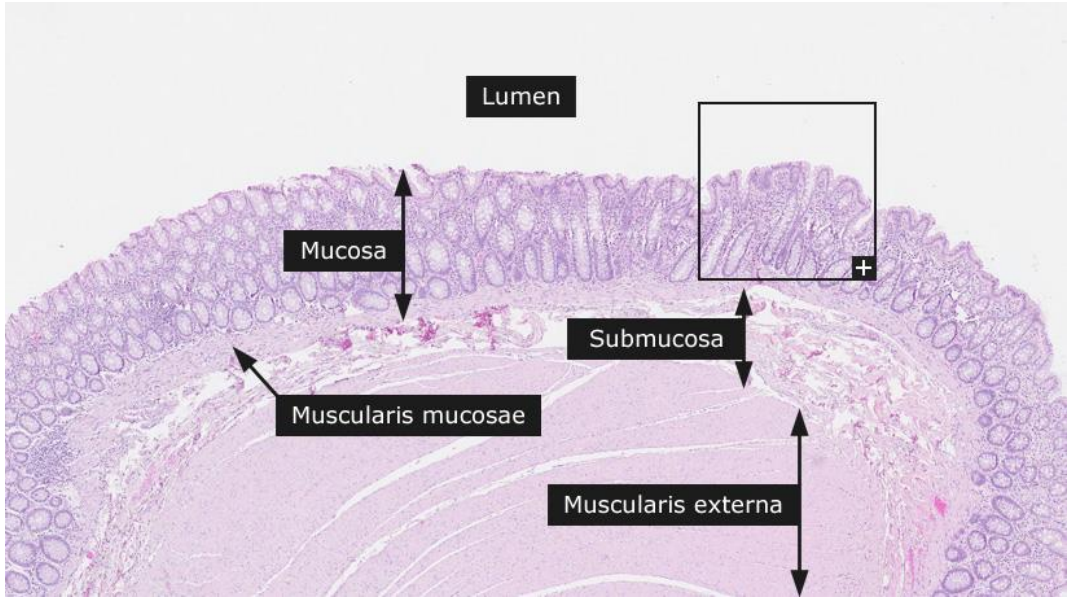
Confluent,
Colon only

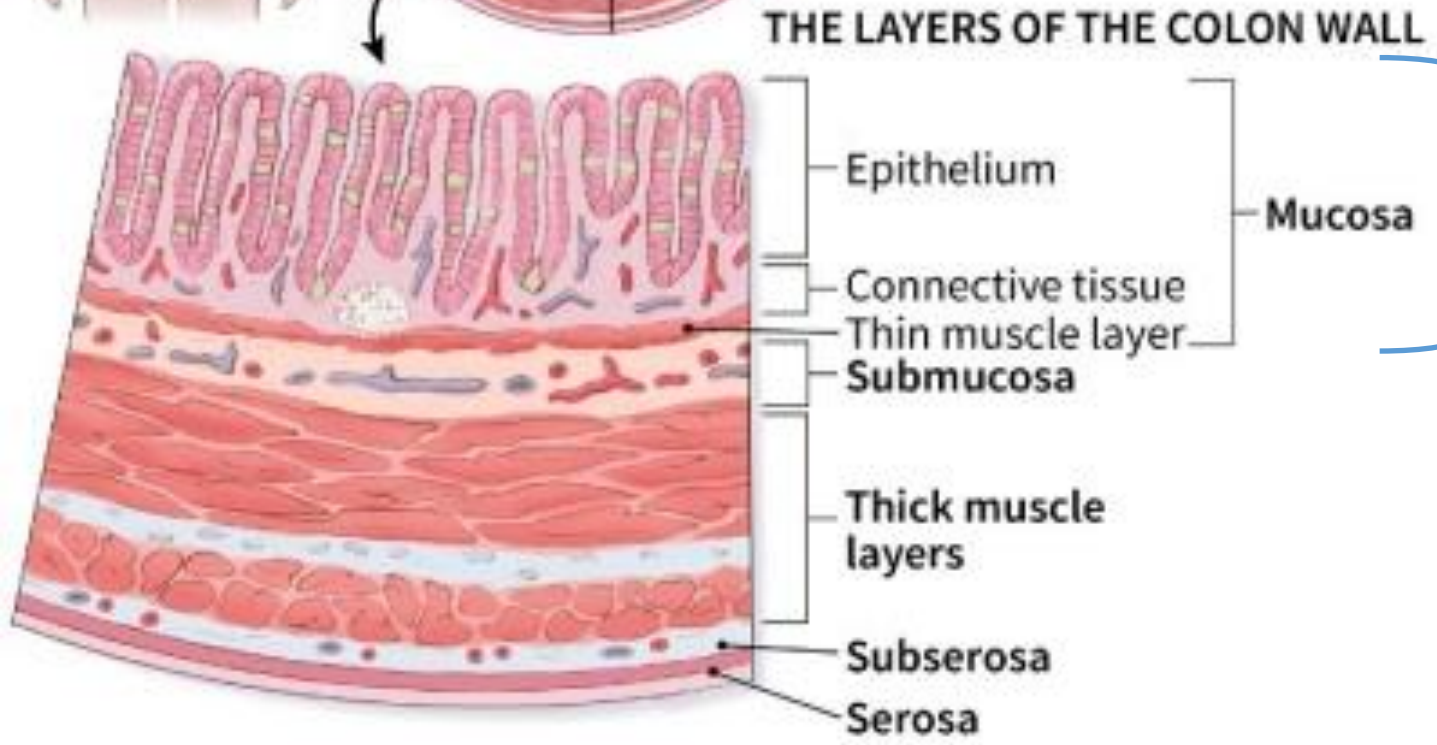
Crohn's Disease



<u>Skip</u> lesions,
Mouth to Anus







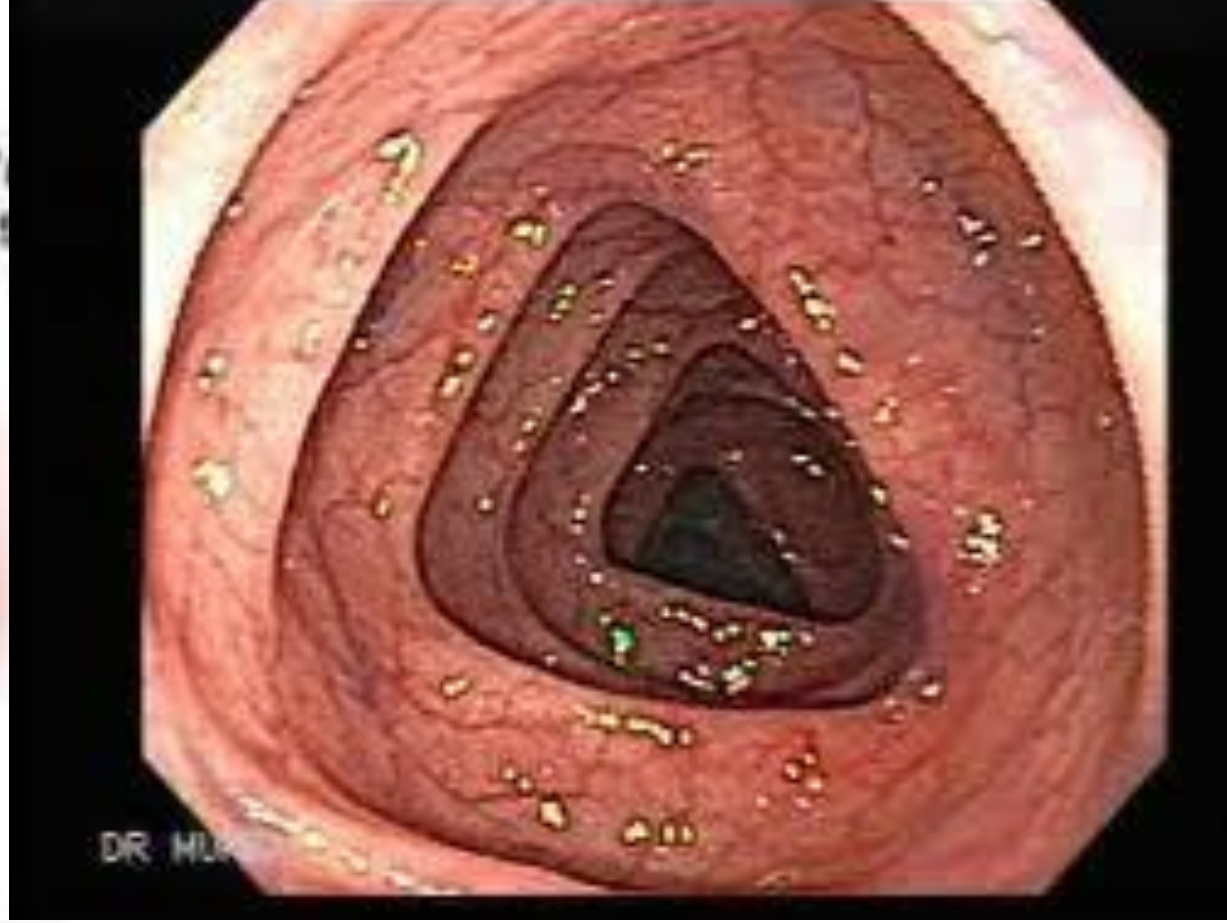
Ulcerative Colitis (mucosal)

Crohn's disease (transmural)

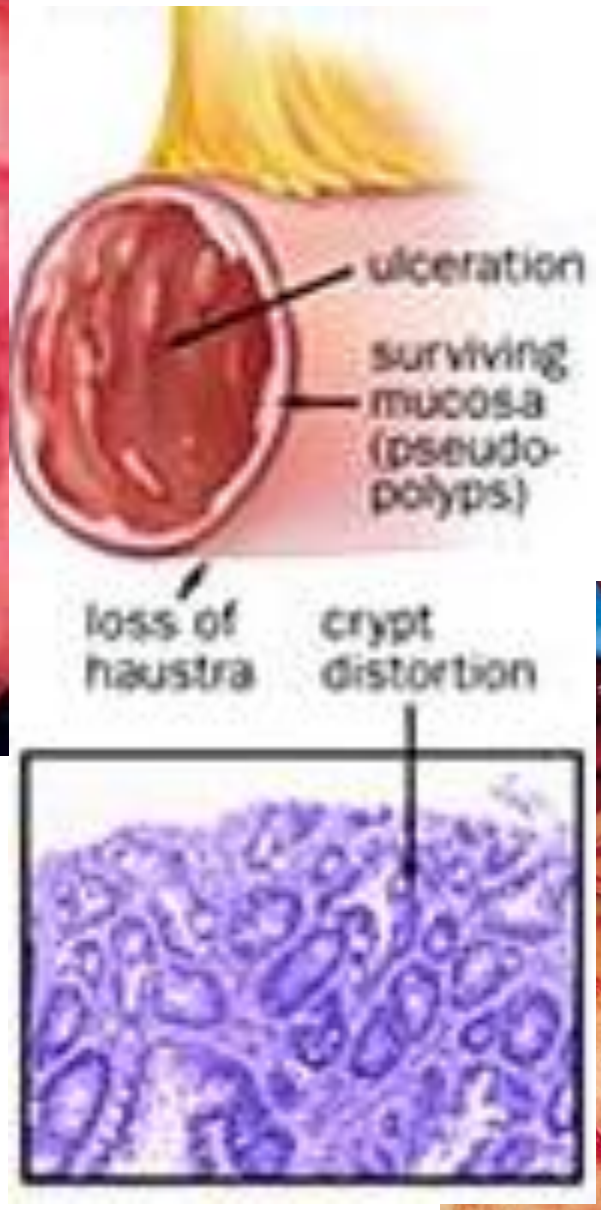
Classic IBD: Distinguishing Characteristics

