Predicting the natural history of IBD

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**Patient 1**

- Age 22
- Frequent cramps and diarrhea for 6 months
- Weight loss 2 kilos
- Ileocolonoscopy + bx
- R/ budesonide
- Doing well afterwards for 1 year

**Patient 2**

- Age 19
- Emergency: acute onset of severe pain RFI, fever 38°C, sick
- Frequent diarrhea with blood and mucus for 6 weeks
- CT scan
- R/ antibiotics
- Colonoscopy + bx
Patient 1

- Age 22
- Frequent cramps and diarrhea for 6 months
- Weight loss 2 kilos
- Ileocolonoscopy + bx
- R/ budesonide
- Doing well afterwards for 1 year

Patient 2

- Age 19
- Emergency: acute onset of severe pain RFI, fever 38°C, sick
- Frequent diarrhea with blood and mucus for 6 weeks
- CT scan
- R/ antibiotics
- Colonoscopy + bx

Will both diseases behave the same?
Natural history of IBD…the questions

1. What is the likelihood of a flare in any given year?
2. Will I ever need steroids?
3. Will the location of my disease remain stable over time?
4. Can you predict my disease behaviour?
5. What is the likelihood of a surgical intervention?
6. Are current therapies able to alter the natural history?
7. What about the risk of colorectal cancer?
8. Is my life expectancy altered?
"Your best bet would be to stay in bed next year."
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Natural course of IBD

Flare

Remission
After the first year of diagnosis, the majority of patients with CD in any population has mild disease activity or is in remission.

Disease activity: CD

<table>
<thead>
<tr>
<th>Disease state</th>
<th>% of lifetime disease course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>24.3</td>
</tr>
<tr>
<td>Mild active disease</td>
<td>27.5</td>
</tr>
<tr>
<td>Severe, drug responsive</td>
<td>0.9</td>
</tr>
<tr>
<td>Severe, drug-dependent</td>
<td>4.3</td>
</tr>
<tr>
<td>Severe, drug refractory</td>
<td>1.8</td>
</tr>
<tr>
<td>Surgery</td>
<td>1.1</td>
</tr>
<tr>
<td>Post-surgery remission</td>
<td>40.1</td>
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</tbody>
</table>

65% of follow up time is characterized by medical or surgical remission

Silverstein et al Gastroenterology 1999
Disease activity: CD

- Flare
- 1 year of remission
- 30% chance of remission in following year
- 80% chance of remission in following year

Veloso FT et al Inflamm Bowel Dis 2001
Disease activity: UC

- 1161 UC patients
- FU 25 years after D/
- 50% in clinical remission every year at any time
- Cumulative probability of a relapsing course is 90% after 25 years of FU
- Activity in the first 2 years after D/ indicates with 70-80% probability an increased probability of 5 consecutive years of active disease

Langholz E et al Gastroenterology 1994
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Requirement of steroids

- Copenhagen County: 56% required corticosteroids
- Olmstead County: 34% (UC) - 43% (CD) required steroids

Munkholm P et al Gut 1994
Faubion et al Gastroenterology 2001
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Make a classification in your IBD patient!

Anatomy

- Symptoms
- Clinical course
- Prognosis
Disease location

- Small bowel: 30%
- Colon: 42%
- Small bowel + Colon: 28%

Farmer Gastroenterology 1975

Bar chart:
- Ileocolonic: 73
- Colonic: 51
Natural history of location

Over 10 years, only 15% of patients have a change in location

Louis E et al Gut 2001
Natural history of Fistulizing CD

• Only 2 Population based studies:
  – Stockholm County
  – Olmsted County

• Stockholm County 1955-1974
  – 826 new diagnoses of CD
  – Cumulative incidence of anal fistulas = 23%
  – Incidence increased with more distal intestinal disease location

Hellers G et al Gut 1980
Other 13%
Entero-enteric 24%
Recto-vaginal 9%
Perianal 54%

Schwartz DA Gastroenterology 2002
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Natural history of behaviour

N=297 CD

% of patients

Diagnosis 5 years 10 years

Inflammatory
Stricturing
Penetrating

Louis E et al Gut 2001
Over a 20 years period, 88% risk of developing stricturing (18%) or penetrating (70%) disease

Cosnes J et al Inflamm Bowel Dis 2002
Location of disease determines the behaviour!

- Ileal disease
- Colonic
  - Ileocolonic

stricturing
inflammatory
penetrating

Farmer RG Gastroenterology 1985
Louis E et al Gut 2001
Cosnes J et al Inflamm Bowel Dis 2002
Natural history of behaviour at 20 yrs

Cosnes J et al Inflamm Bowel Dis 2002
<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio</th>
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</thead>
<tbody>
<tr>
<td>Homozygous CARD15</td>
<td>7.44</td>
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<tr>
<td>Homozygous CARD15+ileal disease</td>
<td>17</td>
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</table>

Brant S et al, Inflamm Bowel Dis 2003; 9: 281-289
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At 1 year following start of CS therapy, 40% of CD and 30% of UC patients will need surgery.

