Medical Therapy for Pediatric IBD: Efficacy and Safety

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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

How To Know Which Therapy Is "Right" For Your Child

Aminosalicylates (5-ASA)

- Reduce inflammation in the bowel
- Oral and rectal preparations
- Release in different areas of the GI tract
- Generally well tolerated
- Side effects: headache, GI symptoms; 3-5% will have allergy

Includes:

- **Mesalamine**
- **Pentasa**
- **Apriso**
- **Lialda**
- **Asacol**
- **Colazol**

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)

Turner D, et al. *J Crohns Colitis* 2014; 8:1464-1470, Breton et al. *Inflamm Bowel Dis,* 2019.

Corticosteroids

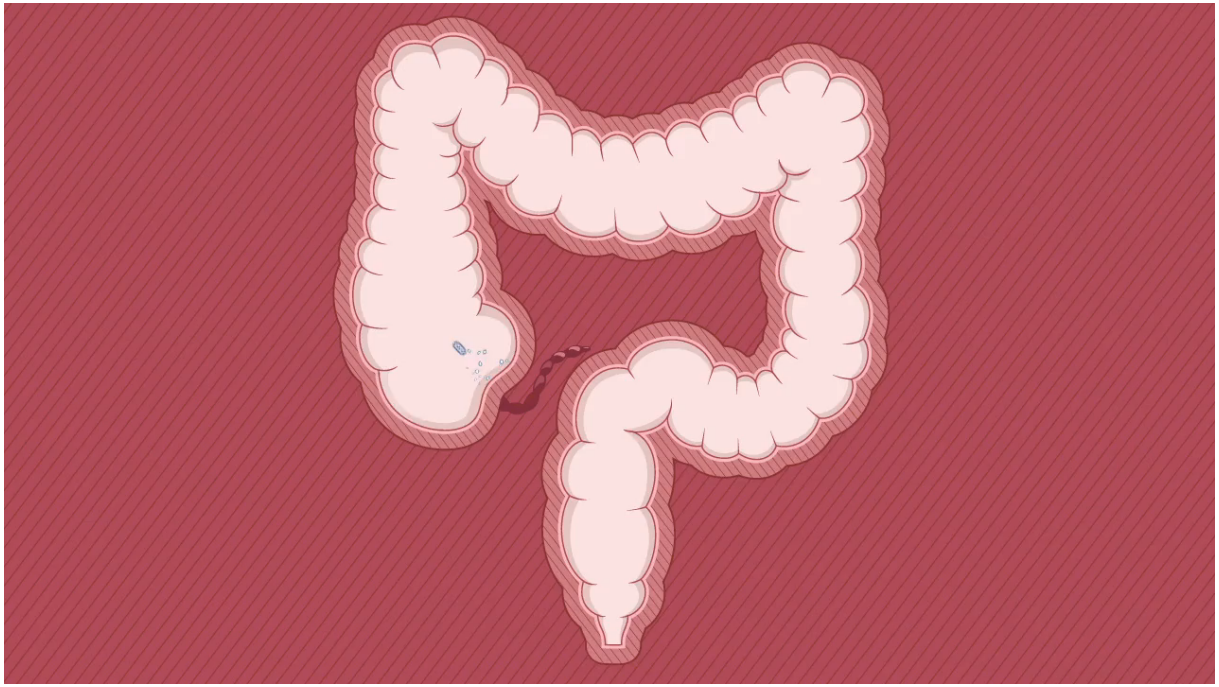
- Oral (prednisone), IV (Solumedrol), or rectal
- Decreases active inflammation
- Indication: Acute symptomatic management
- Works quickly to improve symptoms
- Does not promote healing of GI tract
- **Not** indicated for maintenance therapy

Corticosteroids: Safety and 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

