Iron deficiency anaemia in IBD

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Outline

- Epidemiology
- Terminology
- Basic science
  - Iron homeostasis
  - Bowel mucosal injury
- Clinical features
- Diagnosis
- Treatment

Introduction

- Anaemia is the commonest EIM
- Found more in hospitalized and newly diagnosed patients
- Iron deficiency most prevalent cause of anaemia
- More common in Crohn’s than UC
- Must be diagnosed and treated early

Table 3.2 ***Global anaemia prevalence and number of individuals affected***

Population group	Prevalence of anaemia		Population affected	
	Percent	95% CI	Number (million)	95% CI
Preschool-age children	47.4	45.7-49.1	293	283-303
School-age children	25.4	19.9-30.9	305	238-371
Pregnant women	41.8	39.9-43.8	56	54-59
Non-pregnant women	30.2	28.7-31.6	468	446-491
Men	12.7	8.6-16.9	260	175-345
Elderly	23.9	18.3-29.4	164	126-202
Total population	**24.8**	**22.9-26.7**	**1620**	**1500-1740**

Anaemia definition

- Children 6 months to <5 years: 11 g/dL
- Children 5 to <12 years: 11.5 g/dL
- Children 12 to <15 years: 12 g/dL
- Non-pregnant women: 12 g/dL
- Pregnant women: 11 g/dL
- Men ≥15 years: 13 g/dL

