



# WHAT'S NEXT IN PEDIATRIC INFLAMMATORY BOWEL DISEASE?

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# Educational Objectives

- Distinguish between the signs, symptoms, and complications of ulcerative colitis and Crohns disease
- Describe diagnostic methods in practice for inflammatory bowel disease
- Identify current and future treatment and therapy options for inflammatory bowel disease

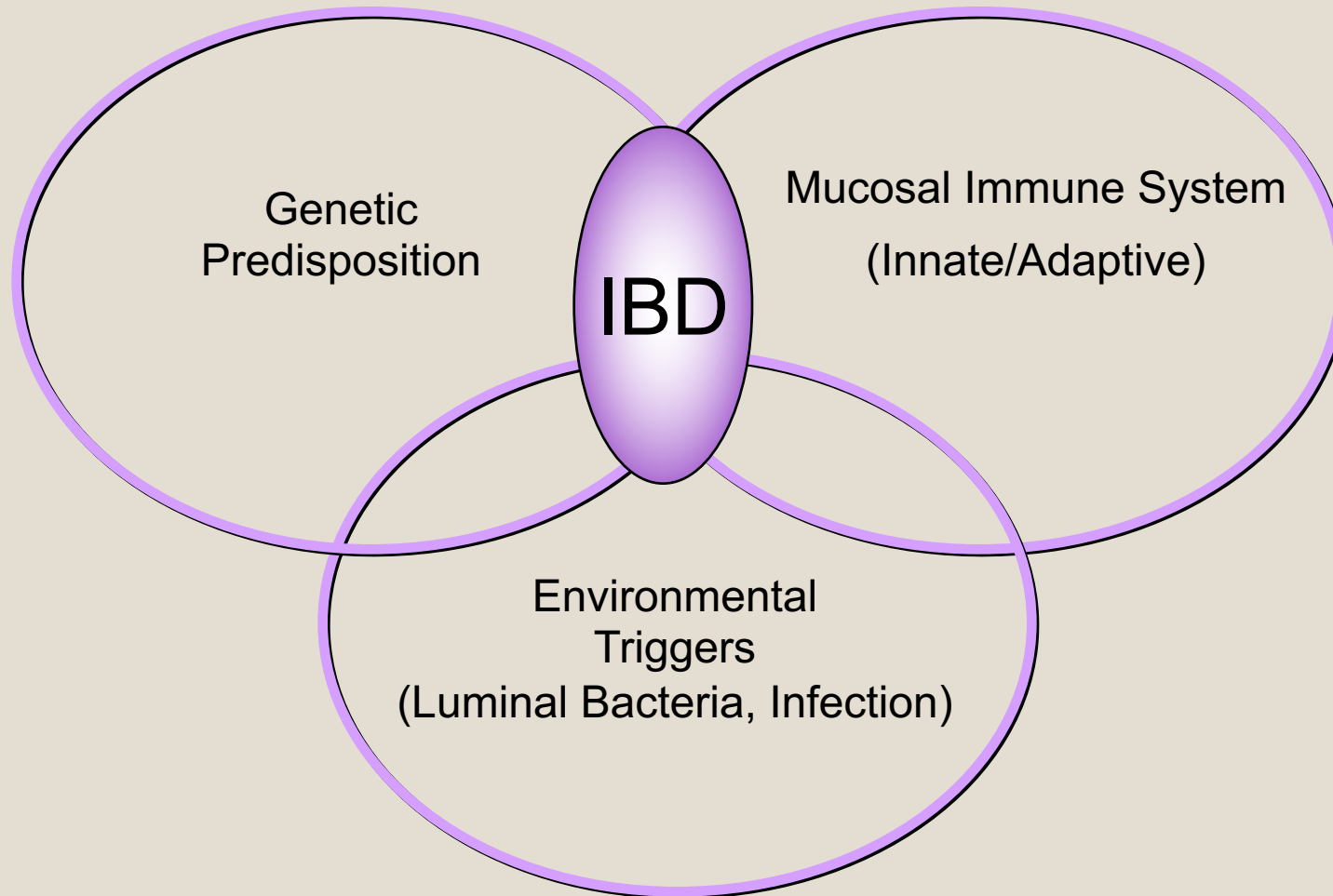
# Disclosures

- Abbvie Speakers Bureau
- Pfizer Speakers Bureau
- Prometheus Labs Physician Advisory Board
- This presentation will discuss use of some medications off-label in the pediatric population

# Background: Inflammatory Bowel Disease

- Chronic inflammatory disease of the intestinal tract
- Usually characterized by progressive damage to the gastrointestinal tract
- Pediatrics: risk for complications in growth, malnutrition, bone disease, psychosocial issues
- Pathogenesis poorly defined
- IBD is being identified more frequently in the US

# Etiologic Theories in Inflammatory Bowel Disease



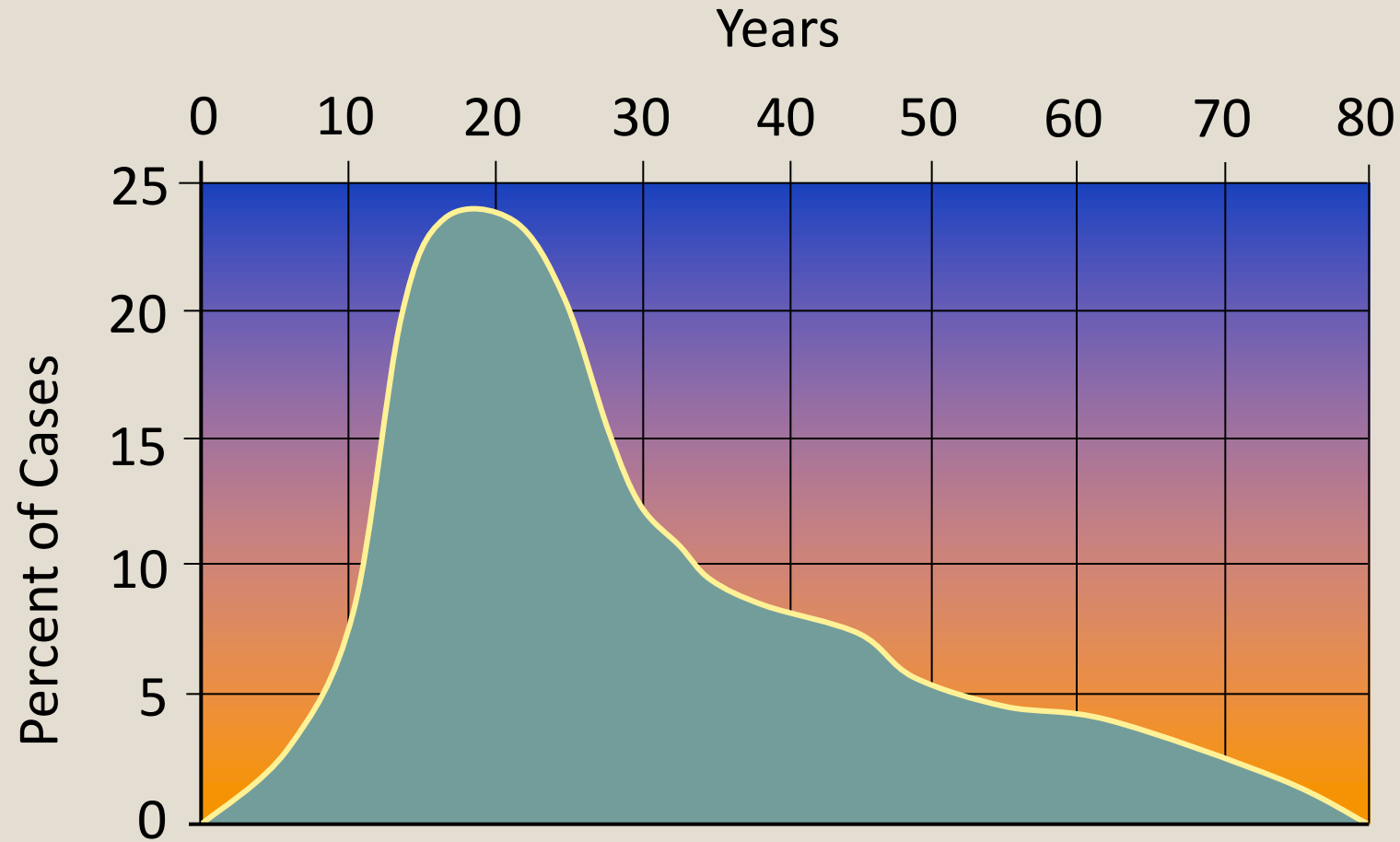
# IBD in Pediatric Patients

- Similarities with adults
  - Disease and therapy are generally the same
  - Differential diagnosis is commonly similar for patients over the age of 5 years
- Differences with adults
  - **More aggressive disease in pediatrics**
  - Lack of specific pediatric data
  - Lack of child-appropriate formulations
  - **Unique growth and development problems**

# How Common is Pediatric IBD in U.S.?

- Incidence increasing among children
- Ten percent, or 140,000, of the estimated 1.6 million Americans who suffer from IBD are under the age of 18.
- Approximately 20 percent of patients have another family member with IBD, and families frequently share a similar pattern of disease.
- IBD, which has been detected in infants as young as 18 months, can be particularly hard to diagnose in children.

# Age of Onset of IBD



**20-25% of IBD cases diagnosed by 20 years**



# Crohn's Disease vs. Ulcerative Colitis

## Crohn's Disease

- Any part of the GI tract
- Discontinuous
- Rectal sparing
- Ileum commonly involved
- Perianal disease
- Transmural inflammation
- Fistulae and abscesses
- Granulomas
- Strictures common

## Ulcerative Colitis

- Colon only (+/- gastritis)
- Continuous
- No rectal sparing
- +/- backwash ileitis
- No perianal disease
- Mucosal inflammation
- Abscesses very rare
- No granulomas
- Strictures rare

# IBD Presentation

- The initial symptoms may be nonspecific weight loss or delayed growth.
  - For example, 80-90 percent of children with Crohn's disease experience weight loss.
  - For this reason, the correct diagnosis can be difficult to make.
  - The average delay in diagnosis is three years from the onset of symptoms.
- Sixty to 90 percent of children with Crohn's disease and 14 percent of children with ulcerative colitis experience growth failure.

# IBD Presentation

- Other symptoms range from mild to severe and life-threatening and include any or all of the following:
  - persistent diarrhea,
  - abdominal pain or cramps, **\*\*\*RLQ TENDERNESS!**
  - rectal bleeding,
  - intermittent fever,
  - inflammation of joints (arthritic-like symptoms),
  - inflammation of skin or eyes, and
  - skin nodules and ulcers.

