

Vitamin B12 deficiency in adults

GUIDELINE

Background

NICE CKS states that deficiency of vitamin B12 or folate are the most common causes of megaloblastic anaemia.

- > Megaloblastic anaemia is characterized by the development of larger than normal red blood cells (macrocytosis), with immature nuclei due to defective DNA synthesis.
 - This results in red cells with a mean cell volume (MCV) above the normal range (greater than 100 femtolitres)
- > Pernicious anaemia (an autoimmune disorder which results in reduced production of intrinsic factor) is the most common cause of severe vitamin B12 deficiency in the UK.
- > Other causes of vitamin B12 deficiency are rare, but include:
 - Drugs — colchicine, metformin, nitrous oxide, proton pump inhibitors, H2-receptor antagonists.
 - Gastric causes — total or partial gastrectomy, congenital intrinsic factor deficiency or abnormality, Zollinger-Ellison syndrome.
 - Inherited — intrinsic factor receptor deficiency (Imerslund Gräsback syndrome).
 - Intestinal causes — malabsorption, ileal resection, Crohn's disease.
 - Nutritional — malnutrition, vegan diet.

Symptoms of deficiency

- > Cognitive changes, dyspnoea, headache, indigestion, loss of appetite, palpitations, tachypnoea, visual disturbance, weakness, lethargy.
- > Neurological complications associated with vitamin B12 deficiency include a loss of cutaneous sensation, loss of mental and physical drive, muscle weakness, optic neuropathy, psychiatric disturbances ranging from mild neurosis to severe dementia, symmetrical neuropathy affecting the legs more than the arms and urinary or faecal incontinence.

Diagnosis

As per NICE CKS on *Anaemia, B12 and Folate Deficiency* it is worth noting that the clinically normal level for serum B12 is unclear, although it is thought that serum B12 of less than 200 nanograms/L (148 picomol/L) is sensitive enough to diagnose 97% of people with vitamin B12 deficiency.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Serum B12 levels are not easily correlated with clinical symptoms, although people levels of less than 100 nanograms/L (75 picomol/L) usually have clinical or metabolic evidence of vitamin B12 deficiency.

In the elderly, low serum B12 concentrations usually in the range 100–160 nanograms/L may occur in the absence of anaemia or macrocytosis, and clinically significant vitamin B12 deficiency may be present even with serum B12 levels in the normal range.

Women taking oral contraceptives may show decreased serum B12 levels because of a decrease in cobalamin carrier protein, however, this may not result in deficiency.

Serum B12 levels fall in pregnant women and are less reliable in determining deficiency.

Note: reference values (and units) may vary between laboratories.

For people with suspected vitamin B12 or folate deficiency, arrange:

- > A full blood count to determine mean cell volume (MCV), haematocrit and haemoglobin levels, and a blood film — which help to identify megaloblastic anaemia.
- > Measurement of serum B12 and folate levels to determine the cause of anaemia.
- > Additional investigations, such as liver function tests, gamma-glutamyl transpeptidase, and/or thyroid function tests to identify the underlying cause. Determining the underlying cause may require specialist referral.

Anti-intrinsic factor antibody (anti-IFAB)

The finding of a low total serum B12 level may be further evaluated by testing for anti-IFAB. If positive, the test has a high positive predictive value (95%) for the presence of pernicious anaemia³

Treatment

The need for IM hydroxocobalamin should be discussed with each patient individually with regards to availability and ability to administer in a community setting.

If prescribing hydroxocobalamin 1mg IM injection is inappropriate e.g. under a pandemic situation, prescribers are advised to use the licensed 1mg cyanocobalamin tablets (Orobalin®).

Parenteral therapy is preferred for faster remission and liver repletion⁵.

Patients with suspected neurological involvement:

DO NOT delay treatment if there is (or is a strong suspicion of) neurological involvement

- > Seek urgent specialist advice from a haematologist.
- > Ideally, management should be guided by a specialist, but if specialist advice is not immediately available, consider the following:
- > Initially administer hydroxocobalamin 1 mg intramuscularly on alternate days until there is no further improvement, then administer hydroxocobalamin 1 mg intramuscularly every 2 months.

