Disease behavior in adult patients—are there predictors for stricture or fistula formation?

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Crohn’s disease behavior: Vienna and Montreal classifications

- **Age at Diagnosis (A)**
  - A1 < 16 yr
  - A2 17–40 yr
  - A3 > 40 yr

- **Location (L)**
  - L1 ileal
  - L2 colonic
  - L3 ileocolonic
  - L4 isolated upper

- **Behavior (B)**
  - B1 nonstricturing-nonpenetrating
  - B2 stricturing
  - B3 penetrating
  - P perianal disease

- **Age at Diagnosis (A)**
  - A1 < 40 yr
  - A2 ≥ 40 yr

- **Location (L)**
  - L1 terminal ileum
  - L2 colonic
  - L3 ileocolonic
  - L4 upper gastrointestinal

- **Behavior (B)**
  - B1 nonstricturing-nonpenetrating
  - B2 stricturing
  - B3 penetrating

Gasche C, et al. Inflamm Bowel Dis 200;6:8-15
Natural history of Crohn’s disease: 90% of patients develop stricturing or penetrating complications

Disease behavior is not a stable given.
More than 70% of CD patients develop complications within 10 y

Cosnes J, et al. Inflamm Bowel Dis 2002;8:244–250
Changes in Crohn’s disease behavior and location

Stricture or fistula both reflect and predict severe/aggressive disease

- Adults: 361 CD patients
  - HR of ~2.1 for strictures and severe CD

- Pediatric population: 989 CD patients
  - Median follow-up 2.8 y
  - HR of ~2.5 for stricture or fistula and the risk for surgery

Loly C, Scand J Gastroenterol 2008;43:948-954
Gupta N, et al. Gastroenterol 2006;130:1069-1077
Predicting severe Crohn’s disease
[the development of non reversible serious lesions]

Stricture or fistula are associated with an increased risk for surgery.

- 60% of patients require surgery within 10 years.
Stricture or fistula at diagnosis predict surgery

- Population-based study, 476 CD patients, diagnosed in 12y
- Mean age at CD diagnosis 34, 71% diagnosed before 40 y
- Inflammatory disease behavior in 76%
- Perianal fistula prevalence:
  4.8% within 6 months, 10.3% at final follow up
- Predictors for surgery stricturing and penetrating phenotypes
- Predictors for disease recurrence:
  - Small bowel localization
  - Stricturing disease
  - Young age<40y

Why do we need disease course and behavior prediction?

- Patient information
- Closer follow-up of patients with worse prognosis
- Top down therapy suggested for patients with predicted aggressive course, may modulate disease course in adult and pediatric CD

Gupta N, et al. Gastroenterol 2006;130:1069-1077
How can we predict disease behavior?

- Clinical
  [Endoscopic]
- Serologic
- Genetic
Clinical factors associated with development of stricture or fistula

Stricture
- Recent diagnosis (after 1987)  
  - (HR 1.3 [1–1.6])
- Jejunal involvement  
  - (HR 3.2 [2.2–4.7])
- Ileal involvement  
  - (HR 2.5 [1.9–3.3])
- No colonic involvement  
  - (HR 2.0 [1.6–2.4])
- No anoperineal disease  
  - (HR 1.4 [1.1–1.8])

Fistula
- Age <40 yr  
  - (HR 1.3 [1–1.5])
- Non-caucasian  
  - (HR 1.3 [1.1–1.6])
- Anoperineal lesions  
  - (HR 2.6 [2.3–3.0])
- No oesophagogastroduodenal involvement  
  - (HR 1.4 [1.1–1.9])

5-year disabling Crohn’s disease

Beaugerie L, et al. Gastroenterology 2006;130:650-656
Seksik, et al. Gastroenterology 2007; 132 a17.80
Loly C, Scand J Gastroenterol 2008;43:948-954
Predictors of disabling Crohn’s disease

Score is based on the number of predictive factors at diagnosis:
age <40, steroid treatment, perianal lesions

Beaugerie L, et al. Gastroenterol 2006;130:650-656
Deep colonic ulcers are risk factors for colectomy in Crohn’s disease.

