Approach to Anaemia II

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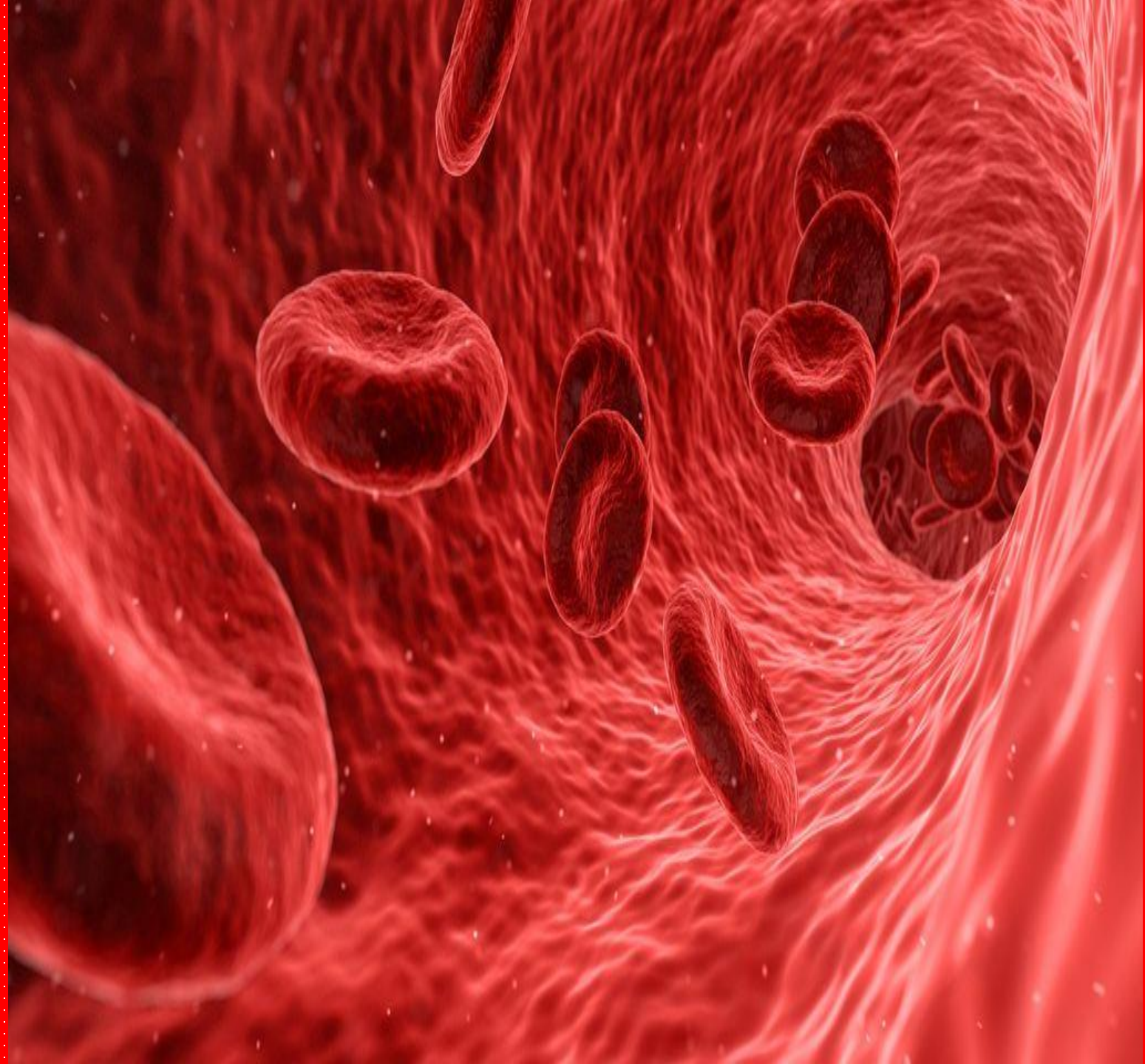


Learning Objectives

At the end of this session, learners should be able to do the following:

- Be familiar with algorithmic approach to diagnosis of anaemia.
- Understand presentation, pathogenesis and management of:

➢ Iron deficiency anaemia.

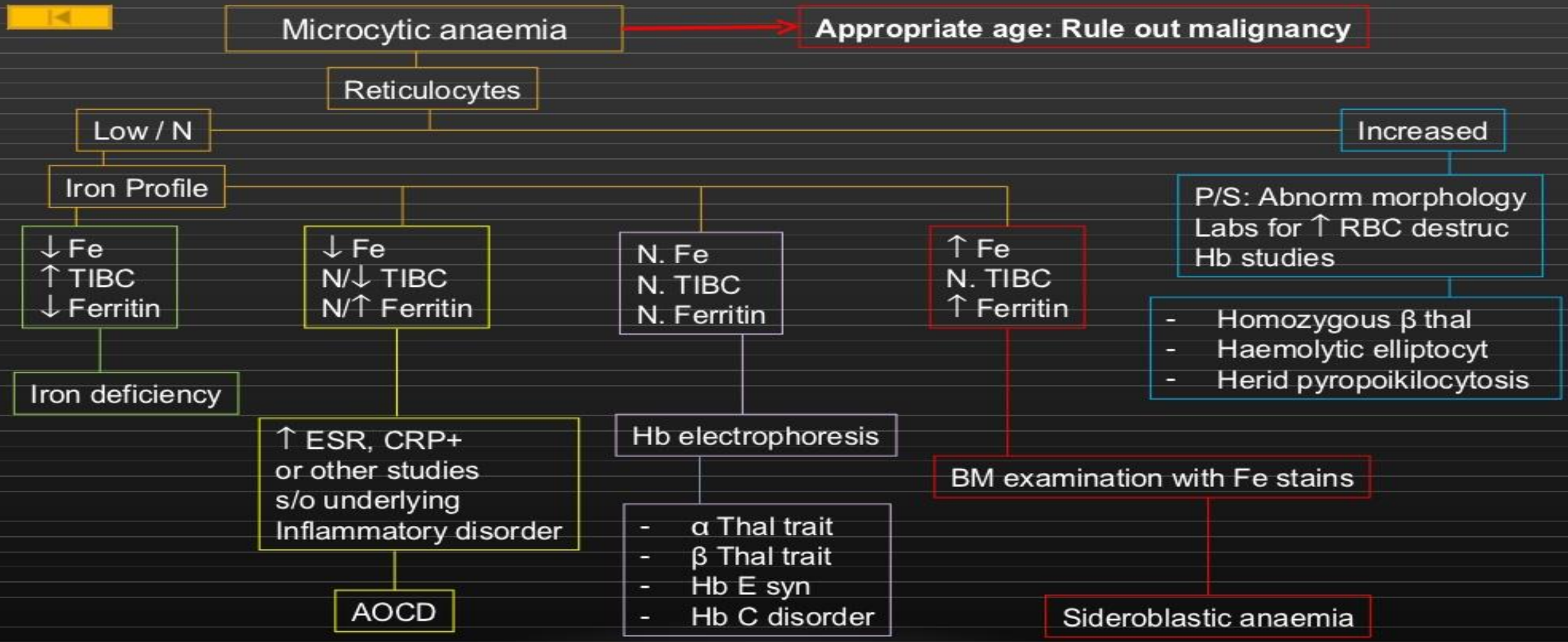
➢ Vitamin B_{12} deficiency anaemia.

