SUMMARY OF THE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF COBALAMIN & FOLATE DISORDERS

ISSUED BY

THE BRITISH COMMITTEE FOR STANDARDS IN HAEMATOLOGY

April 2014

This is a summary of the main conclusions and recommendations of the recently updated guidelines on diagnosing and treating Vitamin B12 and Folic Acid deficiency.
The draft report was published in January 2014 and is a thorough evaluation of how Vitamin B12 and folic acid deficiency is diagnosed and treated that takes into consideration the large number of research papers that have been published since the last guidelines were issued in 1994.

These new guidelines were originally intended to be published in June 2012 but were postponed following a meeting between the society and representatives of the Department of Health although whether the postponement was solely due to that meeting is not confirmed.
The full Draft guidelines contains 9,950 words and so this summary concentrates on the main issues addressed by the report and doesn't include any references to the papers.

Medical professionals associated with the PA Society all welcome the new recommendations and are generally pleased with the result. The main conclusion of the report is that there are several issues surrounding the current Combined Binding Luminescence Assay that is used to determine B12 status and that research is needed to address these problems. However, all who have had sight of the report are disappointed that the single most common cause of complaint by members (the frequency of replacement therapy injections) is not addressed at all but refers the reader to the British National Formulary.

Summary of Key Recommendations:

- The clinical picture is the most important factor in assessing the significance of test results assessing cobalamin status since there is no ‘gold standard’ test to define deficiency.
- Serum cobalamin remains the first line test currently, with additional second line plasma methylmalonic acid to help clarify uncertainties of underlying biochemical/functional deficiencies. Plasma homocysteine may be helpful as a second line test, but is less specific than methylmalonic acid. The availability of these second-line tests is currently limited.
- Serum holotranscobalamin (Active B12-test) has the potential as a first line test, but an indeterminate ‘grey area’ may still exist.
- Definitive cut-off points to define clinical and subclinical deficiency states are not possible, given the variety of methodologies used and technical issues, and local reference ranges should be established.
- In the presence of discordance between the test result and strong clinical features of deficiency, treatment should not be delayed to avoid neurological impairment.
- Treatment of cobalamin deficiency is recommended in line with the British National Formulary. Oral therapy may be suitable and acceptable provided appropriate doses are taken and compliance is not an issue.
- Serum folate offers equivalent diagnostic capability to red cell folate and is the first line test of choice to assess folate status.

A. Tests to confirm/diagnose cobalamin deficiency

The grades are based on recommendations
1=strongly recommended – read as recommended; 2=weak – read as suggest.
The Quality of available evidence is given as A, B or C.
A=strong evidence; B=moderate evidence and C=more research is needed.

Recommendations

- A blood film showing oval macrocytes and hypersegmented neutrophils in the presence of an elevated MCV may alert the clinician to the presence of underlying cobalamin or folate deficiency (Grade 2B)
- Cobalamin and folate assays should be assessed concurrently due to the close relationship in metabolism (Grade 1A)
- The writing group (the authors) recommends adoption of reporting for cobalamin assay results in pmol/L (Grade 2C)
- A serum cobalamin cut-off level of either 148 pmol/L (200 ng/L) or one derived from a local reference range should be used as evidence of cobalamin deficiency in the presence of a strong clinical suspicion (Grade 2B)
- The report providing the result of a serum cobalamin assay should include the following
  o The interpretation of the result should be considered in relation to the clinical circumstances
  o Falsely low serum cobalamin levels may be seen in the presence of folate deficiency or technical issues
  o Neurological symptoms due to cobalamin deficiency may occur in the presence of a normal MCV (Grade 2C)
- Plasma tHcy and/or plasma MMA, depending on availability, may be considered as supplementary tests to determine biochemical cobalamin deficiency in the presence of clinical suspicion of deficiency but an indeterminate serum cobalamin level (Grade 2B)
  o Although plasma tHcy is a sensitive marker of cobalamin deficiency, plasma MMA is more specific
  o Both assays have to be interpreted in relation to renal function
- Holotranscobalamin is suggested as a suitable assay for assessment of cobalamin status in a routine diagnostic laboratory in the future (Grade 1B)

B. Tests to determine the aetiology of cobalamin deficiency

Recommendations

- All patients with anaemia, neuropathy or glossitis, and suspected of having pernicious anaemia, should be tested for anti-intrinsic factor antibody regardless of cobalamin levels (Grade 1A).
- Patients found to have a low serum cobalamin level in the absence of anaemia, and who do not have food malabsorption or other causes of deficiency, should be tested for IFAB to clarify whether they have an early/latent presentation of pernicious anaemia (Grade 2A).
- Anti-gastric parietal cell antibody testing for diagnosing pernicious anaemia is not recommended (Grade 1A).

C. Treatment of cobalamin deficiency

Recommendations

- Treatment of established cobalamin deficiency should follow the schedules in the British National Formulary (Grade 1A).
- Initial treatment with oral cobalamin may not be appropriate in pernicious anaemia, but may be considered in maintenance or correction of suboptimal levels in asymptomatic patients (Grade 2C).