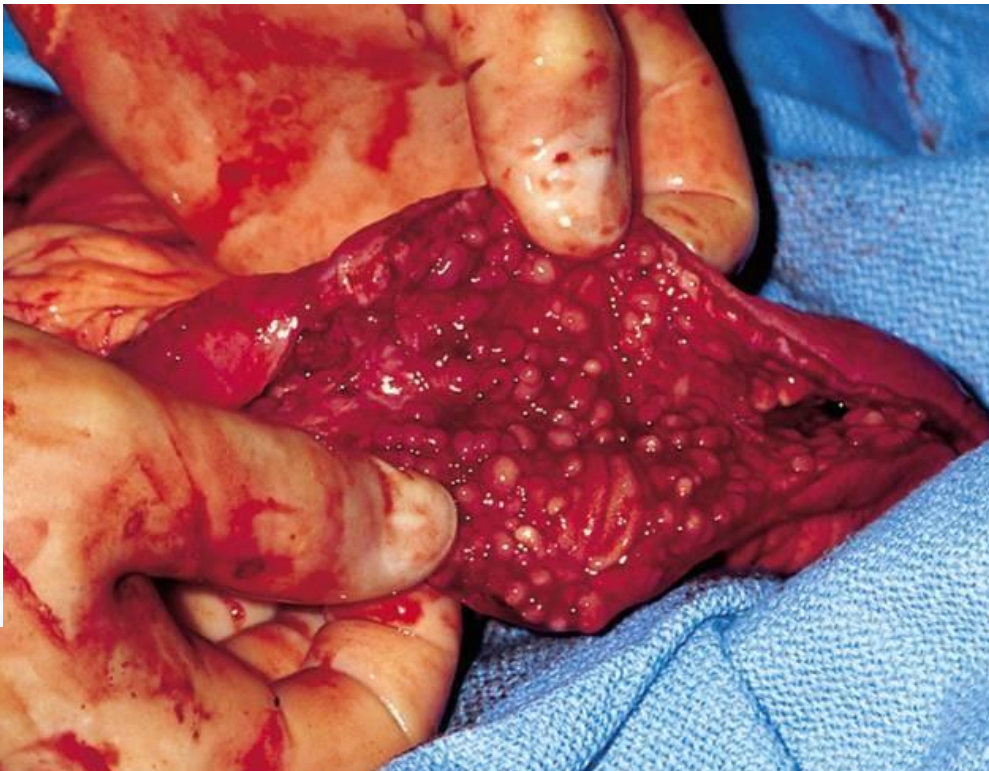
	Ulcerative Colitis	Crohn's disease
Symptoms	Bloody diarrhea	Rarely bloody, Weight loss, Diarrhea, Abd Pain, EIM's
Disease involvement	Colon only	Any part of the GI tract
Rectal disease	Rectal involvement	Rectal sparing
Perianal disease	Absent	Common
Pattern of distribution	Continuous	Skip lesions
Tissue involvement	Mucosal	Transmural
Colonoscopy findings	Confluent ulceration, friability (bleeding mucosa), Aphthous ulcers	Aphthous ulcers, serpiginous ulcers, Cobblestoning 'skip' lesions
Histologic findings	No granulomas	Non-caseating granulomas in ~20%
Effect of smoking	Protective in some	Predicts aggressive course
Disease complications	Severe colitis, Toxic Megacolon, Colon cancer	Fistulae, Strictures Colon or Small Bowel cancer

Normal Colon

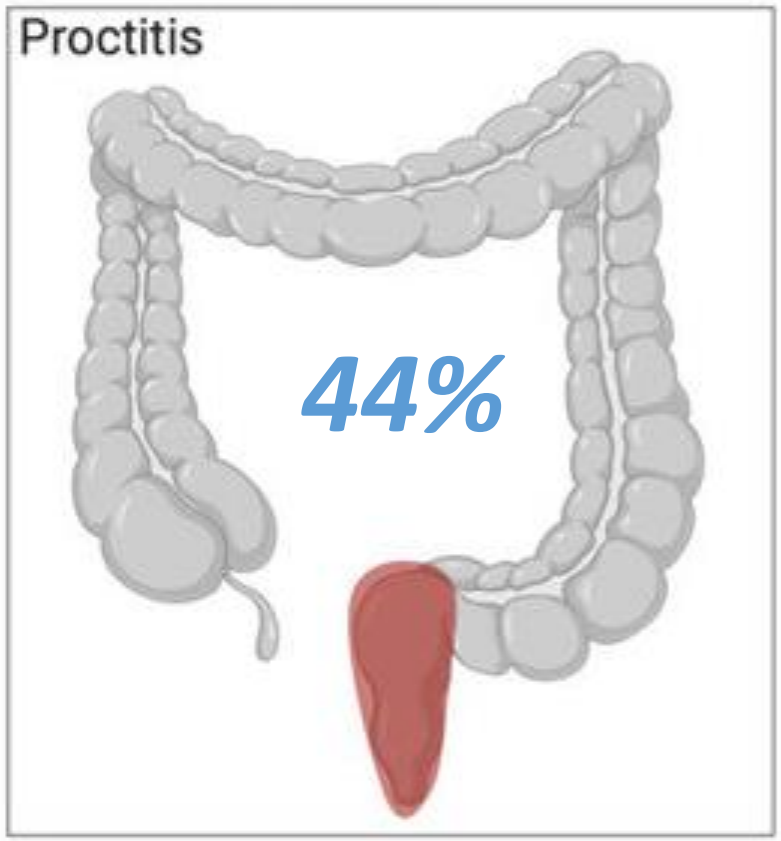


Ulcerative Colitis

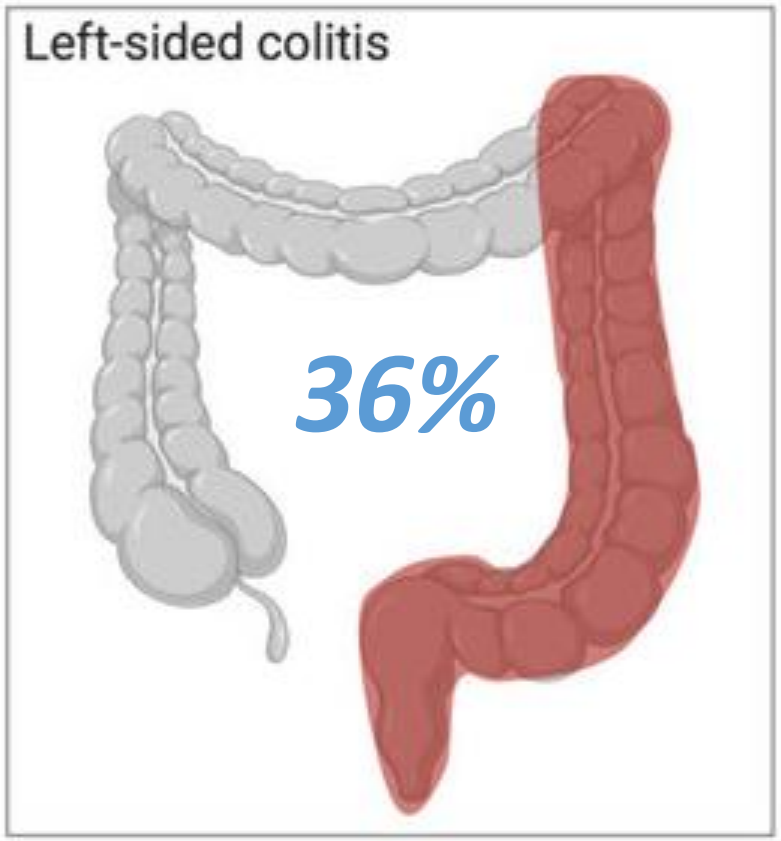




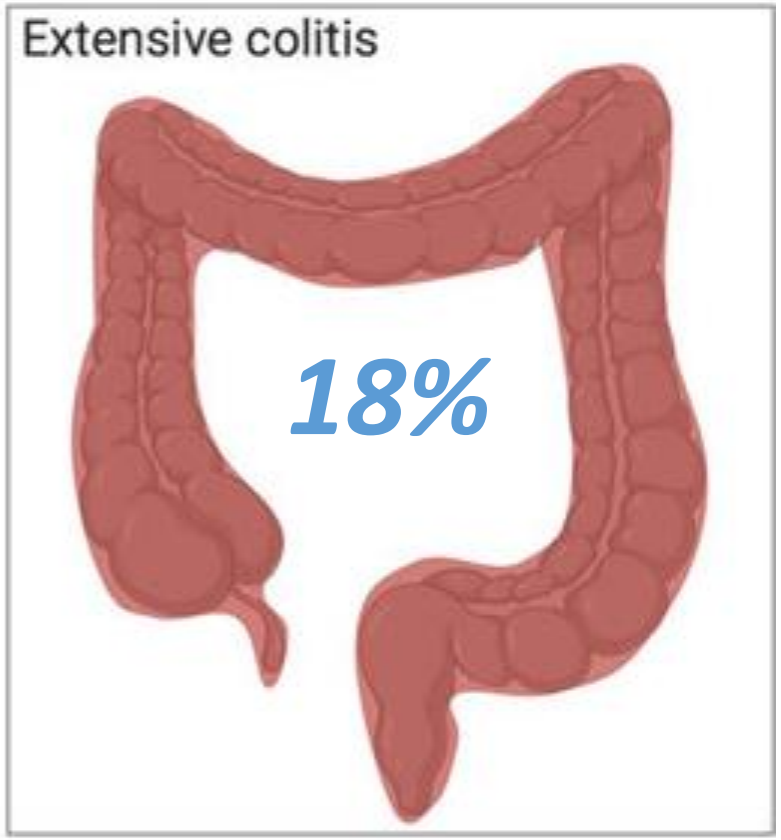
Affected Site of Disease: Ulcerative Colitis



