



ADVANCES 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

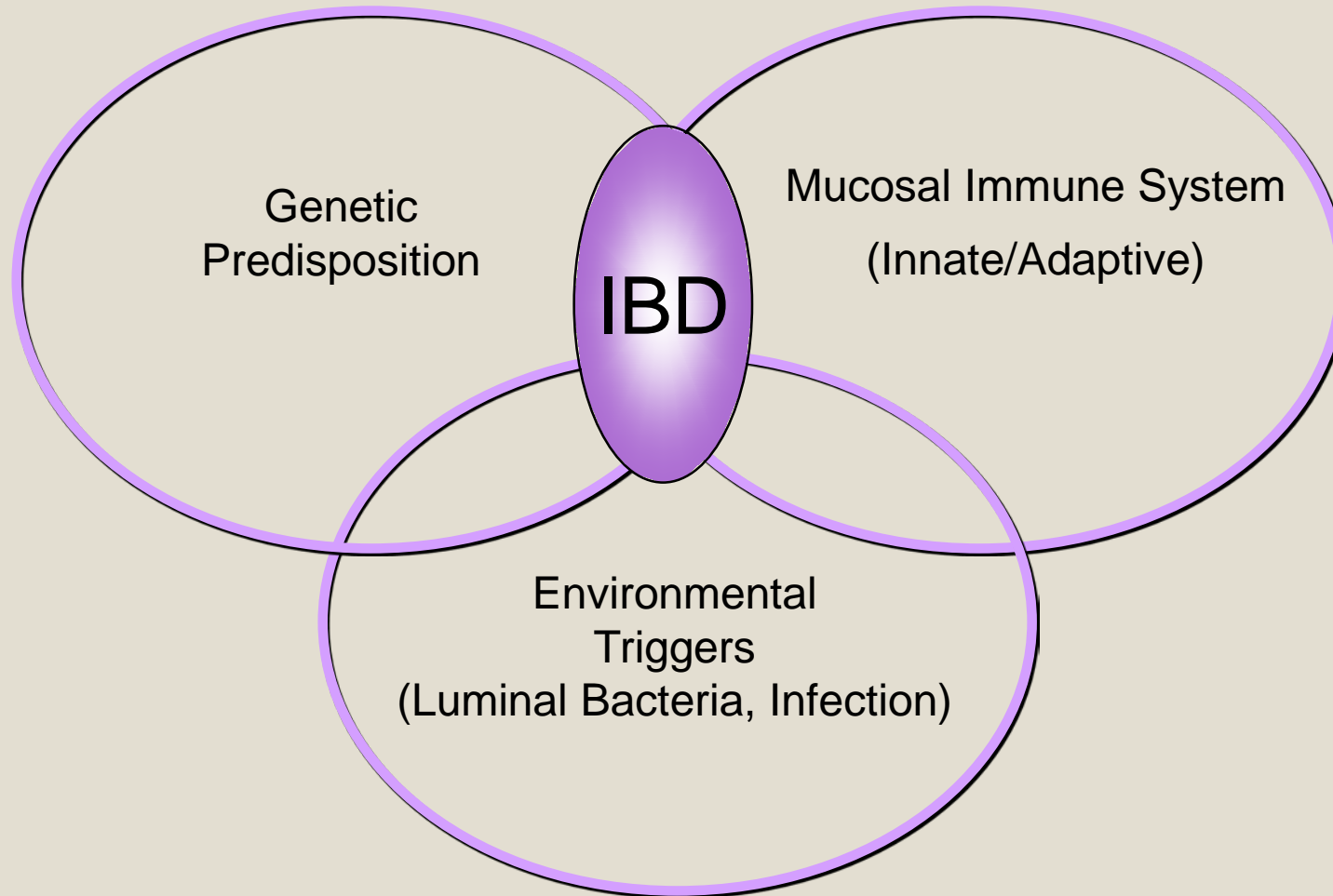
Disclosures

- Abbvie Speakers Bureau
- 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



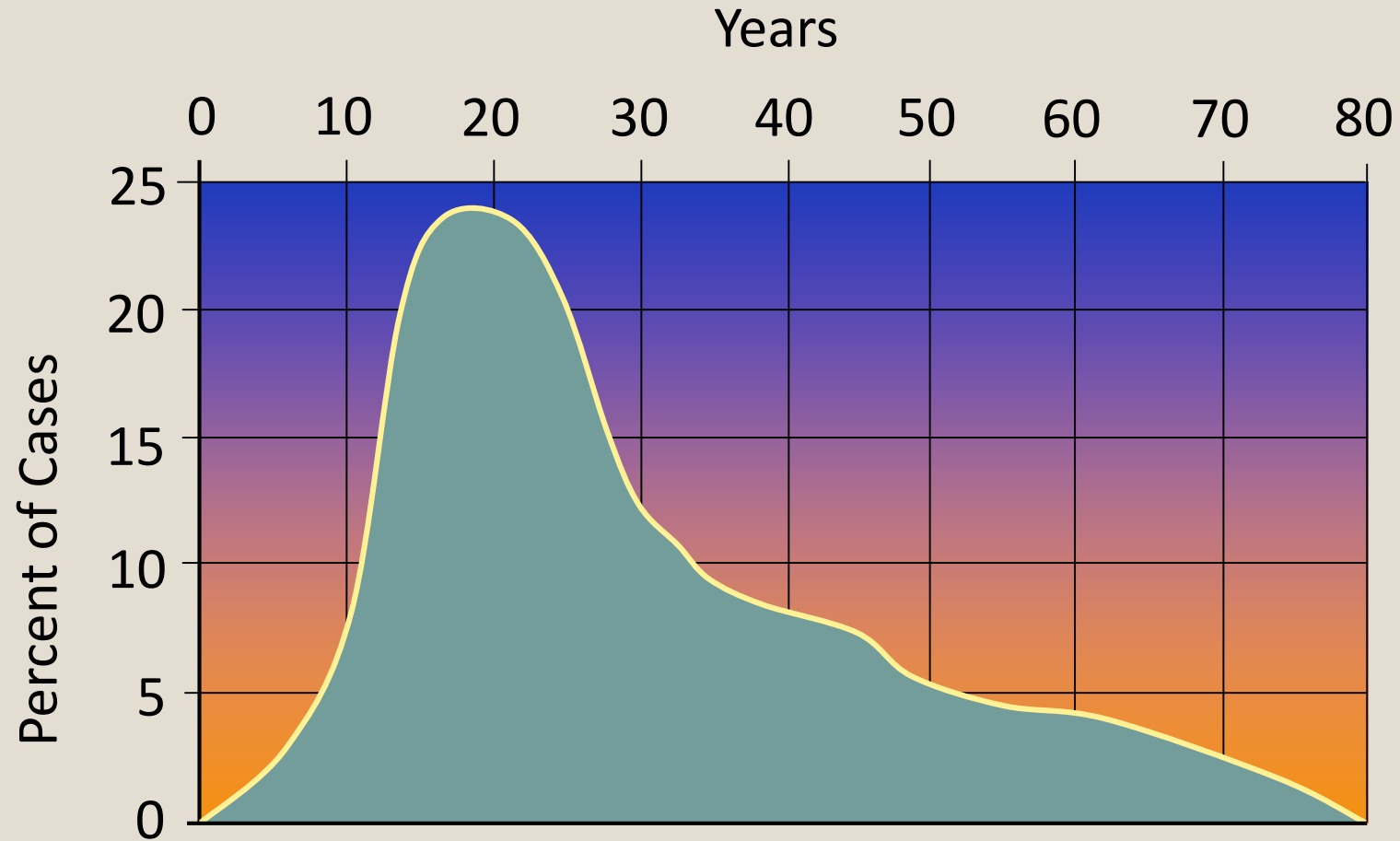
IBD in Pediatric Patients

- 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.

