

Approach to anaemia

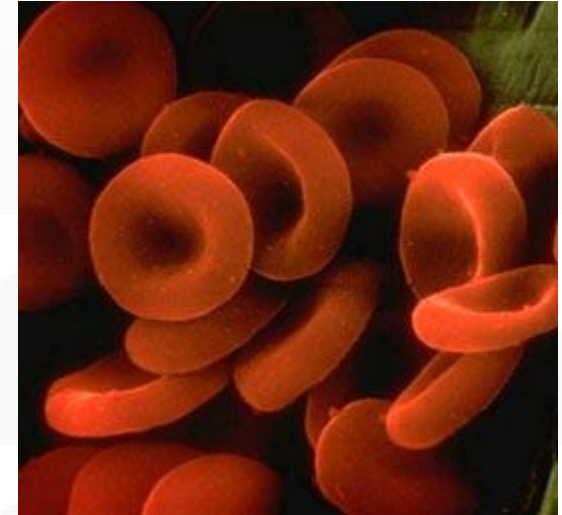
Dr Alasdair Patrick

Gastroenterologist

Consultant Physician

CMDHB

MacMurray Gastroenterology



Overview

- History and clinical exam
- Ways to think about anaemia
 - Kinetic and morphological approach
- Microcytosis
 - Thallasaemia and iron deficiency
- Macrocytosis
 - B12/folate and other causes
- Normocytic anaemia
- When to refer

History very important

- Presenting symptoms
 - Duration of anaemia
 - Overt bleeding
 - GI tract
 - Menstruation
 - Upper and lower GI tract symptoms
 - Alarm Symptoms
- Past medical history
 - Liver disease
 - IBD
 - Skin, joint
 - Haematological
- Drugs and Alcohol
 - NSAID, Asprin, Alendronate, warfarin, iron, phenytoin
- Nutrition and eating habits
- Travel
 - Worldwide most common cause of low iron is parasites
- Family History
 - Cancer, coeliac disease, Thallasaemia



Is Clinical exam important?

- Signs of anaemia
 - Palms, nails beds and conjunctiva
 - Conjunctiva pallor
 - Hb <100 sensitivity = 18.6%
 - Hb < 90 sensitivity = 50%
- Stigmata of chronic liver disease



Is clinical exam important?

- Haematological disease
 - Petichae, ecchymoses, lymph nodes, hepatosplenomegaly, bone pain
- PR exam
 - Sensitivity for colorectal cancer 5%
 - Sensitivity for GI bleeding not well studied



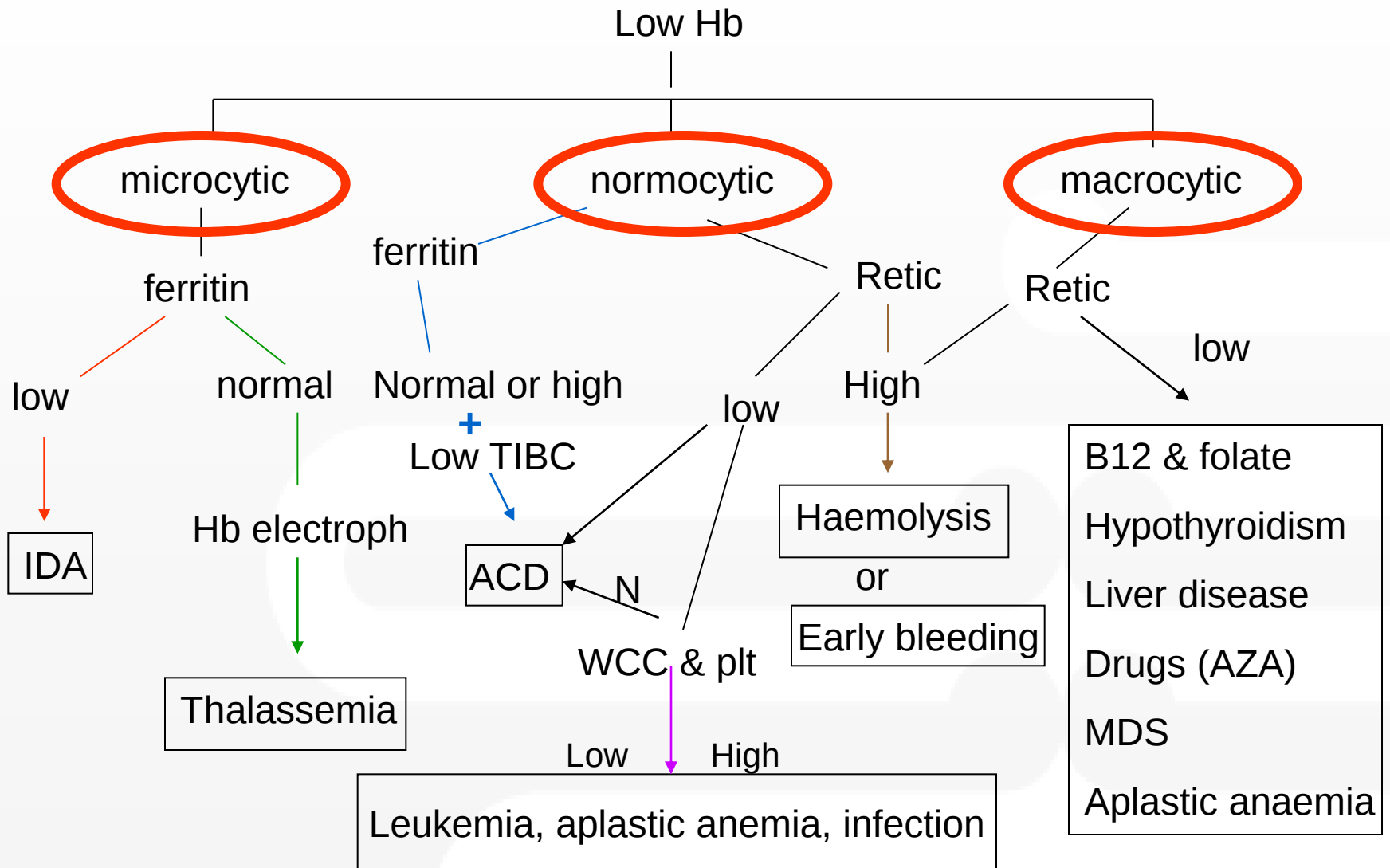
Ways to think about anaemia

- Morphological approach
 - Based on MCV
 - Micro, macro and normocytic
- Kinetic approach
 - Decreased production vs increased destruction
 - Useful when normocytic

Morphological approach

- Divide into groups depending on MCV

Microcytic	Normocytic	Macrocytic
Iron def Thalessaemia Chronic Disease	Acute blood loss Haemolytic Marrow infiltration Chronic Disease	B12 Folate Alcohol Reticulocytosis Hypothyroid



