Can We Predict the Course of Crohn's Disease and Why Does It Matter?

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Can we predict patients who will have a “progressive” course?
Progression of Digestive Disease Damage and Inflammatory Activity

**Prognosis - Clinical**

- **Traditional Risk Factors for “Bad Course”**
  - Young age at diagnosis
  - Smoking
  - Early penetrating (or stricturing) disease
  - Early need for steroids
  - High initial CRP
  - Perianal disease
  - Ileal and upper GI tract disease


Beaegerie Gastro 2006; 130:650
Cosnes IBD 2002; 8:244
Thia, Gastro 2010; 139:1147
Binder, Gut 1985; 26: 146
### Predicting a “Disabling Course”

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate P value</th>
<th>Multivariate OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 40</td>
<td>.0004</td>
<td>2.1 (1.3-3.6)</td>
</tr>
<tr>
<td>Ileal disease</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>.09</td>
<td></td>
</tr>
<tr>
<td>Perianal disease</td>
<td>.01</td>
<td>1.8 (1.2-2.8)</td>
</tr>
<tr>
<td>Steroids for first flare</td>
<td>.0001</td>
<td>3.1 (2.2-4.4)</td>
</tr>
</tbody>
</table>

Beaugerie L. Gastroenterology 2006;130:650-6

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### Clinical Predictors of “Complicated Disease”

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Hazard ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colon only</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>Ileocolonic</td>
<td>5.6</td>
<td>2.3 – 13.9</td>
</tr>
<tr>
<td>Ileal</td>
<td>7.8</td>
<td>3.5 – 17.4</td>
</tr>
<tr>
<td>Upper GI Tract</td>
<td>9.5</td>
<td>3.0 – 30.1</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;16</td>
<td>Reference</td>
<td></td>
</tr>
<tr>
<td>16-40</td>
<td>2.1</td>
<td>0.8 – 5.2</td>
</tr>
<tr>
<td>41+</td>
<td>1.3</td>
<td>0.5 – 3.5</td>
</tr>
</tbody>
</table>

Thia et al. Gastroenterology 2010;139:1147-55
Predictors of “Rapid Progression to Surgery”

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current smoker</td>
<td>3.09 (1.47–6.51)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.82 (1.05–3.18)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2.07 (1.04–4.10)</td>
</tr>
<tr>
<td>Ileal localization only</td>
<td>2.22 (1.30–3.81)</td>
</tr>
<tr>
<td>Oral corticosteroid use in 1st 6 months</td>
<td>3.79 (1.90–7.55)</td>
</tr>
</tbody>
</table>


Prognosis of CD Patients with Severe Endoscopic Lesions

- **SELS** defined as deep ulcerations >10% of mucosal area with at least one colonic segment
- Risk of colectomy associated with severe endoscopic lesions, high CDAI, absence of immunosuppression

![Graph showing the percentage of patients with severe endoscopic lesions over time](image)
Potential Role of Serologic and Genetic Testing

• Diagnosing Disease
• Predicting Development of Disease
• Predicting Course of Disease

Ideal Biomarkers

• Easy to measure
  – Noninvasive
  – Reproducible
  – Inexpensive
• Responsive to change
• High PPV and NPV
Genetic Markers of Disease Course: NOD2

- Meta-analysis of 49 studies
- Summary relative risk estimates

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrating or stricturing disease (B2/B3)</td>
<td>1.17 (1.10 – 1.24)</td>
<td>67%</td>
</tr>
<tr>
<td>Perianal disease</td>
<td>1.03 (0.92 – 1.16)</td>
<td>53%</td>
</tr>
<tr>
<td>Surgery</td>
<td>1.58 (1.38 – 1.80)</td>
<td>64%</td>
</tr>
</tbody>
</table>


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Do Serologic Patterns Predict Phenotypes and Prognosis?

