Vitamin B12 treatment guideline

What are the signs of B12 deficiency?

• Haematological (in order of increasing severity)
  Isolated red cell macrocytosis without anaemia
  Macrocytic anaemia (esp if MCV >110fl)
  Pancytopenia (esp if MCV >120fl)
• Neurological or psychiatric
  Peripheral neuropathy
  Cognitive change e.g. dementia
  Optic neuritis
• Gastrointestinal due to malabsorption
• Other (rare)
  Angular cheilosis
  Sore beefy red tongue

When to check Vitamin B12 levels:

• Macrocytosis (MCV>100fl) or macrocytic anaemia
• Previous gastric surgery/inflammatory bowel disease/Coeliac disease
• Iron deficiency anaemia not responding to adequate oral iron
• Neuropsychiatric symptoms where the cause is not known

Causes of Vitamin B12 deficiency:

• Inadequate dietary B12 (rare, usually only in strict vegans)
• B12 Malabsorption
  ▪ Pernicious Anaemia (PA), commonly associated with other
    Autoimmune conditions (especially vitiligo and thyroid disease)
  ▪ Long term use of PPI or H2-antagonist drugs
  ▪ Chronic alcoholism
  ▪ Pancreatic failure
  ▪ Coeliac disease (more commonly causes iron and/or folate deficiency
    but up to 30% of patients can have B12 deficiency)
  ▪ Gastrectomy
  ▪ Small bowel (especially terminal ileal) surgery
  ▪ IBD
  ▪ Drugs – Biguanide (eg Metformin) therapy, Cholestyramine, Slow K

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Foods containing vitamin B12

The following foods are good sources of vitamin B12. Including these foods regularly in the diet should help to prevent vitamin B12 deficiency:

• Liver/liver pâté (note that pregnant women should avoid liver/liver pâté).
• Eggs.
• Cheese.
• Milk.
• Meat - for example, beef, lamb and pork.
• Fish.
• Fortified breakfast cereals.
• Marmite®.
• Fortified oat, rice and soya milks.
• Fortified soya yoghurts.
• Fortified spreads.
• Fortified yeast extract.

People who are vegan should aim to include foods that are fortified with vitamin B12, at least three times a day. If these foods are not consumed in adequate amounts, the Vegan Society recommends a vitamin B12 supplement which can be purchased from a pharmacy or health food shop.
### Serum Vitamin B12 WITHOUT neurological symptoms

**Folate levels should be checked and low levels treated accordingly**

<table>
<thead>
<tr>
<th><strong>197-771ng/L</strong></th>
<th>Normal level</th>
</tr>
</thead>
<tbody>
<tr>
<td>No action required</td>
<td>Stores adequate for 2 years</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>150-196ng/L</strong></th>
<th>Borderline Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia?</td>
<td>Consider other causes*</td>
</tr>
<tr>
<td>NO</td>
<td>Recheck serum B12 after 2 months</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>120-150ng/L</strong></th>
<th>Low level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-intrinsic factor antibody (IFA) positive?</td>
<td>Yes</td>
</tr>
<tr>
<td>NO</td>
<td>Are other causes * of B12 deficiency possible?</td>
</tr>
<tr>
<td>YES</td>
<td>Hydroxocobalamin 1mg IM 3x/week for 2 weeks and then every 3 months lifelong – diagnosis of Pernicious Anaemia inferred</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Less than 120ng/L</strong></th>
<th>Very low level</th>
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</thead>
<tbody>
<tr>
<td>Contact haematology SpR on call for advice</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Low B12 of unknown significance.</strong></th>
<th>Consider low dose oral cobalamin daily for 4 weeks – 50microgram tablets can be purchased from a pharmacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat B12 normal.</td>
<td>Low B12 borderline</td>
</tr>
</tbody>
</table>

| **Consider other causes*** | Recheck serum B12 after 3-4 months |

| **Low B12 of unknown significance.** | Consider long term low dose oral cobalamin if clinically indicated. 50microgram tablets can be purchased from a pharmacy - 1-3 tablets once daily |

| **Consider Hydroxocobalamin 1mg IM 3x/week for 2 weeks and then every 3 months.** | Patient may prefer to use OTC cobalamin instead with annual monitoring |

| **Consider Hydroxocobalamin 1mg IM 3x/week for 2 weeks and then every 3 months lifelong.** | **Check serum folate - secondary folate deficiency can occur in B12 deficiency, both may need to be replaced** |

