4:45 – 5:30 pm

IBD in Pediatrics

SPEAKER
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Presenter Disclosure Information

The following relationships exist related to this presentation:

- Jennifer Strople, MD: Speakers Bureau for AbbVie Inc. Consultant for AbbVie Inc.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Objectives

- Review the pathogenesis of inflammatory bowel disease (IBD)
- Differentiate between adult and pediatric IBD presentations
- Review the natural course of pediatric Crohn's disease (CD) and ulcerative colitis (UC)
- List the health concerns unique to pediatric IBD

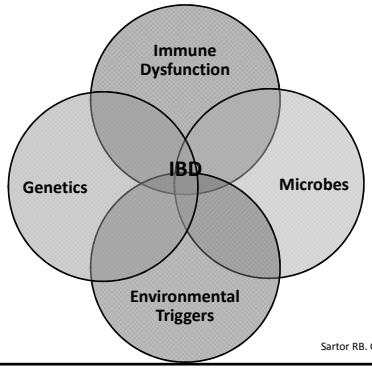
Inflammatory Bowel Disease

Group of idiopathic chronic disorders characterized by chronic inflammation of the GI tract

Ulcerative Colitis **Crohn's Disease**

Inflammatory Bowel Disease Unclassified

What Causes IBD?



Sartor RB. Gastroenterol 2008

Genetic Susceptibility

- Positive family history is the greatest single risk factor for IBD
  - Not explained by simple Mendelian inheritance
  - Genetic influence is greater in CD than UC
  - Monozygotic twins: 35-50% concordance for CD, 6-16% concordance for UC
- Genetic defects
  - Innate Immune Response (NOD2, ATG16L1)
  - Adaptive Immune Response (IL23R,STAT3, MHC, IL10R)
  - Barrier Function (PTGER4)

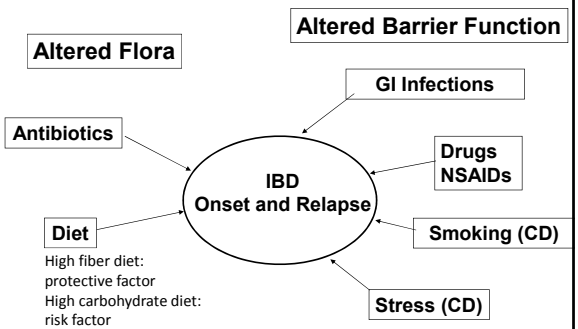
Orholm M et al. Scand J Gastroenterol 2000
Tysk C et al. Gut 1998
Spehlmann ME et al. Inflamm Bowel Dis 2008
Abraham C et al. N Engl J Med 2009

Microbiome: The Evidence

- Commensal bacteria required for chronic inflammation in experimental models
- Decrease diversity of fecal microbiota
  - Decreased Firmicutes relative to healthy controls
  - Decreased ratio of protective species
  - Decreased species that produce short chain fatty acids
- Therapeutic benefits of antibiotics in CD & pouchitis
- Fecal diversion treats CD and pouchitis

Frank DN et al. Proc Natl Acad Sci 2007
Sartor RB. Gastroenterology 2008

Environmental Triggers



High fiber diet:
protective factor
High carbohydrate diet:
risk factor

Ponder A, et al. Clin Epidemiol 2013

Epidemiology of Pediatric IBD

- Approximately 25% of IBD occurs in pediatric age group
  - Male predominance of CD, no sex difference in UC
- Pediatric incidence in the US
  - CD—4.5/100,000
  - UC—2/100,000
- Pediatric prevalence in the US
  - CD—43/100,000
  - UC—28/100,000
- 2010 Census Data--Estimated that 50,000 children are presently suffering from IBD

Kugathasan S et al. J Pediatr 2003
Kappelman Met al. Clin Gastroenterol Hepatol 2007

Increasing Incidence of IBD

Systematic review of trends in pediatric IBD:
-78% showed ↑ incidence of IBD
-60% showed ↑ incidence of CD
-20% showed ↑ incidence of UC

Loftus CG et al. Inflamm Bowel Dis 2007
Benchimol EI et al. Inflamm Bowel Dis 2011

