Guidelines for the Investigation and Management of Vitamin B12 and Folate Deficiency

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Cobalamin (B12) and Folate Deficiency

These pathways are based on guidance from the British Committee for Standards in Haematology. This stated that because of the wide variability in methods to measure B12 and folate local pathways should be clinically orientated and based on locally generated normal ranges, with standardised international units.

The new ranges were derived from ranges stated in the new BCSH guidelines after modification for differences between laboratories as recommended in these guidelines. We assessed our method performance against other UK laboratories from UK NEQAS results and adjusted the BCSH ranges based on the observed bias in our method compared with the UK average performance. These were then verified by comparison with a set of 300 normal volunteer samples from the local area. The effect of the proposed changes were then modelled on a set of >50,000 real results from our current method/system.

The outcome of the above evaluation is that we expect:

- 4.5% of patients will have a result below the lower limit (this lower limit equates to the 3rd percentile for the 300 healthy volunteers).
- 9.5% of patients will have a result in the indeterminate range and a repeat suggested at 8 weeks (this cut-off equates to 11th percentile for the 300 healthy volunteers).
- 71% of these repeats will have normal values.

The change in the ranges looks large but our new method gives results about 21% lower than the previous method and the change of units reduces the reported number by a further 26%.

Normal Ranges in Hull and East Yorkshire

The normal ranges for B12 and folate levels based on the above methodology are:

B12 (115 to 1000 pmol/L) (B12 levels just within the normal range can lead to symptoms so results 115-150 should be assessed on an individual basis)

Folate (>3µg/L)

Diet assessment and advice is essential as dietary deficiency can be easily corrected.
Foods high in B12 include: fish and shellfish, beef, liver, dairy products, eggs.
Foods high in folate include: green vegetables, beans and pulses, citrus fruit.

There are two pathways for investigation and management for B12 depending on the indication for it being tested and one for folate.

Cobalamin Deficiency

There are many pitfalls for the investigation of haematinic deficiency **and routine testing should not be undertaken**. Symptoms of deficiency are usually non-specific, screening tests are not sensitive or specific and assays for cobalamin (B12) and folate show wide variation within the same patients and between methods and are difficult to interpret.

B12 and folate should always be assessed together due to the close relationship of metabolism. However, once a patient has commenced B12 replacement there is no further need for it to be measured again.

Currently cobalamin is the only routine test available for the assessment of B12. Other tests may become available locally in the future to assist decision making for treatment in cases of borderline results. Some specialist tests sent to other labs are available for better understanding of B12 metabolism.

There are few absolute indications for B12 assessment. The interpretation of B12 outside these indications is more complex and results should be interpreted with caution.

Absolute indications for measuring vitamin B12:

1. **Unexplained anaemia**
2. **Neurological signs or cognitive impairment**
3. **Post gastric and bariatric surgery**
4. **Failure to thrive, movement disorders and developmental delay in infants**
5. **Objective evidence of B12 deficiency – glossitis**