Confined to Rectum



Up to Splenic Flexure



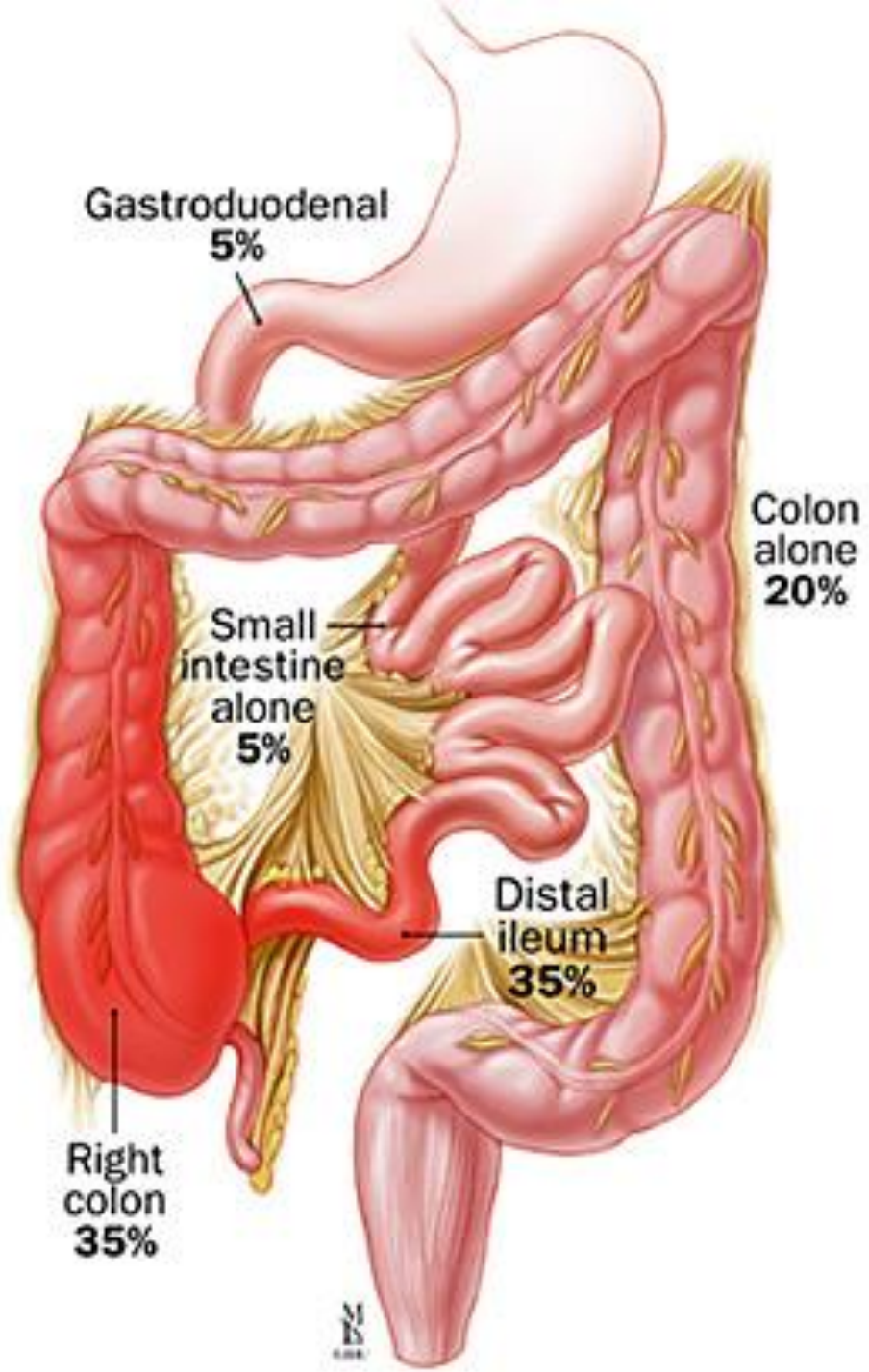
Beyond Splenic flexure
Often involving entire colon
(pancolitis)

Langholz et al. Scand J Gastroenterol. 1991;26:1247-1256

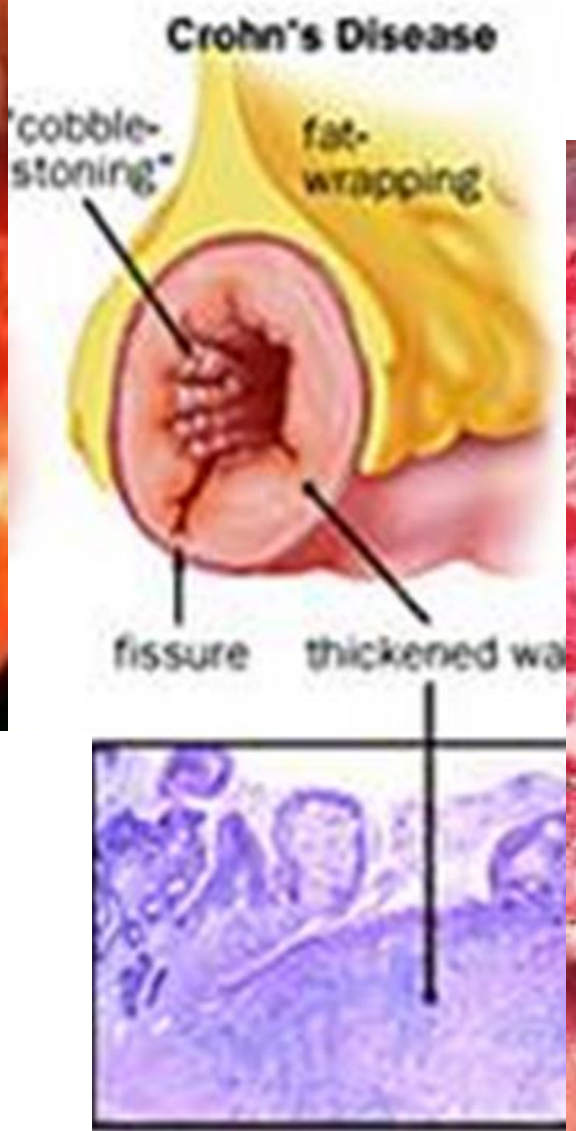
Crohn's Disease

Majority of Crohn's patients have Ileal and/or Colonic disease

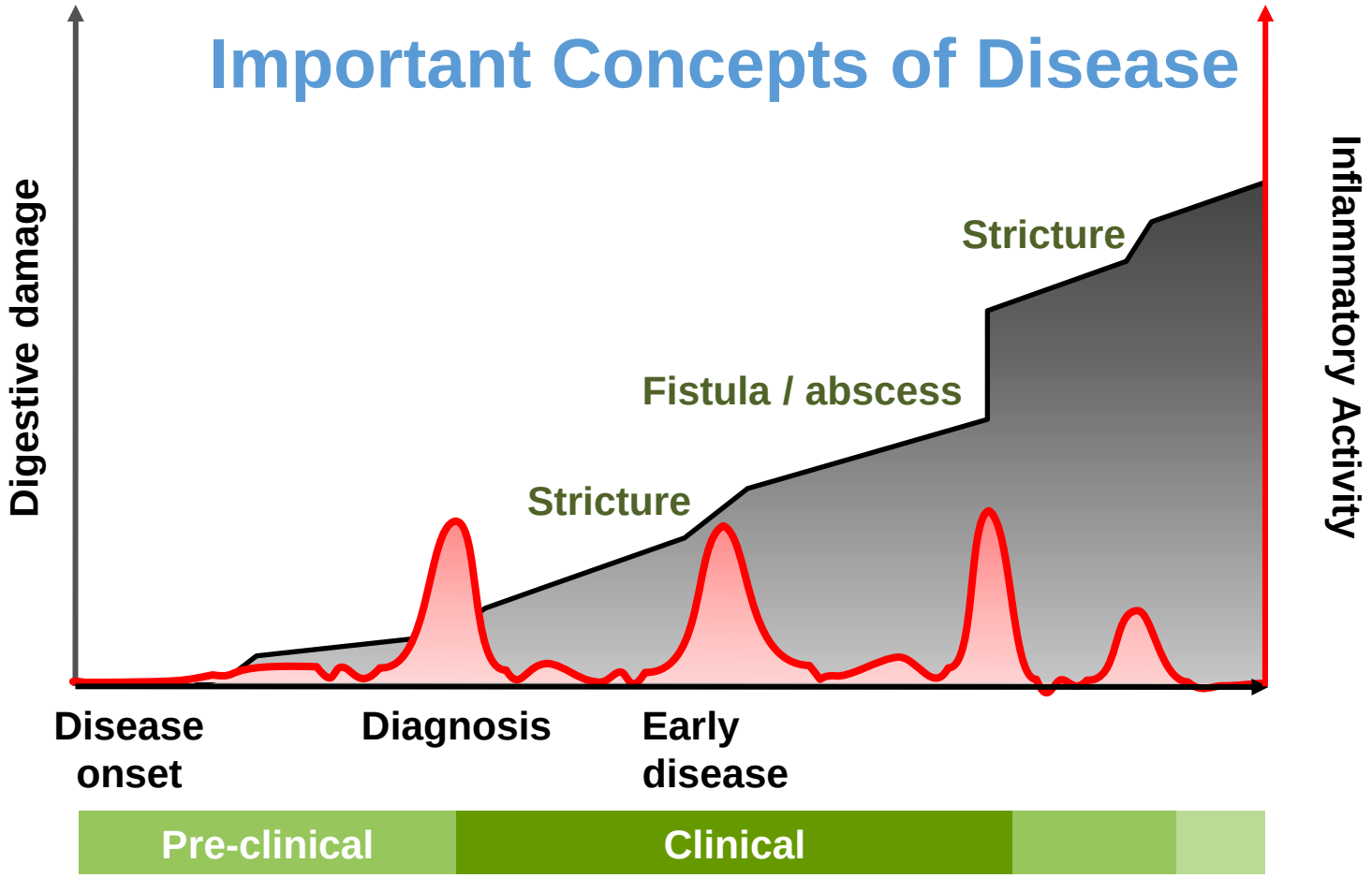
Modern day studies suggest we may be under diagnosing Upper GI (UGI) Crohn's, perhaps as common as 5-25% of CD patients w/UGI CD



Crohn's Disease



Relapsing & Remitting Inflammatory Time Course



- Life-long, chronic disease, without cure
- Waxing & waning disease course with ‘flare’ & ‘remission’
- Complications and bowel damage accumulate

Pariente B, Cosnes J, Danese S, et al. Development of the Crohn's disease digestive damage score, the Lémann score. *Inflamm Bowel Dis*. 2011;17(6):1415–1422.

Key Concepts

Ulcerative colitis involves only the colon and affects the inner most intestinal lining (mucosa).

Crohn's disease can affect mucosa through the wall of the intestine (transmural) at any area of the intestine from mouth to anus, although ileum & colon most commonly involved.

In CD: Unchecked disease over a lifetime can result in strictures, fistulae and abscesses

In UC: Unchecked disease can lead to scarring and atony of the colon if not bloody diarrhea alone.

In Both: Unchecked disease can increase the lifetime risk of intestinal cancer

Medical Treatment Concepts

AVOID long-term steroids due to numerous and predictable side effects & adverse events.
Instead, favor Steroid-Sparing therapies.

Late start of Steroid Sparing therapy does ***NOT*** prevent complications of disease (stricture, fistula, abscess, cancer, flare).
Rather, start Steroid sparing therapy ***EARLY*** !

Many treatments require higher doses of a medicine known as ***Induction*** treatment.
This is followed by a dose provided at regular intervals every few weeks or months known as ***Maintenance*** treatment.

