Inflammatory Bowel Disease

Jeremy Nightingale
Consultant Gastroenterologist
St Mark’s Hospital, Harrow
Art of managing IBD

Professor John Lennard-Jones
Ulcerative Colitis

- Chronic relapsing diarrhoea (nocturnal) with blood / mucus / urgency
- Inflammation of colon mucosa
- Starts in rectum

- Incidence 10 / 100,000
- Prevalence 240 / 100,000
Crohn’s Disease

- Chronic relapsing abdominal pain / diarrhoea / weight loss / reduced growth
- Transmural inflammation of bowel with granulomas
- Affects mouth to anus
- Skip lesions
- Fistulas / strictures
- Incidence 6 / 100,000
- Prevalence 145 / 100,000
Mechanism of Crohn’s Disease

Apthous ulcer

Transmural inflammation

Deep fissure
Abscess
Fistula
Surgery in 2 - 4 years

Mucosal hypertrophy
Fibrosis

Stricture
Surgery in 8 - 10 years
Evolution of Crohn’s Phenotypes over 20 years (n = 2002)

Cosnes J et al. Inflamm Bowel Dis 2002; 8: 244-50

Twenty-year actuarial rates were:
- inflammatory: 12%
- stricturing: 18%
- penetrating: 70%
Inflammatory Bowel Disease
Extra-intestinal Manifestations

Skin
- Erythema nodosum
- Pyoderma gangrenosum

Eyes
- Episcleritis / iritis

Joints
- Arthropathy
- Sacro-iliitis/ ankylosing spondylitis

Liver
- Sclerosing cholangitis
  (cholangiocarcinoma)
# Inflammatory Bowel Disease

## Aetiological factors

<table>
<thead>
<tr>
<th></th>
<th>Ulcerative colitis</th>
<th>Crohn’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Genetic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>identical twins</td>
<td>1/17</td>
<td>8/18</td>
</tr>
<tr>
<td></td>
<td>CARD15 / NOD2</td>
<td></td>
</tr>
<tr>
<td><strong>Environmental</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>smoking</td>
<td>non-smokers</td>
<td>smokers</td>
</tr>
<tr>
<td>season</td>
<td>spring / autumn</td>
<td></td>
</tr>
<tr>
<td>anatomy</td>
<td>appendix present</td>
<td>faecal stream</td>
</tr>
<tr>
<td>infection</td>
<td>sulphate reducing bacteria</td>
<td>mycobacteria</td>
</tr>
<tr>
<td></td>
<td>CMV</td>
<td></td>
</tr>
<tr>
<td>diet</td>
<td>milk</td>
<td>refined sugar</td>
</tr>
<tr>
<td>society</td>
<td>Western / urban</td>
<td>Western / urban</td>
</tr>
<tr>
<td>stress</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Autoimmune</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>anti-colon antibodies</td>
<td></td>
<td>reduced macrophage function</td>
</tr>
</tbody>
</table>
Assessment of IBD

Exclude infection

Ulcerative Colitis
- Extent
- Severity

Crohn’s Disease
- Locations
- Behaviour
- Activity

Nutrition
Complications
Extent of Ulcerative Colitis

Montreal Classification. Gut 2007

Extensive colitis
E3

(Pancolitis)

Left- sided colitis
E2

(Procto-sigmoiditis)

Proctitis
E1
## Severity of Ulcerative Colitis


**Montreal Classification. Gut 2007**

<table>
<thead>
<tr>
<th></th>
<th>Severe</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea (stool/day) *</td>
<td>&gt;6 + blood</td>
<td>&lt;4 +/- blood</td>
</tr>
<tr>
<td>Evening Temp (°C) *</td>
<td>&gt;37.5</td>
<td></td>
</tr>
<tr>
<td>Heart rate (min) *</td>
<td>&gt;90</td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>tender</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin*</td>
<td>&lt; 10 gm / dl</td>
<td></td>
</tr>
<tr>
<td>ESR*</td>
<td>&gt;30 mm / hr</td>
<td></td>
</tr>
<tr>
<td>Albumin</td>
<td>&lt; 35 g / l</td>
<td></td>
</tr>
<tr>
<td>Abdominal x-ray</td>
<td>mucosal islands</td>
<td>dilated abnormal colon</td>
</tr>
</tbody>
</table>

