Guideline for the management of Vitamin B12 deficiency in adults (18yrs and over)

Anaemia or strong clinical suspicion e.g. visual disturbance, memory loss, psychiatric abnormalities, loss of peripheral nerve function that can result in impaired sensation, movement or organic function with no other identifiable cause, glossitis

- <150ng/L
- 150-199ng/L → Offer patient dietary advice and recheck in 3 months. Patient may purchase OTC cyanocobalamin 50-100mcg od. Check folate levels***
- ≥200ng/L & no symptoms: no further investigation. If anaemia present: offer dietary advice/OTC cyanocobalamin 50-100mcg OD for 3 months

B12 dropped to <150ng/L

Asymptomatic and B12 ≥200ng/L. Continue with dietary control, no further investigation

B12 remains 150-199ng/L or ≥200ng/L in patient with strong clinical suspicion → Check IFAB

- Positive
- Negative

Check Intrinsic Factor Antibody (IFAB) but proceed to treatment regardless. Check folate levels***

- No neurological symptoms** → **IM hydroxocobalamin 1000mcg on alternate days for 2 weeks**

  Maintenance *(see overleaf for action during coronavirus pandemic / in similar circumstances):*
  - Dietary cause: OTC oral cyanocobalamin 50-150mcg daily
  - Non-dietary cause: IM hydroxocobalamin 1000mcg **every 3 months** for life

- Neurological Symptoms** → **Seek *specialist advice (include IFAB result)**

  Management as per specialist advice but if recommendation delayed, initiate treatment with:
  IM hydroxocobalamin 1000mcg on alternate days until no further symptomatic Improvement

  Maintenance: *(see page 3 for action during coronavirus pandemic / in similar circumstances):*
  IM hydroxocobalamin 1000mcg **every 3 months** for life—if advised by specialist

Positive:
- No neuro symptoms → IM hydroxocobalamin 1000mcg on alternate days for 2 weeks
- Neuro symptoms → Seek *specialist advice (include IFAB result)

Negative:
- Neuro symptoms → Seek *specialist advice (include IFAB result)
- No neuro symptoms → Continue with dietary control (+/- oral OTC cyanocobalamin), no further investigation

Specialist recommendation only ← Ensure patient has adjusted diet, purchased OTC cyanocobalamin, and taken these tablets for 3 months. Patient to continue with OTC cyanocobalamin while *specialist advice is sought.

Red flags:
Discuss with Haematology (via Advice & Guidance)
- Hb<60g/dl associated with low reticulocyte count
- Presence of nucleated red blood cells (NRBC) on peripheral blood film and associated low platelets (<100) and/or low neutrophils (≤1)

Refer to Gastro
- Confirmed pernicious anaemia (raised IF antibodies) - increased risk of gastric cancer with autoimmune gastritis

Key points to consider:

***Specialist advice:**
Seek advice from most appropriate clinician, considering cause (gastro) or symptoms (neuro) or patient factors (care of older person)

- Remote advice usually sufficient. Consider advice and guidance
- Check response to B12 replacement with repeat Full Blood Count (FBC) and reticulocytes at 7-10 days after starting IM replacement—if no improvement in haemoglobin/low reticulocytes discuss with Haematology via Advice & Guidance
- There is no need to recheck serum B12 in patients on IM treatment. FBC should be used to monitor response to B12 replacement

** **Neurological symptoms**

- Vision problems
- Memory loss
- Pins and needs (paraesthesia)
- Loss of physical co-ordination (ataxia), which can affect your whole body and cause difficulty speaking or walking
- Damage to parts of the nervous system (peripheral neuropathy), particularly in the legs

If neurological problems do develop, they may be irreversible.