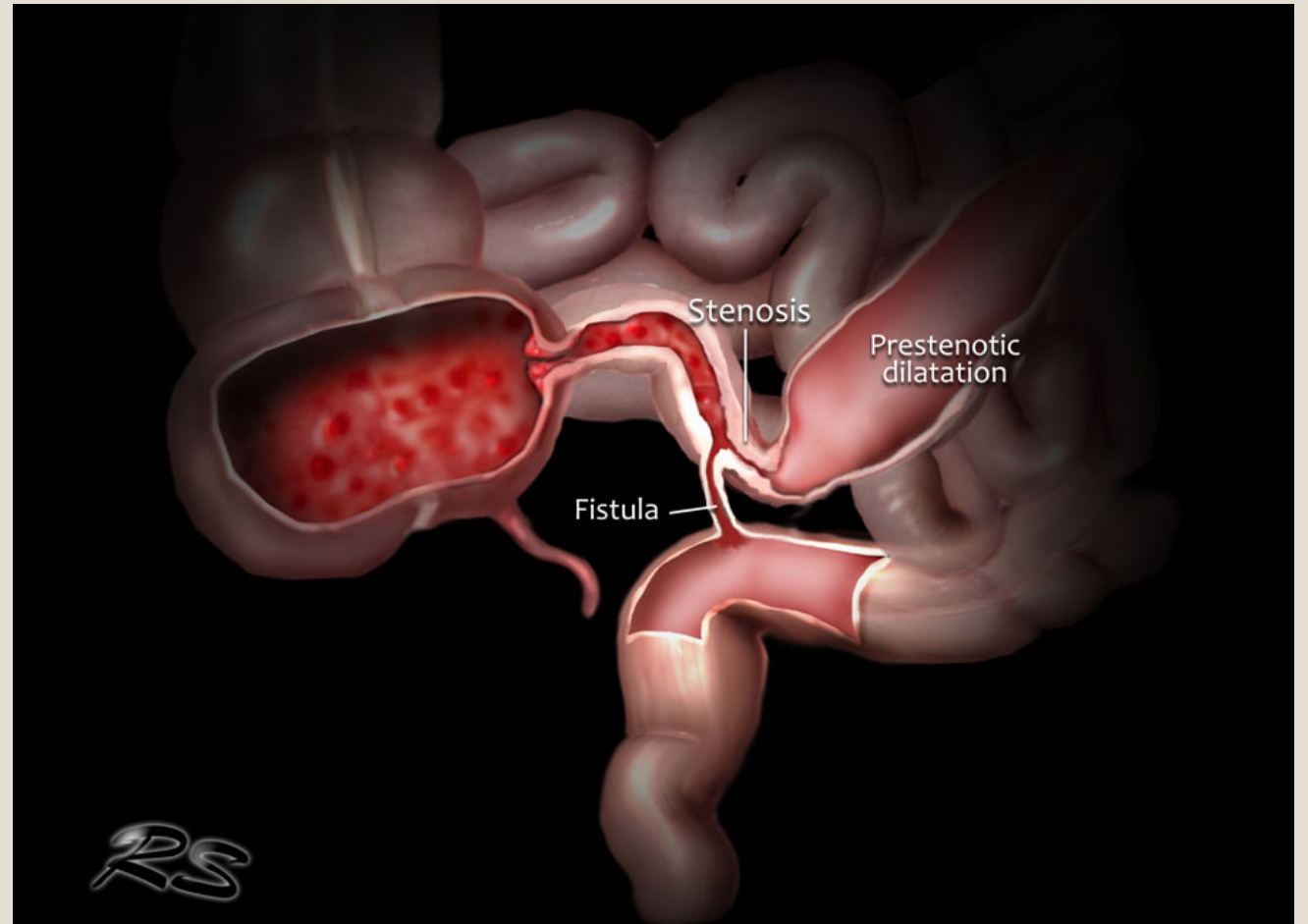
Initial Laboratory Evaluation

- 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

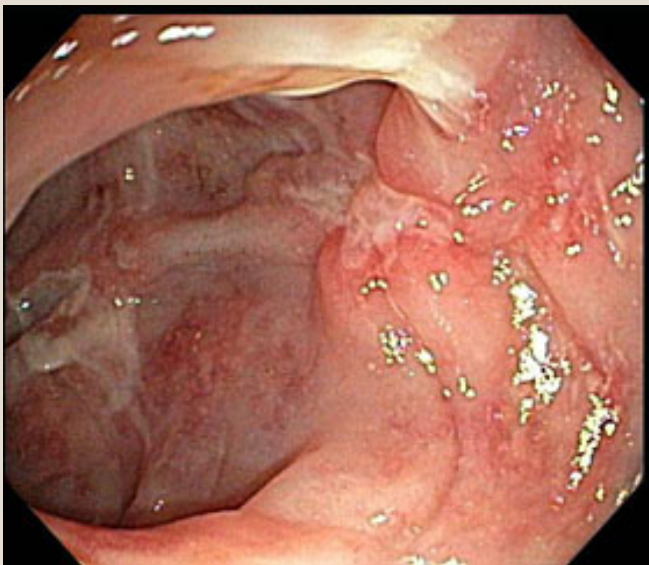
LOW HGB
LOW ALB
HIGH CRP
HIGH ESR

Radiology Testing

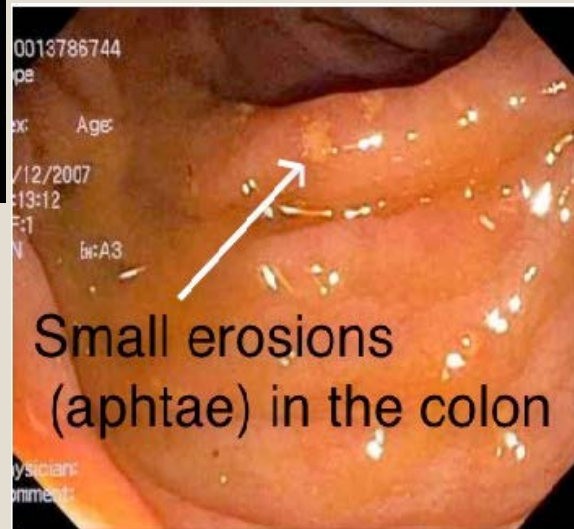
- Upper GI with Small Bowel Follow-Through
 - Cheapest
 - Easiest to do – no IV's
 - Least detailed
 - Most radiation
- CT enterography
 - More detail than UGI/SBFT with less radiation
 - Faster than MRI
- MR enterography
 - No radiation
 - Best image quality
 - Most expensive
 - May need anesthesia



Endoscopy/Colonoscopy Crohn's disease



Patchy Colitis



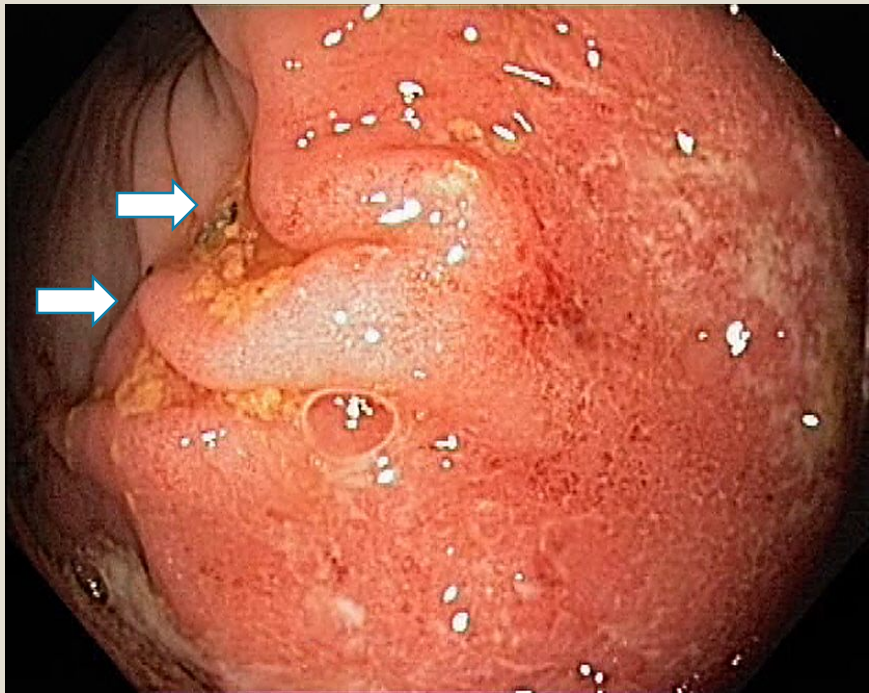
**Small erosions
(aphtae) in the colon**