Clinical Presentation

Classic Presentation

- Gastrointestinal (approx 80%)
  - Abdominal Pain
  - Diarrhea
  - GI bleeding
  - Nausea/vomiting
  - Early satiety
  - Weight loss
  - Oral ulcerations
  - Perianal disease

Atypical Presentation

- Systemic
  - Growth Failure
  - Anorexia
  - Malaise
  - Fever of unknown origin
- Endocrine
  - Pubertal Delay
- Hematologic
  - Anemia
    - Micro, macro, or normocytic

Extraintestinal Manifestations

- May be precede GI symptoms
- 25-35% of patients with IBD
- Parallel disease activity, or have course independent of intestinal disease
- CD--extraintestinal manifestations more common with colonic disease

Phenotypic Characteristics of Pediatric IBD

- More severe/extensive disease in pediatric patients
- Rapid early progression is often seen
- Crohn's disease
  - "Panenteric" disease common
    - Upper tract involvement at diagnosis in 36-50%
  - Isolated colonic disease more common in young children
    - 63% in children < 8 y/o compared to 35% in >8 y/o
  - Less isolated ileal disease

Van Limbergen J et al. Gastroenterology 2008
Heyman MB et al. J Pediatr 2005

Phenotypic Characteristics of Pediatric IBD

- Ulcerative colitis
  - Left sided and pancolonic disease more common in children
    - 60-80% of children present with pancolitis, compared to 20-30% of adult onset disease
  - Proctitis is a rare presentation in pediatrics
  - Reclassification to CD over time in 2-13%

Van Limbergen J et al. Gastroenterology 2008
Heyman MB et al. J Pediatr 2005
Abraham BP et al. J Clin Gastroenterol 2012

Non-Classical Phenotypic Characteristics of Pediatric UC

- Small anal fissures/skin tags (<5 mm)
- Oral ulcers
- Gastritis without aphthae
- Relative rectal sparing
- Periappendiceal inflammation without pancolitis
- Histological patchiness

J Pediatr Gastroenterol Nutr 2007

Natural History of Pediatric CD

- Disease location not fixed
  - Children with less extensive disease have disease progression within two years
    - 39% have progression (n=143)
- CD behavior evolves
  - Inflammatory phenotype at presentation
  - Both stricturing and penetrating disease phenotype increase with time
  - Perianal disease complicates other disease behaviors

Van Limbergen J et al. Gastroenterology 2008
Vernier-Massouille G et al. Gastroenterology 2008

Risk Factors for Surgery in Pediatric CD

- Older age at diagnosis
- Female gender
- Greater disease severity
- Small bowel or perianal disease
- Poor growth at diagnosis
- Treatment with steroids at diagnosis
- Stricturing or penetrating disease

Gupta N et al. Gastroenterology 2006
Schaefer ME et al. Clin Gastroenterol Hepatol 2010
Siegel C et al. Inflamm Bowel Dis. 2011
Vernier-Massouille G et al. Gastroenterology 2008

Natural History of Pediatric UC

- 2 large pediatric IBD centers (n=171)
  - 43% had mild disease, 57% had moderate/severe disease at presentation
  - 80% had resolution of symptoms with therapy within 6 months of diagnosis
  - At 1 year…
    - 55% symptom free, 38% chronic intermittent disease, 7% persistent symptoms
    - Colectomy risk: 5%
  - At 5 years…
    - Colectomy risk: 19%

Hyams JS et al. J Pediatr 1996

Risk Factors For Surgery in Pediatric UC

- Disease severity at presentation
  - Mild disease—colectomy risk 9% at 5 years
  - Moderate/severe—colectomy risk 26% at 5 years
- Extensive disease
  - Colectomy risk 29% at 5 years
- Extraintestinal manifestations at diagnosis
- Elevated WBC and anemia at diagnosis
- Elevated CRP at diagnosis

Hyams JS et al. J Pediatr 1996
Gower-Rousseau C et al. Am J Gastroenterol 2009
Moore JS et al. Inflamm Bowel Dis

