Pernicious Anaemia/IDA

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GI HEPATOLOGY ECHO OF SUB-SAHARAN AFRICA
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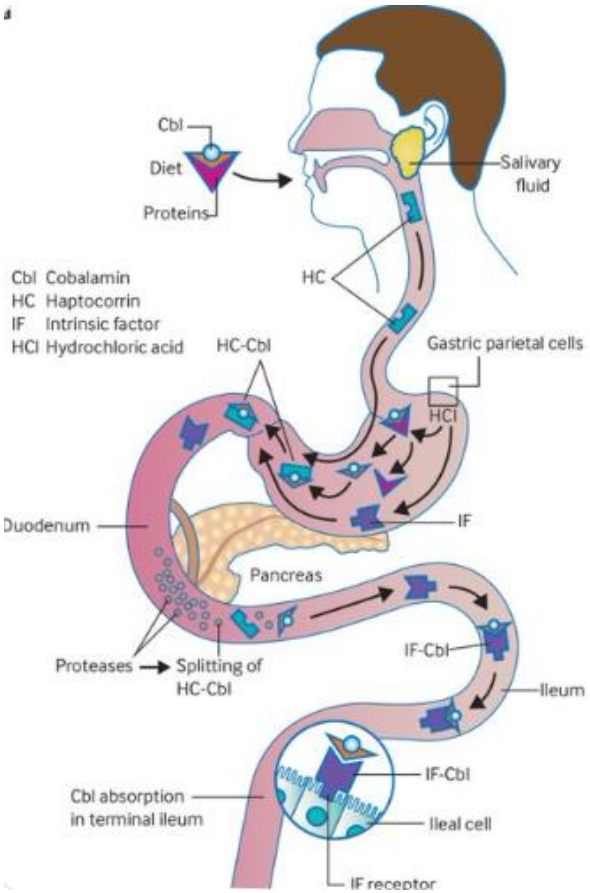
Pernicious Anaemia

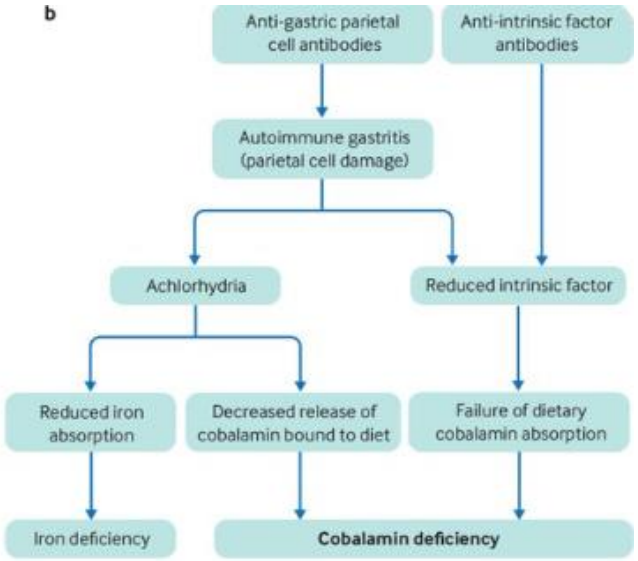
- Autoimmune disease that affects the gastric mucosa and results in gastric atrophy
- Antibodies are produced against cells of the stomach or against IF
- This leads to destruction of parietal cells and failure to produce intrinsic factor, resulting in vitamin B_{12} Malabsorption
- Most common cause of cobalamin deficiency anaemia worldwide

Pernicious Anaemia

- More common in temperate climate
- Affects both sexes equally
- Age of presentation is > 60 yrs (median age 70-80)
- The relationship between PA and H pylori is still unclear
- Genetic: PA has a familial link with < 19% having a family member with PA
- Genotypes HLA- DRB1*03 and DRB1*04 associated with PA and other AI disease

Absorption of B_{12}





Absorption of B_{12}

- In stomach, B_{12} is combined with intrinsic factor (IF) which is synthesised by the gastric parietal cells
- The IF-B_{12} complex can bind to a specific surface receptor in distal ileum where it is absorbed and IF destroyed
- Vitamin B_{12} is absorbed into portal blood where it becomes attached in the plasma to transcobalamin which deliverers B12 to bone marrow and other tissues

Causes of macrocytic anaemia	Causes of cobalamin deficiency
Hypoplastic anaemia, myelodysplastic syndrome	Total or partial gastrectomy Gastric bypass or other bariatric surgery Ileal resection or organ reconstructive surgery
Folate deficiency	Corpus-predominant *Helicobacter pylori* gastritis
Liver disease (alcoholic, advance cirrhosis, poor dietary intake)	Inflammatory bowel disease, tropical sprue
Haemolytic anaemia, response to haemorrhage	Imerslund–Gräsbeck and other syndromes
Drugs (e.g., methotrexate, azathioprine, 6-mercaptopurine, acyclovir, 5-florouracil, phenobarbital)	Protein-bound vitamin B12 malabsorption
Chronic obstructive pulmonary disease	Mild atrophic gastritis
	Use of metformin or drugs that block stomach acid
	Vegan of vegetarian diet, or diet low in meat and dairy products

Chronic Gastritis

loss of gastric mucosal folds and thinning of the gastric mucosa

Type A (autoimmune)

