

Medical Therapy for Pediatric IBD: Efficacy and Safety

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How do we choose a therapy?



Goals of Therapy in Pediatric IBD

- Induce and maintain clinical remission
- Improve quality of life
- Achieve optimal growth
- Minimize drug toxicity
- Optimize surgical outcomes
- Heal mucosal lining
- Alter the natural course of the disease

More to Follow...

- Diet
 - Anti-inflammatory diet
 - Enteral nutrition therapy
- Probiotics
- Alternative and Complementary therapies

Aminosalicylates (5-ASA)

- Reduce inflammation in the bowel
- Oral and rectal preparations – “topical”
- Release in different areas of the GI tract
- **Ulcerative colitis**: effective for induction and maintenance of remission
- **Crohn disease**: efficacy unclear for induction or maintenance of remission
- Generally well tolerated
- Side effects: headache, GI symptoms; 3-5% will have allergy

Antibiotics

- Decrease inflammation by changing or eliminating bacteria in GI tract
- Multiple indications for Crohn
 - Perianal disease
 - Abscess
 - Prevent post-operative recurrence
 - Treatment of mild or moderate disease
- Ulcerative colitis
 - Triple or quadruple antibiotics for refractory severe UC

Flagyl
(metronidazole)



Cipro
(ciprofloxacin)



Corticosteroids

- Oral (prednisone), IV (Solumedrol), or rectal
- Suppress active inflammation
- Indication: Acute symptomatic management
- Works quickly
 - Provides immediate symptomatic relief
 - Does not promote healing of GI tract
- **Not** indicated for maintenance therapy
 - Lose efficacy, side effects

Corticosteroids: Common Side Effects

- Growth retardation
- Increased risk of infection
- Contribution to ↓ bone mineral density
- Excessive weight gain
- Cosmetic
 - Acne, moon facies, hirsutism
- Psychological
 - Sleep disturbance, mood instability

Budesonide – “Topical” Steroid

UCERIS (budesonide)

UCERIS is not indicated for Crohn's disease; it is indicated for the induction of remission in patients with active, mild to moderate UC

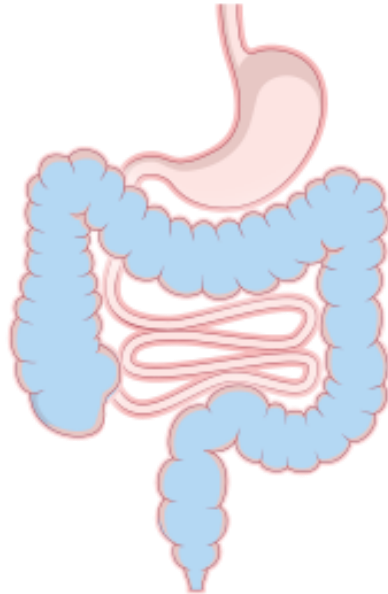
TARGET:

Full length of colon

MMX® technology:

Pill dissolves at pH ≥ 7.0 , the approximate pH level near the entry to the colon

Dosage: 9-mg tablet QD



Entocort® EC (budesonide)

Entocort® EC is not indicated for UC; it is indicated for the treatment of active, mild to moderate Crohn's disease involving the ileum and/or ascending colon

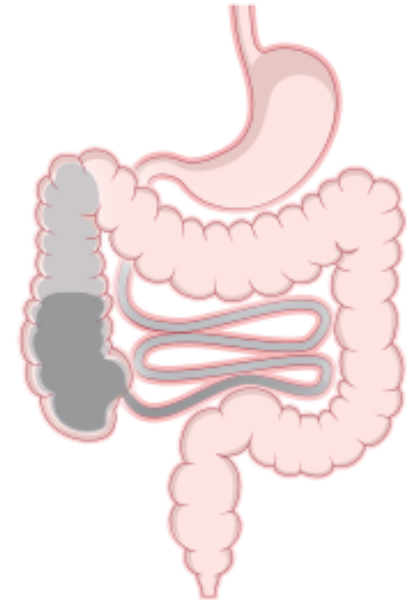
TARGET:

Ileum/ascending colon

Controlled ileal release:

Pill dissolves at pH > 5.5 , the approximate pH level of the duodenum

Dosage: 3 mg x 3 capsules QD



Immunomodulators

- Suppress immune response that triggers intestinal damage in IBD
- Maintenance of remission
- Steroid sparing
- Alone vs. in combination with biologics

6-MP/Imuran

- Daily dosing
- Oral administration
- 3-4 months for max.

Methotrexate

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

No live vaccines

6-MP/AZA and MTX Adverse Effects

6-MP/AZA

- Nausea
- ↓ white blood cell count
- Liver toxicity
- Pancreatitis
- Increased infection risk
- Increased skin cancer risk
- Slightly increased lymphoma risk

Methotrexate

- Nausea
- ↓ white blood cell count
- Liver toxicity
- Poor appetite
- Increased infection risk
- Reaction at injection site
- No documented increased cancer risk
- Teratogenic

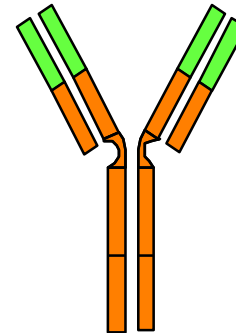
Biologic Therapies

- Many pathways lead to overactive immune system resulting in inflammation in the intestine
- Biologics are medications engineered to interfere in these pathways to stop inflammation
- Used to treat moderate to severe Crohn disease and ulcerative colitis

Biologics

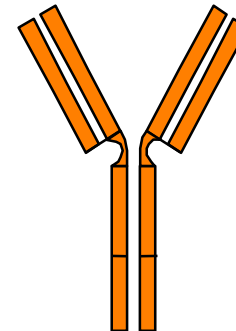
- Anti-TNF therapy
 - Infliximab (Remicade)
 - Adalimumab (Humira)
 - Golimumab (Simponi)
 - Certolizumab (Cimzia)
- Integrin Antagonists
 - Vedolizumab (Entyvio)
 - Natalizumab (Tysabri)
- Anti-IL-12/IL-23
 - Ustekinumab (Stelara)

