



CLINICAL GUIDELINES

Vitamin B12: Treatment of Deficiency in Adults

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained. Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

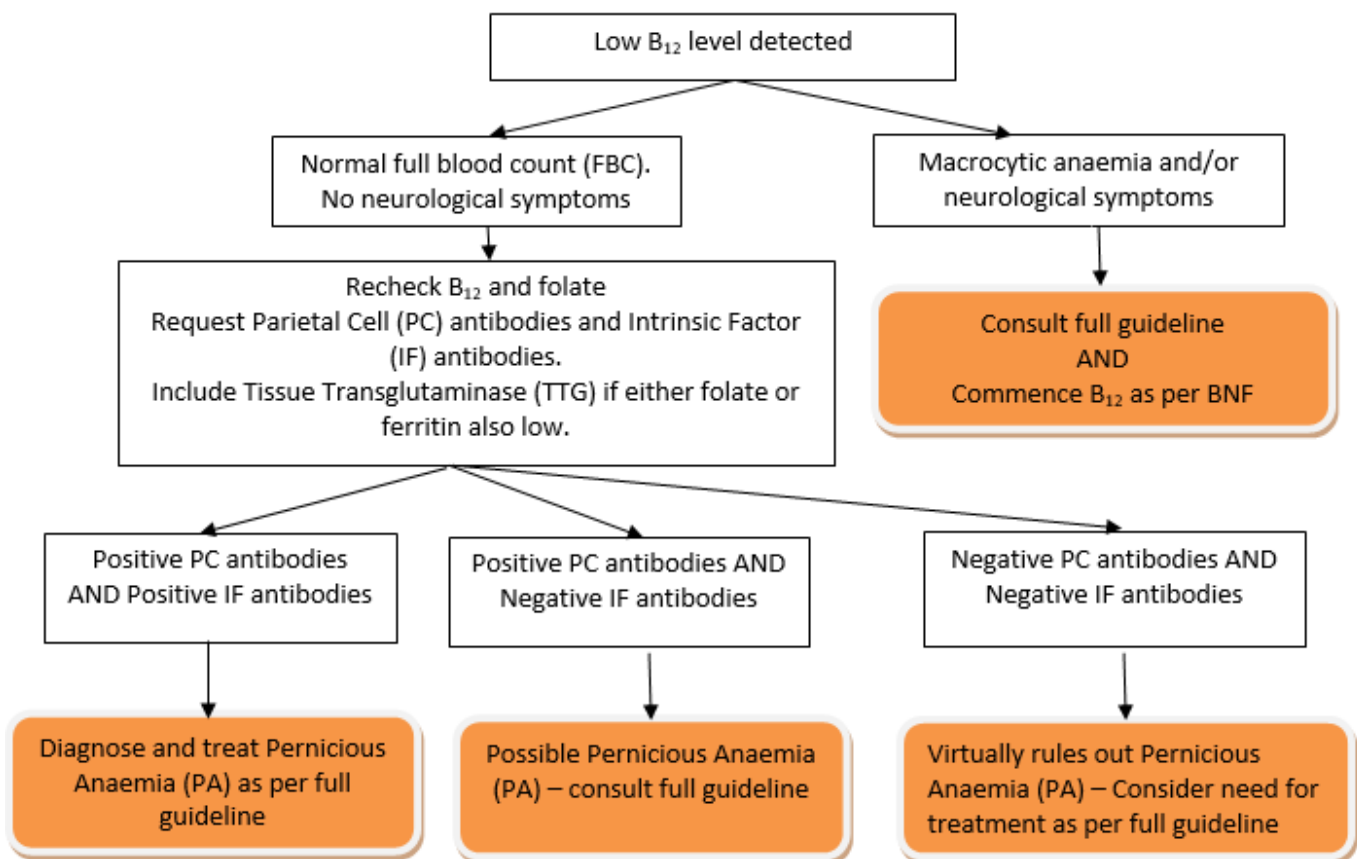
SCOPE:

This guidance gives advice on how to treat adults who are at risk of B₁₂ deficiency or who are known to have deficient/insufficient levels of vitamin B₁₂.