Faubion et al Gastroenterology 2001

Risk factors:
- Small bowel disease
- Perianal fistulas

Risk factors for recurrence after surgery:
- Females (RR 1.2)
- Small bowel disease (RR 1.8)
- Perianal fistulas (RR 1.4)

n=1.936 CD
Disease behaviour and surgery

- 770 CD patients undergoing intestinal resection
- For perforating or non-perforating indications
  - 77% of perforating and 71% of fistulising patients who underwent a second surgery had that for the same indication than for their first operation

- Perforating disease: more rapid recurrence
- Stricturing disease: slow recurrence

Greenstein AJ et al Gut 1988
• Increases risk for CD (X2)
• More severe disease course
• Increased risk for surgery
• Increased risk for postoperative recurrence

CD

UC

• Protects against UC

NO SMOKING
## Appendectomy and risk of UC

<table>
<thead>
<tr>
<th>Sample size</th>
<th>Pooled</th>
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<tr>
<td></td>
<td>UC</td>
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<tr>
<td>Total</td>
<td>2770</td>
</tr>
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<td></td>
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</table>

*Koutroubakis & Vlachonikolis AJG 2000 Jan;95(1):171-6*

* Adjusted OR for heterogeneity
Appendectomy and disease course

N=259 UC – 20 with prior appendectomy

- No influence on:
  - disease extent
  - need for IS treatment
  - colectomy rates

Appendectomy may delay onset but not course of the disease

Selby WS Am J Gastroenterol 2002
Appendectomy and disease course

Cosnes J et al Gut 2002
Previous appendectomy (OR 0.4) and current smoking (OR 0.6) independent factors protecting against colectomy

Cosnes J et al Gut 2002
Appendectomy and disease course

- Incidence of flares assessed prospectively
- Period 1997 – 2000

Previous appendectomy is associated with less severe course of UC

Cosnes J et al Gut 2002
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Treatment goals: are we changing the natural history?

- Alleviate symptoms
- Remission
- Off steroids
- Maintenance of remission
- Mucosal healing
- Cure

Azathioprine, infliximab
Change in management

N= 2573 (565 patients seen <3 months after diagnosis)

Cosnes J et al Gut 2005
Change in management

Step up
1. 5-ASA
2. Corticoids
3. If tapering unsuccessful, start azathioprine
4. If no disease control with AZA, start anti-TNF

Top down
1. Anti-TNF: 3 infusions together with start AZA

Outcome?

Hommes D et al DDW 2005
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IBD and cancer

- Great variability in cancer incidence!

- At 30 years:
  - Hospital studies: 40% cumulative cancer rates
  - Population studies: 13.5%

- For pancolitis:
  - Hospital studies: 50% cumulative cancer rates
  - Population studies: 16.5%

Hordijk, Shivananda et al Scand J Gastroenterol 1989
UC and cancer

- 3117 UC patients
- Population-based
- FU 1-60 years after D/
- Risk groups:
  - Extensive colitis
  - Young age at onset
  - UC patients with familial risk
  - UC + PSC

The risk of colorectal cancer in patients with UC begins to increase at 8 years from diagnosis.

Two approaches to prevent:
- Total colectomy
- Endoscopic surveillance

In the absence of:
- Prospective studies
- Cost-effectiveness analyses
- Studies comparing QOL in patients with either strategy
- The choice must be made on an individual basis

Ekbom A et al Lancet 1990
Cancer surveillance: recommendations

- **UC proctitis**: no data to support special recommendations beyond those for the general population

- **Pancolitis/left-sided <8 years**: same as general population

- **Pancolitis/left-sided >8 years**: colonoscopy every 1-2 years with 2-4 biopsies every 10 cm or prophylactic colectomy
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UC and mortality

Langholz E et al Gastroenterology 1992
Winther K et al Gastroenterology 2003
Winther K et al Gastroenterology 2003
CD and mortality

<table>
<thead>
<tr>
<th>Author</th>
<th>Ref</th>
<th>Region</th>
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<td>Loftus EV Jr</td>
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<td>Palli D</td>
<td>Gut 1998</td>
<td>Florence</td>
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<td>Probert CS</td>
<td>Gut 1992</td>
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<td>Munkholm P</td>
<td>Gastroenterol 1993</td>
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<tr>
<td>Jess T</td>
<td>Gastroenterol 2003</td>
<td>Copenhagen County</td>
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<td>1.30</td>
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Graph: Cumulative survival rate (%) over years of follow-up after diagnosis.
Natural history of IBD…the answers

1. 50-60% of patients are in remission during any given year
2. 40-50% (CD) and 30% (UC) patients will need steroids during the first year
3. The location of the disease remains stable over time
4. The disease behaviour changes over time with increasing risk for stricturing/penetrating disease with longer disease duration
5. Disease location influences behaviour: ileal disease will tend to evolve towards stricturing disease and ileocolonic/colonic towards penetrating
6. Cumulative risk of surgery 15 years after D/ is 80% (CD) and 30% (UC)
7. Current therapies have not (yet) shown to alter natural history although follow up time is short and lack of prospective studies
8. Risk of colorectal cancer begins to increase 8 years after diagnosis and is greatest in patients with pancolitis and PSC
9. Life expectancy of CD patients is slightly lower (seen at longer follow up after diagnosis) and most pronounced in women <50 yrs at diagnosis
10. Life expectancy of UC patients is generally normal except for patients >50 of age and extensive colitis at diagnosis