**Remicade
(infliximab)**



75% Human

**Humira
(adalimumab)**



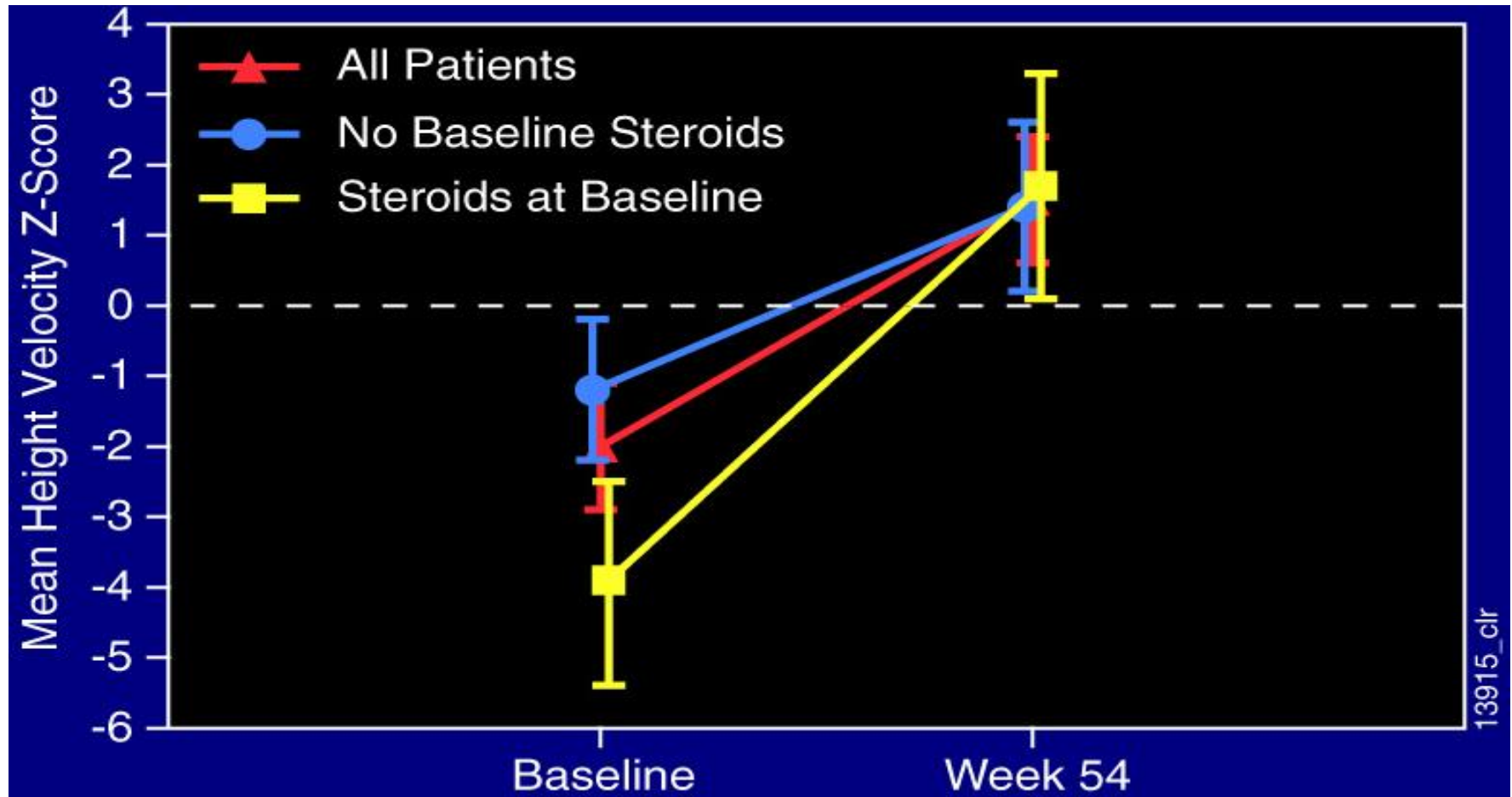
100% Human

Remicade (infliximab)

Humira (adalimumab)

- Moderate to severe Crohn's disease
 - Decreases steroid requirement
 - Mucosal healing
 - Healing of perianal disease
 - Improvement of growth
 - Bone health
 - Prevention of post-operative recurrence
- Ulcerative colitis
 - Treatment of moderate to severe disease
 - Prevention of surgery

Improved Growth with Infliximab



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Anti-TNF α Therapy

Remicade (infliximab)

- Intravenous infusion
- Loading dose
 - 0, 2, 6 weeks
- Maintenance dose
 - Every 8 weeks
- Can escalate if necessary

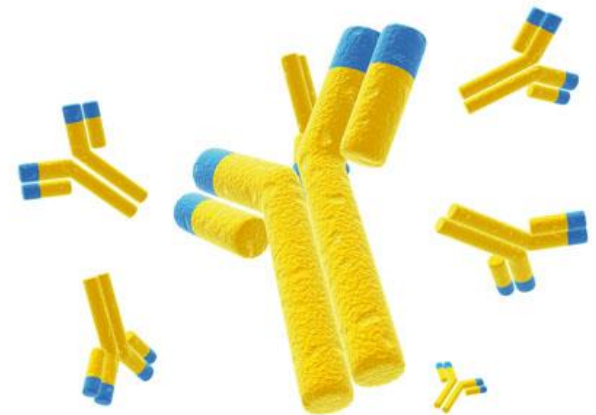
Humira (adalimumab)

- Subcutaneous injection
 - Now Citrate Free Humira
- Loading dose
 - Multiple injections wk 0,2
- Maintenance dose
 - Every 2 weeks
- Can escalate if necessary

Need to pre-screen for tuberculosis
No live vaccines

Anti-TNF α Therapeutic Monitoring

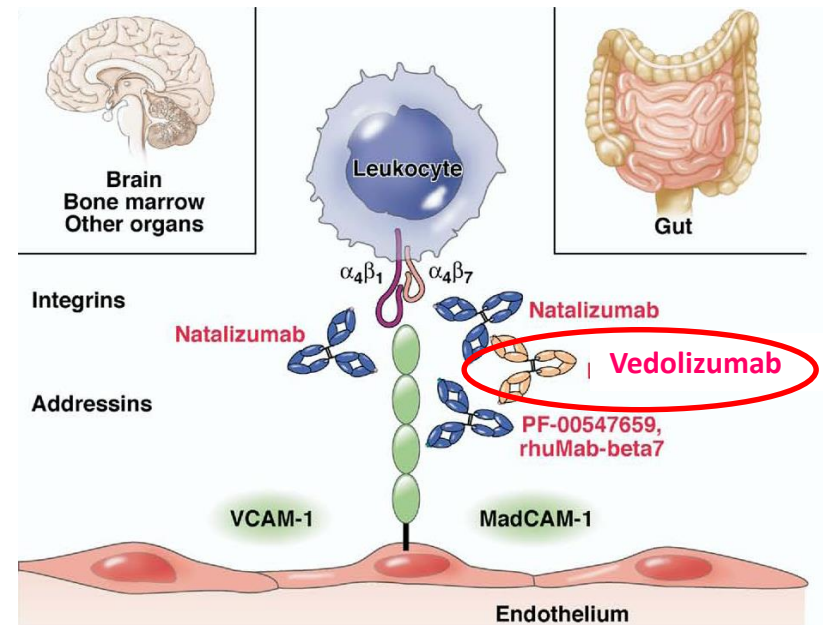
- Measure trough level/antibodies against medicine
- “Sub-therapeutic drug level”
 - Less likely to be effective
 - Increase dose and/or decrease interval
- Antibodies against medication
 - Less likely to be effective
 - Can optimize dose
 - Add immunomodulator
 - Might have to switch agents



Vedolizumab (Entyvio)