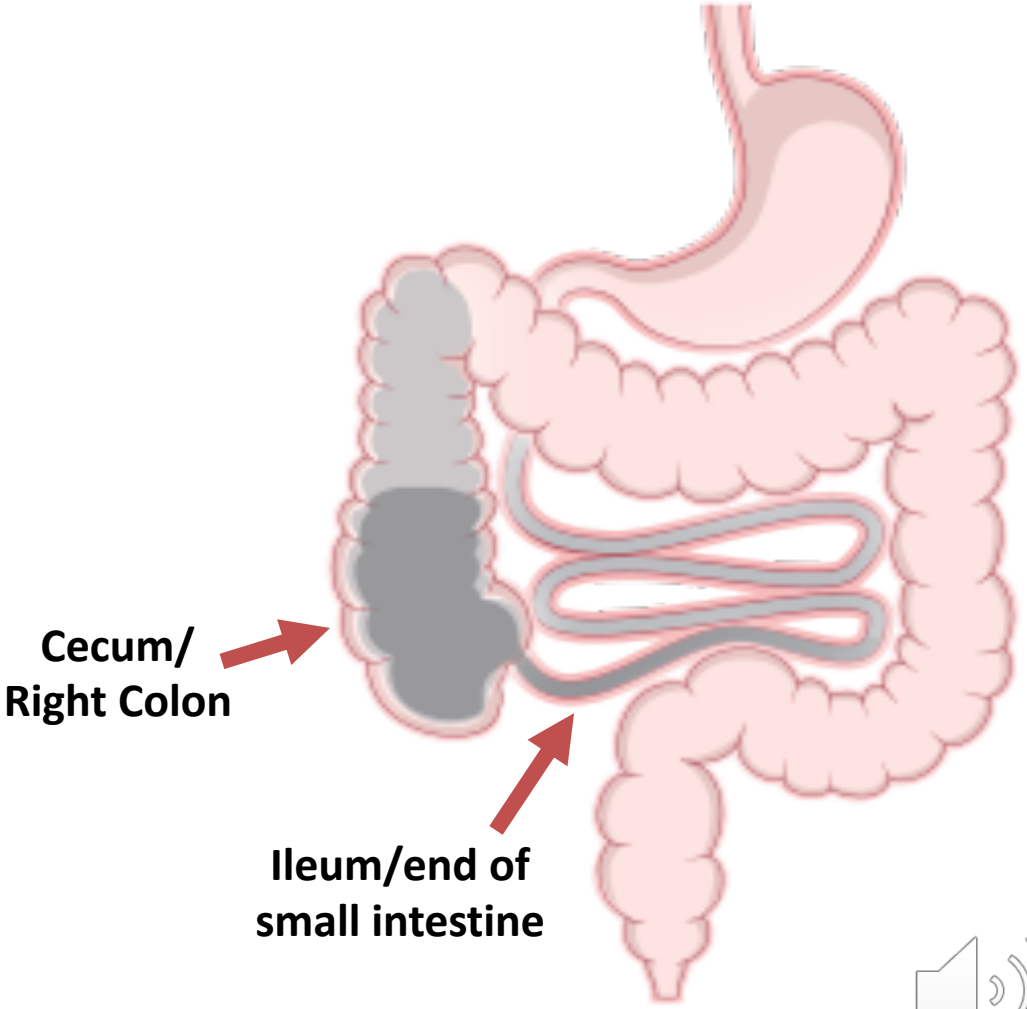
Uceris

- Budesonide
- As effective as prednisone, less side effects
- For colonic disease
- 1 pill (9mg) daily



Entocort EC

- Budesonide
- For Crohn disease
- Targets ileum and beginning of colon
- 3 pills (3mg each) daily



Diet Therapies

- Important part of every child's care plan
- Anti-inflammatory diet
- Exclusive Enteral Nutrition
- Food based exclusion diets
  - Crohn disease exclusion diet
  - Specific carbohydrate diet

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.
- CD and UC

Methotrexate

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

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

Anti-TNFα Therapy

Remicade (infliximab)

- Intravenous infusion
- Loading dose
  - 0, 2, 6 weeks
- Maintenance dose
  - Every 4-8 weeks

Humira (adalimumab)

- SQ (under skin) injection
- Loading dose
  - Multiple injections wk 0, 2
- Maintenance dose
  - Every 1-2 weeks

