IBD

Stool tests: Are they useful?

Ingvar Bjarnason
Professor of Digestive Diseases
King’s College Hospital
London
UK
1965-2000

- Endoscopy
- Enteroscopy (capsule, push, balloon)
- Colonoscopy

Good for diagnosis
Provide no functional information
Endoscopy
Superb for diagnosis

Transformed Gastroenterology

Provides no functional information
Why stool tests?

Neurologists
Urologists
Rheumatologists
Respiratory phys,
Gastroenterologists

CSF
Urine
Synovial fluid
Sputum

Stool analyses provide direct information on the gastrointestinal tract
Faecal stool tests: Potential uses

- To distinguish between IBD and IBS
- To assess laboratory disease activity in IBD
- To assess responses to treatment
- To assess prognosis of disease
- Research uses
The history of stool tests

- Coproscopy:
  - Visual stool examination practiced since antiquity
  - Microscopy for parasites, white cells, etc.
- Faecal fats, radioisotopic tests (RBC, proteins, etc.)
- Radioimmunoassay + ELISA
  - Tumor necrosis factor
  - Myeloperoxidase
  - Lactoferrin
  - Calprotectin
Intestinal inflammation

- 111Indium White Cells
- Abdominal scintigraphy
- 4 day faecal 111Indium excretion

Results
- 100% sensitive for detection of IBD
- Faecal excretion correlates with histological and clinical disease activity indices in Crohn’s and UC
Validation:

Faecal calprotectin
Faecal lactoferrin

Validation against 111In White cells
Equal sensitivity

Angriman et al Clin Chim Acta 2007 in press
Langhorst et al. Inflamm Bowel Dis 2005;11:1085-1091
Calprotectin v. 111IndWBC

- Faecal calprotectin excretion over 4 days (mg)
- Calprotectin concentration in single stool (mg/L)

4 day faecal 111Indium excretion

- 3800
- 1487
Faecal Calprotectin con.

- 116 patients with Crohn’s disease
- Various disease activity
Faecal Calprotectin

Can we discriminate between Patients with and without Intestinal inflammation?

602 (-275) = consecutive patients referred with lower GI symptoms to GI outpatients that required imaging

Tibble et al. Gastroenterology 2002;123:450-460
<table>
<thead>
<tr>
<th>Test</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calprotectin</td>
<td>27.8</td>
</tr>
<tr>
<td>Intestinal permeability</td>
<td>8.9</td>
</tr>
<tr>
<td>CRP</td>
<td>4.2</td>
</tr>
<tr>
<td>ESR</td>
<td>3.2</td>
</tr>
<tr>
<td>ROME = IBS</td>
<td>13.3</td>
</tr>
<tr>
<td>Normal Calp. + ROME</td>
<td>&gt; 50</td>
</tr>
</tbody>
</table>
Normal calpro and + ROME

- Virtually excludes organic intestinal disease
- Does not warrant any diagnostic imaging
Calprotectin predicts relapse in asymptomatic IBD

- 81 asymptomatic patients underwent the calprotectin test
- Follow up for 1 year
- 55% relapsed

- Faecal calprotectin
- Relapse: 122 mg/L
- Non-rela: 36 mg/L

- At 50 mg/L the test has 90% sensitivity and 83% specificity for predicting relapse

Tibble et al Gastroenterology 2000;119:15-22
Costa et al GUT 2005;54:364-368
Calprotectin as a predictor of relapse in IBD

Gastroenterology 2000;119:15-22

![Graph showing the relationship between calprotectin levels and relapse in IBD over time.](image)

- U.C < 250 mg/L
- C.D < 250 mg/L
- U.C > 250 mg/L
- C.D > 250 mg/L

**p < 0.0001**
Calprotectin predicts relapse in asymptomatic patients with IBD

Can we treat these at risk patients and Prevent the clinical relapse?
Study Design

- Open, prospective, randomised controlled trial
- Number of patients: 66
- Asymptomatic with calprotectin > 250

<table>
<thead>
<tr>
<th>Screening</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Evaluation visits Month 2-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Unchanged treatment</td>
</tr>
</tbody>
</table>
## Remission in Month 6

<table>
<thead>
<tr>
<th></th>
<th>Adacolumn</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>21 (72%)</td>
<td>10 (32%)</td>
</tr>
<tr>
<td>Relapse</td>
<td>8 (27%)</td>
<td>21 (68%)</td>
</tr>
</tbody>
</table>
Survival analysis

\[ p < 0.05 \]