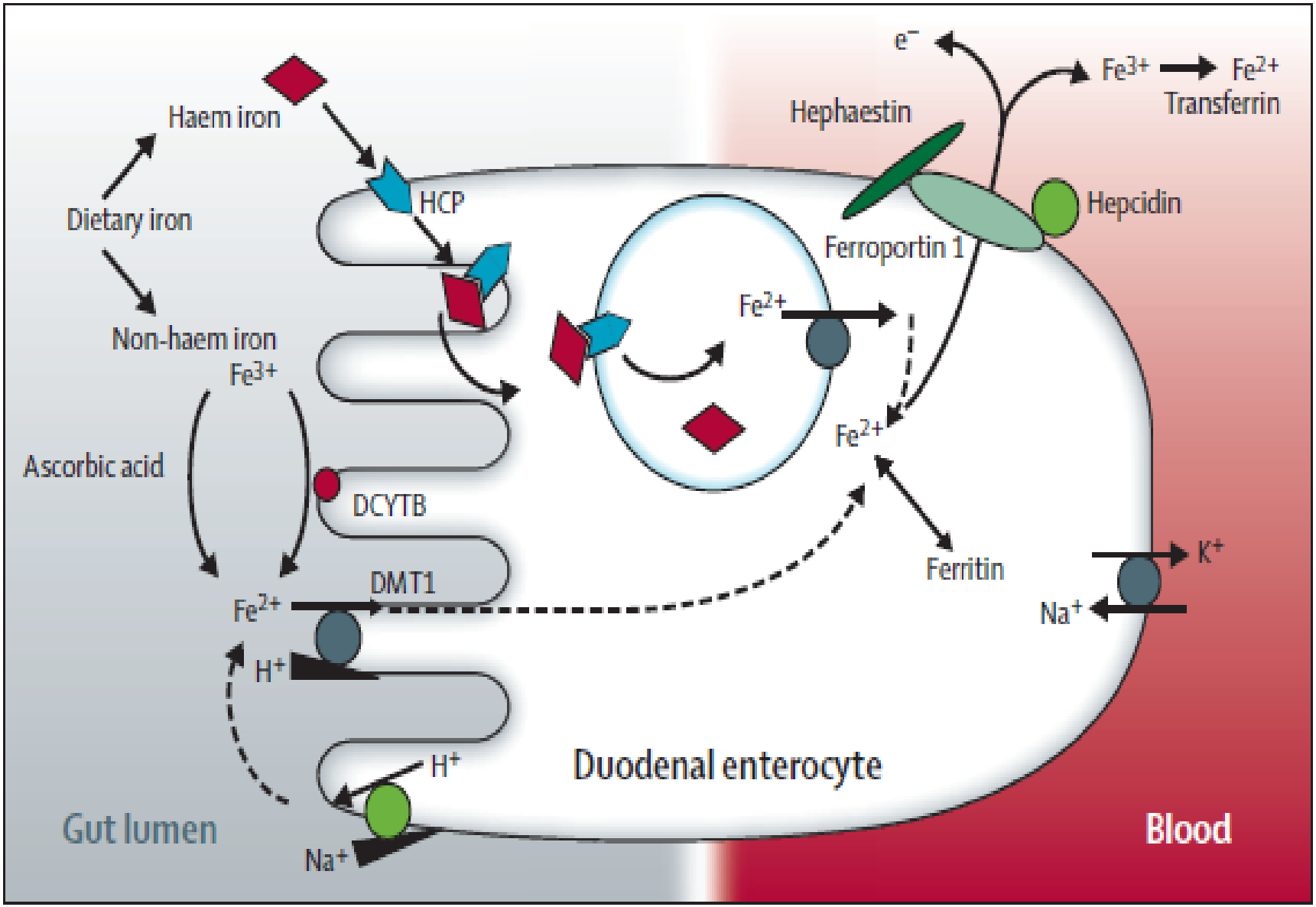
Iron restricted erythropoeisis

- Absolute iron deficiency
  - Reduced Iron stores

- Functional iron deficiency
  - Insufficient iron available for erythropoeisis despite normal or elevated iron levels
    - Anaemia of chronic disease
    - Erythropoesis stimulating agents

Iron homeostasis

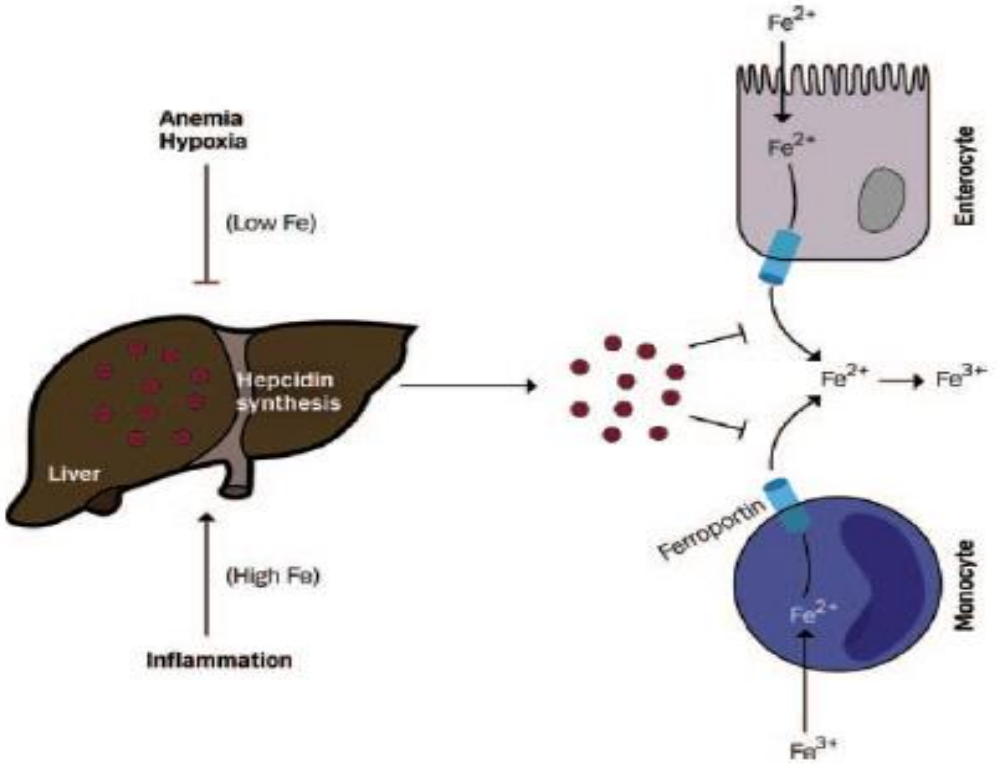
- About 20-25mg iron needed daily for haem synthesis
- 1-2mg of that acquired from diet
- Remainder recycled from senescent RBC
- No active Iron excretion -concentration must be regulated at site of absorption
- 1-2mg obligatory loss daily


Haem iron
Dietary iron
Non-haem iron
Fe^{3+}
Ascorbic acid
HCP
DCYTB
DMT1
Fe^{2+}
H^+
H^+
Na^+
Gut lumen
e^-
Hephaestin
Fe^{3+}
Fe^{2+}
Transferrin
Hepcidin
Ferroportin 1
Fe^{2+}
Fe^{2+}
Ferritin
K^+
Na^+
Duodenal enterocyte
Blood

