Can I Predict the Clinical Outcome of my IBD Patient?

Fairmont Royal York, Salon A
Sunday, Feb 9/2014, 11h00-11h40

Speakers: Sharyle Fowler, University of Saskatchewan and David Rubin, University of Chicago
Accreditation

This event has been approved as an accredited (Section 1) group learning activity as defined by the Maintenance of Certification program of the RCPSC. It has been produced under RCPSC guidelines for the development of co-developed educational activities between CAG and Forest Laboratories Canada Inc.
Name: Dr. Sharyle Fowler

Financial Interest Disclosure
(over the past 24 months)

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
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<tbody>
<tr>
<td>AbbVie</td>
<td>Speaker, Advisory Board</td>
</tr>
<tr>
<td>Janssen</td>
<td>Speaker, Advisory Board</td>
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<tr>
<td>Shire</td>
<td>Speaker</td>
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Slides noted by * were prepared by an industry partner
Name: Dr. David Rubin

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<th>Company/Commercial Enterprise</th>
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<td>Abbvie aka Abbott Immunology</td>
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<td>X (Registry)</td>
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<td>X (Registry)</td>
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<td>Co-founder, non-profit medical education organization</td>
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Learning Objectives

At the end of this session, participants will be able to:

• Identify clinical, serologic and endoscopic predictors for poor prognosis in patients with IBD

• Describe the use of serologic, endoscopic and fecal biomarkers to assess the risk of clinical relapse in patients with IBD
### 2014 CDDW/CASL Winter Meeting

#### CanMEDS Roles Covered:

<table>
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<th>Description</th>
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<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>(as <em>Medical Experts</em>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. <em>Medical Expert</em> is the central physician Role in the CanMEDS framework.)</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>(as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)</td>
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<tr>
<td><strong>Collaborator</strong></td>
<td>(as <em>Collaborators</em>, physicians effectively work within a healthcare team to achieve optimal patient care.)</td>
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<tr>
<td><strong>Manager</strong></td>
<td>(as <em>Managers</em>, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)</td>
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<tr>
<td><strong>Health Advocate</strong></td>
<td>(as <em>Health Advocates</em>, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)</td>
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<tr>
<td><strong>Scholar</strong></td>
<td>(as <em>Scholars</em>, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)</td>
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<tr>
<td><strong>Professional</strong></td>
<td>(as <em>Professionals</em>, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)</td>
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Case – Ms KB

• 20 yo F referred for 1 year history of intermittent bloody diarrhea
• Symptoms deteriorated over past 1 month
• 4-5 BMs/day + 1-2 BMs over night
• Watery stools + blood on the toilet paper
• Tenesmus and urgency
• Wt loss – 30-40 lbs in 1 year, 10 lbs past month
• Denies extra-intestinal manifestations of IBD
Case – Ms KB

• Physical exam – unremarkable (including perianal area)

• Labs from Family MD
  – WBC 8.0, Hgb 106 (MCV 72.8), Plt 388
  – ESR 41, CRP 41
  – Albumin 35
  – Ferritin 21, B12 N
  – Liver enzymes, electrolytes, renal function N
  – TSH, celiac serology N
Case - KB

• Labs at 1st clinic visit
  – WBC 8.0, Hgb 97 (MCV 70.3), Plt 467
  – ESR 74, CRP 61
  – Albumin 31
  – Liver enzymes, electrolytes, renal function N
  – TPMT, HepB serology ordered
Case - KB
Questions

- How would you rate the severity of this case?
- What tools do you routinely use to assess severity and predict disease prognosis?
- What tools do you wish you had better access to for predicting prognosis?
Definitions

• Severe disease – definitions vary
  – More than 2 steroid courses
  – Steroid dependence
  – Hospitalization
  – Disabling chronic symptoms
  – Need for immunosuppressive therapy
  – Penetrating or stricturing complications
  – Presence of perianal disease
  – Need for surgery
Risk Assessment Tools

• Presentation at diagnosis
• Laboratory markers
• Serological markers
• Stool markers
• Genetic markers
• Response to initial therapy?
Differing Patterns of Crohn’s disease Behavior

IBSEN study: Patients choosing 1 of 4 theoretical, predefined disease courses (n=197)

- **n=85 (43%)** Decrease in symptom severity
- **n=37 (19%)** Chronic continuous symptoms
- **n=6 (3%)** Increase in symptom severity
- **n=63 (32%)** Chronic relapsing symptoms

Missing data: n=6 (3%)

Long-term evolution of Crohn’s disease behavior

Cosnes J, et al. Inflamm Bowel Dis 2002;8:244–50
Long-term evolution of Crohn’s disease behavior (population-based study)

American population-based cohort of individuals diagnosed with Crohn’s disease 1970–2004 (n=306); evaluated for initial phenotype and cumulative probability of complications estimated using Kaplan-Meier

Progression of digestive damage and inflammatory activity in a theoretical patient with Crohn’s disease

How much damage has occurred before diagnosis?

