Treatment of Pediatric IBD: What is Different?

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Overview

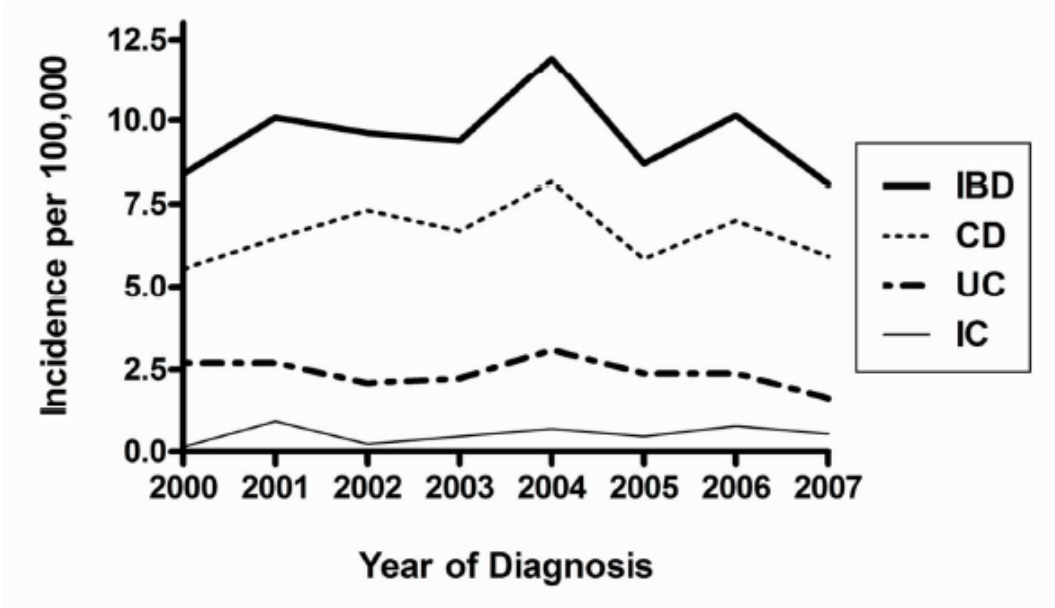
- Is Pediatric IBD the same disease?
- Treatment considerations

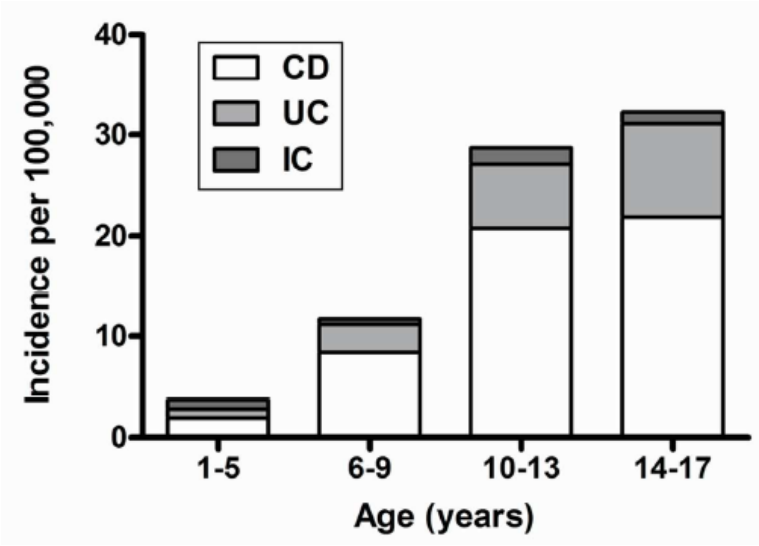
Overview

- Is pediatric IBD the same disease?
  - Epidemiology
  - Presentation and symptoms
  - Phenotype and natural history
- Treatment considerations

Epidemiology: Pediatric IBD is a rare disease

Incidence of Pediatric IBD





Overall incidence: 9.5 per 100,000
CD twice as common as UC in childhood
Both CD and UC very rare prior to age 6, with sharp increase thereafter
Slight male predominance for both diseases, especially CD

Adamiak, Inflamm Bow Dis, 2013

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Prevalence: Pediatric IBD

- Prevalence Estimates from US Commercially Insured population (< age 20)
  - Crohn's disease: 58 per 100K
  - Ulcerative Colitis: 34 per 100K
- Extrapolation to US population
  - Crohn's disease: 38K
  - Ulcerative Colitis: 23K
- ~5% of IBD patients in the U.S. are children
- Classified as "rare diseases" by NIH
  - FDA Orphan Drug Designation

Kappelman, DDaS, 2013

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Common Presentations of Pediatric IBD

Crohn's disease (n=386)

- Abdominal pain - 86%
- Diarrhea - 78%
- Blood in stool - 49%
- Weight loss – 80%
- Fever – 38%
- Perianal lesions – 44%