➢ Folate deficiency anaemia.

➢ Anaemia of chronic disease.

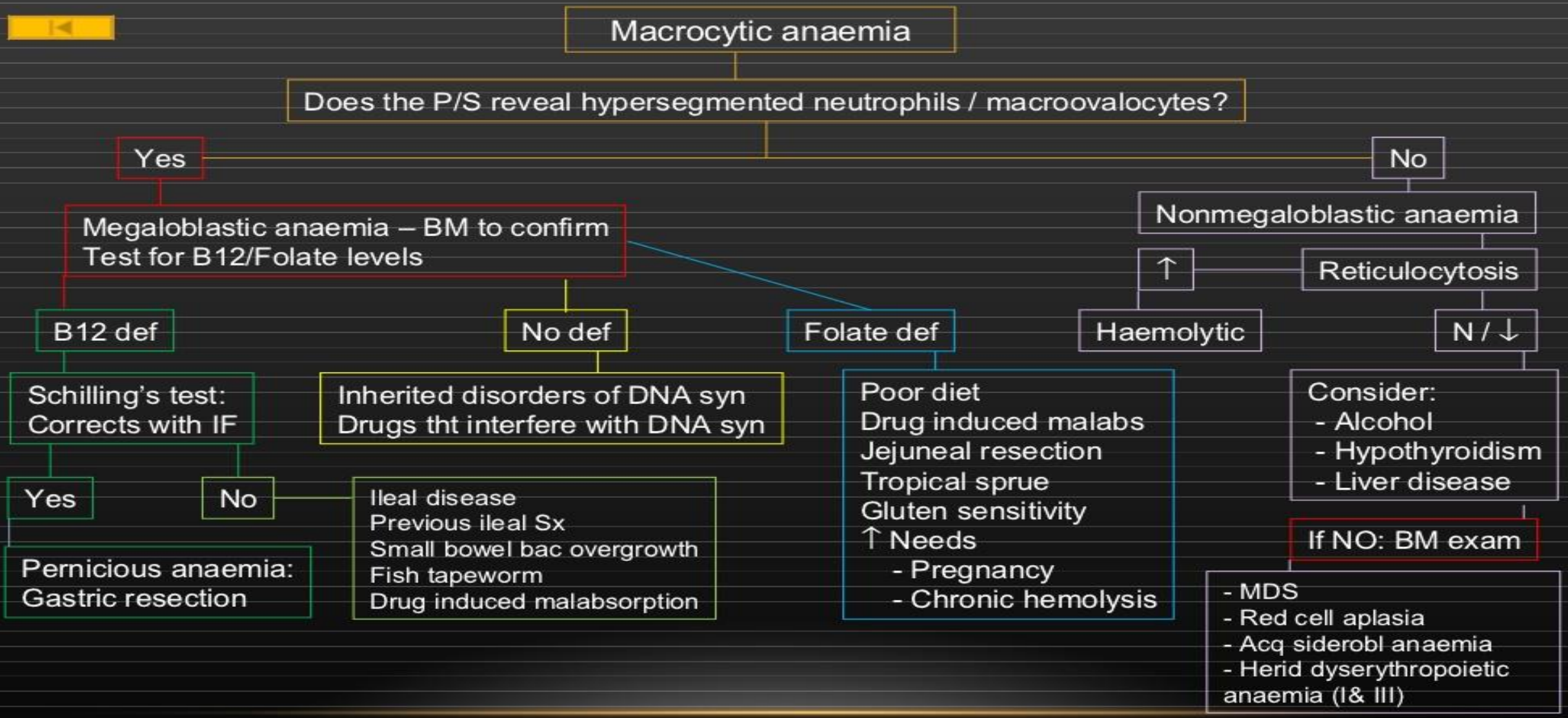
➢ Autoimmune haemolytic anaemias.

Approach to microcytic anaemia



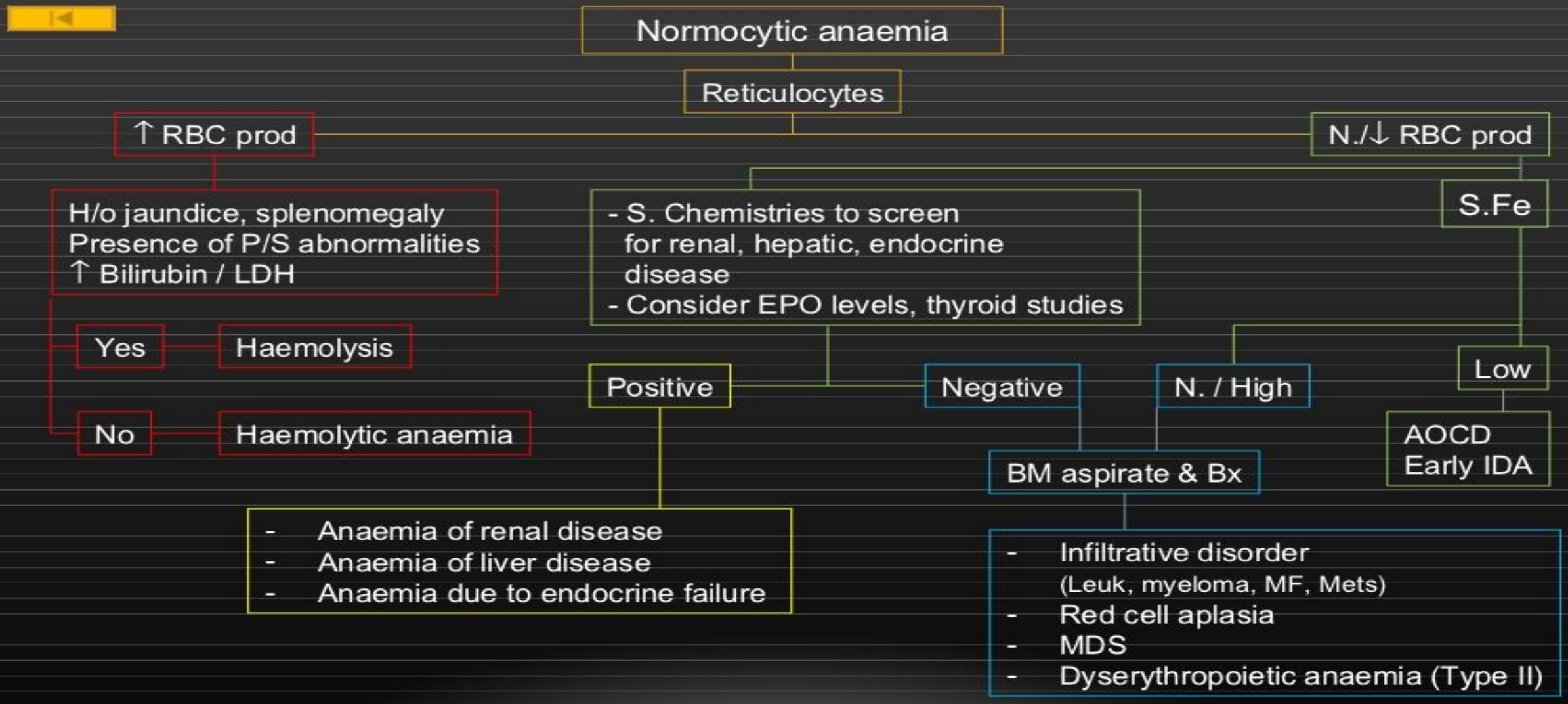
(Ref: Bertil Glader: Anaemia: General Considerations, Wintrobe's Clinical Haematology 11/e, 2004: 951-978)