Probability of colectomy in patients with or without Severe Endoscopic Lesions (SELs) defined by deep ulcers covering >10% of at least 1 colonic segment.

Mucosal healing predicts remission

- In patients with CD, fever at diagnosis and medical treatment without steroids were significant predictors for mucosal healing.

- Mucosal healing significantly associated with less inflammation after 5 years.

\[ p = 0.02 \]

Froslie KS. Gastroenterology 2007;133:412
Clinical predictors of stricture or fistula

- Age < 40
- Disease location (small bowel-strictures)
- Perianal disease
- Steroid use

- [No mucosal healing?]
## Serologic response can predict disease behavior

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Directed against</th>
<th>Sensitivity/specificity (%)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>pANCA</td>
<td>Neutrophil cytoplasm (colonic bacteria?)</td>
<td>60-70 in UC 90</td>
<td></td>
</tr>
<tr>
<td>ASCA</td>
<td>Mannans, <em>Saccharomyces cerevisiae</em></td>
<td>60-70 (can be as low as 35) 95</td>
<td>Young diagnosis age Need for surgery FS, IP NOD2 association</td>
</tr>
<tr>
<td>OmpC</td>
<td>Outer membrane porin C, <em>E coli</em></td>
<td>31-55%</td>
<td>IP disease, need for surgery Longer duration</td>
</tr>
<tr>
<td>Anti-I2</td>
<td>I2 protein, <em>Pseudomonas fluorescens</em></td>
<td></td>
<td>FS disease, need for surgery</td>
</tr>
<tr>
<td>CBir1</td>
<td>Flagellin of commensal bacteria (clostridium?)</td>
<td></td>
<td>SB IP FS pANCA+CD&gt; pANCA+UC</td>
</tr>
</tbody>
</table>

References:
- Rump JA, Immunobiology, 1990
- Duerr RH, Gastroenterology 1991
- Rutgeerts P, Gastroenterology 1998
- Vermeire S, Gastroenterology 2001
- Cohavy O, Infect Immun 2000
- Landers CJ, Gastroenterology 2002
- Lodes MJ, JCI 2005
- Targan SR, Gastroenterology 2005
- Papp M, Am J Gastroenterol 2008
- Amre DK, Am J Gastroenterol 2006
- Forcione DG, et al. GUT 2004
<table>
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<th>Directed against</th>
<th>Sensitivity/ specificity (%)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>gASCa</td>
<td>covalently-bound mannan</td>
<td>50-56</td>
<td>Young diagnosis age, Shorter duration, perianal disease, AZA use, FS/IP, NOD2 association</td>
</tr>
<tr>
<td>ALCA</td>
<td>Laminaribioside</td>
<td>15-27</td>
<td>Young diagnosis age, FS/IP</td>
</tr>
<tr>
<td>ACCA</td>
<td>Chitobioside</td>
<td>11-20</td>
<td>Longer duration (high levels), non inflammatory behavior</td>
</tr>
<tr>
<td>AMCA</td>
<td>Mannobioside</td>
<td>11-28</td>
<td>NOD2 association, Shorter duration</td>
</tr>
</tbody>
</table>

Dotan I, Gastroenterology 2006;131:366-378
Ferrante M, GUT 2007;56:1394-1403
Papp M, Am J Gastroenterol 2008;103:665-681
Crohn’s disease stratification: it’s quality and quantity...