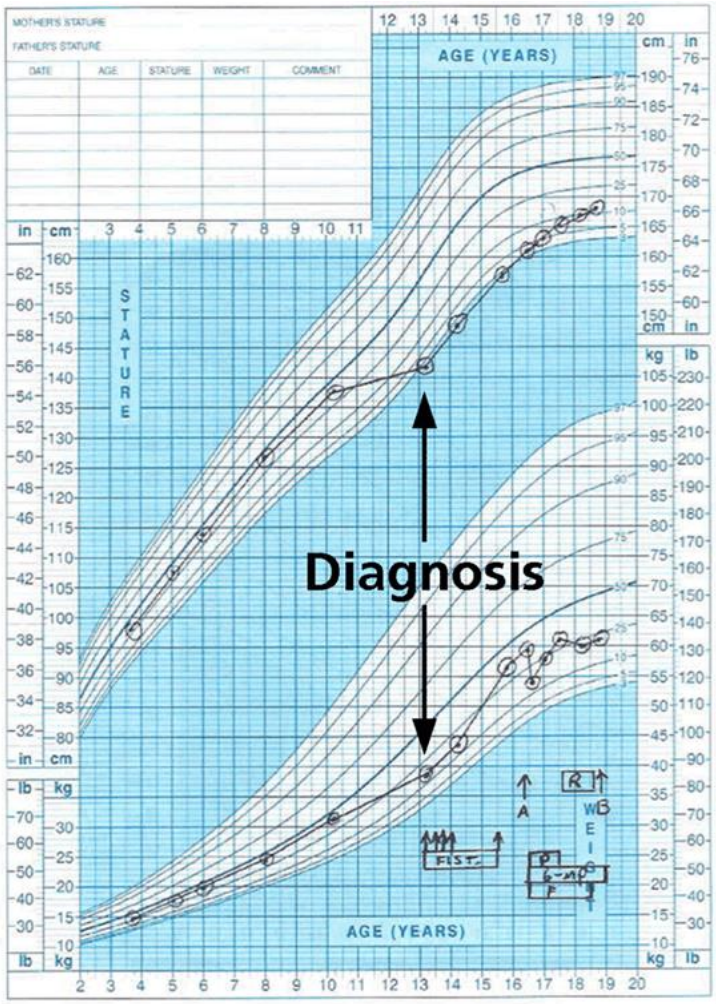
Ulcerative colitis (n=195)

- Abdominal pain 69%
- Diarrhea – 93%
- Blood in stool – 95%
- Weight loss – 55%
- Fever – 15%

Griffiths and Buller in Walker: Pediatric Gastrointestinal Disease (2000)

What's different: Growth

- ~ 3% patients present with growth failure as predominant symptom
- More common in CD than in UC
- Adult height compromised
  - CD: 32-88%
  - UC: 9-34%
- Etiology of growth failure
  - Intestinal inflammation
  - Inadequate oral intake
  - Diarrhea and nutrient losses
  - Steroids



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What's different: Bone Health

- Maximum accumulation of calcium in your bones occurs in mid-teen years.
- Decreased bone mineral density common in children and adolescents with IBD
- Etiology multifactorial
  - Poor calcium absorption/intake; vitamin D deficiency
  - Decreased physical activity
  - Inflammation
  - Steroid use

What's different: Pubertal Delay

- Pubertal delay in ~1/4 of children with CD
  - Delay usually 6-12 months
- Pubertal delay much less frequent in UC

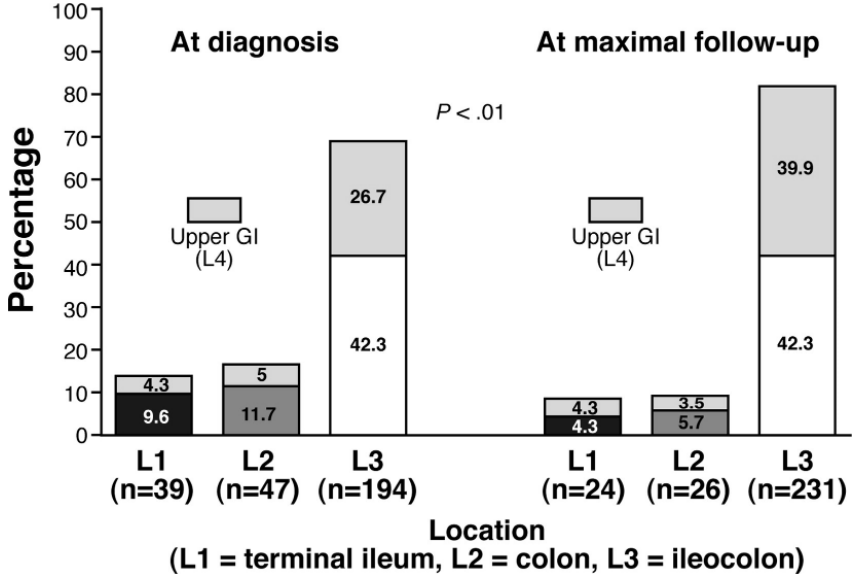
What's different: psychosocial impact

- Psychosocial impact of IBD well-appreciated in adults
- Effects compounded in pediatrics
  - Being a teen is hard enough!
  - Being different (having a chronic illness) makes it tougher
  - Embarrassing symptoms/steroid side effects impact self-image
  - Complicated medical/dietary regimens, procedures, frequent clinic visits, and hospitalizations are all added stressors
- Depression well described in children with IBD
  (Szigethy *et al.* 2004 and 2014. *JPGN*)
- Children with IBD have poorer school functioning compared to healthy children

  (Mackner *et al.* 2012. *J Clin Beh Psych)*

Phenotype and Natural History: CD

- More extensive disease distribution
  - 69% with L3 at dx; 82% at max follow-up
  - 36% UGI at dx; 48% at max follow up
- Behavior: B1 predominant
  - At 5 years
    - Pediatric: 73%
    - Adult: 66%



