Pediatric and Adolescent Issues in IBD

Sandra C. Kim, M.D.
Dept. of Pediatrics, Div. of Gastroenterology
and
The Center for Gastrointestinal Biology and Disease
University of North Carolina at Chapel Hill
Children Are Not Small Adults!
Epidemiology of Pediatric IBD

• 1-2 million Americans; ~100,000 < 18 years
• ~25% of IBD patients will develop disease before age 18
• Overall incidence 7/100,000 children, with significant rise >10 yrs of age (Kugathasan, et al. 2003. J Pediatr)
• ~50% increase in children with IBD over past decade (Benchimol, et al. 2009. Inflamm Bowel Dis)

The Cost Of Disease In Pediatric IBD

- Annual disease-attributable costs for IBD: $6.3 billion
- Overall per patient costs greater in children vs. adults

Pediatric IBD Has Unique Characteristics

- Similarities between pediatric and adult IBD
  - GI symptoms
  - Extra-intestinal manifestations
- Presentation is more severe in children
  - UC: Higher incidence of pancolitis (>80%)
  - Crohn’s disease: Greater progression to surgery; more aggressive disease phenotypes
- Growth and pubertal delay
- Psychosocial impact of disease
# Symptoms in Pediatric Crohn’s

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classic Presentation</td>
<td>78.6 %</td>
</tr>
<tr>
<td>(Abdominal pain, diarrhea, weight loss)</td>
<td></td>
</tr>
<tr>
<td>Extraintestinal predominant</td>
<td>8.4 %</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>3.7 %</td>
</tr>
<tr>
<td><strong>Growth Failure</strong> predominant</td>
<td>3.3 %</td>
</tr>
<tr>
<td>Anemia</td>
<td>2.7 %</td>
</tr>
<tr>
<td>Anorexia, weight loss</td>
<td>2.0 %</td>
</tr>
<tr>
<td>Ex-lap for abdominal pain</td>
<td>1.3 %</td>
</tr>
</tbody>
</table>

Kugathasan et al. 2003. *J Pediatr*
Growth and Nutritional Status in IBD
Growth Failure in IBD

• More common in Crohn’s disease vs. UC
  • Issues are noted both pre-and post-diagnosis
• Decreased height percentiles in 36-39%; adult height compromised
  (Sawczenko, et al. 2006. Pediatrics)
• Decreased height velocity
  (Walters, et al. 2008. Inflamm Bowel Dis)
  • Crohn’s disease: 32% - 88%
  • UC: 9% - 34%
• “Growth window” crucial
• *Growth good marker for disease activity
Factors Affecting Growth

- Disease severity/degree of inflammation
  - Inflammatory cytokines (IL-6, TNF)
  - Corticosteroid therapy
  - Inadequate oral intake
  - Malabsorption
- Interval from onset of symptoms to diagnosis
- *Disease location: small intestinal/jejunal
  - Timing of surgery
Pubertal Delay in IBD

- Similar factors affecting growth affect onset of puberty
  - May not be made up later in life
- Delayed age of peak height velocity (middle of puberty) in Crohn’s disease (Hildebrand, et al. 1994. JPGN)
  - ~1/4 children with Crohn’s
  - Delay usually 6-12 months
  - Possibility of catch – up growth
- *Treat disease, not the growth failure, if possible!
Pediatric IBD Algorithm

**Nutrition**

- **Satisfactory**
  - Follow-up 6 months
  - Annual RD evaluation
- **At Risk**
  - Follow-up 4 weeks
  - Satisfactory
  - At Risk
  - Failure
  - 1. Reassess Disease Activity & Escalate Rx if patient not in Remission
  - 2. RD Referral *
- **Failure**
  - Overw/ Obesity (>85th %ile)
  - RD Referral/ Nutrition Ed for wt loss
  - Consider Further Medical Eval
  - Follow-up 6 months
  - Satisfactory
  - At Risk
  - Failure
  - 1. Reassess Nutrition*  
  - 2. Increase Calories  
  - 3. Consider Endocrine Consult
  - Follow-up 3 months
  - Satisfactory
  - At Risk
  - Failure
  - 1. Reassess Disease Activity  
  - 2. Steroid Sparing Regimen  
  - 3. Tanner Stage &  
  - 4. Consider Endocrine Consult Bone Age
  - 5. RD Referral *
  - Follow-up 3 months
  - Satisfactory
  - At Risk
  - Failure
  - Consider Tube Feedings