Mechanism of Anaemia in IBD

- Blood loss form ulcerated mucosal surfaces
- Anaemia of chronic diseases-Hepcidin
- Nutritional deficiencies
- Resection
- Medications

Effect of inflammation



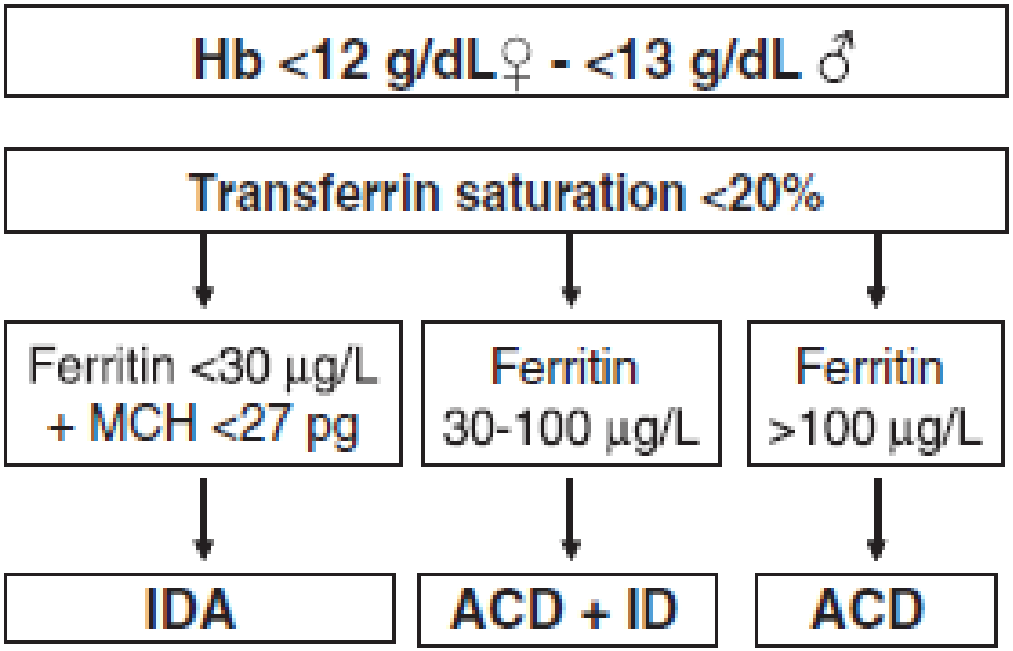
Clinical features

- May be symptomatic in the absence of anaemia
- Impaired quality of life
- Cognitive, motor and behavioural impairment
- Increase in pregnancy complications

Diagnosing IDA in IBD

- Basic laboratory screening
  - FBC
  - Ferritin
    - Without inflammation: <30µg
    - With inflammation: <100µg
  - Transferrin: <20%
  - CRP
  - Reticulocytes

Diagnosing IDA in IBD



Differentiating IDA from ACD

- Soluble transferrin receptor level
  - Not affected by chronic inflammation
  - High in IDA
- sTfR/Log Ferritin index

- For functional anaemia:
  - Percentage of hypochromic cell index
  - Reticulocyte haemoglobin
  - Zinc protoporphyrrin

Therapeutic goals

- Treat underlying disease
- Normalise haemoglobin
- Replenish stores: Ferritin >100µg up to 400µg
- Avoid the need for transfusion
- Improve quality of life

Oral treatment

- Ferrous formulations: FeSO4, Fumarate, gluconate
- Inexpensive and convenient to take
- Unfavourable side effect profile- up to 70%
- Food content may decrease/increase uptake
- Ferric form: Ferric polymaltose

Ferric formulation

- Complex between Ferric iron and Maltose
- Can be effective in patients who have failed or are intolerant to Ferrous
  - No interaction with food components
  - Does not induce ROS
- Can be an alternative to IV iron
- Commonest S/E: Gastrointestinal upset

Effects of Iron on inflammation

- Iron is a key growth and virulence factor for microbes
- Formation of a hydroxyl free radical which mediates tissue injury
- Activation of NFκβ
- Impaired intracellular killing of pathogens by macrophages

Is there evidence for adverse effects

- Oldenburg et al
- IL 10-/- vs. Wild type mice given oral and rectal iron
- Increase in pro-inflammatory cytokines
- No significant increase in histological inflammation

In humans...

