Natural History and Predictors of Course in Pediatric and Adult Ulcerative Colitis

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Disclosures

- Janssen Biotech: consultant, Advisory Board, research support
- Abbvie: Advisory Board, consultant
- Takeda: consultant
- Soligenix: consultant
- UCB: consultant
- Celgene: consultant
- Lilly: consultant
- Receptos: consultant
- Boehringer Ingelheim: consultant
• Pathophysiology, Epidemiology
• Clinical expression: Adults vs. Children
• Standard of Care: Adults vs. Children
• Therapies and Natural history: Adults vs. children
• Predictors of course
• Age: How low can you go?
• Is UC a disease for which partial extrapolation is reasonable?
Ulcerative Colitis - Pathophysiology

A chronic inflammatory disorder of the colon that results from an inappropriate activation of the mucosal immune system by antigens derived from both the host epithelium and enteric flora in genetically susceptible individuals.
IBD Pathogenesis

Primary factors

- Genome
- Microbiome
- Exposome
- Immunome

Secondary factors

- Epigenome
- DAMPs
- Neuro-endocrine system
- Cell differentiation
- Altered tissue homeostasis
- Adipose tissue
- Others

Early IBD

Late IBD

Disease evolution

Before IBD

After IBD

Courtesy of Claudio Fiocchi, MD
200 susceptibility genes identified
Key pathways arising from gene discovery in Crohn's disease and ulcerative colitis.

C W Lees et al. Gut 2011;60:1739-1753

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Shared Genes With Other Immune Mediated Disorders

Figure 1. The global map of inflammatory bowel disease: red refers to annual incidence greater than 10/105, orange to incidence of 5–10/105, green to incidence less than 4/105, yellow to low incidence that is continuously increasing. Absence of color indicates...

Jacques Cosnes, Corinne Gower-Rousseau, Philippe Seksik, Antoine Cortot
Gastroenterology, Volume 140, Issue 6, 2011, 1785–1794.e4
Age Distribution

Figure 2. Age-specific prevalence of ulcerative colitis in the United States.

# Clinical Expression: The Same in Children and Adults

<table>
<thead>
<tr>
<th>Feature</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
<tr>
<td>Bleeding</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>XXXX</td>
<td>XXXX</td>
</tr>
<tr>
<td>Arthritis</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Axial spondyloarthropathy</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Liver disease</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Other: pyoderma gangrenosum, erythema nodosum, uveitis, episcleritis</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>
Disease Extent: Generally more extensive in children

<table>
<thead>
<tr>
<th>Disease extent</th>
<th>Adults(^1)</th>
<th>Adults(^2)</th>
<th>Children(^3)</th>
<th>Children(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distal</td>
<td>12%</td>
<td>22%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Left sided</td>
<td>38%</td>
<td>37%</td>
<td>20%</td>
<td>23%</td>
</tr>
<tr>
<td>Extensive</td>
<td>48%</td>
<td>42%</td>
<td>75%</td>
<td>69%</td>
</tr>
</tbody>
</table>

\(^1\)Lancet 2016;387:156,  \(^2\) APT 2015;43:540,  \(^3\)Gastroenterology 2008;135:1114,  \(^4\) PROTECT Study
Endoscopic and Histologic Appearance of Disease Is the Same in Adults and Children

Infiltration of lamina propria with inflammatory cells, crypt abscesses, architectural distortion, basal plasmacytosis
Natural History Is What Happens When There are No Good Therapies

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Study cohort</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hardy¹</td>
<td>1933</td>
<td>95 adults</td>
<td>75% mortality at 1 year</td>
</tr>
<tr>
<td>Truelove/Witts²</td>
<td>1955</td>
<td>Adult UC treated with HC</td>
<td>6% HC and 15% control pts died within 6 months</td>
</tr>
<tr>
<td>Goel³</td>
<td>1973</td>
<td>25 hospitalized children with UC</td>
<td>20% died (post-colectomy), 19 had chronic disease</td>
</tr>
<tr>
<td>Michener⁴</td>
<td>1979</td>
<td>336 children</td>
<td>35% colectomy, 5% died (cancer); 69% chronically ill</td>
</tr>
<tr>
<td>Langholz⁵</td>
<td>1994</td>
<td>1161 adults</td>
<td>30% colectomy by 15 years</td>
</tr>
</tbody>
</table>

