Guidance for Primary Care on the Interpretation of Haematinics

B12, Folate and Ferritin

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References:

NICE Clinical Knowledge Summary (CKS) on B12 and Folate Deficiency: https://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#diagnosis
NICE CKS on Iron Deficiency: https://cks.nice.org.uk/anaemia-iron-deficiency#diagnosis
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**Vitamin B12**

B12 deficiency does not usually require secondary care referral.

Replacement is usually given by IM injection. Oral replacement may be appropriate for mild deficiencies where the IF antibody result is negative.

It is not appropriate to measure B12 in patients on supplements. Monitor response to therapy using the full blood count (Hb and MCV).

**Box 1**
Causes of low B12 include:
- Pregnancy, OCP, HRT (not thought to represent a functional B12 deficiency)
- Medications: metformin, PPI, anti-convulsants e.g. phenytoin, antibiotics, colchicine
- Vegetarian/vegan/poor diet
- Malabsorption – consider other features of malabsorption/pancreatic insufficiency
- Pernicious anaemia – consider history of autoimmune disease and/or family history
- Folate deficiency
- Parasitic infection, HIV, Myeloma

**Box 2**
*B12 levels are not easily correlated with clinical features, and low levels may not represent a functional B12 deficiency.*

Features of B12 deficiency may include:
- Macrocytic anaemia (MCV >101 fl)*
- Glossitis
- Paraesthesia, unsteadiness, peripheral neuropathy

*Note co-existing iron deficiency/thalassaemia trait may mask macrocytosis*
Folate

It is not appropriate to measure folate in patients on supplements. Monitor response to therapy using the full blood count (Hb and MCV). Serum folate should always be measured with B12; in the presence of true B12 deficiency, serum folate may be elevated.

- **Folate <3.0 μg/L**
  - Folate deficiency.
  - Check B12 levels and commence folate replacement (*symptoms of B12 deficiency can be exacerbated if treated with folate replacement alone*).
  - Consider diet and medication as a cause (see box 3).

- **Folate 3.0 – 3.9 μg/L**
  - Possible folate deficiency.
  - ? Reduced intake over the previous few days
  - ? Symptomatic (see box 4)

- **Folate >3.9 μg/L**
  - Folate deficiency unlikely.
  - Note: serum folate reflects recent folate ingestion and recent high dose biotin intake may cause falsely elevated results; please see [https://tinyurl.com/BiochemInfo](https://tinyurl.com/BiochemInfo) for more information on biotin interference.
  - If strong clinical suspicion of deficiency remains, rule out B12 deficiency and consider discussion with haematology for more specialised testing.

- **Check B12 levels**
  - Commence replacement.

- **Repeat in 6 – 8 weeks. If still low, consider replacement.**

**Box 3**

Conditions associated with low folate include:
- Dietary deficiency/anorexia
- Pregnancy
- Alcoholism
- Malabsorption – consider other features of malabsorption/pancreatic insufficiency
- Haemolysis
- Malignancy
- Medications: Anti-convulsants
- Sample collection immediately post-dialysis

**Box 4**

Features of folate deficiency include:
- Macrocytic anaemia (MCV >101 fl)*
- Angular cheilosis/stomatitis

*Note: co-existing iron deficiency/thalassaemia trait may mask macrocytosis
Ferritin

Serum ferritin is the biochemical test which most reliably correlates with relative total body iron stores; low levels generally indicate low iron stores. For the investigation of iron deficiency, serum ferritin is superior to the measurement of iron and transferrin saturation, which are rarely useful. Monitor response to therapy using FBC (Hb and MCV). There is no need to re-check ferritin levels within 6 – 8 weeks.

<15 μg/L

Iron deficiency confirmed.
Evaluate underlying cause (see box 5) and commence replacement.

15 – 30 μg/L

Iron deficiency likely.
Consider clinical context (see box 6) and commence replacement if appropriate.
Evaluate underlying cause (see box 5).

30 – 150 μg/L (women <60 y)
30 – 260 μg/L (women >60 y)
Or 30 – 400 μg/L (men)

CRP <5 mg/L?
Yes
Iron deficiency unlikely.

No
Iron deficiency not excluded.
Ferritin levels are increased independently of iron status in acute and chronic inflammatory conditions, as well as malignancy and liver disease, which may mask deficiencies. Repeat when the acute phase response has resolved.
For patients with chronic inflammatory conditions, interpretation should be performed cautiously. Consider FBC and fasting transferrin saturation; if <16%, iron deficiency is possible. Note: transferrin saturation is non-specific as pregnancy, OCP and chronic illness can result in low transferrin saturation without iron deficiency.

>150 μg/L (women <60 y)
>260 μg/L (women >60 y)
Or >400 μg/L (men)

Iron deficiency excluded.
Refer to https://tinyurl.com/BiochemInfo for the investigation of hyperferritinaemia.

Causes of iron deficiency include:
- Inadequate diet or malabsorption
- Bleeding, e.g. GI bleeding, menorrhagia or blood donation
- Chronic renal failure and haemodialysis
- Infancy, pregnancy or lactation
- Idiopathic

Features of iron deficiency include:
- Microcytic hypochromic anaemia (MCV <79 fl)
- Symptoms of anaemia – fatigue, dyspnoea, pallor.
- Symptoms of iron deficiency may occur without anaemia: fatigue, lack of concentration, irritability, hair loss, dry skin, angular cheilosis, atrophic glossitis, spoon-shaped nails, and unusual cravings for ice or non-food items (phenomenon known as pica).