**Anemia**

Guidelines

- Haematology: British Society for Haematology (https://b-s-h.org.uk/guidelines/)
- Nephrology: KDIGO (2012 – Anemia in CKD) https://kdigo.org/wp-content/uploads/2016/10/KDIGO-2012-Anemia-Guideline-English.pdf
- Gastroenterology:
    - British Society of Gastroenterology: IDA (https://www.bsg.org.uk/wp-content/uploads/2019/12/Guidelines-for-the-management-of-iron.pdf?x83412)
    - American Journal of Gastroenterology: Small bowel bleeding (https://journals.lww.com/ajg/Fulltext/2015/09000/ACG_Clinical_Guideline__Diagnosis_and_Management.10.aspx)

Definition of Anemia

- <13: Men
- <12: Non pregnant women
- <11 (because of dilution): Pregnant women
- Geriatric population: No specific cut-offs, clinically contextualise; but rule of thumb ~ 10 might be acceptable)

Defining Iron Deficiency

- Ferritin
    - Most important marker
    - **< 15 umg/L definitive IDA (if no co-existent disease)**
    - < 50-100 umg/L (possibly IDA if other ongoing processes like infections)
    - < up to 200 in chronic diseases such as CKD
- Other factors: Low iron, raised TIBC
- CKD/ESRF Thresholds for IDA
    - **Pre-Dialysis/PD Patients: TSAT <20%, Ferritin <100 ng/mL (pre-dialysis and PD pts)**
    - **HD Patients: <20%, Ferritin <200 ng/mL (Haemodialysis pts)**

Pathophysiology of Anemia in CKD

- Iron deficiency – Most common (absolute and functional)
- Other causes include: Decreased EPO production, anemia of chronic disease, nutritional deficiency, blood loss (dialysis, blood taking), reduced RBC survival, marrow suppression

When does anemia become a problem in CKD

- Usually CKD Stage 4-5 (when eGFR <30)
- Anemia is an independent risk factor for adverse cardiovascular outcomes

How hard to hunt beyond CKD for anemia?

- Evaluate as per a general population
- If there is IDA – offer GI referral for endoscopic evaluation before replacement

Optimising iron and EPO status in CKD/ESRF patients

- Targets
    - Hb: Generally **10-11.5**; but needs to be contextualised (eg lower targets if recurrent access thrombosis)
    - Iron:
        - **Non-Dialysis: TSAT > 25%, Ferritin > 200**
        - **Dialysis: TSAT > 30%, Ferritin > 500**

- Non-Dialysis
    - Start PO iron (more convenient when not on HD) when TSAT < 30%
    - Parenteral Iron
        - Indications: Severe iron def (TSAT <12%), severe anemia (Hb<7), SE to PO iron, failure of therapy PO iron
        - Ferrinject preferred over venofer in non-dialysis patients because can load higher dose faster
    - Reassess in about 1 month, if iron replete (TSAT>25%, Ferritin>200) but Hb < 10, then start ESA
    - Usually Recormon: Usually start 4000u SC weekly then uptitrate (check Hb 2-4 weeks later)
    - Option of longer acting ESA like darbepoetin or mircera which allows less frequency dosing (1/week) but more expensive
- Dialysis
    - PD patients
        - Don't do very well with PO iron, but don't have access for IV iron
        - Hence lower threshold for admissions for IV iron therapy
    - HD patients
        - If iron deficient, load IV venofer 100mg once/week for 8-10 weeks
        - Once replete, maintain 100mg once/month

Endoscopic evaluation in IDA

- **Generally offer to all males and post-menopausal female**
- The lower the Hb, the higher the likelihood of malignancy
- But always go back to history and ascertain malignancy risk factors of possible etiologies (e.g. NSAID use for PUD and family history for GI malignancies)
- Nutritional deficiencies rare in local population except vegans without B!2 supplementation
- In young foreign worker population, consider other conditions such as PUD and parasitic infections rather than isolated dietary deficiency

Variability of Iron Studies

- Iron studies affected by multiple factors such as ongoing illness, fasting etc
- While inpatient testing may not be ideal, may have benefits of:
    - Opportunistic screening (as some patients don't make it to outpatient clinics)
    - If serious disorder like cancer, don't want to delay diagnosis

How long are scopes 'valid' for?

- No simplistic answer to 'validity' – Hence need to go back to patient and history what are the suspected diagnoses
- **Lower threshold for repeat OGDs** – Peptic ulcer disease can develop in fairly short intervals
- Higher threshold for repeat colonoscopy – Colonic cancers take ~10 years from dysplasia to frank malignancy
- Will need to weigh risk to benefit in terms of procedural risk and aim of investigations, alongside alternatives (scans)

Utility of FOBT for screen

- Indicated as a screening test for ASYMPTOMATIC, AVERAGE RISK for COLON CANCER – outside this context utility uncertain
- **Generally not recommended for screening for occult BGIT/IDA**, unless a really last resort
- Possibly can be used to sway patients to do endoscopic evaluation if positive
- New generation FIT more specific for LBGIT because of actual haem ring detection (hence less sensitive for UBGIT compared to older Guaic test)

Small bowel evaluation

- **Small bowel bleeding is fairly uncommon (5-10% of all GI bleeds)**
- Consider the following before small bowel evaluation
  - Clinical evaluation for other causes of IDA
  - Repeating OGD and colonoscopy before small bowel evaluation
  - Cross sectional imaging of abdomen to exclude stricturing disease, diseases like GIST
- First line of small bowel evaluation is often video capsule endoscopy – but purely diagnostic, and findings may be non-specific/non-diagnostic
- **Utility of small bowel evaluation is highest in the context of OVERT BGIT**