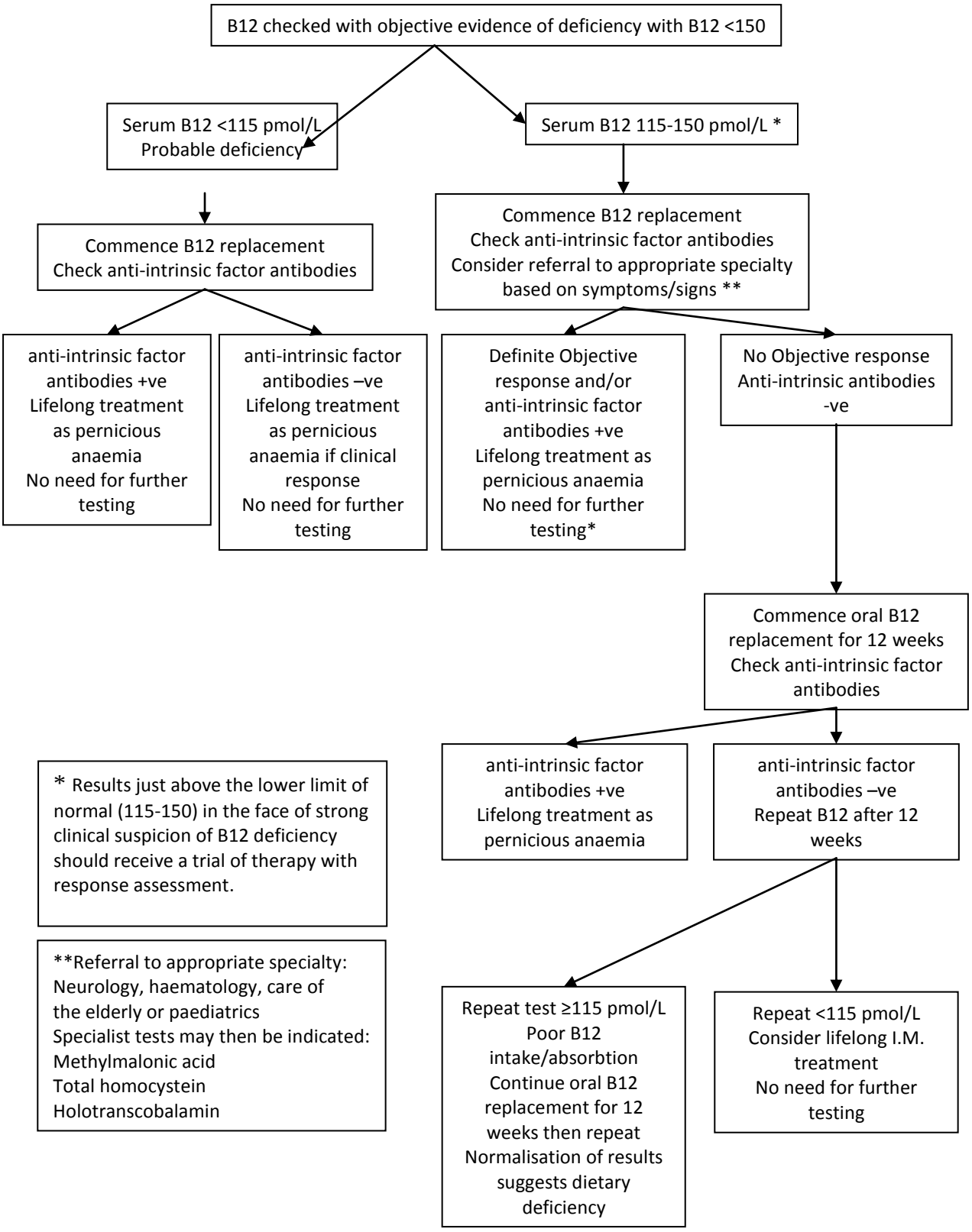
Many non specific symptoms may be caused by B12 deficiency including tiredness, fatigue and other neuropsychiatric symptoms and B12 assessment should only be assessed if no other cause is found.

There are currently no indications for B12 supplementation without assessment of B12 levels. However, post gastric or bariatric surgery guidelines suggests lifelong treatment without assessment or monitoring may prevent deficiency as the majority of patients will eventually require supplementation with IM therapy due to oral supplements being inadequate.

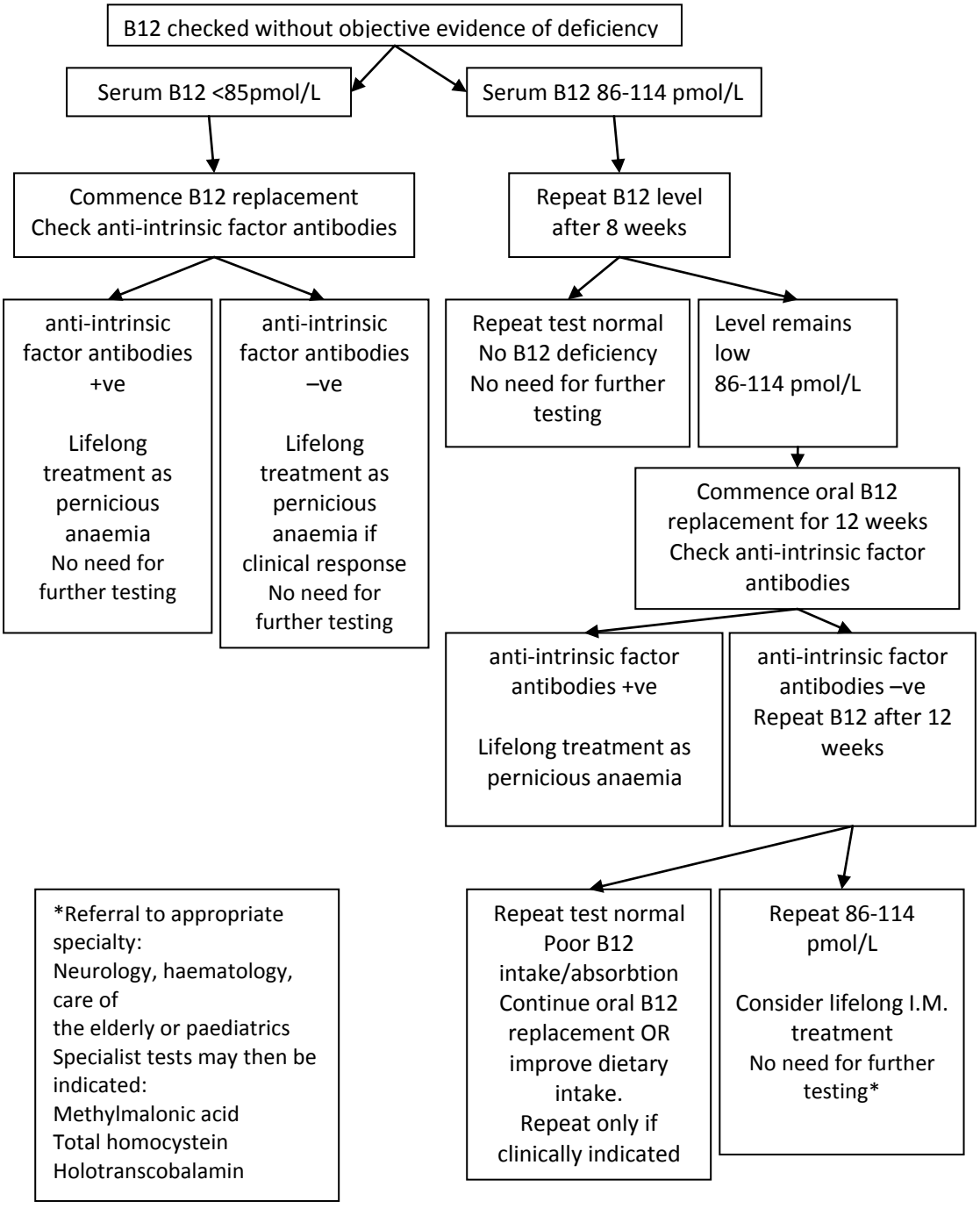
Investigation and management of B12 deficiency can be divided into two based on indications for assessment.

