Investigation and Treatment of Adult Vitamin B12 (Cobalamin) Deficiency in Primary Care

Approved by DMAG January 2020

1. Strong suspicion of cobalamin deficiency with objective parameters e.g. anaemia, glossitis, cognitive impairment, paraesthesia. Check serum cobalamin and folate levels.

   - Serum cobalamin <150ng/L: very probable deficiency
   - Serum cobalamin 150-200 ng/L: probable deficiency
   - Serum cobalamin 200-250ng/L: possible cobalamin deficiency (i.e. falsely normal cobalamin)

Check IFAB levels and initiate IM hydroxocobalamin 1mg ASAP

   Neurological symptoms: Alternate days until no improvement (review after 3 weeks)
   No neurological symptoms: 3 x week for 2 weeks

   - IFAB positive: Pernicious Anaemia
   - IFAB negative + clinical response (see *)
     - Antibody Negative: Pernicious Anaemia
       - Coeliac screen and refer to gastro if positive or diarrhoea/abdo pain
   - IFAB negative & no clinical response

   IM hydroxocobalamin 1mg lifelong

   Neurological symptoms: every 2 months
   No neuro symptoms: every 3 months

   Objective studies of more frequent dosing are absent.
   Further testing of B12 is NOT necessary
   Oral cyanocobalamin is NOT recommended but 1mg tabs (unlicensed in UK) could be considered where IM not tolerated. Dose 1-2mg daily.

   Referral criteria:
   - Haematologist: Pregnancy with profound deficiency (urgent), functional B12 deficiency (urgent), uncertain cause following investigations or suspected blood disorder or malignancy (urgent), failure to respond to treatment.
   - Neurologist: severe neurological symptoms (urgent).
   - Gastroenterologist: suspected malabsorption or gastric cancer

2. Non-specific symptoms in the absence of objective clinical parameters

   - Serum cobalamin <150ng/L: Manage as algorithm 1
   - Serum cobalamin 150 – 200ng/L: Repeat serum cobalamin after 2 months
   - Serum cobalamin in normal range: No further investigation / treatment
   - Persistent serum cobalamin 150 – 200ng/L: Check IFAB levels
     - Consider 4 weeks oral cyanocobalamin 50mcg OD pending IFAB results.
     - Pts should be told to report immediately if symptoms of neuropathy develop as this dose is inadequate for true pernicious anaemia.

   - IFAB positive: Treat as Pernicious Anaemia
   - IFAB negative: Repeat serum cobalamin at 3-4 months
     - Repeat serum cobalamin >200ng/L:
       - NO FURTHER INVESTIGATION.
       - Likely cause is food malabsorption so increase dietary intake (see over).
       - Where increased dietary intake is difficult consider long-term supplementation.
         - 1st line: OTC supplements (min. 50mcg/day)
         - 2nd line: Consider cyanocobalamin 50mcg od or twice yearly IM hydroxocobalamin 1mg.
         - May need to be lifelong in vegans, but for other dietary causes stop after cobalamin corrected and diet has improved. Check levels 6-12 months.
     - IFAB negative: Repeat serum cobalamin at 3-4 months
       - Medication review for drug causes (see over)
       - Deprescribe where possible and retest in 2 months
       - OCP/HRT: increase dietary intake
       - Consider other possible causes of deficiency
         - Coeliac screen and refer to gastro if positive or diarrhoea/abdominal pain
       - Does not require treatment but monitor serum cobalamin every 6-12 months

   - IFAB positive: Treat as Pernicious Anaemia
   - IFAB negative: Repeat serum cobalamin at 3-4 months

   Repeat serum cobalamin 150-200ng/L:

   - Medication review for drug causes (see over)
     - Deprescribe where possible and retest in 2 months
     - OCP/HRT: increase dietary intake
   - Consider other possible causes of deficiency
     - Coeliac screen and refer to gastro if positive or diarrhoea/abdominal pain
   - Does not require treatment but monitor serum cobalamin every 6-12 months

   Repeat serum cobalamin >200ng/L:

   - NO FURTHER INVESTIGATION.
   - Likely cause is food malabsorption so increase dietary intake (see over).
   - Where increased dietary intake is difficult consider long-term supplementation.
     - 1st line: OTC supplements (min. 50mcg/day)
     - 2nd line: Consider cyanocobalamin 50mcg od or twice yearly IM hydroxocobalamin 1mg.
     - May need to be lifelong in vegans, but for other dietary causes stop after cobalamin corrected and diet has improved. Check levels 6-12 months.