Casting a wide net vs targeted testing based on MCV

- Generally targeted
- But always go back to history to further contextualise testing

Incidental microcytosis/macrocytosis

- MCV changes usually precedes anemia, hence advisable to evaluate for cause of micro/macrocytosis in the absence of anemia
- Causes of macrocytosis: B12/folate deficiency, hypothyroidism, liver disease, MDS, myeloma
- Causes of microcytosis: Iron deficiency, thalassemia

Reticulocyte Profile

- Reticulocytes Percentage
- **Reticulocyte Ab (Absolute amount) – Main parameter to consider**
  - Ballpark Figures: 'Normal' retic range should correspond to normal Hb, Hb ~10 : Retic count ~ 150, Hb 7-8: Retic count ~ 150-200
  - Retic count dependent also on rate of blood loss
- Reticulocyte He: Measures amount of Hb in recticulocytes (may be a measure of functional Fe def)
- All hematinic deficiencies cause reduced retic response but response is quickly corrected with replacement

Blood Transfusion

- Generally aim Hb > 7
- Unless IHD, active bleeding then aim > 8

Iron Replacement

- **Require 100-200mg elemental iron/day for iron replacement**
- Diet: Heme iron (liver, red meat, seafood, poultry), non-heme iron (beans, dark green leafy vegetables, fried fruits, iron fortified bread/cereal/pasta)
- PO Formulations

| Oral Iron Preparations | Elemental Iron per tablet | % elemental iron | Tablet Equivalency to Ferrous Fumarate | Other Elements per tablet | Price/tab ($) [SC/PR] | Subsidy Status |
|---|---|---|---|---|---|---|
| Ferrous Fumarate 200mg Tab | 66mg | 33% | 1 | - | 0.05 | S1 |
| Ferrous Sulphate Co Tab [Contains Ferrous Sulphate anhydrous 200mg ] | 65mg | 32% | 1 | Thiamine 3mg, Riboflavin 1.5mg Nicotinamide 10mg | 0.12 | S1 |
| Ferrous Gluconate 300mg Tab | 36mg | 12% | 2 | - | 0.12 | S1 |
| Ferrous Gluconate Co Cap (Sangobion) [contains Ferrous Gluconate 250mg] | 30mg | 12% | 2 | Cyanocobalamin 7.5mcg, Folic acid 1mg, Ascorbic acid 50mg, Manganese 0.2mg, Copper sulphate 0.2mg, Sorbitol 25mg | 0.12 | S1 |
| Iberet Folate SR Tab [contains Ferrous Sulphate 525mg] | 105mg | 20% | 0.6 | Thiamine 6mg, Pyridoxine 5mg, Cyanocobalamin 25mcg, Riboflavin 6mg, Niacinamide 30mg, Folic Acid 800mcg, Calcium Panthothenate 10mg, Ascorbic Acid 500mg. | 0.59 | OTC |
| Iron Polymaltose 50mg/ml Drops (Maltofer) | 50mg/ml | 100% | 1.2mL | - | 13.05/btl (30mL) | S1 |
| Iron Polymaltose 100mg Tab (Maltofer) | 100mg | 100% | 0.7 | - | 0.65 | OTC |

- Preparations
  - Ferrous sulphate: 65mg elemental Fe / tab
  - Sangobion (multiple vitamins): 30mg elemental Fe / tab
  - Polymaltose drops: 50mg elemental Fe / ml
  - Polymaltose tablets: 100mg elemental Fe / tab
- Generally main SE that of constipation
- Vitamin C can increase iron absorption (caution in renal patients as can cause renal stones)

· Parenteral Iron
- Ferrosig (Iron Polymaltose) – IM/IV
- Venofer (Iron Sucrose) – IV; more in renal patients
- Ferrinject (Ferric Carboxymaltose) – IV; more in other patients as can give higher iron boost
- All carry small risk of anaphylaxis

<u>B12 Deficiency</u>

· Diagnosis
- **B12 < 200 probable deficiency; 200-300 possible deficiency**
- While guidelines suggest role of MMA/homocysteine, practically don't check much in Singapore because of cost and limited test availability

· Pernicious Anemia Screening
- Check anti-intrinsic factor; anti-parietal cell is non-specific
- Even if negative in very low B12, to treat as seronegative pernicious anemia

· Treatment of Pernicious Anemia
- IM B12 injections for pernicious anemia
- PO B12 generally not for repleting B12 in pernicious anemia because of significant depletion of stores, mainly for maintenance
- However often times in pernicious anemia, may still choose to maintain with IM B12 monthly
- Dosing – Singapore uses Cyanocobalamin (not that uptodate recommendations based on hydroxocobalamin)
  - **1000mcg IM/SC daily x 7 days THEN**
  - **1000mcg weekly x 1 month THEN**
  - **1000mcg monthly for maintenance**

· Endoscopic Screening
- Older studies showed association with GI ca, but more recent studies haven't seem to show so
- Generally refer based on other factors such as GI symptoms, age etc
- However, because of higher upper GI malignancy risk compared to western population, might consider

<u>Hemolytic Anemia</u>

· **Normal LFT DOES NOT exclude hemolysis** – low grade hemolysis may not cause raised bilirubin/LDH

· **Haptoglobin is SENSITIVE but NOT SPECIFIC**; can be lowered in liver dysfunction

<u>Take Home Points</u>

· Dr Low: Anemia workup in CKD should still be as per the normal patient, thresholds for IDA differ in CKD cohort

· Dr Koh: Treat IDA with respect – could portend malignancy

· Dr Lee: Work up underlying causes of nutritional deficiencies rather than simply supplenting