- Normal MCV & reticulocytosis in early bleeding
- Blood film is useful in microangiopathic and leukoerythroplastic picture
- Early Anaemia of Chronic Disease can be microcytic

Low Hb

microcytic

ferritin

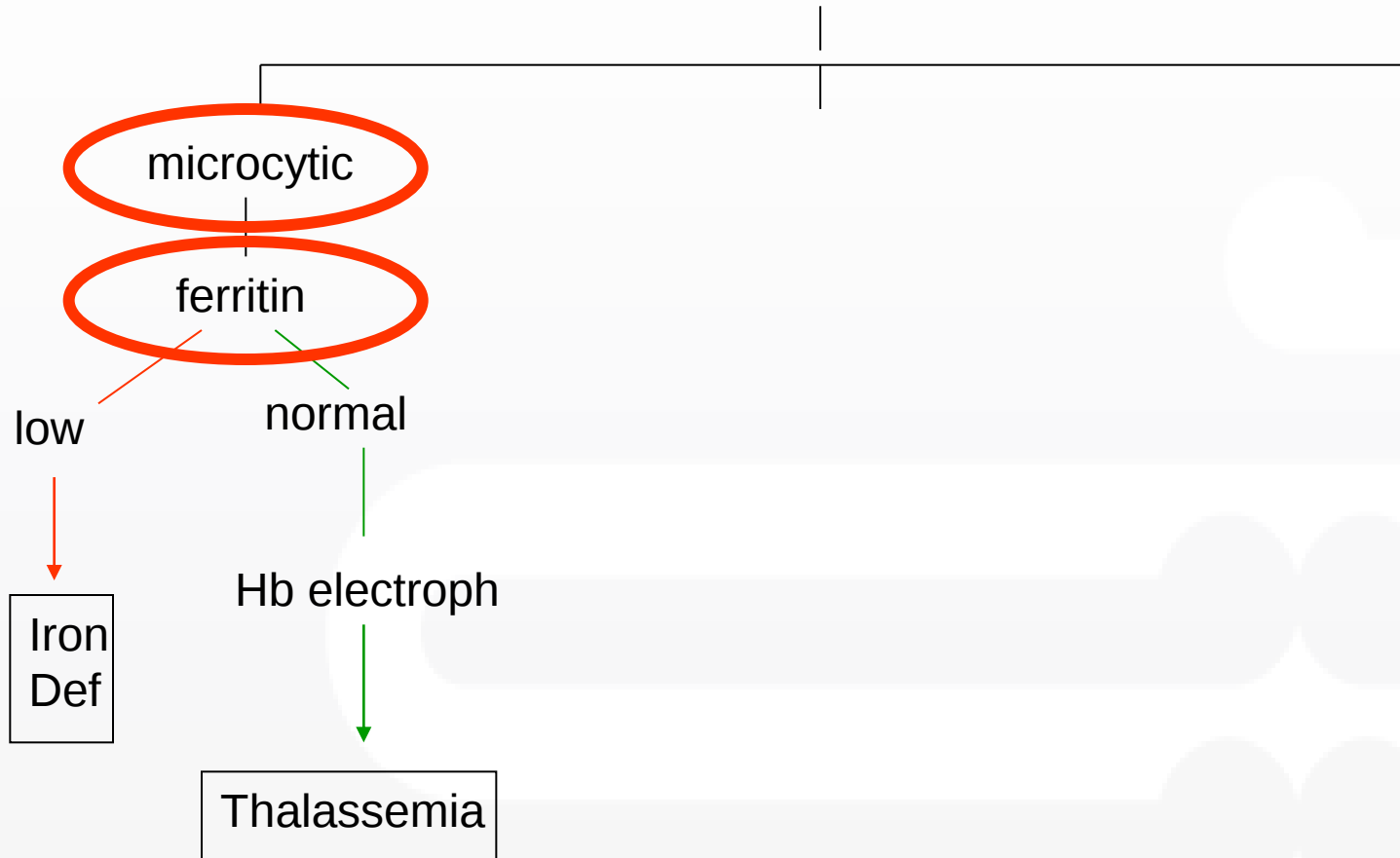
low

normal

Iron
Def

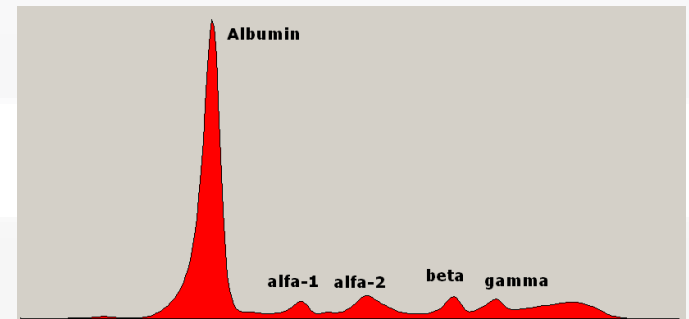
Hb electroph

Thalassemia



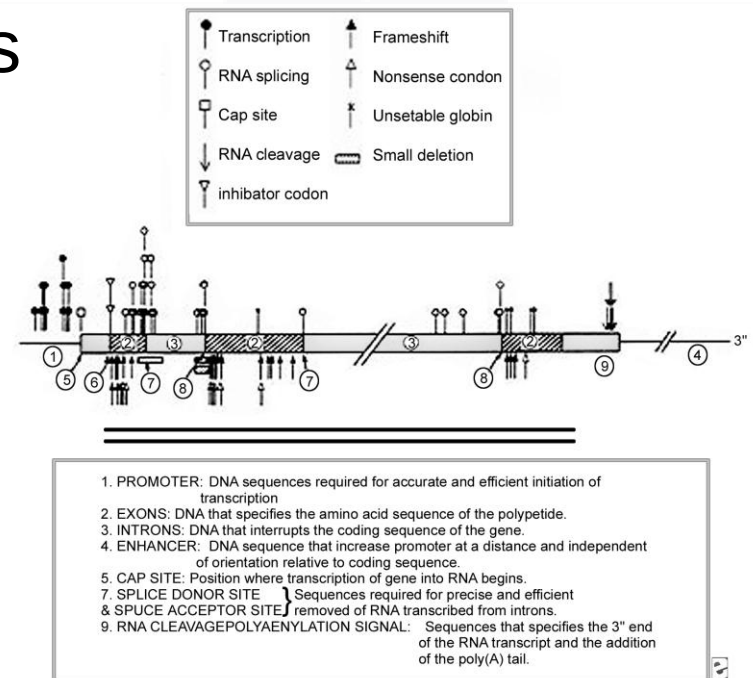
Microcytosis-Thallasaemia

- Normal ferritin
 - Order an electrophoresis
 - Separation of particles under the influence of a spatially uniform electric field
- Thallasaemia
 - Autosomal recessive
 - Two types
 - Degree of anaemia a clue
 - » Major when inherit both genes
 - » Minor when have one