1. Strong suspicion with objective indications for testing
2. Investigation with no strong supporting evidence

1. Management of B12 deficiency with strong suspicion with objective indications for testing. Treatment should be I.M. unless stated.



2. Management of B12 deficiency with no strong supporting evidence. Treatment should be I.M. unless stated.



Referral for second line testing

If there is strong objective evidence of B12 deficiency (macrocytic anaemia, neurological symptoms or failure to thrive) despite normal levels second line testing under specialist guidance is indicated. This guidance needs to be directed by a specialty appropriate to the patient: neurology, paediatrics, care of the elderly or haematology.

Second line testing is complex with significant pitfalls and appropriate tests include:

1. Plasma total homocysteine
   This is raised in B12 deficiency but not specific becoming elevated in folate deficiency, B6 deficiency, renal disease and hypothyroidism.

2. Plasma methylmalonic acid
   This is raised in B12 deficiency but again is not specific being raised in renal disease and by haemoconcentration and small bowel bacterial overgrowth.

3. Holotranscobalamin
   This is more sensitive but not a routinely used test.

Results of second line testing by a specialist require correlation with patient symptoms and response to therapy.

Treatment for B12 deficiency

Current clinical practice within the UK is to treat cobalamin deficiency with hydroxocobalamin in the intramuscular form (outlined in the British National Formulary, BNF, http://www.medicinescomplete.com/mc/bnf/current/PHP5867-drugsused-in-megaloblastic-anaemias.htm).

Standard initial therapy for patients without neurological involvement is 1mg intramuscularly (IM) three times a week for 2 weeks (e.g. Mon, Wed, Fri for 2 weeks).

The BNF advises that patients presenting with neurological symptoms should receive 1mg IM on alternate days until there is no further improvement. However, the GWG recommends a pragmatic approach in patients with neurological symptoms by reviewing the need for continuation of alternate day therapy after 3 weeks of treatment.

Maintenance treatment for patients presenting without neurological deficit is with hydroxocobalamin 1mg IM every 3 months.

Those with initial neurological deficit should receive hydroxocobalamin 1000 micrograms IM every 2 months.

No further testing for cobalamin levels is required once I.M. replacement commenced.

Low dose oral cyanocobalamin 50 – 150 micrograms daily between meals is licensed within the UK and may improve serum cobalamin and biochemical markers in borderline cases. Once commenced B12 levels should only be assessed if clinical suspicion of B12 deficiency develops.

Pitfalls of B12 measurement

There are many pitfalls for the assessment of B12:

Drug use:

- **Metformin**

  Metformin paradoxically reduces the serum cobalamin level but improves intracellular metabolism. Reduced B12 levels in those on metformin are rarely clinically significant and usually improve with dietary improvement of B12 intake.

  B12 should only be assessed in patients with diabetes if objective evidence of deficiency is present including peripheral neuropathy or macrocytic anaemia.

  Low levels should be investigated with anti-intrinsic factor antibodies and should be treated with a short course of B12 (50 micrograms orally for 4 weeks). Response should be assessed clinically and continued if benefit is shown.

  There is no need for prophylactic B12 administration.