- Silva et al: IDA in IBD and non-IBD
- 57 Patients invited, 10 lost to follow up
- Disease severity before and after treatment
- Results
  - 12 (26%) were intolerant
  - 2 IBD patients (6%) had disease relapse
  - No significant increase in disease related markers
  - No significant increase in ROS in rectal biopsies

Table 3. Responses to oral iron therapy for 4 weeks in patients with anaemia due to ulcerative colitis, Crohn's disease, active IBD and non-IBD causes

	Ulcerative colitis ($n = 14$)			Crohn's disease ($n = 19$)			Active IBD ($n = 7$)			Non-IBD ($n = 14$)		
	Before iron	After iron	*P*-value	Before iron	After iron	*P*-value	Before iron	After iron	*P*-value	Before iron	After iron	*P*-value
Simple Colitis Clinical Activity Score	3.5 (2.6)	5 (3.2)	0.014*	–	–	–	–	–	–	–	–	–
Harvey–Bradshaw Index	–	–	–	3.1 (1.7)	3.7 (3.4)	0.1	–	–	–	–	–	–
IBDQ (score/224)	164 (12)	175 (9)	0.016*	177 (36)	178 (25)	0.525	167 (57)	180 (55)	0.094	–	–	–
Non-IBD Symptom Score	–	–	–	–	–	–	–	–	–	2.4 (2.2)	2.5 (1.6)	0.765
Haemoglobin (g/dL)	12.3 (1.9)	12.7 (1.0)	0.004*	10.0 (1.6)	11.7 (1.6)	<0.001*	10.0 (3.5)	13.2 (1.3)	0.016*	10.2 (1.2)	11.9 (0.9)	0.002*
Ferritin (mcg/L)	5 (8)	25 (26)	0.002*	4 (8)	16 (9)	<0.001*	3 (4)	15 (20)	0.016*	5 (1.5)	19 (8)	0.004*
Platelets ($\times 10^9$/L)	320 (95)	280 (121)	0.04*	338 (162)	341 (177)	0.075	321 (308)	280 (164)	0.016*	344 (134)	283 (117)	0.01*
ESR (mm/h)	21 (35)	17 (41)	0.052	40 (30)	19 (38)	0.016*	19 (28)	6 (12)	0.031*	9 (24)	6 (25)	0.742
CRP (mg/dL)	5 (4)	7 (19)	0.063	16 (20)	22 (21)	0.424	5 (15)	5 (6)	0.5	5 (1)	5 (13)	1.000
Albumin (g/L)	44 (6)	43 (3)	0.91	38 (8)	39 (10)	0.073	42 (11)	43 (10)	0.188	46 (5)	45 (4)	0.008*

Use of oral Iron in IBD

- Can be used for mild anaemia (Hb>10)
- Elemental Iron doses of up to 100mg
  - e.g. Approx 65mg in 200mg $FeSO_4$
- **Disease must be quiescent**
- Aim for Ferritin >100µg/L
- Check levels after 4 weeks
- Continue for 6 months after Hb normalization

Iron refractory IDA (IRIDA)

- Defective gene TMPRSS6 that controls Matriptase 2
- Uninhibited Hepcidin production
- Low MCV, MCH, % transferrin saturation and normal-low Ferritin
- Can check TSAT/Hepcidin ratio
- May respond to IV iron

Intravenous Iron

- Previously associated with severe S/E
- Preferred route for supplementation in IBD
- Can be used for
  - Moderate to Severe anaemia –Hb <10
  - Intolerance to oral Iron or inadequate response
- Disadvantages
  - High cost
  - Infusion reactions, Hypophosphatemia

Formulations available

- Iron Sucrose- Venofer®
- Iron dextran- Cosmofer®
- Iron Isomaltoside 1000- Monofer®
- Ferric Carboxymaltose- Ferinject®
- Iron gluconate- Ferrlecit®
- Ferumoxytol- Rienso®