Thalassaemia

- Excessive rbc destruction
 - Shortened to less than 100 days
- Hb made of two proteins
 - Alpha and beta globulins
- Alpha
 - Asians and Arabs
- Beta
 - Mediterranean



Thalassaemia

- Major
 - Refer to haematology
 - Need transfusions
- Minor usually requires no treatment
 - No further investigations needed

Low Hb

microcytic

ferritin

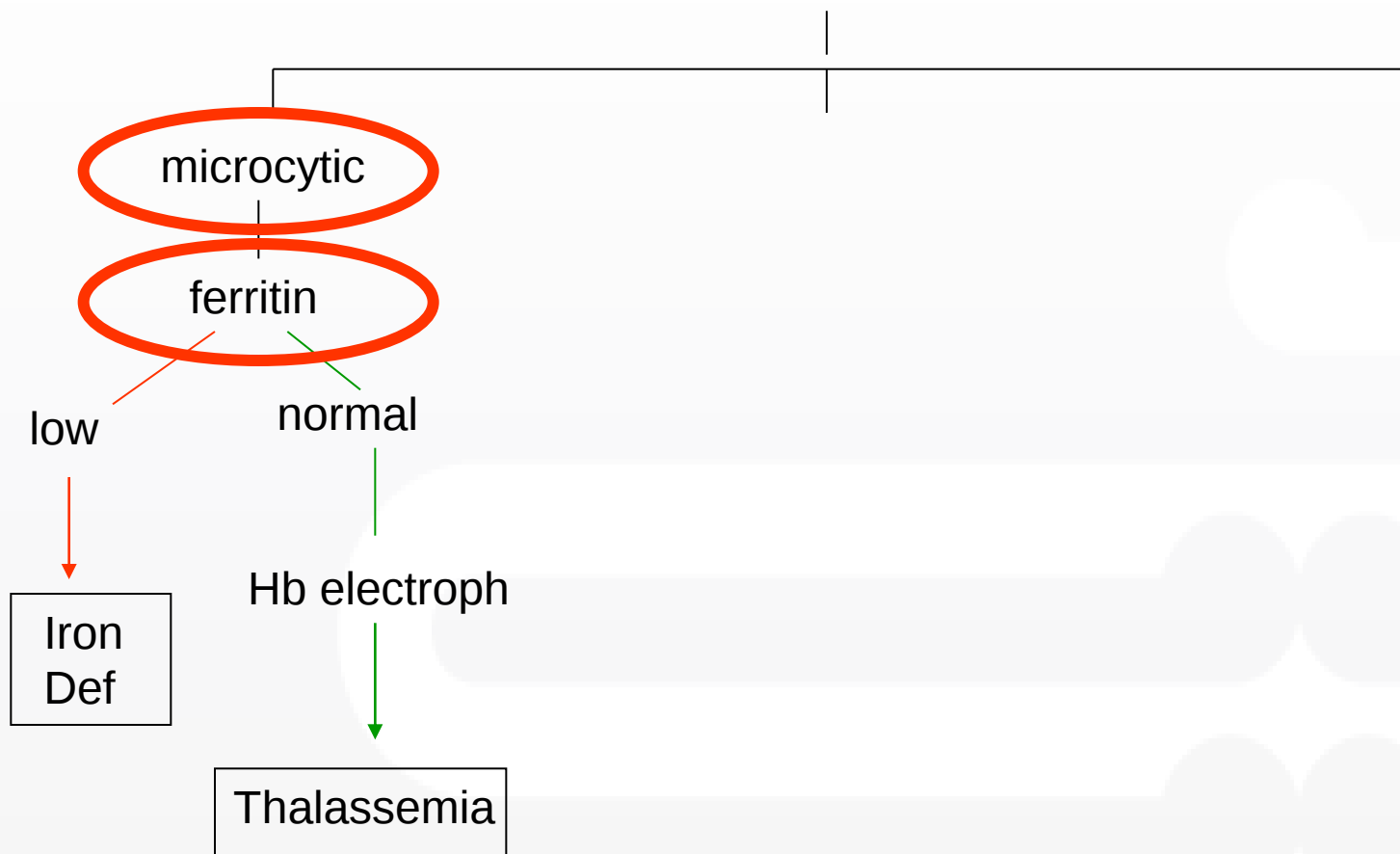
low

normal

Iron
Def

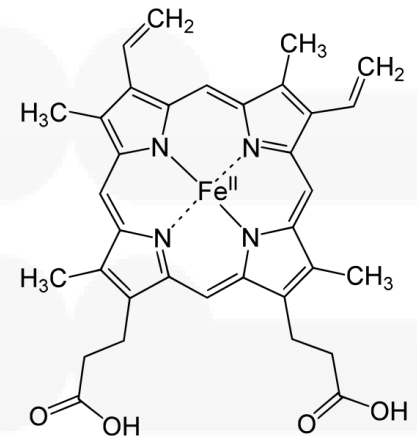
Hb electroph

Thalassemia



What is iron?

- Iron
 - Essential for many forms of life as is an electron donor and acceptor
 - Good transporter
 - In many food sources
 - Heme and non heme
 - If was free in a cell it would catalyze free radical formation
 - Needs to be bound

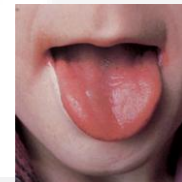


Components of iron

- Normal person has 5g of iron
 - 2.5g in Haemoglobin
 - 2g in ferritin complexes
 - Protein that releases iron in a controlled fashion
 - 400mg in cells
 - 3-4mg in plasma bound to transferrin
 - Highest turnover of iron (24x ferritin)
 - Transferrin receptors on cells
 - Tiny amount of free iron

History and exam

- Pica
 - Perverted appetite for substances not fit as food
 - Dirt = geophagia
 - Paper= amylophagia
 - Ice = Pagophagia
- Beeturia
 - Red urine after eating beets
 - Due to changes in gut bacteria
- Signs now rare



Components of iron



- Iron
 - Second best measure of stores
- Transferrin
 - Goes up in IDA as body tries to compensate
 - Increased by oral contraceptive
- Transferrin saturation
 - Low in IDA but normal in chronic disease
- Ferritin
 - Best measure of stores
 - Acute phase protein- check CRP

Further bloods tests

- Serum transferrin receptor
 - Derived from bone marrow erythroid precursors
 - Proportional to erythropoietic rate
 - Inversely related to iron stores
 - Goes up when there are low iron stores

Iron deficiency vs chronic disease

Type	Fe	Transferrin	TS	Ferritin
Iron deficiency	↓	↑	↓	↓
Chronic disease	↓	↓	N	Variable

Iron absorption is low and utilisation by the BM is impaired in Chronic Disease

Low ferritin “rules of thumb”

- Interpreting ferritin when inflammation is present
 - Divide ferritin by 3
- Relative risk of cancer is 31 (7-109)
- Gastroscopy: 36% yield
- Colonoscopy: 25% yield
 - Capsule endoscopy yield 66%

3 ways it can be low

- Dietary deficiency
 - Heme iron well absorbed
 - Meat, fish and poultry
 - Non heme iron
 - Fruits, veggie, nuts and grain
 - Tea, coffee, fiber and calcium reduce absorption
- Poor absorption
 - Coeliac disease, H pylori, gastrectomy, PPIs
- Blood loss

RARE IN NZ!