**Moderate:** “between severe and mild”

with 4 - 6 stool / day
### Treatment of Mild / Moderate Left Sided Ulcerative Colitis / Proctitis

**Bowel with colitis**

<table>
<thead>
<tr>
<th>Location</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>suppository*</td>
</tr>
<tr>
<td>Rectum and sigmoid</td>
<td>foam*</td>
</tr>
<tr>
<td>Rectum, sigmoid and descending colon</td>
<td>liquid enema*</td>
</tr>
</tbody>
</table>

*: Aminosalicylate or non-absorbable steroid
Treatment of Mild / Moderate Extensive Ulcerative Colitis

Ulcerative colitis Management in adults, children and young people.
June 2013, NICE clinical guideline 166

- Mesalazine (5 amino-salicylic acid)

- Prednisolone or Beclometasone dipropionate
  Campieri M et al. Aliment Pharmacol Therap 2003; 17:1471-1480

- Thiopurine (Azathioprine / 6-Mercaptopurine)

- Calcineurin inhibitor (Tacrolimus)
Treatment of Extensive Ulcerative Colitis

Mesalazine

Asacol®

2.4 gm bd

Pentasa®

2-3 gm bd
Thiopurine Pathway

Hepatotoxicity

6-MMP

6-MTIMP

Immunosuppression
Bone marrow toxicity

Glutathione

Thiopurine methyl transferase (TPMT)

AZA → 6-MP → 6-TIMP → 6-TGN

If 6-TG > 235 pmol / 10^8 RBC
62% remission
Osterman MT et al. Gastroenterology 2006; 130:1047-53

Xanthine oxidase

6-Thiouric acid
Severe Extensive Ulcerative Colitis
Severe Extensive Ulcerative Colitis

Mesalazine
IV steroids
Surgical reviews
(LMWH / Antibiotics)

What next when no response at 3-5 days?
Severe Extensive Ulcerative Colitis

- Antiviral (CMV)
- Ciclosporin
- Infliximab
  (Adalimumab, Golimumab, Vedolizumab)
Comparison of Ciclosporin and Infliximab in Severe Ulcerative Colitis refractory to Intravenous Steroids


<table>
<thead>
<tr>
<th></th>
<th>Ciclosporin (n=58)</th>
<th>Infliximab (n=57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical response at day 7</td>
<td>50 (86%)</td>
<td>48 (84%)</td>
</tr>
<tr>
<td>Colectomy at 3 months</td>
<td>17%</td>
<td>21%</td>
</tr>
</tbody>
</table>
Disease Location and Behaviour in Crohn’s Disease. Olmsted County, Minnesota from 1970 to 2004

Thia KT et al. Gastroenterology 2010; 139: 1147-55

Location

Behaviour

2 / 3 have terminal ileal disease
Activity of Crohn’s Disease

CDAI: *Gastroenterology* 1976;70:439-444

Harvey-Bradshaw: *Lancet* 1980;I:514

- Stool frequency
- Abdominal pain
- General well being
- Complications
- Abdominal mass
- Antidiarrhoeal drugs *
- Haematocrit *
- Weight *

* : CDAI only
Is there active Crohn’s disease or a chronic stricture?

- History
- Examination
- Inflammatory markers
  - platelets
  - albumin
  - CRP
  - Faecal calprotectin
- Radiology
Low Fibre Diet

_Avoid_

Vegetables / fruit
Nuts
Wholemeal products

_Eat_

Dairy products
Refined flour
Potato without skin
Meat / fish
Jelly
Soups / drinks

_Good teeth_
Balloon Dilatation

Successful in 76% over 44 (1-103) months

Mueller et al. Aliment Pharmacol Ther 2010; 31: 634-9
Treatment of Active Crohn’s Disease

- Stop smoking
- Mesalazine (colonic disease only)
- Antibiotics
- Steroids (Prednisolone or Budesonide)
- Immunosuppressive drugs (Azathoprine / 6MP / Methotrexate) (Infliximab, Adalimumab, Vedolizumab)
- Nutrition (liquid diets)
Recommended as treatment options for:

• Adults with severe active or active fistulising Crohn’s disease.

• Disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy.

• Given as a planned course of treatment until treatment failure (including the need for surgery), or until 12 months after the start of treatment, whichever is shorter.

• Disease should be reassessed and treatment only be continued if clear evidence of on-going active disease.
Improving Efficacy of Biological Drugs

• Earlier treatment
• Combine with Immunosuppressive drug
• Reduce time between doses / increase dose
• Measure - blood levels
  - antibodies
• Change to another biological drug
Oral Supplements for Crohn’s Disease

Harries AD et al. Lancet 1983; i: 887-90

29 undernourished patients

2 months cross-over study

Normal diet

V

Normal diet plus supplement (Ensure plus®) = 3000 kcal / day
Oral supplements for Crohn’s Disease

Harries AD et al. Lancet 1983; i: 887-90

**Nutrition**

↑ weight *

↑ mid-arm muscle circumference *

**Inflammation**

↓ serum orosomucoid *

↑ albumin *

* p< 0.05
Complications of IBD

- Tiredness
- Strictures and fistulas
- Anaemia (Fe, B₁₂ or folate)
- Malnutrition / short bowel
- Growth failure (in children)
- Gallstones and renal stones
- Amyloid
- Neoplasia
  - Colonic and sites of chronic inflammation
  - Sclerosing cholangitis
  - Thiopurine related (skin and lymphoma)
- Psychological effects
Enterocutaneous fistula(s)
Acute Intestinal Failure Management
Enterocutaneous Fistula(s)

• **Immediate**
  - Water / electrolytes (Na⁺, Mg²⁺)
  - Sepsis
  - Wound management
  - Pain control

• **Early**
  - Nutrition (refeeding risks)
  - Reduce stoma / fistula output
  - Psychosocial
  - Mobility

• **Late**
  - Anatomy - mapping - fistula - site / drainage - gut - length / quality
  - Procedure – Not days 10 – 100
  - Disease treatment
Intestinal Failure

Main diagnoses:

Abdominal surgery: Date(s):

ANATOMY

Remaining small bowel length: cm

Urological

Gynaec

Other problems:

Venous
Types of Patient with a Short Bowel

Jejunum-colon

Jejunostomy
## Risk of Developing Colorectal Cancer in Ulcerative Colitis or Crohn’s Colitis

*NICE clinical guideline 118 – Colonoscopic surveillance 2011*

<table>
<thead>
<tr>
<th>Years</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>30</td>
<td>18</td>
</tr>
</tbody>
</table>

### Highest risk

- extensive colitis
- moderate or severe active inflammation
- primary sclerosing cholangitis
- colonic stricture in the past 5 years
- dysplasia in the past 5 years
- colorectal cancer in first-degree relative < 50 years
# Course of Ulcerative Colitis

<table>
<thead>
<tr>
<th>Description</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>intermittent attacks</td>
<td>60 - 75</td>
</tr>
<tr>
<td>Single attack</td>
<td>4 - 10</td>
</tr>
<tr>
<td>Continuous trouble</td>
<td>5 - 15</td>
</tr>
</tbody>
</table>

*Recto-sigmoid disease*

Becomes extensive 5 - 15
Colectomy for Ulcerative Colitis

Failed medical therapy acute attack chronic ill-health

Dysplasia / carcinoma

35% with total colitis have colectomy within 25 years
Clinical Course - Crohn’s Disease

**Medical therapy**
60% relapse within a year (pre-azathioprine)

**Surgical therapy***
30 - 35% have surgery within 3 years
70% lifetime risk of surgery
50 - 60% relapse within 10 years of surgery
half of these have repeat surgery