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Small bowel disease</th>
<th>Fibrostenosis</th>
<th>Internal Perforation</th>
<th>Small bowel surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASCA</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>pANCA</td>
<td>-</td>
<td>-</td>
<td>Not associated</td>
<td>-</td>
</tr>
<tr>
<td>I2</td>
<td>+</td>
<td>+</td>
<td>Not associated</td>
<td>+</td>
</tr>
<tr>
<td>OmpC</td>
<td>Not associated</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Mow WS. Gastroenterology 2004;126:414-24
Risk of Crohn’s Disease Progression and Positive Serology

Antibodies:
- Anti-L2, anti-OmpC, anti-CBir1, ASCA

Graph:
- Time to Disease Progression (months)
- Probability of Non-progressive CD
- N=70


Serologic Sums Predict Survival without Surgery

536 pediatric patients with all disease distributions

Adapted from Dubinsky et al. Clin Gastroenterol Hepatol 2008;6:1105-1111
Combination of genetic and quantitative serological immune markers are associated with complicated Crohn's disease behavior

- Cross-sectional study
- Banked blood from well-characterized CD patients ($n = 593$)
- Serological biomarkers (ASCA-IgA, ASCA-IgG, anti-OmpC, anti-CBir1, anti-I2, pANCA).
- In a patient subset ($n = 385$), $\text{NOD2}$ (SNP8, SNP12, SNP13) genotyping
- Complications included stricturing and penetrating disease behaviors
- For each serologic marker, complication rates were stratified by quartile (Quartile Sum Score)
- Performance of model integrating serologic and genetic markers demonstrated by area under the receiver operating characteristic curve

Higher QSS is Associated with a Greater Risk of CD Complications

Problem with Cross Sectional Survey

57% of Patients already had complication at time of blood draw

Longitudinal Status of Serologies Predicts CD Phenotype Before Diagnosis (PREDICTS Study)

Methods
• 100 patients with incident CD (ICD-9 codes)
• Serum samples from DOD Serum Repository (2, 4, 6, years before and at diagnosis)
• Disease type at diagnosis (ICD-9, CPT codes)
  – Complicated (stricturing, intestinal penetrating, or history of resection) vs. uncomplicated

Results
• Titers of 4 CD-associated markers (ASCA-IgA, ASCA-IgG, anti-A4-Fla2, anti-FLaX) prior to diagnoses were higher in complicated vs uncomplicated CD

Serum markers are detectable well before the diagnosis of CD and can predict development of complications

Outcomes of Corticosteroid Therapy for Crohn’s Disease

Immediate Outcome (n=74)
- Complete Remission: 58% (n=43)
- Partial Remission: 26% (n=19)
- No Response: 16% (n=12)

1-Year Outcome (n=73)
- Prolonged Response: 32% (n=24)
- Steroid Dependent: 28% (n=21)
- Surgery: 38% (n=28)

Steroid use is a risk factor but 50% of patients in the community never see steroids!


What have we learned?

- IBD is Chronic & Progressive
- Symptoms do not reflect “inflammatory burden”
- Treating to biologic targets improve long-term outcomes
- The earlier the better
- Get the most out of initial therapy
- PK/PD Makes a difference
AGA Clinical Pathway for Crohn’s Disease

Assessing Inflammatory Status

- Assess inflammatory status
  - Perform clinical lab testing: CBC, CRP, CMP, Fecal calprotectin, ESR
  - Select imaging modalities (if indicated)
    - Perform endoscopy
      - Perform CT-enterography OR magnetic resonance enterography

- Assess symptoms/signs
  - Fever
  - Abdominal pain
  - GI bleeding
  - Localized tenderness
  - Weight loss
  - Joint pain
  - Cutaneous signs

*Selection depends on local expertise and experience with imaging modalities. Magnetic Resonance Enterography is preferred due to the reduction in ionizing radiation, particularly for younger patients. If patient is less than 50 years of age, we suggest using Magnetic Resonance Enterography.

†Consideration could be given as to whether to make treatment decisions based on inflammatory markers versus confirming with colonoscopy. This may depend on whether there was historically good correlation between the biomarker selected and colonoscopy in the specific patient.

