Anaemia and GI Blood Loss

Dr Satish Keshav DPhil FRCP
John Radcliffe Hospital
Nuffield Dept of Medicine
University of Oxford
Mr T J, age 85
Dizzy and unwell – August in France.
No dyspepsia.
No wt loss.
No change in bowel habit.
On Aspirin 75mg.
Hb 7 and low MCV.
History

- Transfused 3 units of Blood.
- Symptoms improved.
- Aspirin stopped.
- Not on any other medications
- In UK, noticed melaena intermittently.
History

- Perforated DU in 1940s after the war.
- Normal Ba enema- 1993.
Unremarkable apart from abdominal scar

- Hb 10.4  MCV 76  MCHC 23 ↓
- Iron 6.8  Sat. 9%  Ferritin 14 ↓
- Urea 7  Cr 93  normal LFT  INR 1
- TTG Ig A Ab < 1
- GI investigations
Upper Endoscopy
Healing antral ulcer
Colonoscopy
89 patients with Occult blood loss.
- 34 had Oesophagitis, Gastritis or gastric erosions
- 13 had colon cancer
- No diagnosis was established in 14 patients.
- 8 patients had concurrent upper GI and Ca Colon
- Most of them had no symptoms of colonic disease.
- The presence of proximal lesion should not preclude evaluation of the colon.

BMJ 1997 Jan 18;314(7075):206-8
### Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>13%</td>
<td></td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>10%</td>
<td></td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>All Other Sites</td>
<td>17%</td>
<td></td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.

Source: American Cancer Society, 2005.
## Probability of CRC

<table>
<thead>
<tr>
<th></th>
<th>Birth to 39 (%)</th>
<th>40 to 59 (%)</th>
<th>60 to 79 (%)</th>
<th>Birth to death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>.07 (1 in 1484)</td>
<td>.90 (1 in 111)</td>
<td>3.96 (1 in 25)</td>
<td>5.90 (1 in 17)</td>
</tr>
<tr>
<td>Females</td>
<td>.06 (1 in 1586)</td>
<td>.69 (1 in 145)</td>
<td>3.04 (1 in 33)</td>
<td>5.54 (1 in 18)</td>
</tr>
</tbody>
</table>

Modified from American Cancer society, Surveillance research, 2005
Beginning at age 50, men and women should follow one of the following examination schedules:

- A fecal occult blood test (FOBT) every year
- A flexible sigmoidoscopy (FSIG) every five years
- Annual fecal occult blood test and flexible sigmoidoscopy every five years*
- A double-contrast barium enema every five years
- A colonoscopy every ten years

*Combined testing is preferred over either annual FOBT, or FSIG every 5 years alone.

People who are at moderate or high risk for colorectal cancer should talk with a doctor about a different testing schedule
GI Bleeding

• GI bleeding may originate anywhere from the mouth to the anus and may be overt or occult.
  • Hematemesis or emesis with red blood indicates an upper GI source of bleeding (almost always above the ligament of Treitz) that is often brisk, usually from an arterial source or varix.
  • "Coffee grounds" result from bleeding that has slowed or stopped, with conversion of red Hb to brown hematin by gastric acid.
  • Hematochezia usually indicates lower GI bleeding but may result from vigorous upper GI bleeding with rapid transit of blood through the bowels.
  • Melena typically indicates upper GI bleeding, but a small-bowel or right colon bleeding source may also be the cause.
• About 100 to 200 mL of blood in the upper GI tract is required to produce melena, which may continue for several days after severe hemorrhage and does not necessarily indicate continued bleeding.
### Causes of GI Bleeding

#### Upper GI tract
- Duodenal ulcer: (20–30%)
- Gastric or duodenal erosions: (20–30%)
- Varices: (15–20%)
- Gastric ulcer: (10–20%)
- Mallory-Weiss tear: (5–10%)
- Erosive esophagitis: (5–10%)
- Angioma: (5–10%)
- Arteriovenous malformation: (< 5%)

#### Lower GI tract (percentages vary with the age group sampled)
- Diverticular disease
- Colonic carcinoma
- Colonic polyps
- Inflammatory bowel disease: ulcerative proctitis/colitis, Crohn’s disease, infectious colitis
- Colitis: radiation, ischemic
- Angiodysplasia (vascular ectasia)
- Internal hemorrhoids
- Anal fissures

#### Small-bowel lesions
- Meckel’s diverticulum, tumors, angioma, arteriovenous malformations
Causes of GI Bleeding
## Causes of GI Bleeding

<table>
<thead>
<tr>
<th>Age</th>
<th>&lt;60yr</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>60-79 yr</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>&gt;80 yr</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