Aphthous Ulcerations

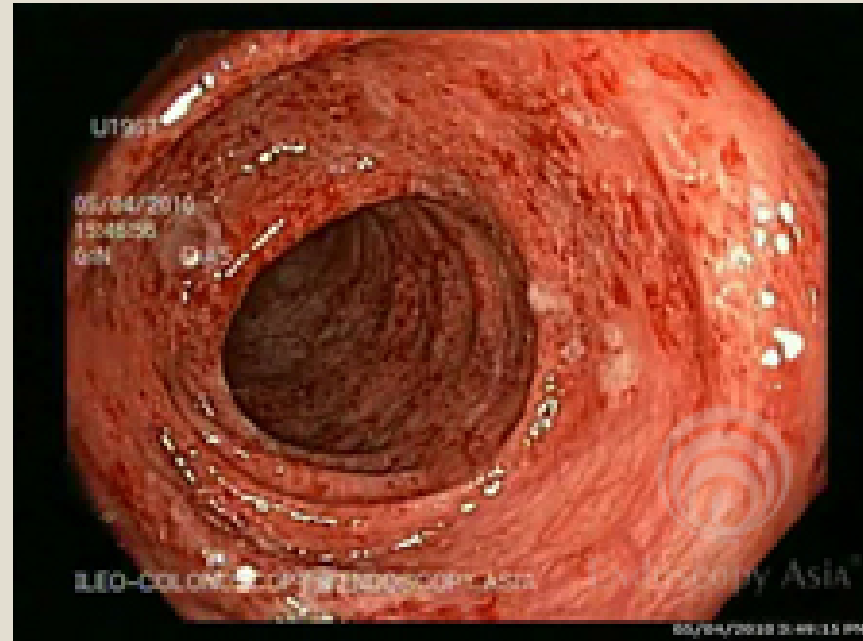


Crohn's ileitis

Endoscopy/Colonoscopy - Ulcerative Colitis

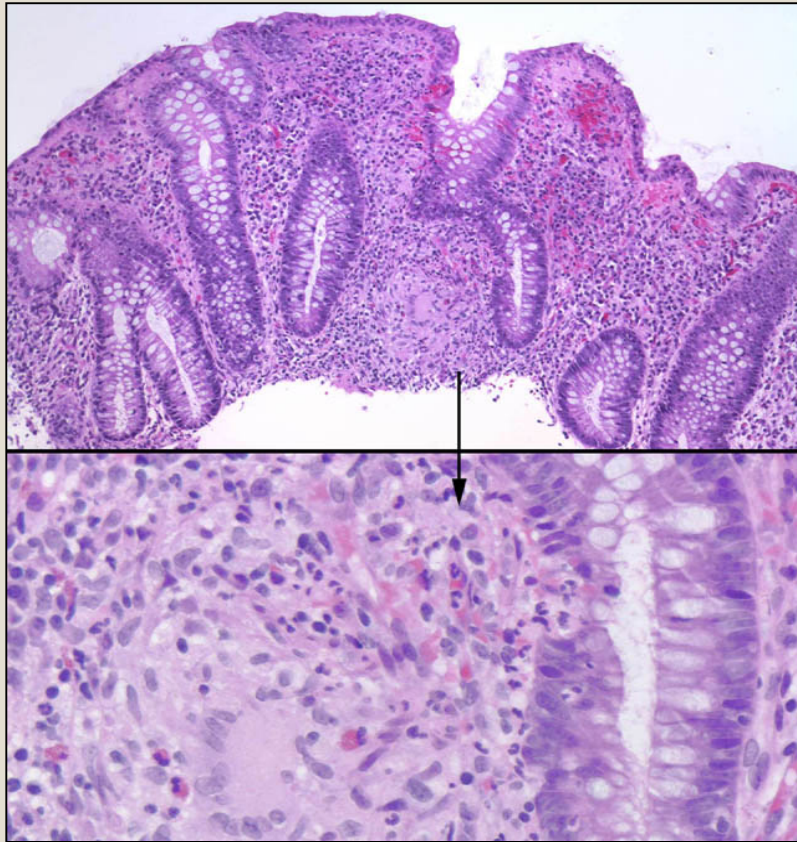


Colitis with Transition Zone



Pancolitis

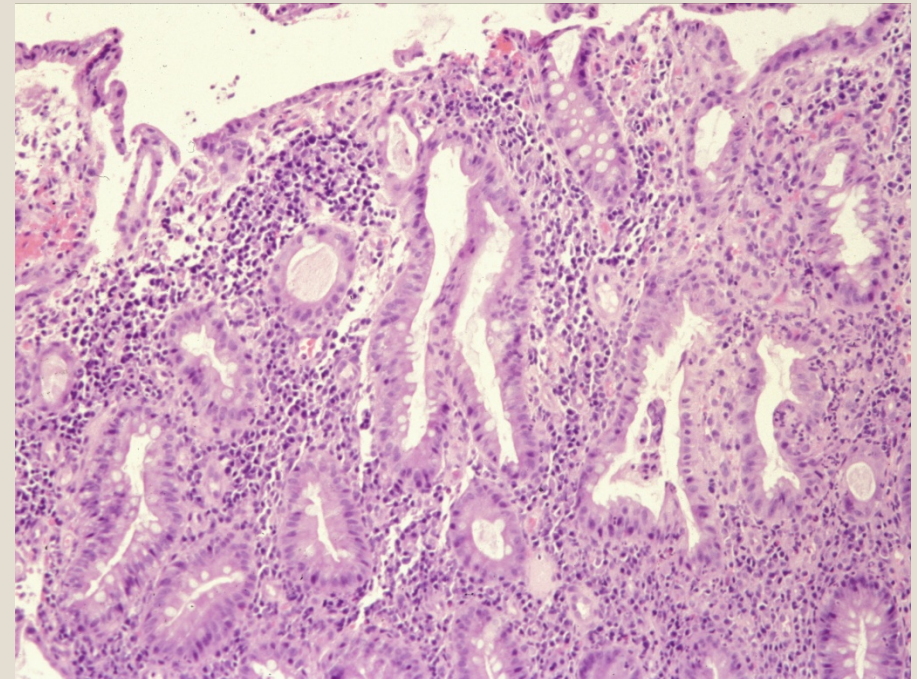
Histopathology



Colitis with Granuloma

Colitis

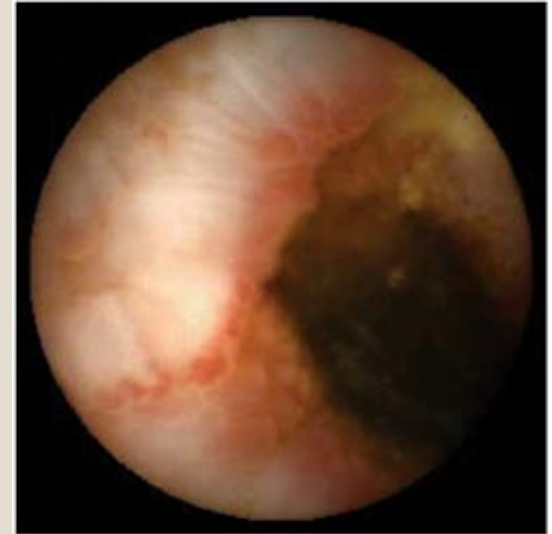
- Crypt branching, distortion
- Crypt abscess
- Hypercellular