Vernier-Massouille, Gastro, 2008

Van Limbergen, Gastro, 2008

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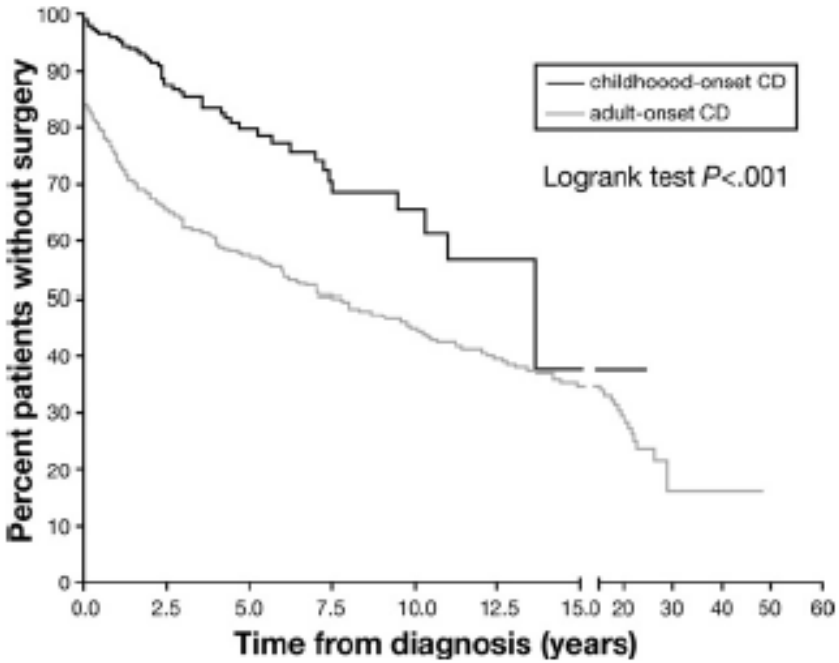
Surgery in Pediatric CD

- Cumulative probability of surgery by 5 years
  - 20% pediatric onset
  - 43% adult onset
- Time to surgery greater in pediatric vs adult CD
  - ? More extensive distribution less amenable to surgery
  - > B1 (inflammatory)



Van Limbergen, Gastro, 2008

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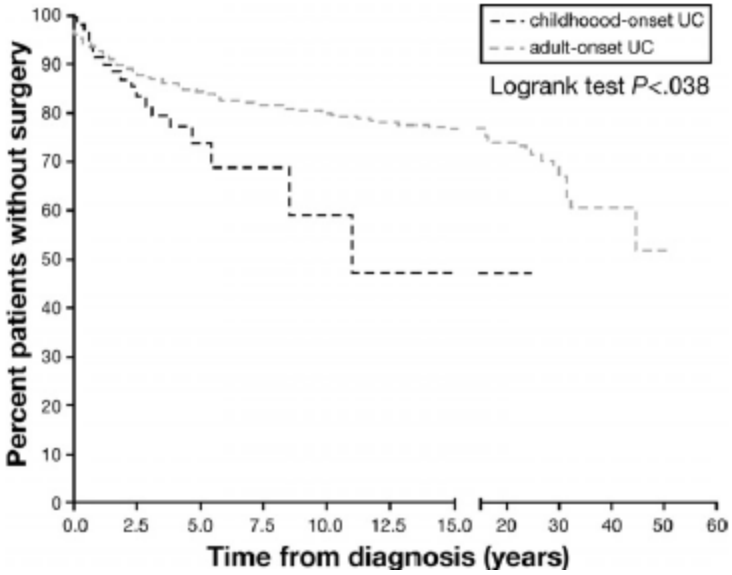
Phenotype and Natural History: UC

- More extensive disease distribution
  - Ped UC: 82% with pancolitis at max follow-up
  - Adult UC: 48% pancolitis at max follow-up
- Colectomy by 5 years
  - 26% pediatric onset
  - 16% adult onset



Van Limbergen, Gastro, 2008

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Pediatric vs Adult IBD: Different diseases?

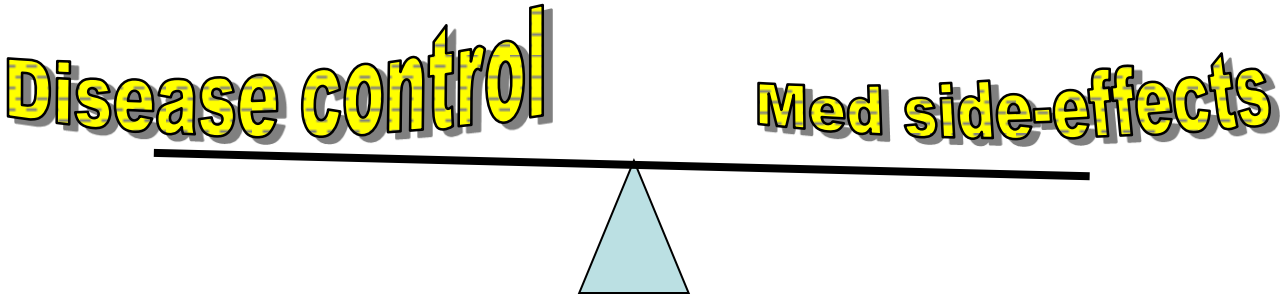
- Pediatric IBD rare disease
  - Orphan drug implications
- Gastrointestinal and EI symptoms similar
  - Unique developmental aspects of pediatric IBD:
    - growth and pubertal delay
    - diminished bone density
    - psychosocial impact
- Disease extent often greater in pediatric IBD
- CD: more often inflammatory; less surgery
- UC: higher need for colectomy

Overview

- Is pediatric IBD the same disease?
- Treatment considerations

Treatment Considerations

- Available treatment options largely the same
  - Greater off-label use
  - Sometimes a barrier for insurance authorization
- As with adults, treatment decisions involve balancing the risks and benefits
  - Including risks of un/under-treated IBD
- General treatment considerations underscore differences between pediatric and adult IBD



Consideration #1: Urgency of Treatment

- Children experience life faster
  - Greater consequences of “missing out” due to illness
- Finite “window” for development
  - Growth
  - Bone mineral density
  - Psychosocial
- Urgent need to commence **effective** medical therapy!