Medical Treatment Options

Corticosteroids
Mesalamines
Immunomodulators: 6-MP, Azathioprine
Methotrexate

Monoclonal Antibodies (aka, Biologics)
- Cytokine Blockade
  - Anti-TNFs: Infliximab, Adalimumab, Certoluzimab, Golimumab
  - Anti-IL-12/23: Ustekinumab
- Lymphocyte Trafficking Inhibitors
  - Anti-Integrin: Vedoluzimab

Small Molecule Therapies (non-protein/antibody)
- Janus Kinase Inhibitors: Tofacitinib, Upadicitinib
- S1P: Ozanimod

IBD Therapeutics: Evolution to Revolution

Surgery & Steroids remained the mainstay of therapy

for the entire 20th century

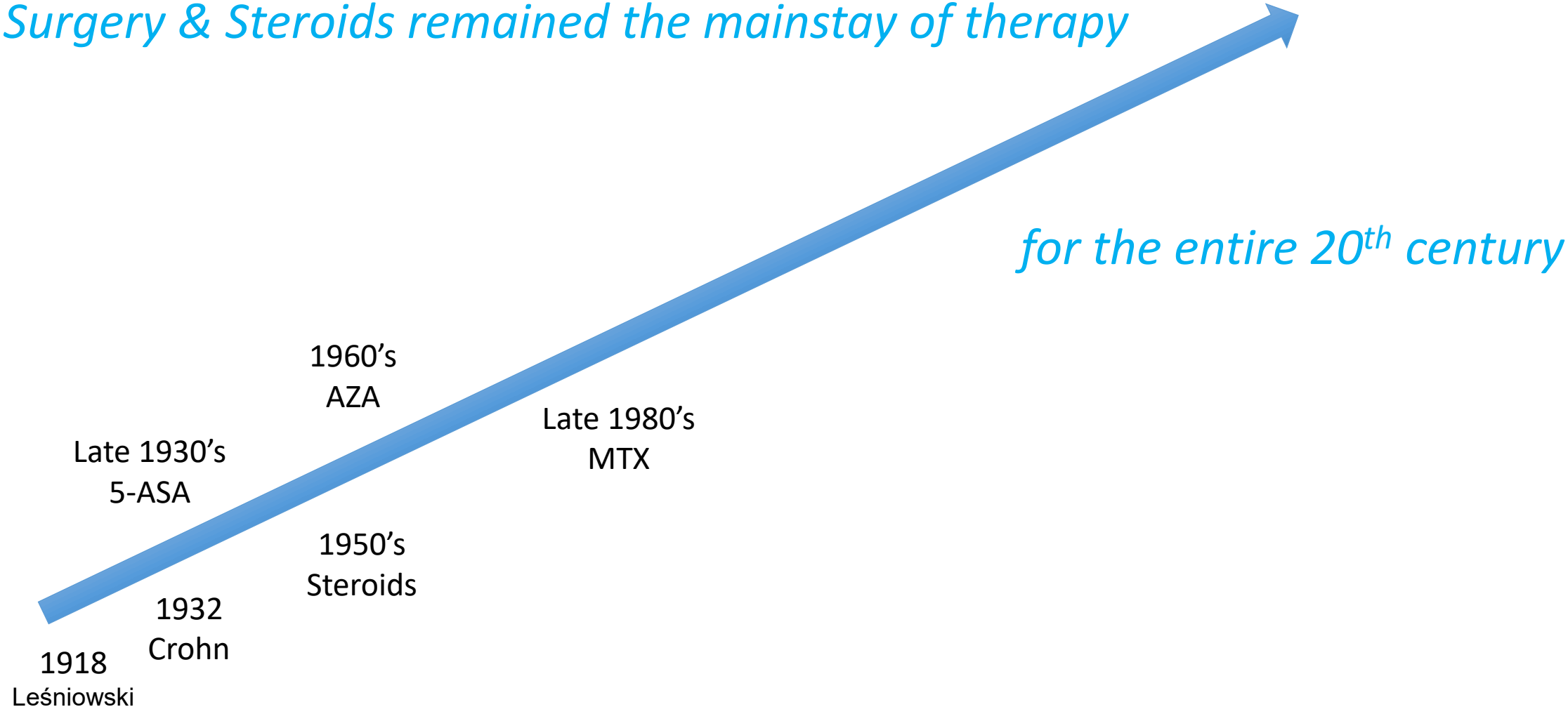


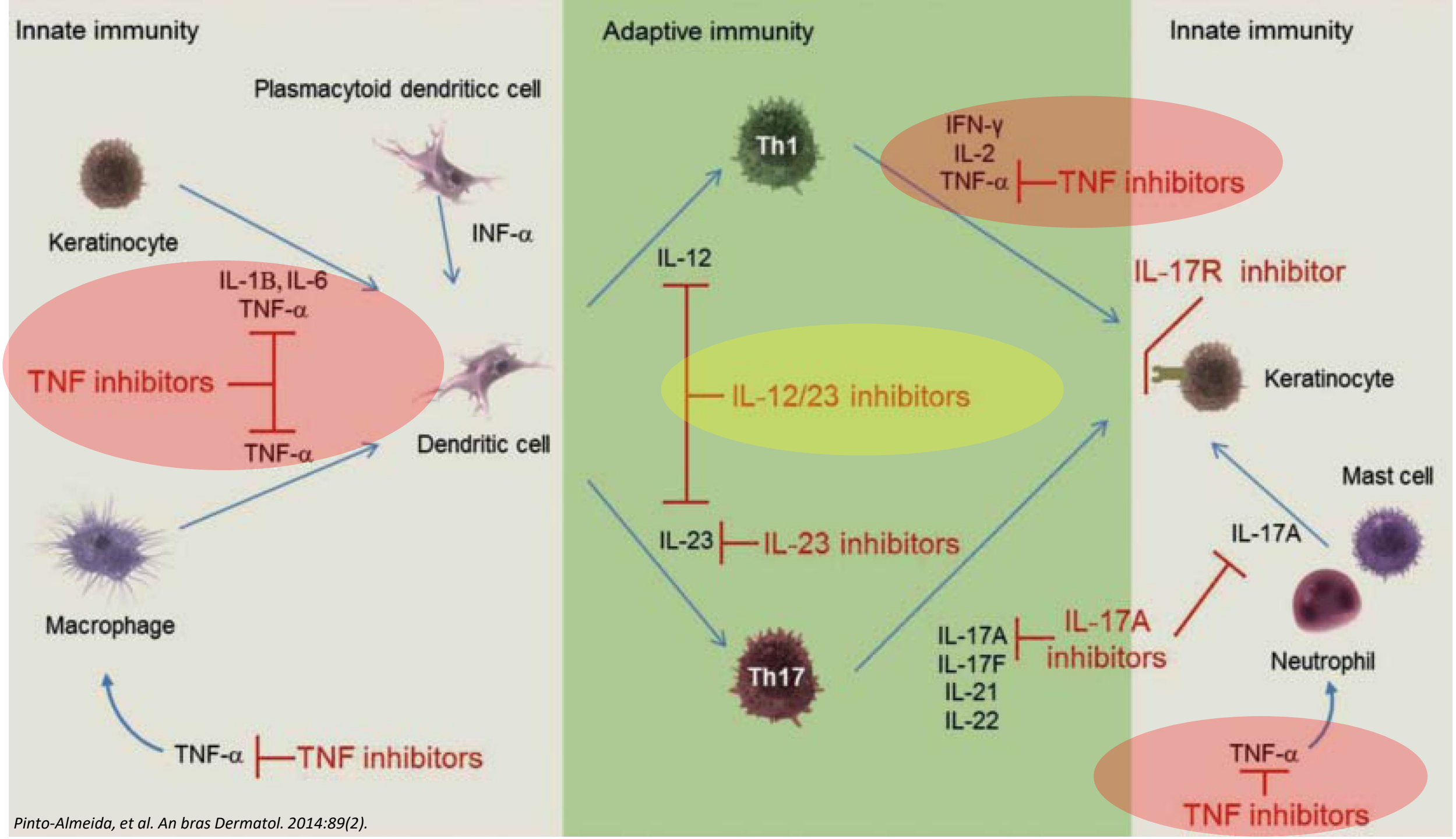
Image per Dr. Nandi

Corticosteroids

- Rapid onset
- IV in hospitalized patients
- PO outpatient, 40-60 mg/day w/gradual taper by 5 mg/week
- Chronic therapy assoc'd w/intolerable side effects & adverse events

Prednisone : 'The all the time eating, bone thinning , shaking , weight gaining, so you can never sleep again medicine !

- Budesonide: Limited systemic circulation so minimal to no side effects, only helpful in Mild-Moderate ileo-colonic disease



Pinto-Almeida, et al. An bras Dermatol. 2014:89(2).

IBD Therapeutics: Evolution to Revolution

Expanding arsenal

Recent highlights include
New MOAs !
IV to SC formulae !
Effective oral therapeutics !

