3rd Annual Baylor University Medical Center
IBD Center Conference:
Treating IBD in 2018 - How Close Are We to the Promise of Personalized Medicine?
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Risk Stratification in IBD

Themos Dassopoulos, M.D.
Director, Baylor Scott and White Center for IBD
Adjunct Professor of Medicine, Texas A&M University
Themistocles.Dassopoulos@BSWHealth.org
Tel: 469-800-7189; Cell: 314-686-2623

BaylorScott&White
CENTER FOR INFLAMMATORY BOWEL DISEASES

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
- Hospitalization
- Surgery
- Relapse
- Steroid use
- Poor quality of life
- Disability
- 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% (29.8-32.6%)
- 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*

Fumery Clin Gastroenterol Hepatol 2018
*Froilkis Gastroenterology 2013

Trends in UC Therapy (population-based cohorts)

Steroids

- Olmsted: One year after starting steroids, 49% of patients in sustained remission, 22% steroid-dependent, and 29% with colectomy[1]

Immunomodulators[2]

- 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
- IMM initiated earlier, from 23 mos. (1991-1997) to 10 mos. after diagnosis (2006–2010)

Anti-TNF[2]

- Copenhagen County-Hungary cohort: 4% at 5 years and 6-7% at 7 years
- Dutch Cohort: 4% when diagnosed 1998-2005, 10% when diagnosed 2006-2010
- RCT meta-analysis: lower hospitalization (OR 0.48, 0.29-0.80) and surgery (OR 0.67, 0.46-0.97)[3]

[1]Faubion Gastroenterology 2001
[2]Fumery Clin Gastroenterol Hepatol 2018
[3]Mao Aliment Pharmacol Ther 2017

CD Outcomes (population-based cohorts)

- Location at diagnosis
  - Ileal (L1): 25-30%
  - Colonic (L2): 35-40%
  - Ileocolonic (L3): 30-40%
  - L3 increasing ?
- Behavior at diagnosis
  - Inflammatory (B1): 55-80%
  - Stricturing (B2): 5 - 25%
  - Penetrating (B3): 5 - 25%
  - B1 increasing?
- Change of Behavior : B1 → B2/B3
  - Hungary:
    - 21% at 5 years
  - Olmsted:
    - 19% at 90 days
    - 22% at 1 year
    - 51% at 20 years
  - ACCESS (Asia-Australia):
    - 20% at 1 year

Aniwan Gastroenterol Clin NA 2017

CD Outcomes (population-based cohorts)[1]

Clinical course

- **10% of patients go into prolonged clinical remission**[2]
- Steroids at diagnosis is a sentinel event: 28% with steroid-dependence and 38% with bowel resection by one year[3]
- Steroid dependence in 1/3[2]

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%
- Omlsted
  - 5 years: 38%
  - 10 years: 48%
  - 20 years: 58%
- Meta-analysis (2013)[4]
  - One year: 16.3% (11.4-23.2%)
  - 5 years: 33.3% (26.3-42.1%)
  - 10 years: 46.6% (37.7-57.7%)

[1]Aniwan Gastroenterol Clin NA 2017; [2]Peyrin-Biroulet Am J Gastroenterol 2010; [3]Faubion Gastroenterology 2001; [4]Frolkis Gastroenterology 2013;

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

Low Risk	High Risk
Limited anatomic extent	Extensive colitis
Mild endoscopic disease	Deep ulcers
	Age at diagnosis <40

No Risk	Possible Risk	High Risk
Family history	HLA	Steroid-requiring disease
Unknown Risk	Smoking	History of hospitalization
Microbiome	Male gender	*C. difficile* infection
		CMV infection

Dassopoulos Gastroenterology 2015

IBSEN: CRP at diagnosis Colectomy

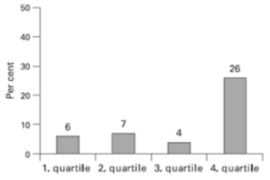
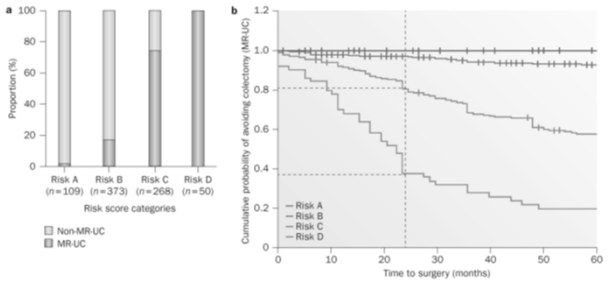


Figure 1 Percentage of patients with ulcerative colitis that is extensive (n = 129) who underwent colectomy during the first 5 years after diagnosis by C-reactive protein (CRP) quartile. The fourth quartile includes patients with CRP above 23 mg/l.