Clinical Predictors of Disabling Disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Non-disabling, % (n = 166)</th>
<th>Disabling, % (n = 957)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Below 40 years</td>
<td>77.1</td>
<td>87.7</td>
<td>.0004</td>
</tr>
<tr>
<td>40 years or above</td>
<td>22.9</td>
<td>12.3</td>
<td></td>
</tr>
<tr>
<td><strong>Location of disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small bowel only</td>
<td>44.6</td>
<td>32.8</td>
<td>.002</td>
</tr>
<tr>
<td>Small bowel + colon</td>
<td>25.9</td>
<td>39.4</td>
<td></td>
</tr>
<tr>
<td>Colon only</td>
<td>29.5</td>
<td>27.8</td>
<td></td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>50.3</td>
<td>57.4</td>
<td>.09</td>
</tr>
<tr>
<td>Ex- or nonsmoker</td>
<td>49.7</td>
<td>42.6</td>
<td></td>
</tr>
<tr>
<td><strong>Perianal lesions at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>17.5</td>
<td>26.4</td>
<td>.01</td>
</tr>
<tr>
<td>No</td>
<td>82.5</td>
<td>73.6</td>
<td></td>
</tr>
<tr>
<td><strong>Steroids for first flare</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>37.3</td>
<td>65.2</td>
<td>.0001</td>
</tr>
<tr>
<td>No</td>
<td>62.7</td>
<td>34.8</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative incidence of surgical resection in CD after corticosteroid exposure

38% at 1-year

Faubion et al, *Gastroenterology* 2001; 121: 255
CRP

• An acute phase reactant
• Genetically determined
  – Up to 30% of CD and 50% of UC pts do not produce CRP

**CRP**

- **IBSEN cohort**
- **CRP at diagnosis, 1 and 5 years**
  - 454 UC
  - 200 CD

- **CD**
  - Increased risk of surgery with CRP > 53 mg/l (L1 disease)
  - OR 6.0 (95% CI 1.1 to 31.9), p=0.03

- **UC**
  - Increased risk of surgery with CRP > 23 mg/l (E3 disease)
  - OR 4.8 (95% CI 1.5-15.1), p=0.02

Prognosis and Severe Lesions

- Retrospective cohort
- 102 patients with active CD
- Severe endoscopic lesions (SEL)
  - extensive and deep ulcerations >10% of at least one colonic segment
- Risk of colectomy
  - SEL at index colonoscopy
  - high CDAI
  - absence of immunosuppression during f/u

Serologic Markers

• Markers of immune response to microbial antigens
  – Anti-*Saccharomyces cerevisiae* antibody (ASCA)
  – Perinuclear anti-neutrophil cytoplasmic antibody (pANCA)
  – *Escherichia coli* outer membrane porin (OmpC)
  – *Pseudomonas fluorescens*-associated sequence (I2)
  – Flagellin (CBir1)
“Immune Reactivity” and Prognosis

• 796 pediatric CD patients
• Sera tested for anti-Cbir1, anti-OmpC, ASCA, pANCA
• Assessed associations between serology scores and clinical outcomes
  – development of B2 or B3 behavior
  – need for surgery

“Immune Reactivity” and Prognosis

Poor prognostic factors for Crohn’s disease patients

• Disease location and behavior
  – Extensive small bowel disease
  – Severe upper GI disease
  – Rectal disease
  – Perianal disease
  – Early stricturing/penetrating disease
  – Deep ulcers

• Risk factors
  – Smoking
  – Young age at diagnosis (<40)
  – Genetic and serological profile scores?