Medical Therapies for Pediatric IBD

Induction of remission

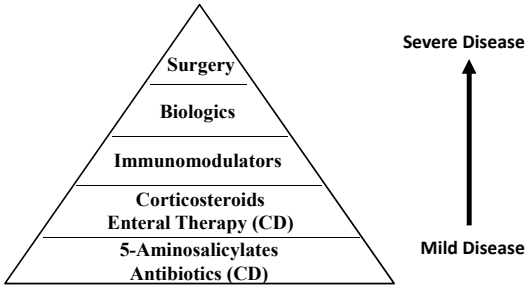
- Corticosteroids
- Anti-TNF therapy
- 5-aminosalicylates (UC)**
- Enteral therapy (CD)

Maintenance of Remission:

- 5-aminosalicylates (UC)**
- Antibiotics (CD)*
- Enteral therapy (CD)
- Immunomodulators*
- Anti-TNF therapy
- Anti-integrins*

*Not FDA approved in pediatrics
**Only balsalazide is FDA approved in pediatrics

Therapeutic Pyramid for IBD



Adapted from Lichtenstein GR et al. Inflamm Bowel Dis 2004; S2-S10

Courtesy of the Crohn's & Colitis Foundation of America

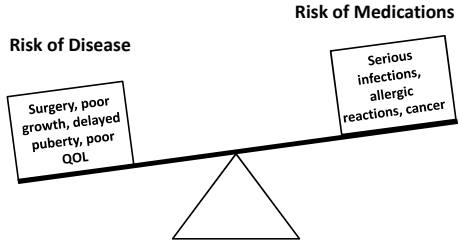
Goals of Therapy

- Induce symptomatic remission
- Maintain remission (avoid relapse)
- Prevent complications
  - Disease related
  - Medically induced
- Promote normal growth and development
- Minimize exposure to steroids
- Improved quality of life

Future Goals for Treating IBD

- Personalized medicine
  - Customizing treatment plans for each patient
  - Stratifying treatment based on prognosis and diseases features
- Use of more reliable markers for inflammation
- More aggressive treatment following complications to prevent recurrence
- Promote healing of the mucosa
- Modify disease course

Balancing Risks



Courtesy of the Crohn's & Colitis Foundation of America

Issues Unique to Pediatric IBD

- Growth Failure
- Pubertal Delay
- Bone Disease
  - Failure to obtain peak bone mass
- Impaired Psychosocial Development
- Immunizations
  - failure to receive primary series of vaccinations

Issues Unique to Pediatric IBD

- **Growth Failure**
- **Pubertal Delay**
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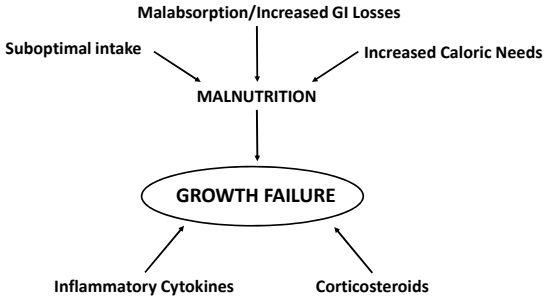
Growth Failure in Pediatric IBD

- Decreased height percentile at diagnosis: up to 39%
- Decreased height velocity at diagnosis: 88% of patients with CD
- Up to 60% will have a decreased in height percentiles during course
- Deficits in adult heights: 7-35%
  - Skewing of adult heights toward the lowest percentiles

Courtesy of the Crohn's & Colitis Foundation of America

Motil et al. Gastroenterology 1992
Markowitz et al. J Pediatr Gastroenterol Nutr 1993

Growth Failure in Pediatric IBD



Courtesy of the Crohn's & Colitis Foundation of America

Balliger AB et al. Gut 2000
Heuschkel R et al. Inflamm Bowel Dis 2008
Kleinman RE et al. J Pediatri Gastroenterol Nutr 2004
Wong SC et al. J Pediatri Gastroenterol Nutr 2006

Sex Differences in Growth Failure

- Boys more vulnerable to growth impairment
  - Cumulative incidence: 12.6% in boys, 4% in girls
  - Timing of onset of disease, later onset of growth spurt, longer duration of puberty
- IGF-1 plays a central role
  - IGF-1 levels reduced in males compared to females
    - Relationship similar across Tanner Stages
- IGF-1 z-scores inversely associated with ESR and CRP