KEY POINTS:

1. The vast majority of patients with a low serum Vitamin B₁₂ level do NOT have Pernicious Anaemia (PA). However PA is an important diagnosis NOT to miss.
2. Metformin, proton pump inhibitors (PPIs), folate deficiency, pregnancy, oral contraceptive pills (OCPs) and other drugs discussed in the full guideline are the most common causes of a low serum Vitamin B₁₂. They do NOT require B₁₂ replacement unless B₁₂ deficiency anaemia or neuropathy is suspected.

WHAT TO DO WITH A LOW B₁₂ LEVEL



BACKGROUND:

Vitamin B₁₂ deficiency can take years to manifest as the body has significant stores of the vitamin. Symptoms of anaemia such as fatigue and lethargy, dyspnoea, faintness, palpitations, headache, tinnitus, anorexia, angina (if the person has pre-existing coronary artery disease) may be present but are not diagnostic. Patients may also present without anaemia. Vitamin B₁₂ deficiency should be suspected if the person reports unexplained neurological symptoms e.g. paraesthesia, numbness, cognitive changes, or visual disturbance.

Low B₁₂ levels predominantly affect older adults with prevalence rates of around 5% in 65–74 year olds, and more than 10% of people over 75 according to [NICE CKS, Anaemia - B₁₂ and folate deficiency](#).

CAUSES OF VITAMIN B₁₂ DEFICIENCY / LOW SERUM B₁₂ LEVELS

Note: not all patients with low B₁₂ levels in serum have true B₁₂ deficiency. Low levels in serum do not always reflect reduced supply of B₁₂ to the tissues.

- Pernicious anaemia (PA) - (Autoimmune Atrophic Gastritis). Vitamin B₁₂ combines with Intrinsic Factor (IF), which is produced by parietal cells in the stomach, to form an IF-B₁₂ complex, which then allows absorption to take place in the terminal ileum. Pernicious anaemia is an auto-immune disorder which results in reduced production of IF and therefore reduced absorption of B₁₂.
- Inadequate dietary intake of B₁₂ - Vitamin B₁₂ is present in virtually all animal tissues including eggs. Vitamin B₁₂ is not generally present in plant foods, but many foods are fortified with B₁₂ including breakfast cereals, soya drinks, and yeast extracts such as marmite.
- Dietary deficiency is rare in younger people but occurs more frequently in older people living in institutional environments. Individuals adhering to a vegan diet may be at risk of B₁₂ deficiency.
- Intestinal causes e.g. malabsorption, ileal resection, Crohn's disease.
- Hormonal causes - low serum B₁₂ levels are found in 20% of pregnancies. This occurs without anaemia or any other laboratory features of tissue B₁₂ deficiency. Low serum B₁₂ levels can similarly be found in women with the progesterone implant or taking the oral contraceptive.
- Medications e.g. colchicine, metformin, anticonvulsants, long term Proton Pump Inhibitors (PPIs) or H₂ blockers may cause low levels which do not require treatment unless there is associated B₁₂ deficiency anaemia or suspected neuropathy.
- Folate deficiency per se may cause B₁₂ levels to be low. **Although dietary deficiency is the most common cause of a low serum folate** all patients with combined low folate **and** B₁₂ levels should have a tissue transglutaminase (TTG) level checked (to exclude coeliac disease) regardless of the presence or absence of gastro-intestinal symptoms of malabsorption.
- Recently the syndrome of food-cobalamin malabsorption has been described. In this syndrome patients have a negative Parietal Cell (PC) and Intrinsic Factor (IF) antibody screen. The absorption of vitamin B₁₂ bound to food is impaired but the absorption of free vitamin B₁₂ such as in oral vitamin B₁₂ supplements, is normal. This appears to be related to altered acid levels in the stomach. It is common in the elderly and in those taking antacid therapies. Predisposing factors are as follows:
 - Atrophic gastritis, chronic helicobacter pylori infection (HP infection)
 - Microbial proliferation, AIDS
 - Long term ingestion of antacids or biguanides (e.g. metformin)
 - Chronic alcoholism
 - Gastrectomy, gastric bypass surgery
 - Pancreatic exocrine failure
 - Idiopathic (age related)