Approach to macrocytic anaemia



(Ref: Bertil Glader: Anaemia: General Considerations, Wintrobe's Clinical Haematology 11/e, 2004: 951-978)

Approach to normocytic anaemia



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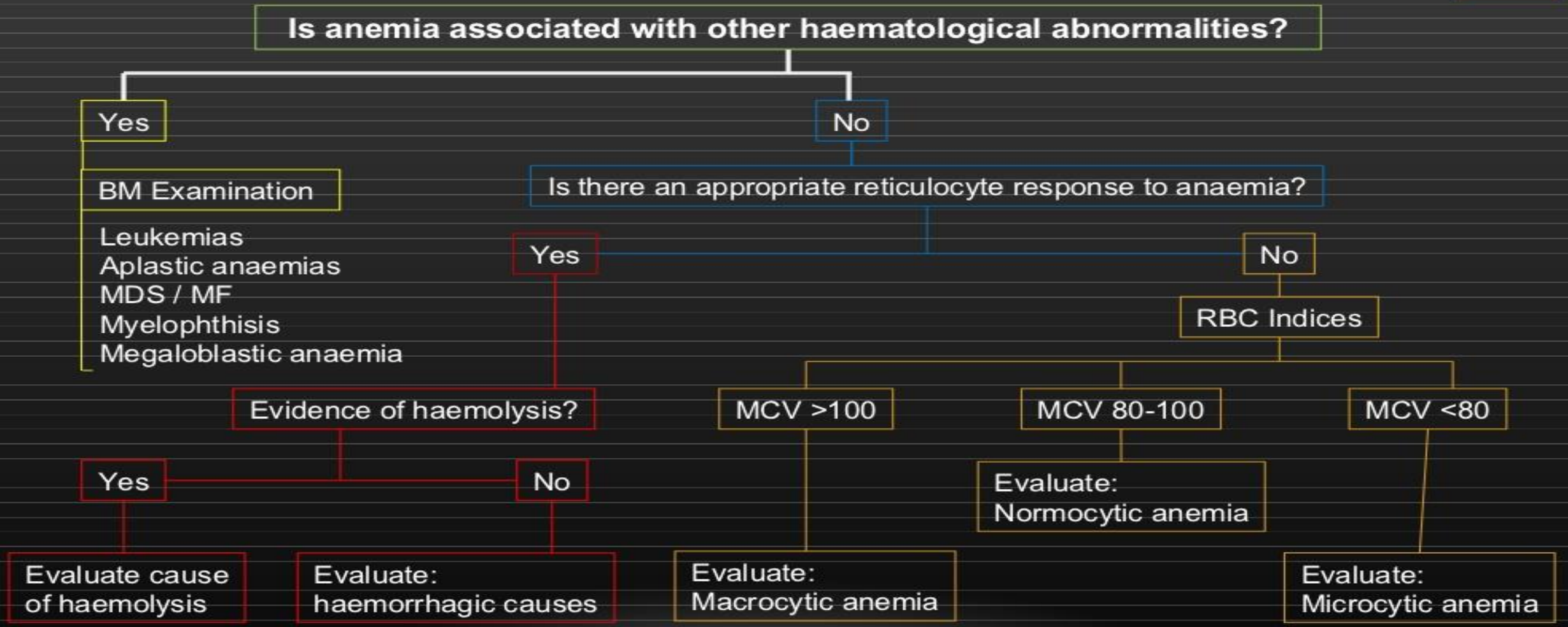
Anaemia with suspected Haematologic abnormalities



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Iron Deficiency Anaemia

- Iron deficiency is the most common cause of anaemia in the world
- The body has limited ability to absorb iron.
- Iron frequently lost through haemorrhage.
- Most iron occur in insoluble ferric (Fe^{3+}) form, which has poor bioavailability.
- Ferrous (Fe^{2+}) is more readily absorbed.

- Iron classified as:

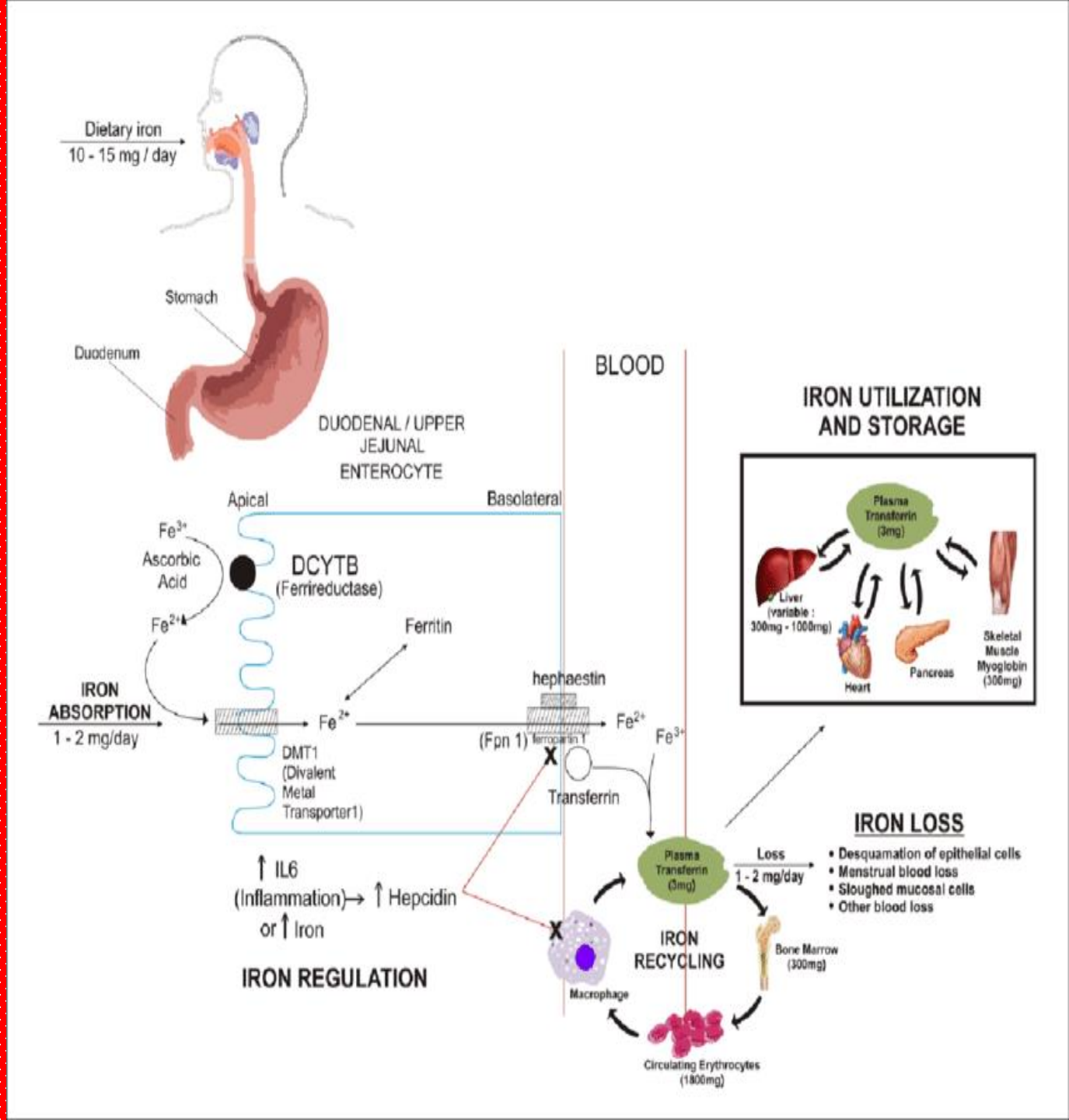
➢***Non-haem*** iron , mainly derived from cereals

➢***Haem*** iron derived from haemoglobin and myoglobin in red or organ meats.

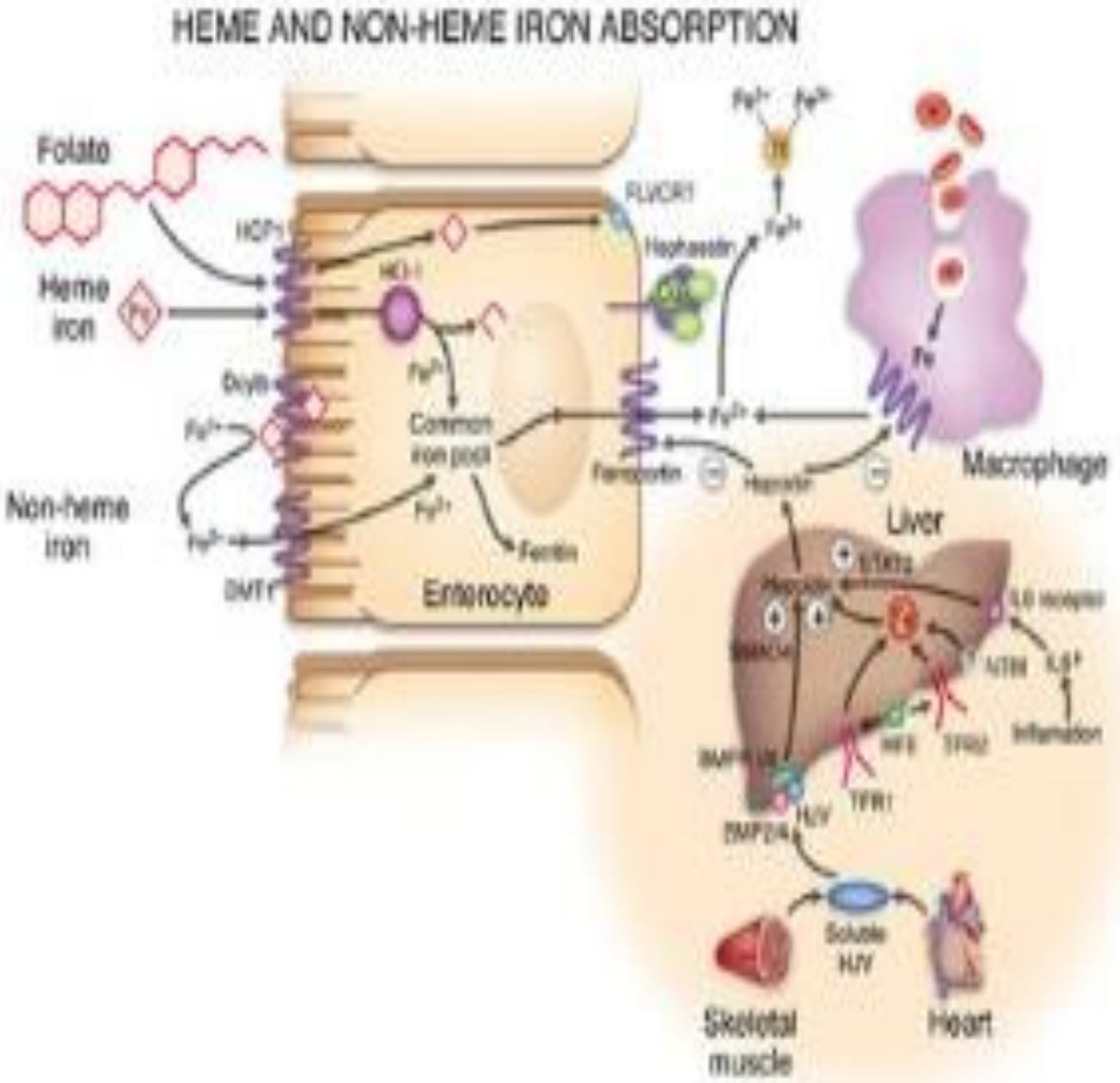
- Haem iron is better absorbed than non-haem iron

Iron absorption

- Most haem iron is absorbed in the proximal intestine.
- Intestinal haem transporter, haem carrier protein 1(HCP1) is the main carrier protein.
- HCP1 highly expressed in the duodenum and upper jejunum.
- HCP1 expression is upregulated by hypoxia and iron deficiency
- Non-haem iron absorption occurs primarily in the duodenum.