Coeliac disease

- NZ prevalence 1/87
- Blood testing
 - Tissue transglutaminase
 - Sensitivity 95-99%
 - Specificity 95-99%
 - Should normalize in 3-6 months
 - HLA DR2/DQ8
 - Not changed by diet
 - Sensitivity 99.6%
 - Specificity only 30%
 - Other tests are outdated



Coeliac risk for family members

- Risk for the relatives
 - Monozygotic twins 75%
 - HLA identical siblings 40%
 - First degree relatives with 2 siblings 17%
 - First degree relatives 5-11%

Coeliac disease

- Clinical symptoms and mucosal response
 - Clinical response to GFD may be excellent
 - But some have residual symptoms
 - These may be IBS
 - Response may not equal healing
 - 3-10% are refractory and these have high risk of lymphoma
 - Incomplete mucosal recovery is common
- Follow up biopsy recommended

Complications of Coeliac Disease

- Nutritional deficiencies
 - Low bone density
 - Anemia- Fe, Folate, B12
- Dermatitis herpetiformis
 - Other skin disorders
- Other immune diseases
- Associated conditions
- Microscopic colitis 33%
- Bacterial overgrowth 10%
- Sepsis
- Refractory CD*
 - 41% ulcerative jejunoileitis
 - 30% mesenteric cavitations
 - 30% hyposplenism
 - 40% progress to EATL
- NHL 4X general pop risk (SIR 3.6)
- Small bowel adenoCa
- Other cancers
 - Primary liver
 - ?gastric & esophageal
 - CRC SIR 1.5 (ascending and transverse)

*Krauss and Schuppan Gastros Endos Cli 2006 (16): 317-327

Low ferritin- Blood loss

- Non gastrointestinal
 - Menstruation, Blood donation, Haematuria
- Gastrointestinal
 - **Common:**
 - Aspirin/NSAID use 10–15%
 - Colonic carcinoma 5–10%
 - Gastric carcinoma 5%
 - Benign gastric ulceration 5%
 - Angiodysplasia 5%
 - **Uncommon:**
 - Oesophagitis 2–4%
 - Oesophageal carcinoma 1–2%
 - Gastric antral vascular ectasia 1–2%
 - Small bowel tumours 1–2%
 - Ampullary carcinoma <1%
 - Ancylostoma duodenale <1%

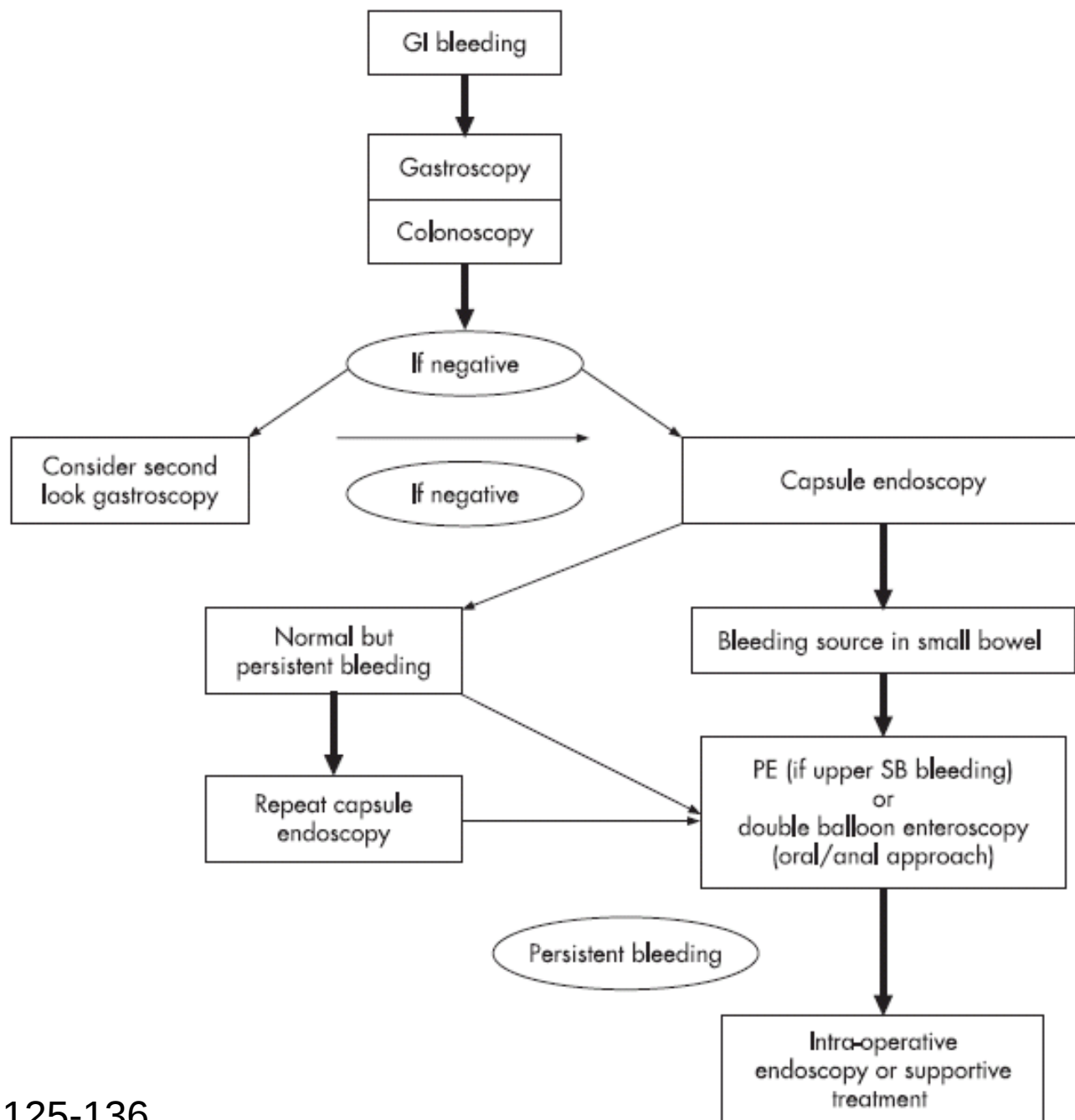
Investigations for Iron Deficiency

British Gastro guidelines

- Coeliac serology
- Men and post menopausal woman
 - OGD and colonoscopy
 - If normal then capsule endoscopy
- Investigation also indicated if:
 - Over 50
 - No response to iron therapy
 - Family history of cancer