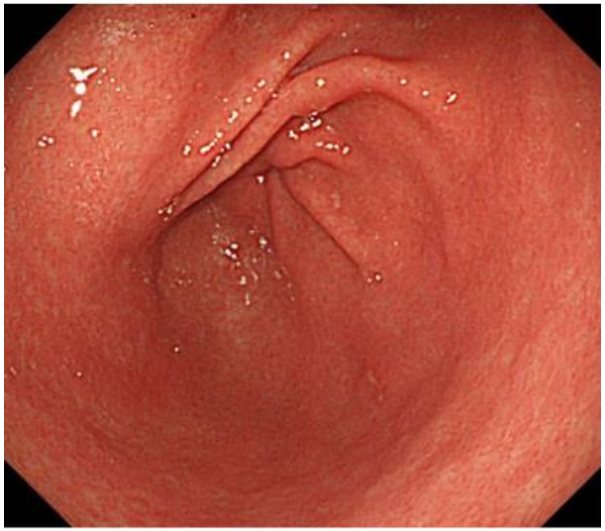
Involves the fundus and body, spares the antrum

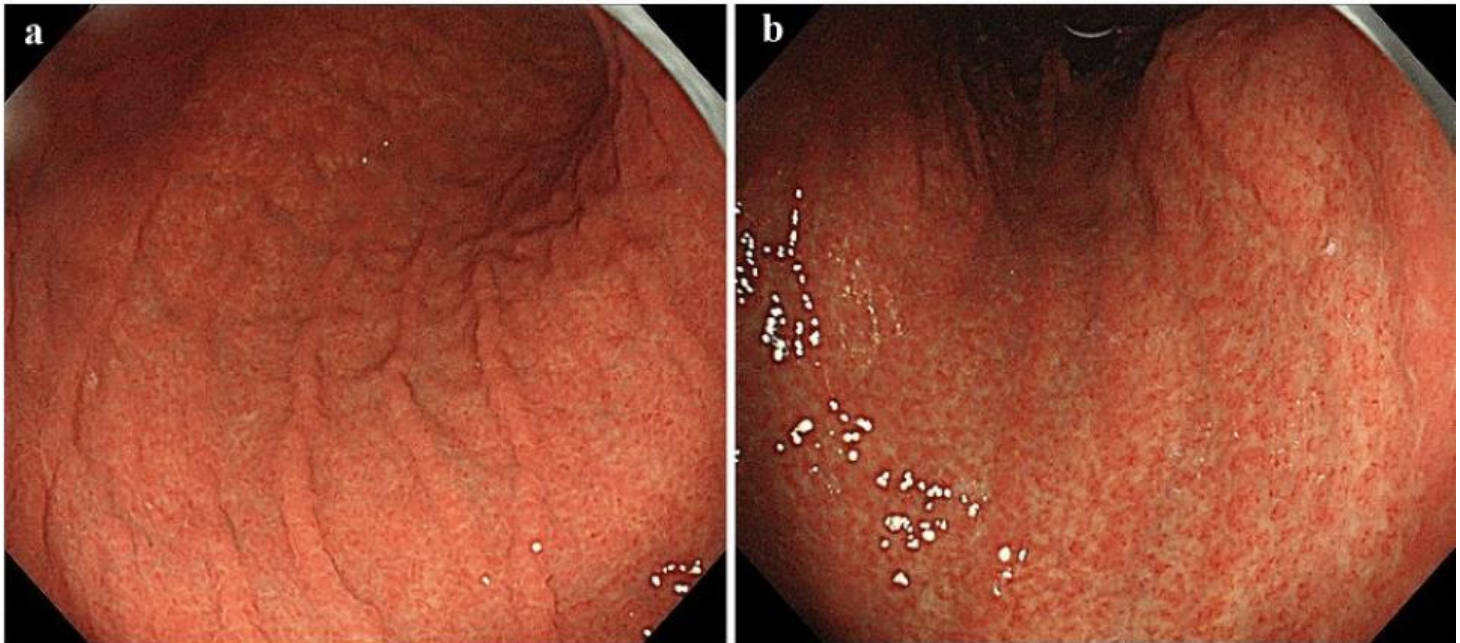
Type B (non-autoimmune)
Involves antrum, fundus & body

TABLE 1. TYPES OF CHRONIC GASTRITIS.