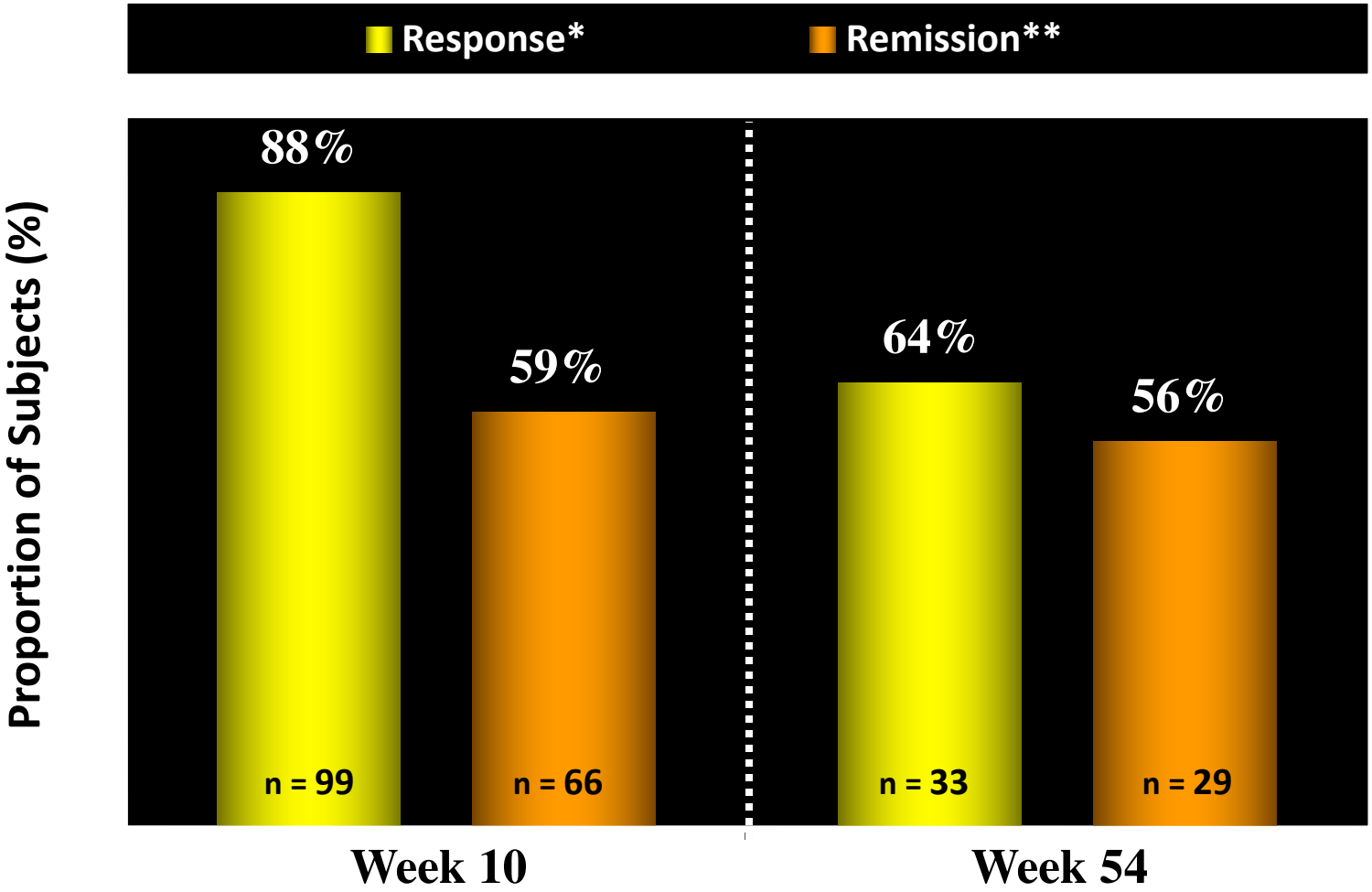
No live vaccines

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

REACH (Pediatric Crohn Disease Study)