Consideration #2: Avoidance of steroids

- Steroid side effects compounded in pediatrics
  - Growth
  - Bone density
  - Appearance (acne, cushingoid)
    - Kids particularly sensitive to body image
  - Other psychosocial effects

In general, pediatric IBD patients have a greater need to achieve rapid disease control with steroid-sparing

Consideration #3: Treatment Effectiveness

- Medical treatment may be more effective in pediatric IBD
  - Shorter disease duration
  - For CD:
    - More “inflammatory” disease

Population	Study	Disease duration (years)
Adult	ACCENT I (infliximab)	7.9
Pediatric	REACH (infliximab)	2.2

Hanauer, Lancet, 2002
Hyams, Gastro, 2007

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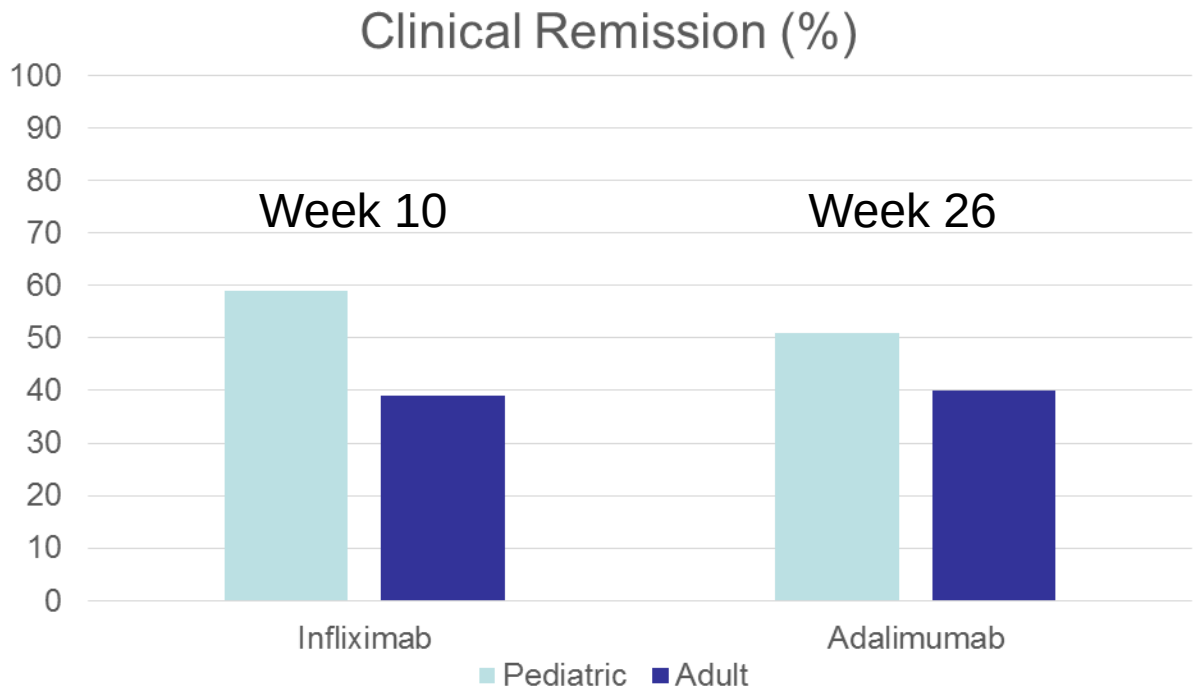
Effectiveness of anti-TNF



Data from ACCENT I and REACH
Different study designs; outcome measures

Data from CHARM and IMAgINE 1
Different study designs, Ped data converted to CDAI of week 4 response; CHARM only in week 4 responders

Hanauer, Lancet, 2002
Hyams, Gastro, 2007
Colombel, Gastro, 2007
Hyams, Gastro, 2012

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Consideration #3: Extent of disease

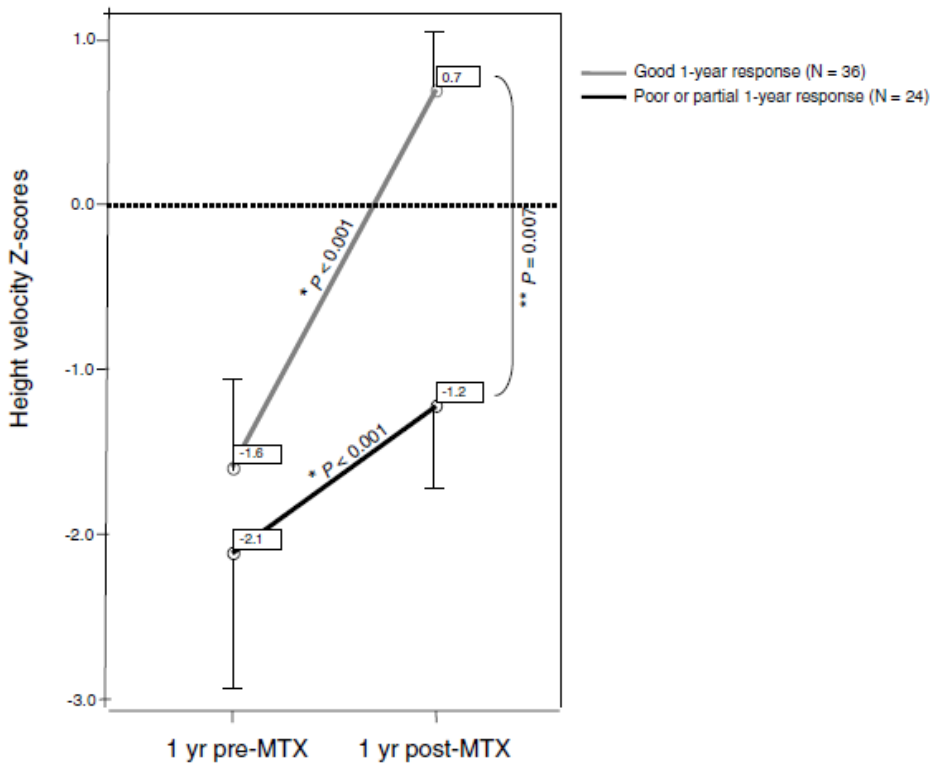
- Disease location more extensive in pediatric IBD
- Limits effectiveness of topical agents
  - Ileal release budesonide for Crohn's
  - Topical rectal therapy in UC