- Non-haem iron is reduced from the ferric to the ferrous form by a brush border ferrireductase
- Divalent metal transporter1 (DMT1) transports iron (and other metals) across the apical (luminal) surface of the mucosal cells
- Iron become internalized through transporter molecule ferroportin on basolateral aspect of enterocyte into blood stream and bind to transferrin
- Hepcidin regulates iron absorption by binding to ferroportin causing its internalization and degradation.



- Iron deficiency anaemia develops when there is inadequate iron for haemoglobin synthesis
- Causes of IDA include:

Reproductive	**Menorrhagia**
GIT	Hook worm infestation, Oesophagitis,Oesophageal varices, Hiatus hernia, Peptic ulcer, Inflammatory bowel disease,Haemorrhoids,Carcinoma(stomach, colorectal), Angiodysplasia
Malabsorption	Coeliac disease, Atrophic glossitis, Gastrectomy
Physiological	Growth spurts, Pregnancy
Dietary	Vegan
Genitourinary system	Haematuria
Others	PNH,Frequent venesection e,g.blood donation

- Clinical features include:

➢ PICA-abnormal cravings e.g. for ice or soil

➢ Brittle nails

➢ Spoon-shaped nails (koilonychia)

➢ Atrophy of the papillae of the tongue

➢ Angular stomatitis

➢ Brittle hair,

➢ A syndrome of dysphagia and glossitis (Plummer–Vinson or Paterson–Brown–Kelly syndrome.

➢ Clinical features of underlying cause if any e.g.Portal hypertension with bleeding varices

Investigations

Blood count and film.

- Microcytosis
- Hypochromasia
- Poikilocytosis
- Anisocytosis
- Target cells are seen.
- ↑RDW

Iron studies

- ↓Serum iron
- ↑Iron-binding capacity
- ↓Serum ferritin.
- ↑Serum soluble transferrin receptors.
- ↓Transferrin saturation

Other investigations

- Upper & lower GI endoscopy
- Stool M/C/S & occult blood
- Pelvic USS
- Bone marrow biopsy

Treatment

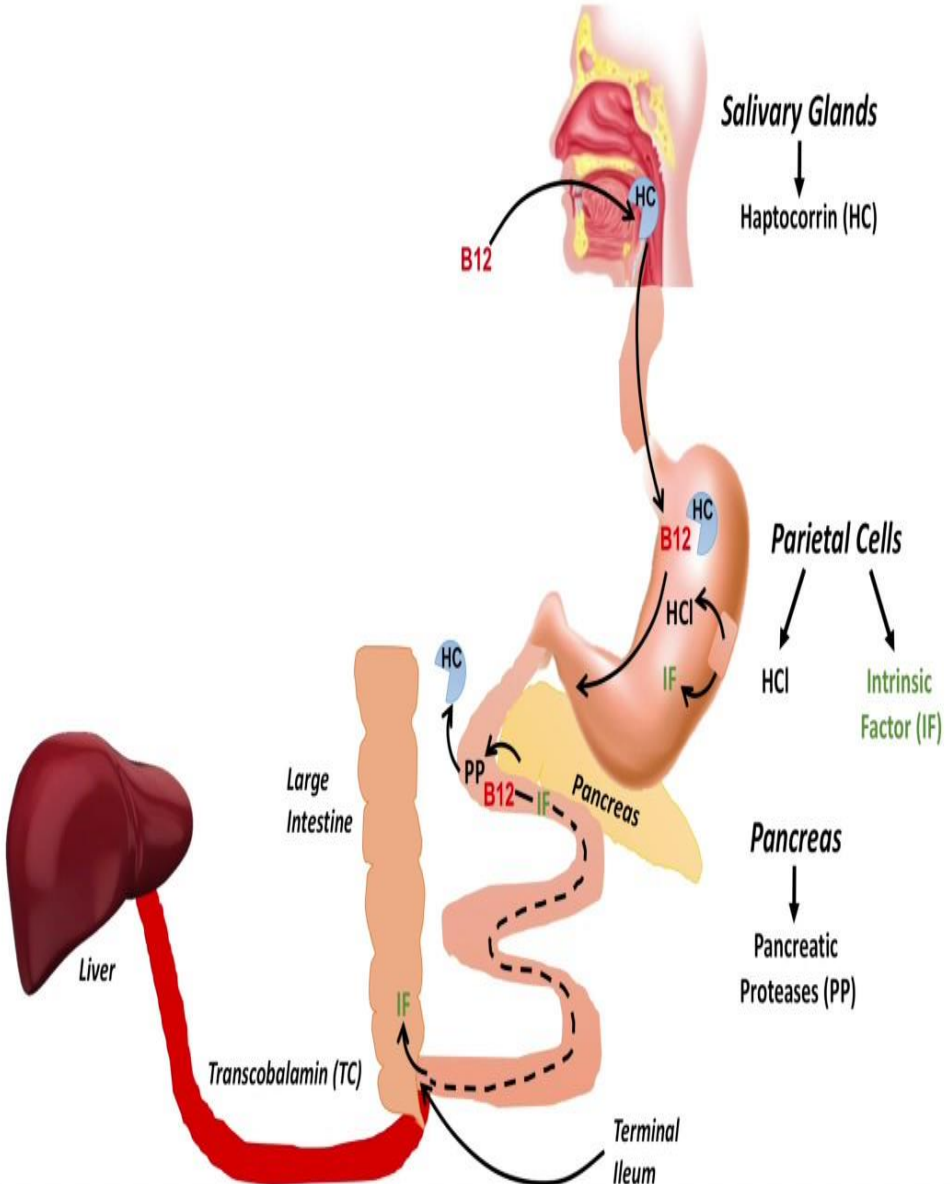
- Look for and treat the underlying cause
- Give iron to correct the anaemia and replace iron stores.
- Give oral iron such as ferrous sulphate (200 mg three times daily)
- Iron replacement should be for 6 months.
- When Hb and MCV are normal it should taken for at least 6 months to replenish Fe stores.
- In severe IDA, Ferrous sucrose infusion can be given up to 1000mg over 2 weeks.
- Response to iron therapy can be monitored using the reticulocyte count and Hb level, with an expected rise in haemoglobin of 1 g/dL per week