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



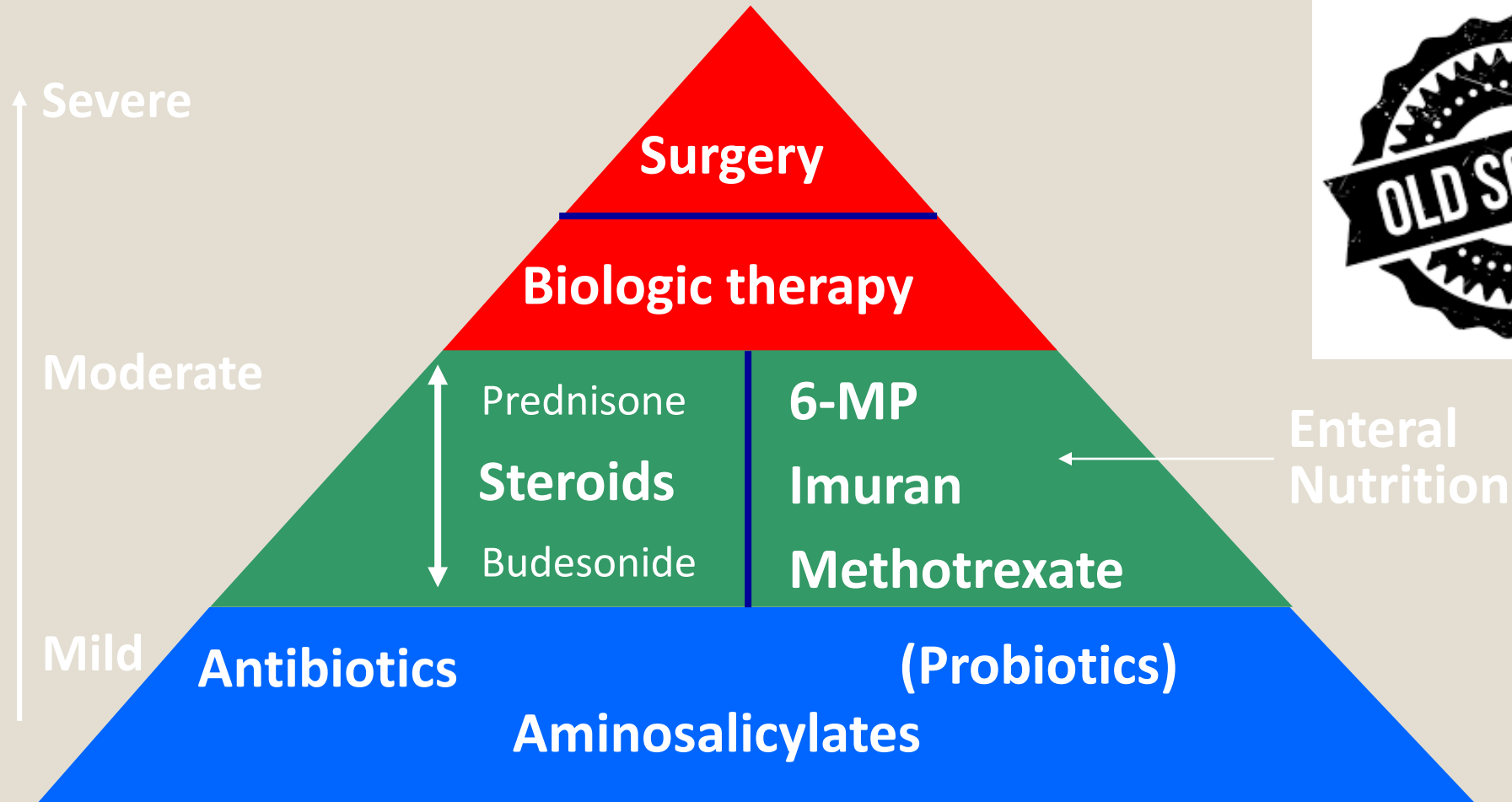
Treatment of Pediatric IBD→Goals

- **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



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

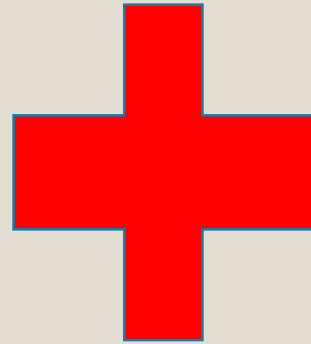
Entyvio (vedolizumab) – UC/Cr
Takeda; $\alpha 4\beta 7$ - 2014

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

2018 – JAK/STAT
XELJANZ
(tofacitinib)

Treatment of Pediatric IBD → Goals

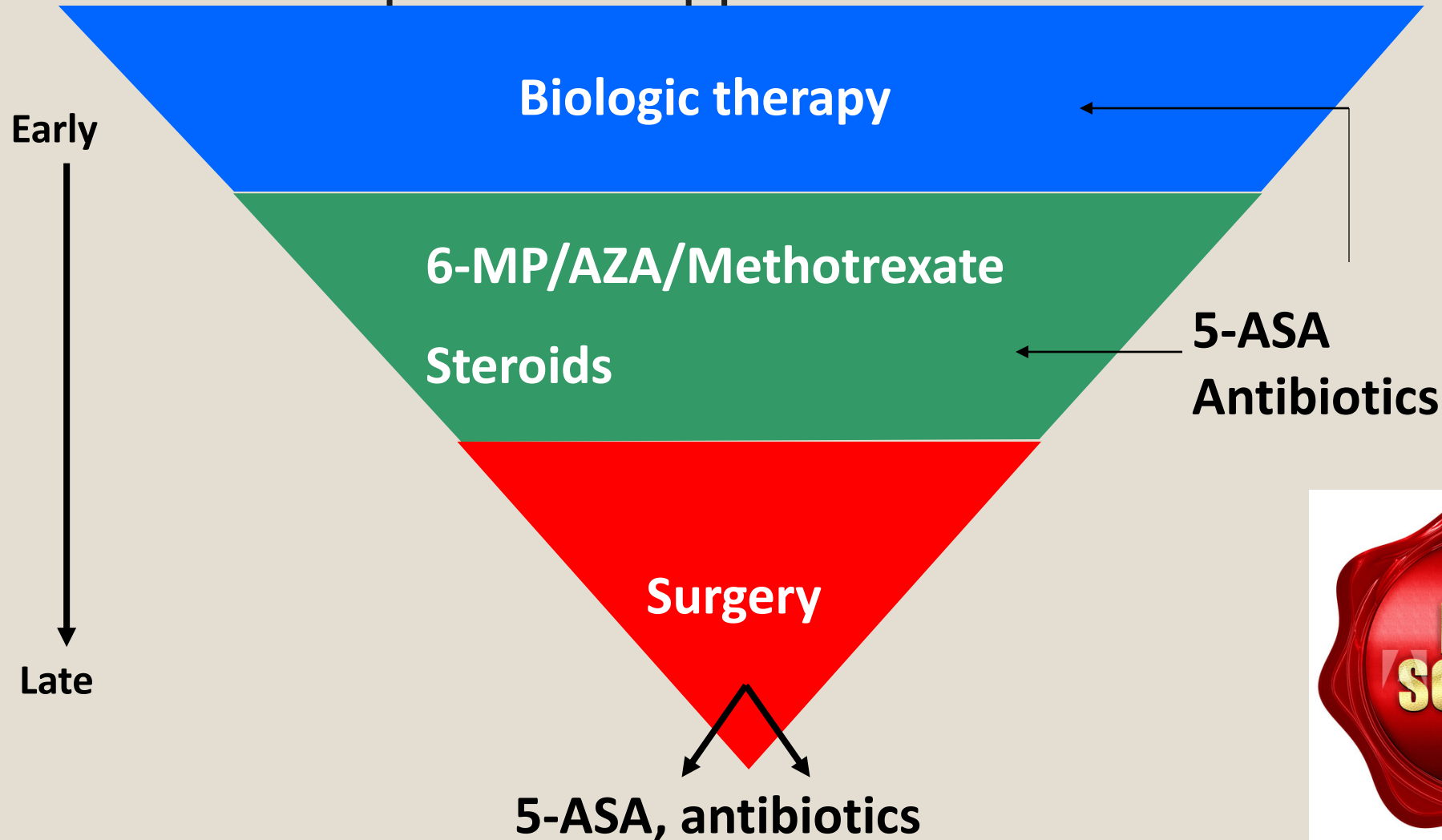
- **Improve growth and nutrition**
- Improve quality of life
- Maximize therapeutic response
- Minimize toxicity
- Prevent disease complications
- Maximize adherence
- **Promote psychological health**



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



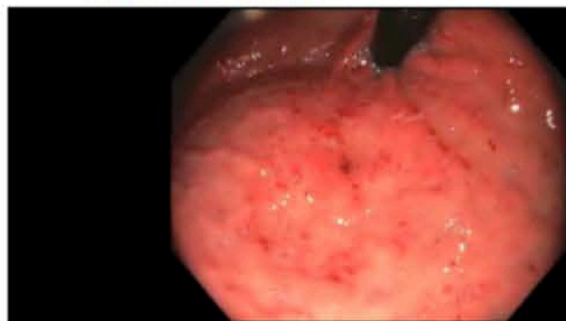
9 Gastric Fundus :
*Inflammation



10 Gastric Fundus :
*Inflammation



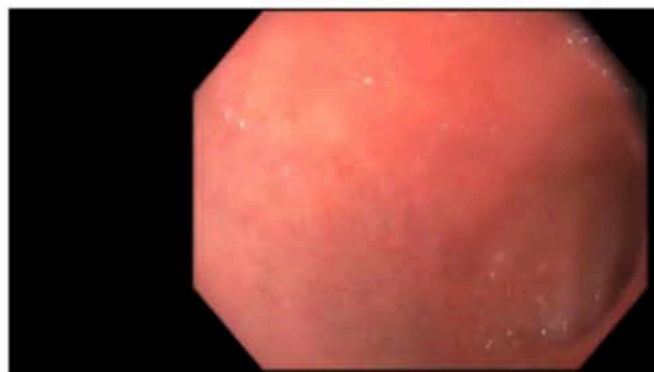
11 Gastric Antrum :
*Inflammation



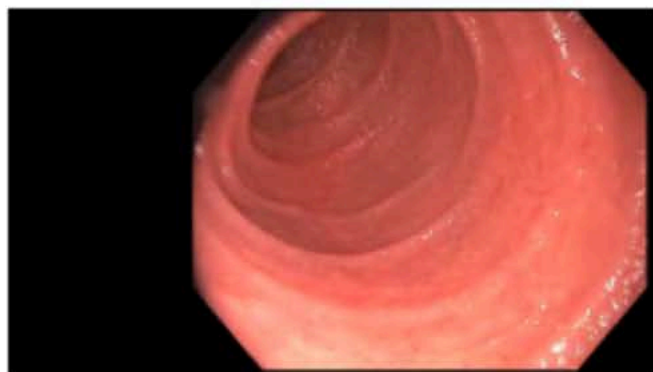
12 Gastric Fundus :
*Inflammation



13 Gastric Body :
*Inflammation



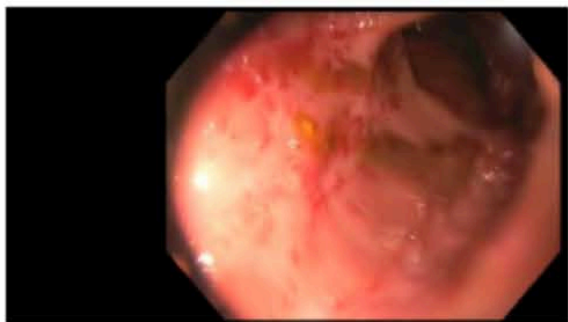
14 Duodenal Bulb : Atrophic



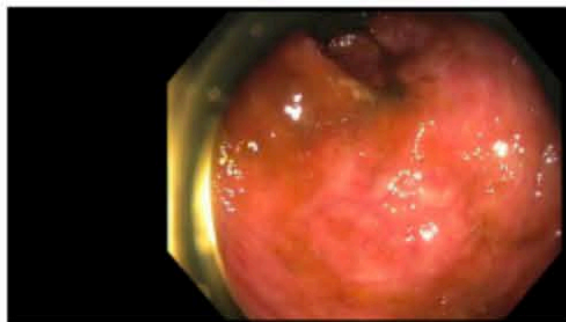
15 2nd Portion of the
Duodenum : Atrophic