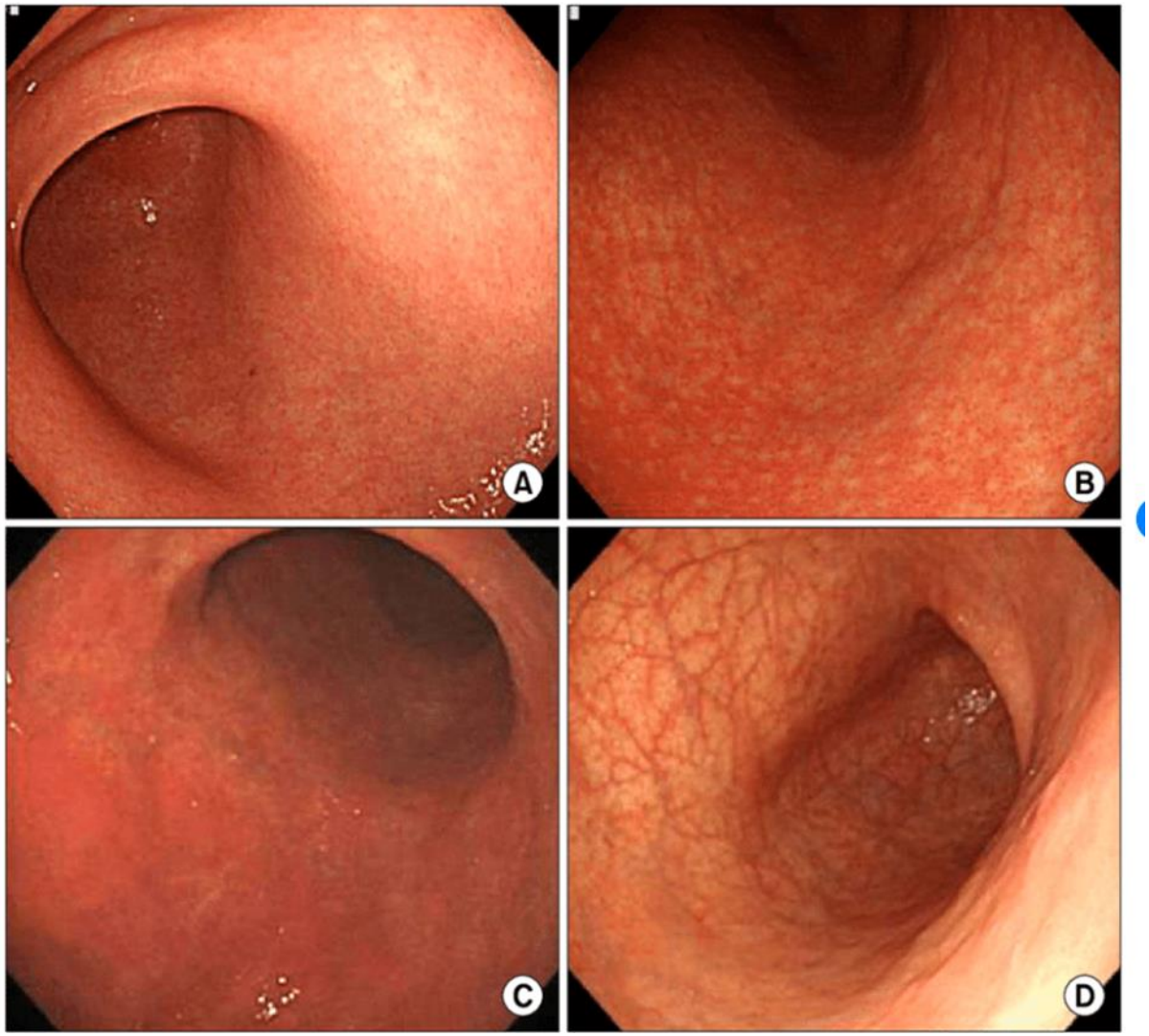
Type A gastritis
Antrum spared
Antibodies to parietal cells and intrinsic factor
Low serum pepsinogen I concentrations
Achlorhydria
Hypergastrinemia and gastric carcinoids
Vitamin B_{12}–deficient megaloblastosis
Type B gastritis
Antrum involved
Helicobacter pylori infection
Hypogastrinemia

