

## Guidelines for the investigations & management of Vitamin B12 deficiency

### Background

We are frequently asked for advice on the cause of a patient's vitamin B12 (cobalamin) deficiency and its management. For the patients with a very low serum B12 level (<100ng/l) and anaemia, macrocytosis or neurological symptoms, the treatment is simple: load the patient with vitamin B12 parenterally (by IM injection) and continue with maintenance vitamin B12 by IM injection every 3 months indefinitely (see below for more details). The cause of the vitamin B12 deficiency may be more difficult to define but this guideline should help you to find a cause in the majority of these more serious cases.

This document is designed not just to provide guidance on a management plan for these patients but also to provide some background information to support better understanding of the issues involved. **However, if you are in a rush, please go straight to the suggested management algorithm on page 5.**

Requests for serum vitamin B12 levels continue to rise. Surrey Pathology Services performed 32,500 vitamin B12 measurements in 2016 compared with 18,000 in 2010. Many of these tests are requested in the absence of any haematological, neurological or gastrointestinal problems. Such asymptomatic patients usually have moderately or mildly low vitamin B12 levels of 150-180ng/l. In this situation, it is common not to find a cause for the vitamin B12 deficiency which makes it difficult to know how best to manage the patient.

### Presentation

#### Sources of dietary vitamin B12

Vitamin B12 is found in foods of animal origin including milk, cheese, yoghurt and eggs. Vitamin B12 deficiency of dietary origin is therefore only found in strict vegans. The recommended daily requirement of vitamin B12 is small (1-2 µg/day) compared with total body stores (2000-5000 µg) much of which is stored in the liver. This explains why it takes a long time, usually years, for vitamin B12 deficiency to develop.

#### Vitamin B12 absorption

Dietary vitamin B12 is freed from the food protein by pepsin in the acid gastric environment and binds to haptocorrin, a protein secreted in saliva. In the small intestine, haptocorrin is degraded by pancreatic enzymes, the vitamin B12 is released and binds with intrinsic factor (IF), itself secreted by gastric parietal cells. The physiological pH changes which occur in both the stomach and the proximal small bowel are necessary for optimum B12 absorption. The IF-B12 complex is carried through the small intestine and binds to receptors in the terminal ileum where it is actively absorbed. A small fraction (1-2%) of the daily intake is passively absorbed across the entire absorptive surface of the intestinal tract.

### Indications for measuring serum vitamin B12 level

- Haematological (in increasing order of severity)
  - Isolated red cell macrocytosis
  - Macrocytic anaemia (esp. if MCV >110fl)
  - Pancytopenia (esp. if MCV >120fl)
- Neurological or psychiatric
  - Peripheral neuropathy
  - Cognitive change e.g. dementia
  - Optic neuritis
- Gastrointestinal
  - Investigation of possible malabsorptive process
- Other (rare)
  - Angular cheilosis
  - Sore beefy red tongue

Haematological complications of vitamin B12 deficiency can present in the absence of neurological problems and *vice versa*.

### Causes of vitamin B12 deficiency

- Inadequate vitamin B12 in diet
  - Strict Vegan
- Oral contraceptive pill
  - The reduced serum B12 level is thought to be due to a reduction in the level of the vitamin B12-carrying protein (transcobalamin) rather than a deficiency of vitamin B12 *per se*.
  - Vitamin B12 malabsorption
    - Pernicious anaemia (PA)
      - Caused by loss of gastric parietal cells due to autoimmune atrophic gastritis resulting in reduced IF production
      - Commonly associated with other autoimmune conditions (esp. vitiligo and thyroid disease) and slightly increased risk of gastric carcinoma.
      - Familial tendency
- Long term use of PPI or H<sub>2</sub>-antagonist drugs
- Chronic alcoholism
- Pancreatic failure
- Coeliac disease
  - this much more commonly causes iron and/or folate deficiency
  - but 10-30% of coeliac patients can have evidence of vitamin B12 deficiency
- Gastrectomy
- Small bowel (esp. terminal ileal) surgery

- Generalised malabsorption
  - e.g. tropical sprue
- Inflammatory bowel disease
  - esp. that affecting the terminal ileum e.g. Crohn's disease
  - Blind loop syndrome and/or small bowel bacterial overgrowth
  - bacteria compete for and break down IF-B12 complex
- Drugs
  - Biguanide (e.g. Metformin) therapy (inhibits vitamin B12 absorption)
  - Cholestyramine
  - Slow K
- Fish tapeworm (*Diphyllobothrium latum*) infestation
  - Mostly seen in Scandinavia where eating raw fish is more common
- Rarities e.g.
  - Nitrous oxide (N<sub>2</sub>O)
  - cob(I)alamin oxidised to cob(III)alamin
  - Deficient/defective IF
  - Disorders of cobalamin transport
  - e.g. defective transcobalamin II or TC II receptor
  - Inborn errors of metabolism

A careful clinical history, concentrating on the patient's diet, drug therapy and previous medical history is therefore important in elucidating the cause of vitamin B12 deficiency. Other features such as a family history and signs of autoimmune disorders (esp. thyroid disease and vitiligo) may point towards a diagnosis of pernicious anaemia.