Consideration #4: Treatment Outcomes

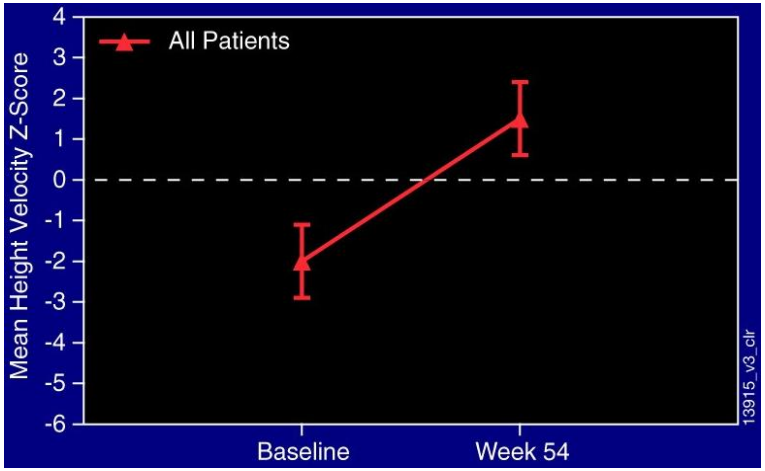
- As in adult IBD, treatment outcomes include:
  - Improving GI and EI symptoms
  - Normalizing laboratory abnormalities (hgb, alb, crp, esr)
  - Nutritional status
  - Mucosal healing
- Pediatric specific outcomes:
  - Growth
  - Bone density
  - Psychosocial

Effective Treatment Improves Growth

Methotrexate



Infliximab



Adalimumab

	Baseline	Week 52
Height Velocity Z score	-0.4	2

Turner, AJG, 2007
Hyams, Gastro, 2012
Walters, AIBD, *Dec 2006*

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Effective Treatment Improves Growth

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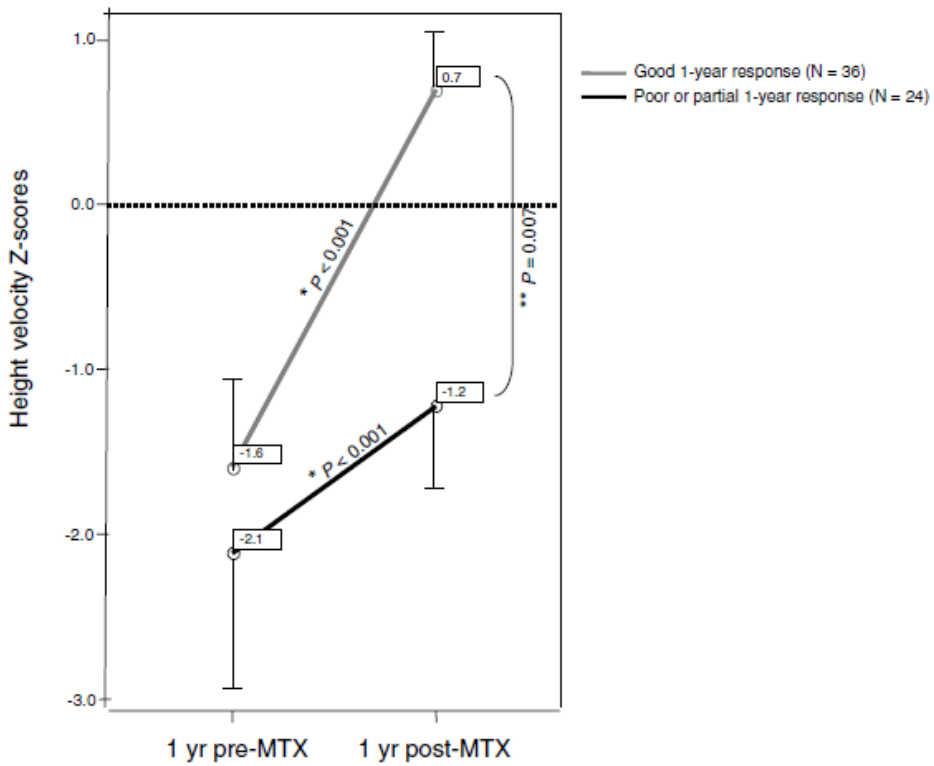

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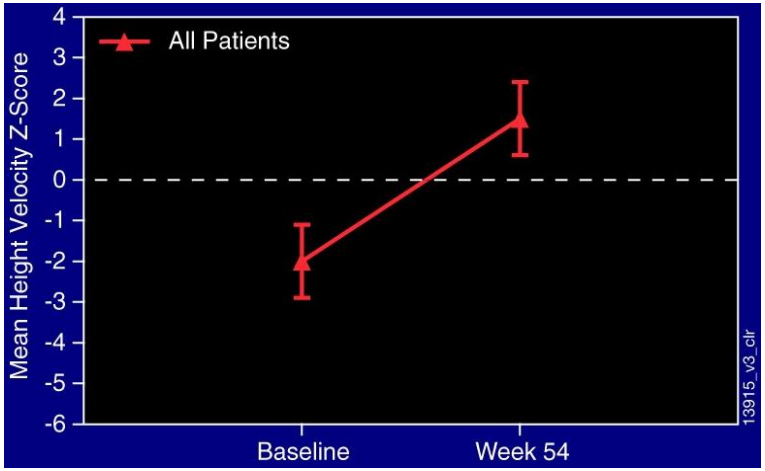

Adalimumab

	Baseline	Week 52
Height Velocity Z score	-0.4	2

- **Effective treatment also improves bone health and psychological functioning**