Early autoimmune gastritis

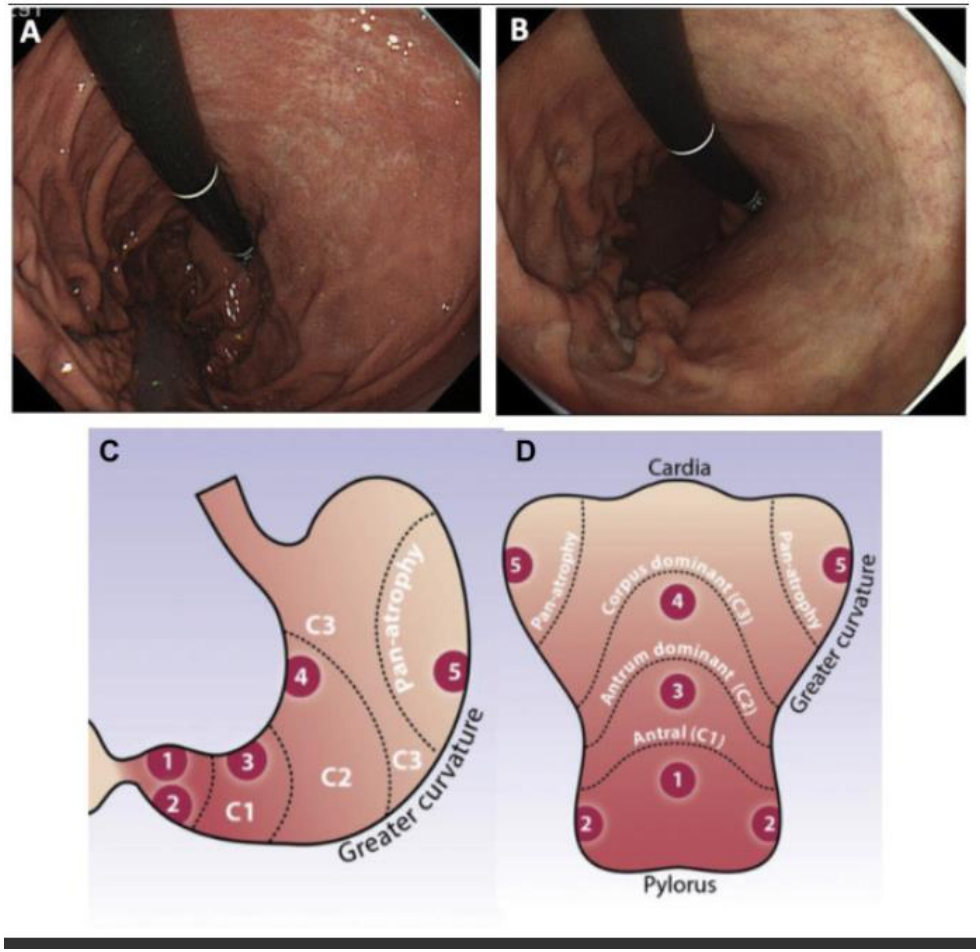




Atrophic changes



Atrophic gastritis



Gastrointestinal complications

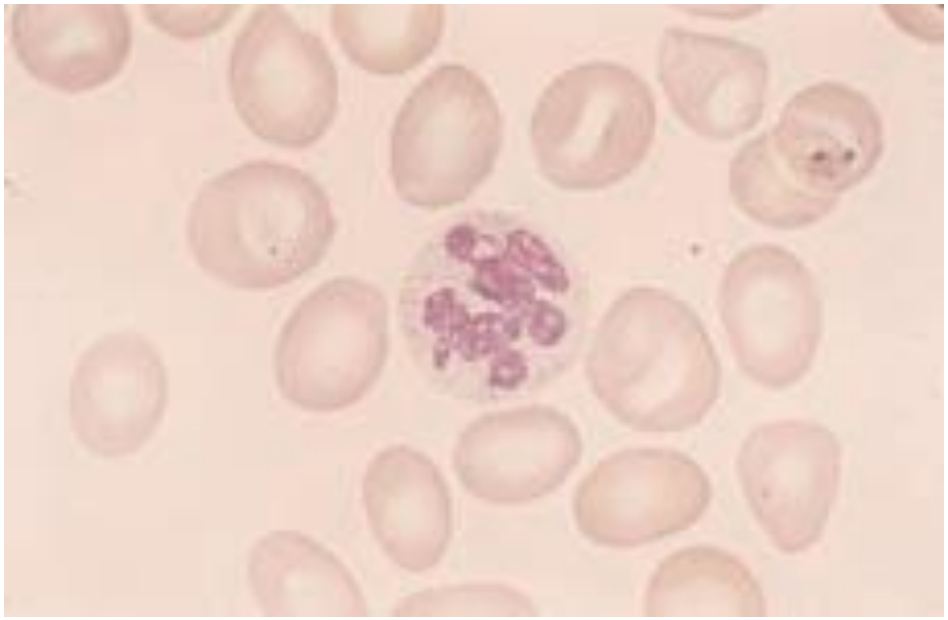
- Tongue smooth and beefy red – atrophic glossitis
- Megaloblastosis of the epithelial cells of the small intestines may result in diarrhoea and malabsorption
- Intestinal metaplasia risk factor for adenocarcinoma
- Achlorhydria and bacterial overgrowth may also lead to formation of carcinogenic nitrosoamines
- ↑ risk of gastric carcinoma + gastric carcinoid tumours

Neurologic complications

- Peripheral neuropathy (glove and stocking paraesthesia)
- Sub-acute combined degeneration
- Mixture of posterior column lesion : vibration & position sense & sensory ataxia with + Romberg sign
- Lateral column lesions limb weakness, spasticity & extensor plantar responses
- Cerebral: mild personality defects, memory loss, frank psychosis (megaloblastic madness)

Investigation

- Macrocytic anaemia with ↓ in in absolute reticulocytes
- Oval macrocytes
- Hypersegmented neutrophils
- Pancytopenia rates 5 – 37%
- Severe cases of PA present with pseudothrombotic microangiopathy: heamolysis, thrombocytopenia and schistocytosis with high mean LDH levels