**Growth**

- **Satisfactory**
  - Follow-up 6 months
  - Annual RD evaluation
  - Reassess Growth in 6 months
- **At Risk**
  - Follow-up 2-4 weeks
  - Satisfactory
  - At Risk
  - Failure
  - 1. Reassess Nutrition*  
  - 2. Increase Calories  
  - 3. Consider Endocrine Consult
  - Follow-up 3 months
  - Satisfactory
  - At Risk
  - Failure
  - Consider Tube Feedings

* nutritional labs, food record, set calorie/WT goals, oral supplements, vitamins-minerals
Overall Principles in Managing Growth Failure

- Optimize nutrition: careful assessment and appropriate supplementation
- Re-assess disease activity even if labs normal, no other GI symptoms present
- Consultation with endocrinologist
- AVOID steroids!
  - Maintenance medications (Biologics; immunomodulators)
  - Surgery timed/used judiciously
Bone Density Issues in IBD

- Maximum calcium accretion occurs in mid-teen years
  - May not be made up later in life
- Decreased bone mineral density common in pediatric IBD patients
  - Poor calcium absorption/inadequate calcium intake and vitamin D deficiency
  - Decreased physical activity
- Steroid use increases short and long term risk
Bone Health and Inflammation

- Osteoprotegerin (OPG) and receptor activator of NF-kB (RANKL)
  - Bone homeostasis maintained
  - Increased in inflamed intestinal tissue
  - Inverse correlation with BMD
- Children with IBD have elevated OPG levels
  (Sylvester et al. 2006. J Peds)
  - Correlates with T – cell activation/IFN-\(\gamma\)
  - Increase in inflammatory cytokines (ie.IL-6) suppresses bone formation
    (Paganelli, et al. 2007. Inflamm Bowel Dis)
- *Highlights significance of controlling inflammation
Bone Structure Maintenance in IBD

  • Musculoskeletal outcomes using pQCT
  • Bone strength: trabecular and cortical volumetric BMD
• Steroid use does not affect bone loss
• *Decreased vBMD, muscle mass at diagnosis*
• Trabecular BMD not completely recovered
  • Affected by pubertal stage at diagnosis
Pediatric IBD

Nutrition
Calcium, vitamin D
Caloric/Protein intake
Vitamin K

Delayed sexual maturation
\(\downarrow\) IGF-1
Inactivity
\(\downarrow\) Lean tissue mass
Medications

Immune Factors
T cells (INF-\(\gamma\), RANKL)
Cytokines
Intestinal OPG?

Growing Bone

Modeling
- Bone formation
  - Endochondral
  - Periosteal
- Bone resorption
  - Endosteal

Bone shaping and growth

Remodeling
- Bone resorption
  - Faster
- Bone formation
  - Slower

Maintenance of bone mass

Sylvester. 2005. Inflammm Bowel Dis
Goals of Treatment in Pediatric IBD

• **Immediate goals**
  • Suppress inflammation to heal the intestinal mucosa
  • Decrease/alleviate symptoms

• **Continued goals**
  • Prevent disease relapse
  • Avoid complications
  • *Restore normal growth*, nutritional status

• **Ultimate goals**
  • Treatment should be reasonable, cost-effective
  • Improve quality of life
  • Alter the natural history of disease favorably
Corticosteroids in Pediatric IBD

- Initially effective in inducing remission; concerns of dependency
- Debilitating effect on children and adolescents
  - Psychosocial impact
  - Neurological changes
  - Physical appearance
- Negative impact on growth and bone metabolism
- Absence of GI symptoms **not** acceptable if child is stunted, cushingoid
Treatment Issues in Pediatric IBD

• Limited data in pediatric IBD therapy
  • Treatment extrapolated from adult studies
  • Not “one size fits all”

• Similar efficacy in inducing remission
  • Sample sizes smaller in pediatric studies

• Similar toxicities, but longer drug exposures
  • Impact of lifetime therapy duration

• Outcomes for clinical trials needs to consider pediatric – specific outcomes
  • Growth parameters
  • Markers of bone metabolism
Thiopurines and Pediatric Crohn’s

- Prospective, double-blind, placebo-controlled study evaluating whether 6-MP decreases need for corticosteroids
- Total steroids: Significantly less by 6 months
- *Key: Steroid-sparing regimen

Methotrexate in Pediatric Crohn’s

- Retrospective, longitudinal cohort study in children who failed 6-MP/ AZA therapy (Turner, et al. 2007. AJG)

