Derbyshire Shared Care Pathology Guidelines

Vitamin B12 (including Folate)

What are the signs/symptoms of B12/folate 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
- Other (rare)
  - Angular cheilosis
  - Sore beefy red tongue

When to check Vitamin B12/folate 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

Serum folate measurement provides equivalent information to red cell folate

Red cell folate assays are affected by pre-analytical and analytical variables and measurement is not recommended

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
Management of Vitamin B12 deficiency

![Flowchart diagram of Vitamin B12 levels and management]

**Serum Vitamin B12**
- **197 – 771 ng/L**
  - Normal level
  - No action required
  - Stores adequate for 2 years
- **150 – 196 ng/L**
  - Borderline level
  - Does the patient have neurological symptoms or anaemia?
    - NO
      - Consider GI causes
      - Dietary deficiency is rare
      - Re-check serum B12 after 2 months
    - YES
      - i.m. B12 replacement indicated (see page 3)
- **<150 ng/L**
  - Low level
  - If symptomatic (e.g. anaemia, glossitis, paraesthesia), a presumptive diagnosis of PA can be made in the absence of another cause of vitamin B12 deficiency or macrocytosis.
  - Lifelong i.m. B12 replacement indicated (see page 3)

**Anti-intrinsic factor antibody (IFA) testing**
Although IFA is extremely specific for pernicious anaemia (positive predictive value 95%), it has a low sensitivity of 40–60%, meaning that only about half of people with pernicious anaemia will have anti-intrinsic factor antibody (i.e. its absence does not rule out a diagnosis of pernicious anaemia). For this reason, the routine reflex testing of IFA when vitamin B12 levels are low is expensive with a low detection rate.
Low B12 of unknown significance
Measurement of B12 levels for non-specific symptoms (tiredness, neuropsychiatric symptoms or screening) particularly in the elderly population often leads to the discovery of borderline B12 levels in the absence of anaemia or other significant features. These patients may include previously undiagnosed or latent pernicious anaemia, patients with food malabsorption and patients on long term PPI or H₂-antagonist drugs or metformin.

Second line tests to confirm cobalamin deficiency (Methylmalonic acid, Plasma total homocysteine, Holotranscobalamin) are not currently available and the low sensitivity of IFA as outlined above means its measurement in these cases is unhelpful. Management should therefore be based on clinical judgement.

Over the counter (OTC) B12 replacement (Reference CKS NICE guidelines and in consultation with Derbyshire Medicines Management)
Low dose oral cyanocobalamin is now listed as BLACK. You may wish to trial a short 4 week course of OTC B12, which 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.

If mild deficiency is thought to be diet related, advise people to take oral cyanocobalamin tablets 50–150 micrograms daily between meals. In vegans, treatment may need to be life-long, whereas in other people with dietary deficiency, replacement can be stopped once the B12 levels have been corrected and the diet has improved (do not check more often than 12 weekly). You may also wish to give dietary advice about foods that are a good source of B12: eggs, foods which have been fortified with B12 (some soy products, some breakfast cereals and breads), meat, milk and other dairy products, salmon and cod.

Vitamin B12 Replacement
Intramuscular:
- Pernicious Anaemia requires lifelong treatment with parenteral vitamin B12
  Hydroxocobalamin 1mg 3 times a week for 2 weeks then 1mg every 2-3 months, lifelong

- Macrocytic anaemias with neurological involvement
  Hydroxocobalamin 1mg alternate days until no further improvement, then 1mg every 2 months

- Macrocytic anaemias without neurological involvement
  Hydroxocobalamin 1mg 3 times a week for 2 weeks followed by either:
  - If not thought to be diet related, 1mg i.m.every 2-3 months for life
  - If dietary deficiency is suspected, OTC B12 replacement as above or a twice-yearly 1mg hydroxocobalamin injection

The clinical picture is the most important factor in assessing the significance of Vitamin B12 levels.
Treatment should not be delayed in the presence of discordance between test results and clinical features to avoid neurological impairment.
Management of Folate levels:

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<tr>
<th>Serum Folate</th>
<th>Range</th>
<th>Status</th>
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<tr>
<td></td>
<td>3.9 - 26.8 ug/L</td>
<td>Normal</td>
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<tr>
<td>&lt;3.9 ug/L</td>
<td>Deficient</td>
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- Secondary folate deficiency can be seen if concomitant vitamin B12 deficiency. Both may need to be replaced.

- **Check vitamin B12 levels in all people before starting folic acid** — treatment with folate alone could improve wellbeing but mask underlying B12 deficiency, and allow neurological disease to develop.

  **For combined B12 and folate deficiency, B12 replacement must be started at least 24 hours before folic acid is started**

- Diet is the commonest cause of low folate levels. Take a dietary history and correct any dietary deficiencies. In folate deficient megaloblastic anaemia give folic acid 5mg daily for 4 months. Up to 15mg daily may be necessary for malabsorption states.

- **Give dietary advice about foods that are a good source of folic acid** — good sources of folate include: Asparagus, Broccoli, Brown rice, Brussels sprouts, Chickpeas, Peas

When to refer:

- 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.

Contacts

RDH Duty Haematologist (via switchboard) 01332 340131
CRH Consultant Haematologist Via Consultant Connect or Crhft.cabadviceandguidance@nhs.net

References


NICE Clinical Knowledge Summary (Apr 2018). Anaemia – B12 and Folate Deficiency
https://cks.nice.org.uk/anaemia-b12-and-folate-deficiency

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<td>May 2018</td>
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<td>Dr Chris Millar, Dr Rowena Faulkner, Dr P Blackwell, Mrs H Seddon</td>
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