The Natural History We Want To Avoid

• Ulcerative colitis – poor quality of life; uncontrolled inflammation requiring colectomy; cancer
Standard of Care Non-biologic Therapies for Ulcerative Colitis: Adult vs. Child

• The mainstay of therapy for pediatric or adult ulcerative colitis are aminosalicylates
  Effective for both induction and maintenance of remission for mild to moderate disease

• Abundance of adult trials, paucity of pediatric trials for efficacy and safety. Most pediatric data are from observational studies

• Adult success rates around 50%¹
• Cautiously note overall similarity in efficacy though many methodologic confounders
• Non-adherence a big issue in both populations

Ford et al. Am J Gastroenterol 2011;106:601
Outcome at 1 Year Children with Ulcerative Colitis Treated With 5-ASA±CS in First 30 Days (n=213)

Corticosteroid free, rescue and surgery free

Zeisler et al. JPGN 2013;56:12
Immediate and Long-Term Outcomes of Corticosteroid Therapy in Ulcerative Colitis

1 Month
- Complete Response: 54% (60%)
- Partial Response: 30% (24%)
- No Response: 16% (16%)

1 Year
- Prolonged Response: 49% (50%)
- Steroid-Dependent: 22% (45%)
- Surgery: 29% (5%)

(Agent, n=63), Pediatric, n=62

Thiopurine Treatment in Pediatric UC

133 children treated with 6-MP/azathioprine without concomitant biologic or previous calcineurin Rx

Adult data: 6 m – 1 yr, range 53%-63%


Hyams et al., Am J Gastroenterol 2011;106:981
Clinical Remission at Week 8: Infliximab Pediatric Trial (T72) Compared to ACT 1 and ACT 2

- **REMICADE 5 mg/kg q8w Maintenance**
  - T72: 24/60 (40.0%)
  - ACT: 88/242 (29.8%)

- **ACT 1 and ACT 2 Placebo**
  - 25/244 (10.2%)

Mucosal Healing at Week 8: Infliximab Clinical Trial (T72) Compared to ACT1 and ACT2

Colectomy: The last choice natural history

- Often great resistance
- Medically refractory severe disease-life threatening, no choice
- Chronic disease –poorly responsive to medical therapy, impaired quality of life; medication toxicity, somewhat elective
- Dysplasia
- Improved use of current therapies and emerging therapies changing likelihood
Cumulative Probability of Colectomy by Disease Activity at Diagnosis (1975-1995): Children, Pre-biologic era

Mild vs moderate/severe, \( P<0.03 \), * 2 IBD centers

Cumulative Probability of Colectomy, Pediatric Center 1988-2002

Overall rate of colectomy
5 years: 20%

Rate of colectomy by disease extent
29% for extensive disease

1st year high risk for extensive disease

Cumulative Probability of Colectomy: Manitoba, 1987-2008

**Figure 1.** Overall colectomy rate.

Targownik et al. Am J Gastroenterol 2012;107:1228
Cumulative Probability of Colectomy, Manitoba, by Age dx

Targownik et al. Am J Gastroenterol 2012;107:1228
## Factors Associated with Poor Outcomes: Adults

<table>
<thead>
<tr>
<th>Factor</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis</td>
<td>Younger age associated with more severe disease, higher relapse, and higher risk of colectomy</td>
</tr>
<tr>
<td>Smoking status</td>
<td>Non-smokers and ex-smokers do worse than current smokers</td>
</tr>
<tr>
<td>Sex</td>
<td>Conflicting, though some evidence that males do worse; many confounders</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>Conflicting, though ; CLEC7A, MDR, HLA DRB1, hMLH1 associated with refractory disease</td>
</tr>
<tr>
<td>Disease extent</td>
<td>Extensive disease, worse outcomes</td>
</tr>
<tr>
<td>Histopathologic severity</td>
<td>More severe, worse outcomes</td>
</tr>
<tr>
<td>Early hospitalization</td>
<td>Markedly worse outcomes</td>
</tr>
<tr>
<td>Elevated acute phase reactants</td>
<td>Increased CRP, ESR associated with worse outcomes</td>
</tr>
<tr>
<td>Other labs</td>
<td>Anemia, hypoalbuminemia associated with worse outcomes</td>
</tr>
</tbody>
</table>

