NHS
Coventry and Warwickshire Pathology Services

Guideline for Primary Care: Investigation and management of B12 / Folate deficiency

Scope

- Intended for use by the NHS Coventry and Warwickshire Integrated Care Board GP practices and Medicines Optimisation Team (MOT).

Aims

- To aid prescribers to decide when to take vitamin B12 levels and how to treat vitamin B12 deficiency by raising awareness of national guidance.
- To support the review of all existing prescriptions of cyanocobalamin/hydroxocobalamin for appropriateness of prescribing.

Background

- The incidence of pernicious anaemia in the UK population is estimated [extrapolated from National Health and Nutrition Examination Survey (NHANES) reports in the United States] to lie between 1–5/100 000 per annum, i.e., a rare disease[1].
- Reflex testing of all low cobalamin samples in a routine diagnostic laboratory is therefore expensive with a low detection rate[1].
- A history of other autoimmune disease e.g. hypothyroidism, and family history (Banka et al, 2011) increases the pre-test probability of pernicious anaemia[1].

Accepted indications for B12/folate testing[2]

Reference ranges: B12 211-911 ng/L Folate more than 5.4 ug/L

• Unexplained macrocytosis (MCV >100fL) • Unexplained anaemia, if MCV high or normal • Dementia. Unexplained neuropsychiatric illness. • Peripheral neuropathy. Optic atrophy. • Organ-specific autoimmune disease (e.g. hypothyroidism) • FH of pernicious anaemia	• Malabsorption, including coeliac disease • Terminal ileal Crohn's disease. Atrophic gastritis • Long term metformin treatment • Previous Gastric or terminal ileal resection if not already on B12 supplements as prophylaxis • Poor nutritional status, as part of nutrition assessment

What monitoring is required after treatment for vitamin B12 or folate deficiency has started?[3]

- Perform a full blood count and reticulocyte count:
    - Within 7–10 days of starting treatment;
        - 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).
    - After 8 weeks of treatment, and also measure ferritin and folate levels.
        - The mean cell volume (MCV) should have normalised.
    - On completion of folic acid treatment to confirm a response.
- Measuring B12 levels is unhelpful as levels increase with treatment regardless of how effective it is, and retesting is not usually required.
- However, B12 can be measured 1–2 months after starting treatment if there is no response.
- Neurological recovery may take some time — improvement begins within one week and complete resolution usually occurs between six weeks and three months.

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

Dietary advice for patients with no neurological involvement[3]

Give dietary advice about foods that are a good source of vitamin B12 — good sources of vitamin B12 include[2]:

- Eggs
- Foods which have been fortified with vitamin B12 (for example some soy products, and some breakfast cereals and breads) are good alternative sources to meat, eggs, and dairy products
- Meat
- Milk and other dairy products
- Salmon and cod

Management of diet related vitamin b12 deficiency[3,4];

- Oral cyanocobalamin should NOT routinely be prescribed for patients suspected of having or likely to have diet-related vitamin B12 deficiency. Such patients should be advised to purchase a supply instead.
- For patients with medically diagnosed vitamin B12 deficiency (diet related) it is reasonable to prescribe oral cyanocobalamin at NHS expense at a dose 50-150micrograms daily between meals.
- Alternatively prescribe hydroxocobalamin IM 1mg injection- twice yearly

Management of B12 deficiency

Patients on hormone replacement therapy (HRT) and oral contraception[1]

- Asymptomatic women taking oral contraception or HRT with mildly reduced serum cobalamin (150-211 ng/l) do not require further investigation but should be advised to review their dietary intake of cobalamin-rich foods, and cobalamin supplements may be considered.

Poor absorption due to gastrointestinal surgery or disease[5]

Procedure	Frequency of B12 monitoring	Management
Sleeve gastrectomy	3, 6, and 12 months, annually thereafter	Hydroxocobalamin IM 1mg every 3 months[5]
Roux-en-Y gastric bypass	3, 6, and 12 months, annually thereafter	Hydroxocobalamin IM 1mg every 3 months[5]
Duodenal switch (BPD/DS)	3, 6 and 12 months, annually thereafter	Hydroxocobalamin IM 1mg every 3 months[5]

Food bound cobalamin malabsorption (FBCM)[1]

- FBCM has been used to define a group of disorders characterized by gastric hypochlorhydria due to age-related gastric atrophy or secondary to drugs such as the proton pump inhibitors[1].
- Patients with food-bound cobalamin malabsorption may benefit from low dose oral replacement[1].
- The degree of food-bound cobalamin malabsorption can vary, therefore a pragmatic approach would be to start with a low dose and titrate as necessary.