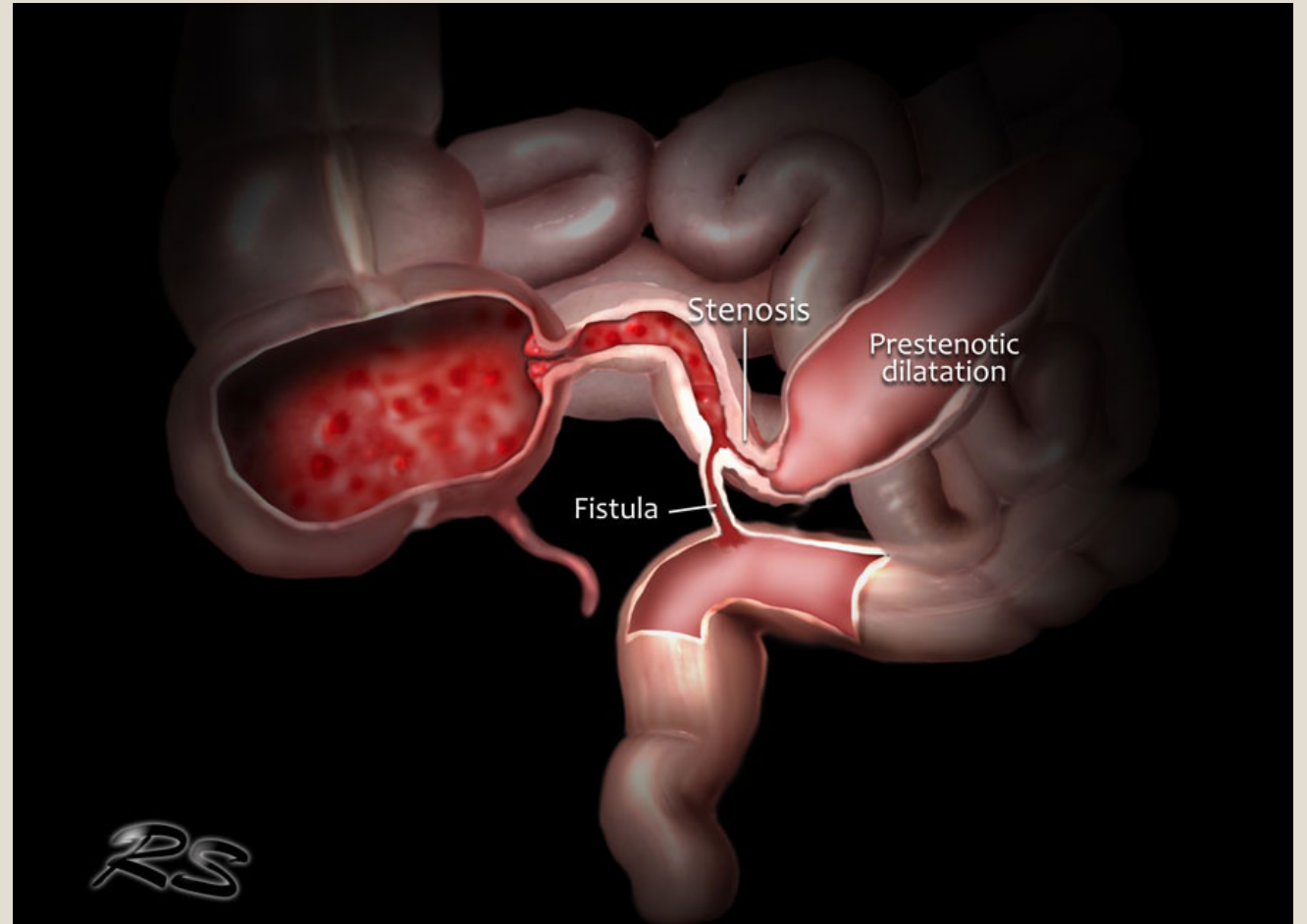
# Initial Laboratory Evaluation

- Complete blood count and differential
  - Anemia, thrombocytosis common
- ESR, CRP
  - Typically elevated with active inflammation
- Comprehensive metabolic panel
  - Screen for liver abnormalities
  - [Hypoalbuminemia](#) → Highly suggestive
- Rule out enteric infection, celiac disease
- IBD Serology: promising, but not proven

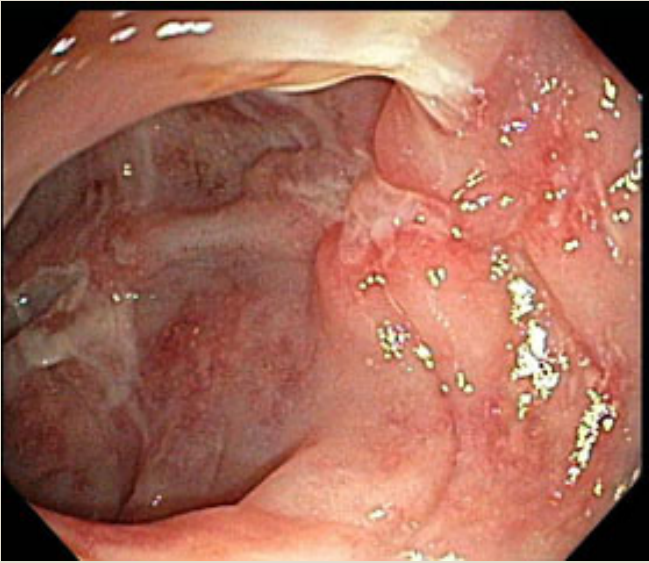
LOW HGB  
LOW ALB  
HIGH CRP  
HIGH ESR

# Radiology Testing

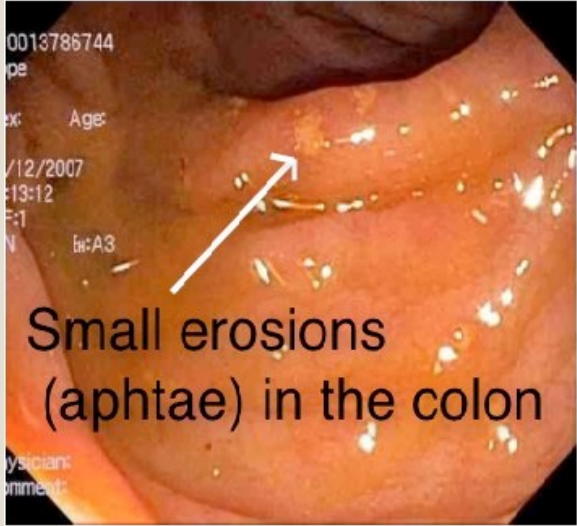
- Upper GI with Small Bowel Follow-Through
  - Cheapest
  - Easiest to do – no IV's
  - Least detailed
  - Most radiation
- CT enterography
  - More detail than UGI/SBFT with less radiation
  - Faster than MRI
- MR enterography
  - No radiation
  - Best image quality
  - Most expensive
  - May need anesthesia