Clinical Remission



* ↓ from baseline of ≥ 15 points in PCDAI score & PCDAI score ≤ 30

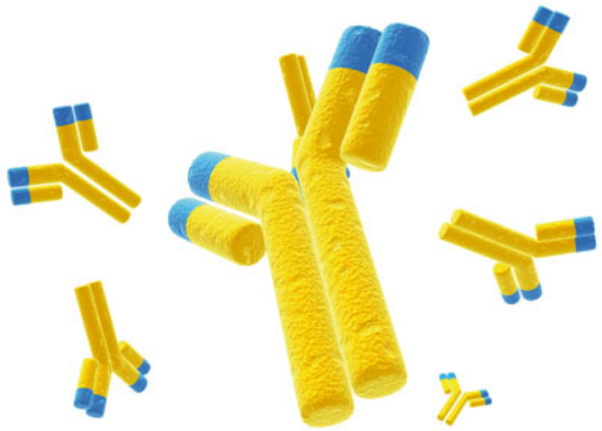
** PCDAI score ≤ 10

Hyams, et al. *Gastroenterology* 2007;132:863-73

Anti-TNFα Therapeutic Monitoring

- Measure drug level of the medication
- Measure antibodies against the medication

- Can guide therapy plan (dosage, frequency)
- Helps determine if there needs to be a medication change



Biosimilars

- Very similar to biologic counterpart
- Minor differences in clinically inactive components
- No clinically meaningful difference in terms of safety, purity, and potency

Biosimilars

Adalimumab

- Abrilada
- Cyltezo
- Hadlima
- Amgevita
- Hyrmioz

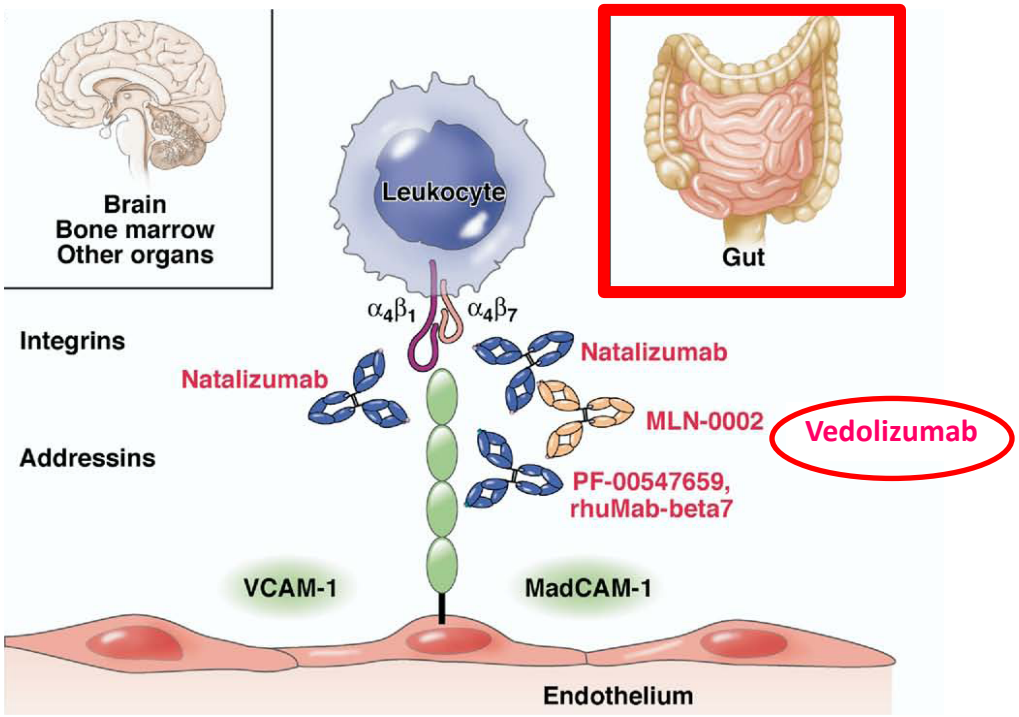
Infliximab

- Inflectra
- Ixifi
- Renflexis
- Avsola

Vedolizumab (Entyvio)