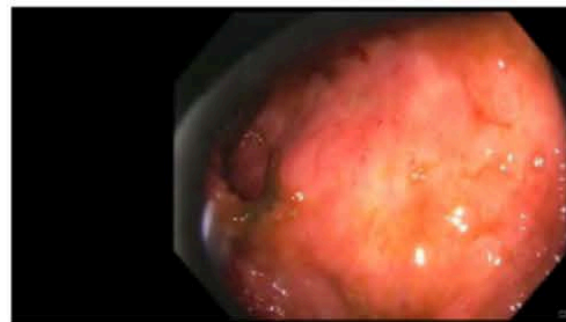
16 2nd Portion of the
Duodenum : Atrophic;



1 Rectum : Crohn's - Simple Endo Score



2 Rectum : Crohn's - Simple Endo Score



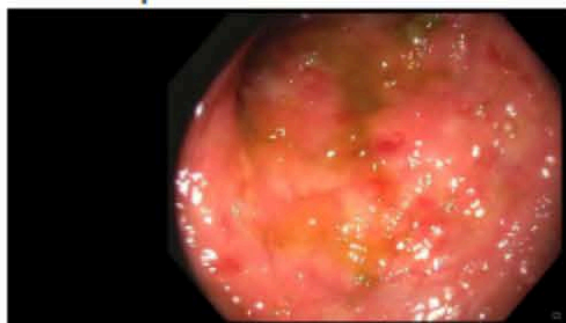
3 Sigmoid Colon : Crohn's - Simple Endo Score



4 Sigmoid Colon : Crohn's - Simple Endo Score



5 Sigmoid Colon : Crohn's - Simple Endo Score



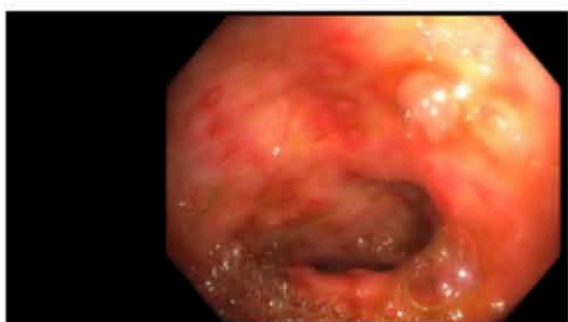
6 Sigmoid Colon : Crohn's - Simple Endo Score



7 Descending Colon : Crohn's - Simple Endo Score



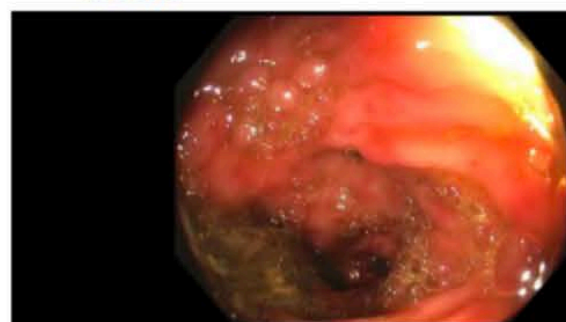
8 Descending Colon : Crohn's - Simple Endo Score



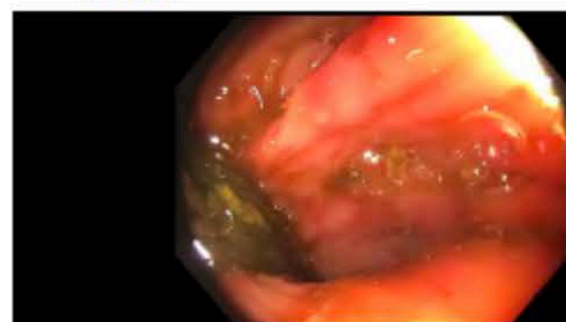
9 Descending Colon : Crohn's - Simple Endo Score



10 Descending Colon : Crohn's - Simple Endo Score



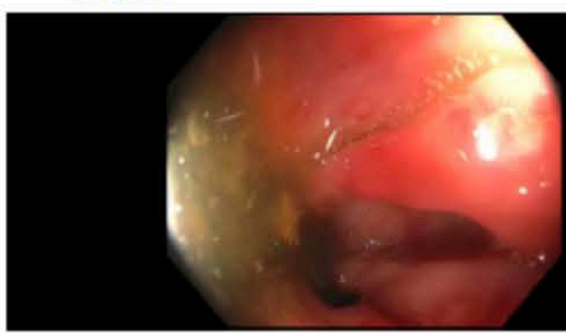
11 Descending Colon : Crohn's - Simple Endo Score



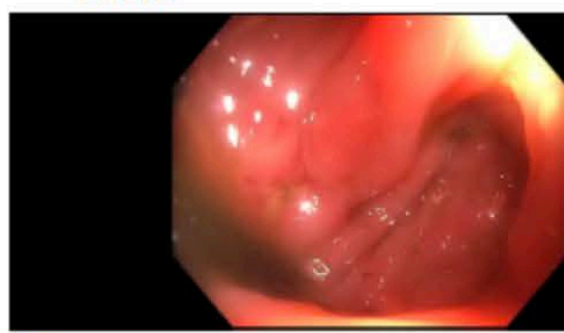
12 Descending Colon : Crohn's - Simple Endo Score



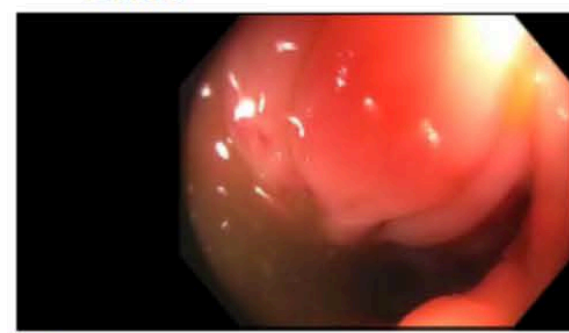
13 Splenic Flexure : Crohn's - Simple Endo Score



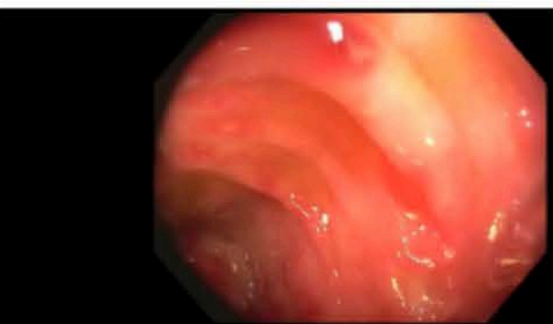
14 : Crohn's - Simple Endo Score



15 Transverse Colon : Crohn's - Simple Endo Score



16 Transverse Colon : Crohn's - Simple Endo Score



17 Transverse Colon : Crohn's - Simple Endo Score



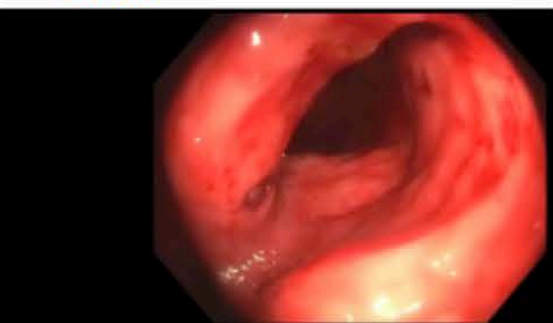
18 Transverse Colon : Crohn's - Simple Endo Score