Cumulative reactivities (higher levels/more markers) were associated with:

- Stricturing or penetrating disease behavior in adult and pediatric populations
- Small bowel location
- Need for surgery
- Relapsing course of pediatric CD
- NOD2 and TLR4 variants (controversy)

Dotan I, Gastroenterology 2006;131:366-378
Dubinsky MC, Am J Gastroenterol 2006;101:360-367
Forcione DG, GUT 2004;53:1117-22
Desir B, CGH 2004;2:139-46
Henckaerts L, GUT 2007;56:1536-42
Dassopoulos T, Inflamm Bowel Dis 2007;13:143-151
Papp M, Am J Gastroenterol 2008;103:665-681
Crohn’s disease progression:
Serologic response predicts timing

Antibodies (gASCA, ALCA) appear >10 years before CD onset in CD but not control patients

Average level of serologic markers before and after diagnosis

<table>
<thead>
<tr>
<th>Marker</th>
<th>Before Disease Onset</th>
<th>After Disease Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>gASCA</td>
<td>54.5</td>
<td>107.6</td>
</tr>
<tr>
<td>ALCA</td>
<td>23.0</td>
<td>36.7</td>
</tr>
<tr>
<td>ACCA</td>
<td>71.7</td>
<td>96.6</td>
</tr>
</tbody>
</table>

Steady increase in antibody levels as disease progresses

Serologic markers units by year post onset

- 0-3 years (n=98)
- 4-9 years (n=103)
- 10-15 years (n=82)
- >15 years (n=90)

Time to first complication (fistula or abscess)
Shorter for ASCA+ vs ASCA-
Shorter for pANCA- vs pANCA+

Israeli E, Gastroenterology 2006 (abstr)
Amre DK, Am J Gastroenterol 2006;101:645-52
Dassopoulos T, Inflamm Bowel Dis 2007;13:143-51
Dubinsky MC, Am J Gastroenterol 2006;101:360-367
Serologic predictors of stricture or fistula

913 Adult CD patients
ALCA ACCA AMCA gASCA OmpC
Score 0=no serologic markers
Score 5=all markers positive

Number of immune responses

Genotype-phenotype correlations

Presence of NOD2 variants determined seroreactivity
gASCA, ALCA, AMCA associated with NOD2 NOD2 genotype and seroreactivity synergism in predicting fibrostenotic disease
Dose response between the number of mutant NOD2 alleles and ASCA prevalence and titers

Devlin SM, Gastroenterology 2007
Papp M, Am J Gastroenterol 2008;103:665-681
Ippoliti AF, Gastroenterol 2006 (abstr)
Dassopoulos T, Inflamm Bowel Dis 2007;13:143-51
Genotype-phenotype correlations

% gASCA positivity in CD patients with NOD2/CARD15 variants
n=850, p<0.0001, Titers 62 vs 47 U p<0.0001

% ALCA positivity in CD patients with NOD2/CARD15 variants
n=800, p=0.002, Titers 41 vs 47 U p=0.003

% ACCA positivity in CD patients with TLR4 variants
n=791, p=0.003

Henckaerts L, et al. GUT 2007;56:1536-42
Genetics predictors of stricture or fistula

- 1684 CD patients, The Netherlands: *NOD2, IBD5, DLG5, ATG16L1, IL23R*
- CD patients with stricturing or penetrating disease—significantly more risk alleles
- Patients needing surgical intervention—more risk alleles
- *ATG16L1* -associated with stricturing and perianal disease

Risk stratified approach for treatment decisions

Top Down: early treatment with immunomodulators

“Complication Risk Test”: combined clinical, serologic, genetic factors
- May assist in deciding whom to treat top down vs. step up
- May enable improved matching of aggressive, expensive treatment specifically to potentially complicated patients
- Prevent complications
- Increase patients quality of life
Summary

Disease behavior in adult patients—are there predictors for stricture or fistula formation?

- Stricture or fistula are complicated CD phenotypes
- Stricture or fistula are aggressive CD, and predict disabling/complicated CD
- Stricture or fistula may be predicted using clinical, serologic and genetic markers
- Combined serologic and genetic markers and higher titers—predict disease aggressiveness, behavior, rate of development
- Long term, prospective studies are required
Conclusions

Disease behavior in adult patients—are there predictors for stricture or fistula formation?

• Should we predict disease course? Yes we should

• Can we predict disease course Yes we can...(as good as it gets..)

• Future perspectives: better combination of clinical, genetic and serologic indices for a prospectively effective risk score
Thank You!