Iron deficiency with no anaemia

- 3 times as common as Iron Deficiency
 - 0.9% prevalence of malignancy
- Recommendations are the same
 - > 50 years old (non menstruating) with hypoferritinemia
 - No response
 - Family history

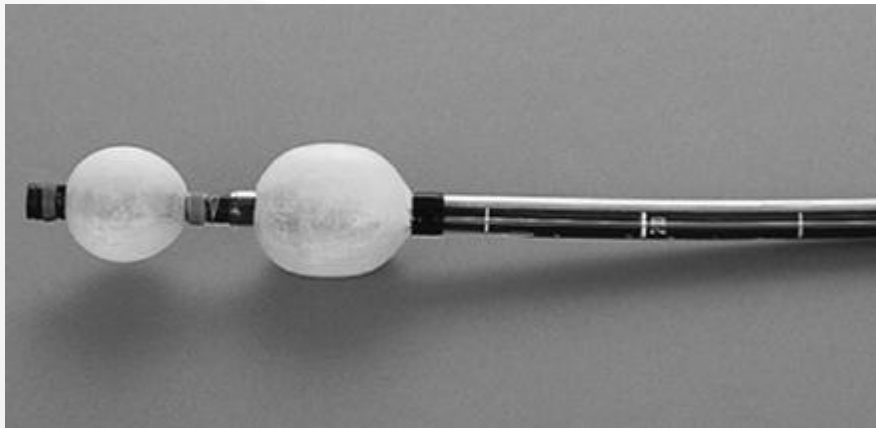


Capsule endoscopy

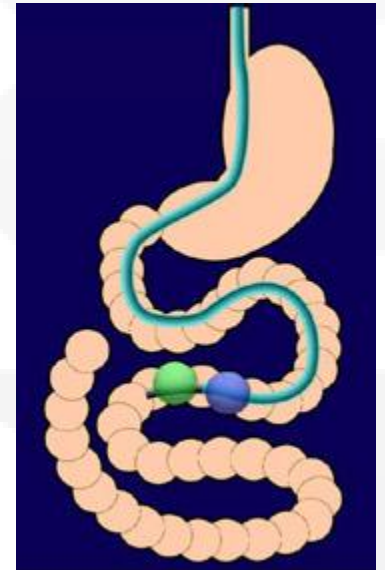


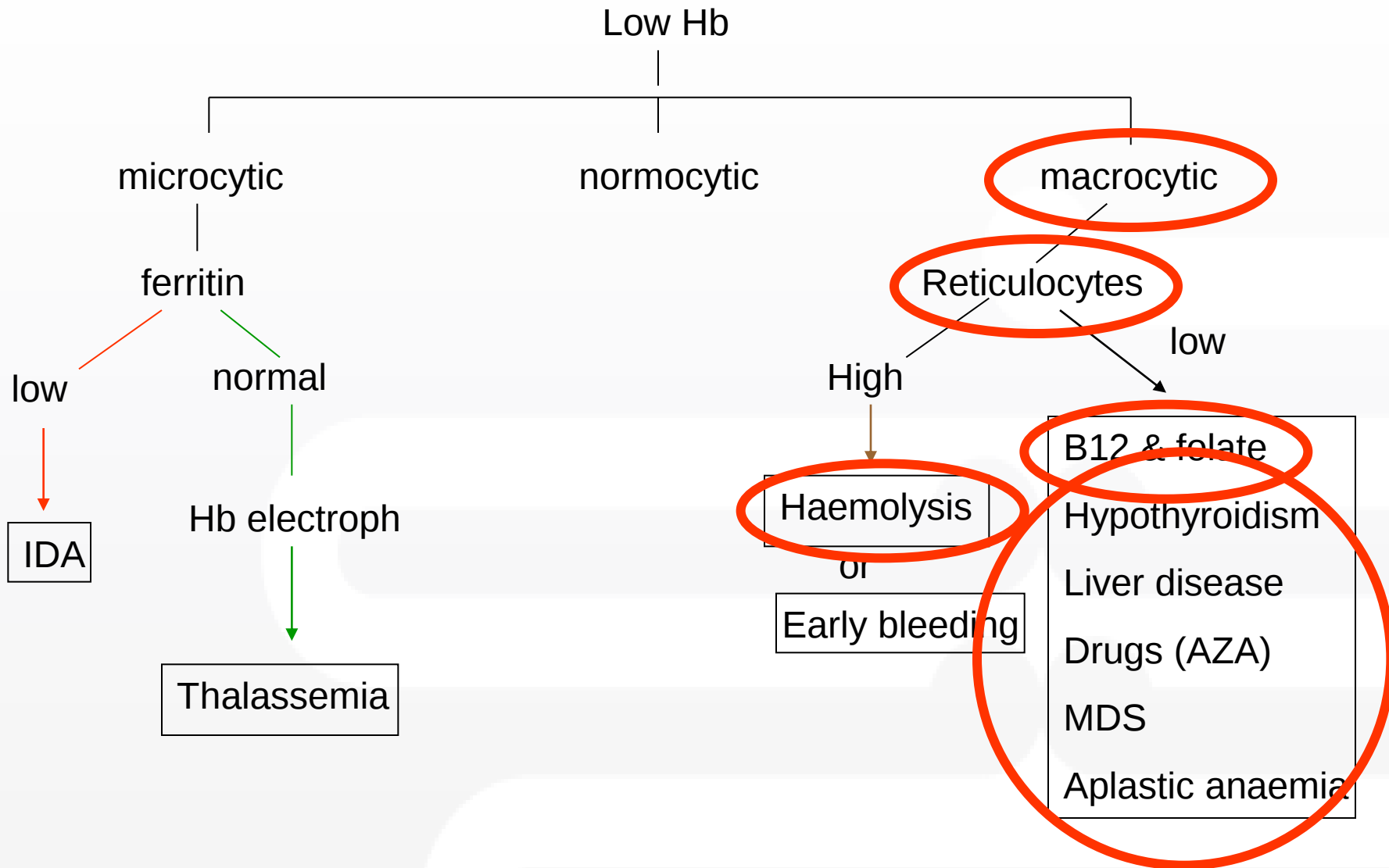
Yield is 2/3

Balloon Enteroscopy



Full bowel visualization can be achieved





Haemolysis

- Other blood tests
 - Low Haptoglobins
 - Binds free Hb then this complex is removed by the spleen
 - High LDH
 - Enzyme that converts pyruvate to lactate
 - Is abundant in red blood cells
 - High bilirubin
 - Coombes test
 - Blood film

Haemolysis

Table 3. Causes Of Hemolysis

Congenital	Hereditary spherocytosis Glucose-6-phosphate dehydrogenase deficiency (G6PD) Sickle cell disease
Acquired	Autoimmune Cold and warm agglutinins Drug-induced Microangiopathic hemolytic anemia (MAHA), disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS) Paroxysmal nocturnal hemoglobinuria (PNH) Mechanical valve