# Endoscopy/Colonoscopy Crohn's disease



**Patchy Colitis**



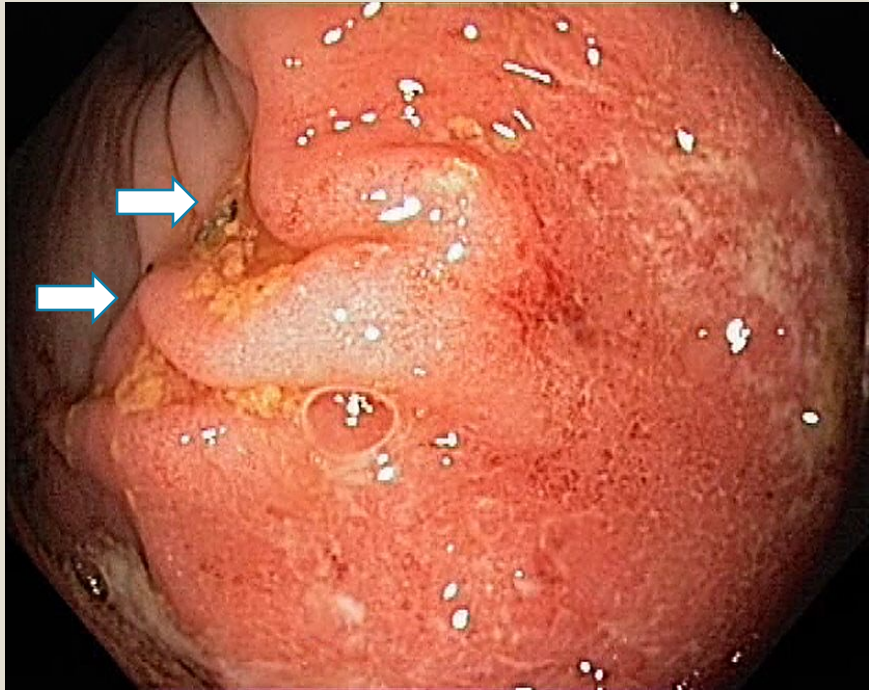
**Aphthous Ulcerations**



**Crohn's ileitis**



# Endoscopy/Colonoscopy - Ulcerative Colitis

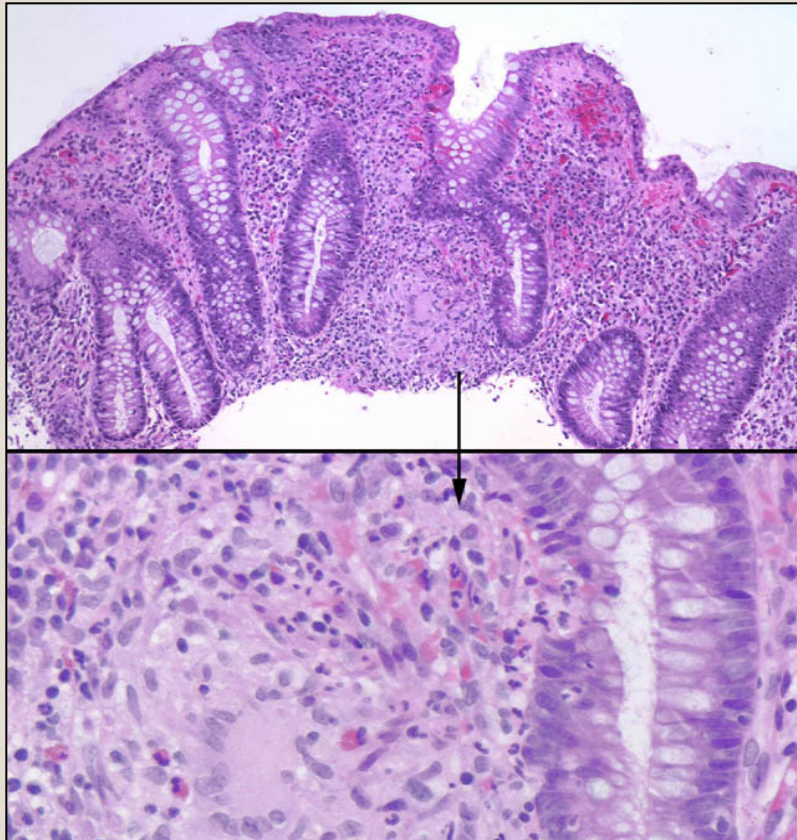


**Colitis with Transition Zone**



**Pancolitis**

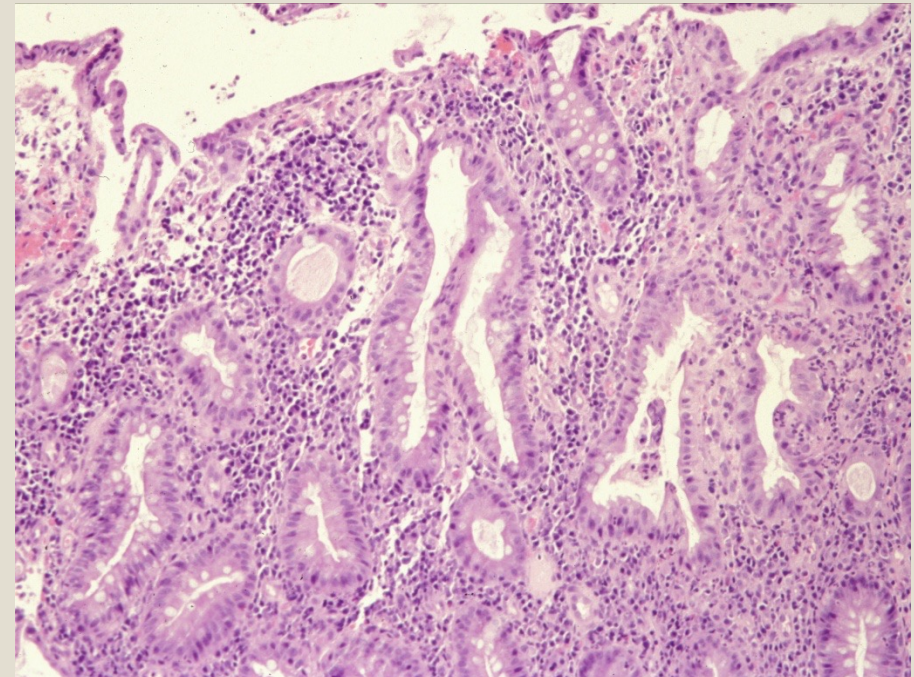
# Histopathology



**Colitis with Granuloma**

## **Colitis**

- Crypt branching, distortion
- Crypt abscess
- Hypercellular

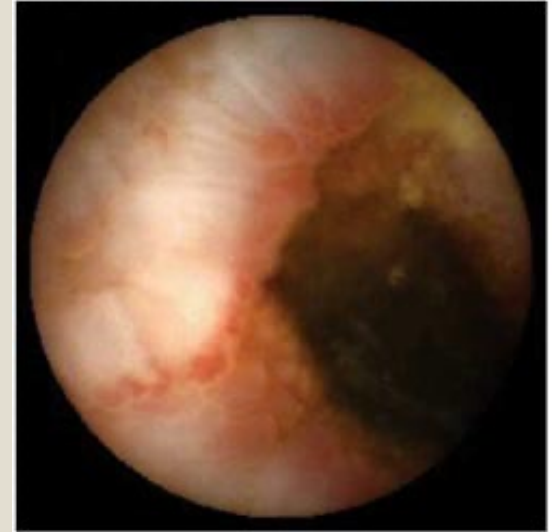






# Capsule Endoscopy

- Relatively easy to swallow
  - Endoscopically placed in younger patients
- Can visualize entire small bowel
- **MUST** rule out intestinal stricture prior to placement
- 8 hours of footage to review



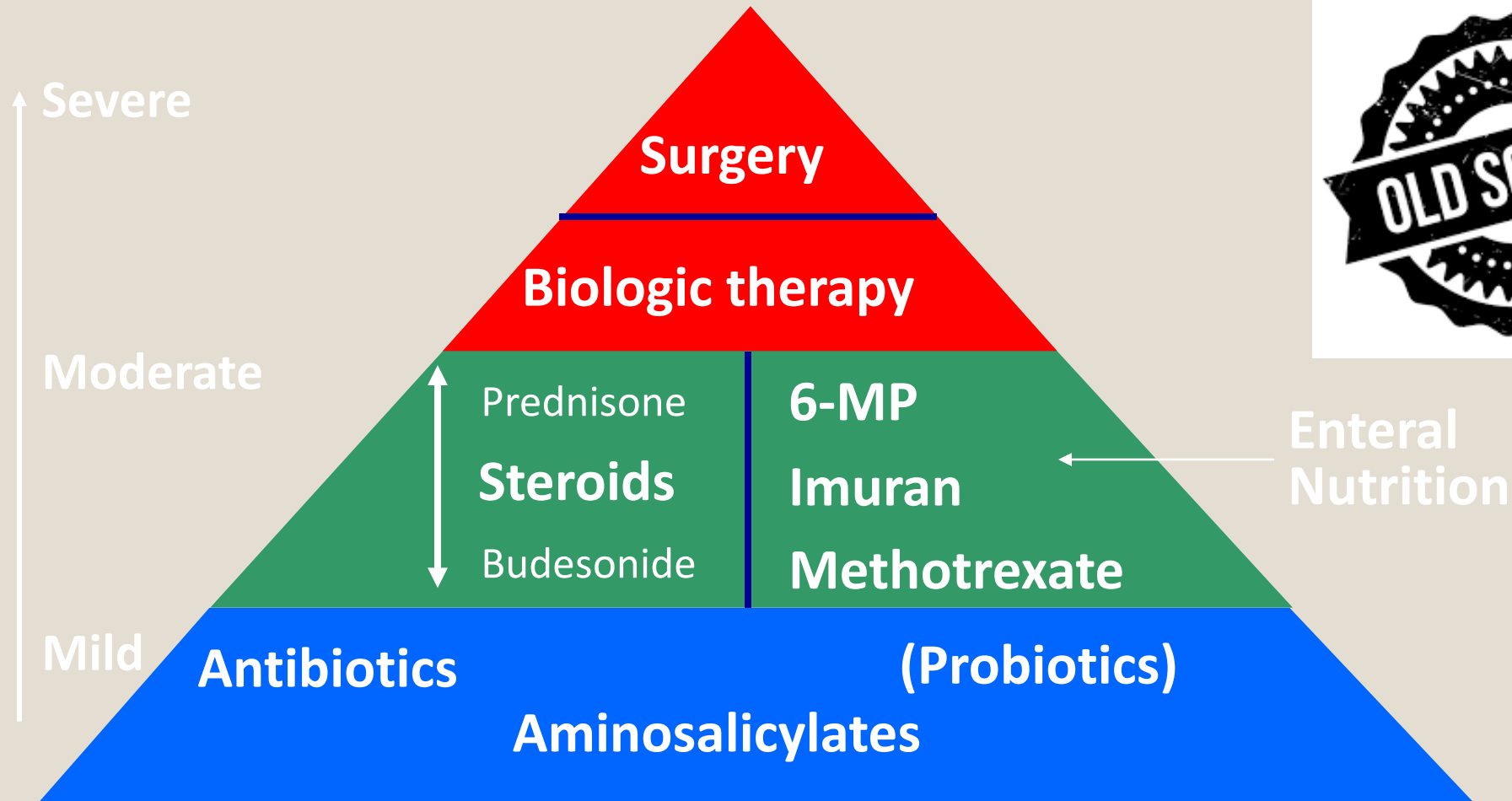
# Treatment of Pediatric IBD→Goals

- **Improve growth and nutrition**
- Improve quality of life
- Maximize therapeutic response
- Minimize toxicity
- Prevent disease complications
- Maximize adherence
- **Promote psychological health**

Treat to  
Target:  
Clinical  
Remission



# Pediatric IBD “Step-Up” Algorithm



Enteral  
Nutrition

# IBD – Approved Drugs Timeline

## Orals

1950 1955 1960 1965 1970 1975 1980 1985 1990

**Azulfidine (sulfasalazine)**  
Pharmacia & Upjohn – 1950

**Cortef (hydrocortisone)**  
Pharmacia & Upjohn – 1952

**Rheumatrex (methotrexate)**  
DAVA – 1953

**Purinethol (mercaptopurine)**  
Teva – 1954

**Imuran (azathioprine)**  
Prometheus – 1968

**Deltasone (prednisone)**  
Pharmacia & Upjohn – 1972

**Dipentum (olsalazine)**  
Alaven – 1990

**Asacol (mesalamine)**  
Warner Chilcott - 1992

**Entocort (budesonide)**  
AstraZeneca – 1997

## Biologics

1995 2000 2005 2010 2015

**Remicade (infliximab) - UC**  
J&J; TNF - 1998

**Remicade (infliximab) - Cr**  
J&J; TNF - 2005

**Humira (adalimumab) - Cr**  
Abbvie; TNF - 2007

**Cimzia (certolizumab) - Cr**  
UCB; TNF - 2008

**Tysabri (natalizumab) - Cr**  
Biogen;  $\alpha 4\beta 1, \alpha 4\beta 7$  - 2008

**Humira (adalimumab) - UC**  
Abbvie; TNF - 2012

**Simponi (golimumab) - UC**  
J&J; TNF - 2013

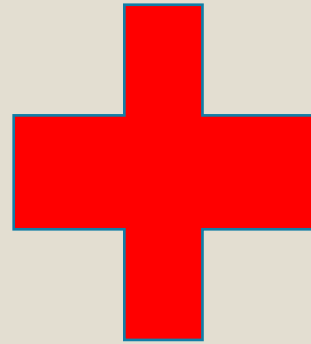
**Entyvio (vedolizumab) – UC/Cr**  
Takeda;  $\alpha 4\beta 7$  - 2014

**Stelara (ustekinumab) - Cr**  
J&J; IL-12 / IL-23 - 2016 (projected)

2018 – JAK/STAT  
XELJANZ  
(tofacitinib)

# Treatment of Pediatric IBD → Goals

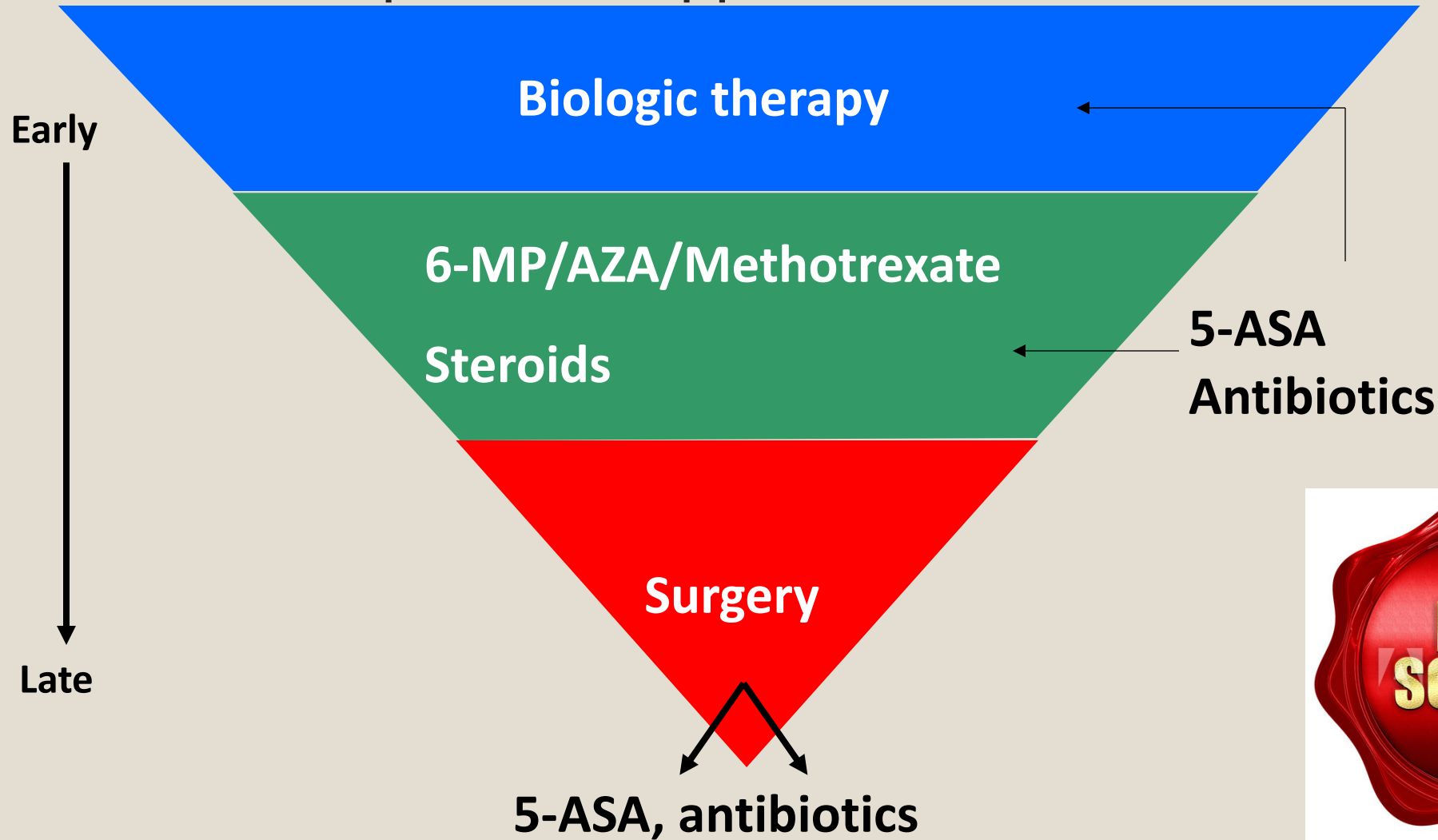
- **Improve growth and nutrition**
- Improve quality of life
- Maximize therapeutic response
- Minimize toxicity
- Prevent disease complications
- Maximize adherence
- **Promote psychological health**