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

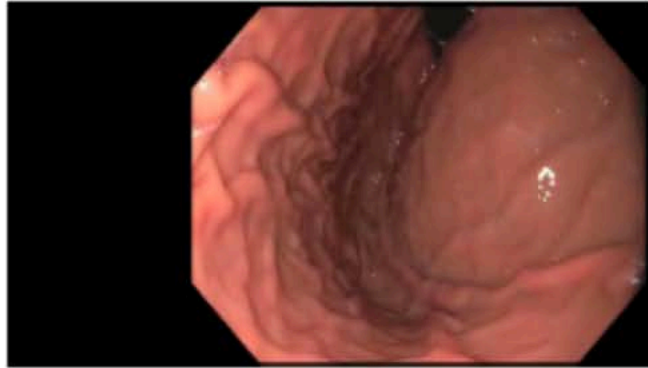


23 Rectum : Crohn's - Simple Endo Score

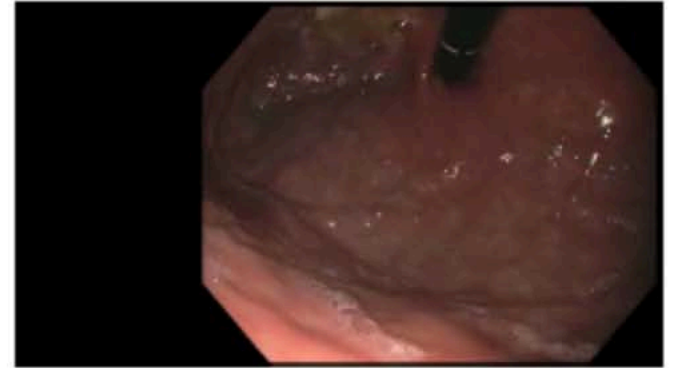
After 12 weeks of Total Enteral Nutrition



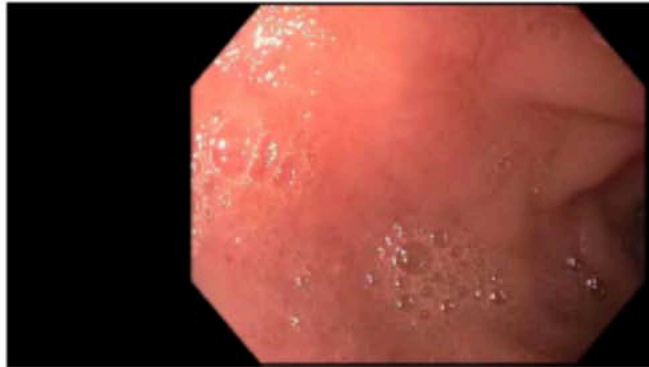
4 Pre-pyloric Stomach :
Normal



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



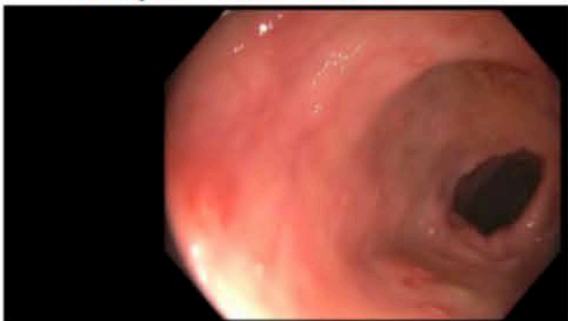
2 Sigmoid Colon : Crohn's - Simple Endo Score



3 Sigmoid Colon : Crohn's - Simple Endo Score



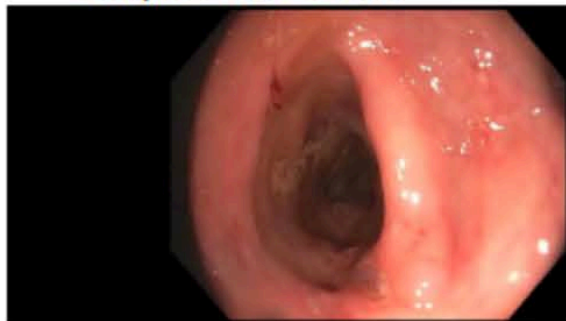
4 Sigmoid Colon : Crohn's - Simple Endo Score



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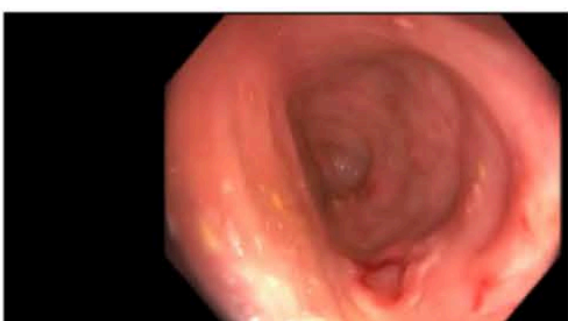
6 Descending Colon : Crohn's - Simple Endo Score



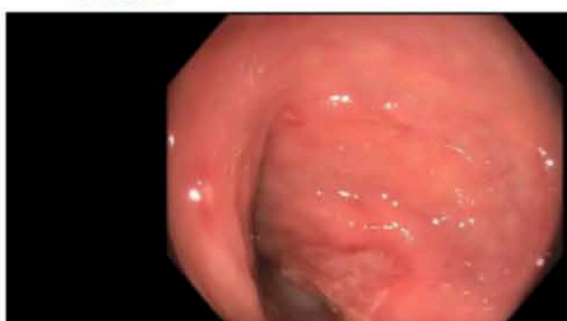
7 Descending Colon : Crohn's - Simple Endo Score



8 Descending Colon : Crohn's - Simple Endo Score



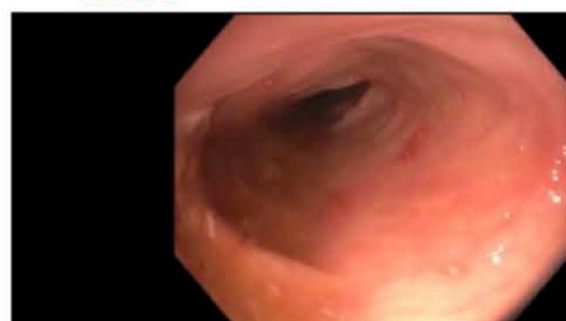
9 Descending Colon : Crohn's - Simple Endo Score



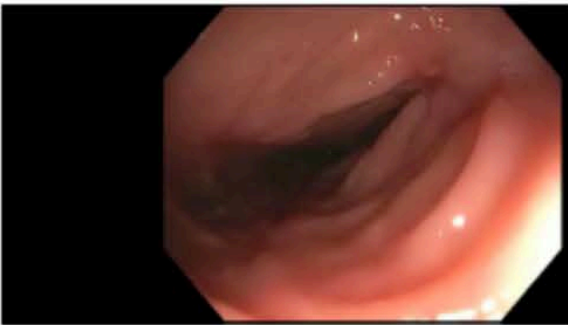
10 Descending Colon : Crohn's - Simple Endo Score



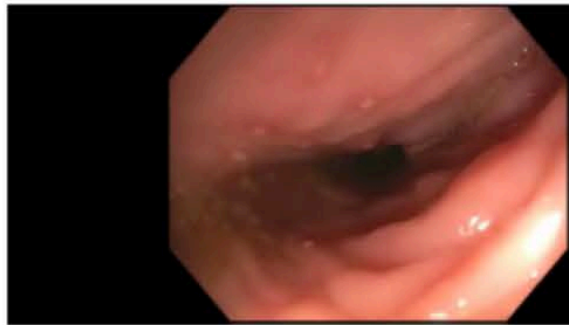
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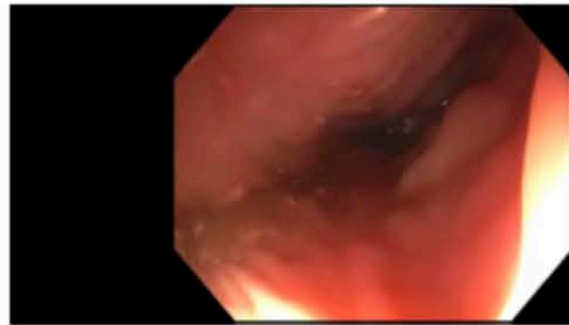
12 Transverse Colon : Crohn's - Simple Endo Score