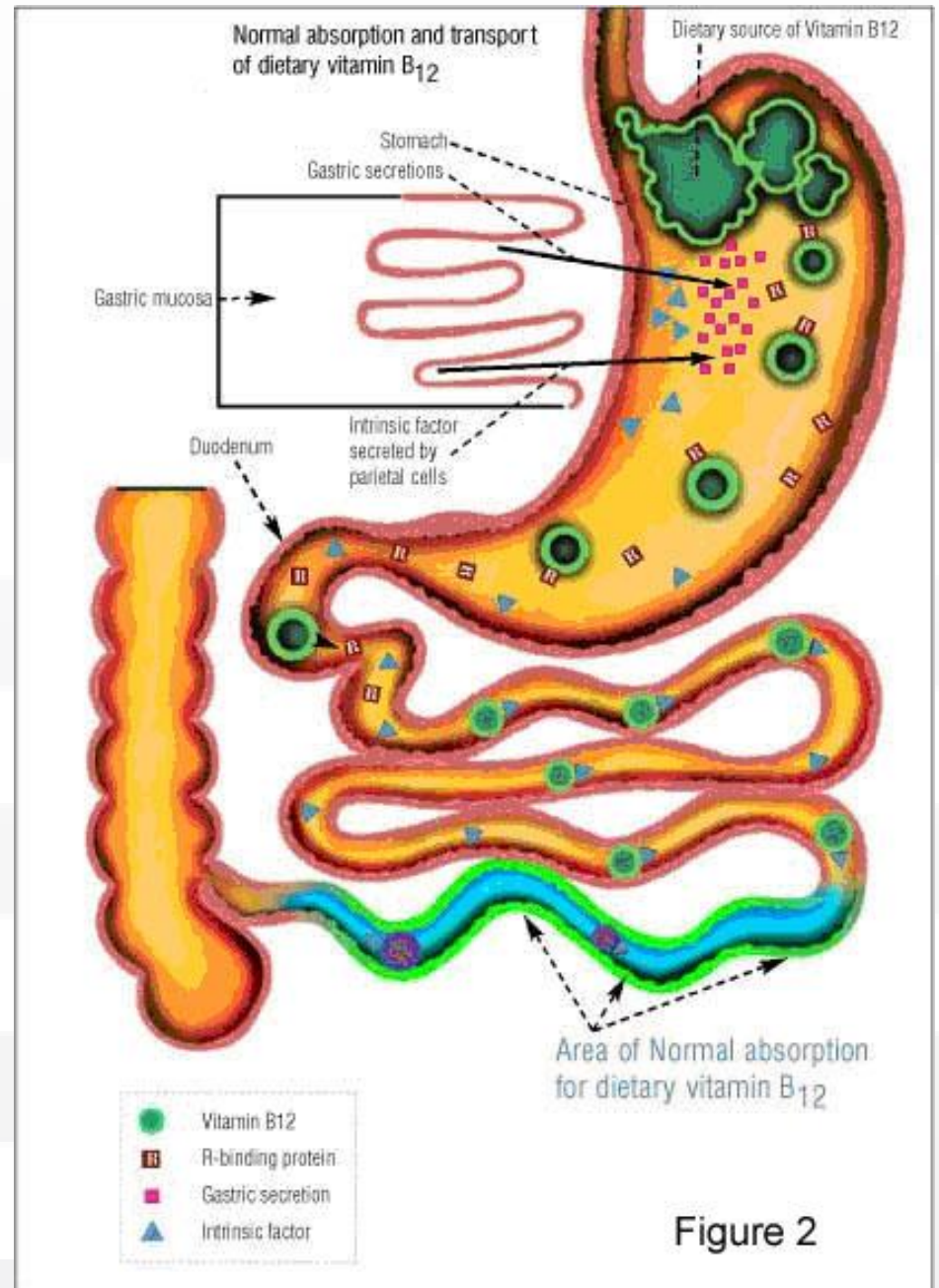
All cases of haemolysis need hematology referral

B12 and folate

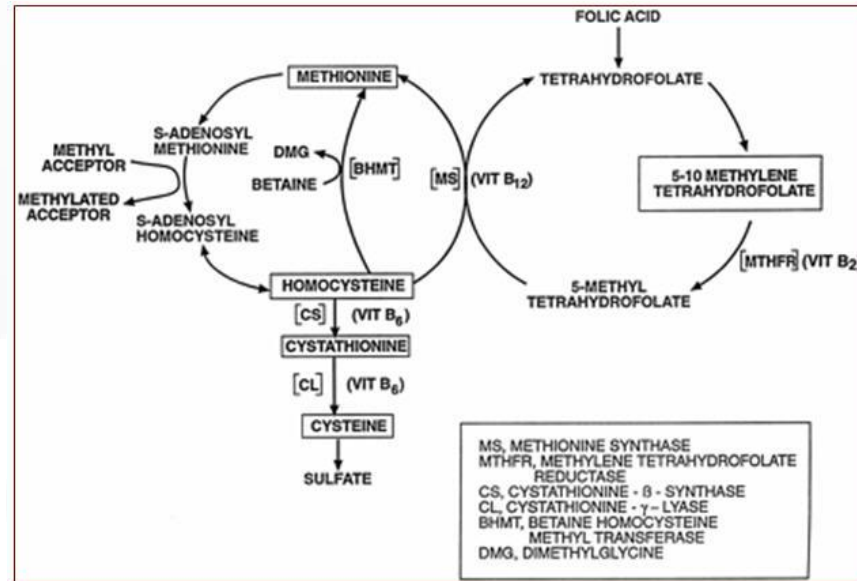
- B12
 - Serum levels vary widely in individuals
 - Differences of more than 100 seen in 21%
 - Check level at least twice
 - Stores are vast therefore slow process
- Folate
 - Varies over short term
 - Red cell folate is time averaged stores
 - Found in leafy green vege and fruit
 - Food enriched sources

B12

- Occurs naturally in animal products
 - Eggs, meat and milk



Blood tests in B12 deficiency



If unclear whether true deficiency

Check:

Methylmalanoic acid

Homocysteine

These are high in 98% of B12 deficiency

Pernicious anaemia

- Failure to absorb B12 due to loss of gastric parietal cells
- Historically prognosis was very poor
 - Death within 3 years
 - Associated with other autoimmune diseases
- 2-3 times increase risk of gastric and bowel cancer

Blood tests in Pernicious anaemia

- Intrinsic factor antibodies
 - Diagnostic of pernicious anaemia
 - Only found in 50% of cases
- Parietal cell antibodies
 - Not diagnostic but suggestive
 - Found in 90% of cases
- Gastroscopy plus biopsy to diagnose
 - Treatment is B12 injections