Turner, AJG, 2007
Hyams, Gastro, 2012
Walters, AIBD, *Dec 2006*

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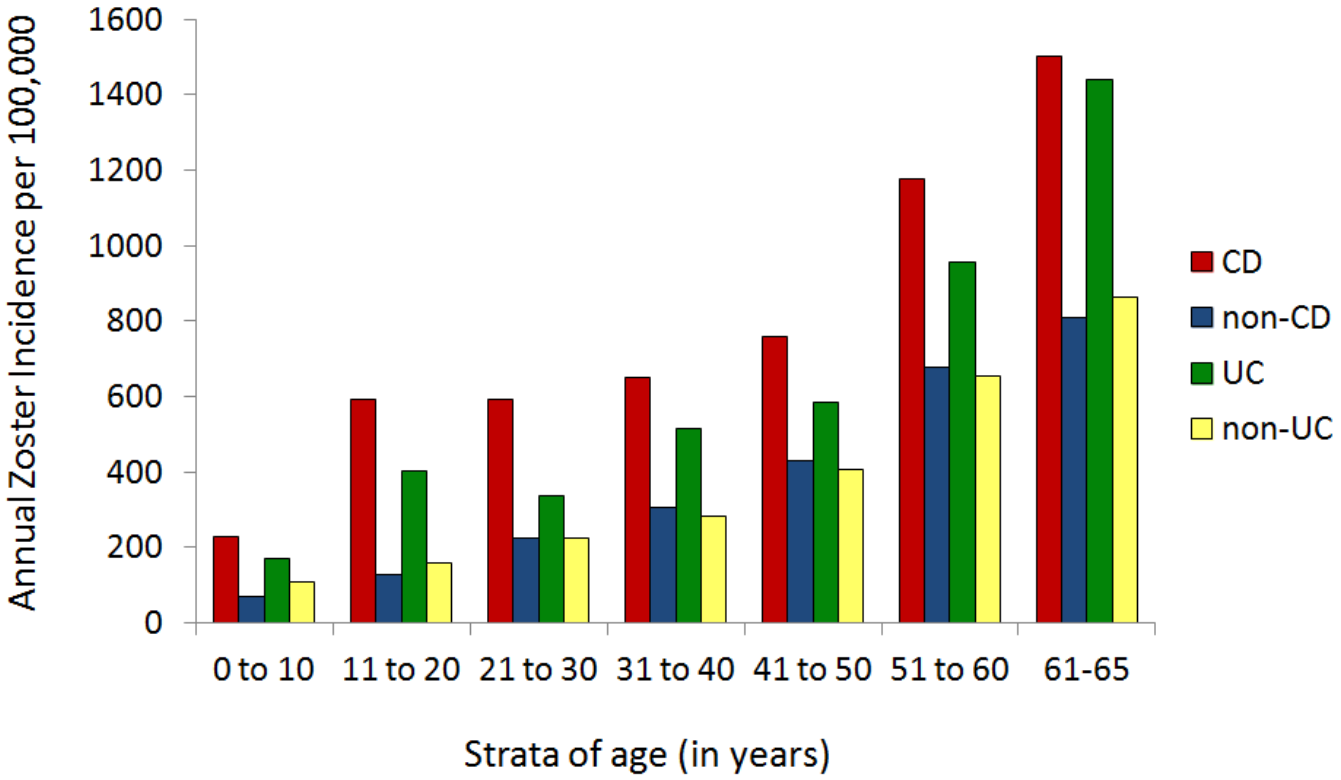
Consideration #5: Different risks

- Treatment decisions should be made based on absolute risk
  - Not relative risk
- Absolute risk of many treatments may be less in children
  - Risk of serious infection and malignancy increase with age in general population
  - Comorbidities less frequent in children

Infections: Herpes Zoster

Figure 2: Incidence of Zoster by Age in CD, UC and non-IBD populations



Long, Aliment Pharmacol Ther, 2013

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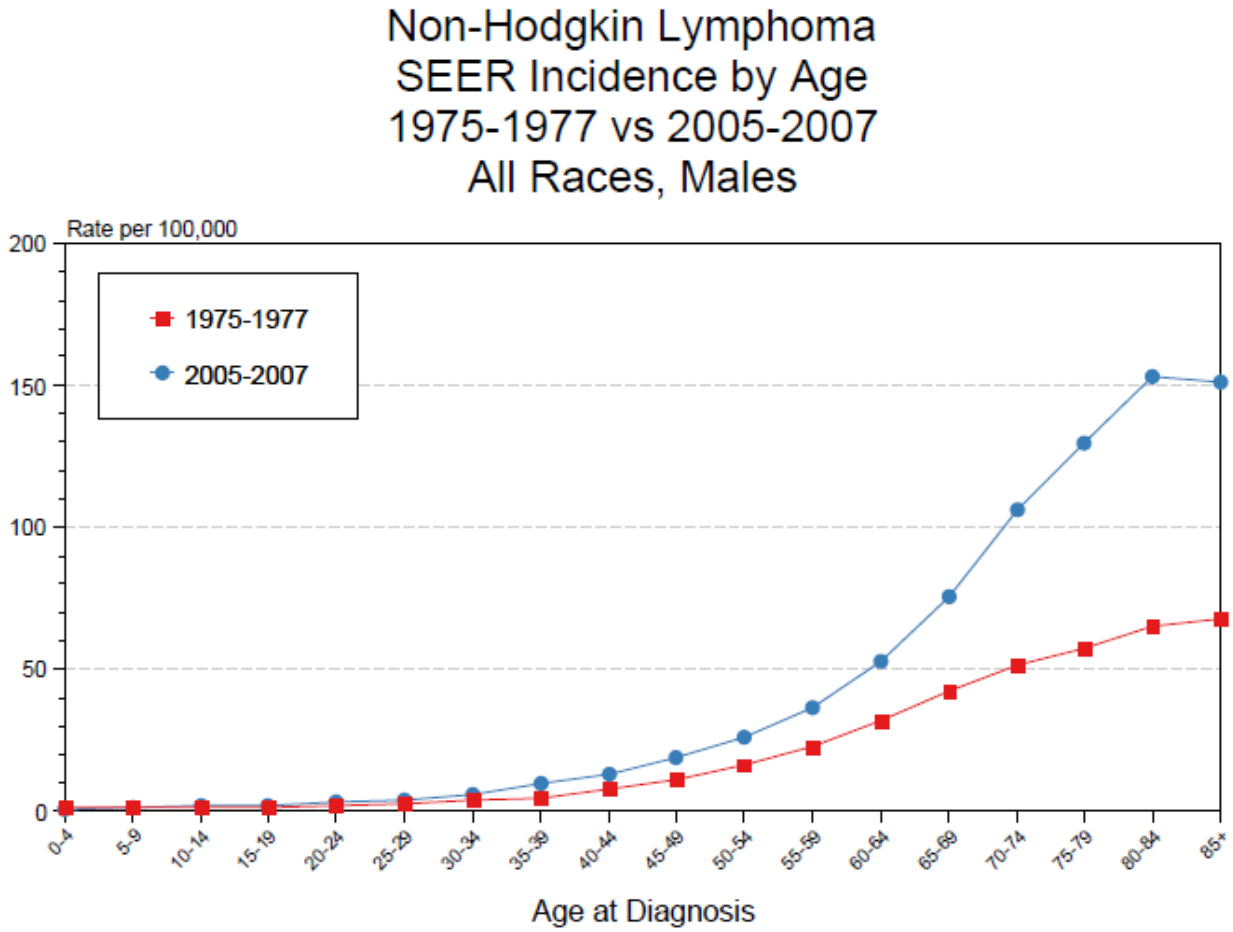
Lymphoma-background incidence