- Children with Crohn’s disease
  - N = 60 (mean 14 ± 2 yrs)
  - Thiopurine failure/intolerant; infliximab-naive

- Results:
  - 12 months: 53% steroid-free remission
  - 36 months: 35% steroid-free remission
Growth Velocity Improved with MTX

*Key: Alternative immunomodulator; improved growth velocity

Turner, et al. 2007. AJG
Anti-TNF Therapy in Children

- Debate between top-down vs. bottom-up
  - Not as applicable for children
- Benefits of anti-TNF therapy
  - Steroid-sparing
  - Mucosal healing
  - Reversal of growth failure/nutritional status
- Concerns with anti-TNF therapy
  - Adverse events
  - *Long-term sequelae: malignancies
Infliximab in Pediatric Crohn’s Disease (REACH)

- Multicenter, randomized, open-label study
  (Hyams et al. 2007. Gastroenterology)
- Children with Crohn’s disease on stable doses of medications
  - N = 112 (6 - 17 yrs)

- Results:
  - Week 10: 88% with response; 59% remission
  - Week 54: 64% with response; 56% remission

- *Key: Steroid-sparing regimen; positive effect on growth
Infliximab and Growth Velocity (REACH)

*Greatest benefit: Patients with >1 year delay in bone age and corticosteroids at enrollment

Hyams. et al. 2007. Gastroenterology
Infliximab and Bone Density

• Biochemical markers of bone metabolism measured from patients in REACH study (Thayu, et al. 2008. Clin Gasto Hepatol)

• Bone formation markers increased, while resorption measures decreased
TEENAGERS
TIRED OF BEING HARASSED BY YOUR PARENTS?
ACT NOW!!
MOVE OUT, GET A JOB, PAY YOUR OWN WAY, WHILE YOU STILL KNOW EVERYTHING!!
Psychological Moratorium
(Erikson, 1956)

“This period (adolescence) can be viewed as a psychological moratorium during which the individual, through free role experimentation, may find a niche in some section of his society, a niche which is firmly defined and that seems to be uniquely made for him.... In finding (one’s identity) the young adult gains an assured sense of inner continuity and social sameness which will bridge what he was as a child and what he is about to become ....only trial and error can lead to the most felicitous avenues of action and self expression. Adolescence is not an affliction but a normative crisis...”
Psychological Challenges Facing Children with IBD

• Greater risk of low self-esteem, poor social functioning, and depression

• Specific issues facing our patients:
  • Defining what it means to have a chronic illness
  • Coping with procedures, frequent clinic visits, and hospitalizations
  • Adhering to complicated medical and dietary regimens
  • Maintaining adequate support systems at home and school
  • Transitioning from adolescence to college
Depression and Self-Image

• Depression present in children with IBD (Szigethy, et al. 2004. JPGN)
  • Increased disease activity and corticosteroid treatment correlates with depression
  • Children manifest depression symptoms
• Quality of life and social interactions impacted
  • ~1/3 – 1/2 children with limitations in ADL
  • Parental perceptions of children with IBD
• Body image and disordered eating patterns also prevalent
Helping Adolescent Patients Manage Their Disease

• Healthcare providers must be proactive
• Ensure disease knowledge is well – established
• Set goals that can be reached
• Develop open, interactive relationship
• Encourage optimism and use praise for even the small successes
• Gradual increase in responsibility for self – management in disease
Transitioning of Care

“The goal of a transition program is to achieve for each chronically ill patient a continuum of care that includes normalization of social and emotional development and the acquisition of independent living skills.”

- NASPGHAN Medical Position Statement 2002
The UNC TR_xANSITION Program

Designed to teach and enhance disease self-management skills and self - *activation* to adolescents & young adults with chronic health conditions, allowing for better health outcomes as adults.

*Activation*: a process of gaining knowledge, skill, and confidence.
UNC T.R\textsubscript{x}A.N.S.I.T.I.O.N. Score™

- **Type** of Chronic Illness
- **Rx** Medications
- **Adherence**
- **Nutrition**
- **Self-Management**
- Informed about reproductive health Issues
- **Trade/School**
- **Insurance**
- **Ongoing** Adult Support
- **New Health Care Providers**
UNC TRxANSITION Program: How Do We Assess?