Treat to Target:  
Endoscopic  
Remission!



# Pediatric IBD “Top-Down” Approach





# STEP 1: INDUCE REMISSION

# Systemic Corticosteroids

- Oral (prednisone), IV (Solumedrol), or rectal
- Suppress active inflammation
- Indication: IBD flare
- Provide immediate symptomatic relief
  - Do not promote GI tract mucosal healing
- **Not** indicated for maintenance therapy



# Entocort (Budesonide)

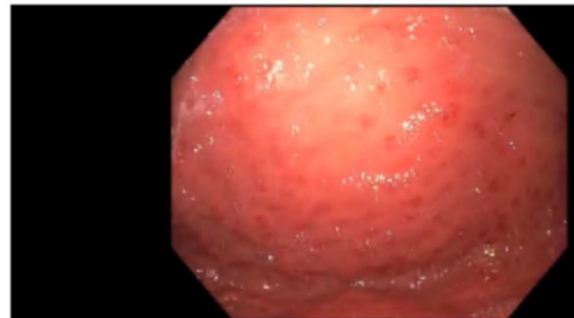
- Rapid hepatic clearance formulation
  - Released in the terminal ileum
- Considerably less steroid side effects
- Effective for ileocolonic Crohn's disease
- Not effective for UC, Crohn's colitis or gastritis
- Role as maintenance therapy unclear
  - Evidence of some steroid side effects (growth suppression)

# Uceris (Budesonide)

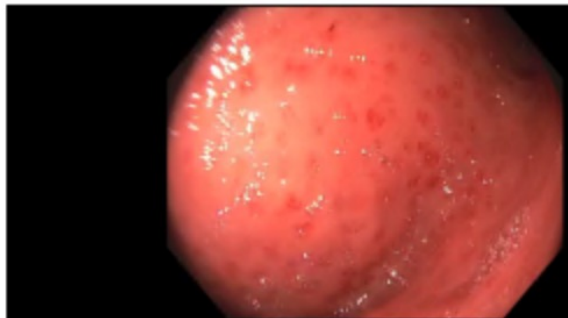
- UCERIS tablets are designed to work directly in the colon, where UC is located.
- The medicine travels intact through the digestive system until it reaches the colon and dissolves.
- Once it dissolves, UCERIS tablets provide a slow release of medicine in the colon.

# Enteral Nutritional Therapy

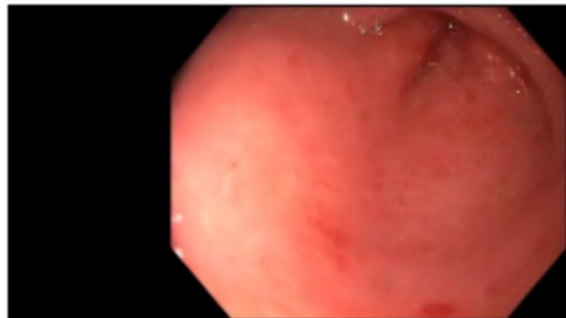
- Improves nutrition for **all** IBD
- Effective **therapy** for pediatric Crohn's
- 100% of calories by formula
- Usually requires NG tube
- As effective as steroids for improving symptoms, **more effective** for healing of GI inflammation
- Likely mechanism → Change in intestinal microflora



**6** Gastric Body :  
\*Inflammation



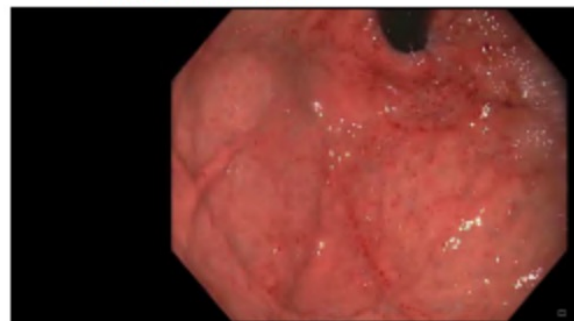
**7** Gastric Body :  
\*Inflammation



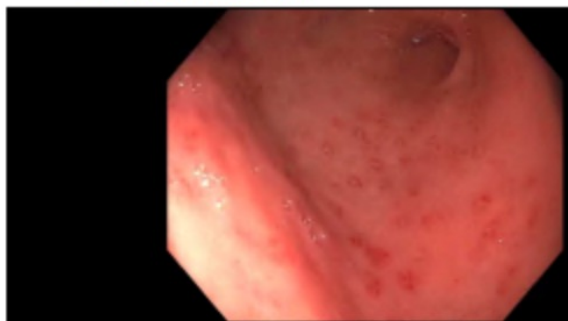
**8** Gastric Body :  
\*Inflammation



**9** Gastric Fundus :  
\*Inflammation



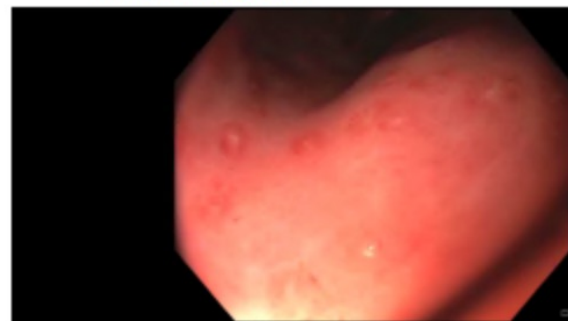
**10** Gastric Fundus :  
\*Inflammation



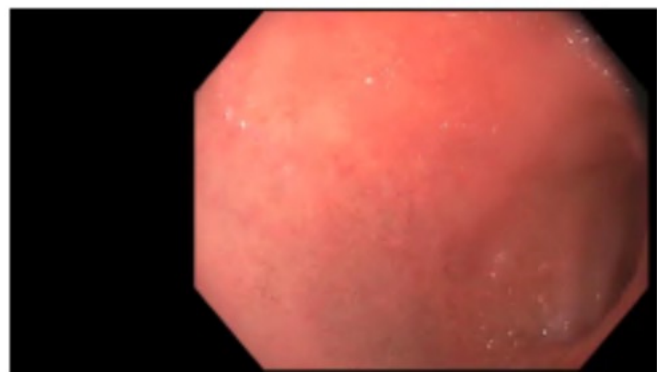
**11** Gastric Antrum :  
\*Inflammation



**12** Gastric Fundus :  
\*Inflammation



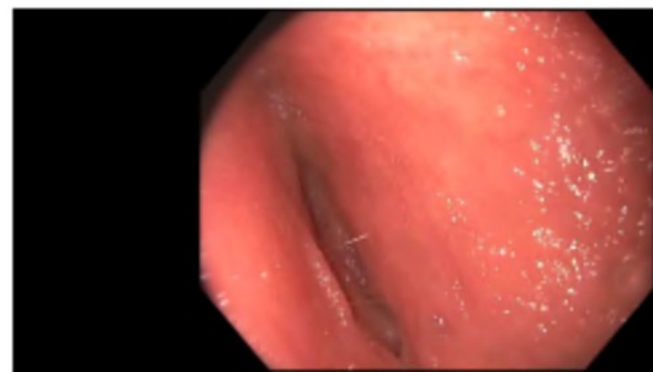
**13** Gastric Body :  
\*Inflammation



**14** Duodenal Bulb : Atrophic

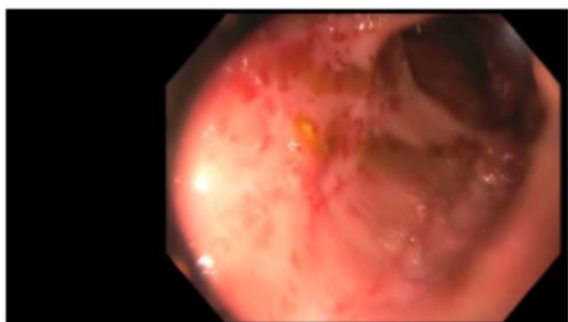


**15** 2nd Portion of the  
Duodenum : Atrophic

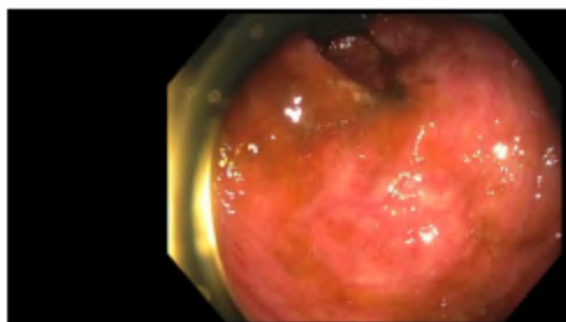


**16** 2nd Portion of the  
Duodenum : Atrophic;

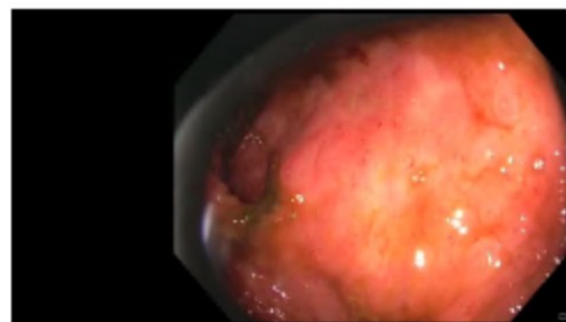




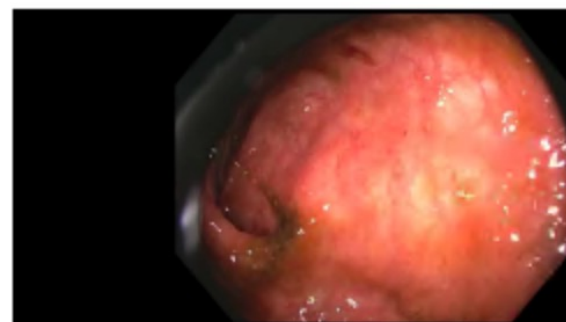
**1** Rectum : Crohn's - Simple Endo Score