Gut specific anti-adhesion molecule

- Inhibits intestinal T-lymphocyte migration into tissue
- 2014: Approved for adult Crohn disease and UC
- IV infusion
- Similar dosing schedule to Remicade

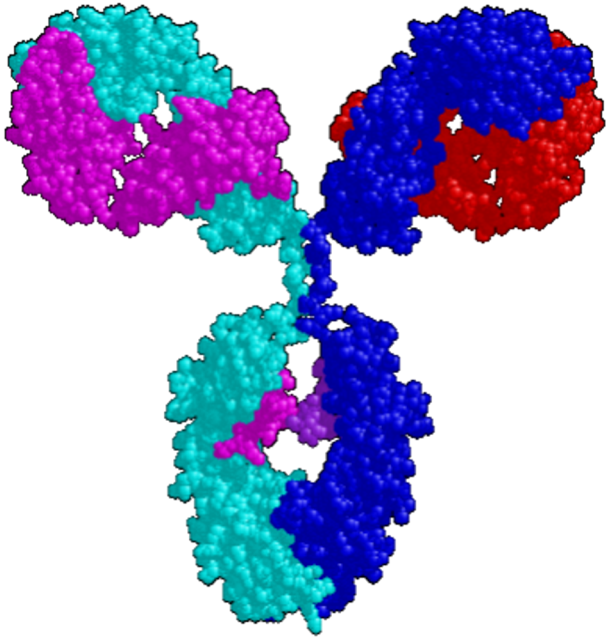


Ustekinumab (Stelara)

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

- Initially used for psoriasis and arthritis
- 2016: Approved for treatment of Crohn disease
- 2019: Approval for UC
- Side effect profile favorable

- **Induction:** IV infusion in GI suite
- **Maintenance**: Subcutaneous injection self-administered every 1-2 months



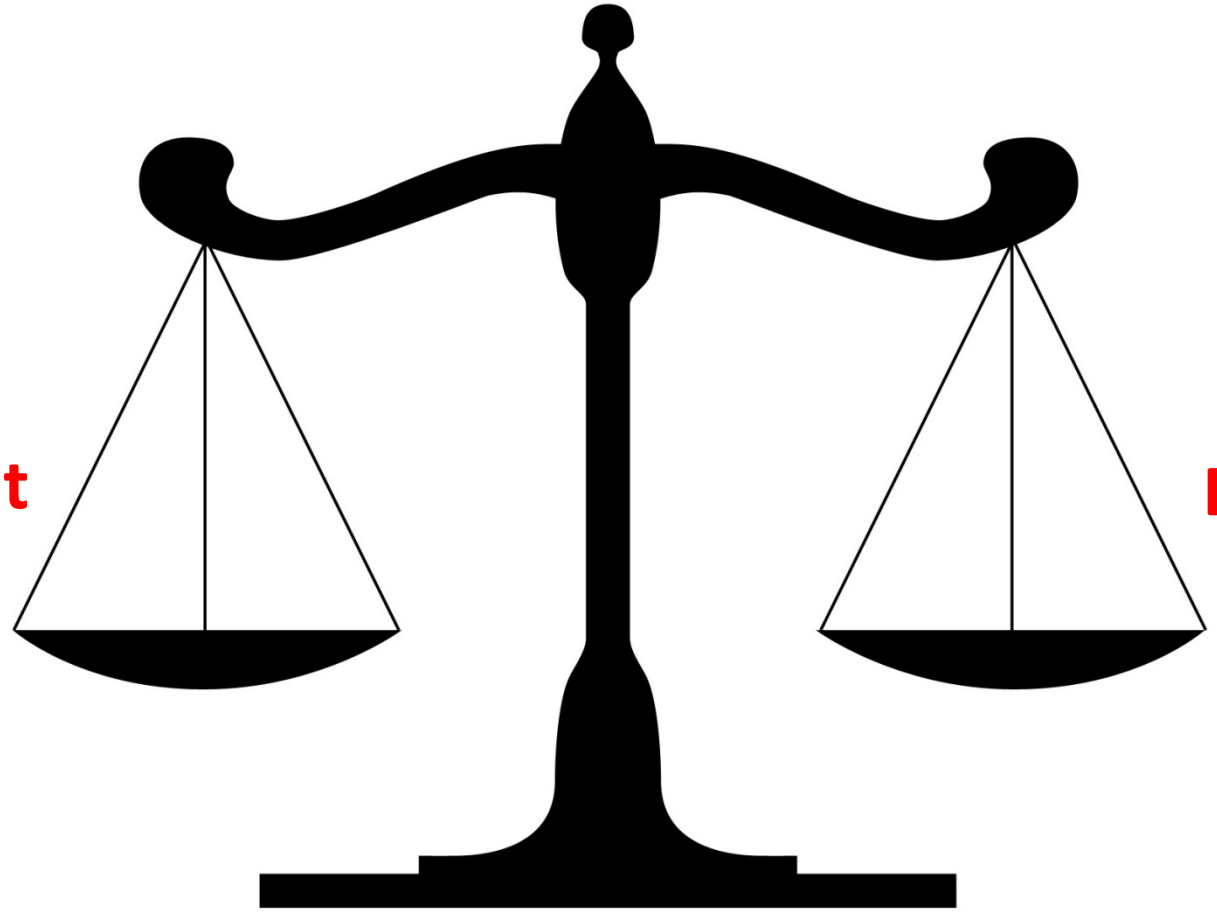
Sandborn WJ et al. *N Engl J Med* 2012; 367:1519-1528