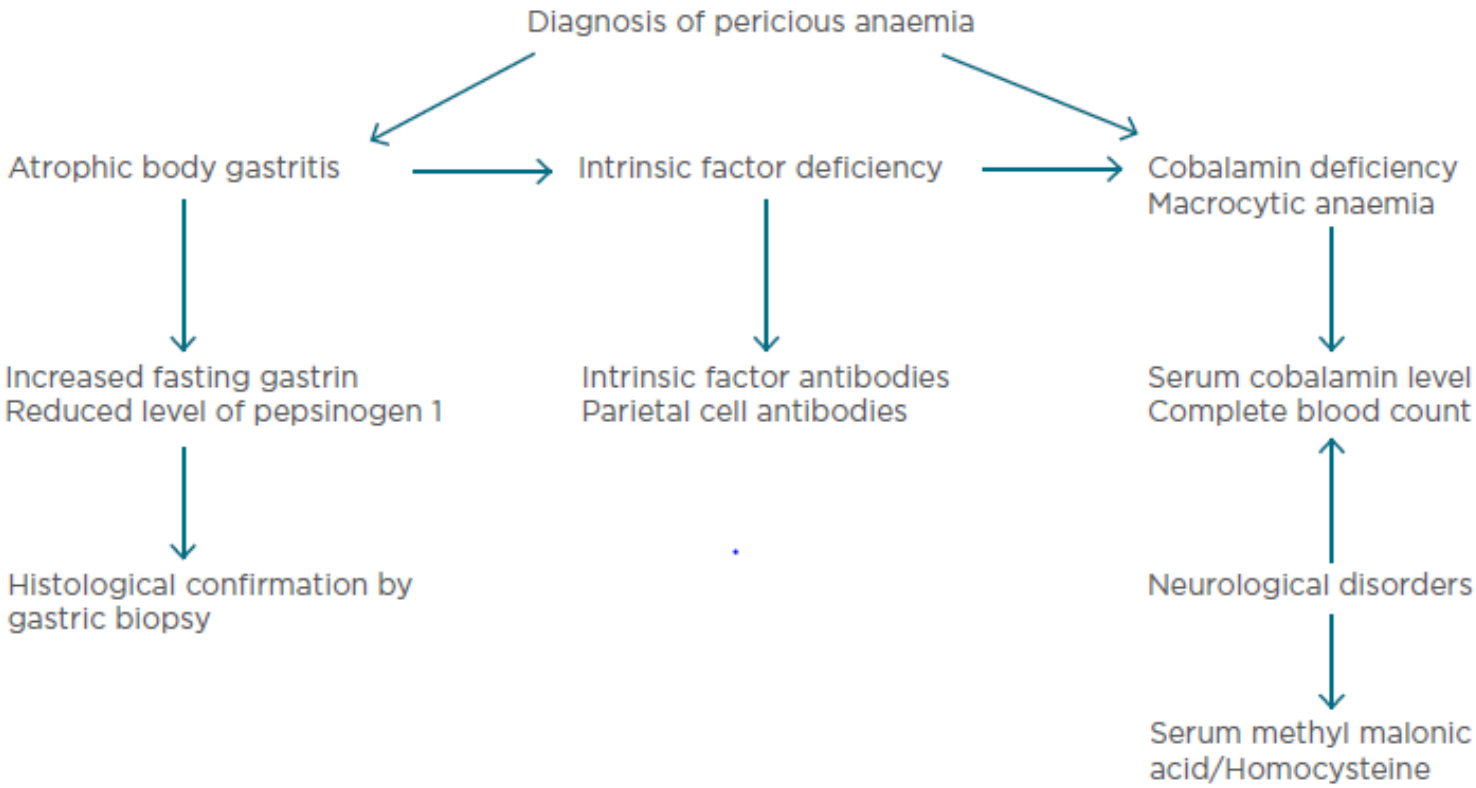


Laboratory diagnosis

- Megaloblastic anaemia (MCV > 100)
- Low B12 levels (< 200 pg/ml)
- Gastric atrophy (gold standard with topography)
- Presence of antibodies to gastric parietal cell or IF

Investigation

- NB to differentiate between B12 and folate deficiency as tx of B12 with folate may reverse megaloblastic blood picture but neurologic complication may worsen
- Measurement of serum holotranscobalamin II
  - Fall before vitamin B_{12}
- ↑ Methylmalonic acid level is specific for B12 deficiency
- Serum homocysteine is less specific because also elevated in folate deficiency


Diagnosis of pericious anaemia
Atrophic body gastritis
Intrinsic factor deficiency
Cobalamin deficiency
Macrocytic anaemia
Increased fasting gastrin
Reduced level of pepsinogen 1
Intrinsic factor antibodies
Parietal cell antibodies
Serum cobalamin level
Complete blood count
Histological confirmation by
gastric biopsy
Neurological disorders
Serum methyl malonic
acid/Homocysteine

Associations with other Autoimmune disease

- Hashimoto's thyroiditis (3-32%), commonest
- Insulin dependent diabetes mellitus (3-4%)
- Addison's disease
- Primary ovarian failure
- Primary hypoparathyroidism
- Graves' disease
- Vitiligo (2-8%)
- Myasthenia gravis
- Lambert- Eaton syndrome

Treatment

- Vitamin B12 administered parenterally
  - intramuscular injection of 1000 mcg every day for the first week
  - Then weekly for a month
  - Followed by monthly injections

PA requires lifelong treatment

Can give oral (1000 -2000ug) per day if tolerated and if IM contraindicated i.e. clotting disorder, but NOT for neurological complications