### Differential diagnosis of a macrocytosis (MCV >100fl)

In almost all of these cases the condition causes macrocytosis by inhibiting cell division of the red cell precursors in the bone marrow – less cell division gives rise to larger red cells.

- *Alcohol and/or liver disease* (esp. if macrocytosis accompanied by thrombocytopenia but no or only mild anaemia)
- *Vitamin B12/folate deficiency*
- *Pregnancy and newborn*
- *Hypothyroidism*
- *Haemolytic anaemia* (where macrocytosis results from the presence of increased numbers of reticulocytes, which are larger than mature red cells, in the blood)
- *Myelodysplasia*
- *Drugs* esp anti-metabolites that interfere with DNA synthesis and cell division e.g.
  - Hydroxycarbamide
  - Azathioprine
  - Methotrexate
  - Trimethoprim
  - Zidovudine (AZT) and other nucleoside reverse transcriptase inhibitor treatments for HIV
  - *Aplastic anaemia* or other causes of 'bone marrow stress'
  - *Acquired sideroblastic anaemia* (very rare)

## Investigations to help define the cause of the vitamin B12 deficiency

Anti-intrinsic factor (anti-IF) antibodies – highly specific (95-100%) for PA but not very sensitive (only positive in 50-60% of patients with PA)

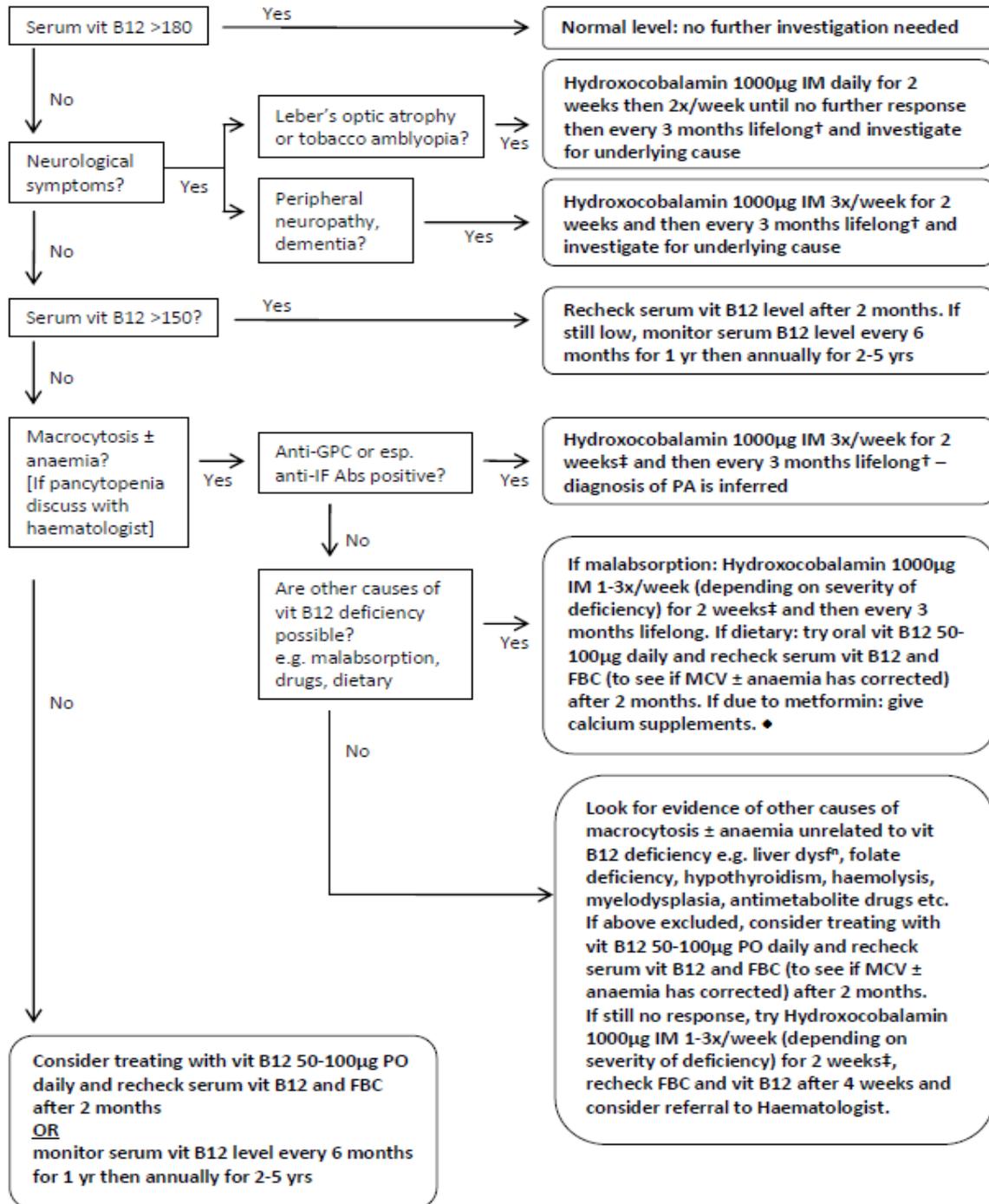
- Anti-gastric parietal cell (anti-GPC) antibodies – reasonably sensitive (80-90%) for PA but not as specific as anti-IF antibodies – this is one of the tests that make up the autoimmune screen.
- NB. A positive anti-GPC and/or anti-IF antibody test does not require repeating – to do so is a waste of resource.
- Thyroid function tests and anti-thyroid antibodies
- Test for coeliac disease
  - Tissue transglutaminase (tTG)
- Tests for generalised malabsorption (if symptoms are suggestive) – we suggest that the faecal tests are only requested by a Gastroenterologist
  - Serum
    - Calcium and vitamin D
    - Folate
    - Ferritin
  - Faecal
    - Fats
    - Elastase
- Schilling test (**NO LONGER AVAILABLE IN THE UK**)
  - This was a test designed to provide objective evidence of some form of vitamin B12 malabsorption (part 1) and whether it was corrected with the additional of oral IF (part2) or after a course of antibiotic therapy (part 3).
  - The radioactively-labelled cobalamin is now difficult to source and the oral intrinsic factor required for the part 2 test is no longer available in the UK.
  - In practice, in an audit performed in a large DGH in the South of England in the early 2000s, almost all patients with a serum vitamin B12 <100ng/l had evidence of vitamin B12 malabsorption whilst virtually none of the patients with serum vitamin B12 >150ng/l did