Method: Mantel-Haenszel

GROUP
- Ada
- Unchanged
New indication for treatment in IBD

- Calprotectin identifies a group of patients at significant risk of clinical relapse
- Treatment reduces relapse rates
- Asymptomatic patients with calprotectin < 250 may not need continuous 5-ASA etc.
Treatment of established active IBD
Calprotectin in a patient with CD receiving Remicade (Infliximab)
Calprotectin and CRP levels in patients with CD before and after Remicade
Calprotectin levels in IBD patients with active disease and during mucosal healing

Calprotectin mg/L
Log scale

Crohn’s disease
active / remission

Ulcerative colitis
active / remission

* p< 0.0001

Mucosal healing

Scand J Gastro 2004
Faecal calprotectin

- Active IBD
- Prednisolone
- Elemental diet
- Azathioprine
Research uses: Effect of NSAIDs on IBD

Case reports

- Cause relapse of Crohn’s and UC
- Occurs within a week of treatment
- Seen with indomethacin, naproxen, diclofenac, etc.
Prevalence of relapse of IBD with NSAIDs

Patients with quiescent IBD

Relapse (%)
50
40
30
20
10
0

Paracetamol (n = 26)
Naproxen (n = 32)
Diclofenac (n = 29)
Indomethacin (n = 22)

Within 9 days of taking the drugs

Mechanism of relapse

80 patients with IBD taking NSAIDs

<table>
<thead>
<tr>
<th>Drug</th>
<th>COX-1</th>
<th>COX-2</th>
<th>Topical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Naproxen</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nabumetone</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>

Relapse defined clinically (CDAI)
Inflammation by calprotectin
Paracetamol

Naproxen

Nabumetone

Nimesulide

Fecal Calprotectin

Week 0 1 4

Paracetamol

Naproxen

Nabumetone

Nimesulide

Fecal Calprotectin

Week 0 1 4

Fecal Calprotectin

Week 0 1 4
Research uses: Subclinical intestinal inflammation in IBD relatives
49 patients and 151 of their 220 (58%) first degree relatives were studied for the presence of intestinal inflammation by the faecal caplropectin test.

49% of relatives had intestinal inflammation.

Inheritance pattern = additive trait
Variant component analyses

Ankylosing spondylitis: Prevalence of intestinal inflammation

Ileocolonoscopy
Mielantis & Veys: 354 patients
Ileal inflammation was found in 40-80%

Ileal biopsies showed the same prevalence and type of abnormality as in ileal Crohn’s disease
Intestinal inflammation in AS relatives

- 47 and 124 of 213 (58%) first degree relatives were studied for the presence of intestinal inflammation

41% of relatives had intestinal inflammation

Inheritance pattern = additive trait
Variant component analyses

Gastroenterology. 2003;125:1598-1605
Subclinical intestinal inflammation

- First degree relatives of patients with Crohn’s disease and AS have a “common” genetic abnormality that results intestinal inflammation
Are AS and IBD patients related?

- The three following databases were assessed for the purpose of this study:
  - 1. Genealogic information on 610,920 people in Iceland during the past 11 centuries
  - 2. All living Icelanders diagnosed with AS (n=205)
  - 3. All living Icelanders diagnosed with IBD (n=1384)
- The relative risk for AS and IBD was assessed by comparison with 10,000 random sample from the Icelandic population. A cross-risk ratio was used to estimate possible relatedness between the AS and the IBD cases. A kinship coefficient (KC) for AS and IBD was estimated.
AS and IBD patients are related

SUMMARY

- Relative risk IBD-first degree
  - IBD-IBD 4.4
  - AS-AS 96
  - AS IBD 3.3
- Relative risk falls off rapidly = compatible with additive genes
- The KC of the IBD+AS patients was $12.9 \times 10^{-5}$ and control group ($8.5 \times 10^{-5}$) ($p=0.0001$). 1st – 7th meiosis, the KC of the IBD+AS patients remained significantly larger than the KC of the control group.
Pathogenesis?

Similar genetic factors \[\rightarrow\] Subclinical intestinal inflammation

Environmental factors?

AS \[\rightarrow\] Crohn’s
Faecal tests provide direct functional data

- Can be used for diagnostic screening (IBD v IBS)
- Useful for assessing disease activity in IBD
- Useful for assessing responses to treatment
- Provide prognostic information in IBD (altering clinical practice)
- Unlimited research potential!