### Shock

- None 0
- Pulse >100
- Syst BP <100 2

### Co-morbidity

- None 0
- Cardiac failure, or any major comorbidity 2
- Dissemin. Malignancy 3

### Endoscopic diagnosis

- M-W tear, no lesion seen 0
- All other diagnoses 1
- Malignancy of upper GI 2

### Stigmata of recent haemorrhage (SRH)

- None, or dark spots only 0
- Blood in upper GI tract 1
- Adherent clot, visible 2

### Predicted Mortality

<table>
<thead>
<tr>
<th>Initial Risk Score</th>
<th>Final Risk Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-endoscopy</td>
<td>Post-endoscopy</td>
</tr>
<tr>
<td>0</td>
<td>0.2%</td>
</tr>
<tr>
<td>1</td>
<td>2.4%</td>
</tr>
<tr>
<td>2</td>
<td>5.6%</td>
</tr>
<tr>
<td>3</td>
<td>11.0%</td>
</tr>
<tr>
<td>4</td>
<td>24.6%</td>
</tr>
<tr>
<td>5</td>
<td>39.6%</td>
</tr>
<tr>
<td>6</td>
<td>48.9%</td>
</tr>
<tr>
<td>7</td>
<td>50.0%</td>
</tr>
<tr>
<td>8+</td>
<td>-</td>
</tr>
</tbody>
</table>
Causes of GI Bleeding
Causes of GI Bleeding
Causes of GI Bleeding
Causes of GI Bleeding
Causes of GI Bleeding
Causes of GI Bleeding

[Images of digestive tract]
Causes of GI Bleeding
Ulcerative colitis and Crohn’s disease = IBD

- Prevalence: 150:100 000
- Incidence: 5-15:100 000
- Incidence of Crohn’s rising year on year
- Presents at any age, commonest in 3rd decade
- 25% diagnosed before age 18 years
- Crohn’s most prevalent in westernized countries
- Ulcerative colitis distributed worldwide
Ulcerative colitis & Crohn’s
Ulcerative colitis & Crohn’s

Ulcerative colitis & Crohn’s disease

**Ulcerative colitis**
- From rectum to variable distance proximally
- Mucosal inflammation only
- Neutrophils, eosinophils, lymphocytes
- Antibody responses to colonic antigens
- Moderate systemic inflammatory response

**Crohn’s disease**
- May involve any part of bowel, non-contiguous
- Transmural inflammation
- Lymphocytes and macrophages, granulomas
- Antibody responses to enteric organisms/antigens
- Marked systemic inflammatory response
Anaemia is common in IBD

Prevalence at diagnosis 32 %
Sjöberg D et al. Sv gastrodagarna 2011:

- Prevalence in outpatients with IBD

Anaemia
- Hb < 130 g/l ♂
- Hb < 120 g/l ♀

## Causes of anaemia in IBD

<table>
<thead>
<tr>
<th>Common</th>
<th>Occasional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Vitamin B\textsubscript{12} deficiency</td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>Folate deficiency</td>
</tr>
<tr>
<td>Drug-induced (sulfasalazine, thiopurines)</td>
<td>Drug-induced (sulfasalazine, thiopurines)</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Myelodysplastic syndrome</td>
</tr>
<tr>
<td>Aplasia (often drug-induced)</td>
<td>Inborn hemogobinopathies or disorders of erythropoiesis</td>
</tr>
</tbody>
</table>
CRP and Fe levels distinguish anaemia in CD and UC

Scattergram and medians of CRP and Fe in CD and UC

** P<0.05

Sivanesan S et al unpublished data
CRP, Fe, %Saturation, Ferritin in CD and UC

Scattergram and medians of CRP, Fe, %Satn, Ferritin in CD and UC

** P<0.05

Sivanesan S et al unpublished data
Anaemia in Ileo-anal Pouch

117 Patients with ileo-anal pouches, >12 months after surgery

Mean Hb: 12.8g/dl (+/-1.9) (range: 6.6 - 16.4)
Mean ferritin: 64.0μg/l (+/-86.1) (range: 2.9 - 433.5)

Anaemia: 35.9% (42/117)
Microcytosis: 17.1% (20/117)
Hypoferriataemia: 21.6% (16/117)

B12 deficiency: 5.3%
Folate deficiency: 12.1%

Gilchrist J, Amin, I et al unpublished data
Ulcerative colitis
Anaemia in IBD

INFLAMMATION

Bleeding
Anaemia in IBD

- Bleeding
- INFLAMMATION
- TNF-α
- IFN-γ
- IL-1
- EPO
Hepcidin

Iron Availability

Bleeding

IL-6

Reduced Iron absorption

Oral Iron

TNF-α
IFN-γ
IL-1

EPO

INFLAMMATION

Bleeding
**Hepcidin**

**Iron Availability**

**Bleeding**

**IL-6**

**Reduced Iron absorption**

**Oral Iron**

**Iron sequestration**

**ANAEMIA**

**Oral Iron**

**EPO**

**Bleeding**

**TNF-α**

**IFN-γ**

**IL-1**

**INFLAMMATION**
Iron uptake and use

- Dietary iron: 1-2 mg/day
- Iron uptake in the duodenum:
  - Plasma
  - TF-Fe(III)
- Iron uptake in macrophages:
  - Fe(II)
  - DMT1
  - DCYTB
  - Ferritin
  - Hephaestin
- Excess iron:
  - Liver
  - Fe(II)
  - Fe(III)