Food based malabsorption associated with gastric atrophy (age related or associated with long term PPI use) is the likely cause of 30 to 50% of cases of sub-clinical B₁₂ deficiency. The NHSGGC reference ranges for B₁₂ and folate are as follows:

Serum B ₁₂	200 – 900 pg/ml
Serum Folate	3 - 20 ng/ml

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Vitamin B₁₂ deficiency - as defined by serum vitamin B₁₂ levels below the reference range on two separate occasions a month apart - is a common finding; however the identification of significant pathology either underlying or secondary to this deficiency is not.

The clinical picture is the most important factor in assessing significance of serum vitamin B₁₂ results. Definitive cut off points for clinical and subclinical deficiency are not possible.

- The test measures total, not metabolically active, vitamin B₁₂. It does however have a sensitivity of diagnosing 97% of patients with true B₁₂ deficiency.
- The levels are not easily correlated with clinical symptoms, although people with vitamin B₁₂ levels less than 100 pg/ml usually have clinical or metabolic evidence of vitamin B₁₂ deficiency.
- In 97% of people with true vitamin B₁₂ deficiency, the serum vitamin B₁₂ level is below 180 pg/ml.
- Clinically significant vitamin B₁₂ deficiency is only very rarely present with vitamin B₁₂ levels in the normal range but can occur, particularly in elderly people.

The B₁₂ assay is a frequently requested test, generating many results out with the reference range and thus reported as abnormal. Determining the relevance and appropriate management of these results has been highlighted as an area of concern by many GPs locally. Our aim is to provide a simple means of assessing and replacing vitamin B₁₂ which will ensure adequate treatment of those with genuine B₁₂ deficiency or underlying disease whilst minimising the treatment and investigative burden of those with clinically insignificant low B₁₂ levels.

WHEN TO MEASURE VITAMIN B₁₂:

It is appropriate to measure serum B₁₂ in the following circumstances. Serum folate should also be measured at the same time:

- **Macrocytosis** (MCV > 100fl). Note: Liver disease, alcohol and hypothyroidism should also be considered as possible causes of a macrocytosis.
- **Unexplained anaemia**
- **Unexplained neurological signs and symptoms** e.g. peripheral neuropathy, visual loss and dementia
- **Severe depression** (especially in the elderly)
- **Gastro-intestinal symptoms** e.g. glossitis, abnormal taste, bowel malabsorption or unexplained diarrhoea. Levels should also be monitored in patients who have had surgical resections or radiotherapy to stomach/small intestine
- **Vegan Diet** (long term)
- **Hypothyroidism** - there is a high incidence of hypothyroidism in patients with PA and vice versa.

WHEN NOT TO MEASURE VITAMIN B₁₂:

- Tiredness is **not** an indication for serum vitamin B₁₂ assay.
- Serum vitamin B₁₂ assays should **not** be performed as first line in any routine haematological screen.
- Hormonal preparations (oral and depot), combined oral contraceptive treatment (OCT), depot progesterone implants and pregnancy, lower serum vitamin B₁₂ levels without causing tissue deficiency or macrocytosis. Therefore it is generally **not helpful to check serum vitamin B₁₂ in females taking progesterone preparations, combined OCT or who are pregnant** unless there is a clinical indication such as described above.