Kotlyar DS, CGH, 2015

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NNH vs background incidence

Number Needed to Treat (Harm) to Cause 1 Additional Lymphoma per Year

Age (*y*)	Lymphoma incidence[a,b]	NNH if relative risk of lymphoma = 2	NNH if relative risk of lymphoma = 3	NNH if relative risk of lymphoma = 4	NNH if relative risk of lymphoma = 5
20–29	7.25	6897	4598	3448	2759
30–39	9.45	5291	3527	2646	2116
40–49	15.6	3205	2137	1603	1282
50–59	29.9	1672	1115	836	669
60–69	59.0	848	565	424	339
70–79	102.5	488	325	244	195

Kotlyar DS, CGH, 2015

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Kotlyar DS, CGH, 2015

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Exception: HSTCL

Hepatosplenic T cell lymphoma

- Rare, often fatal
- Male predominant (>90%)
- 17/25 cases (68%) < 35 years of age
- Most reported case on combination therapy with thiopurine + anti-TNF

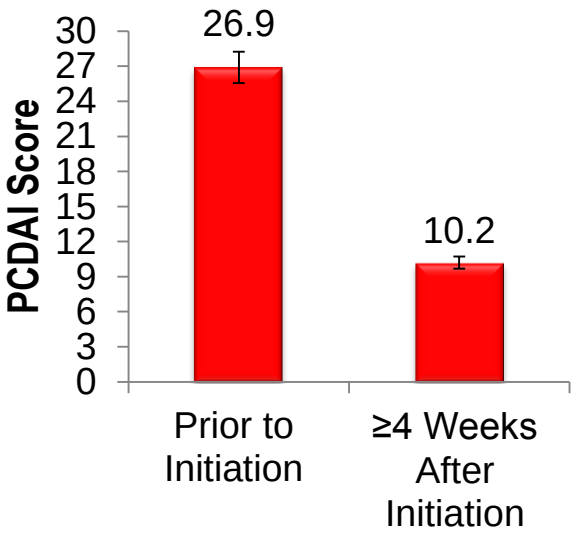
Consideration #6: Greater focus on nutrition

- Increased attention to:
  - nutrition, growth, skeletal health
  - corticosteroid avoidance
- Nutritional therapy more widely utilized in pediatric IBD

Enteral Therapy in Crohn's Disease

- Effective in children and adults with Crohn's disease for induction and maintenance (50-75%)
- EEN vs. corticosteroids (peds)
  - Better remission rates
  - Positive effect on growth
  - Mucosal healing
- EEN may be more effective in children than adults
- Efficacy not demonstrated in UC

CHOP EEN Experience



Zachos, *et al* (2007). *Cochrane Database*
Gupta. *et al (*2013). *Inflamm Bowel Dis*

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Consideration #7: Limited data

- Even in 2017, many important treatment decisions in pediatric IBD are made with limited data!
  - Few well-designed clinical trials
  - Some multi-center cohorts
  - Many single-center retrospective reports
- Much extrapolation from adult data
- We need more high-quality pediatric clinical trials
- Pediatric IBD community is very invested
  - Well established multi-center collaborations
- **We can pull this off!**

PRO-KIIDS and Risk

- PRO-KIIDS
  - CCFA sponsored Pediatric IBD Research Network
  - ~ 30 participating centers
- Risk
  - Inception cohort to identify the genetic, microbiological, and immunological factors predictive of more severe CD
  - ~1,100 children from 28 centers recruited <u>before diagnosis</u>
  - Primary manuscript now in press at major medical journal

