Pediatric IBD

• Incidence
  – 2-4 new cases/100,000 pop./year

• Presentation
  – Overt: diarrhea, blood in stool, abdominal pain, vomiting, fevers
  – Subtle: chronic anemia, fatigue, growth deceleration
  – Extra-intestinal manifestations
# IBD Spectrum

<table>
<thead>
<tr>
<th>CROHN’S DISEASE</th>
<th>ULCERATIVE COLITIS</th>
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<tbody>
<tr>
<td>Anywhere in GI tract</td>
<td>Colon only</td>
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<tr>
<td>Transmural</td>
<td>Superficial</td>
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<tr>
<td>“Skip” lesions</td>
<td>Continuous</td>
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<tr>
<td>Noncaseating granulomas</td>
<td>Crypt abscesses</td>
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<tr>
<td>Complications</td>
<td>Fewer complications</td>
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<tr>
<td>– Stricture, fistula, abscess</td>
<td>Colectomy may be curative in refractory cases</td>
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<tr>
<td>Can recur after surgical resection</td>
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Indeterminate (features of both)
IBD Diagnosis

• Clinical presentation
• Screening labs
  – CBC/diff, electrolytes, UA, lipase, ESR, CRP
  – Stool culture, guaiac, other studies – as indicated by symptoms
• Imaging
  – Fluoroscopy (UGI, SBS, barium enema)
  – CT of abdomen/pelvis with contrast
• Endoscopy with biopsies
  – EGD
  – Colonoscopy
Diagnostic Issues

- Risk and constraints of invasive studies delay the diagnosis
- IBD considered relatively rare in children
  - 2-5% of all IBD cases occur in ages < 10 years
- For management and prognostic decisions need to differentiate between IBD subtypes
  - Up to 15% of cases remain indeterminate
    - Clinical and pathological features of both
Serodiagnostic Testing in IBD

- **ANCA** (Anti-neutrophil cytoplasmic antibody)
  - pANCA (perinuclear ANCA)
  - Elevated in UC
    - First published by Duerr R et al, Gastroenterology 1991; 100: 1385-91

- **ASCA** (Anti-\textit{Saccharomyces cerevisiae} mannan antibodies)
  - Elevated in Crohn’s disease

- Studies evaluating these tests in children are limited
Prometheus™ IBD First Step Assay

• Commercially available
  – Send out via GI Lab to Prometheus Laboratories, San Diego, CA

• 4 markers
  – DNAse-sensitive pANCA IgG
  – ASCA IgG
  – ASCA IgA
  – Anti-OmpC IgG and IgA
    • Outer membrane porin of *E. coli*
    • Associated with Crohn’s disease
    • No previous published data on its diagnostic value
Methods

• pANCA
  – Enzyme-linked immunosorbent assay (ELISA)
  – Fixed neutrophils incubated with sera
    • Neutrophil-bound Ab labeled using goat anti-human IgG conjugated to alkaline phosphatase
    • P-nitrophenol added for colorimetric reaction
    • Absorbance measured at 405 nm to measure titer
    • Positive titers based on reference values from adult UC patients
  – Indirect immunofluorescence on ANCA ELISA + samples
    • Perinuclear staining pattern
    • Disappearance after DNAse treatment confirms nuclear antigen
Methods

- **ASCA**
  - **ELISA**
    - Microtiter plates coated with phosphopeptidomannans from yeast *S. cerevisiae* and sera added
    - Bound Ab labeled by alk.phos.-conjugated goat anti-human IgG and IgA
    - Absorbance compared to values from pool of sera collected from well-defined CD patients
  - **Cutoff for positivity (ELISA units = EU)**
    - IgA: 20 EU/mL
    - IgG: 40 EU/mL
Methods

• OmpC
  – ELISA
    • Microtier plates coated with purified outer membrane porin antigens isolated from *E. coli*
    • Sera added and bound Ab labeled by alk. Phos.-conjugated goat anti-human IgG and IgA
    • Absorbance measured and compared to standard curve
    • Standards from pooled sera collected from well-defined CD patients
Validation

- Recent study in children/young adults
- Prometheus IBD First Step Assay on samples from 198 patients in Pediatric GI practice
  - CD (n=81), UC (n=54)
    - Dx established by clinical, imaging, endoscopic criteria
    - Clinical scores used to evaluate disease severity
    - Charts re-reviewed at end of study period to determine outcome
  - Controls (n=63)
    - Functional abdominal pain, IBS, uncomplicated GERD, diarrhea-NOS
DNAse-sensitive pANCA

- Positive in
  - 70% of UC pts.
  - 18% of CD pts.
  - 3% of controls
    - Patients with higher pANCA titers were more likely to have UC

- No relationship between pANCA titer and disease severity (Kozarek score)

- All patients who were pANCA+ had IBD involving the entire colon or left colon
ASCA IgG and IgA

- Highly specific for CD
  - IgG: 98% (one control was +), IgA: 100%
- Sensitivity
  - IgG: 37%, IgA: 41%, either: 44%
- Better at telling CD from UC than pANCA is at distinguishing UC from CD
- Lower ASCA titers correlated inversely with severity (Pediatric CD Activity Index)
- ASCA+ patients were more likely than ASCA- pts
  - to have ileal or ileal/right colon disease ($p < 0.001$)
  - to require ileal resection ($p < 0.05$)
Anti-OmpC

- Positive in
  - 24% of CD pts
  - 11% of UC pts
  - 5% of controls
- Identified 6 additional IBD pts not detected by the other assays
- No relationship between Anti-OmpC and disease severity or risk of surgery
Overall Assay

- Positive screening test = at least one positive marker
- Specificity = 97%
- Sensitivities
  - CD: 65%
  - UC: 76%
- Positive predictive value approaches 80%
  - In population referred specifically to exclude IBD
  - Much lower in general GI or peds population
  - Findings of this pediatric study in agreement with previous studies in adults and children

*Histology is still gold standard in first decade of 21st century*