Cyanocobalamin 50microgram tablets are Green on the formulary but are expensive on NHS so patients should be encouraged to purchase cheaper OTC supplements.

Prescribing should follow NHS England OTC guidance for vitamins i.e. proven deficiency due to chronic medical condition or surgery resulting in malabsorption.
What are the signs/symptoms of B12/folate deficiency?

**Haematological (in order of increasing severity)**
- Isolated red cell macrocytosis without anaemia
- Macrocytic anaemia (esp if MCV >110fl)
- Pancytopenia (esp if MCV >120fl)

**Neurological or psychiatric**
- Peripheral neuropathy
- Cognitive change e.g. dementia
- Optic neuritis

**Other (rare)**
- Angular cheilosis
- Sore beefy red tongue

What are the causes of vitamin B12 deficiency?

- **Pernicious anaemia (commonest cause)**
- **Gastric causes**
  - e.g. gastrectomy, gastric resection, atrophic gastritis, *H. Pylori* infection, gastric bypass, congenital intrinsic factor deficiency or abnormality
- **Intestinal causes**
  - e.g. malabsorption, ileal resection, Crohn’s disease affecting the ileum, chronic tropical sprue, HIV or radiotherapy to the cervix (causing irradiation of the ileum)
- **Inadequate dietary intake (e.g. vegan)**
- **Chronic alcoholism**
- **Drugs**
  - e.g. metformin, colchicine, neomycin or anticonvulsants. Long-term use of H₂ receptor antagonists & PPIs can worsen deficiency.

It is also important to note that:
- Women on OCP may show decreased B12 levels due to decreased cobalamin carrier protein, rather than a deficiency state
- Pregnancy may cause falsely low B12 levels because of the increased plasma volume rather than actual deficiency, which makes it very difficult to diagnose in pregnancy. For further information about B12 deficiency in pregnancy see: [https://www.sps.nhs.uk/articles/how-should-severe-vitamin-b12-deficiency-in-pregnancy-be-managed/](https://www.sps.nhs.uk/articles/how-should-severe-vitamin-b12-deficiency-in-pregnancy-be-managed/)

How should tests be interpreted?

The **clinical picture is the most important factor** in assessing the results of serum cobalamin. Definitive cut off points for clinical and subclinical deficiency are not possible. See algorithms overleaf and bear in mind:

- The test measures total, not metabolically active vitamin B12.
- Levels are not easily correlated with clinical symptoms.
- Clinically significant vitamin B12 deficiency may be present when levels are in the normal range, especially in the elderly.
- About 50% with pernicious anaemia will have Intrinsic Factor Antibodies (IFAB). If IFAB is present, pernicious anaemia is very likely, but its absence does not rule out a diagnosis of pernicious anaemia.

How should response to treatment be assessed?

If patient presented with anaemia, check FBC & reticulocytes 10 days following initiation of treatment and repeat FBC at 8 weeks to ensure normalisation of Hb.

What dietary advice should patients be given?

Advise consumption of foods rich in vitamin B12 e.g. some soy products, breakfast cereals, breads, meat, eggs & dairy products.

[https://www.nhs.uk/conditions/vitamin-b12-or-folate-deficiency-anaemia/treatment](https://www.nhs.uk/conditions/vitamin-b12-or-folate-deficiency-anaemia/treatment)

[https://www.vegsoc.org/B12](https://www.vegsoc.org/B12)

What are review criteria for discontinuation of IM hydroxocobalamin that may have been initiated inappropriately?

- **Patient was asymptomatic or associated pathology** at initiation
- **Only 1 borderline result** for serum cobalamin (150–200ng/l)
- **IFAB negative** (where previously tested)