Gut specific anti-adhesion molecule

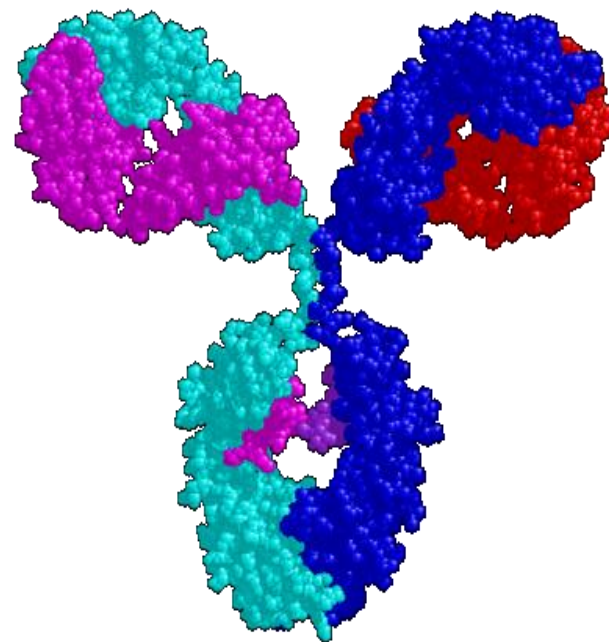
- Inhibits intestinal T-lymphocyte migration into tissue
- 2014: Approved for adult Crohn disease and UC
- CHOP: >75 patients
- Published on early experience



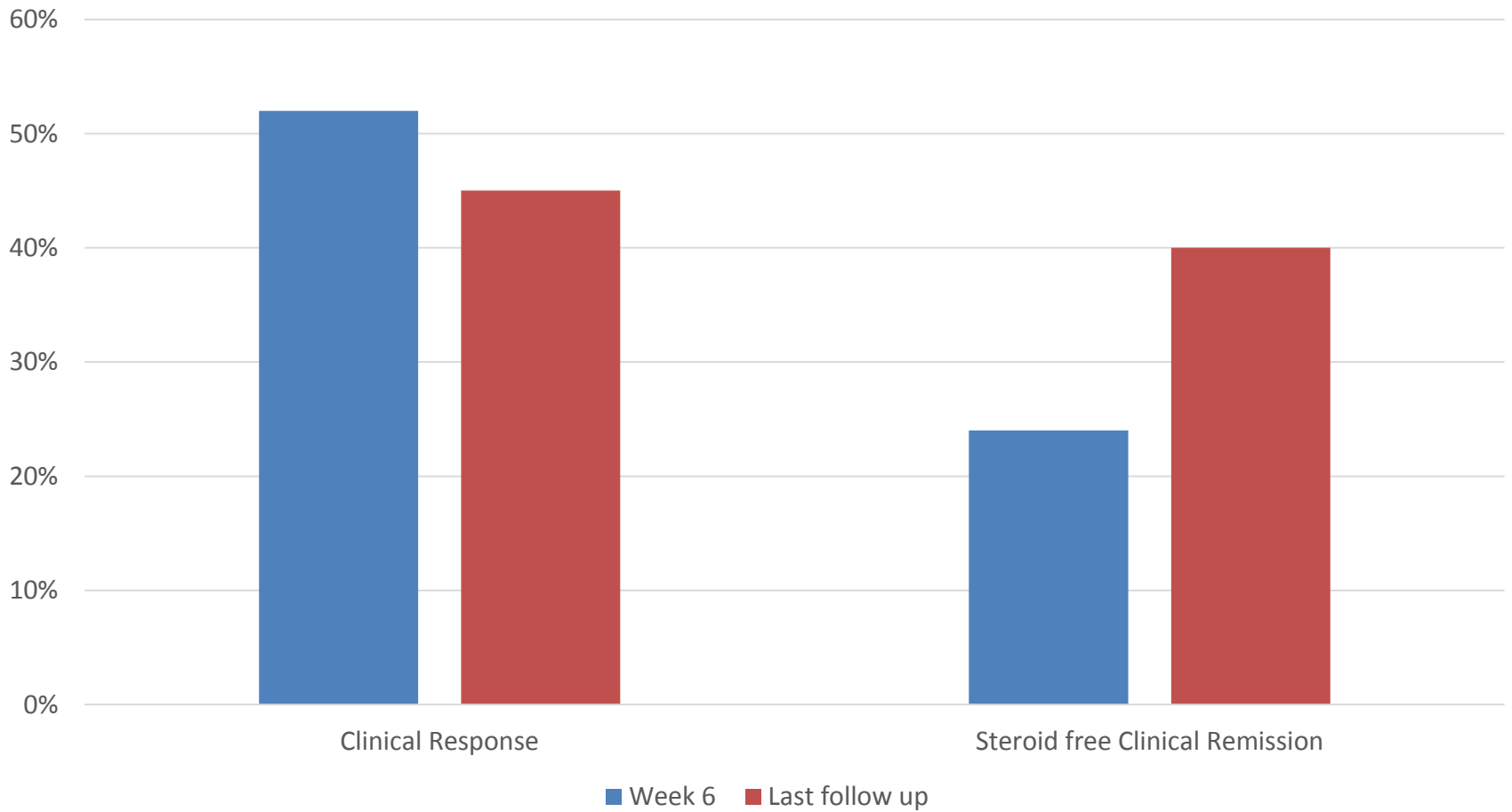
Ustekinumab (Stelara®) for Active Crohn Disease

Prevents binding of IL-12 and IL-23 to receptors

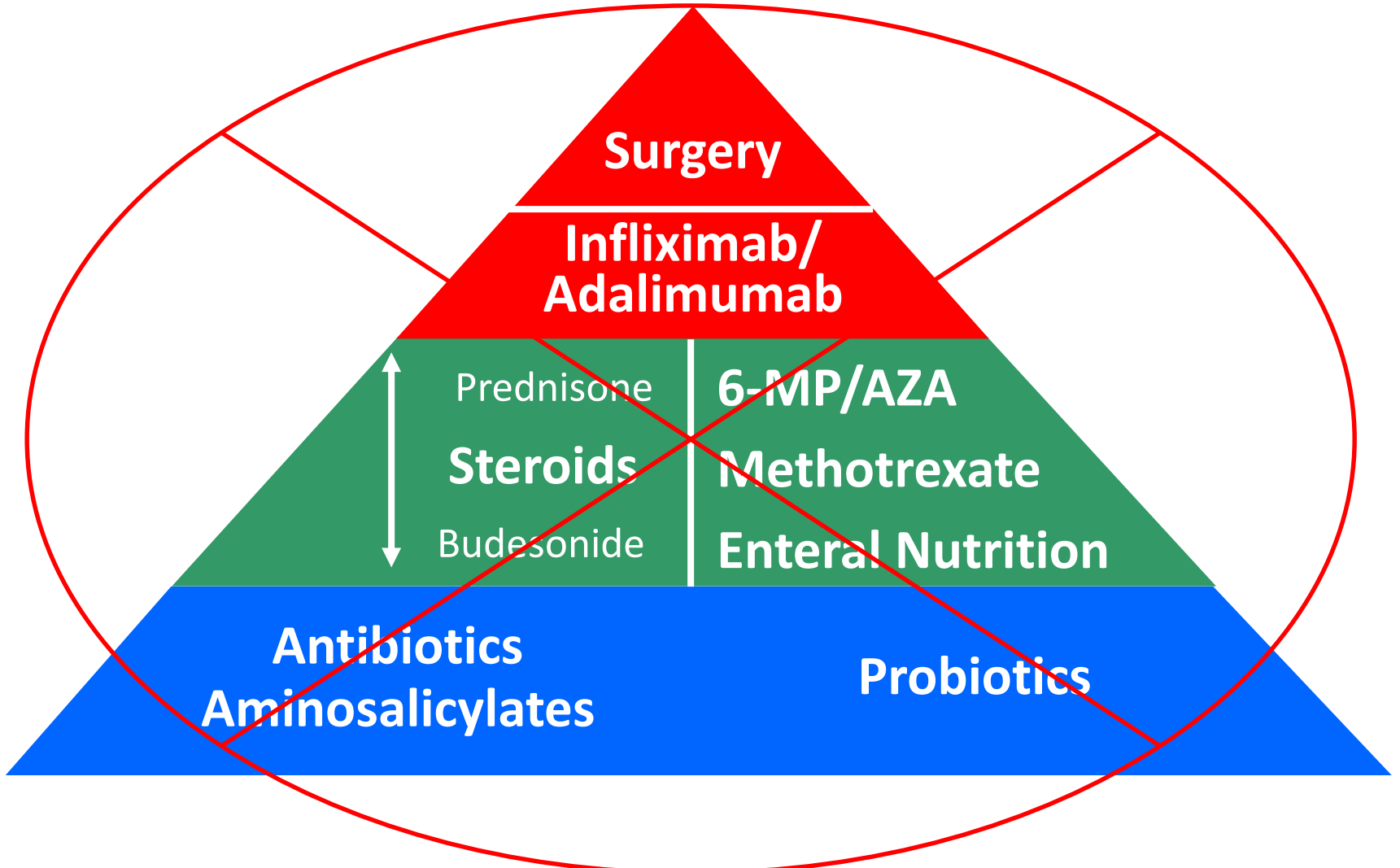
- Initially used for psoriasis and arthritis
- 2016: Approved for treatment of Crohn disease
- Side effect profile favorable
- **Induction:** IV infusion in GI suite
- **Maintenance:** Subcutaneous injection self-administered every 1-2 months