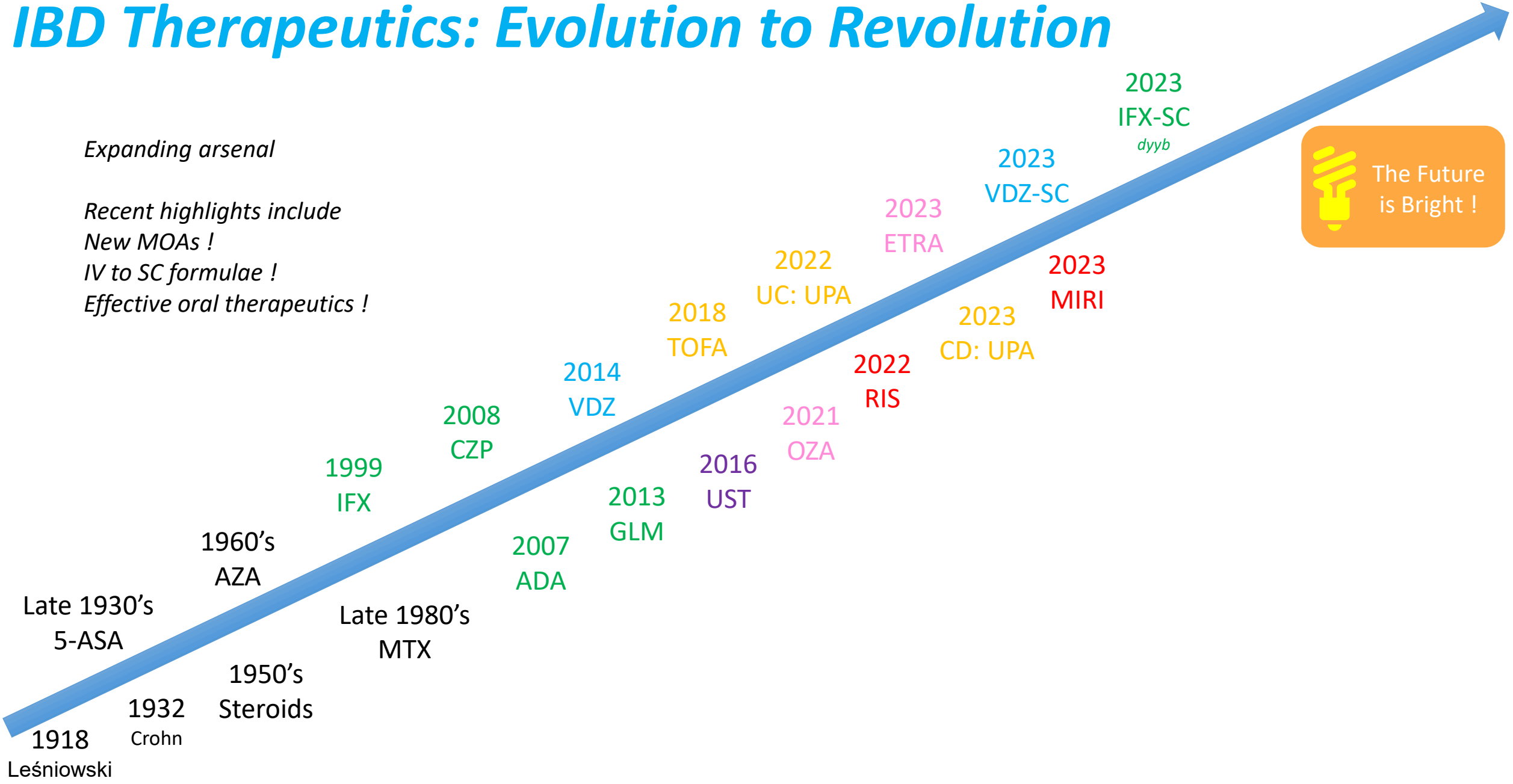
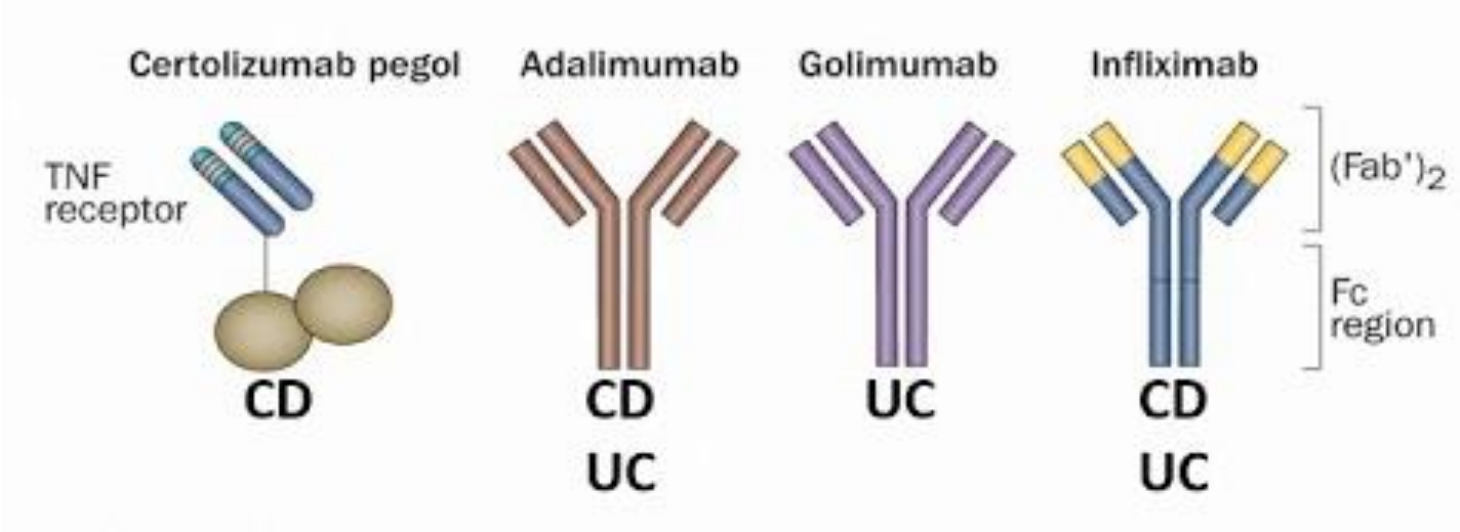


Image per Dr. Nandi

Biologics : Anti-TNFs



Introduced in 1998
Anti-cytokine therapy:
Tumor Necrosis Factor

Some agents approved for Crohn's and/or UC

Depending on type, administered via
IV infusion or Subcutaneous injection

Side Effects rare, Possible increased risk of
- Infection (Screen for Hepatitis B and Tuberculosis)
- Skin cancer
- Infusion reactions
- Heart failure
- Developing antibodies against the Anti-TNF agent (immunogenicity)

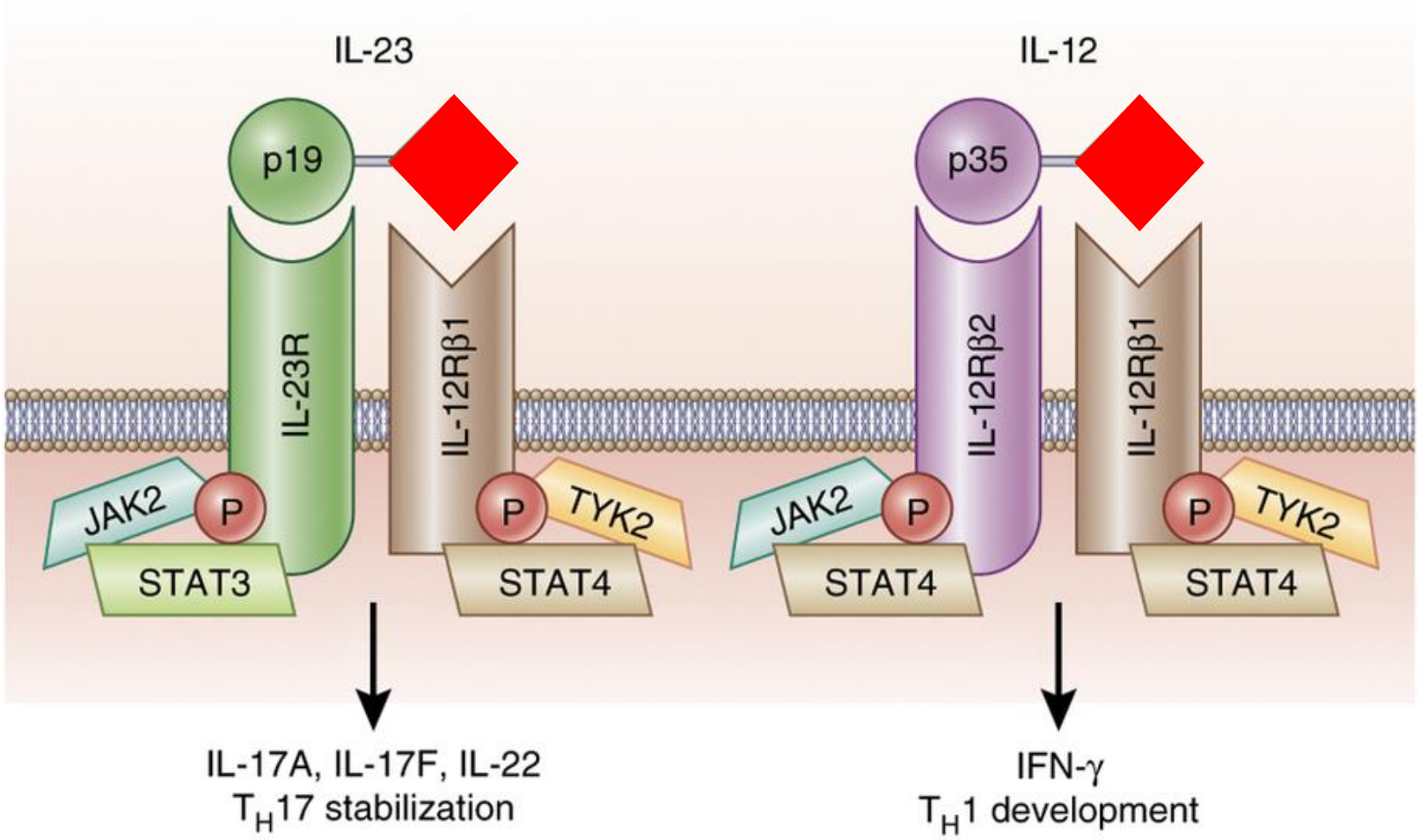
Biologics : Anti-IL-12/23 - Ustekinumab

Antibody directed to p40 subunit shared by both IL-12 and IL-23

Approved for both Crohn's and UC

Good efficacy, Less immunogenic

Screen for Hepatitis B and Tuberculosis



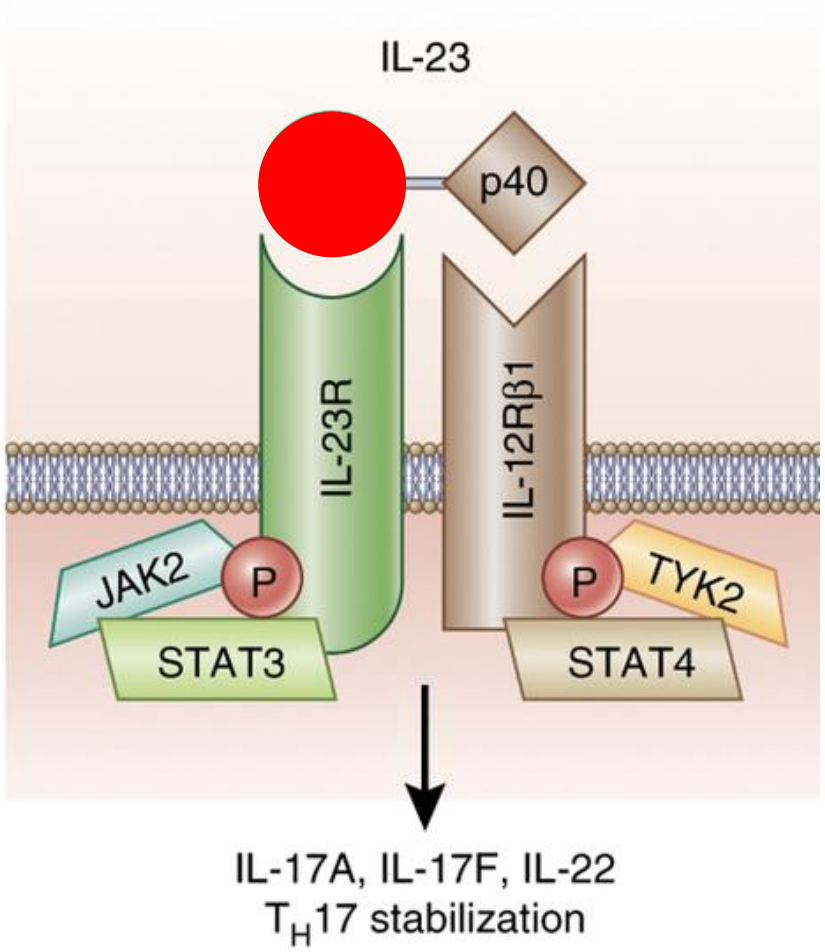
Biologics : Anti-IL-23 – Risankizumab, Mirikizumab