Source: https://www.nhs.uk/conditions/vitamin-b12-or-folate-deficiency-anaemia/complications/

Blood tests

- FBC to determine mean cell volume (MCV), haematocrit and haemoglobin levels, and a blood film—which help to identify megaloblastic anaemia.
- Measurement of serum cobalamin and folate levels—to determine the cause of anaemia.
- Reticulocyte count and iron studies—it is not uncommon to see multiple deficiencies
  - ◊ ***If a folate deficiency is identified, treatment should be initiated with cobalamin therapy before adding in folate therapy (as per the usual treatment pathway)
  - ◊ If an iron deficiency is also present start iron replacement and investigate the iron deficiency as appropriate as per the usual treatment pathway
- Additional investigations, such as liver function tests, gamma-glutamyl transpeptidase, and/or thyroid function tests—to identify the underlying cause.

Source: https://cks.nice.org.uk/topics/anaemia-b12-folate-deficiency/diagnosis/investigations/

The British Society for Haematology (BSH) issued the following guidance on Vitamin B12 replacement during the COVID-19 pandemic:

Where Vitamin B12 deficiency is not thought to be diet related, i.e. due to pernicious anaemia, prior gastrectomy, bariatric surgery, achlorhydria, pancreatic insufficiency, short bowel syndrome, bacterial overgrowth, inflammatory bowel disease):

NICE Clinical Knowledge Summary 2019 recommends: administer hydroxocobalamin 1mg IM every 2-3 months for life.

BSH advice during COVID-19 pandemic for patients established on IM hydroxocobalamin:

- The need for IM hydroxocobalamin should be discussed with each patient individually. It is recommended that screening questions for COVID-19 infection are asked before patients attend their GP surgeries. Alternatives to attending the GP surgery such as local pharmacies or home administration by district nurses should be explored.
- As an alternative, where there is good compliance with treatment, oral cyanocobalamin can be offered at a dose of 1mg per day until regular IM hydroxocobalamin can be resumed, i.e. once GP surgeries are able to do so safely, aiming to have a shortest possible break from regular injections.
- Patients should be advised to monitor their symptoms and should contact their GP if they begin to experience neurological or neuropsychiatric symptoms such as pins and needles, numbness, problem with memory or concentration or irritability.
- Patients who are self-administering IM hydroxocobalamin should continue to do so but the BSH do not recommend a patient switching to self-administration during the COVID-19 pandemic since instruction is likely to be difficult.

Where B12 deficiency is thought to be diet related:

NICE Clinical Knowledge Summary 2019 recommends: advise people either to take oral cyanocobalamin tablets 50-150 micrograms daily between meals or have a twice yearly hydroxocobalamin 1mg injection. In vegans, treatment may need to be life-long, whereas in other people with dietary deficiency replacement treatment can be stopped once the vitamin B12 levels have been corrected and the diet has improved.

BSH advice during COVID-19 pandemic for patients established on IM hydroxocobalamin:

- An alternative is to offer oral cyanocobalamin tablets, 50-150mcg, daily between meals. The BSH recommend reassessing serum B12 prior to recommencing IM hydroxocobalamin.
- Some patients (excluding patients with vegetarian or vegan diets) may be vitamin B12 replete if they have already been receiving vitamin B12 supplementation and may be able to stop supplementation for up to a year.
- All patients should be counselled to take their dose on an empty stomach to maximise absorption.
- Give dietary advice about foods that are a good source of vitamin B12:
  - eggs, meat, milk, other dairy products and fish (salmon and cod)
  - foods fortified with vitamin B12 (e.g. some soy products and some breakfast cereals and bread) are good alternatives.

Reference: BSH guidance on B12 replacement during the COVID-19 pandemic, 01.05.2020, British Society for Haematology, https://b-s-h.org.uk/media/18275/bsh-guidance-b12-replacement-covid-1901052020finalv.pdf Accessed 02/07/2020