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

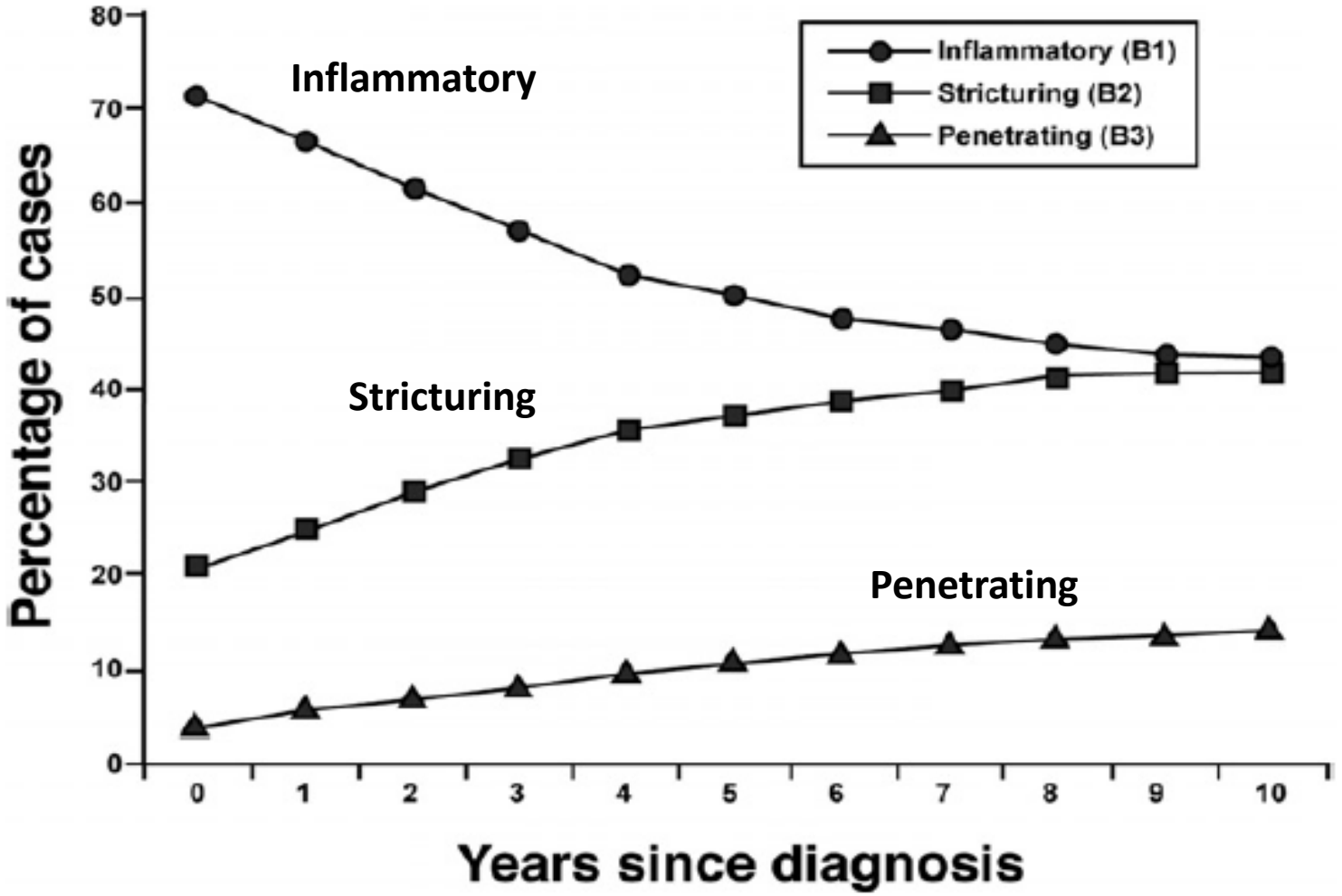
Risk of Treating vs. Not Treating

Risk of Treatment



Risk of Disease