Iron utilization:
- Red blood cells
- Ferritin
- Hephaestin

Iron homeostasis: Ferroportin

20-30 mg/day
Iron uptake and use blocked

Hepcidin
Serum Ferritin in IBD

Serum Ferritin (µg/L)

A: In the absence of inflammation:

Definite  Probable  Unlikely  Excluded

B: In the presence of inflammation:

Definite  Highly probable  Probable  Possible  Unlikely  Excluded
FIGURE 2. Correlation between hemoglobin concentrations and quality-of-life questionnaire (CCVEII-9) score.
### Intravenous Iron Therapy

<table>
<thead>
<tr>
<th>Trade names(^b) (US, Europe)</th>
<th>High MW Iron Dextran</th>
<th>Low MW Iron Dextran</th>
<th>Iron Gluconate</th>
<th>Iron Sucrose</th>
<th>Ferric Carboyx-maltose(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer</td>
<td>Luitpold Pharmaceuticals</td>
<td>Cosmofer Pharmacosmos</td>
<td>Sanofi-Aventis</td>
<td>Venofer Int.</td>
<td>Vifo Int.</td>
</tr>
</tbody>
</table>

**Chemical properties\(^c\)**

<table>
<thead>
<tr>
<th>MW [kD]</th>
<th>Complex stability</th>
<th>Acute toxicity</th>
<th>Dosing(^b)</th>
<th>Test dose required</th>
<th>Maximal dose</th>
<th>Max. infusion time</th>
<th>Max. injectable single dose</th>
<th>Max. injection time</th>
<th>Safety profile(^d)</th>
<th>Risk of dextran-induced anaphylaxis</th>
<th>Relative risk of serious adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>265</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td>62.5–125 mg</td>
<td>360 min</td>
<td>100 mg</td>
<td>10 min</td>
<td>Yes</td>
<td>Yes</td>
<td>High</td>
</tr>
<tr>
<td>165</td>
<td></td>
<td></td>
<td></td>
<td>Yes</td>
<td></td>
<td>360 min</td>
<td>100 mg</td>
<td></td>
<td></td>
<td>Yes</td>
<td>Moderate</td>
</tr>
<tr>
<td>&lt; 50</td>
<td>Low</td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes(^a)/No</td>
<td>Low</td>
</tr>
<tr>
<td>30–100</td>
<td>Moderate</td>
<td>Medium</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Yes(^a)/No</td>
<td>Lowest</td>
</tr>
<tr>
<td>&gt; 100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n.a.</td>
</tr>
</tbody>
</table>

---

\(^a\) Calcium ferrocyanide

\(^b\) Intramuscular administration

\(^c\) Total iron content

\(^d\) Adverse events

---

*Note: The table compares different iron therapy options, including their chemical properties, dosing requirements, and safety profiles.*
**Table 2.** Number (%) of patients with normal levels of hemoglobin, serum ferritin, or transferrin saturation after iron replacement therapy

<table>
<thead>
<tr>
<th></th>
<th>Hb ≥ 12/13 g per 100 ml</th>
<th>Ferritin ≥ 100 μg/l</th>
<th>Ferritin ≥ 30 μg/l</th>
<th>TFS ≥ 16%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Crohn study</strong></td>
<td>31 (79.5)</td>
<td>37 (94.9)</td>
<td>39 (97.5)</td>
<td>30 (76.9)</td>
</tr>
<tr>
<td><strong>Colitis study</strong></td>
<td>14 (70.0)</td>
<td>14 (70.0)</td>
<td>16 (80.0)</td>
<td>6 (30.0)</td>
</tr>
<tr>
<td><strong>Predict study</strong></td>
<td>11 (37.9)</td>
<td>25 (86.2)</td>
<td>29 (100.0)</td>
<td>5 (17.9)</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td>56 (63.6)</td>
<td>76 (86.4)</td>
<td>84 (95.5)</td>
<td>41 (47.1)</td>
</tr>
</tbody>
</table>

Hb: hemoglobin; TFS: transferrin saturation.
Data are presented as n (%).
Iron deficiency anaemia in GI disease is potentially serious:
- Always consider Colon Cancer, especially in those over 50
- Consider unusual causes
- Consider specialist referral

Iron deficiency in GI disease is not only due to bleeding:
- Inflammation may reduce iron absorption
- Consider coeliac disease!
- Is the diet adequate?

Therapy of iron deficiency is evolving:
- Iron deficiency is not corrected by blood transfusion
- Intravenous iron is a viable option
- Monitor and maintain treatment