Antibody directed to p19 subunit unique to only IL-23

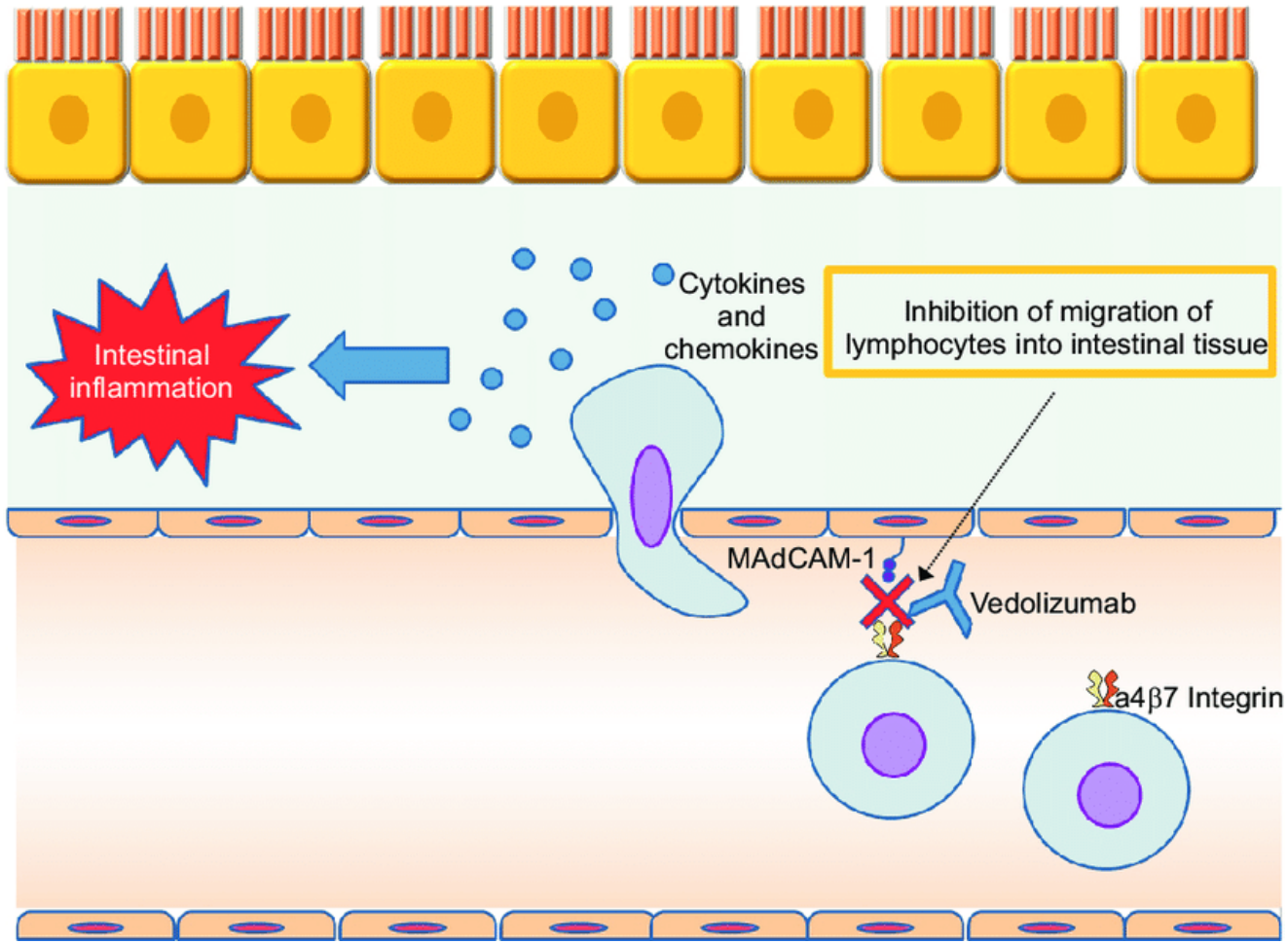
RIS - Approved for Crohn's
MIRI – Approved for UC

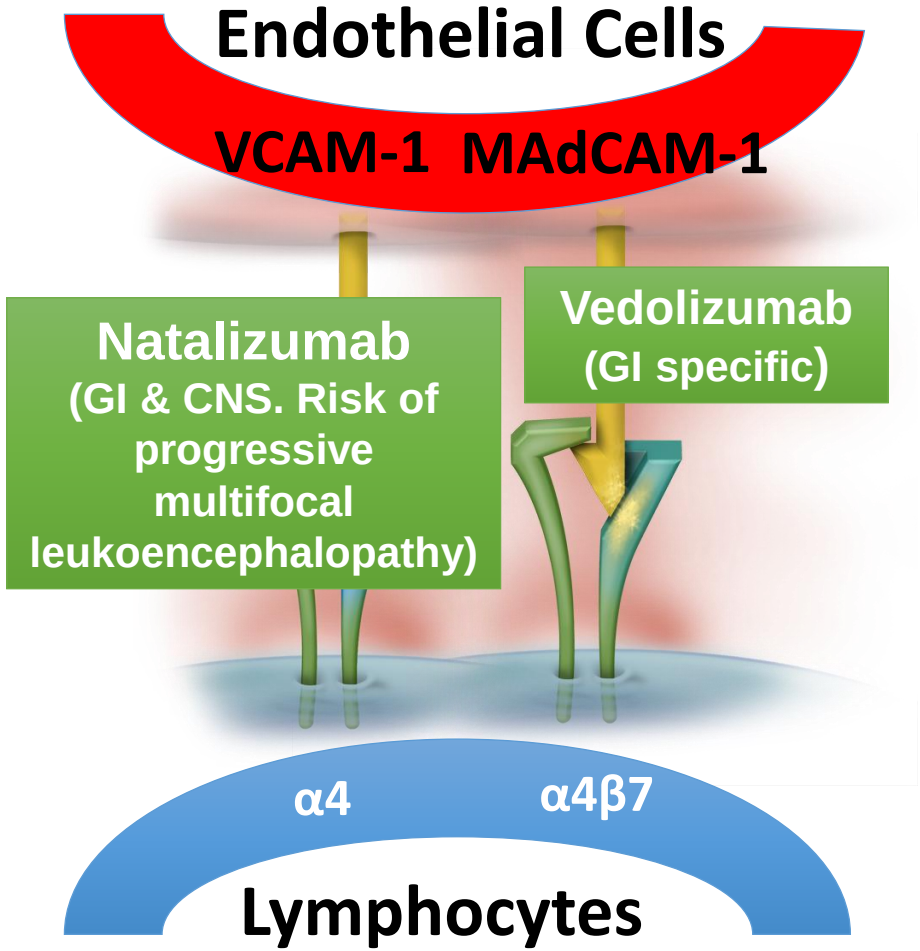
Good efficacy, Less immunogenic

Screen for Hepatitis B and Tuberculosis



Biologics : Anti-Integrin - Vedoluzimab





Does NOT block cytokines. Instead, prevents leukocytes from traveling to gut.
Vedoluzimab does not affect CNS, therefore no reported PML. Natalizumab not utilized in modern practice.
Vedoluzimab does ***NOT*** reactivate dormant Hepatitis B or Tuberculosis.

Small Molecule : JAK Inhibitor – Tofacitinib, Upadicitinib

Cytokine-Receptor binding promotes JAK polymerization

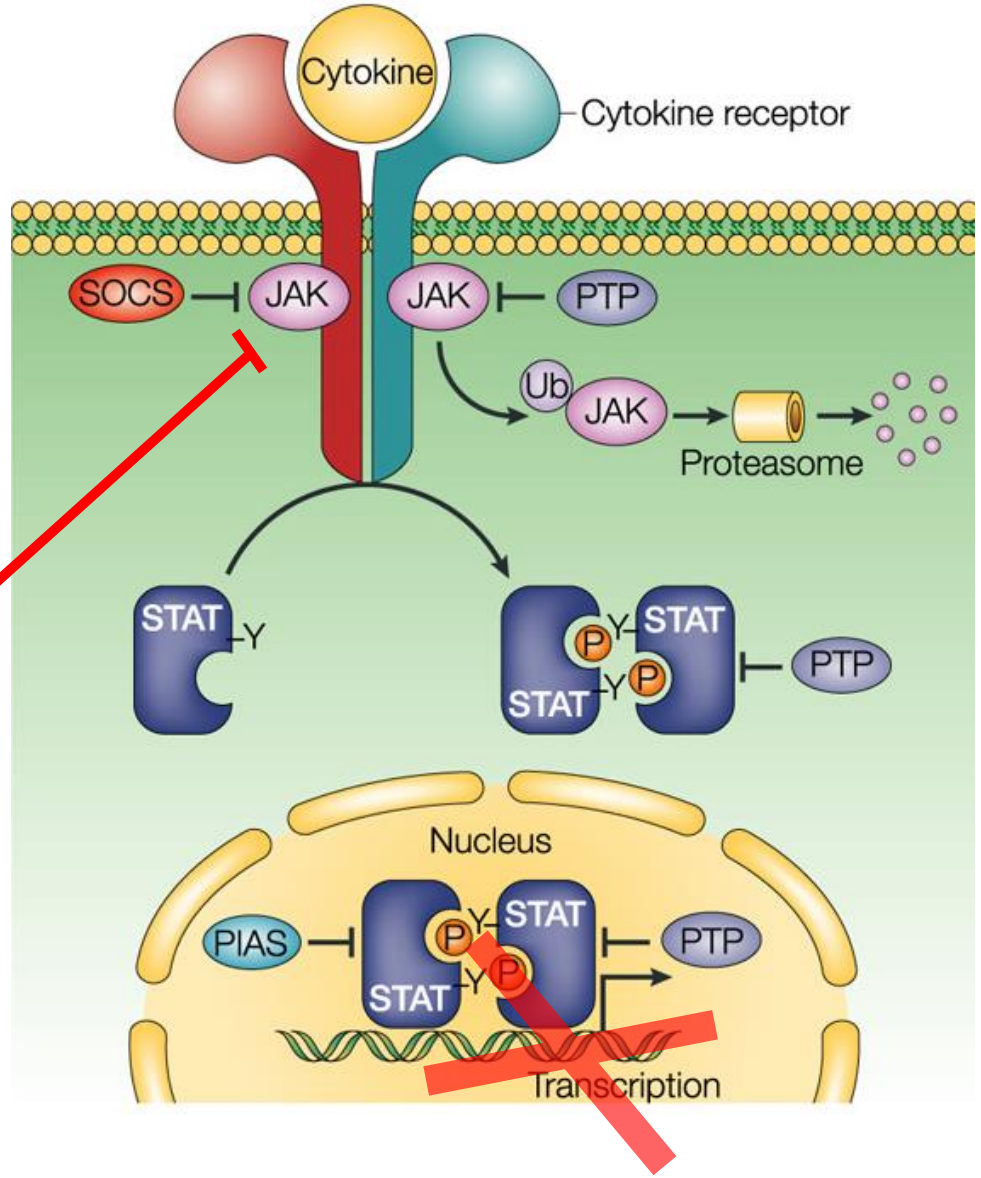
In turn, JAK phosphorylates STATs

Phosphorylated STATs promote transcription & cytokine synthesis.

JAK's are synthetic, not proteins delivered orally.