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*Consider other causes:
- Anaemia?
- Other causes of macrocytosis/anaemia unrelated to B12 deficiency e.g. liver dysfunction, folate deficiency, hypothyroidism, haemolysis, myelodysplasia, antimetabolite drugs etc.
- **Check serum folate**
- Secondary folate deficiency can occur in B12 deficiency, both may need to be replaced.

**Repeat B12 normal.**

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**Repeat B12 borderline.**
Serum Vitamin B12 WITH neurological symptoms

197-771ng/L
Normal level
No action required
Stores adequate for 2 years

150-196ng/L
Borderline Level
Hydroxocobalamin 1mg IM 3x/week for 2 weeks and then every 2 months lifelong

120-150ng/L
Low level
Check for Macrocytosis and anaemia. If pancytopenia discuss with haematologist
Anti-intrinsic factor antibody (IFA) positive?
YES
Diagnosis of Pernicious Anaemia inferred
NO
Are other causes * of B12 deficiency possible?
NO
Hydroxocobalamin 1mg IM 3x/week for 2 weeks and then every 2 months lifelong
YES

Less than 120ng/L
Very low level
Contact haematology SpR on call for advice

Folate levels should be checked and low levels treated accordingly

Look for evidence of other causes of macrocytosis+/- anaemia unrelated to B12 deficiency e.g liver dysfunction, folate deficiency, hypothyroidism, haemolysis, myelodysplasia, antimetabolite drugs etc.

Hydroxocobalamin 1mg IM 3x/week for 2 weeks and then every 2 months lifelong

**Check serum folate- secondary folate deficiency can occur in B12 deficiency, both may need to be replaced
*Other causes include; malabsorption, diet, Combined Oral Contraceptive pill (COCP), pregnancy, drug induced
  • Drug induced B12 deficiency –includes Metformin, Trimethoprim, Colchicine, Neomycin, anticonvulsants, long term use of PPI or H2-antagonist drugs.
  • 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
  • Pregnancy and COCP cause altered B12 binding to plasma protein, so borderline/low levels are commonly seen, which may not indicate true deficiency

** In the event of combined B12 and folate deficiency, always start B12 twenty four hours ahead of folate to protect neurones. In severe B12 or folate deficiency supplementation may cause severe hypokalaemia as red cell production restarts

There is no need to monitor serum vitamin B12 levels in patients receiving regular parenteral vitamin B12 treatment

Patients treated with oral repletion therapy need to have their initial response to treatment monitored with vitamin B12 levels after 3-4 months. A short 4 week course (at least 50 microgram daily) may be of benefit if B12 levels are borderline on 2 occasions but it is important to note that this dose is not adequate for true pernicious anaemia. Patients should be given strict instructions to seek immediate medical attention if neuropathy symptoms develop
A variety of food supplements containing other strengths of vitamin B12 can be purchased from health food shops. Some products may not be suitable for vegans and the patient should be advised about checking labels.

When to refer:

Uncomplicated vitamin B12 deficiency does NOT require routine referral for Haematology outpatient assessment

• Consider referring to Haematology if there is a failure to respond to therapy i.e. there is not a prompt rise in Hb (Note: Vitamin B12 levels do not require re-checking if the patient is already on replacement therapy. The FBC can be used to monitor response).
• Consider referral to/discussion with appropriate specialty if vitamin B12/folate deficiency plus gastrointestinal disease or neurological symptoms or dementia.

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