Risk Stratification in IBD

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Old IBD Treatment Paradigm

• “Treat disease according to disease extent and severity”
• Disease treated based on current inflammatory burden
• Long-term risks not considered
• Assess current burden and longitudinal risk

What risks are we talking about?

• Morbidity
• Mortality
• Relapse
• Steroid use
• Poor quality of life
• Disability

• Hospitalization
• Surgery
• Colonic neoplasia
• Colostomy
• Short gut

Risk stratification

• Differences in the risk of disease progression and complications
• Predictors of progressive and complicated disease

- Prognostic scores
- Risk-stratified therapeutic approach

Examples of risk-stratified management

Colitis-associated colon cancer
• Differences in risk of progression to colonic dysplasia/cancer
• Predictors:
  - Duration and extent of colitis
  - Inflammatory activity
  - Primary sclerosing cholangitis
• Risk-stratified surveillance

Post-operative recurrence of CD
• Differences in risk of clinical and surgical recurrence
• Predictors: Endoscopic recurrence
• Risk-stratified treatment based on Rutgeerts score

UC Outcomes (population-based cohorts)

- Location at diagnosis
  - Proctitis: 29.4% (25.3-34.7%)
  - Left-sided: 40.1% (32.6-44.6%)
  - Extensive: 30.5% (28.8-32.6%)

- Disease progression
  - Proctitis to left-sided: 28%-30%
  - Proctitis to extensive: 14%-16%
  - Left-sided to extensive: 21%-34%

- Hospitalizations
  - At diagnosis: 10-15%
    - One year: 17-29%
    - 5 years: 29-54%
    - 10 years: 39-66%

- Cumulative colectomy rates
  - 1-year: 4.4%
  - 5-years: 10.1%
  - 10 years: 14.6%

  Significant decrease over time*
**Trends in UC Therapy (population-based cohorts)**

**Steroids**
- **Olmsted**: One year after starting steroids, 49% of patients in sustained remission, 22% steroid-dependent, and 23% with colectomy.

**Immunomodulators**
- In pre-biologic era, IMM use at 1, 5, and 10 years was 5%, 12%, and 12%.
- In biologic era, IMM use increased 2-3 fold: 11%–20% at 1 year and 17%–27% by 7 years.

**Anti-TNF**
- Copenhagen County-Hungary cohort: 4% at 5 years and 6-7% at 7 years.
- RCT meta-analysis: lower hospitalization (OR 0.48, 0.29-0.80) and surgery (OR 0.67, 0.46-0.97).  

**CD Outcomes (population-based cohorts)**

**Clinical course**
- 10% of patients go into prolonged clinical remission.
- Steroids at diagnosis is a sentinel event: 28% with steroid-dependence and 38% with bowel resection by one year.
- Steroid dependence in 1/3.

**Hospitalizations**
- Two thirds of patients require hospitalization.
- Half of hospitalizations are in first year.
- 20% annual hospitalization rate thereafter.

**Surgery**
- Norway, Hungary, Denmark:
  - One year: 14-15%
  - 5 years: 25-30%
  - 10 years: 38-52%
- Olmsted:
  - 5 years: 38%
  - 10 years: 48%
  - 20 years: 58%
- Meta-analysis (2013):
  - One year: 16.3% (11.4-23.2%)
  - 5 years: 33.3% (26.3-42.1%)
  - 10 years: 46.6% (37.7-57.7%)

**Risk Stratification in UC**
- Progression of mild disease.
- Hospitalization in patients with moderate disease.
- Colectomy in patients with severe disease.
- Colectomy in all patients.

**Colectomy Risk in UC**

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited anatomic extent</td>
<td>Extensive colitis</td>
</tr>
<tr>
<td>Mild endoscopic disease</td>
<td>Deep ulcers</td>
</tr>
<tr>
<td>Age at diagnosis &lt;40</td>
<td>High CRP and ESR</td>
</tr>
<tr>
<td>Steroid-requiring disease</td>
<td>History of hospitalization</td>
</tr>
<tr>
<td>C. difficile infection</td>
<td>CMV infection</td>
</tr>
</tbody>
</table>

**IBSEN: CRP at diagnosis Colectomy**

**Change of Behavior**: B1 → B2/B3
- Hungary:
  - 21% at 5 years
  - Olmsted:
    - 19% at 90 days
    - 51% at 1 year
  - ACCESS (Asia-Australia):
    - 20% at 1 year
46 SNPs explained 48% of the variance for colectomy risk

Risk stratification in CD

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Moderate/high Risk</th>
<th>Not listed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limited anatomic extent</td>
<td>Extensive anatomic extent</td>
<td>L2/L3/L4</td>
</tr>
<tr>
<td>Age at diagnosis &gt;30</td>
<td>Age at diagnosis &lt;30</td>
<td>CRP</td>
</tr>
<tr>
<td>No perianal and/or severe rectal disease</td>
<td>Perianal and/or severe rectal disease</td>
<td>NOD2</td>
</tr>
<tr>
<td>Superficial ulcers</td>
<td>Deep ulcers</td>
<td>ASCA</td>
</tr>
<tr>
<td>No prior surgical resection</td>
<td>Prior surgical resection</td>
<td>Smoking</td>
</tr>
<tr>
<td>Inflammatory behavior</td>
<td>Strictureing and/or penetrating behavior</td>
<td></td>
</tr>
</tbody>
</table>

IBSEN: CRP at diagnosis predicts outcomes in CD

Predictors of Complicated CD

- Prospective inception cohort study at 28 sites in the US and Canada
- 913 children with 9% developing complications
- The validated model included age, race, disease location and serologies
- Sens 66% (51–82), Spec 63% (55–71), and NPV 95% (94–97)
- Ruminococcus implicated in stricturing complications
- Veillonella implicated in penetrating complications
- Ileal genes controlling extracellular matrix production were associated with stricturing in the risk model (HR 1·70, 95% CI 1·12–2·57)
Putting it all together

- We need models to predict behavior based on:
  - Clinical characteristics (age at diagnosis, disease location, smoking)
  - Biochemical tests (CRP)
  - Endoscopic findings
  - Genotype
  - Serotype
  - Microbiome
  - Immunome, Proteome, miRNA ...
- And we then need tools to visualize risk

A user-friendly tool to calculate risk of CD complications

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fecal occult blood</td>
<td>2.4 (1.15 - 4.31)</td>
</tr>
<tr>
<td>Post-operative disease</td>
<td>1.7 (1.13 - 2.61)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.7 (1.05 - 2.71)</td>
</tr>
<tr>
<td>ESR</td>
<td>1.2 (1.05 - 1.35)</td>
</tr>
<tr>
<td>HLA-DR</td>
<td>0.97 (0.84 - 1.15)</td>
</tr>
<tr>
<td>Smoking status</td>
<td>2.7 (1.39 - 3.95)</td>
</tr>
</tbody>
</table>

Example Patient 41

Inclusion criteria

- Moderate-severe active CD:
  - CDAI ≥220
  - SES-CD ≥7
  - elevated biomarker, CRP>5 or FeCal >250

AND

- CD at moderate-high risk for complications
  - Clinical assessment
  - CD Personalized Risk and Outcome Prediction Tool (PROSPECT)
  - Criteria defined by the 2014 AGA CD Clinical Care Pathway

Where do we go from here?

- We need validated risk stratification tools to
  1) Estimate prognosis
  2) Inform decision making

Assessment of IBD therapies should include efficacy and safety stratified by risk