Usually recurs at resection site

*: resection, stricturoplasty or defunctioning
Summary

- **Ulcerative Colitis**
  - Extent and severity
  - Topical therapy for left sided disease
  - Mesalazine and immunosuppressive drugs for extensive disease
  - Ciclosporin after IV steroids

- **Crohn’s Disease**
  - Sites, behaviour and activity
  - Active - mesalazine, immunosuppressive drugs, nutrition and biologicals. STEP UP
  - Strictures - low fibre diet, balloon dilatation
  - Enterocutaneous fistula(s) treat sepsis and wait

Multidisciplinary Team
Surgery for Crohn’s Disease

Close liaison between physician and surgeon

Before surgery

• Treat sepsis (drain abscess)
• Improve nutrition
• Define anatomy

Surgery

• Resection
• Stricturoplasty
• Defunction
Early Treatment of IBD

Infliximab

“top-down” Vs “step-up”

5 ASA
## Nutritional Assessment

**Malnutrition Universal Screening Tool (MUST)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg / m^2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>18.5 - 20</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>% WL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5 - 10</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>ill + no food</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5 days</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

1: *medium risk*, 2+: *high risk*
Follow-up of Inflammatory Bowel Disease

Annual review / SOS
6 monthly review if on azathioprine

Current state (weight, activity)
Complications (illness or treatment)
  Anaemia
  Kidney / Liver tests
  Cancer
Actions before Immunosuppressive Therapy
Rahier JF et al. (ECCO) J Crohns Colitis 2014; 8: 443-68

- TPMT testing
- Current infection (dormant)
  - HIV, Hep B, C, Varicella, EBV
  - Chest X-ray / IGRA or Quantiferon *
- Vaccination
  - Varicella or Hep B if sero-negative
  - Pneumocococcus
  - Influenza (annually)
  - HPV (regular cervical smears)
  - Travel - dead vaccines (Hep A)

*: Anti-TNF therapy
Malignancies

- Increased risk of colorectal cancer – surveillance colonoscopies
  - 10 years pan-colitis
  - 15 years for left sided colitis
Mortality with Clostridium *difficile* in patients with IBD
Ananthakrishnan AN et al. Gut 2008;57: 205-10

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n</th>
<th>mortality odds ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD</td>
<td>77,366</td>
<td>1.0</td>
</tr>
<tr>
<td><em>C. difficile</em></td>
<td>44,400</td>
<td>2.2</td>
</tr>
<tr>
<td>IBD + <em>C. difficile</em></td>
<td>2,804</td>
<td>4.7</td>
</tr>
</tbody>
</table>

Don’t forget stool microscopy and culture
# Placebo Response in Ulcerative Colitis


<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Improved</strong></td>
<td>%</td>
</tr>
<tr>
<td>Clinically</td>
<td>52</td>
</tr>
<tr>
<td>Sigmoidoscopically</td>
<td>59</td>
</tr>
</tbody>
</table>

- **11** controlled trials
- **185** patients
- **2 - 6 weeks**
Compliance with Treatment in Patients with Ulcerative Colitis

*Bernal I et al. Dig Dis Sci 2006;51: 2165-9*

<table>
<thead>
<tr>
<th>Not taking</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short - term</td>
<td>20</td>
</tr>
<tr>
<td>Long - term</td>
<td>50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Forget &gt;1 dose / week</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Oral mesalazine</td>
<td>45</td>
</tr>
<tr>
<td>- Azathioprine</td>
<td>25</td>
</tr>
</tbody>
</table>
Endoscopic balloon dilatation of strictures

Mueller et al. Aliment Pharmacol Ther 2010; 31: 634-9

- 55 patients, 93 balloon dilations.
- Terminal ileum 39, ileo-caecal 17.

- Successful in 76% over 44 (1-103) months.

- 24% required surgery. All had de novo strictures in the terminal ileum and were significantly longer than ileal strictures that responded to endoscopic treatment. 7.5 (1-25) cm vs. 2.5 (1-25) cm; p = 0.006.