## Management of vitamin B12 deficiency

In general, **patients presenting with significant haematological and/or neurological consequences need to be treated promptly and effectively with vitamin B12 replacement via the parenteral route** – the effectiveness of oral therapy might be compromised if a malabsorptive condition is the cause of the deficiency.

The management of patients with apparently **asymptomatic** vitamin B12 deficiency is a source of considerable debate. These patients usually have a serum vitamin B12 >150ng/l. It is worth confirming the 'deficiency' by repeating the serum vitamin B12 level (beware: the laboratory computer system may reject requests for vitamin B12 levels within 42 days of the previous request – please make it clear on the e-request/form why you are repeating the test in a short time-frame). If the level is still low, a significant proportion of these patients will go on to develop symptomatic vitamin B12 deficiency in the future. You then have a choice:

- monitor the vitamin B12 level on an annual basis or
- treat with oral vitamin B12 supplements and monitor the serum vitamin B12 level after 2-3 months to see if it improves. Treating these patients with parenteral vitamin B12 supplementation would seem somewhat heavy-handed.



**NB.** This algorithm is NOT applicable to pregnant patients. MCV may rise physiologically to 105fl in pregnancy. Pregnancy causes a physiological lowering of B12 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. If clinical concern, please discuss with a haematologist.

- There is no need to monitor serum vitamin B12 levels in patients receiving 3 monthly parenteral vitamin B12 treatment.
- We suggest adding folic acid 5mg PO daily for 4 weeks for patients with anaemia due to vitamin B12 deficiency. This avoids the possibility of inducing folate deficiency consequent upon the increased normoblastic red cell production that should follow after providing a source of the previously deficient vitamin B12.

It has been suggested that an increased intake of calcium reverses the vitamin B12 malabsorption induced by metformin. Bauman WA et al, *Diabetes Care* 2000 (23) 1227-31

Hydroxocobalamin has replaced the use of cyanocobalamin as the form of vitamin B12 of choice for parenteral therapy: it is retained in the body for longer than cyanocobalamin.

The rationale for treating patients with apparently asymptomatic but significantly reduced levels (<150ng/l) of serum vitamin B12 is that some of these patients show biochemical evidence of subclinical vitamin B12 deficiency e.g. increased levels of plasma homocysteine and methylmalonic acid and some will develop symptomatic problems if left untreated.

Patients treated with oral repletion therapy need to have their initial response to treatment monitored with vitamin B12 levels after 2-3 months followed by 6-12 monthly tests to ensure an ongoing response.

## Related documents

Guidelines for the diagnosis and treatment of cobalamin and folate disorders: British Committee for Standards in Haematology, BJHaem, Volume 166, Issue 4, pp 496–513, Aug 2014 - <http://onlinelibrary.wiley.com/doi/10.1111/bjh.12959/full>

British National Formulary on line (Nov 2017)

10 minute consultation - Vitamin B12. B Hudson, *British Medical Journal* 5 June 2010 (vol 340) pages 1245-6

Postgraduate Haematology 6<sup>th</sup> ed, AV Hoffbrand, D Catovsky, EGD Tuddenham & AR Green; Wiley Blackwell

## Further sources of information

### Information for patients

Vitamin B12 deficiency anaemia – [www.patient.co.uk/health/Anaemia-\(Pernicious\)-and-Vitamin-B12-Deficiency.htm](http://www.patient.co.uk/health/Anaemia-(Pernicious)-and-Vitamin-B12-Deficiency.htm)

Pernicious Anaemia Society – [www.pernicious-anaemia-society.org](http://www.pernicious-anaemia-society.org)

### Information for clinicians

Please contact a member of the Clinical Haematology Team via your local hospital switchboard for further advice

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