Long-Term Evolution of Pediatric Crohn Disease is Structural Damage



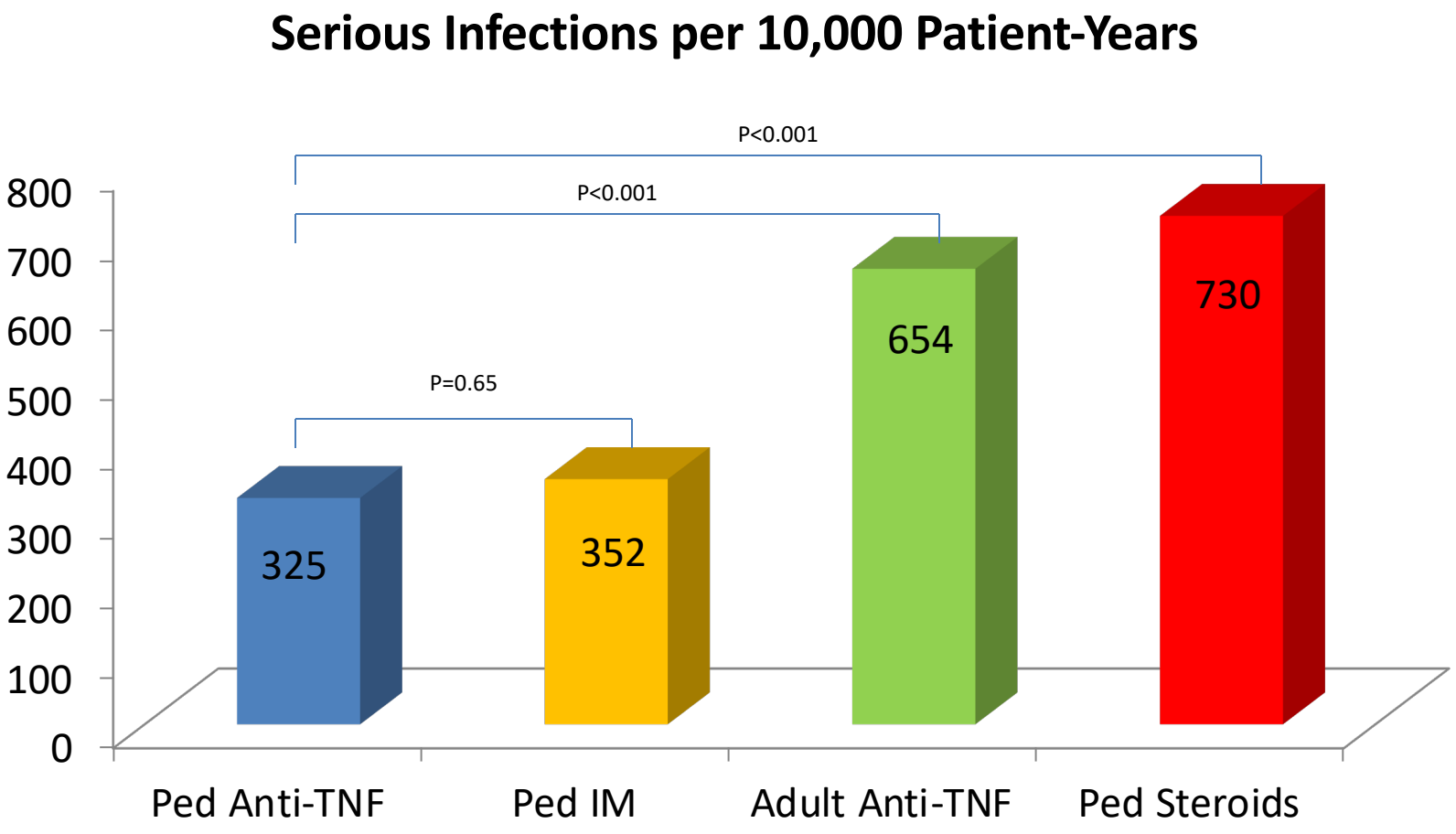
Vernier-Massouille G et al. *Gastroenterology* 2008