Henriksen Gut 2008

46 SNPs explained 48% of the variance for colectomy risk



Haritunians Inflamm Bowel Dis 2010

Risk stratification in CD

Assess current and prior disease burden

Low Risk	Moderate/high Risk	Not listed
Limited anatomic extent	Extensive anatomic extent	L2/L3/L4
Age at diagnosis >30	Age at diagnosis <30	CRP
No perianal and/or severe rectal disease	Perianal and/or severe rectal disease	NOD2
Superficial ulcers	Deep ulcers	ASCA
No prior surgical resection	Prior surgical resection	Smoking
Inflammatory behavior	Stricturing and/or penetrating behavior	

Sandborn Gastroenterology 2014

IBSEN: CRP at diagnosis predicts outcomes in CD

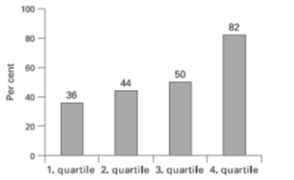


Figure 2 Percentage of patients with Crohn's disease with L1 (n = 46) who underwent intestinal resection during the first 5 years after diagnosis by C-reactive protein (CRP) quartile. The fourth quartile includes patients with CRP above 53 mg/l.

Henriksen Gut 2008

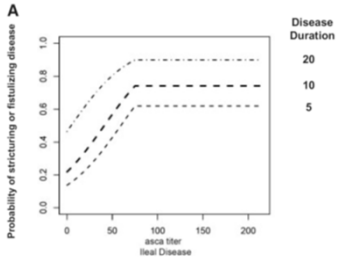
Predictors of Complicated CD

TABLE 3. Odds Ratio for Having Stricturing or Fistulizing Disease Versus Inflammatory Disease

	OR	(95% CI)	*P*
ASCA (/25 U)	2.7	(1.5, 46.7)	0.001
Age at diagnosis (/10years)	1.4	(0.9, 15.9)	0.175
Family history of IBD	3.6	(0.5, 28.1)	0.220
CD	0.1	(0.0, 0.9)	0.039
# *NOD2/CARD15* mutations	1.6	(0.7, 3.4)	0.233
Tobacco use (ever)	0.4	(0.1, 1.3)	0.128
Ileal disease	7.4	(1.6, 33.6)	0.010
Use of steroids	1.0	(0.3, 3.8)	0.955
Disease duration (/10 years)	4.7	(2.3, 24.2)	0.000

Dassopoulos Inflamm Bowel Dis 2007

Predictors of Complicated CD



Dassopoulos Inflamm Bowel Dis 2007

Predicting complicated CD in newly diagnosed children

- 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)

Kugathasan Lancet 2017

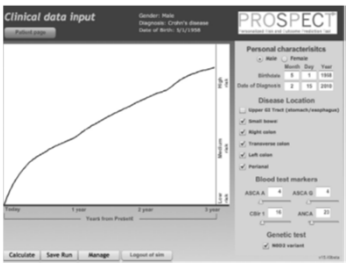
Putting it all together

- 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

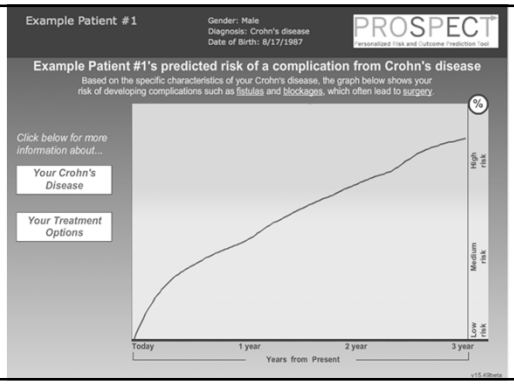
A user-friendly tool to calculate risk of CD complications

Table 3 | Multivariate analysis for the risk of Crohn's disease complication

Variable	Hazard ratio (95% CI)
Small bowel disease	2.12 (1.05–4.29)
Left colonic disease	0.73 (0.49–1.09)
Perianal disease	4.12 (1.01–16.88)
Ln ASCA	1.35 (1.16–1.58)
Ln CBir1	1.29 (1.07–1.55)
Ln ANCA	0.77 (0.62–0.95)
NOD2 frameshift mutation	2.13 (1.33–3.40)
Perianal × log ASCA	0.63 (0.42–0.94)



Siegel Aliment Pharmacol Ther 2016



Triple Combination Therapy in High Risk CD

- Triple Combination Therapy
  - Vedolizumab 300 mg IV at Weeks 0, 2, 6, 14 and 22
  - Adalimumab 160 @ week 0, 80 @ week 2, then 40 q2wk to week 26
  - Methotrexate 15 mg/week to week 34
- Monotherapy Phase
  - Vedolizumab 300 mg IV every 8 weeks (wk 30-102)

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