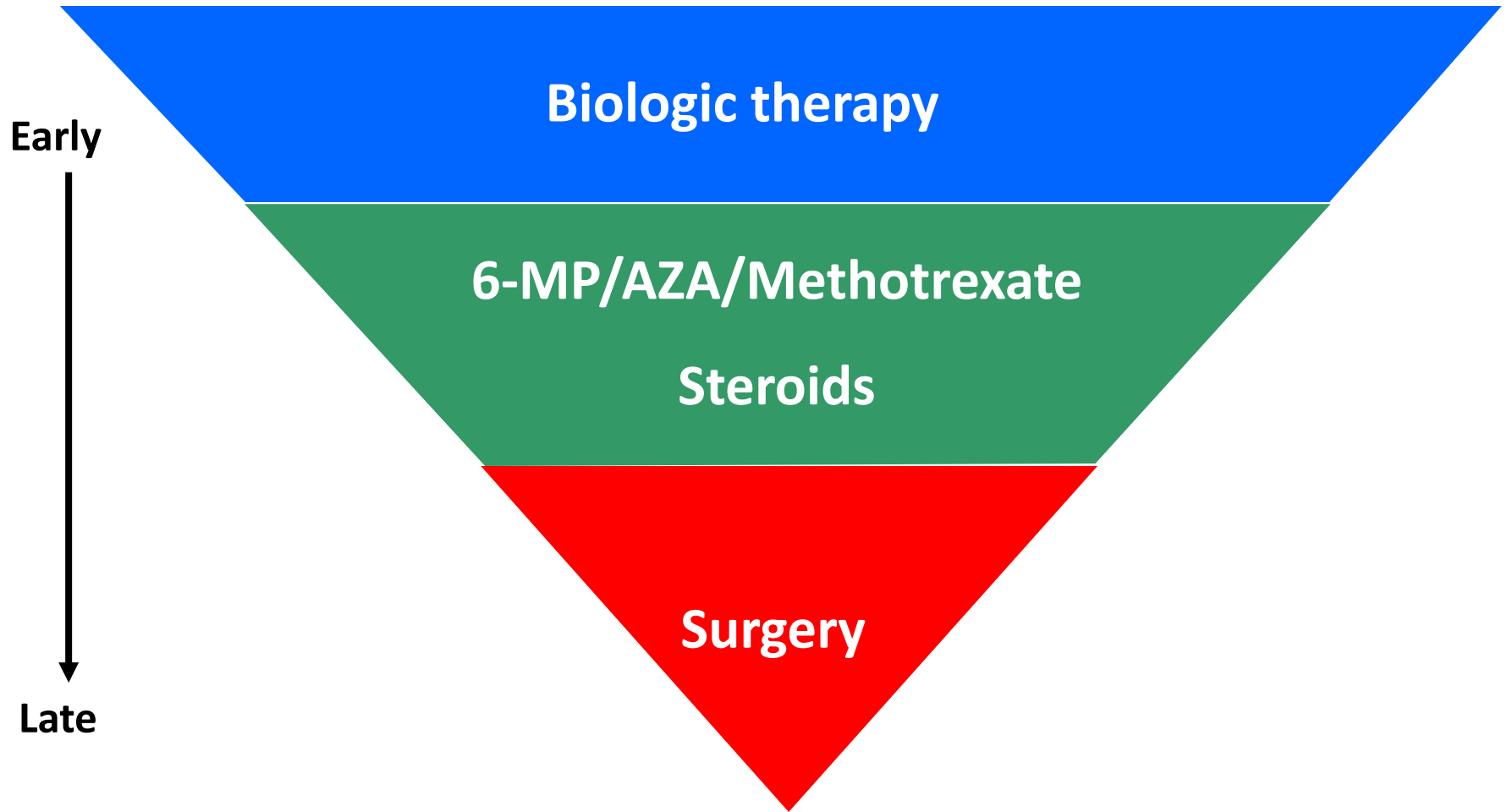
Ustekinumab Experience at CHOP



Traditional Pediatric IBD “Step-Up” Algorithm



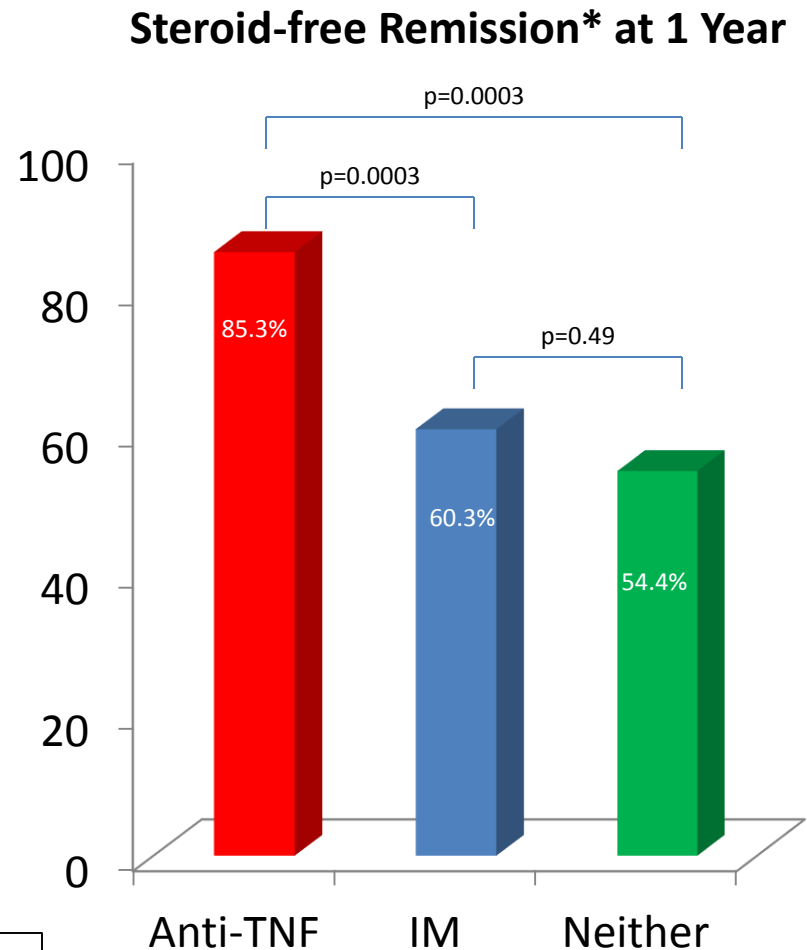
Does Early Use of Biological Therapy Improve Outcomes?