Medication / condition that may reduce levels of vitamin B12	**Comments**
Metformin (for longer than 12 months)	• Usually improved with increased dietary B12 intake • Only assess if objective evidence of deficiency is present including peripheral neuropathy or macrocytic anaemia • If low levels check IFAB and should be treated with a short course of OTC oral cyanocobalamin (50micrograms orally for 4 weeks). Response should be assessed clinically and continued if benefit is shown • No need for prophylactic B12 administration
Proton pump inhibitors and H2 antagonists	• OTC oral replacement (25—100 micrograms orally) may be appropriate **if** objective evidence of deficiency is found
Anticonvulsants	• If no objective features of B12 deficiency—no need for replacement • OTC oral replacement (25—100 micrograms orally) may be appropriate **if** objective evidence of deficiency is found
Oral contraceptives and hormone replacement therapy	• Only be assessed if objective symptoms develop and this is the only indication for treatment • OTC oral replacement (25—100 micrograms) orally may be appropriate **if** objective evidence of deficiency is found
Colchicine	• Low levels can easily be increased with dietary supplementation
Antibiotics	• Low levels can easily be increased with dietary supplementation
Gastrointestinal surgery	• Both gastrectomy and bariatric surgery can lead to B12 deficiency and require regular monitoring and replacement if levels are falling despite good dietary intake. Oral replacement is often **inadequate** in these patients since the cause is likely malabsorption
Pregnancy	• This can be measured during pregnancy however serum levels fall during pregnancy therefore these are less reliable. If a deficiency is identified (low levels and/or symptoms) follow pathway as for non-pregnant people
Vegetarian and vegan diets	• Vegetarians and vegans are at increased risk of B12 deficiency especially during pregnancy and when breastfeeding • Monitoring should be considered, especially at high-risk times, and OTC oral supplementation (cyanocobalamin 50mcg daily) may be required

Vitamin B12 frequently asked questions

1. **If laboratory results show low (<150ng/L) vitamin B12 levels can oral supplementation be considered?**
   The NICE Clinical Knowledge Summary recommends that the intramuscular (IM) route should be used in all deficiency cases where there are neurological symptoms as an acute dose (hydroxocobalamin 1mg on alternate days for two weeks). Usually IM will then be used as maintenance. However, if the cause is dietary and the patient does not display neurological symptoms, OTC oral supplementations may be used.

2. **What if the patient is unwilling to have the IM route?**
   If the deficiency is thought to be diet related and not due to lack of intrinsic factor, then it is possible to use oral cyanocobalamin. It is available as cyanocobalamin 50mcg tablets which may be **purchased over the counter**. Parenteral therapy is preferable for deficiency symptomatic patients, as it is retained in the body for longer than oral tablets. Malabsorption is frequently a cause of deficiency, in such cases, oral supplements are unlikely to be effective. This should be explained to the patient, although any decision to inject will obviously require informed patient consent. If this is not obtainable, the patient may choose to purchase OTC, but should be advised this may not be as effective as injection in their circumstances.
   (Please note that Vitamin B Co strong tablets do not contain any vitamin B12 and therefore cannot be used to treat B12 deficiency).

3. **How do you treat low vitamin B12 patients with Type 2 diabetes (on metformin longer than 12 months)?**
   Give patient dietary advice to increase their vitamin B12 levels, advise them to supplement with OTC oral cyanocobalamin. Monitor serum B12 every 6 months. If still low check IFAB. If positive, then treat lifelong with IM hydroxocobalamin every three months. If IFAB is negative, the reduced level may be purely as a result of metformin, increase doses of cyanocobalamin to 150mcg daily, if still not able to raise B12 levels, treatment with three injections of IM hydroxocobalamin with subsequent monitoring of serum B12 at 6 monthly intervals is suggested.

4. **What if a person is still symptomatic despite maintenance IM vitamin B12 treatment?**
   If levels were borderline to begin with and only treated due to symptoms, then this suggests the B12 has not been effective. Trial withdrawal and investigate other causes of symptoms. If initially B12 deficiency, retest the B12 level: if remains low, seek specialist advice. If this is corrected to normal levels, continue maintenance dose interval and investigate other causes of symptoms. If a person's symptoms recur before the next injection is due, seek specialist advice from a haematologist.

5. **What dose of cyanocobalamin is recommended for purchase?**
   If mild deficiency is thought to be diet related, advise people to take oral cyanocobalamin tablets 50-150 micrograms daily between meals. Doses within this range are safe and sufficient to prevent dietary deficiency. Example products are shown on page 6.