There are approved sublingual and intranasal preparations

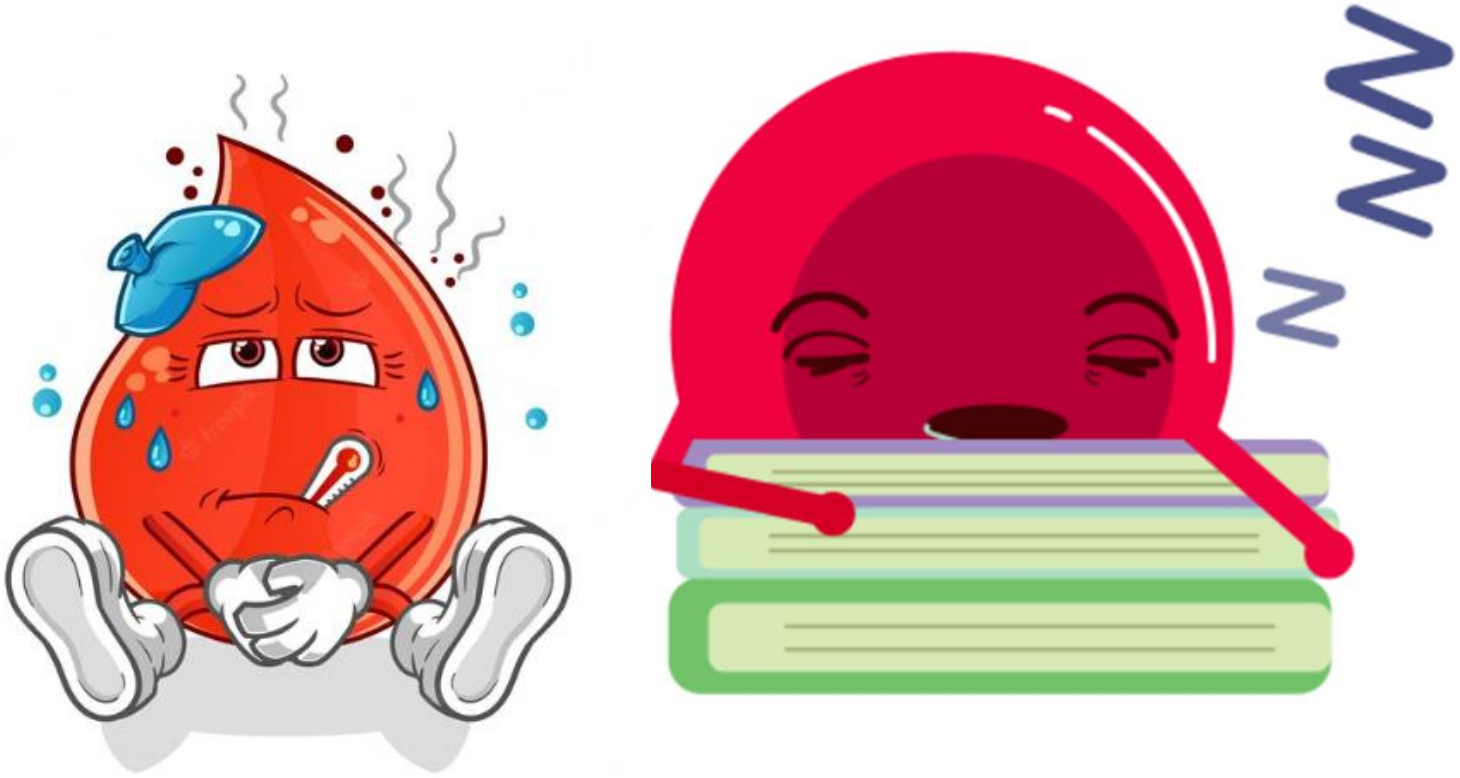
Monitoring

- ↑ in reticulocyte count within 3 days of Tx
- ↓ levels of methylmalonic acid first 5 days of Tx
- Sustained normalisation of B12 occurs following 2 weeks of therapy
- Macrocytosis correction takes place during the first month
- Surveillance is mandatory to detect early + long term consequences i.e. GC, carcinoids

Surveillance

- Advanced atrophic gastritis (severe atrophic changes in both antrum & corpus – high quality endoscopy every 3 years
- Advanced AG & family hx of gastric cancer – every 1-2 years after dx
- No surveillance for mild to moderate atrophy
- Autoimmune gastritis endoscopy every 3-5 years
- If neuroendocrine tumors were removed - surveillance endoscopy every 1-2 years

Iron deficiency anaemia



Introduction

- Most common nutritional disorder worldwide
- Accounts for half of anaemia cases
- Affects 3% of adults & slightly more common in women < 50yrs
- Can results from inadequate intake, decreased iron absorption, increased iron demand & increased iron loss

Introduction

- Menstrual loss is common cause of IDA in premenopausal women
- In adult men and post menopausal women often due to chronic blood loss from GI tract
- IDA may be first presentation of colonic or oesophago-gastric carcinoma

Table 1 Pathological disorders associated with iron deficiency anaemia

Chronic blood loss	
Digestive tract	Neoplastic—most commonly colonic adenocarcinoma
	Inflammatory—for example, peptic ulceration, IBD
	Vascular malformations—angiodysplasia
	Parasitic—for example, hookworm
Genito-urinary tract	Haematuria, pathological gynaecological bleeding—all causes, including malignancy
Respiratory tract	Recurrent epistaxis, haemoptysis—all causes
Malabsorption syndromes	
Hypochlorhydria	Atrophic gastritis
	Helicobacter pylori infection
	Gastrectomy/gastric bypass
	Proton-pump inhibitors
Iron chelation	Tea, coffee, calcium, flavonoids, oxalates, phytat
	Wide range of antacids, Pica syndrome
Enteropathies	Coeliac disease
	Crohn's disease
	NSAID enteropathy
	Rarer enteropathies, for example, Whipple's disease, bacterial overgrowth
Small bowel surgery	Small bowel resection/bypass
Genetic disorders	Iron-refractory iron deficiency anaemia
	Divalent metal transporter 1 deficiency anaemia
Associated with the anaemia of chronic disease	
Chronic heart failure	
Chronic kidney disease	
Chronic inflammatory disorders	For example rheumatoid arthritis, inflammatory bowel disease

Initial clinical assessment

- Detailed history
- Initial investigation of confirmed IDA include urinalysis or urine microscopy, gynae causes
- Screening for coeliac disease
- Appropriate cases endoscopic examination of upper and lower GI tract
- Men & post menopausal women with newly diagnosed IDA gastroscopy and colonoscopy should be first line of GI investigations