- **Proton pump inhibitors and H2 antagonists**

  Prolonged use of proton pump inhibitors cause gastric hypochlorhydria leading to reduced separation of B12 from food. This usually causes a subclinical deficiency but oral replacement (25-100 micrograms orally) may be appropriate if objective evidence of deficiency is found.

- **Anticonvulsants**

  Phenytoin, barbiturates and primidone all reduce the level of circulating B12. In the absence of objective features of B12 deficiency there is no need for replacement.

- **Oral contraceptives and hormone replacement therapy**

Both the OCP and HRT reduce cobalamin levels but this is rarely clinically significant. Levels should only be assessed if objective symptoms develop and this is the only indication for treatment.

- **Colchicine**

  Colchicine reduces B12 absorbtion. Low levels can easily be increase with dietary supplementation.

- **Antibiotics**

  Neomycin and pyrazinamide reduce absorbtion of B12. Low levels can easily be increase with dietary supplementation. Pyrazinamide can causea more general malabsorbtion syndrome.

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.

Pregnancy

- Pregnancy causes a physiological lowering of plasma cobalamin levels by up to 30% by the third trimester. B12 levels should not routinely be measured during pregnancy. Empirical treatment of cobalamin deficiency should be given if paraesthesia, neuropathy or megaloblastic anaemia occurs.

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 oral supplementation may be required.

Other medical disorders

- **HIV**

  Prior to the use of highly active antiretroviral therapy (HAART) up to 20% HIV-infected patients had a low vitamin B12 level. This figure has fallen to less than 9% of patients on therapy. However, few patients prior to therapy have real vitamin B-12 deficiency. The reduced levels are usually due to reduced carrier proteins and reduced white cell count, where most B12 is stored.

- **Myeloma**

  Paraproteins can reduce the level of serum B12 giving artificially low results and rarely reflect true deficiency.

Raised B12

Vitamin B12 does not accumulate to toxic levels. Raised B12 s associated with underlying medical conditions including liver disease, renal failure and myeloproliferative disorders (polycythaemia, chronic myeloid leukaemias and hypereosinophilic syndrome). Liver disease causes release of cobalamin from stores into the circulation, renal disease reduces its excretion and cMPDs increase the number of B12 containing red and white cells.
Raised B12 should lead to assessment for the above conditions and referral to the appropriate specialty.

Folate Deficiency

Folate is an umbrella term for all the biological active forms of the vitamin and folic acid is the synthetic form used in medicines and fortified foodstuffs.

All folates are absorbed in the terminal ileum and almost 50% is stored in the liver.

Folate is essential for DNA synthesis. Clinical signs of deficiency are seen first in rapidly turning over cells such as in the bone marrow and gastrointestinal tract leading to megaloblastic anaemia and glossitis.

Tests for folate assess either serum levels or red cell levels.

Serum folate reflects recent folate intake and can lead to false normal results. Abnormally low folate can be seen in patients with anorexia, recent alcohol intake, pregnancy or on anticonvulsants.

Red cell folate reflects the folate level present in red cells throughout their life span but is affected more readily by preanalytical variables including need for a whole blood sample, sample processing requiring red cell lysis and dilution of the folate released. This processing makes red cell folate a more time consuming and expensive test.

Folate and B12 should always be assessed together due to the close relationship of metabolism and overlap of clinical symptoms deficiency causes.

Indications for folate assessment:

1. Unexplained anaemia/macrocytic anaemia/megaloblastic anaemia
2. Excess alcohol intake especially with coexisting liver disease
3. Exfoliative skin diseases
4. Post gastric and bariatric surgery

Indications for folate supplementation without assessment of folate levels are:

1. Pregnancy
2. Haemolytic anaemia – autoimmune haemolysis, red cell membrane disorders and haemoglobinopathies.

Folate should be considered to be low if the level is <3 micrograms/L. Below this level megaloblastic anaemia is more common.

Treatment of folate deficiency

The BNF has outlined the treatment of folate deficiency as follows:
Folate deficient megaloblastic anaemia (due to dietary insufficiency, pregnancy or antiepileptics): 5 mg of folic acid daily is taken for 4 months, except in pregnancy where it is continued until term, and up to 15 mg daily for 4 months is suggested in malabsorptive states. Chronic haemolytic states and renal dialysis: the prophylactic dose suggested is 5 mg daily to weekly, depending on the diet and rate of haemolysis. Pregnancy: the prophylactic dose suggested is 400 micrograms daily, increased to 5mg daily if BMI >30, in diabetes or other risk factors.

Pitfalls of Folate measurement

1. Serum folate levels are affected by recent folate intake giving false reassurance.
2. Serum folate is reduced in the immediate post renal dialysis period so should not be measured at these times.
3. Medications including anticonvulsants lower the serum folate level.

References

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