Vitamin B_{12} Deficiency

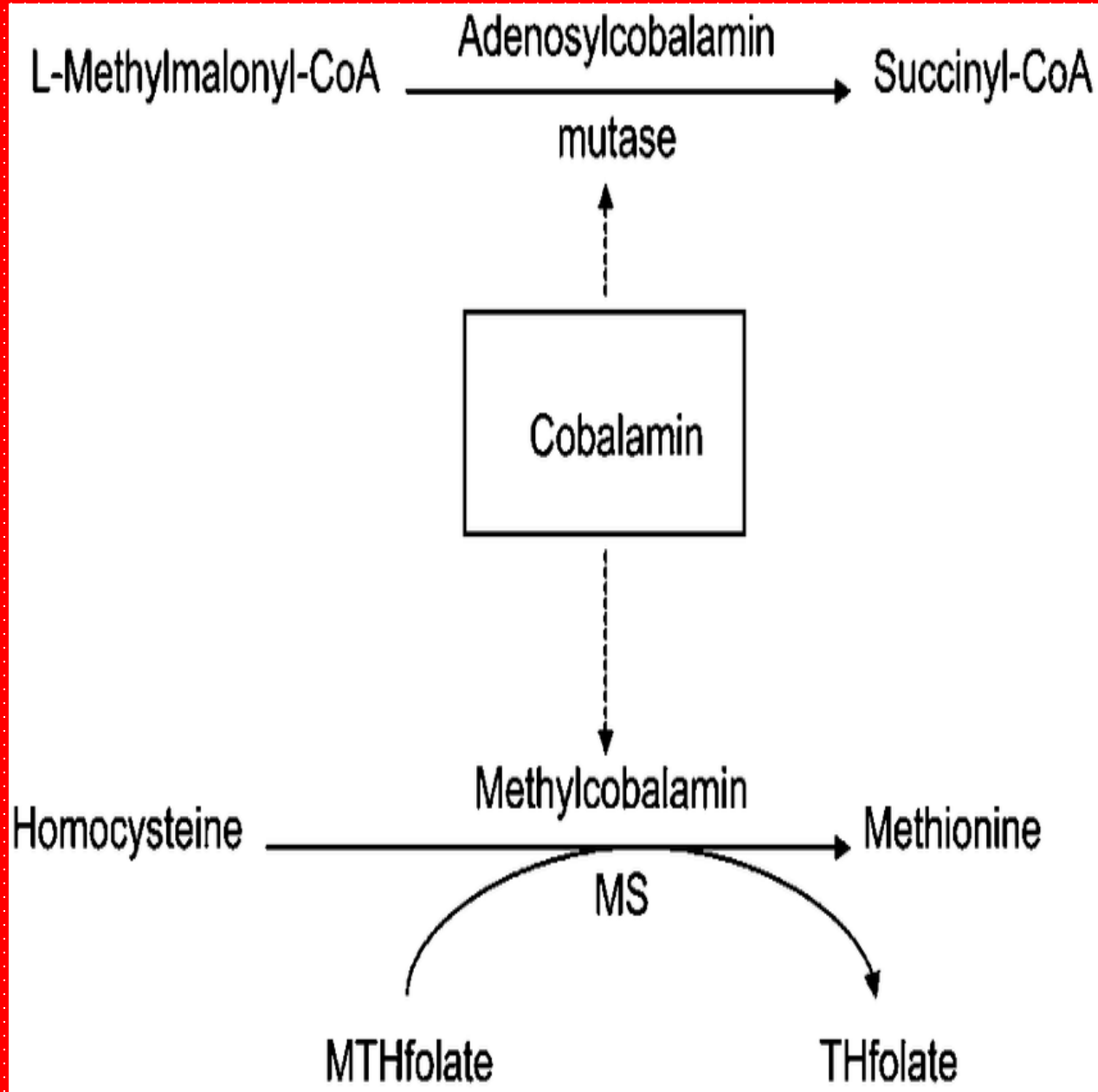
- Vitamin B_{12} is synthesized by certain microorganism
- Humans do not synthesize Vitamin B_{12} and dependent on animal sources.
- It is found in meat, fish, eggs and milk, but not in plants.
- Average adult stores about 2–3 mg, mainly in the liver
- It may take 2 years or more after absorptive failure before B_{12} deficiency develops.
- Main natural cobalamins are:
  - **Deoxyadenosyl-cobalamin**
  - **Methyl-cobalamin**
  - **Hydroxocobalamin .**

- Main function of B_{12} is methylation of homocysteine to methionine
- Demethylation of methyl THF polyglutamate to THF takes place at the same time.
- THF is a substrate for folate polyglutamate synthesis that is key in DNA synthesis.
- Vitamin B_{12} also has a neurological function.
- Deoxyadenosyl cobalamin is a coenzyme for the conversion of methylmalonyl CoA to succinyl CoA
- Succinyl CoA plays a key role in the citric acid cycle, ketone metabolism and heme synthesis.

Vitamin B_{12} Digestion



Vitamin B_{12} Metabolism



Absorption of Vitamin B_{12}

- Vitamin B_{12} is absorbed in the terminal ileum.
- Initially vitamin B_{12} binds to a protein (‘R’ binder) derived from saliva.
- Released from the ‘R’ binder by pancreatic enzymes to bind to intrinsic factor(IF).
- IF is secreted by gastric parietal cells along with H^+ ions.
- It combines with vitamin B_{12} and carries it to specific receptors on the surface of the mucosa of the ileum
- Vitamin B_{12} enters the ileal cells while intrinsic factor remains in the lumen and is excreted.
- Vitamin B12 is transported from the enterocytes to the bone marrow and other tissues by the glycoprotein transcobalamin II (TCII)

Causes of Vitamin B_{12} Deficiency

Low dietary intake	Vegans
Impaired absorption	
Stomach	Pernicious anaemia,Gastrectomy.Congenital deficiency of intrinsic factor
Small bowel	Ileal disease or resection, Bacterial overgrowth, Tropical sprue, pancreatitis, coeliac Disease, Fish tapeworm(Diphyllobothrium latum)
Abnormal utilization	Congenital transcobalamin II deficiency Nitrous oxide (inactivates B_{12})
Drugs	Metformin

Pernicious anaemia(PA)

- PA is an autoimmune disorder characterized by atrophic gastritis with loss of parietal cells in the gastric mucosa.
- It occurs more frequently in fair-haired and blue-eyed individuals and those with blood group A.
- There is consequent failure of intrinsic factor production and vitamin B_{12} malabsorption.
- Clinical features include

➢Yellow lemon skin discolouration

➢Glossitis

➢Angular stomatitis

Neurological features include:

- A progressive polyneuropathy involving the peripheral nerves
- Involvement of the posterior and lateral columns of the spinal cord→subacute combined degeneration of the spinal cord.
- Symmetrical paraesthesiae in the fingers and toes
- Early loss of vibration sense and proprioception
- Progressive weakness and ataxia.
- Paraplegia may result
- Dementia, psychiatric problems, hallucinations, delusions
- Optic nerve atrophy

Investigations

Haematological findings

- Shows the features of a megaloblastic anaemia

Serum vitamin B12

- Usually well below

Bone marrow

- Shows the typical features of megaloblastic erythropoiesis

Serum methylmalonic acid (MMA) and homocysteine(HC)

- Raised in B12 deficiency.