Patients with NO neurological involvement

Non-Dietary related deficiency:

- > Initially administer hydroxocobalamin 1 mg intramuscularly three times a week for 2 weeks
OR prescribe 1 mg cyanocobalamin (Orobalin®) TWO tablets twice a day between meals for 8 weeks.

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- > For maintenance in non-dietary deficiency, administer hydroxocobalamin 1 mg intramuscularly every 2–3 months for life or alternatively, if prescribing IM is inappropriate, 1mg cyanocobalamin (Orobalin®) tablets once a day until regular IM injections can be resumed.
- > Patients should be advised to monitor their symptoms and contact the GP if they begin to experience neurological symptoms such as pins and needles or lack of concentration/problems with memory.

Dietary related deficiency

- > Initially administer hydroxocobalamin 1 mg intramuscularly three times a week for 2 weeks or prescribe 1mg cyanocobalamin (Orobalin®) TWO tablets twice a day between meals⁵ for 8 weeks.
- > Once replete, as confirmed by blood tests detailed below, advise patients to self-care with oral cyanocobalamin tablets 50–150 micrograms daily between meals which can be purchased over-the-counter in a community pharmacy.
- > **Prescribers are encouraged to stop hydroxocobalamin injections or tablets in dietary-related deficiency when patients are replete and no longer require supplementation.**
- > In vegans, self-care supplementation 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.
- > Give dietary advice about foods that are a good source of vitamin B12. Examples can be found on the NHS website <https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-b/>
- > In certain circumstances where treatment is unavailable, many dietary deficient patients may be vitamin B12 replete with adequate levels within the liver, and therefore may be able to safely stop taking supplements for up to one year⁴.

Monitoring

The following monitoring is recommended after treatment has started¹

For IM ONLY:

Within 7–10 days of starting treatment: FBC, reticulocyte count

A rise in the haemoglobin level and an increase in the reticulocyte count to above the normal range indicates that treatment is having a positive effect.

If there is no improvement, check serum folate level (if this has not been done already).

For IM and PO:

After 8 weeks of treatment: FBC, reticulocyte count, iron and folate levels.

The mean cell volume (MCV) should have normalised.

On completion of folic acid treatment to confirm a response if required.

Ongoing monitoring is unnecessary unless a lack of compliance with treatment is suspected, anaemia recurs, or neurological symptoms do not improve or progress.

Measuring serum B12 levels is unhelpful as levels increase with treatment regardless of how effective it is, and retesting is not usually required. However, serum B12 can be measured 1–2 months after starting treatment if there is no response.

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Neurological recovery may take some time — improvement begins within one week and complete resolution usually occurs between six weeks and three months.

Costing Information (Drug Tariff prices²)

Cyanocobalamin 50 microgram tablets x 50 costs £11.42.

50 microgram daily - annual cost / patient = £83.37

150 microgram daily - annual cost / patient = £250.10

Hydroxocobalamin 1mg/ml solution for injection x 5 costs £10.28

1mg every 2 months - annual cost / patient = £ 12.34

1mg every 3months - annual cost/ patient = £ 8.22

1mg every 6 months (Dietary related and/or have normal anti-intrinsic factor antibody) annual cost / patient = £ 4.11

Cyanocobalamin (Orobalin®) 1mg tablets x 30 costs £9.99⁶

Treatment – 2mg twice daily for 8 weeks/ patient = £74.59

Maintenance – 1mg daily – annual cost/ patient = £121.55

References

1. NICE CKS on [Anaemia, B12 and Folate Deficiency](#) (February 2019) (Accessed online on 17/11/20)
2. [Drug Tariff](#) November 2020 (Accessed online on 17/11/20)
3. British Society for Haematology Guidelines [Diagnosis of B12 and Folate Deficiency](#) (Accessed online on 05/12/19)
4. [British Society for Haematology \(BSH\) guidance on Vitamin B12 Replacement During the COVID-19 Pandemic](#) (Accessed online on 19/08/20)
5. Orobalin® [Summary of Product Characteristics](#) (Accessed online on 17/11/20)
6. [BNF Online - Cyanocobalamin](#) (Accessed online on 17/11/20)