Folate deficiency

Intake vs Utilisation

Diet **COMMON**

Coeliac disease
Antifolate drugs

Pregnancy
Lactation
Adolescence

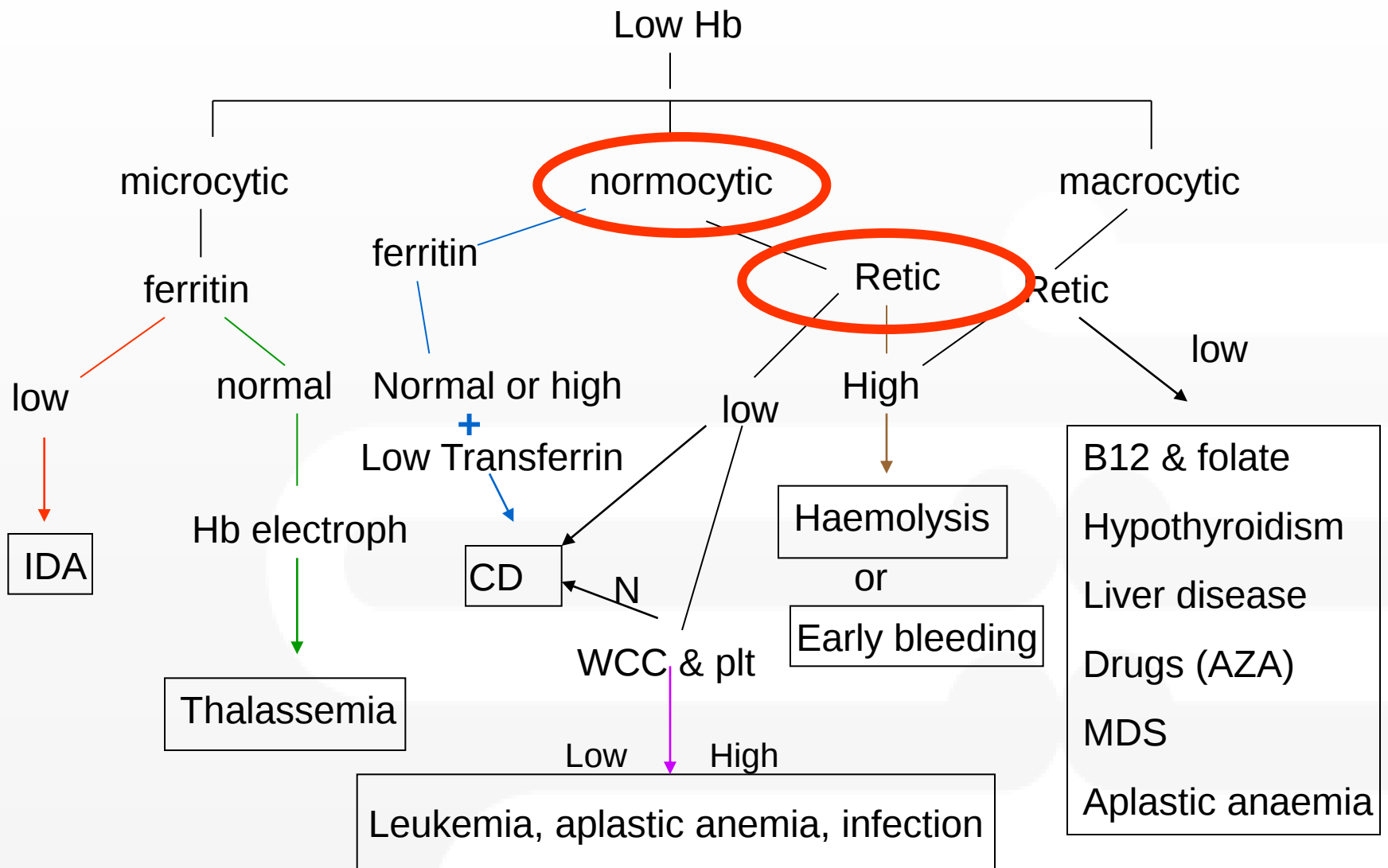
Excess turnover of cells:
Haemolysis, malignancy

- **NO** neuropathy

Importance of the gut

- Region of the gut important:

Iron	Duodenum
B12	Gastric, duodenal or Terminal ileum
Folate	Duodenum and jejunum



- Normal MCV & reticulocytosis in early bleeding
- Blood film is useful in microangiopathic and leukoerythroplastic picture
- Early Anaemia of Chronic Disease can be microcytic

Kinetic approach

Low

Reticulocyte count

High

Decreased RC production

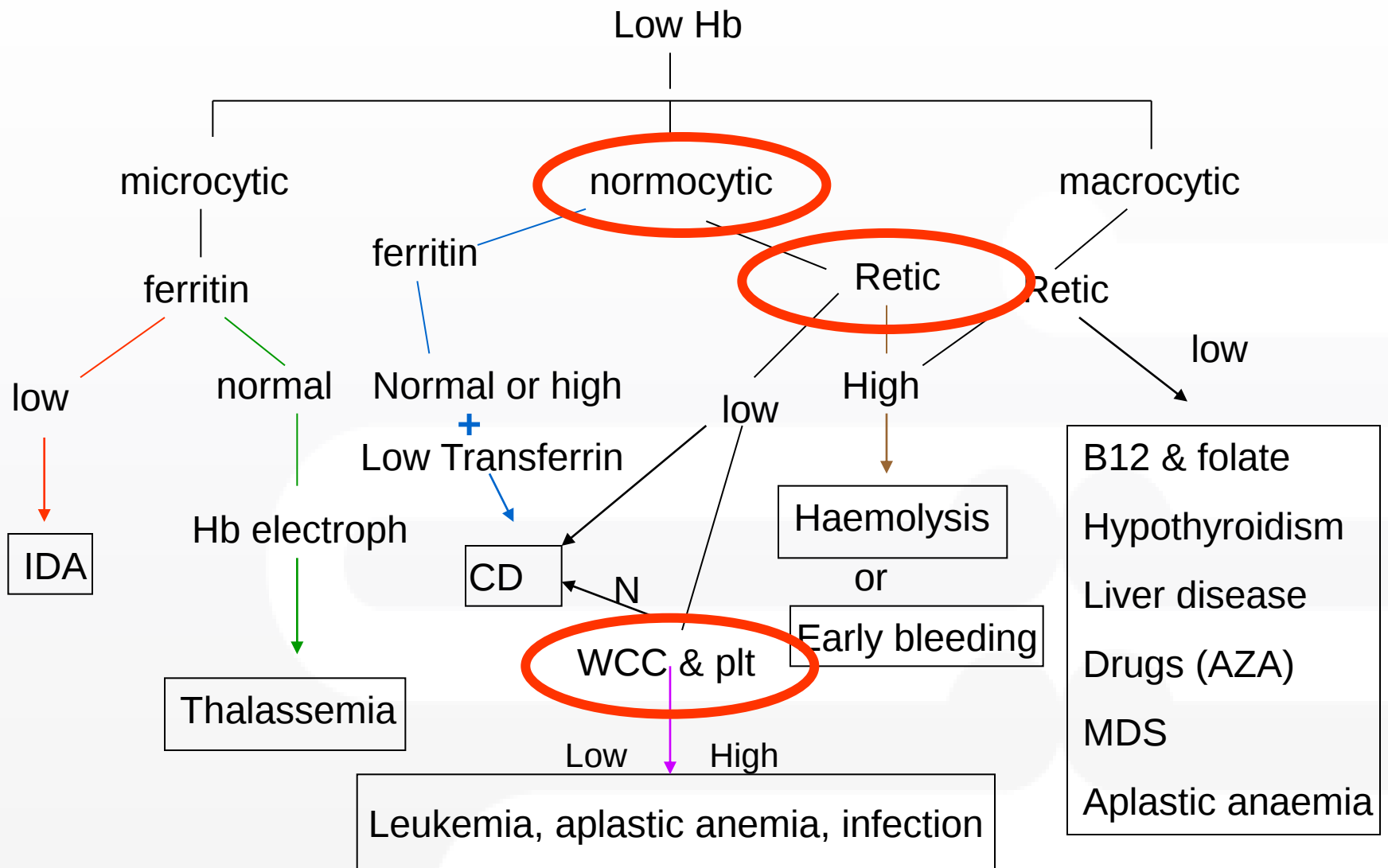
- Anaemia of chronic disease
- Low nutrient (Fe, B12, folate)
- Bone Marrow disease (MDS, tumor infiltration)
- BM suppression (Drugs, chemo Tx)
- Low hormones (EPO, T4, testosterone)