Low serum cobalamin on metformin

- The use of metformin has been linked to reduced B12 levels, however the mechanism of this remains unknown[1].
- Routine testing of B12 in patients with metformin, is not recommended however it is recommended that serum cobalamin is checked in the presence of strong clinical suspicion of deficiency only.
- If serum cobalamin levels are reduced, patients should have tests for gastric parietal cells Abs (GPC) (and intrinsic factor if GPC positive);
  - If positive, lifelong treatment with replacement hydroxocobalamin (as per algorithm 1 or 2 depending on presenting symptoms) should be given.
  - If negative, consider oral cyanocobalamin (50 micrograms for one month) and monitor levels every 6 months, then at yearly intervals[1].
- In any of the above instances, metformin therapy should not be stopped[6].

Folate Management

Folate 3.5 – 35.4µg/l with normal Hb/MCV.
Borderline low folate, with normal FBC. Consider 3 month Rx of folic acid and dietary advice - but 4 months in BNF for megaloblastic anaemia. Can haem help to confirm?

Folate-3.5– 35.4µg/l with low Hb or MCV high.
Borderline low folate, with abnormal FBC. Assess for poor diet and malabsorption. Suggest check TTG to exclude coeliac disease. Consider therapeutic trial of folic acid (5mg OD for 1 month) while dealing with underlying cause[2].

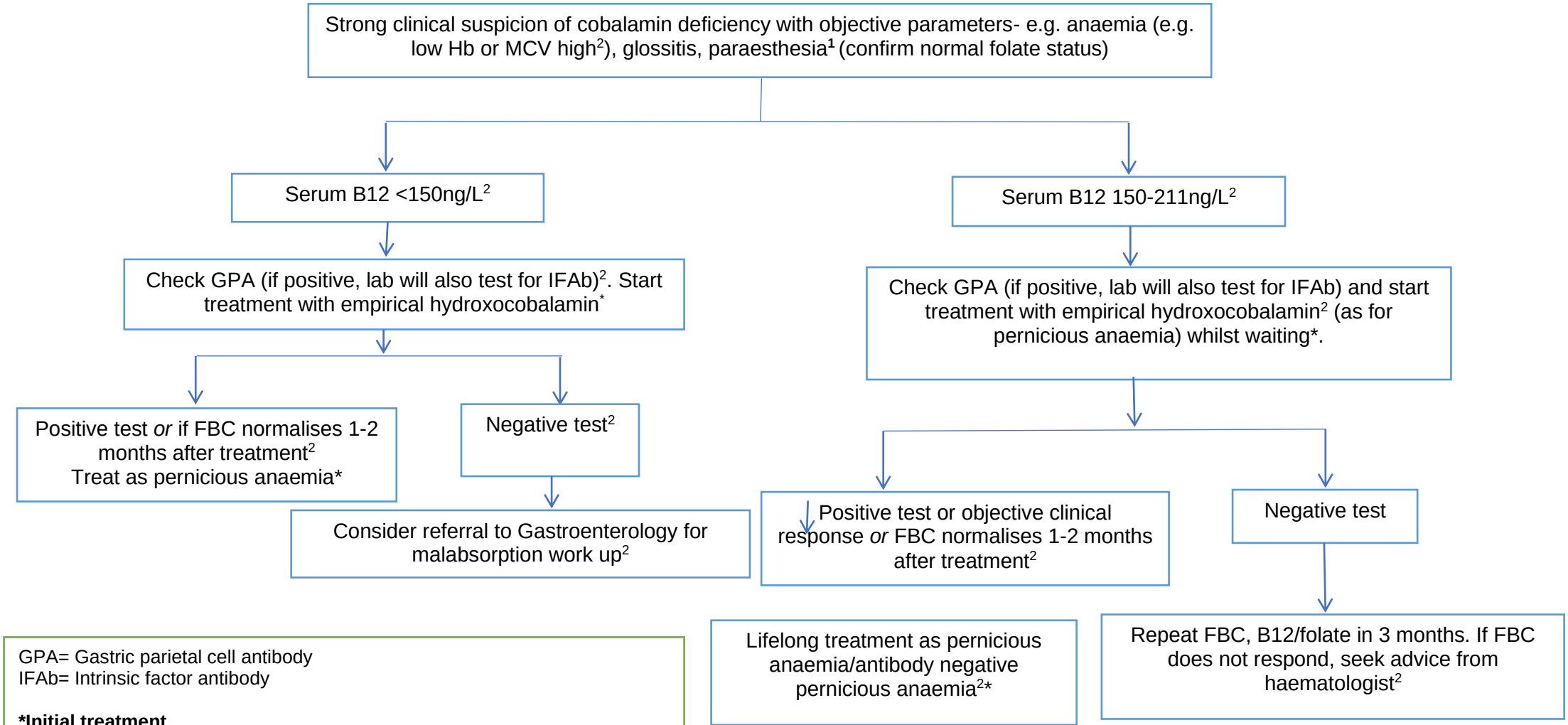
Folate- below 3.5µg/l with normal or abnormal Hb/MCV.
Significantly low serum folate. Assess for poor diet and malabsorption. Suggest check TTG to exclude coeliac disease. Consider therapeutic trial of folic acid (5mg OD for 1 month) while dealing with underlying cause[2].