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

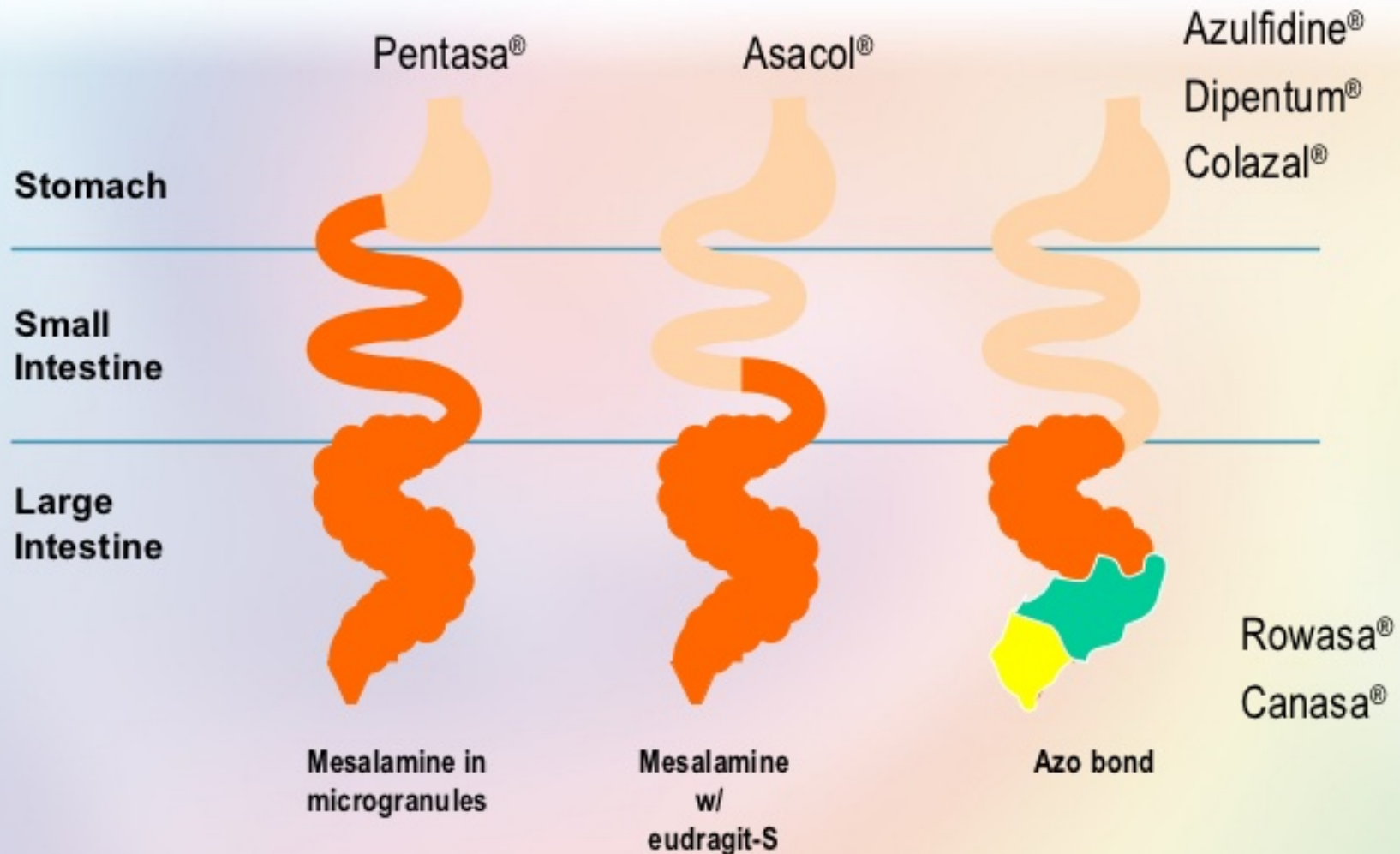


**STEP 2: MAINTAIN
STEROID-FREE
REMISSION**

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 VSL#3
- This is approved in ulcerative colitis and pouchitis
- Contains 23 strains of bacteria

Immunomodulators

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

6-MP/Imuran

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

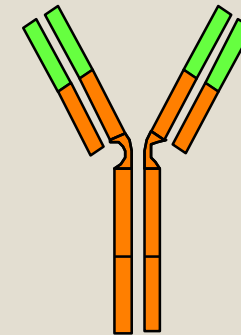
Methotrexate

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

Biologic Therapies

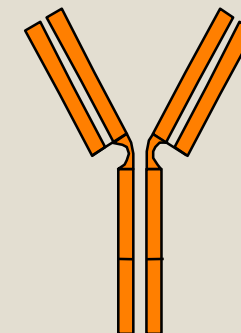
- Pro-inflammatory cytokines contribute to inflammation in IBD
 - TNF α is elevated in IBD patients
- Biologics block and neutralize cytokines
- Used to treat moderate to severe IBD not responding to other therapy
 - Infusion (Infliximab = Remicade, Infliximab biosimilars = Inflectra, Renflexis)
 - Injectable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

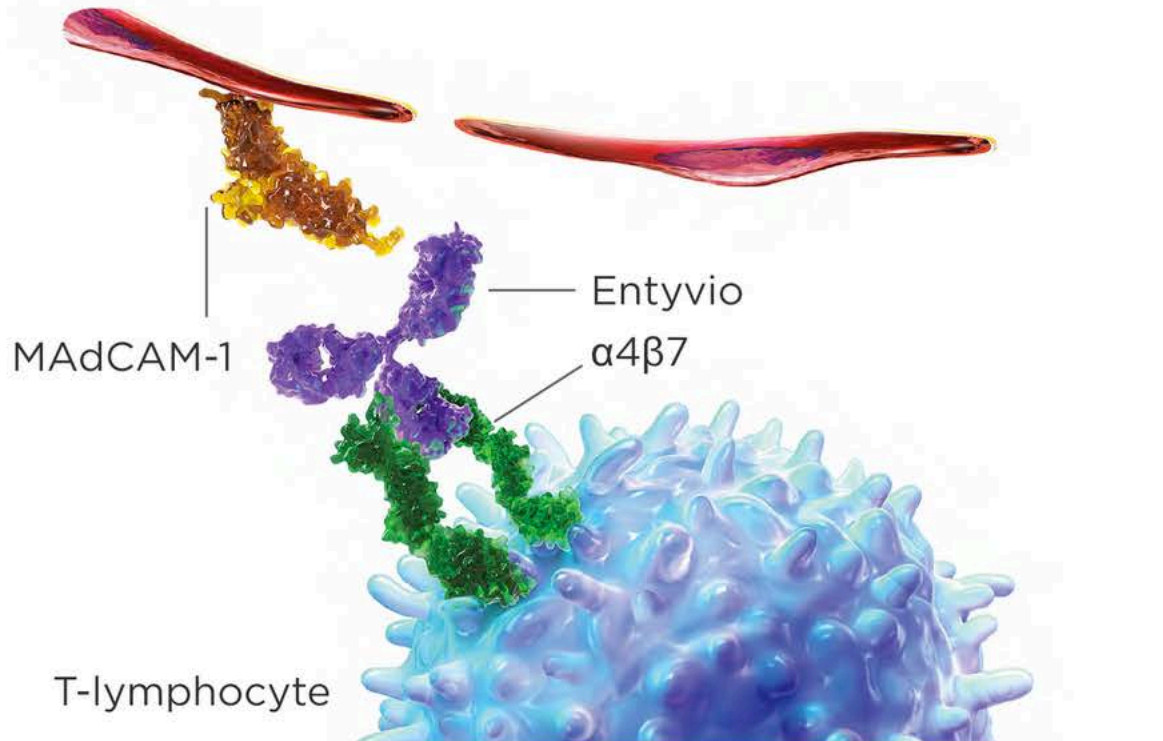
Vedolizumab (Entyvio)

- 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

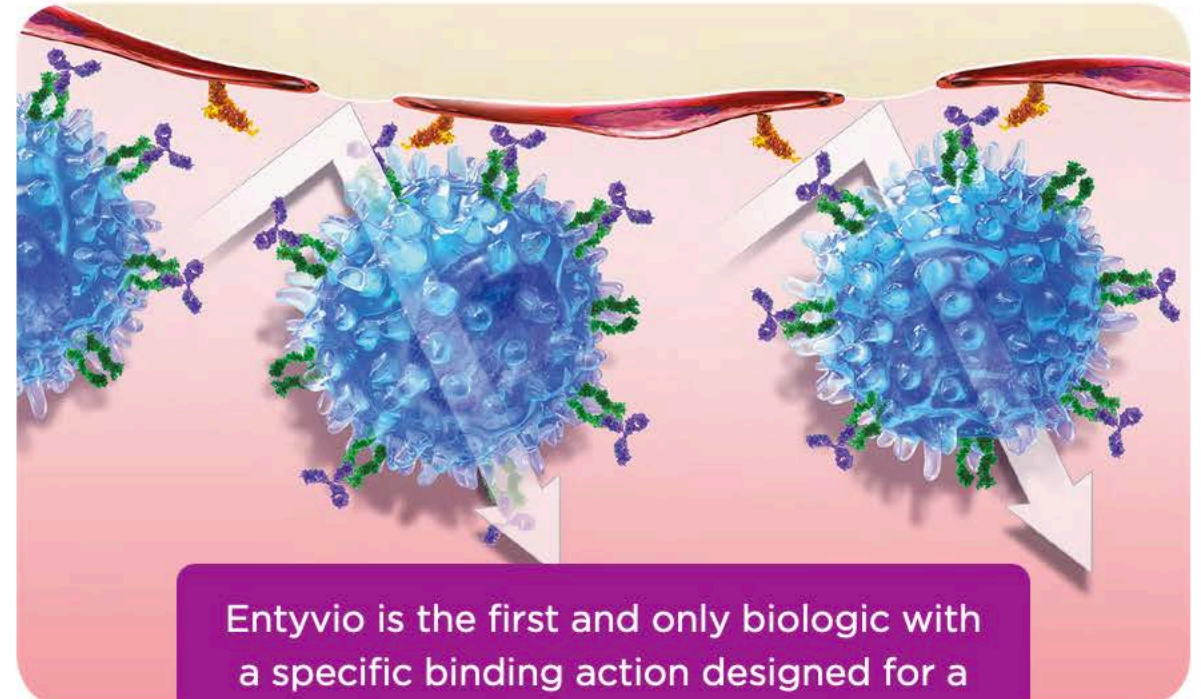
1

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.