Diagnosis

- Ferritin most sensitive, specific & cost effective test for IDA in the absence of inflammation
- Ferritin < 15mcg/L consistent with IDA but cut off 30mcg/L improves sensitivity from 25- 92% specificity 98%
- Ferritin > 100mcg/L generally exclude IDA in patients with no inflammatory states

Diagnosis

- Evidence of anaemia Hb < 13g/dL in men < 12g/dL non-pregnant women & Hb < 11g/dL pregnant women
- Low ferritin
- ↓TSAT ,↓ iron, ↑ TIBC, ↑cell zinc protoporphyrin, ↑serum transferrin receptor ↓ reticulocyte Hb
- Up to 40% patients with IDA will have normocytic erythrocytes

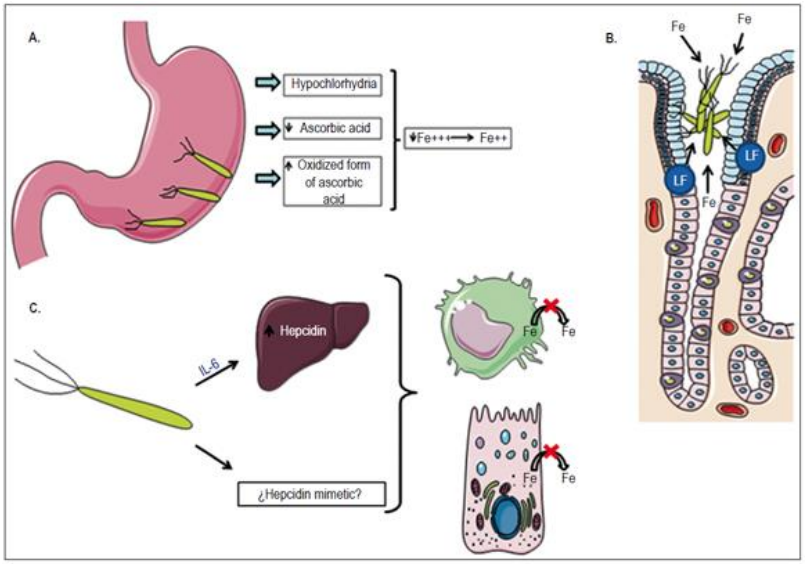
IDA vs. Anaemia of chronic disease

- Ferritin is an acute phase reactant therefore in patients with chronic inflammation or infection ferritin < 50 mcg/mL IDA is likely
- Can be difficult to differentiate IDA vs. ACD
- In heart failure IDA dx → ferritin <100 mcg/L or < 300 mcg/L + TSAT < 20%
- In CKD IDA dx → ferritin < 100 mcg/L or 200 mcg/L + TSAT <20%
- In IBD IDA dx → ferritin < 20 mcg/L or iron saturations < 15% or active disease: ferritin < 100 mcg/L + iron saturation < 15%

Diagnosis

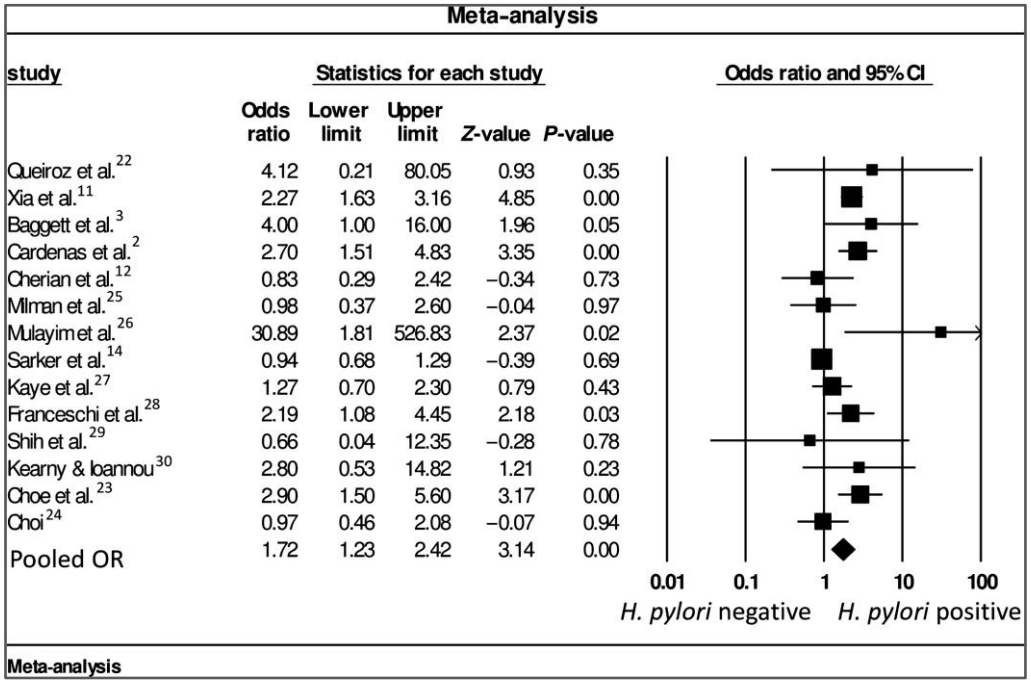
- If no inflammation & ferritin level indeterminate (31- 99 mcg/L): Low iron level , low transferrin saturation, high TIBC
- Soluble transferrin receptor and erythrocyte propophyrin testing or bone marrow biopsy can be considered if diagnosis remains unclear