Case - KB

- Started on prednisone and azathioprine
- Partial improvement in symptoms
- Approval obtained for anti-TNF – started early Jan/13
- Complete resolution of symptoms soon after
Can we predict disease relapse?
Fecal calprotectin

- Neutrophil-derived protein
- Constitutes up to 60% of cytosolic protein
- Anti-proliferative and anti-microbial properties
- Resistant to metabolic degradation by intestinal bacteria
- Stable at room temp for 7 days

http://www.cafepress.ca/+calprotectin_protein_molecule_large_poster,660561858
# Calprotectin to Predict Relapse

<table>
<thead>
<tr>
<th>Author</th>
<th>Patients</th>
<th>Cut off</th>
<th>Sensitivity for relapse (%)</th>
<th>Specificity for relapse (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costa</td>
<td>UC</td>
<td>150 μg/L</td>
<td>89</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>87</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>D’Inca</td>
<td>UC</td>
<td>130 mg/kg</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>CD</td>
<td>65</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>Garcia-Sanchez</td>
<td>CD + UC</td>
<td>120 μg/g</td>
<td>80</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>Ileal CD</td>
<td>223 μg/g</td>
<td>83</td>
<td>50</td>
</tr>
<tr>
<td>Tibble</td>
<td>UC + CD</td>
<td>250 μg/g</td>
<td>90</td>
<td>83</td>
</tr>
<tr>
<td>Kallel</td>
<td>Colonic CD</td>
<td>340 μg/g</td>
<td>80</td>
<td>91</td>
</tr>
<tr>
<td>Gisbert</td>
<td>UC + CD</td>
<td>150 μg/g</td>
<td>69</td>
<td>69</td>
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</table>

Calprotectin to Predict Relapse

<table>
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<tr>
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<th>UC</th>
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<tbody>
<tr>
<td></td>
<td>Relapse</td>
<td>Non-relapse</td>
</tr>
<tr>
<td>Calprotectin (mg/L)</td>
<td>122 (98-229)*</td>
<td>42 (31-49)*</td>
</tr>
<tr>
<td>ESR</td>
<td>21 (8-35)</td>
<td>13 (6-20)</td>
</tr>
<tr>
<td>CRP</td>
<td>13.1 (6-46)</td>
<td>9.1 (3-15)</td>
</tr>
</tbody>
</table>

* p<0.0001

CD – n=43
UC – n=37

STORI

- CD pts (n=115) in CS-free remission x 6 months
- Treated with IFX + anti-metabolite ≥ 1 year
- IFX stopped, f/u ≥ 1 year (median 29 months)

- 52/115 relapsed (43.9 ± 5%)
- Risk factors:
  - male sex
  - absence of resection
  - WBC >6.0, Hgb <145, CRP ≥ 5.0 mg/L
  - calprotectin ≥ 300 μg/g
  - steroid use within 12-6 months prior
  - CDEIS >0
  - IFX TL ≥ 2 mg/L

Louis E, et al. Gastroenterology 2012;142:63-70
STORI w/u CDEIS and IFX TL

- $\leq 3/9$ risk factors – 5% (0.5-29.3%) risk of relapse over 1 year
- $\leq 2/7$ risk factors – 15.2% (5.9-35.7%) risk of relapse over 1 year

Louis E, et al. *Gastroenterology* 2012;142:63-70
Can we predict prognosis of ulcerative colitis?
Natural History of Ulcerative Colitis
Circa 1993

• Within 2 years of diagnosis
  – 17% experience colonic hemorrhage
  – 13% experience toxic colitis
• Disease progresses in many patients
• Complications highest among pancolitis patients
• High rate of colectomy
• Increased risk of colon cancer

Disease Progression in Ulcerative Colitis

<table>
<thead>
<tr>
<th></th>
<th>Farmer¹</th>
<th>Stonnington²</th>
<th>Leijonmarck³</th>
<th>Langholz⁴</th>
<th>Sinclair⁵</th>
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</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>1116</td>
<td>182</td>
<td>1586</td>
<td>1161</td>
<td>537</td>
</tr>
<tr>
<td>Type of practice</td>
<td>Referral</td>
<td>Community</td>
<td>Community</td>
<td>Community</td>
<td>Community</td>
</tr>
<tr>
<td>Initial extent &lt; pancolitis</td>
<td>63%</td>
<td>~67%</td>
<td>63%</td>
<td>80%</td>
<td>89%</td>
</tr>
<tr>
<td>Extension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From proctitis</td>
<td>46%</td>
<td>29%</td>
<td>Not given</td>
<td>Not given</td>
<td>30% at 10 years</td>
</tr>
<tr>
<td>From left-sided colitis</td>
<td>70%</td>
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<th>Langholz(^4)</th>
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<td>537</td>
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<tr>
<td><strong>Period of study</strong></td>
<td>1960-83</td>
<td>1935-79</td>
<td>1955-84</td>
<td>1962-87</td>
<td>1967-76</td>
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Predictors of Poor Response or Colectomy