JAK inhibition ultimately prevents cytokine production

Approved for UC only
No efficacy in CD

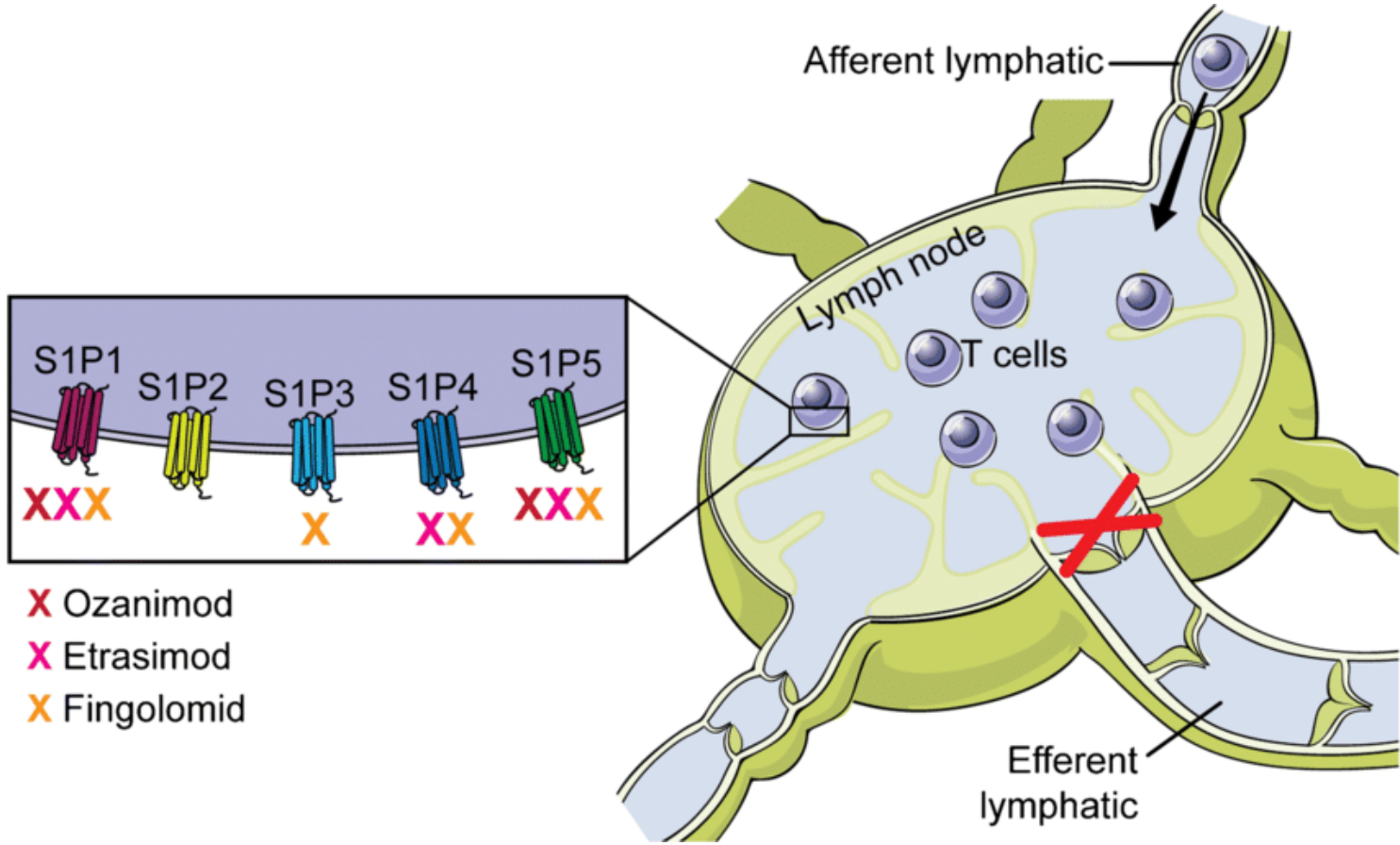


Small Molecule : S1P Antagonist – Ozanimod, Etrasimod

S1P receptors help modulate which lymphocytes migrate to which organs for immune surveillance.

Ozanimod binds specific S1P receptor subtypes to predominantly prevent lymphocyte migration to the intestine.

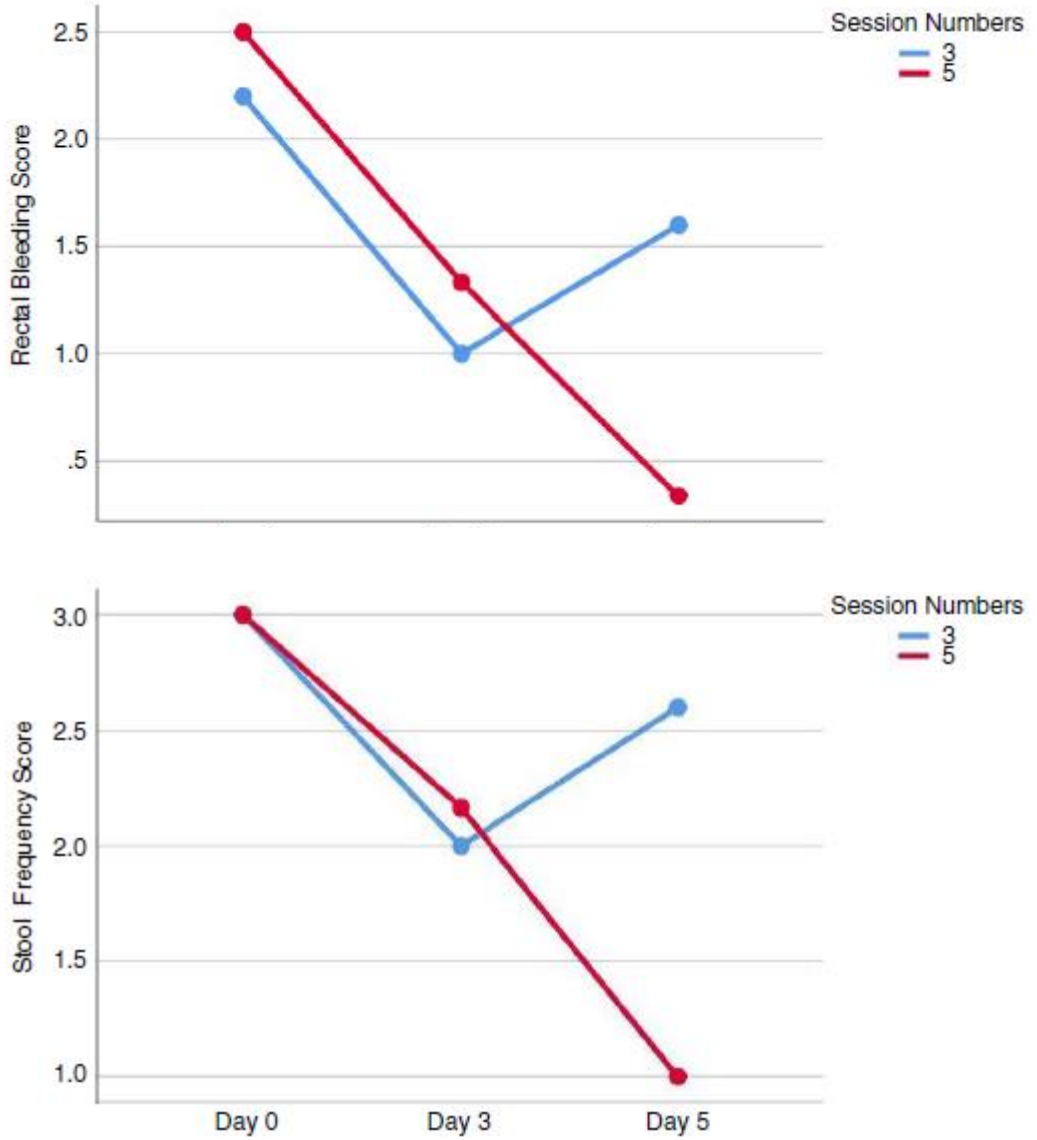
Approved for UC only
No efficacy in CD



Hyperbaric Oxygen Therapy: UC

HBOT prevented a 2nd line biologic from being instituted in 85% of cases.

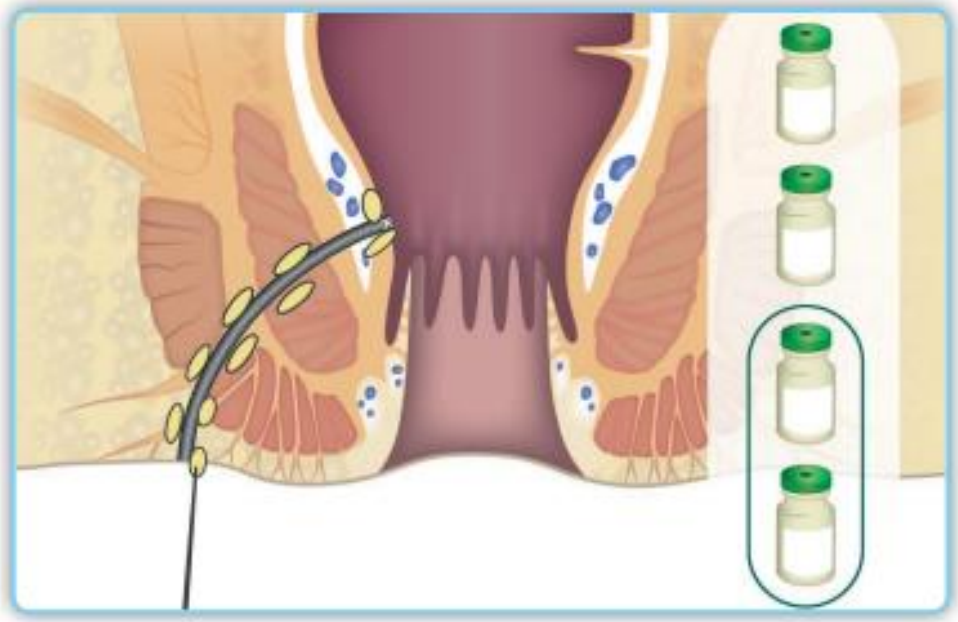
5 days superior to 3 days of HBOT



Dulai PS, et al. Aliment Pharmacol Ther. 2020 Sep;52(6):955-963.