HOW FREQUENTLY TO MEASURE VITAMIN B₁₂:

If on initial haematologic assay, the serum vitamin B₁₂ level is reduced, a repeat serum vitamin B₁₂ assay should be requested approximately one month later, or earlier if symptoms necessitate prompt clinical intervention.

Note - TTG should also be checked if B₁₂ **and** folate levels are low regardless of the presence of symptoms of malabsorption.

Parietal Cell (PC) and Intrinsic Factor (IF) antibodies should be tested in addition at this stage. PC and IF antibody testing is undertaken by the Immunology Laboratory – Previous advice was to sample before starting B₁₂ therapy because the assay in use gave false positive result if the B₁₂ level was > 440pg/ml, This assay has now been replaced and a positive IF antibody result is now reliable even if the patient has started B₁₂ replacement and has a high serum Vitamin B₁₂ level.

See Appendix 1 for a summary table explaining interpretation of results and Appendix 2 for a flowchart on action to take.

- The absence of Parietal Cell (PC) antibodies virtually rules out a diagnosis of pernicious anaemia (PA).
- PC antibodies have high sensitivity but low specificity for PA. Positive PC antibodies are a relatively common finding (seen in up to 10% of individuals) and are therefore not diagnostic in isolation. A negative result is valuable (PA most unlikely) but positive results can be found in iron deficiency and in patients with other autoimmune diseases apart from PA e.g. hypothyroidism.
- IF antibody positivity is strongly predictive for pernicious anaemia and should be considered diagnostic unless clinical features suggest otherwise.
- IF antibody is only present in 50% of cases of PA so a negative result does not rule out a diagnosis of PA i.e. high specificity but low sensitivity
- Less than 5% of cases of PA are negative for both PC and IF antibodies hence the importance of checking for both PC and IF antibodies.

Many causes of low serum vitamin B₁₂ levels apart from hormonal (OCT, progesterone, pregnancy), PA or coeliac disease will respond to oral vitamin B₁₂ replacement (see below) and this can be used as a screening test. A patient responding to oral therapy can then be managed with dietary adjustment and the B₁₂ level re-checked in 3 to 4 months (see flowchart – Appendix 2). If B₁₂ remains low thereafter, replacement should be commenced with intramuscular (IM) hydroxocobalamin and/or pre-disposing factors such as treatment with PPIs addressed if clinically appropriate. Some patients with type 2 diabetes on metformin may require life-long therapy with IM hydroxocobalamin.

Regular monitoring of patients on maintenance IM B₁₂ replacement therapy is not normally considered necessary. Patients with confirmed PA should however have TFTs checked on an annual basis.

WHEN TO REFER TO SECONDARY CARE:

Hospital referral should be reserved for those with severe symptoms or in whom standard investigations fail to clarify the cause of a clinically significant deficiency.

- Seek urgent advice from a haematologist or neurologist if the person has neurological symptoms.

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- Refer to a haematologist or gastroenterologist if the cause of low vitamin B₁₂ is uncertain following investigations.
- Refer to haematologist if macrocytic anaemia does not respond to appropriate B₁₂ replacement.
- Refer to a gastroenterologist if:
 - Malabsorption of vitamin B₁₂ (other than due to pernicious anaemia) or folate is suspected.
 - The person has PA and upper gastrointestinal symptoms. Gastric carcinoma should be excluded if a patient with PA develops iron deficiency or upper GI symptoms.