• Conducted on each patient who comes to pediatric IBD clinic
  • Ages 12-20 yrs
  • Initial enrollment, then q 6 month f/u visit

• Scoring based on knowledge
  • 0 = none; 0.5 = some; 1 = adequate

• Overall score calculated on total score divided by total number of questions asked to get overall % of correct answers
# UNC TRxANSITION Score

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N</th>
<th>%</th>
<th>Score</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.4</td>
</tr>
<tr>
<td>Male</td>
<td>42</td>
<td>45%</td>
<td>6.06 (1.32)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>52</td>
<td>55%</td>
<td>6.28 (1.39)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.2</td>
</tr>
<tr>
<td>White</td>
<td>66</td>
<td>70%</td>
<td>6.32 (1.33)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>23</td>
<td>25%</td>
<td>5.74 (1.41)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>5%</td>
<td>6.43 (1.22)</td>
<td></td>
</tr>
<tr>
<td><strong>Caregivers in the home</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.3</td>
</tr>
<tr>
<td>1 caregiver</td>
<td>21</td>
<td>22%</td>
<td>5.92 (1.39)</td>
<td></td>
</tr>
<tr>
<td>2 caregivers</td>
<td>73</td>
<td>78%</td>
<td>6.26 (1.34)</td>
<td></td>
</tr>
<tr>
<td><strong>Insurance type</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Medicaid</td>
<td>26</td>
<td>28%</td>
<td>5.53 (1.27)</td>
<td></td>
</tr>
<tr>
<td>Private</td>
<td>68</td>
<td>72%</td>
<td>6.43 (1.31)</td>
<td></td>
</tr>
<tr>
<td><strong>Oral meds/day (med=4)</strong></td>
<td></td>
<td></td>
<td></td>
<td>0.6</td>
</tr>
<tr>
<td>&lt;= median</td>
<td>50</td>
<td>53%</td>
<td>6.26 (1.48)</td>
<td></td>
</tr>
<tr>
<td>&gt; median</td>
<td>44</td>
<td>47%</td>
<td>6.12 (1.25)</td>
<td></td>
</tr>
</tbody>
</table>
## Baseline TR\textsubscript{X}ANSITION Score by Age

<table>
<thead>
<tr>
<th>TR\textsubscript{X}ANSITION area</th>
<th>Mean (SD)</th>
<th>Regression with age</th>
<th>β</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of illness</td>
<td>0.84 (0.21)</td>
<td>0.029</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>RX (medications)</td>
<td>0.79 (0.20)</td>
<td>0.007</td>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>Adherence</td>
<td>0.80 (0.22)</td>
<td>-0.006</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Nutrition</td>
<td>0.82 (0.25)</td>
<td>0.021</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>Self-management</td>
<td>0.32 (0.24)</td>
<td>0.048</td>
<td>0.0003</td>
<td></td>
</tr>
<tr>
<td>Issues of reproduction</td>
<td>0.32 (0.30)</td>
<td>0.073</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Trade/school</td>
<td>0.51 (0.16)</td>
<td>0.021</td>
<td>0.02</td>
<td></td>
</tr>
<tr>
<td>Insurance</td>
<td>0.48 (0.33)</td>
<td>0.061</td>
<td>0.0009</td>
<td></td>
</tr>
<tr>
<td>Ongoing support</td>
<td>0.90 (0.27)</td>
<td>0.012</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>New health providers</td>
<td>0.42 (0.38)</td>
<td>0.027</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL SCORE</strong></td>
<td><strong>6.18 (1.35)</strong></td>
<td><strong>0.290</strong></td>
<td><strong>&lt;0.001</strong></td>
<td></td>
</tr>
</tbody>
</table>
Goals of IBD Patient Management: Teens and Children

• Identify patients at risk for nutritional/growth failure
  • Early intervention to preserve, restore growth

• Address psychosocial issues
  • Screen for risk factors

• Work towards patient’s self-management of disease
  • Education
  • Self – management skills
  • Preparation towards independence
Integrating Research With Health Care Delivery

- PRO-KIIDS
- Translational Research
- Clinical Trials
- Outcomes Research
- QI initiatives (ImproveCareNow)
- Health care delivery
- NIH Pediatric IBD U01/34 grant

Improving Child Health
Intestinal bacterial antigens

Genetic predisposition

Environmental triggers

Immune response

IBD
Risk Stratification and the Pediatric IBD Research Network

- Genetic makeup
- Environmental exposures
- Bacteria in GI tract
- Immune reactivity

*1100 children with Crohn’s at diagnosis

3 years → 160-200 patients with complication/surgery
IBD Treatment in the Future: Targeted Therapy?

“IBD Panel”

IBD Subtype

Disease Prognosis

Patient-specific treatment plan

Targeted-specific therapy