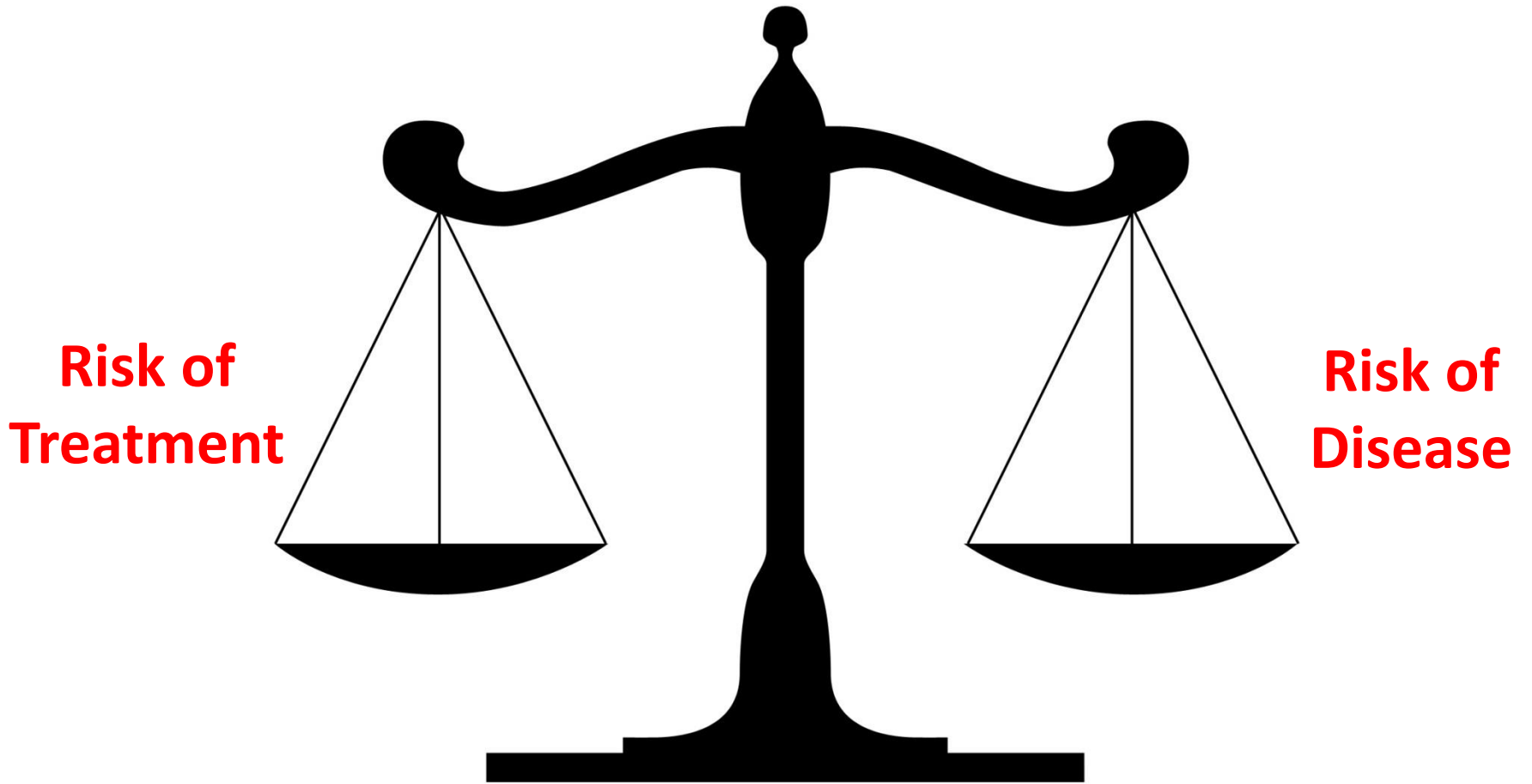
Early Anti-TNF α Therapy in Pediatric Crohn Disease

- Observational cohort of pediatric CD patients (inflammatory)
- Propensity score analysis matched patients on baseline characteristics in 68 triads
 - Early anti-TNF (<3 mo)
 - Early immunomodulator
 - Neither
- Early anti-TNF
 - Higher remission rate
 - Improved height z-score