Autoantibodies

- Anti-parietal cell and anti-intrinsic factor antibodies usually positive
- Anti-parietal cell more specific

Schilling test

- Able to evaluate other causes of B_{12} deficiency such as bacterial over growth

Serum Bilirubin & LDH

- Usually raised due ↑ due ineffective erythropoiesis

Management of Vitamin B_{12} deficiency

- Initially Hydroxocobalamin 1000 μg can be given intramuscularly for 7 days
- It is then at 1000 μg weekly for 4 week
- For patients with PA it is then given every 3 months at 1000 μg for the rest of the patient's life.
- Alternatively, it is now recommended that oral B_{12} is given at 2mg per day.
- Rationale is that 1–2% of an oral dose is absorbed by diffusion and does not require IF.

Folate deficiency

- Folate together with Vitamin B_{12} is a key micronutrient in the synthesis of DNA.
- Major dietary sources of folate are,liver,green vegetables, yeast and nuts.
- Adult body store of folate comprise 10-15mg
- Normal daily requirement of folate is 0.1-0.2mg and may last 4 months in absence of exogenous source.
- Folate absorption occurs rapidly in the proximal jejunum.
- Megaloblastic anaemia patients should not be treated empirically with folate alone.
- If they lack vitamin B_{12},giving folic acid alone would potentially precipitate subacute combined degeneration of the spinal cord

Causes of folate deficiency

Nutritional Poor intake	Old age ,Poor social conditions,Starvation,Alcohol excess (also causes impaired utilization)
Poor intake due to anorexia	Gastrointestinal disease,e.g. partial gastrectomy,coeliac disease, Crohn's disease, Cancer
Antifolate drugs	Phenytoin,Primidone,Methotrexate,Pyrimethamine,Trimethoprim
Physiological excess utilization	Pregnancy,Lactation,Prematurity
Pathological	Haematological disease with excess red cell production,e.g. haemolysis,Malignant disease with increased cell turnover, Inflammatory disease, Metabolic disease, e.g. homocystinuria,Haemodialysis or peritoneal dialysis
Malabsorption	Small bowel bacterial overgrowth

Clinical features

Patient may present as follows:

- Asymptomatic
- Present with symptoms of anaemia,
- Symptoms of the underlying cause.
- Glossitis can occur

Investigations

- FBC shows megaloblastic picture
- ↓RBC folate
- Serum folate may be normal
- In suspected occult gastrointestinal disease small bowel biopsy should be performed
- Evaluate for possible cause

Treatment of folate deficiency

- Folate deficiency can be corrected by giving 5 mg of folic acid daily.
- Treatment should be given for about 4 months to replace body stores.
- Any underlying cause, e.g. coeliac disease, should be treated.
- Prophylactic folic acid is given in chronic haematological disorders where there is rapid cell turnover such as Sickle cell anaemia.

Anaemia of chronic inflammation/Disease

Definition

Anemia of chronic disease(AOCD) is a hypoproliferative anemia that develops in response to systemic illness or inflammation.

- It is the second most prevalent after anemia caused by iron deficiency.
- It is the commonest cause of anaemia among patients with chronic illness.
- A variety of clinical conditions can lead to anemia of chronic disease, including infection, cancer and autoimmune conditions

Pathophysiology

- Anemia of chronic disease appears to be a highly coordinated and genetically conserved adaptive response to systemic disease.
- AOCD is characterized by:

➢ Restriction of Fe absorption from the GIT

➢ Sequestration of Fe into macrophages

➢ Suppression of erythropoietin production, inhibition of erythropoiesis and decreased RBC survival

- Sequestration of Fe within macrophages could have the following beneficial effects:

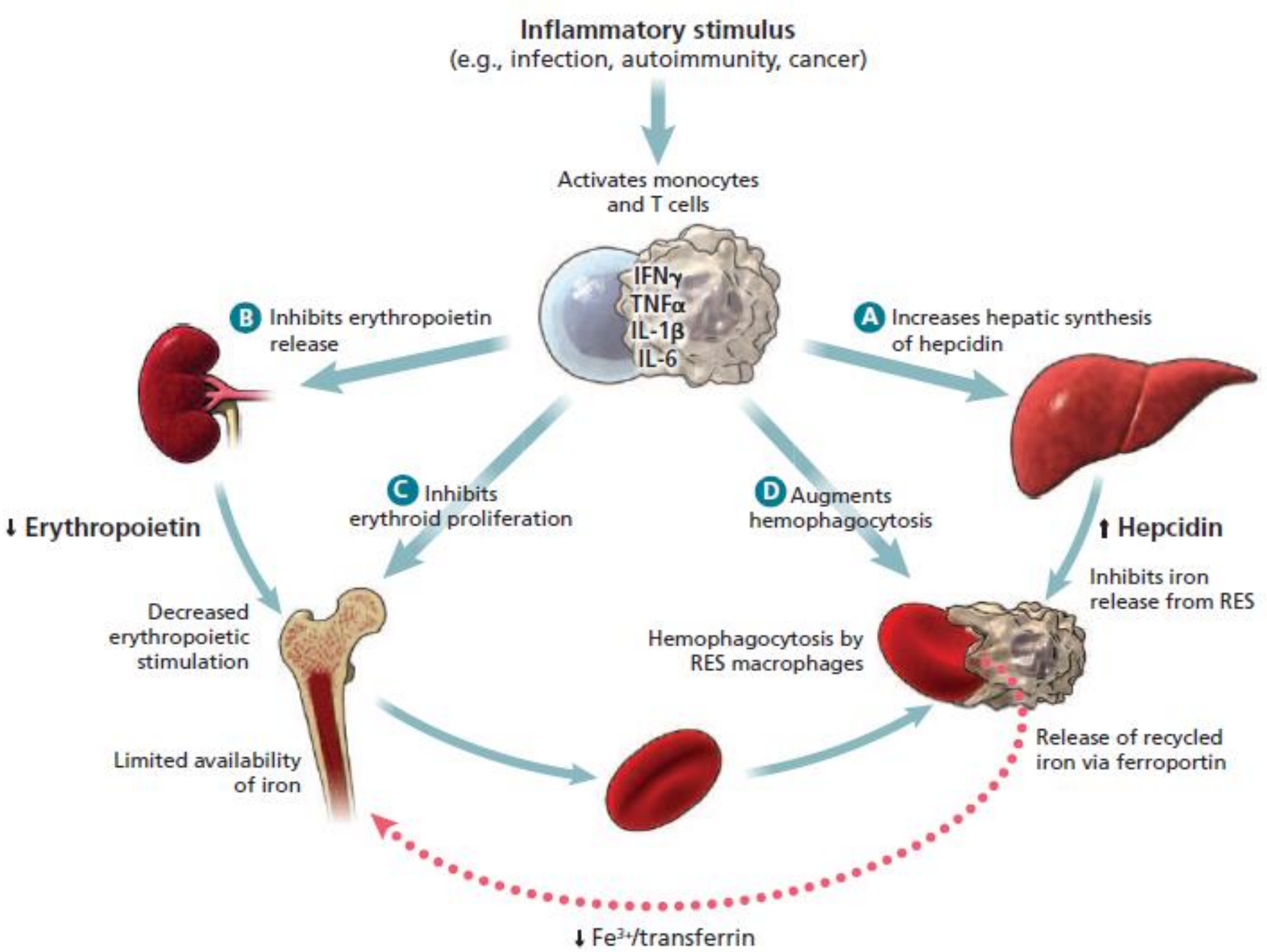
➢ Iron is an essential nutrient required for the growth of many microorganisms.