D. Recommendations on the clinical approach to investigation and treatment of cobalamin associated disorders

Recommendations

- Patients suspected of having pernicious anaemia should be tested for intrinsic factor antibody. Patients found to be positive should have lifelong therapy with cobalamin (Grade 1A).
- Patients negative for intrinsic factor antibody, with no other causes of deficiency, may still have pernicious anaemia as a result of poor sensitivity of the test and should be treated as anti-intrinsic factor antibody negative pernicious anaemia. Lifelong therapy should be continued in the presence of an objective clinical response. (Grade 2A)
- Serum cobalamin level of greater than 148 pmol/L (200 ng/l) in the presence of a strong clinical suspicion of cobalamin deficiency should be evaluated further with MMA, tHcy or HoloTC and a trial of hydroxocobalamin given to ascertain any clinical improvement (Grade 1C).
- In patients with serum cobalamin levels of 'subclinical deficiency' on two occasions, an empirical trial of treatment with oral cyanocobalamin (50 mcg/daily for four weeks) should be given. Strict instructions should be given to patients to seek immediate medical attention if symptoms of neuropathy develop. The cobalamin level should be rechecked after 3 months, and second line tests considered if there is no improvement (Grade 2c).
- No definitive advice can be given on the desirable frequency of monitoring of serum cobalamin in patients with type II diabetes mellitus, but it is recommended that serum cobalamin is checked in the presence of strong clinical suspicion of deficiency (Grade 2B).
- If serum cobalamin levels are reduced, patients should have tests for anti-intrinsic factor antibody since the concurrence of pernicious anaemia with diabetes should be considered. If positive, the patient should have lifelong treatment with replacement cobalamin. If negative, the reduced level may be purely as a result of metformin, although underlying AbNegPA cannot be excluded. Treatment with oral cobalamin may be considered (50mcg for one month), with subsequent monitoring of serum cobalamin after six months and then at yearly intervals is suggested (Grade 2C).
- Currently no recommendations can be given on prophylactic administration with oral cobalamin in patients taking metformin.
- Asymptomatic women taking oral contraception or HRT with mildly reduced serum cobalamin (110 -148 pmol/L; 150-200 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.Grade 1B)
- Serum cobalamin levels fall during pregnancy and are less reliable in determining underlying deficiency (Grade 1A).
- During pregnancy, in the presence of strong suspicion of underlying deficiency, a short course of empirical hydroxocobalamin should be given, with further investigations post-partum (Grade 2C)
- HoloTC may be more reliable than serum cobalamin in determining deficiency in pregnancy, and is recommended as the test of choice, if available (Grade 1B).
- Vegetarians, particularly strict vegans, should be considered for monitoring of their cobalamin level according to clinical assessment (Grade 2C).
- Dietary alterations or oral supplementation may be considered according to the clinical situation (Grade 2C), particularly during pregnancy and breast-feeding.
- Patients who have had bariatric surgery should have their cobalamin status monitored and are likely to need cobalamin supplementation via a route depending upon the type of surgery (Grade 1B).
- Patients with food-bound cobalamin malabsorption may benefit from low dose oral replacement (Grade 2B).

INFANTS

In the presence of clinical suspicion of underlying cobalamin deficiency, even in the presence of normal serum cobalamin levels, further biochemical tests including MMA and tHcy are recommended (Grade 1B). The role of HoloTC in this context is undefined. Further investigation to define any possible genetic abnormalities should be referred to a specialist centre.

No specific recommendation can be made regarding treatment since each case has to be judged individually.

E. Tests to diagnose folate deficiency

Recommendations

A serum folate level less than 7 nmol/L (3 µg/L) is indicative of folate deficiency (Grade 1B).

- Routine red cell folate testing is not necessary since serum folate alone is sufficient in most cases (Grade 1A).
- In the presence of strong clinical suspicion of folate deficiency, despite a normal serum level, a red cell folate may be undertaken, having ruled out cobalamin deficiency (Grade 2B).
- Plasma tHcy can be measured to confirm suspected folate deficiency only in special circumstances; a level above 15 µmol/L could be indicative of folate deficiency but must be assessed in relation to local reference ranges (Grade 2B).

F. Clinical approach to investigation and treatment of folate associated disorders

Recommendation

- Folate status is generally checked in clinical situations similar to those of cobalamin deficiency (Grade 1A).
- Consultation of the British National Formulary and Summary of Product Characteristics is recommended for clarifying any suspicion of low serum folate levels associated with prescribed medications.

Recommendations for future research

In the absence of anaemia or objective clinical signs of cobalamin deficiency, the significance of a low serum cobalamin/folate level can be difficult to determine.
A prospective study on the natural history of subclinical cobalamin deficiency or LCUS with or without abnormal homocysteine/methylmalonic acid is required.
Research on the clinical utility of more sensitive and specific tests is needed.
Research on ways of assessing adequate replacement would be of benefit in titrating the treatment with clinical efficacy.

Recommendations for audit

Laboratory performance of serum cobalamin assay in relation to UK NEQAS[3]

Clinical reason for serum cobalamin request as specified on request forms.
Haemoglobin concentration and mean cell volume, if available, taken at same time as serum cobalamin in the deficiency level and 25% below the local laboratory reference range cut off level.
Clinical audit investigating deficiency states in relation to local reference ranges.
Establishment of clinical cut-off points for deficiency with holotranscobalamin assay.

3. The National External Quality Assessment Service–the UK Body responsible for ensuring all laboratory tests are accurate.