Care with prescribing folic acid alone.

If folic acid is given to a patient who is actually B12 deficient, this may precipitate neurological complications which can be irreversible. Thus, if B12 deficiency cannot be excluded, this should be treated first. Sometimes, combination treatment (B12 and folic acid) is given due to the urgency of the clinical situation, but this may hinder interpretation of which haematinic the patient has responded to[2].

Algorithm 1. Treatment of B12 deficiency in the presence of anaemia and/or neurological symptoms

For patients with neurological involvement seek urgent advice from a haematologist. If advice not immediately available, then consider treatment with hydroxocobalamin 1mg IM on alternate days until no improvement, then every 2 months.[3]



GPA= Gastric parietal cell antibody
IFAb= Intrinsic factor antibody

***Initial treatment**
Pernicious anaemia with neurological involvement- hydroxocobalamin IM 1mg daily on alternate days, until no further improvement[4].
Maintenance- hydroxocobalamin IM 1mg every 2 months for life[3,4]

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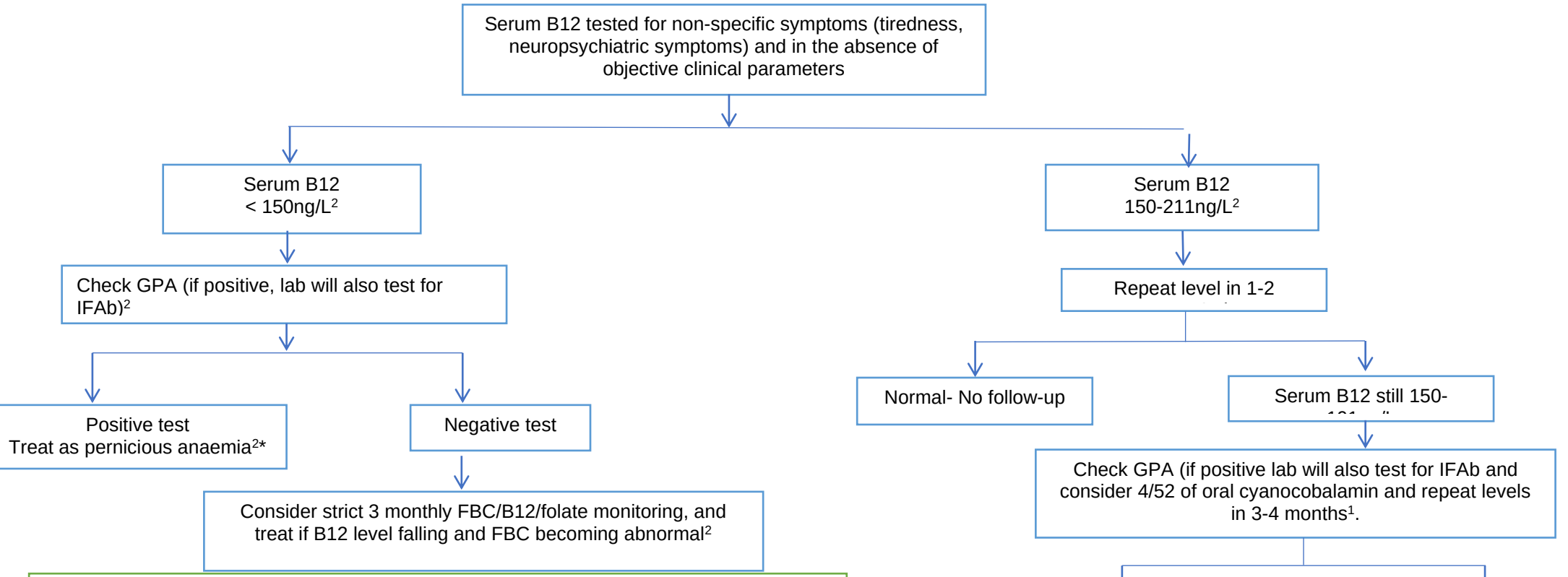
Algorithm 2. Investigation of low B12 without the presence of neurological symptoms



***Initial treatment**:
Pernicious anaemia and other macrocytic anaemias without neurological symptoms;
[4,5]-hydroxocobalamin IM 1mg daily 3x a week for 2/52
Second line (only if IM not tolerated) Orobalin (cyanocobalamin) 1mg tablets- 2 tablets twice a day between meals until remission of symptoms.

Maintenance[2]:
Not thought to be diet related — administer hydroxocobalamin 1mg intramuscularly every 2–3 months **for life**.
If using Orobalin- 1mg daily (if neurological symptoms present, parenteral treatment should be used
****Thought to be diet related*** — advise patients either to purchase OTC oral cyanocobalamin tablets 50–150micrograms daily between meals or prescribe 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.

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References

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6. Wainwright P (2017) Q&A: Metformin and vitamin B12 deficiency. Diabetes & Primary Care 19: 63–6