Mechanisms of IDA in H. pylori



- Blood loss from H. pylori
- Decreased Fe absorption (A)
- H. pylori uses Fe (B)
- Hepcidin decreases release of Fe from macrophages and enterocytes (C)

Meta-analysis on the association between H. pylori and IDA



Pooled **OR 1.72** (95% CI 1.23–2.42); p<.001

Helicobacter, Volume: 22, Issue: 1, First published: 13 July 2016, DOI: (10.1111/hel.12330)

H. pylori and IDA

- The association of H. pylori with unexplained IDA conclusively proven in adults and children[1]
- Recent meta-analyses have shown that H. pylori eradication improves anaemia and increases Hb levels, in particular in those with moderate to severe anaemia[2, 3] and ferritin[4]
- Eradication of H. pylori leads to a reversal of IDA in up to 75% of patients[4]
- Some guidelines recommend eradication of H. pylori in patients with recurrent/unexplained IDA with normal OGD and colonoscopy[5]

1. *Queiroz DMM et al. PLoS One 2013;8:e68833.*
2. *Yuan W et al. Scand J Gastroenterol 2010;45:665–76.*
3. *Qu XH et al. World J Gastroenterol 2010;16:886–96.*
4. *Hudak L et al. Helicobacter. 2017;22:1–16.*
5. *Goddard AF et al. Gut 2011;60:1309–16.*

Anaemia in IBD

- Common extra intestinal manifestation in IBD
- Impaired absorption: chronically inflamed bowel, chronic blood losses, bowel resection & malnutrition
- Oral iron absorption is limited ~ 10- 20% of ingested amount
- Unabsorbed iron exposed to ulcerated intestinal surface → further mucosal damage & changes to gut microbiota
- ECCO guideline Intravenous iron is 1st line therapy in active dx with Hb < 10g/dL

Coeliac Disease

- CD found in 3-5% cases investigated for unexplained IDA
- Seronegative CD is high in the elderly
- CD in the elderly likely to present with malabsorption including IDA
- In older patients bidirectional endoscopy with duodenal biopsy to exclude CD

Imaging GI tract

- Examine upper & lower GI tracts at gastroscopy & colonoscopy
- CT colonography alternative to colonoscopy in certain situations i.e. major comorbidities
- Limited place for contrast CT
- No role for contrast fluoroscopy in IDA

Non-anaemic iron deficiency

- Body stores are depleted → hypoferritinaemia but Hb is normal
- Overall prevalence of GI pathology e.g. malignancy is low
- GI investigation is not warranted in premenopausal women
- Low threshold for investigation in men & postmenopausal women, GI symptoms, family hx

Treatment

- Start tx as soon as dx confirmed by lab investigation
- Treatment & investigation proceed in parallel
- Treat underlying cause once diagnosis made
- The aim is to replenish iron stores & return Hb to normal levels
- Shown to improve QoL, morbidity, prognosis in chronic disease & outcomes in pregnancy

Oral formulations

- British Society of Gastroenterology recommends ferrous preparations – ferrous sulphate first line
  - Cheap
  - Good bioavailability
  - Available in multiple preparations
  - Shown to replenish stores and correct anaemia
- Limitations frequency & severity of side effects
  - Constipation most frequent
  - Nausea
  - Diarrhoea

Oral formulations

- Sodium feredatate (Sytron/ Ecofer)
- Ferric maltol (Feraccru/Accrufer): novel preparation
  - Studies limited to IBD with sustained normal Hb up to 64 weeks
- Sucrosomial iron
  - more efficacy ↑ Hb & ferritin than ferrous sulphate
  - Non-inferior to parenteral iron
- Proton pump inhibitors, gastric acid hypo secretion associated with reduced absorption of dietary iron and iron tablets

Parenteral Iron

- Rapid correction of Hb, fewer side effects & improved safety profile
- Preferred route in patients with
  - GI effects
  - worsening symptoms of inflammatory bowel disease
  - unresolved bleeding
  - renal failure–induced anemia treated with erythropoietin
  - insufficient absorption in patients with celiac disease

Parenteral Iron

- Dexferrum: high molecular weight dextran discontinued due to high incidence of anaphylaxis
- Cosmofer: low molecular dextran still in use, effective & lower incidence of anaphylaxis
- Ferric derisomaltose (Monofer) is an alternative, shorter infusion time
- Iron sucrose (Venofer) slow injection 100-200mg 2-3 times/week

Follow up

- No standard recommendations for follow up after initiation of therapy
- Can recheck CBC every 3months for a year
- Another approach recheck periodically
- No further follow up if patient remains asymptomatic + haematocrit remains normal

Blood transfusion

- Rarely required to tx IDA
  - Slowly developing anaemia adapt to resulting physiological stress
  - Parenteral iron Hb response within a week
- Reserved for severe symptomatic or circulatory compromise
- Recommended in pregnant women with Hb < 6g/dL – abnormal foetal oxygenation
- 1 unit RCC contains 200mg elemental iron therefore will not replenish iron stores in severe IDA

References

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2. Wafa A, Hicham H, Hajar K, et al. Pernicious Anaemia: Mechanisms, Diagnosis and Management. Hematology. 2020 January; 1(1).

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