Factors Associated with Poor Outcomes: Children

<table>
<thead>
<tr>
<th>Factors</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease extent</td>
<td>Extensive, worse outcomes</td>
</tr>
<tr>
<td>Extension of disease</td>
<td>Limited becoming extensive, worse outcomes</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>Worse outcome</td>
</tr>
<tr>
<td>Family history</td>
<td>Associated with disease extension</td>
</tr>
<tr>
<td>Active disease at 3 months after dx</td>
<td>Associated with worse outcomes</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>Hypoalbuminemia at diagnosis associated with worse outcome</td>
</tr>
<tr>
<td>Endoscopic severity</td>
<td>Associated with worse outcomes</td>
</tr>
</tbody>
</table>

Schechter et al. Gut 2015;64:580
A GWAS comparing 324 MR-UC patients with 537 non-MR-UC patients was analyzed using logistic regression and Cox proportional hazards methods. In addition, the MR-UC patients were compared with 2601 healthy controls.
Pediatric vs. Adult HLA for UC

High-density mapping of the MHC identifies a shared role for HLA-DRB1*01:03 in inflammatory bowel diseases and heterozygous advantage in ulcerative colitis

Philippe Goyette¹,³, Gabrielle Boucher¹,³, Dermot Mallon²,³, Eva Ellinghaus⁴, Luke Jostins⁵,⁶, Hailiang Huang⁷,⁸, Stephan Ripke⁷,⁸, Elena S Gusareva⁹,¹⁰, Vito Annese¹¹,¹², Stephen L Hauser¹³, Jorge R Oksenberg¹³, Ingo Thomsen⁴, Stephen Leslie¹⁴,¹⁵, International Inflammatory Bowel Disease Genetics Consortium¹⁶, Mark J Daly⁷,⁸, Kristel Van Steen⁹,¹⁰, Richard H Duerre¹⁷,¹⁸, Jeffrey C Barrett¹⁹, Dermot P B McGovern²⁰, L Philip Schumm²¹, James A Traherne²²,²³, Mary N Carrington²⁴,²⁵, Vasilis Kosmoliaptsis²,³, Tom H Karlsen²⁶–²⁸,³¹, Andre Franke⁴,³¹ & John D Rioux¹,²⁹,³¹

- 969 MHC region were reported from 14308 UC cases and 34241 controls.
- 135 common SNPs were found between Pediatric vs. Adult UC
OR comparison between Pediatric and Adult UC

Differential attributable risk by HLA

Unpublished data, PROTECT Study, U01DK095745
Acute Severe Colitis: Worse Outcomes, Child and Adult
Criteria for Acute Severe Colitis

- Hospitalized
- $\geq 5$ bloody stools daily
- Anemia
- Fever
- Hypoalbuminemia
- Elevated acute phase reactants

A small but disproportionately bad outcome group. Likely more common in children
One Year Outcomes: OSCI Study

128 admissions

Short term colectomy rate: 11 (8.6%)

- 91 response
  - 8 colectomy
  - 7 infliximab
  - 3 colectomy

1 year colectomy rate: 23 (18%)

- 3 colectomy
  - 7 infliximab
  - 7 colectomy

- 1 cyclo
  - 1 response
- 5 response
- 2 colectomy
- 0 colectomy

Turner D et al, Gastroenterology 2010; 138: 2282 -2291
History of medical hospitalization predicts future need for colectomy in patients with ulcerative colitis.
Caution in Very Young Children

• Great care must be taken for very young children (≤2 yrs) where autosomal recessive disorders affecting the immune system may be causative of IBD-like illness- IL-10, IL-10R, XIAP, etc.

• Important that these children not be entered in clinical trials

• Very young children with “wild type” IBD invariably present with a colitis like phenotype making differentiation between Crohn’s disease and ulcerative colitis difficult
Summary

• Ulcerative colitis in adults and children have virtually identical clinical, endoscopic, and histologic features
• In general children have a higher likelihood of corticosteroid, immunomodulator, and biologic exposure than adults, i.e., a more severe phenotype
• However, response to these interventions is similar in adults and children
Fundamental Assumptions For Extrapolation of Drug Trials from Adults to Children: Similarities In...

• Disease pathogenesis
• Pathophysiologic, histopathologic, and pathobiological characteristics
• Criteria for disease definition
• Clinical classification
• Response to intervention
• Disease progression
• Measures of disease progression
Summary

• The use of partial extrapolation to enhance the speed of availability of IBD therapies found to be safe and effective in adults to children appears reasonable

• Dosing and safety cannot be extrapolated