6. **What foods can I advise patients to eat to increase their dietary intake of vitamin B12?**
   Foods that are a good source of vitamin B12: eggs, meat, milk and other dairy products, salmon and cod; as well as foods which have been fortified with vitamin B12 (some soy products, breakfast cereals and breads)

Cyanocobalamin tablets

- Cyanocobalamin tablets are available as a food supplement (immediate-release, modified-release or sublingual tablets) or as a prescription-only medicine that is unlicensed in the UK but can be imported; they can be obtained through community pharmacies (some stock is classified as a wholesaler 'special').
- A list of oral cyanocobalamin preparations currently available for prescribing can be found at https://www.sps.nhs.uk/wp-content/uploads/2020/06/UKMI_QA_Oral-Vitamin-B12-preparations_May-2020.pdf
- Cyanocobalamin tablets must be prescribed as "cyanocobalamin tablets" and should not be written as "vitamin B12 tablets".
- A licensed cyanocobalamin 1mg tablet (Orobalin) has been recently launched in the UK. This is a prescription only medicine (POM) indicated for the treatment of haematological, neurological and other symptoms secondary to vitamin B12 deficiency, malabsorption of vitamin B12, such as due to the absence of intrinsic factor (Pernicious anaemia), stomach resection or disease of the small intestine. It will also be indicated for use during para-aminosalicylic acid therapy, which can cause impaired vitamin B12 resorption.
- Cyanocobalamin 50mcg tablets are available as Pharmacy only medicines or as food supplements.
- Many more preparations, formulations and strengths of oral vitamin B12 are available to purchase as food supplements online or in health food shops and a few are listed on the next page.

Examples of cyanocobalamin available to purchase

(other products are available—there is no preference on what brand is purchased)

Holland and Barrett 100mcg vitamin B12 tablets x 100

£7.69 (price correct as of 23/10/2020). Suitable for vegetarians and vegans

Holland and Barrett 500 mcg vitamin B12 tablets x 100

£9.89 (correct as of 23/10/2020). Suitable for vegetarians and vegans

Holland and Barrett 1000mcg timed release vitamin B12 x100

£14.69 (correct as of 23/10/2020). Suitable for vegetarians and vegans

Myprotein 1000mcg vitamin B12 tablets x60 or x10

£4.99 (x60) or £11.99 (x180) (correct as of 23/10/2020). Suitable for vegetarians and vegans

Nature's Best Vitamin B12 tablets 100mcg vitamin B12 tablets x100

£4.60 (correct as of 23/10/2020). Suitable for vegetarians and vegans

Nature's Best Vitamin B12 tablets 1000mcg vitamin B12 tablets x180

£9.95 (correct as of 23/10/2020). Suitable for vegetarians and vegans

References

- Guideline for the management of Vitamin B12 deficiency (for adults), September 2018, Mid Essex Clinical Commissioning Group
- Anaemia—B12 and folate deficiency, NICE clinical knowledge summary, February 2019. https://cks.nice.org.uk/anaemia-b12-and-folate-deficiency#!management
- British Society for Haematology (BSH) guidance on Vitamin B12 replacement during the COVID-19 pandemic, 01.05.2020. https://b-s-h.org.uk/media/18275/bsh-guidance-b12-replacement-covid-1901052020finalv.pdf Accessed 02/07/2020.
- Guidelines for the diagnosis and treatment of cobalamin and folate disorders, Devalia et al, British Journal of Haematology, June 2014.
- Advice on B12 supplements during COVID pandemic, British Society for Haematology. https://b-s-h.org.uk/about-us/news/covid-19-updates/
- Oral vitamin B12—what are the prescribing considerations and what formulations are available , 29 June 2020. https://www.sps.nhs.uk/articles/oral-vitamin-b12-what-are-the-prescribing-considerations-and-what-formulations-are-available/ Accessed 01/07/2020.
- Oral vitamin B12—what are the prescribing considerations and what formulations are available? May 2020. https://www.sps.nhs.uk/wp-content/uploads/2020/06/UKMI_QA_Oral-Vitamin-B12-preparations_May-2020.pdf Accessed 02/07/2020.