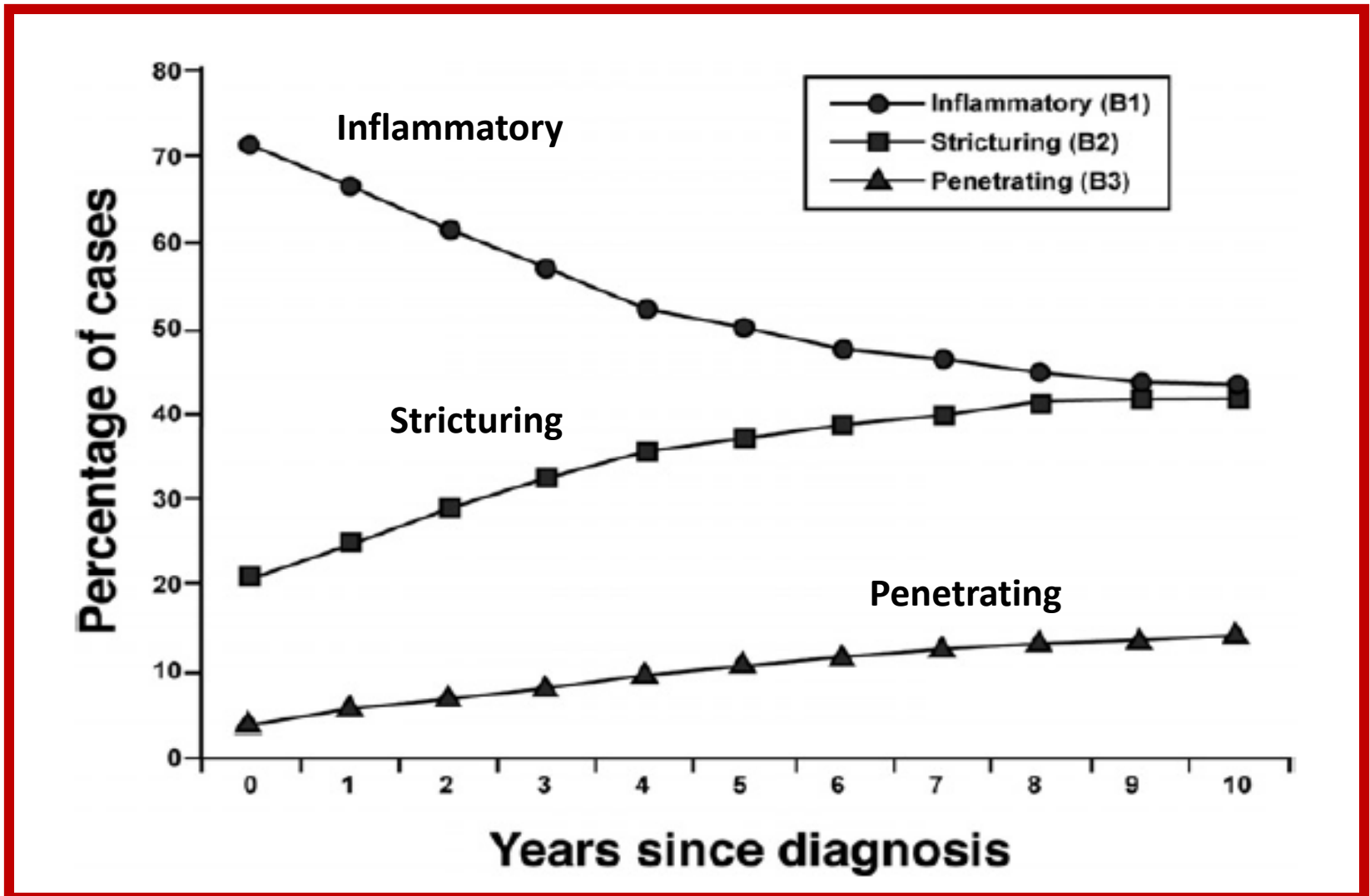
*Remission: PCDAI \leq 10, steroid free, no surgery



Risk of Treating vs. Not Treating



Long-Term Evolution of Pediatric Crohn Disease is Structural Damage



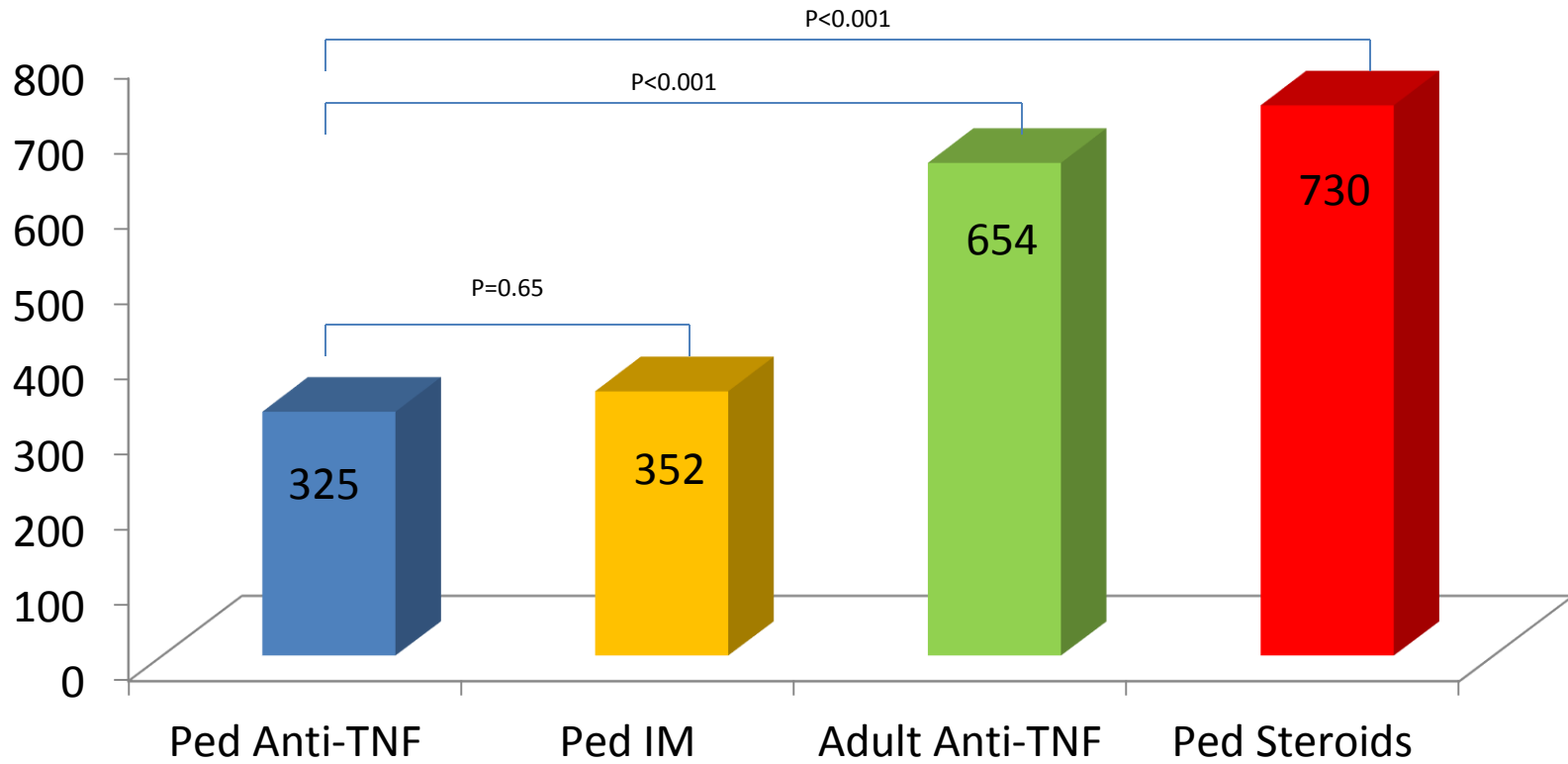
What we (parents, patients and physicians) are most concerned about:

Infection

Lymphoma

Pediatric IBD Risk of Serious Infection: A Systematic Review

Serious Infections per 10,000 Patient-Years



Vaccination

- Ensure that vaccines are up to date at time of diagnosis
- All non-live vaccines should be given
 - Annual flu shot
 - HPV vaccine
 - Consider pneumococcal booster
- Avoid live vaccines if immunosuppressed
 - MMR, Varicella, intranasal flu, others



Risk versus Benefit of Biologics and Immune Suppressants in IBD

Event	Estimated Frequency (annual, pt-years)
Non-Hodgkin Lymphoma (baseline)	2/10,000
Non-Hodgkin Lymphoma (on IM)	4/10,000
Non-Hodgkin Lymphoma (on anti-TNF)	6/10,000
Hepatosplenic T-cell Lymphoma	Unknown
Death from sepsis	4/1000
Tuberculosis	5/10,000