**2** Rectum : Crohn's - Simple Endo Score



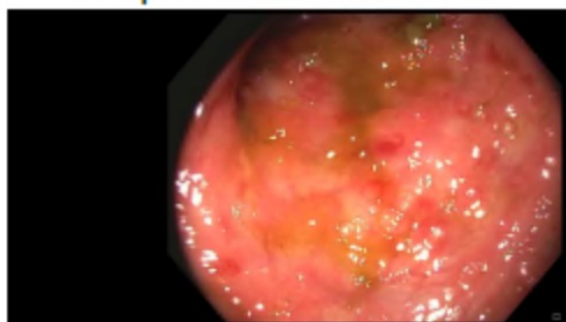
**3** Sigmoid Colon : Crohn's - Simple Endo Score



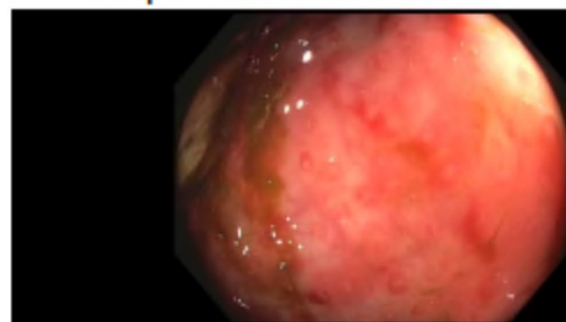
**4** Sigmoid Colon : Crohn's - Simple Endo Score



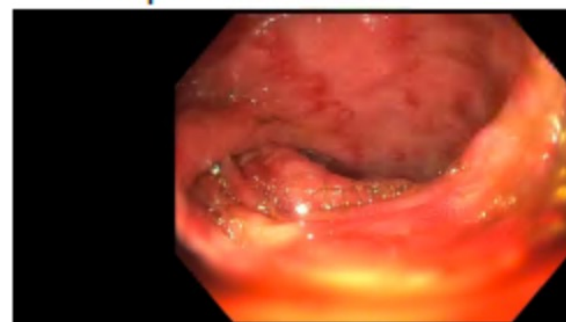
**5** Sigmoid Colon : Crohn's - Simple Endo Score



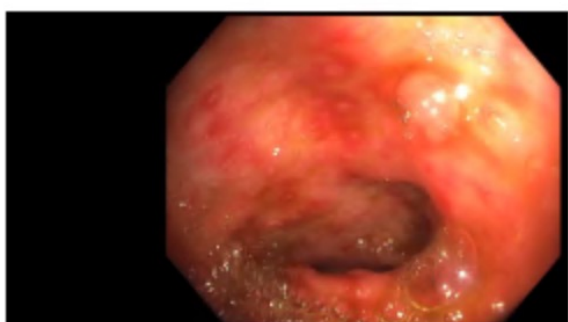
**6** Sigmoid Colon : Crohn's - Simple Endo Score



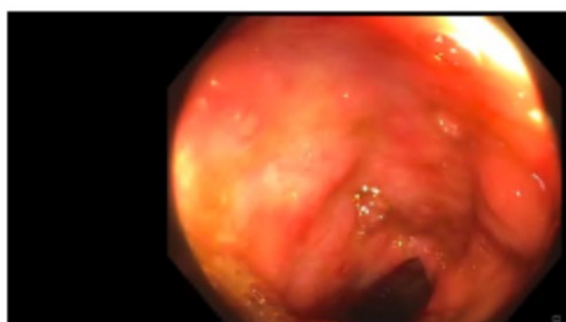
**7** Descending Colon : Crohn's - Simple Endo Score



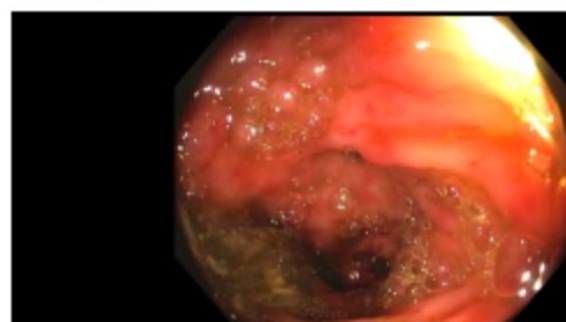
**8** Descending Colon : Crohn's - Simple Endo Score



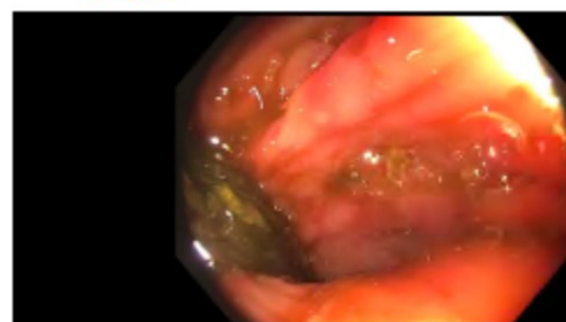
**9** Descending Colon : Crohn's - Simple Endo Score



**10** Descending Colon : Crohn's - Simple Endo Score

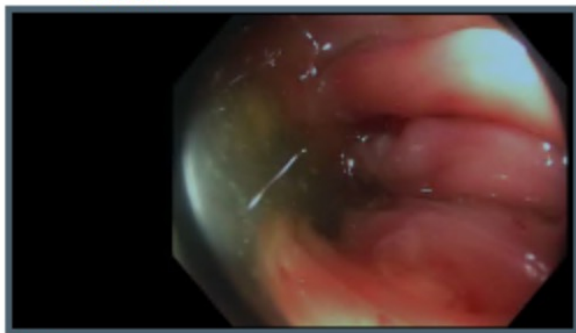


**11** Descending Colon : Crohn's - Simple Endo Score

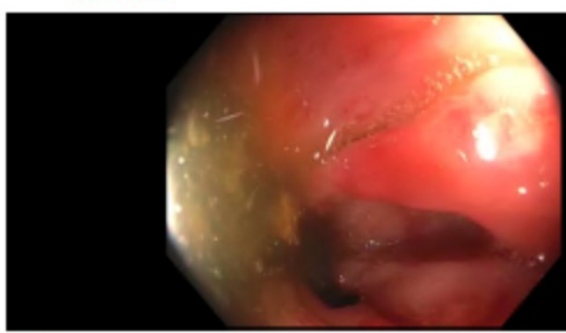


**12** Descending Colon : Crohn's - Simple Endo Score

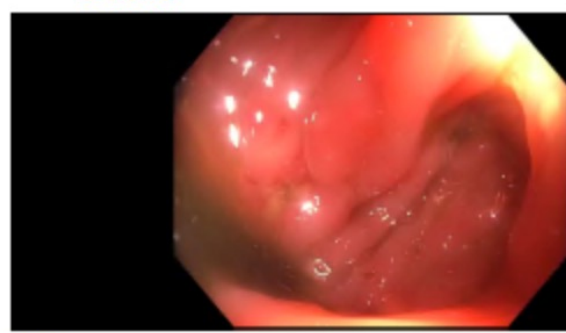




**13** Splenic Flexure : Crohn's - Simple Endo Score



**14** : Crohn's - Simple Endo Score



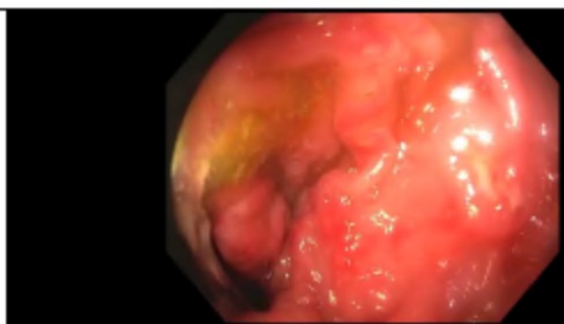
**15** Transverse Colon : Crohn's - Simple Endo Score



**16** Transverse Colon : Crohn's - Simple Endo Score



**17** Transverse Colon : Crohn's - Simple Endo Score



**18** Transverse Colon : Crohn's - Simple Endo Score



**19** Transverse Colon : Crohn's - Simple Endo Score



**20** Transverse Colon : Crohn's - Simple Endo Score



**21** Sigmoid Colon : Crohn's - Simple Endo Score



**22** Sigmoid Colon : Crohn's - Simple Endo Score

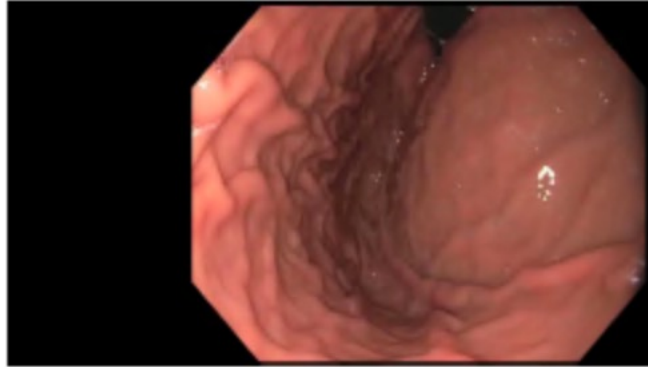


**23** Rectum : Crohn's - Simple Endo Score

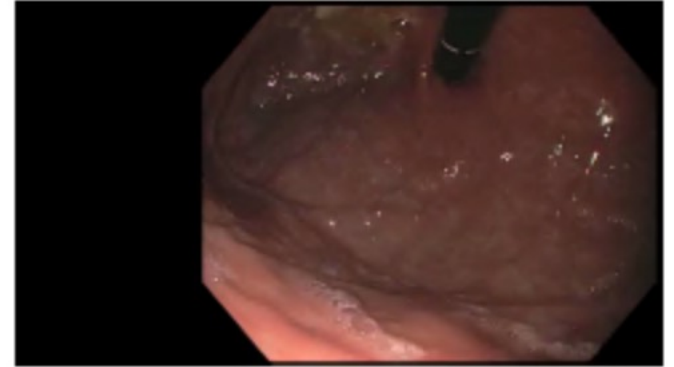
# After 12 weeks of Total Enteral Nutrition