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

Infection

Lymphoma

Pediatric IBD Risk of Serious Infection: A Systematic Review



Dulai PS et al. *Clin Gastroenterol Hepatol* 2014; 12:1443-1451

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

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

Hyams J, et al. *Gastroenterology* 2017 Jun;152(8):1901-1914.e3.

Other Biologics

- Excellent safety profiles
- Antibody formation less prevalent
  - Minimal infusion reactions
- No increase in rate of infections
- Vedolizumab:
  - More gut specific, monitor for extraintestinal findings
  - No cases of progressive multifocal leukoencephalopathy in IBD
  - No increased risk of malignancies

Colombel J-F, *et al*. *Gut* 2017;**66**:839–851

Risk of Disease Often Greater than Risk of Treatment

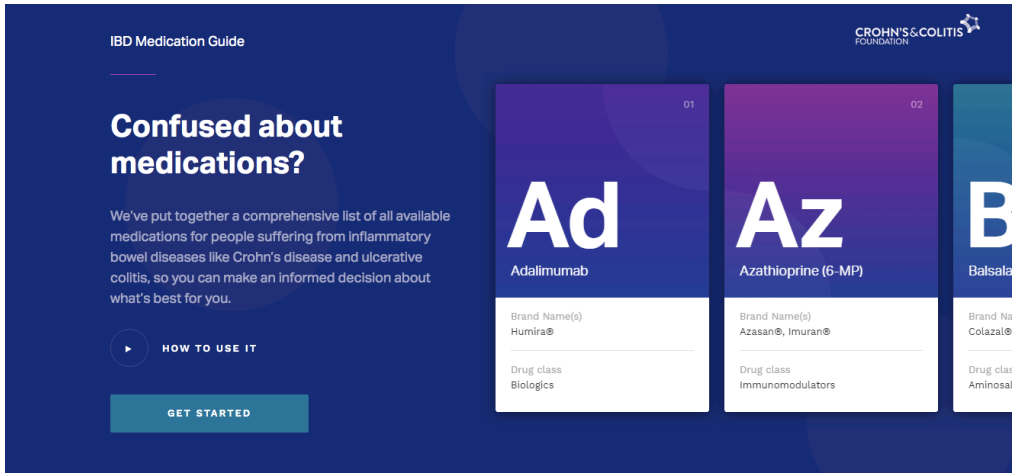
Risk of Treatment

Risk of Disease

Summary of Therapeutic Goals

Resources

CROHN'S & COLITIS FOUNDATION



http://www.ibdmedicationguide.org/