Characteristics of different iron formulations

Iron Preparation	Molecular Weight (kDa)	Carbohydrate Shell	Complex Stability	Maximum Approved Single Dose	Maximum total Dose
Iron dextran, low molecular weight	73	Dextran (branched polysaccharide)	High	200 mg (<30 min)	20 mg/kg
Iron sucrose	43	Sucrose (disaccharide)	Moderate	200 mg (≥30 min)	7 mg/kg (300 mg in some countries)
Iron gluconate	37	Gluconate (monosaccharide)	Low	62.5 mg (5–10 min)	62.5 mg (125 mg in some countries)
Ferric carboxymaltose	150	Carboxymaltose (branched polysaccharide)	High	1000 mg (≥15 min)	20 mg/kg
Iron isomaltoside 1000	150	Isomaltoside (linear oligosaccharide)	High	1000 mg (≥15 min)	20 mg/kg
Ferumoxytol*	721	Polyglucose sorbitol carboxymethylether	High	510 mg (≤1 min)	510 mg

Determining dose

Haemoglobin (g/dL)	Weight <70kg	Weight >70kg
10-12 (Women)	1000mg	1500mg
10-13 (Men)	1000mg	1500mg
7-10	1500mg	2000mg

Frequency of monitoring

- Pts in clinical remission or mild disease can be screened every 6-12 months
- Outpatients with active disease-3 monthly
- Not recommended to repeat iron parameters at least 4 weeks after infusion
- Aim for Ferritin >400µg/L
- Re-treat when Ferritin drops <100µg or Hb drops

Blood transfusion

- The need depends on
  - The rate of bleeding
  - Haemodynamic instability
  - Co-morbidities
  - Haemoglobin level-may be considered if below 7g/dL
- Seldom used in IBD

Take home messages

- Anaemia in IBD should be investigated and treated
- IDA often co-exists with anaemia of chronic disease
- Oral iron for mild anaemia and quiescent disease
- Intravenous iron for severe anaemia

Referrences

.Erin McLean, Mary Cogswell, Ines Egli, Daniel Wojdyla, Bruno de Benoit. Worldwide prevalence of anaemia, WHO Vitamin and mineral Nutrition Information System, 1993-2005. Public Health Nutrition 2007; 12(4): 444-454

- Walter Reinisch, Michael Staun, Sunil Bandar, Manuel Munuz. State of the Iron: How to diagnose and efficiently treat iron deficiency anaemia in inflammatory bowel disease. Journal of crohn's and colitis. 2012; 7: 429-440
- Gisbert JP, Gomollón F. An update on Iron Physiology. World J Gastroenterol 2009; 15(37): 4617-4626
- Ole Haagen Nielsen, Mark Ainsworth, Mehmet Coskun, Gunter Weiss. Management of Iron-Deficiency anaemia in Inflammatory Bowel Disease. Medicine 2015; 94 (23) e963
- Oldenburg B, Koningsberger J.C, Van Berghe Henegouwen. Review article: Iron and Inflammatory Bowel Disease. Aliment Pharmacol Ther 2001; 15:429-438
- Axel U. Dignass et al. European consensus on the diagnosis and management of Iron Deficiency and Anaemia in Patients with Inflammatory Bowel Disease. Journal of crohn's and colitis 2015; 1-12.
- Gunter Weiss, Christoph Tasche. Pathogenesis and treatment of anaemia in inflammatory bowel disease. Haematologica 2010; 95(2): 175-178
- Oldenburg B et al. Iron supplementation affects the production of pro-inflammatory cytokines in IL10 deficient mice. European journal of clinical investigation, 2005; 30: 505-510
- Christoph Gasche et al. Ferric Maltol is Effective in Correcting Iron Deficiency Anaemia in patients with Inflammatory Bowel Disease: Results From a Phase 111 Clinical Trial Programme. Inflammatory bowel Disease 2015; 21: 579-588
- De Silva A.D et al. Efficacy and tolerability of oral iron therapy in inflammatory bowel disease: a prospective, comparative trial. Alimentary Pharmacology and therapeutics. 2005; 22:1097-1105.
- Sindhu Kaitha, Muhammad Bashir, Tauseef Ali. Iron Deficiency Anaemia in Inflammatory Bowel Disease. World J Gastrointest Pathophysiol 2015.15;6 (3): 62-72
- Auerbach Michael. Clinical update: intravenous iron for anaemia. The Lancet 2007; 369:1502-1504
- Blazevic A et al. Severe hypophosphaetemia after intravenous iron administration. The journal of medicine 2014; 72:49-53