Increased cell destruction

- Inherited HA
- Autoimmune
- Infection
- Drugs
- Hypersplenism
- Mechanical
- Microangiopathic

Normocytic anaemia

- Kinetic approach is best for understanding
 - Production vs consumption
- Tests to do:
 - Reticulocyte count
 - Urine, CXR, LFT, Cr, ESR, PEP, WCC, Plt



- Normal MCV & reticulocytosis in early bleeding
- Blood film is useful in microangiopathic and leukoerythroplastic picture
- Early Anaemia of Chronic Disease can be microcytic



Normal WBC and PLT

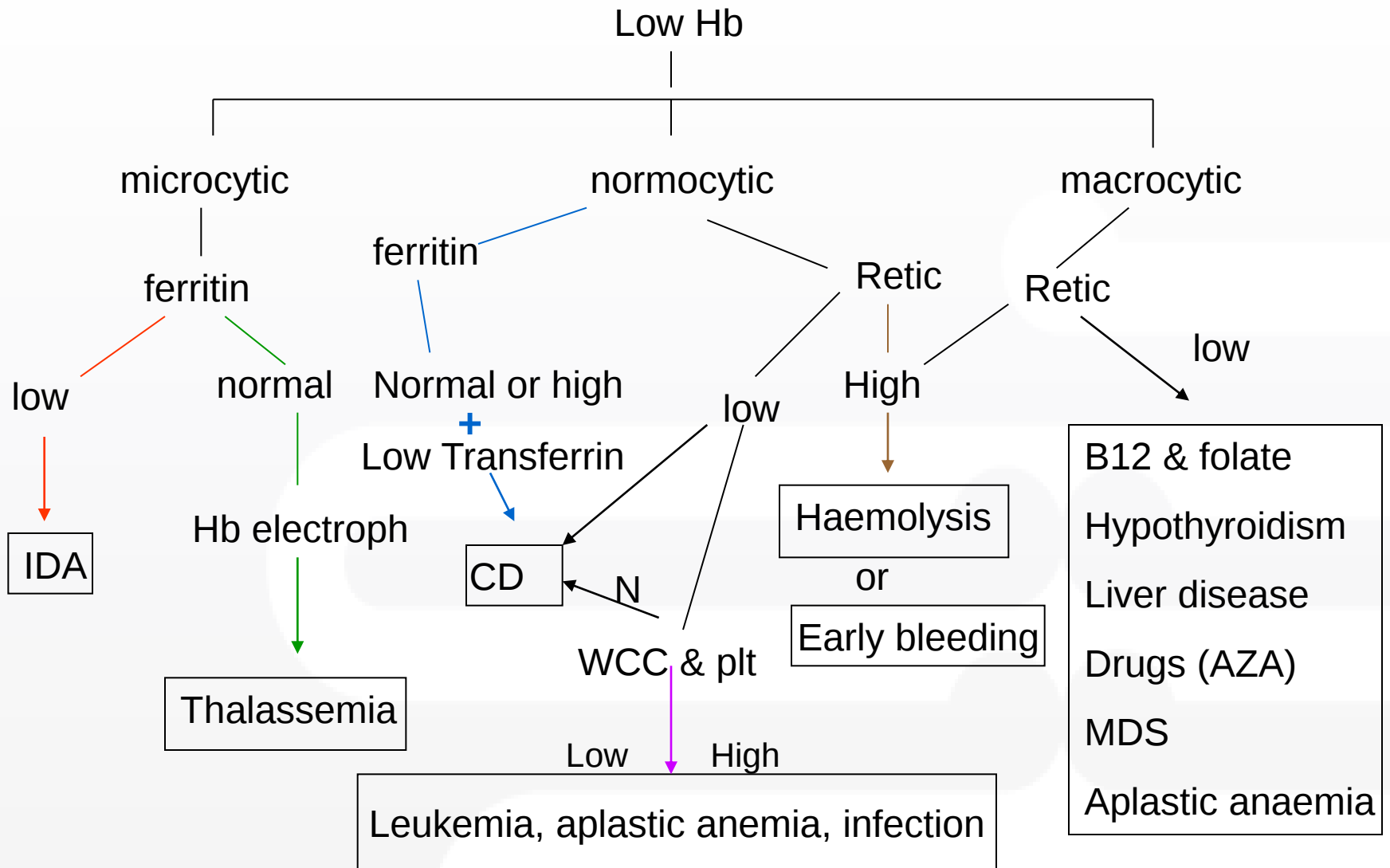
- Hypoplastic anemias
- Transient erythroblastopenia of childhood
- Diamond-Blackfan anemia
- Infections
- Drugs
- Renal disease
- Acute blood loss

Normal or decreased WBC and PLT

- Infection
- Medication associated
- Renal disease
- Splenic pooling (hypersplenism)

Decreased WBC and PLT

- Leukemia
- Aplastic anemia
- Infection



- Normal MCV & reticulocytosis in early bleeding
- Blood film is useful in microangiopathic and leukoerythroplastic picture
- Early Anaemia of Chronic Disease can be microcytic

When to refer anaemia

- Any severe anaemia
- Gastroenterologist
 - Persistent unexplained or progressive
 - High risk iron deficiency or non-responders
 - B12 deficiency
- Hematologist
 - Leucoerythroblastic anaemia
 - Other blood cytopenias
 - Splenomegaly or lymphadenopathy
 - Hemolytic

- Thank you
- Dr Alasdair Patrick
021 681 323