AGA Clinical Pathway for Crohn’s Disease

**Characterizing Risk**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;30 years</td>
<td>&lt;30 years</td>
</tr>
<tr>
<td>Limited</td>
<td>Extensive</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Superficial</td>
<td>Deep</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**AGA Clinical Pathway for Crohn’s Disease**

**Initial Treatment**

**Low-risk patient**
- Ileum and/or proximal colon, none to minimal symptoms
  - Options
    - Budesonide 9 mg/day with or without AZA
    - Tapering course of prednisone with or without AZA

**Moderate/high-risk patient**
- Options
  - Anti-TNF monotherapy over no therapy or thiopurine monotherapy
  - Anti-TNF + thiopurine over thiopurine monotherapy or anti-TNF monotherapy
  - Methotrexate for patients who do not tolerate purine analog in combination with anti-TNF
Does Treating Earlier Make a Difference?

Impact of therapy will depend on degree of structural damage and speed of progression

Costes J et al. Inflamm Bowel Dis. 2002;8:244-250.
Early Aggressive Biologic Therapy versus Conventional Management of Crohn’s Disease

Newly diagnosed* Anti-TNF, antimetabolite, and steroid naive Crohn’s disease (n=133)

Early Aggressive (n=67)
IFX (0/2/6) + AZA
IFX + AZA
+ (episodic)
IFX
Steroids

Conventional Therapy (n=66)
Steroids


*within 4 years

Complete Ulcer Disappearance

Top Down
Step Up

73% 30%

P=0.003

4-week Response According to Prior Therapy with Anti-TNF from Adalimumab CLASSIC vs GAIN studies

CLASSIC (TNF Naive)  GAIN (Prior TNF Rx)

- Placebo
- Adalimumab 160/80mg

Vedolizumab in Crohn’s Disease
Clinical Remission at Week 6 and 10

Clinical Remission at Week 6

- Overall population: 12.1%
- TNF antagonist experience: 15.2%
- Naive: 31.4%

Clinical Remission at Week 10

- Overall population: 12.1%
- TNF antagonist experience: 13%
- Naive: 16%

PBO=placebo; VDZ=vedolizumab

Mean ±% vs placebo (95% CI)

Week 6: Mean ±% vs placebo (95% CI)

- Overall population: 3.0% (-4.5, 10.5)
- TNF antagonist experience: 6.9% (0.1, 13.8)
- Naive: 19.2% (3.3, 35.0)

Week 10: Mean ±% vs placebo (95% CI)

- Overall population: 3.0% (-4.5, 10.5)
- TNF antagonist experience: 6.9% (0.1, 13.8)
- Naive: 19.2% (3.3, 35.0)

P<.001

Redefining Disease Severity in IBD

Impact on Patient
- Symptoms
- QOL
- Disability

Inflammatory Burden
- CRP
- Mucosal lesions
- Disease extent

Complicated Disease Course
- Bowel damage
- Resection
- Perianal disease
- EIMs

Combining Prognostic Markers to Obtain a Unified Molecular Phenotype
“It's tough to make predictions, especially about the future.”
Yogi Berra

Can we predict the course of Crohn’s disease and does it matter?
Prediction is very difficult, especially if it's about the future. Niels Bohr

ECCO Consensus on CD: Definitions and diagnosis
• Genetic factors & serological markers of immune reactivity, alone or in combination, have been unhelpful in predicting the future course of CD at diagnosis.
• Further studies are needed to assess potential predictors in large, phenotypically well-defined cohorts, in order to build an accurate composite predictor index.

• ECCO statement 4A
• No evidence-based recommendation can be made at this time to implement the routine clinical use of genetic tests or serological markers to classify Crohn’s disease.

What have we learned?

• IBD is Chronic & Progressive
• Symptoms do not reflect “inflammatory burden”
• Treating to biologic targets improve long-term outcomes
• The earlier the better
• Get the most out of initial therapy
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