Courtesy of the Crohn's & Colitis Foundation of America

Gupta N et al. Pediatrics 2007
Mason et al. Horm Res Paediatr 2011
Gupta N et al. Inflamm Bowel Dis 2011

Pubertal Development in Pediatric IBD

- Mean age at onset of puberty delayed in both male and female patients with IBD
  - Girls with IBD 12.6 years v. 11.1 years
  - Boys with IBD 13.2 years v. 12.4 years
- Duration of puberty prolonged
- Correlation between age of menarche & height gain
  - Menarche > 15 = Decreased height gain
- Sustained clinical remission can result in catch up growth

Ballinger et al. Pediatric Research 2003: 53:205

Skeletal Health and Pediatric IBD

- Osteopenia and osteoporosis are common in children with IBD
  - Decreased BMD at diagnosis in 43% of CD and 39%, compared to 29% of controls (n=58)
  - Elevated inflammatory cytokines inversely correlated with BMD
- Hypovitaminosis D is prevalent in IBD
  - 25-OH vitamin D levels suboptimal in 58.3%, insufficient in 14.3%, deficient in 5.8% (n=448)
  - Levels inversely associated with ESR

Courtesy of the Crohn's & Colitis Foundation of America

Sylvester FA et al. Inflamm Bowel Dis 2007
Pappa HM et al. J Pediatr Gastroenterol Nut 2011

Risk Factors for Low BMD

- Malnutrition
- Malabsorption
- Inflammation
- Decrease weight baring
- Growth impairment
- Pubertal Delay
- Decreased lean body mass
- Corticosteroids

Pappa H et al. J Pediatr Gastroenterol Nutr 2011

Growth, Puberty and Bone Health

- Growth impairment leads to decreased bone formation
- Sex steroids needed for normal bone mineralization
- Pubertal delay leads to decreased sex steroids
  - Decrease accrual of bone mineral density
    - Period of most rapid bone accrual
      - » Girls: 11-14 y/o
      - » Boys: 13-17 y/o
  - Failure to obtain peak bone mass

Finkelstein JS et al. N Engl J Med 1992
Pappa H et al. J Pediatr Gastroenterol Nutr 2011

NASPGHAN Skeletal Health Clinical Guideline

- DXA encouraged at baseline and every 1-2 years if low BMD noted
- Regular monitoring of linear growth, growth velocity and pubertal development
- Monitor vitamin D levels at least annually
  - Treat hypovitaminosis D with high doses
  - Once optimal status achieved, continue 800-1000 IU daily
- 1000-1600 mg of elemental calcium daily
- Encourage weight bearing activities and resistance training

Pappa H et al. J Pediatr Gastroenterol Nutr 2011

Immunizations in Pediatric IBD

- Ideal world—immunize before start of immunosuppression
- Real world—treatment should not be delayed
- Immunosuppressed children with IBD respond to inactivated vaccines
  - Seroconversion rate for influenza 33% to 85%
- Immunization rates are low
  - 25%-47% receive influenza vaccine
  - 13% not vaccinated against Hepatitis B (n=100)

Courtesy of the Crohn's & Colitis Foundation of America

Mamula P et al. Clin Gastroenterol Hepatol 2007
Lu Y et al. Am J Gastroenterol 2009
Moses J et al. Am J Gastroenterol 2012
Bechimol EI et al. Pediatrics 2013
Huth K et al. Inflamm Bowel Dis 2015

Immunization: Practical Aspects

- Ensure pediatric IBD patients receive recommended immunizations as per ACIP schedule
- Avoid live virus vaccines in immunocompromised patients
- Immunize pediatric IBD patients annually against influenza
- Give pneumococcal vaccination (PCV) to immunocompromised children
  - Immunocompromised Children 6–18 yrs with no previous PCV13:
    - Give first dose, then ≥8 weeks later, give PPSV23
    - Second PPSV23 dose is recommended 5 years after the first

Centers for Disease Control and Prevention

SUMMARY

- Pathogenesis of IBD is multifactorial
  - Interplay of genetics, environment, and microbiome
- Pediatric patients typically present with severe and extensive disease
  - Complications of UC and CD increase with time
- Growth impairment & pubertal delay in are common pediatric IBD
- Be proactive in monitoring bone health and immunizing patients