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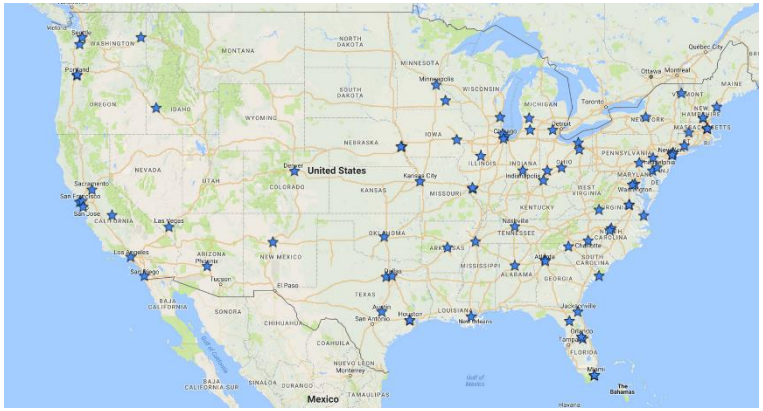
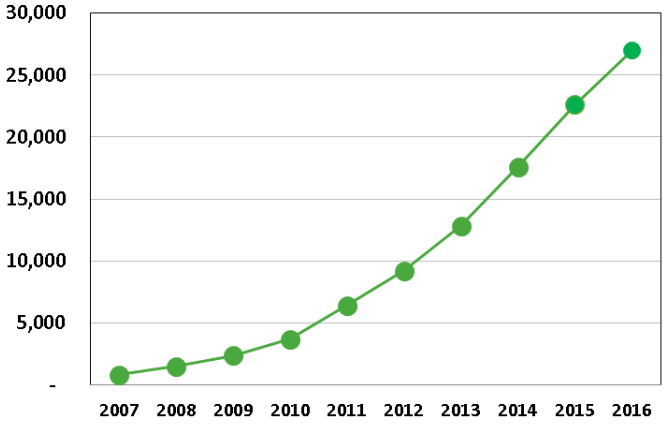
ImproveCareNow

- Learning health network of 95 centers
  - Point of care data collection
  - > 26K patients and 170K visits
  - Largest and fastest growing pediatric IBD registry



- Use of quality improvement to continuously measure and optimize site performance
- Registry to facilitate research
- Increasing focus on communication, engagement, and community building



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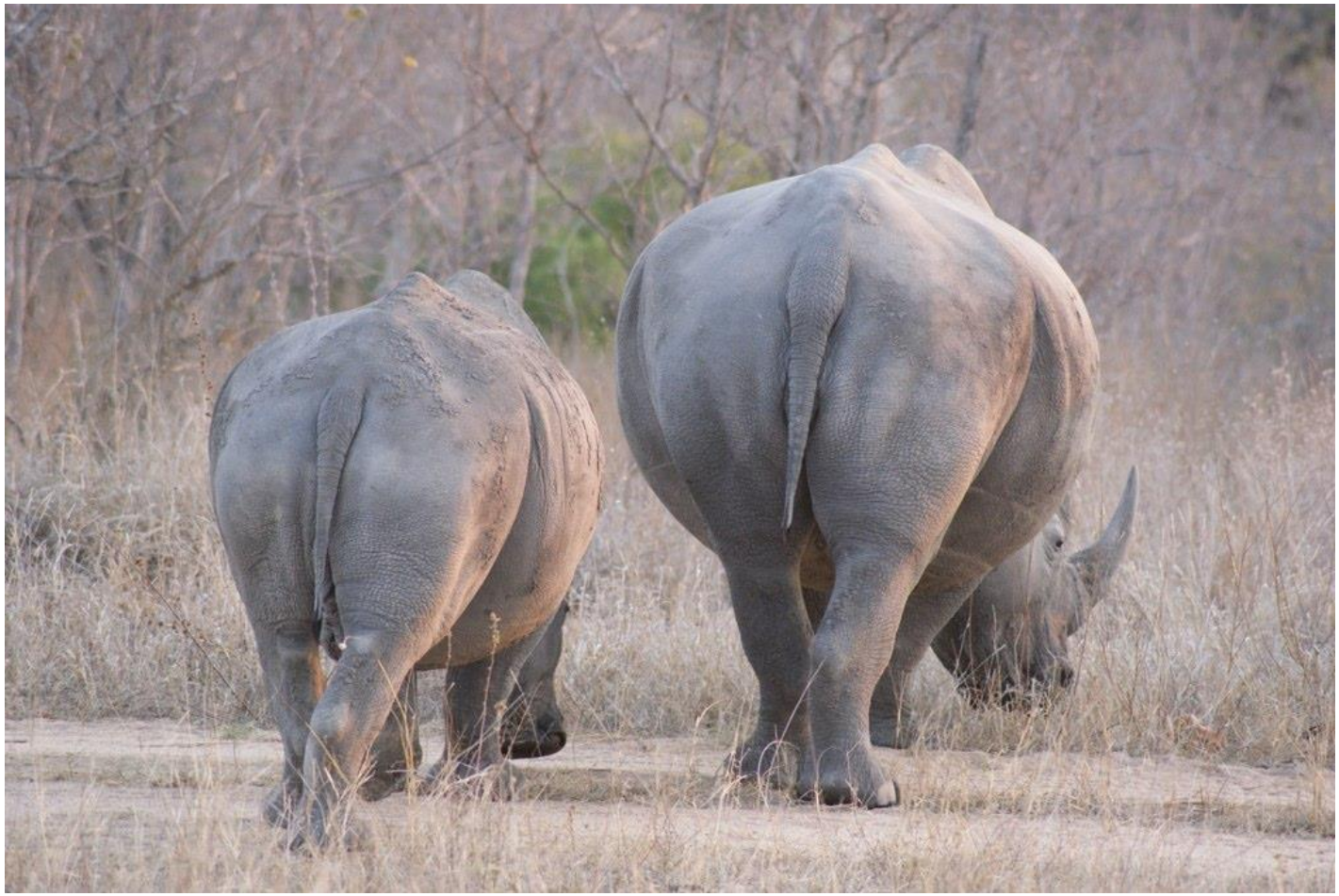
Summary

- Epidemiological, clinical, and phenotypic differences between pediatric and adult IBD
- Treatment options largely the same
- A number of developmental-specific treatment considerations may (slightly) shift the risk-benefit equation
- More pediatric research urgently needed
- **As a community, we have the will and infrastructure to do it!**



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