CORRECTING VITAMIN B₁₂ DEFICIENCY:

- Hydroxocobalamin as intramuscular injection is the preferred form of treatment for confirmed PA and other causes of vitamin B₁₂ deficiency (see below) that do not correct with a trial of oral B₁₂ replacement. It is retained in the body longer than cyanocobalamin and thus for maintenance therapy can be given at intervals of up to 3 months. For this reason IM cyanocobalamin is non-formulary in NHSGGC.
- It is preferable to treat all symptomatic patients (even if the symptoms are mild to moderate) with loading doses as symptomatic benefit is achieved quite quickly. Patients with PA generally feel better within 24 to 48 hours of starting treatment by which time normal haemopoiesis is established in the marrow. The blood reticulocyte count usually rises after a week paralleled by the platelet count, which may rebound temporarily to abnormally high levels. Response may be slower if there is coexistent disease. Suggested loading and maintenance regimes of IM hydroxocobalamin in the current [BNF](#) are as follows –
 - Pernicious anaemia and other macrocytic anaemias **with** neurological involvement - Initially 1 mg once daily on alternate days until no further improvement, then 1 mg every 2 months
 - Pernicious anaemia and other macrocytic anaemias **without** neurological involvement - Initially 1 mg 3 times a week for 2 weeks, then 1 mg every 2-3 months
 - In patients with borderline deficiency who are asymptomatic and have not responded to an initial oral trial of cyanocobalamin it may be appropriate to go straight to 3 monthly hydroxocobalamin injections without loading depending on clinical judgement and taking account of coexistent disease.
- The [BNF](#) lists cyanocobalamin as less suitable for prescribing. Use of oral cyanocobalamin is restricted on the NHSGGC adult formulary to a 4 week trial as a screening test for causes of vitamin B₁₂ deficiency that are reversible with oral replacement (see flowchart). **It should be prescribed for a maximum of 4 weeks and then stopped. Care should be taken to use licensed medicinal products wherever possible rather than unlicensed cyanocobalamin tablets.**
- Proven vitamin B₁₂ deficiency of dietary origin should be corrected by dietary adjustment. There is a warning in the BNF that the currently available cyanocobalamin tablets may not be suitable for vegans. Low cost vitamin preparations containing B₁₂ suitable for vegans are widely available for purchase.
- Excellent advice on maintaining adequate vitamin B₁₂ levels on a vegan diet, via dietary sources or suitable supplements, is available through the [vegan society website](#).