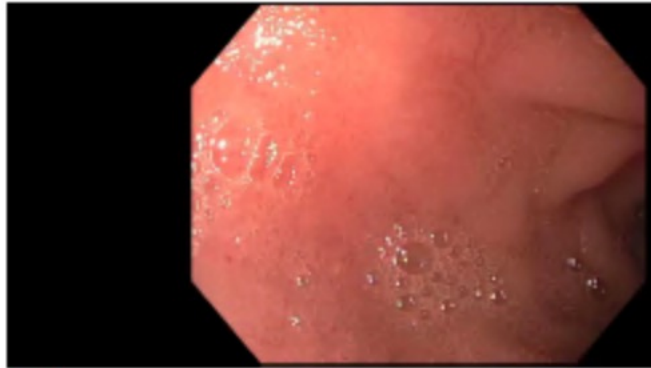
**4** Pre-pyloric Stomach :  
Normal



**5** Gastric Fundus : Normal



**6** Gastric Fundus : Normal



**7** Duodenal Bulb : Normal

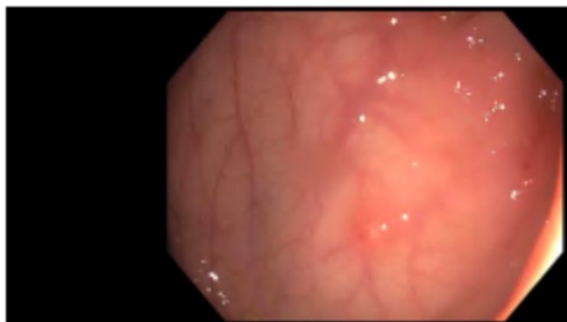


**8** 2nd Portion of the  
Duodenum : Normal

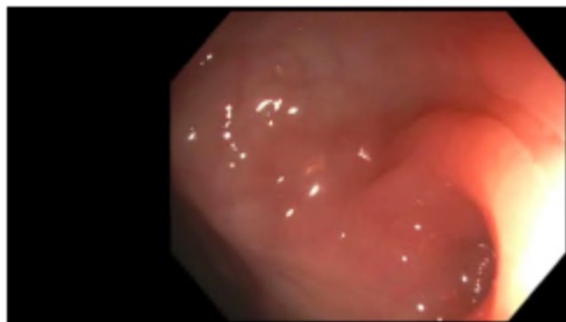




**1** Rectum : Crohn's - Simple Endo Score



**2** Sigmoid Colon : Crohn's - Simple Endo Score



**3** Sigmoid Colon : Crohn's - Simple Endo Score



**4** Sigmoid Colon : Crohn's - Simple Endo Score



**5** Sigmoid Colon : Crohn's - Simple Endo Score



**6** Descending Colon : Crohn's - Simple Endo Score



**7** Descending Colon : Crohn's - Simple Endo Score



**8** Descending Colon : Crohn's - Simple Endo Score



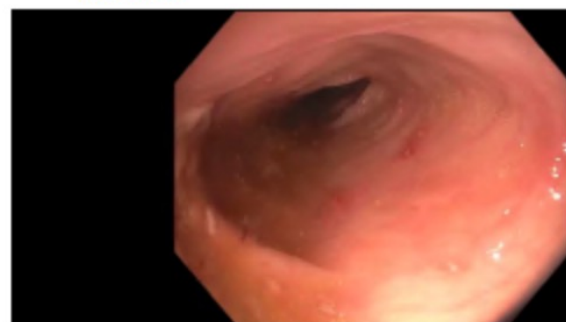
**9** Descending Colon : Crohn's - Simple Endo Score



**10** Descending Colon : Crohn's - Simple Endo Score



**11** Splenic Flexure : Crohn's - Simple Endo Score

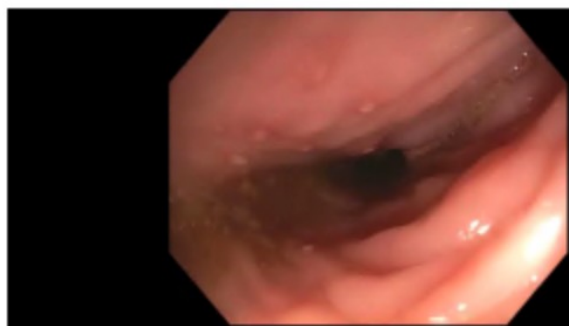


**12** Transverse Colon : Crohn's - Simple Endo Score

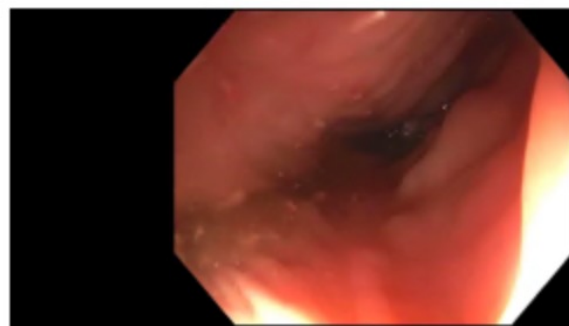




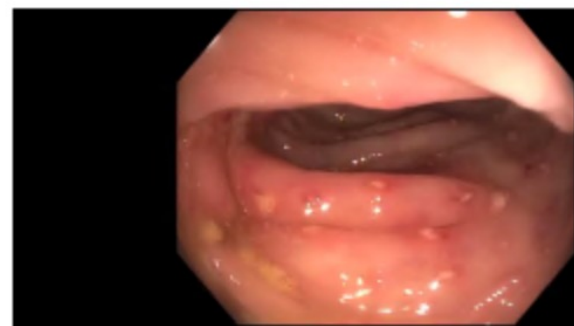
**13** Transverse Colon :  
Crohn's - Simple Endo  
Score



**14** Transverse Colon :  
Crohn's - Simple Endo  
Score



**15** Transverse Colon :  
Crohn's - Simple Endo  
Score



**16** Transverse Colon :  
Crohn's - Simple Endo  
Score

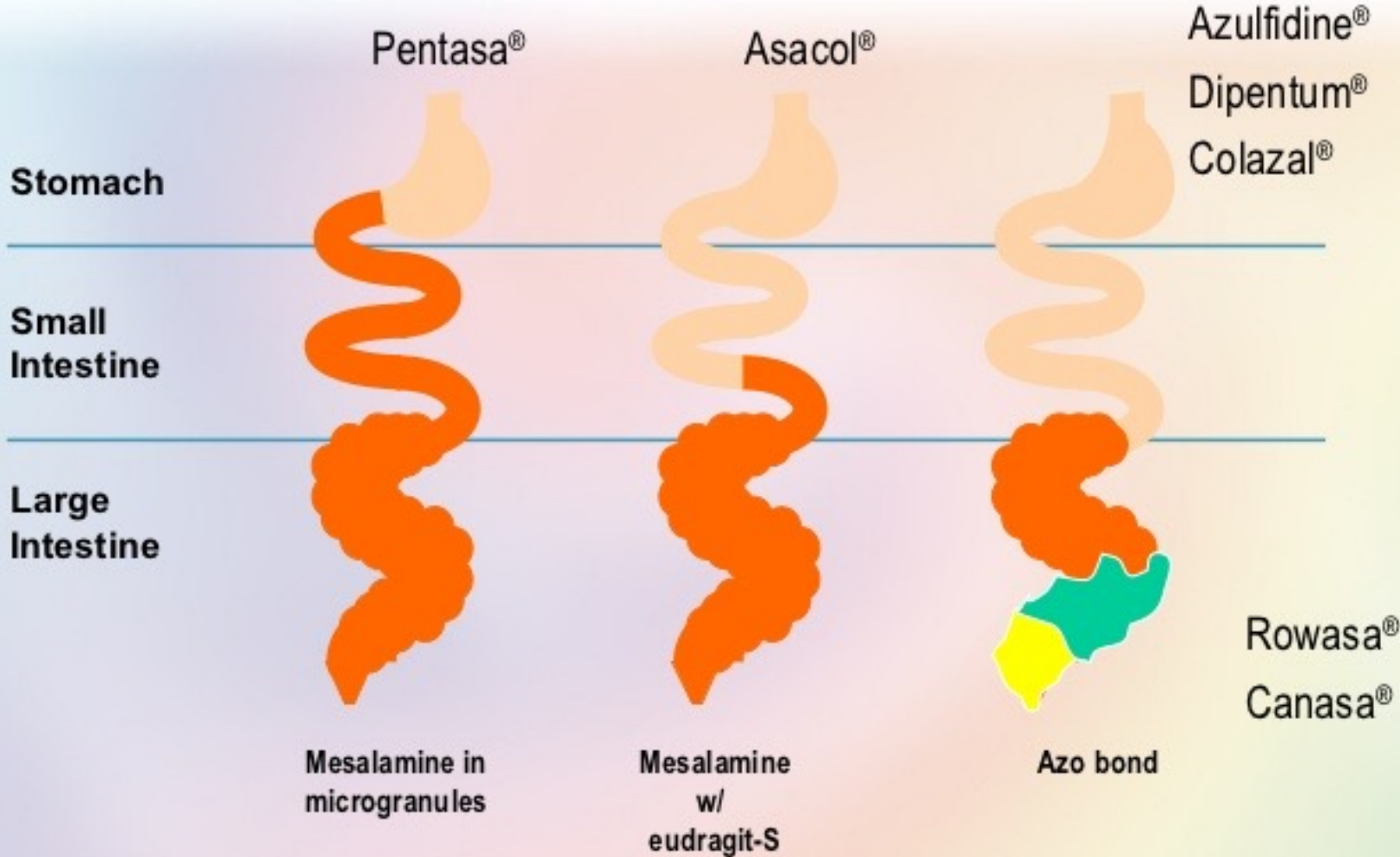


**STEP 2: MAINTAIN  
STEROID-FREE  
REMISSION**

# Aminosalicylates (5-ASA)

- Locally reduce inflammation in the bowel
  - Inhibition of arachidonic metabolism
- Oral and rectal preparations available
- Often a first-line therapy for UC
- Role in decreasing risk of colon cancer
- Well tolerated
  - Headaches, GI complaints most common
  - 3-5% with allergy to medicine
- Adherence can be an issue with large number of pills to be taken multiple times daily

# 5-ASA Release Sites



# Probiotics

- The only probiotic with evidence in inducing remission in pediatric IBD is Visbiome
- This is approved in ulcerative colitis and pouchitis
- Contains 8 strains of bacteria

# Immunomodulators

- Suppress immune response that triggers intestinal damage in IBD
- Induction and maintenance of remission
- Steroid-sparing

## 6-MP/Azathioprine

- Daily dosing
- Oral administration
- 3-4 months for max. efficacy
- **\*Risk of hepatosplenic T-cell lymphoma**

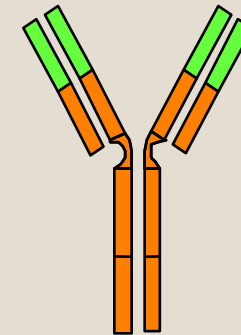
## Methotrexate

- Once weekly dosing
- Oral or subcutaneous
- 6-8 weeks for max. efficacy

# Biologic Therapies

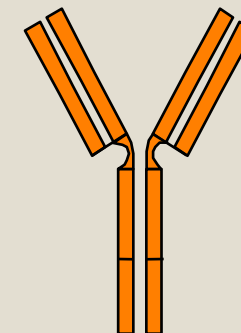
- Pro-inflammatory cytokines contribute to inflammation in IBD
  - TNF $\alpha$  is elevated in IBD patients
- Biologics block and neutralize cytokines
- Used to treat moderate to severe IBD not responding to other therapy
  - Infusion (Infliximab = Remicade, Infliximab biosimilars = Inflectra, Renflexis)
  - Injectable (Adalimumab = Humira)