- Low serum albumin
- ESR >30 mm/h
- Bandemia
- Prolonged flare
- Active infection
- Hospitalization setting
- Severe endoscopic lesions
- Disease duration
- Stool frequency
- Percentage of bloody stools
- Body temperature >37.5
- Heart rate >90 bpm
- Increased CRP
- Toxic megacolon
- Low hemoglobin <10.5 g/dL

CRP=C-reactive protein.
Why is low serum albumin associated with poor prognosis in UC?

• Malnourishment
  – Due to disease
  – More often due to lack of PO intake
• Synthetic dysfunction uncommon
• Loss of protein
  – “leaky bowel”
  – Protein losing colopathy historically well-described

• Impacts treatment options!
Risk of Surgical Resection in Patients with UC After Starting Corticosteroids

185 patients in Olmsted County, MN diagnosed with UC from 1970 to 1993
Non-Adherence Leads to Relapse

Disease Behaviors of Ulcerative Colitis

Figure 1. Four predefined curves, depicting different courses of ulcerative colitis from diagnosis to 10 years’ follow-up. N = the number of non-operated patients (n = 379) reporting on each of them. Data were missing for six patients (1%).

Predictors of Colectomy in Severe Colitis: Poor Prognostic Endoscopic features

- Deep Ulcers
- Extensive Loss of Mucosal Layer*
- Well-like Ulcers
- Large Mucosal Abrasions

*With or without residual mucosal areas.
Severity of Disease Correlates With Colectomy

Severe Endoscopic Colitis (n=46)
- 93% underwent colectomy
- Deep/Extensive Ulcers: 93%
- Mucosal Detachment: 30%
- Large Mucosal Abrasions: 26%
- Well-like Ulcers: 17%

Moderate Endoscopic Colitis (n=39)
- 23% underwent colectomy
- Superficial Ulcers: 77%
- Deep But Nonextensive Ulcers: 8%

Mucosal Healing Correlates to Rate of Colectomy: Results from ACT 1 (infliximab)

0 = NORMAL  1 = MILD  2 = MODERATE  3 = SEVERE
# Histological Inflammation Is a Risk for Neoplasia in UC

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Design</th>
<th>Patients</th>
<th>Inflammation</th>
<th>Risk (OR or HR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gupta (2007)</td>
<td>Cohort</td>
<td>418 patients 65 with any neoplasia</td>
<td>Pathology reports: any neoplasia</td>
<td>HR 1.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>15 with advanced neoplasia</td>
<td>Pathology reports without polypectomy: any neoplasia</td>
<td>HR 3.0</td>
</tr>
<tr>
<td>Rubin (2013)</td>
<td>Case-control</td>
<td>56 cases 90 controls</td>
<td>Average histologic</td>
<td>OR 2.8† (1.4–5.2)</td>
</tr>
</tbody>
</table>

*P<0.001  
†P=0.002  
OR, odds ratio; HR, hazard ratio

Summary: Predicting Prognosis of IBD

• In both Crohn’s and UC, there are clinical features at diagnosis that predict relapse.
• Mucosal healing appears to be one of the most significant predictors of relapse and other outcomes such as surgery and neoplasia.
• An understanding of the prognostic markers in an individual patient should lead to modified approaches to treatment and disease monitoring.
• Evolving treatment paradigms to achieve “deeper” remission may provide better ways to control disease and alter prognosis.
Learning Objectives

At the end of this session, participants will be able to:

• Identify clinical, serologic and endoscopic predictors for poor prognosis in patients with IBD

• Describe the use of serologic, endoscopic and fecal biomarkers to assess the risk of clinical relapse in patients with IBD
Evaluation and Certificate of Attendance

Please visit the CAG website at http://www.cag-acg.org/ to complete the session evaluation and to print your certificate of attendance.

Thank you!