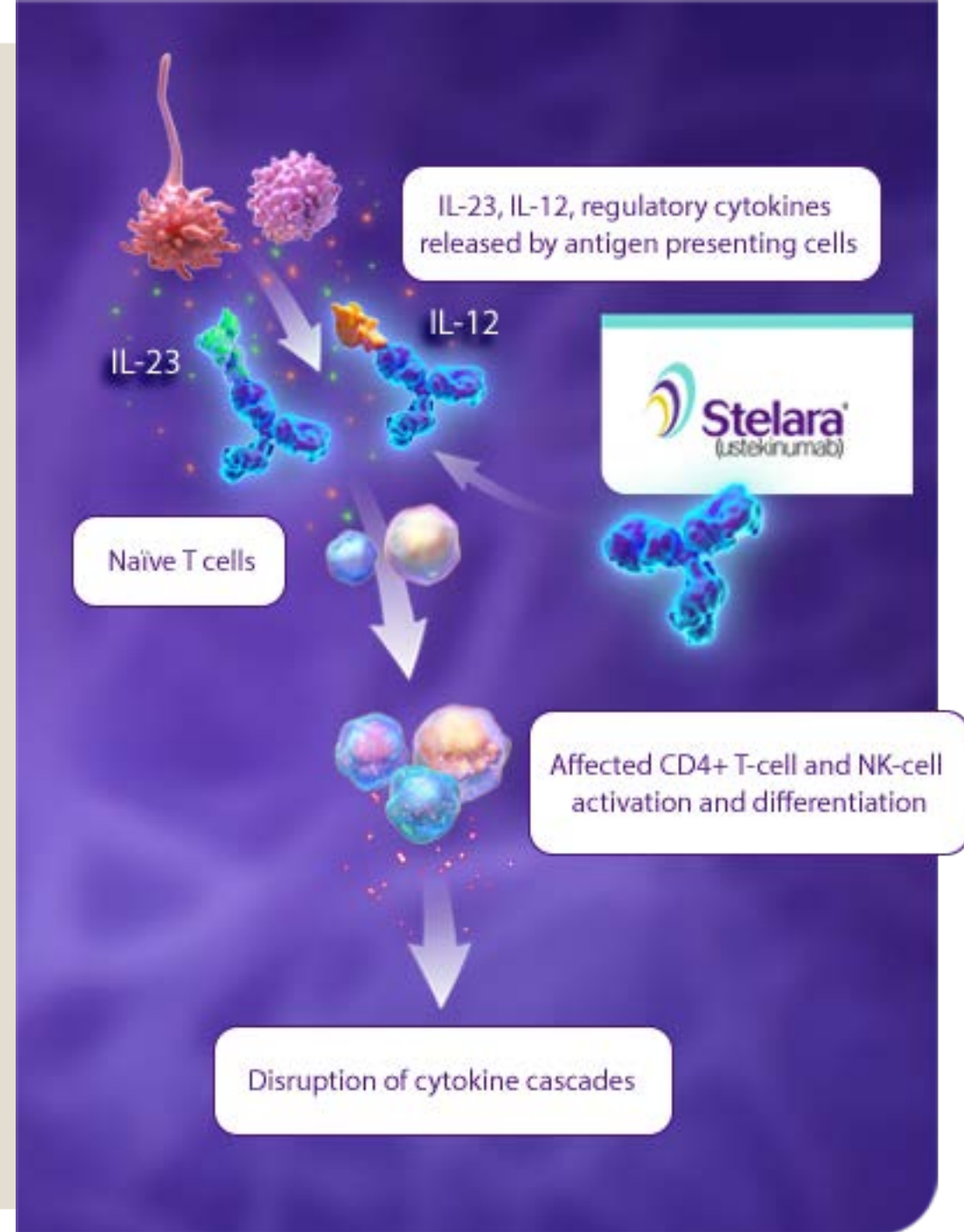
Ustekinumab (Stelara)

- IL12/23 inhibitor
- Approved in Crohns disease

Once every 8 weeks

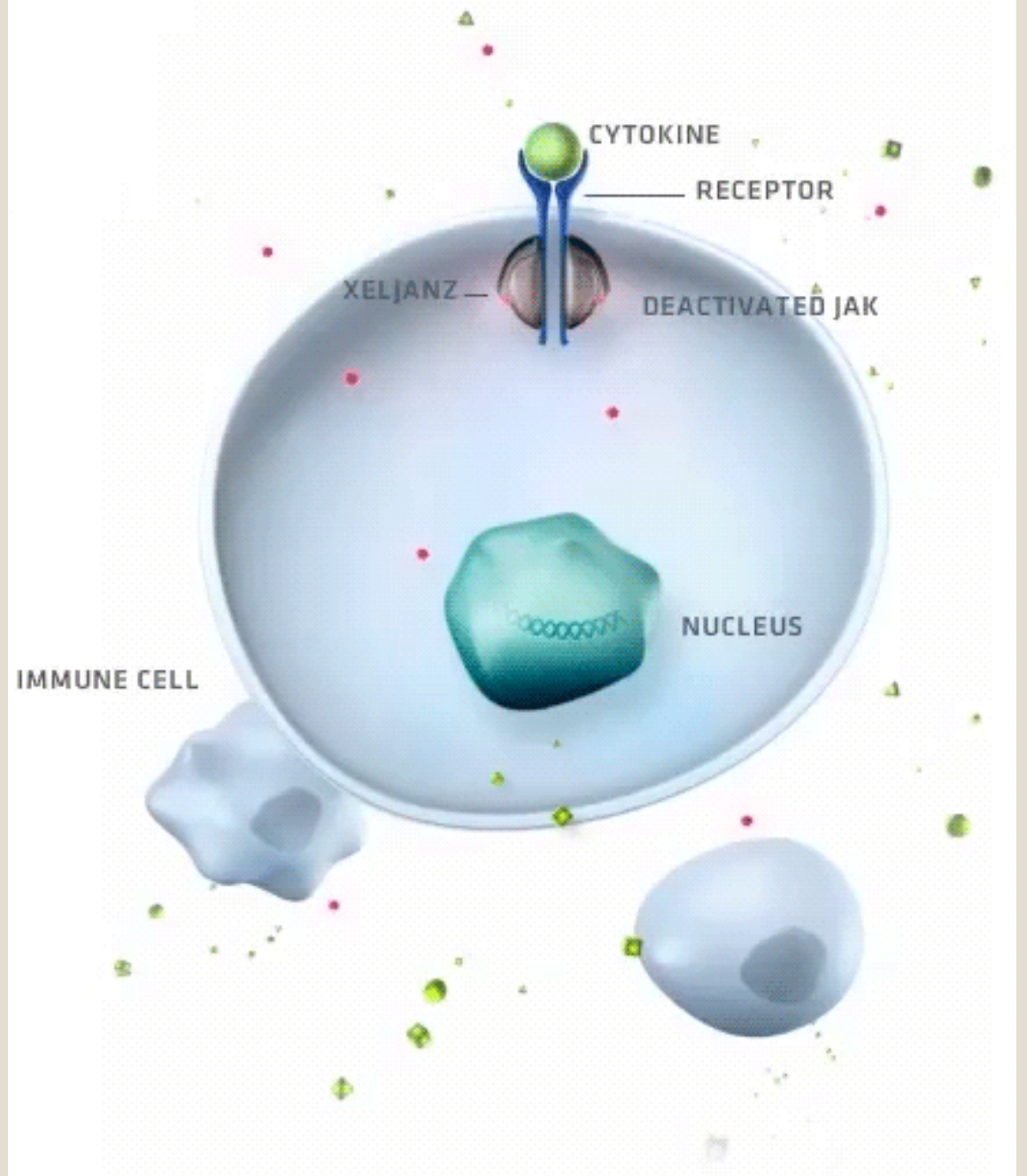
6

INJECTIONS



Tofacitinib (Xeljanz)

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



Future Advances?

- 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