**Remicade**  
(infliximab)



75% Human

**Humira**  
(adalimumab)



100% Human

# Biologics – Anti-TNF

- Pre-screening for TB prior to initiation of therapy
- Infliximab
  - Infusion over 2 hours
  - Loading dose of 0, 2, and 6 weeks
  - Maintenance dose every 8 weeks
- Adalimumab
  - Injection
  - Maintenance dose every 2 weeks
- Side Effect Profile
  - Infection, malignancy, infusion reaction, serum sickness, psoriasis
  - Monitor serum levels and antibodies





# NEW GENERATION BIOLOGICS

Currently FDA approved in adults

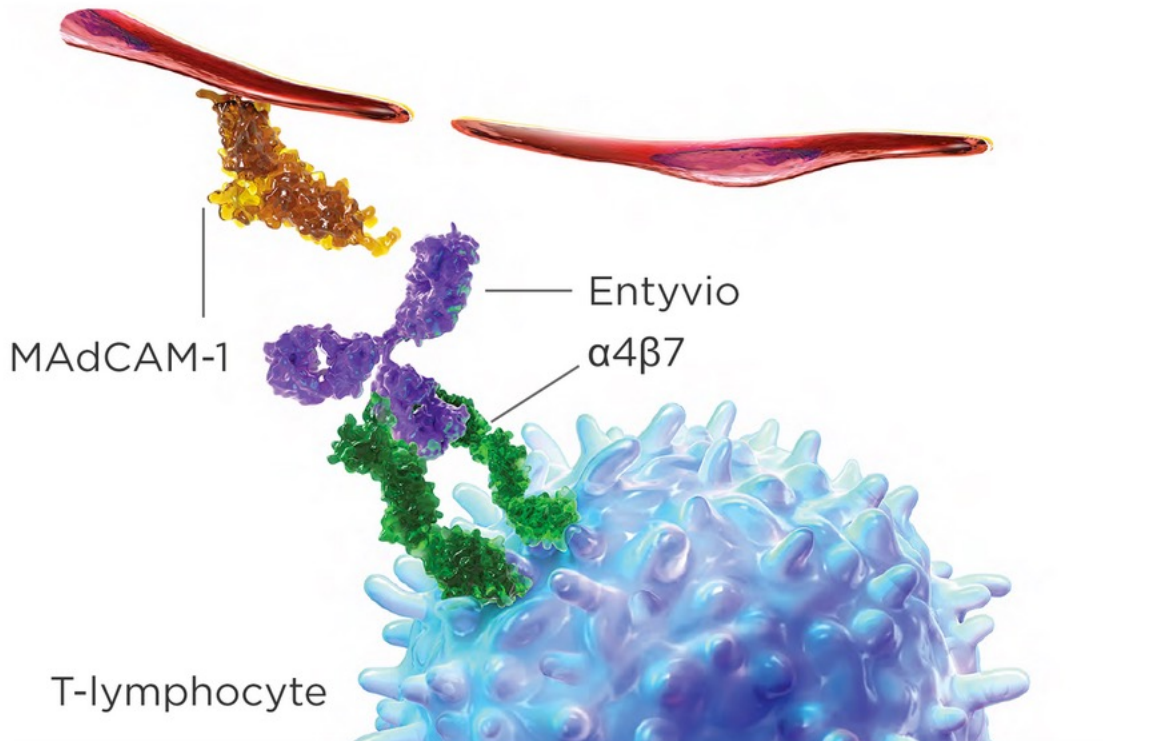
# Vedolizumab (Entyvio)

- Anti-integrin molecule
- Gut-specific
- Prevents inflammatory cytokines from entering the gut
- Infusion every 8 weeks
- Approved in UC and Crohns
- Better data in UC

# Mechanism of Action

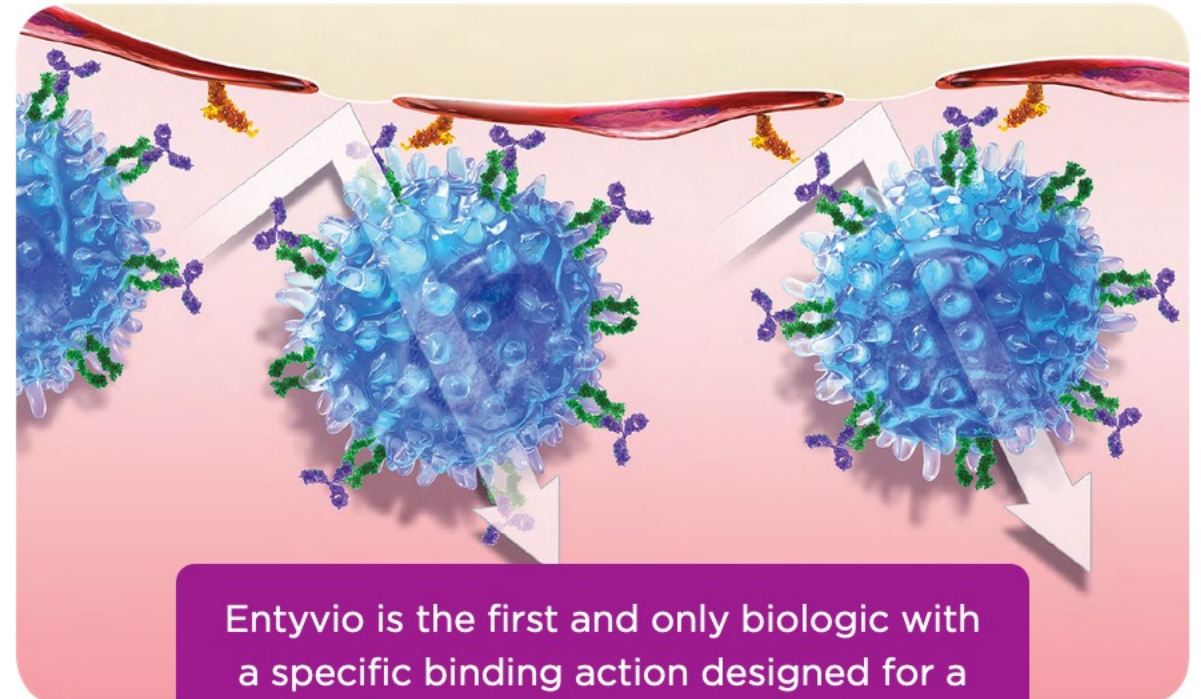
1

**Integrin binding.** Entyvio specifically binds to the  $\alpha 4\beta 7$  integrin and blocks the interaction between the  $\alpha 4\beta 7$  integrin and MAdCAM-1, which is mainly expressed on GI tract endothelial cells.