➢ Iron loading promotes infection and facilitates the growth of malignant cells

➢ Hypoferremia is therefore thought to be an innate antimicrobial strategy.

➢ Decreased bone marrow production reduces nutrient utilization in times of stress

Pathogenetic Mechanism of AOCD



- In inflammatory diseases, cytokines released by activated leukocytes and other cells exert multiple effects that contribute to the reduction in hemoglobin levels
- Cytokines IFN-γ, TNF-α, IL-1β,IL-6 have been implicated in pathogenesis of AOCD.
- Cytokines, especially IL-6 promote hepcidin synthesis in the liver.
- Hepcidin binds to ferroportin on the enterocytes and macrophages leading to internalization and degradation of ferroportin
- This results in sequestration of Fe within the macrophages restricts its absorption for the GIT.

- Overall result is limiting iron availability to erythroid precursors
- There is inhibition of erythropoietin release from the kidney IL-1_{β} and TNF-α
- Direct inhibition of the proliferation of erythroid progenitors IFN-$_{\gamma}$,TNF-α, IL-1_{β}.
- Augmentation of erythrophagocytosis by reticuloendothelial macrophages by ,TNF-α

Clinical features

Patient may present as follows:

- Asymptomatic
- Present with symptoms of anaemia,
- Symptoms of the underlying cause

Investigations

- FBC shows normocytic normochromic picture
- ↓Serum iron
- Normal or ↓Transferrin
- ↓Transferrin saturation
- Normal or ↑ ferritin
- Normal soluble transferrin receptors
- TIBC normal
- ↓Serum erythropoietin

Treatment

- Treat underlying cause
- Transfuse if there is indication or if hemoglobin less than 8 g/dL,
- Give erythropoietic agents e.g. epoetin-alpha, darbopoeitin-alpha, and epoetin-beta.
- Novel agents include:

➢ IL-6 antagonist- Tocilizumab

➢ Direct hepcidin antagonists

➢ Ferroportin agonist

Autoimmune haemolytic anaemias

- Autoimmune haemolytic anaemias (AIHA) are acquired disorders characterized by increased red cell destruction due to autoantibodies on RBCs.
- AIHA usually manifest with a positive direct antiglobulin test(DAT), which detects the autoantibody on the surface of the patient's red cells.
- AIHA is divided into 'warm' and 'cold' types, depending on whether the antibody attaches better to the red cells at body temperature (37°C) or at lower temperatures.
- In warm AIHA, IgG antibodies predominate and the DAT is positive with IgG alone,IgG and complement, or complement only.
- In cold AIHA, the antibodies are usually IgM.

Pathogenesis

- IgM or IgG red cell antibodies which fully activate the complement cascade cause lysis of red cells in the circulation(intravascular haemolysis).
- IgG antibodies frequently do not activate complement and the coated red cells undergo extravascular haemolysis in the RES.
- Some RBCs lose part of the cell membrane through partial phagocytosis and circulate as spherocytes until they become sequestered in the spleen.

Characteristics of AIHAs

	Warm	Cold
Temperature at which antibody attaches best to red cells	37°C	Lower than 37°C
Type of antibody	IgG	IgM
Direct Coombs' test	Strongly positive	Positive
Causes of primary conditions	Idiopathic	Idiopathic
Causes of secondary condition	Autoimmune disorders, e.g. systemic lupus erythematosus Chronic lymphocytic leukaemia Lymphomas Hodgkin's lymphoma Carcinomas Drugs, many including methyldopa, penicillins, cephalosporins, NSAIDs, quinine, interferon	Infections, e.g. infectious mononucleosis, *Mycoplasma pneumoniae*, other viral infections (rare) Lymphomas Paroxysmal cold haemoglobinuria (IgG)

‘Warm’ autoimmune haemolytic anaemias

Clinical features

- Present as a short episode of anaemia and jaundice
- Often remit and relapse and may progress to an intermittent chronic pattern.
- Spleen is often palpable.
- Infections or folate deficiency may provoke a profound fall in the haemoglobin level.
- May be associated with lymphoid malignancies or diseases such as rheumatoid arthritis and SLE or drugs

Investigations

- Haemolytic anaemia is evident.
- Spherocytosis is present as a result of red cell damage.
- DAT is positive, with either IgG alone, IgG and complement, or complement alone on RBC surface.
- Autoantibodies may have specificity for the Rh blood group system.
- Autoimmune thrombocytopenia and/or neutropenia may also be present (Evans' syndrome)

Treatment

- Blood transfusion may be necessary if there is severe anaemia.
- Corticosteroids (e.g. prednisolone in doses of 1 mg/kg daily)are effective in inducing a remission in most patients.
- Splenectomy may be necessary if there is no response to steroids or if remission is not maintained
- Immunosuppressive drugs, such as azathioprine and rituximab, may be effective in patients who fail to respond to steroids and splenectomy.

‘Cold’ autoimmune haemolytic anaemias

Clinical features

- At low temperatures IgM antibodies attach to RBCs and cause them to agglutinate in the cold peripheries of the body.
- Activation of complement may cause intravascular haemolysis when the cells return to the higher temperatures in the core of the body.
- Infections from organisms as Mycoplasma, cytomegalovirus, Epstein–Barr virus (EBV) result in increased synthesis of polyclonal cold agglutinins producing a mild to moderate transient haemolysis.
- Chronic cold haemagglutinin disease (CHAD) after exposure to cold, the patient develops an acrocyanosis similar to Raynaud’s as a result of RBC autoagglutination.

Investigations

- Typical features of haemolytic anaemia present.
- RBCs agglutinate in the cold or at room temperature.
- DAT is positive with complement (C3d) alone.
- Monoclonal IgM antibodies with specificity for the Ii blood group system.

Treatment

- Blood transfusion may be necessary.
- Treat the underlying cause if possible.
- Patients should avoid exposure to cold.
- Steroids, alkylating agent and splenectomy are usually ineffective.
- Treatment with anti-CD20 (rituximab) has been successful in some cases

References

- Oxford Handbook of Clinical Haematology, 2nd Edition
- Oxford Handbook of Clinical Medicine, 9th Edition
- Wintrobe’s clinical Haematology,2004:958-978
- Anaemia:General considerations-Bertil Glader

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Questions??