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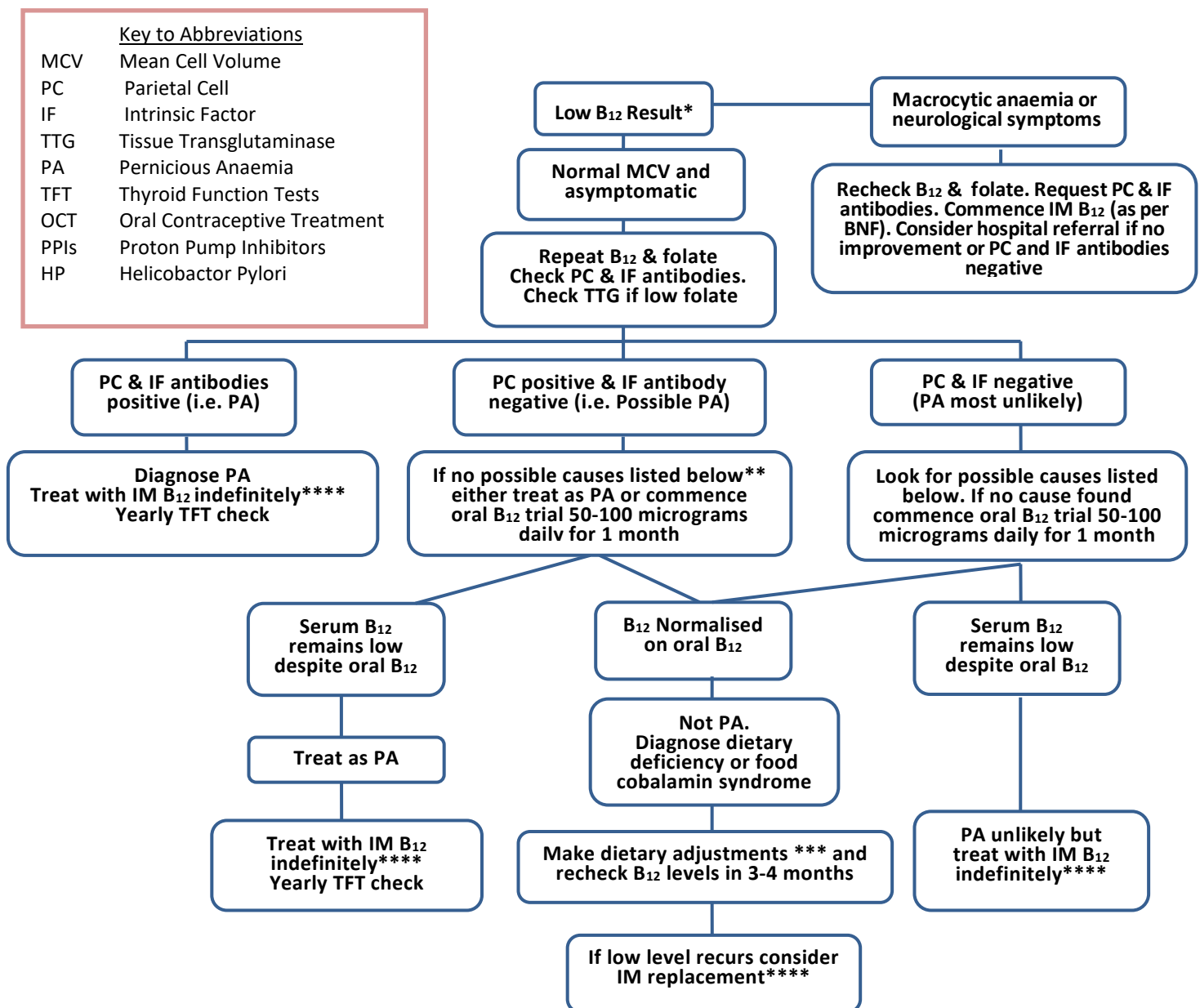
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Appendix 1 - Interpretation of PC / IF Antibody Testing for PA

PC antibody	IF antibody	Interpretation of Results
		<p>PA MOST UNLIKELY</p> <p>The absence of Parietal Cell antibodies virtually rules out a diagnosis of pernicious anaemia (PA). Less than 5% of cases of PA are negative for both PC and IF antibodies.</p>
		<p>DIAGNOSES OF PA</p> <p>IF antibody positivity is strongly predictive for pernicious anaemia and should be considered diagnostic unless clinical features suggest otherwise.</p>
		<p>INCONCLUSIVE – PA POSSIBLE</p> <p>Positive PC antibodies are a relatively common finding (seen in up to 10% of individuals) and are therefore not diagnostic in isolation. IF antibody is only present in 50% of cases of PA so a negative result does not rule out a diagnosis of PA</p>

Appendix 2 - Recommended action on obtaining low B₁₂ result



NOTES:

Pernicious Anaemia

Nowadays a rare cause of low B₁₂

Always check PC and IF antibodies before starting B₁₂. Note < 5% of cases of PA are negative for both PC and IF antibodies

* Low B₁₂ result definition

Serum vitamin B₁₂ levels below the reference range (200-900pg/ml) on two separate occasions a month apart

** Common causes of low B₁₂

1. Pregnancy, OCT, progesterone preparations (low B₁₂ of no clinical significance)
2. Metformin, PPIs. No replacement required unless B₁₂ deficiency anaemia or neuropathy suspected
3. Folate deficiency
4. Chronic Gastritis / HP infection / food cobalamin syndrome

*** Foodstuffs rich in B₁₂

Meat, liver, bovril, fish, cereals, eggs, cheese, milk and fortified foods

**** IM B₁₂ Dosage – see prescribing section of main guideline.

Loading with IM B₁₂ is preferable in all symptomatic patients. Asymptomatic patients as per clinical judgment.