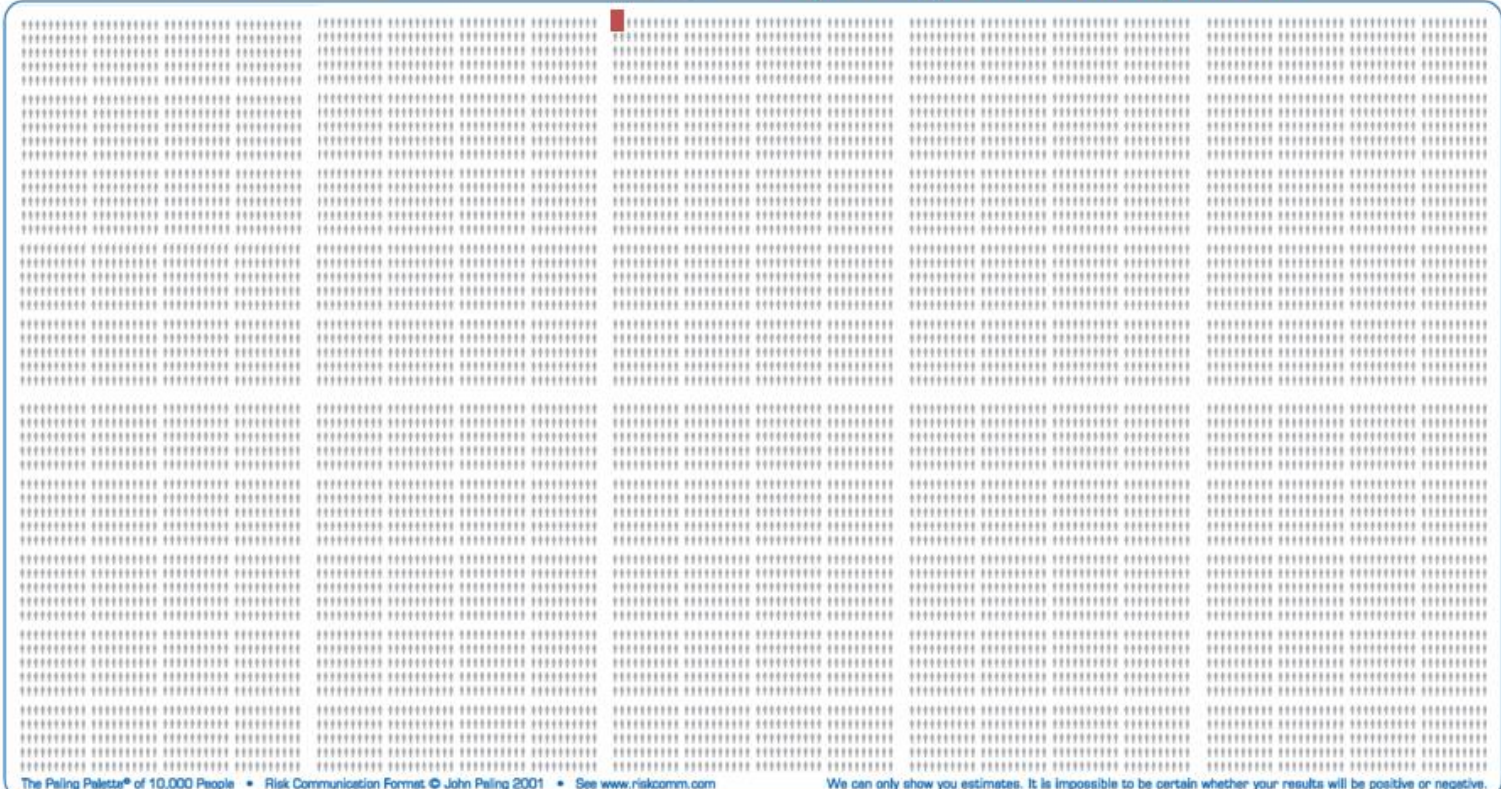
Adapted from Siegel CA. Comprehensive approach to patient risk. Risk versus benefit of biologics and immune suppressants. In: Targan S, Shanahan F, Karp L, eds. Inflammatory Bowel Disease: Translating basic science into clinical practice

Risk of Developing NHL – No immune suppression

Patient with Crohn's disease (without immune suppression)