Stem Cell Therapy : Perianal Fistulizing CD

Darvadstrocel = Expanded allogeneic adipose-derived mesenchymal stem cells



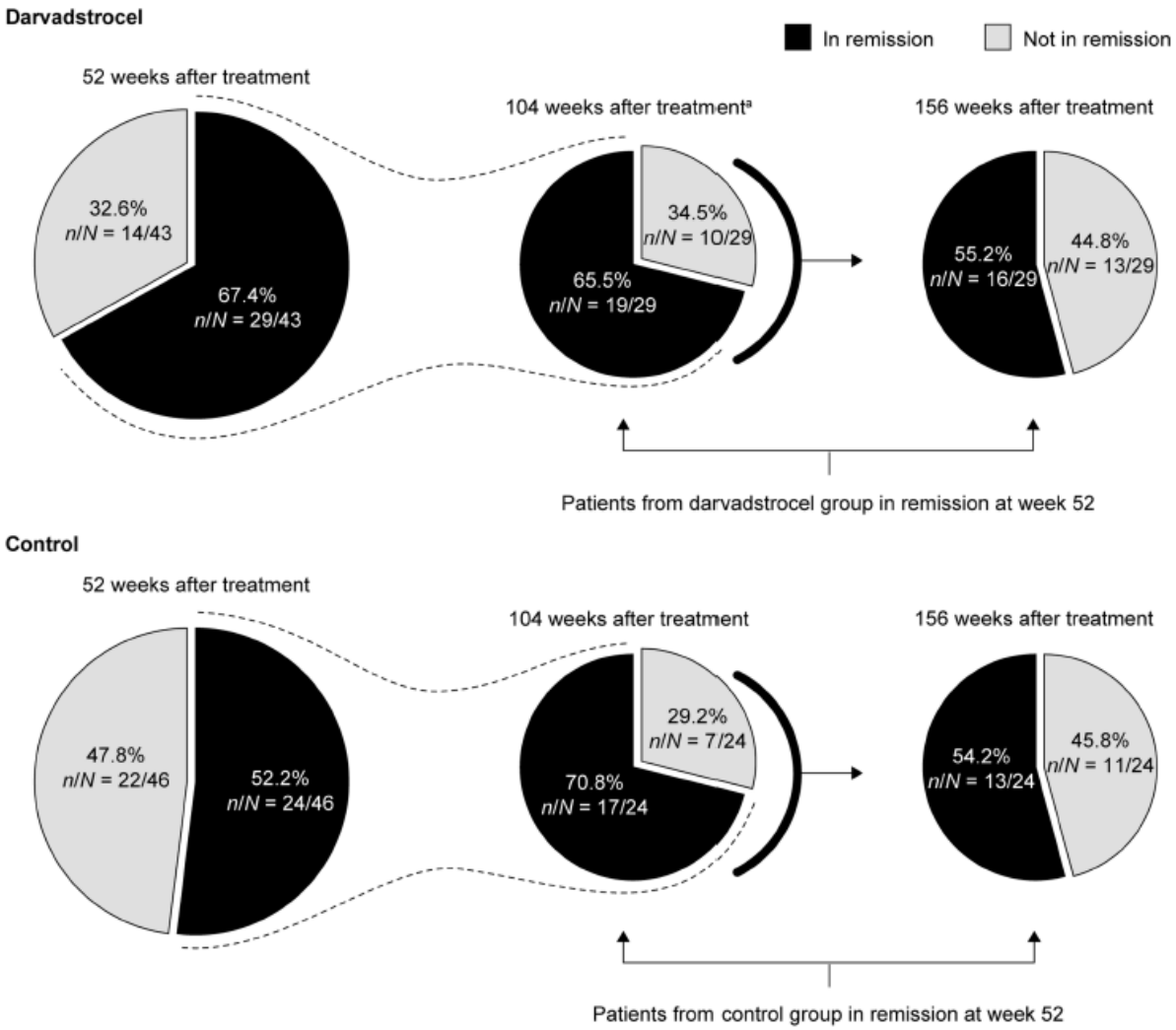


FIGURE 4. Sustained clinical remission in patients with Crohn's disease-related complex perianal fistulas treated with darvadstrocel vs control. [a]DVS group: of the 23 patients in clinical remission 104 weeks after treatment (Figure 3), 4 had not achieved remission by 52 weeks and are therefore not included in those reported to be in sustained remission at 104 weeks (n = 19). Control group: of the 20 patients in clinical remission 104 weeks after treatment (Figure 3), 3 had not achieved remission by 52 weeks and are therefore not included in those reported to be in sustained remission at 104 weeks (n = 17).

Panes J, et al. Inflammatory Bowel Diseases, 2022, 28, 1737–1745.

IMT in Ulcerative Colitis

2017 — *Costello, et al*

Effect of FMT on 8 Week Remission in Mild-Mod UC

Multi-Center, Double-Blind, Autologous-Placebo Controlled, RCT

Intervention: Colonoscopic FMT + Enema x 2 enema over 7 days

Aneroboc pdIMT superior (12 / 38; 32%) to Autologous pIMT (3 / 35; 9%)

2015 — *Moyaeddi, et al*

FMT Induces Remission in Active UC Patients

Single Center, Double-Blind, Placebo Controlled, RCT

Intervention: Weekly IMT x 7 weeks

dIMT superior (9 / 38; 24%) to pIMT (2 / 37; 5%)

2016 — *Paramsothy, et al*

Multidonor Intensive IMT for Active UC

Single Center, Double-Blind, Pooled Donor (3-4) vs Saline Placebo, RCT

Intervention: Colonoscopic Pooled dIMT + Pooled dEnema IMT x 5d/week x 8 weeks

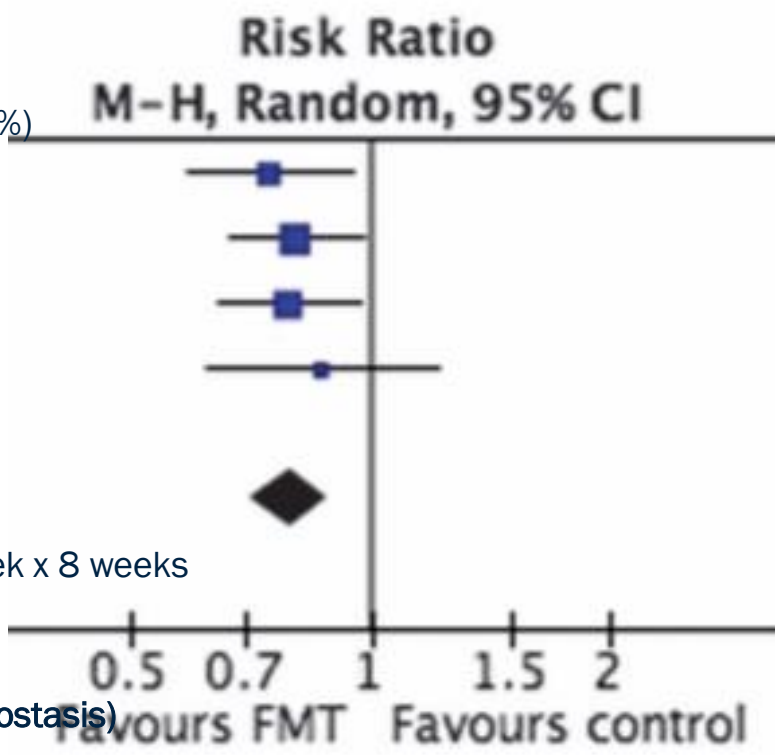
Pooled dIMT superior (11 / 41; 27%) to pIMT (3 / 40; 3%)

2015 — *Rossen, et al*

TURN trial (Trans- plantation of Feces in Ulcerative Colitis; Returning Nature's Homeostasis)

Single Center, Double-Blind, Single Donor vs Autologous-Placebo, RCT

Trended but NO significant difference between dIMT vs aIMT



Note: Ser-287 encapsulated spore Phase 2b for UC did not meet primary endpoints

Narula N, et al. Inflamm Bowel Dis 2017;23:1702–1709

Antibiotic Pre-Administration May Improve FMT Response in UC

Prior Studies

UC vs Controls — Decreased diversity
Decreased *Firmicutes*
– *Clostridia XIVa & IV*
Decreased *Bacteroidetes*

AFM vs AFM + FMT

AFM = Amoxicillin + Fosfamycin + Metronidazole

Combo arm (AFM + FMT) associated w/greater recovery of *Bacteroidetes* and improved response

Question

Is there a difference between self-recovered Bacteroidetes or FMT re-colonized Bacteroidetes ?

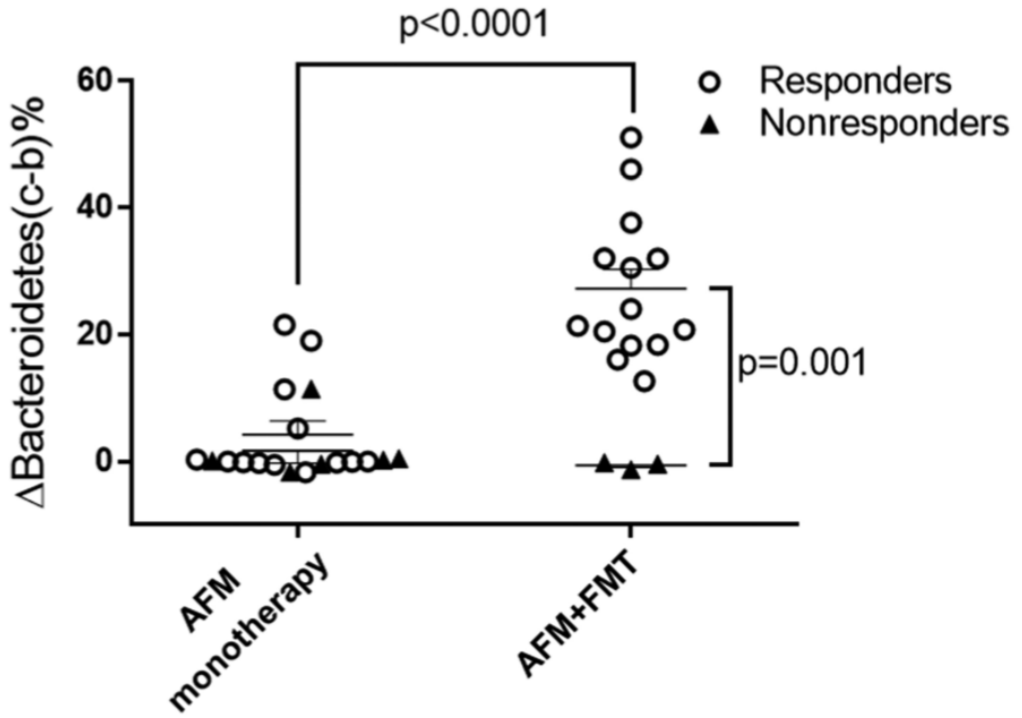


FIGURE 3. The relative abundance of Bacteroidetes following combination therapy with AFM and FMT at 4 weeks posttreatment was significantly higher ($P < 0.0001$) than that in patients receiving AFM monotherapy (n = 17 receiving combination therapy [AFM plus FMT]; n = 19 receiving AFM monotherapy). The proportion of Bacteroidetes increased significantly in the responders (n = 14) compared with that in nonresponders (n = 3) at 4 weeks post-FMT ($P = 0.001$).

Ishikawa D et al. Inflammatory Bowel Diseases, 23(1):1;116-125.

Key Summary Concepts

IBD is a spectrum of immune mediated inflammatory attack of the intestine which may manifest as Crohn's disease, Ulcerative colitis, or Indeterminate colitis.

Increasing incidence/prevalence of disease observed w/more moderate-severe disease.

Early initiation of Steroid sparing therapy (biologics, small molecule) can prevent long-term complications, including cancer, that would otherwise require surgery.

Advances in therapy include new insights into the role of hyperbaric oxygen therapy and/or microbiota restorative therapy in UC and mesenchymal stem cell therapy in perianal fistulizing Crohn's.

Got Questions?

Please Reach Out & Ask :

Neilanjan.Nandi@pennmedicine.upenn.edu

Integrative Healthcare SYMPOSIUM

Friday 1:30pm – 2:30pm

CME: Current & Emerging Advanced Therapeutics in the IBD Landscape

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