2

**Excessive migration blocked.** GI-focused Entyvio selectively inhibits T cell migration to inflamed GI tissue.



# Ustekinumab (Stelara)

- IL12/23 inhibitor
- Approved in Crohns disease

**STELARA®**  
(ustekinumab)

**1**  
IV INFUSION

Given over at  
least one hour

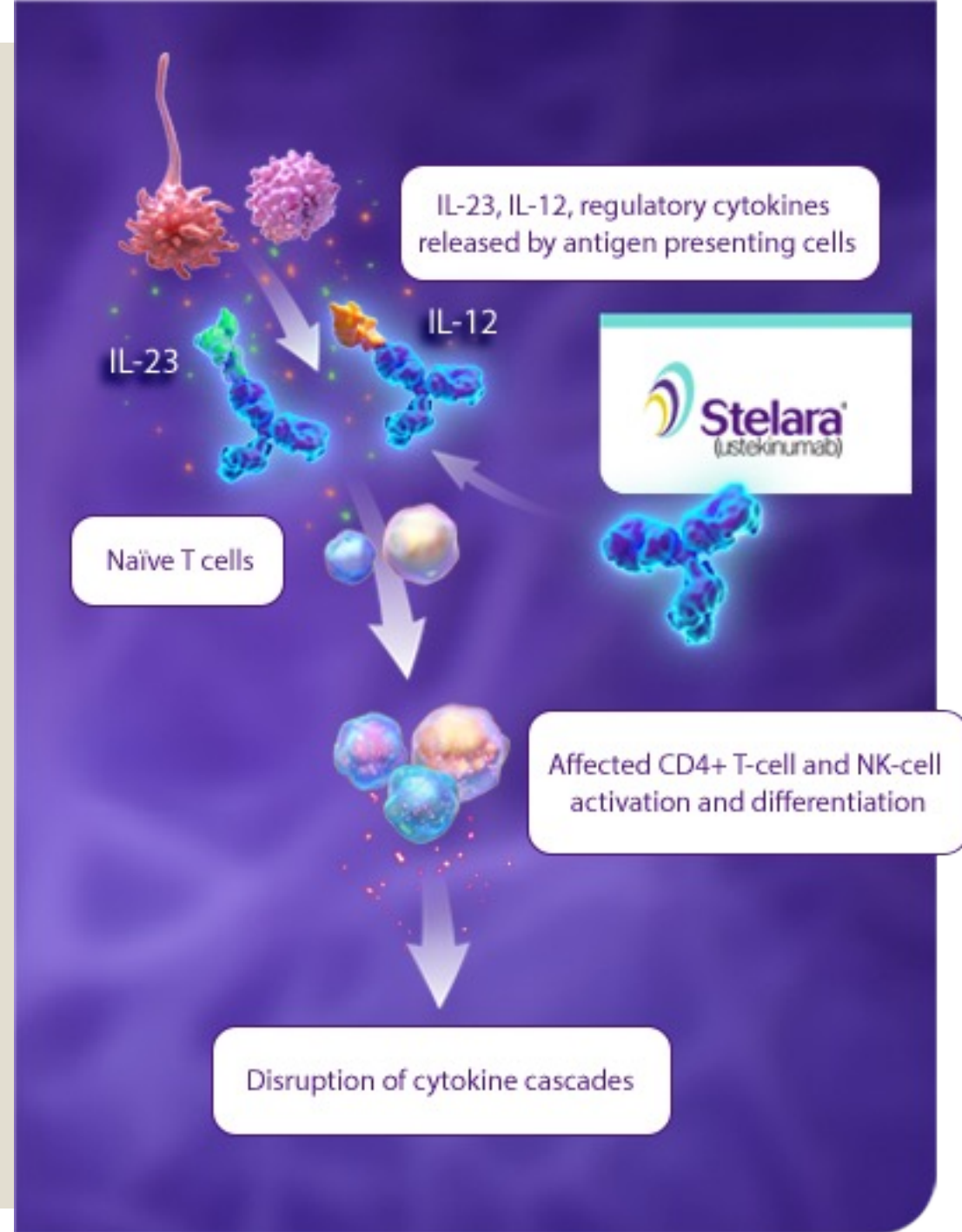


WEEK 0

**6**  
INJECTIONS



Once every 8 weeks





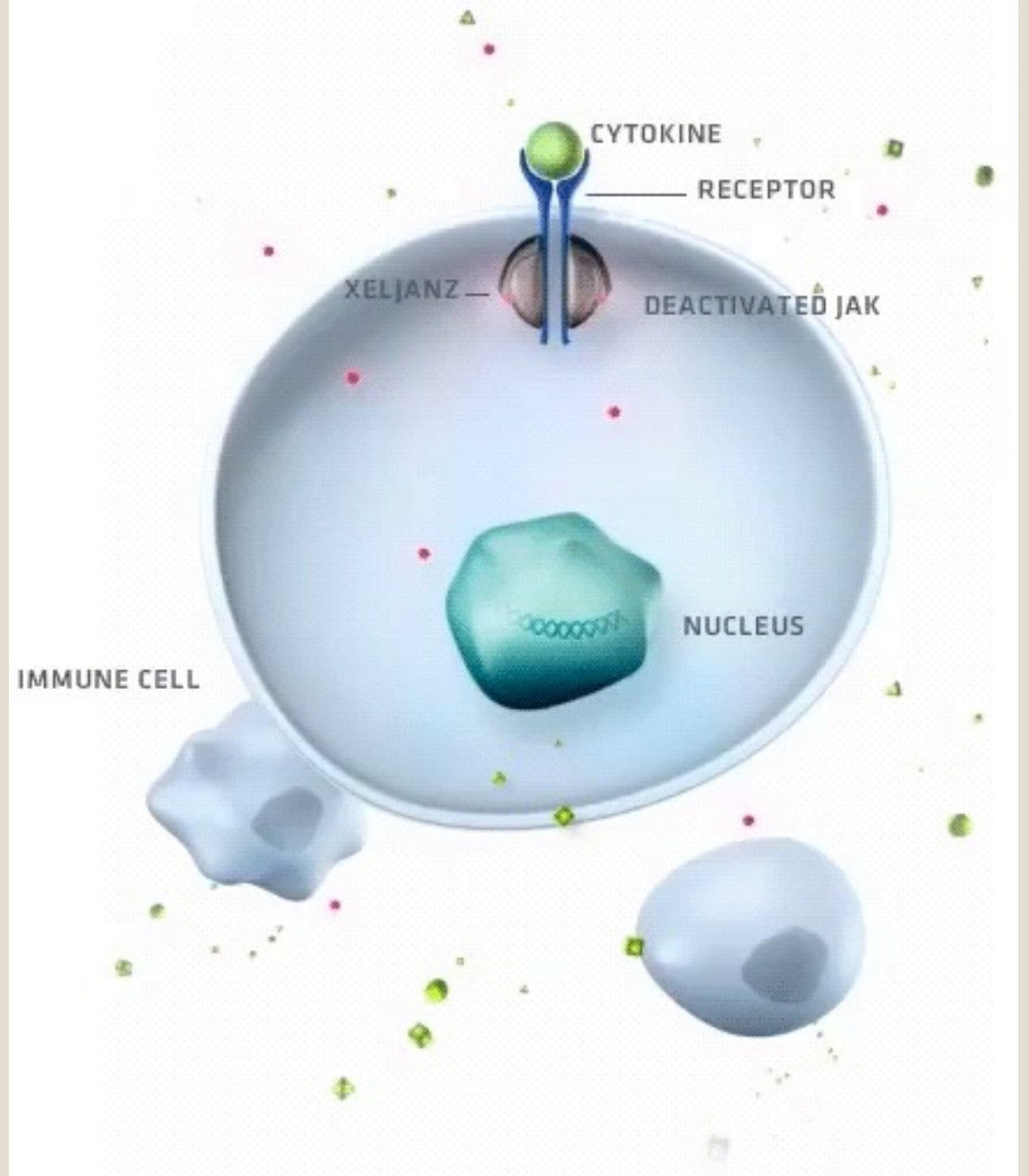


# NEW GENERATION ORAL AGENTS

Currently FDA approved in adults

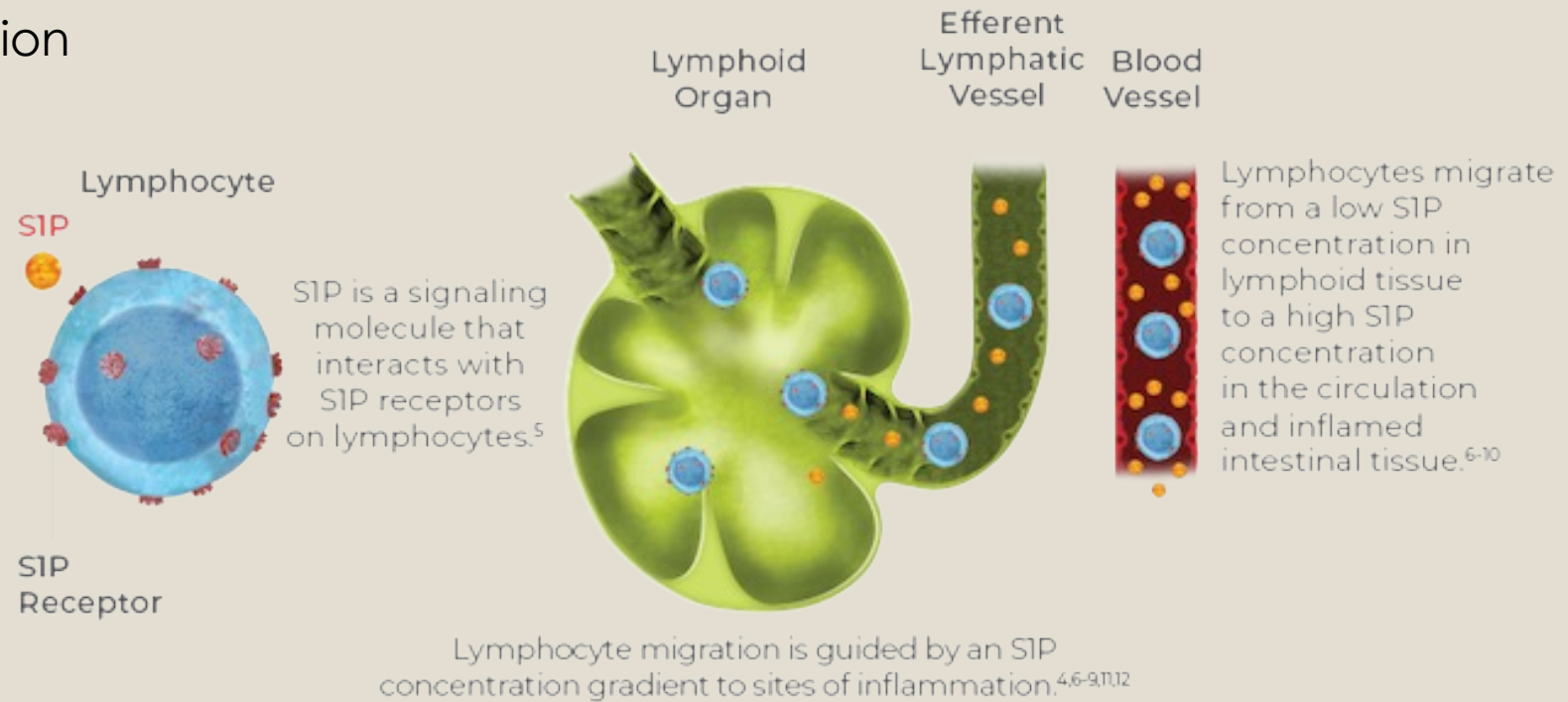
# Tofacitinib (Xeljanz)

- JAK/STAT inhibitor
- Daily oral medication
- Approved in UC



# Ozanimod (Zeposia)

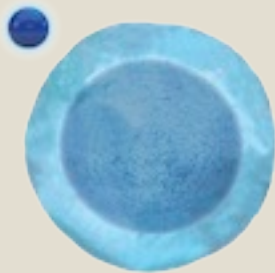
- Sphingosine 1-phosphate (S1P) receptor modulator
- Daily oral medication
- Approved in UC



# Mechanism of Action

The mechanism by which ZEPOSIA exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into the intestine.<sup>1</sup>

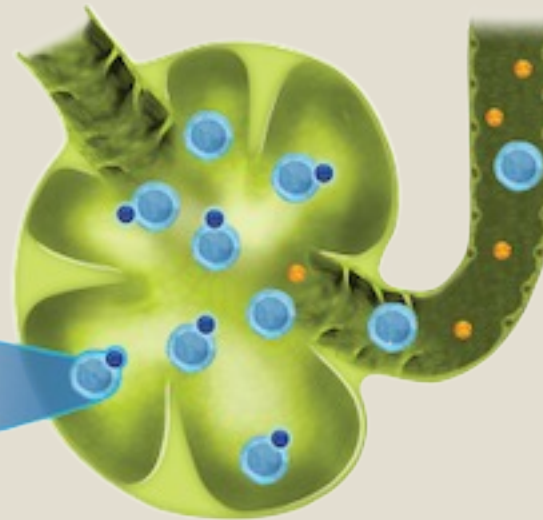
ZEPOSIA  
Small Molecule<sup>14</sup>



ZEPOSIA binds with high affinity to S1P receptors 1 and 5.<sup>1,13,15a</sup>



Lymphoid Organ



Efferent Lymphatic Vessel

Blood Vessel



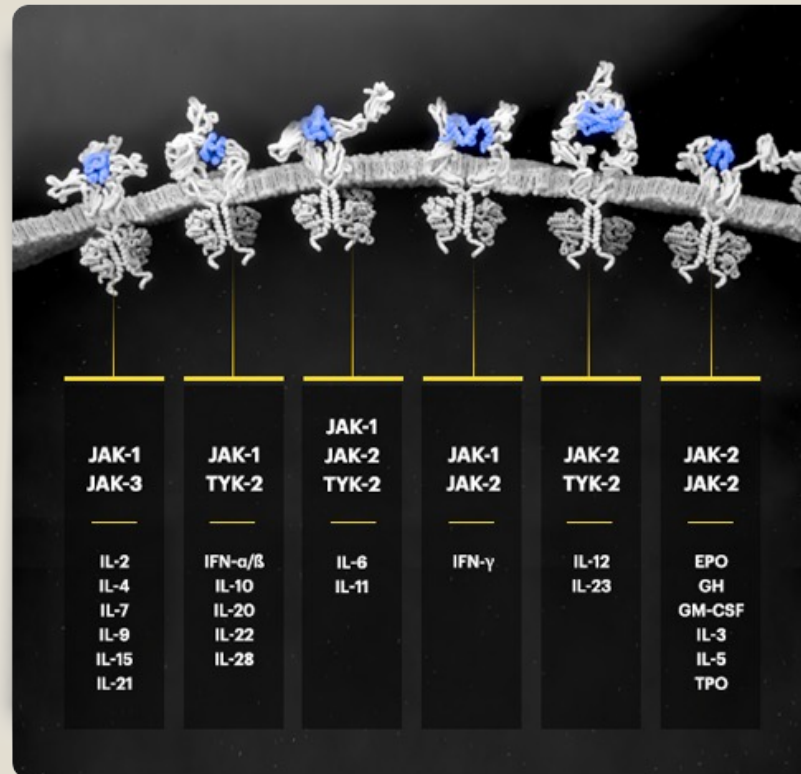
This blocks the capacity of lymphocytes to egress from lymphoid tissue, reducing the number of lymphocytes in the peripheral circulation.<sup>1</sup>

ZEPOSIA induces a sustained internalization of S1P1 receptors.<sup>13,15</sup>



# Upadacitinib (Rinvoq)

- JAK/STAT inhibitor
- Daily oral medication
- Approved in UC



# What's Next?

- Get current biologics approved in pediatrics
- Get new oral agents that are targeted
- Get testing that can be done at the time of diagnosis to predict what treatment will work for each patient
- Get better data on dietary treatments