Ten Thousand People
– pictures to help you see your odds

Estimated annual risk =
2 per 10,000 treated patients

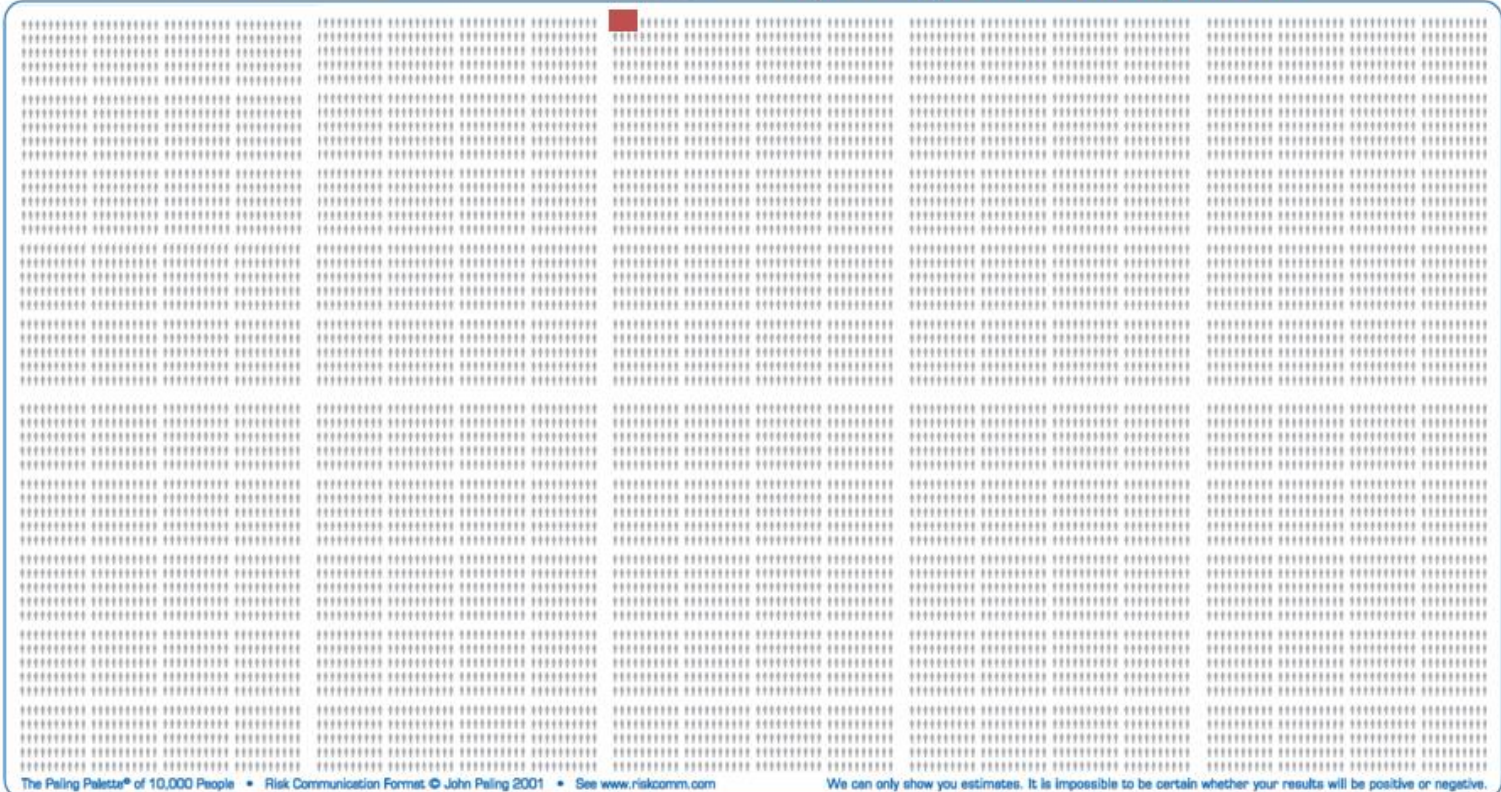


Risk of Developing NHL – Immunomodulator

Patient with Crohn's disease receiving 6MP or Azathioprine

Ten Thousand People
– pictures to help you see your odds

Estimated annual risk =
4 per 10,000 treated patients

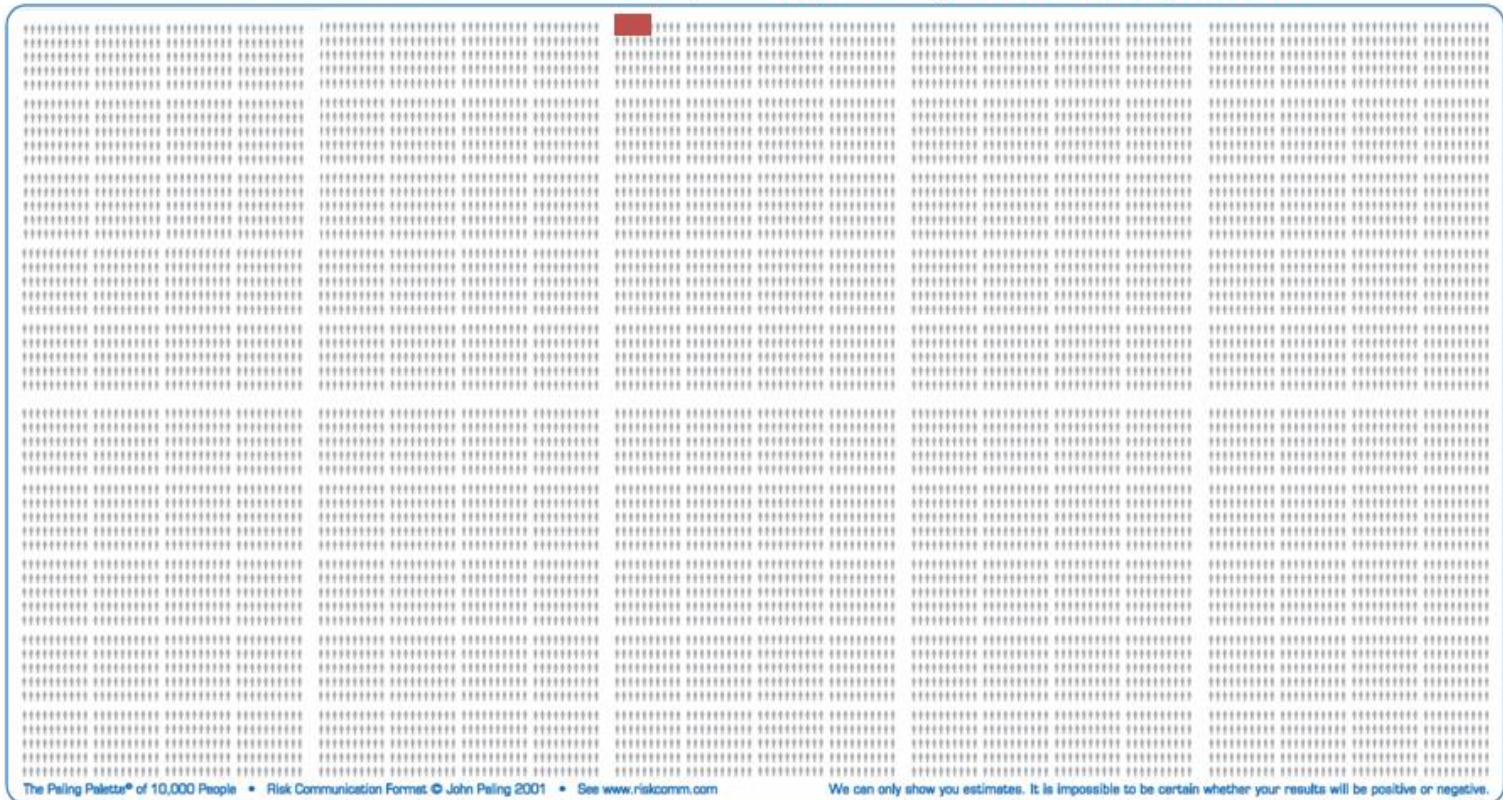


Risk of Developing NHL – Immunomodulator + Anti-TNF α

Patient with Crohn's disease receiving combination anti-TNF + Immunomodulator Therapy

Ten Thousand People
– pictures to help you see your odds

Estimated annual risk =
6 per 10,000 treated patients



Pediatric DEVELOP Registry

- Largest prospective pediatric IBD safety cohort
 - Patients assessed every 6 mo, followed for 20 yrs
 - 5,766 patients enrolled
 - >20,000 PY of follow up
- Infliximab exposed **do not** have higher rate of malignancy than non-exposed
- Statistically significant increased rate of malignancy in thiopurine exposed

Small Molecules

- JAK inhibitors: Tofacitinib (Xeljanz)
 - Daily oral medication
 - Not a biologic: no risk of forming antibodies
 - Blocks JAK-STAT pathway inside of inflammatory cells
 - Decreases cytokines
 - Approved for moderate-severe ulcerative colitis in adults



Risk of Disease Often Greater than Risk of Treatment

**Risk of
Treatment**



**Risk of
Disease**

Summary of Therapeutic Goals



Resources



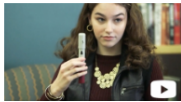
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Center for Pediatric Inflammatory Bowel Disease Resources



How to Give a Subcutaneous Injection Using a Pen



This video from Children's Hospital of Philadelphia (CHOP) demonstrates how IBD patients can give a subcutaneous injection using a pen.

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9 LOCATIONS

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Types of Medications for Crohn's Disease and Ulcerative Colitis

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ABOUT THIS RESOURCE

By: Crohn's & Colitis Foundation
Published: April 7, 2017

The medical treatment of inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis has three main goals:

- **Achieving remission** (the absence of symptoms)
- **Maintaining remission** (prevention of symptoms or flare-ups)
- **Improving your quality of life**

To accomplish these goals, treatment is aimed at controlling the ongoing inflammation in the intestine—the cause of IBD symptoms. There is no standard approach to managing all people with IBD. The symptoms, severity of disease, and how the disease might impact a person down the road vary considerably.

Your healthcare provider will work with you to help decide the right treatment for you. It may take some time for medications to take effect, or sometimes a medication may stop working. The management of Crohn's disease and ulcerative colitis involves dedication to taking your medications as prescribed and maintaining open communication with your healthcare team so you can work together