Summary of B12 documents

Sources quoted

BCSH:

British Committee on Standards in Haematology: Guidelines for the diagnosis and treatment of Cobalamin and Folate disorders.

BMJ:

Vitamin B12 deficiency – Clinical Review.

BMJ 2014;349:g5226 doi: 10.1136/bmj.g5226 (Published 4 September 2014)

NICE:

National Institute for health and Clinical Excellence: Anaemia - B12 and folate deficiency

Scenario: Management.

Shichting Tekort:

Treatment with high dose vitamin B12 been shown to be safe for more than 50 years.

Clinical symptoms should be treated, not blood levels

BCSH1:
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.

BCSH2:

In the presence of discordance between the test result and strong clinical features of deficiency, treatment should not be delayed to avoid neurological impairment.

BCSH4:
Furthermore, patients with strong clinical features of cobalamin deficiency may have serum cobalamin levels which lie within the reference range (false normal cobalamin level).

BMJ1:
If the clinical features suggest deficiency then it is important to treat patients to avoid neurological impairment even if there may be discordance between the results and clinical features

Haematological changes not essential in PA

BCSH3
Neurological presentation (peripheral neuropathy, sub-acute combined degeneration of the cord) may occur in the absence of haematological changes, and early treatment is essential to avoid permanent neurological disability..

BMJ2:
However, it is important to recognise that clinical features of deficiency can manifest without anaemia and also without low serum vitamin B12 levels. In these cases treatment should still be given without delay.

BMJ3:
An estimated 20% of patients with neurological signs do not manifest anaemia.

Referrals:

NICE2:
Seek urgent advice from a haematologist if the person has neurological symptoms

NICE5:
Some experts acknowledge that there is a small group of patients who report a recurrence of their symptoms earlier than 3 monthly.
CKS could find no guidelines or evidence on the management of this group.
Feedback from expert reviewers differs with regard to whether or not more frequent intramuscular injections of hydroxocobalamin 1 mg are required, and if they are, what regimen to suggest.
In the absence of evidence and expert consensus, CKS suggest seeking specialist advice in this situation

Problems with B12 serum assay – interference by anti-IF

BCSH5:
A number of assays are registered on the UK NEQAS scheme, and the overall coefficient of variation of performance between different assays is 5-15%, with intermethod biases of plus 10% or minus 20% from the all-laboratory trimmed mean.

BCSH6:
Some assays may give false normal results in sera with high titre anti-intrinsic factor antibodies(Carmel and Agrawal 2012, Hamilton, *et al* 2006, Hamilton, *et al* 2010).

Problems with anti-IF antibody test

BCHS7:
IFAB is positive in 40-60% of cases(Ungar 1967) i.e. low sensitivity, and the finding of a negative intrinsic factor antibody assay does not therefore rule out pernicious anaemia (hereafter referred to as AbNegPA).

NICE1:
Anti-intrinsic factor antibody is extremely specific for pernicious anaemia, with a high positive predictive value of 95%, but a low sensitivity of 40–60%. This means that about half of people with pernicious anaemia will have anti-intrinsic factor antibody [Andres et al, 2004; Longmore et al, 2007]. If anti-intrinsic factor antibody is present, pernicious anaemia is very likely, but its absence does not rule out a diagnosis of pernicious anaemia [Devalia et al, 2014].

Further testing of serum B12

BCSH8:
No further testing for cobalamin levels is required.

NICE6:
Ongoing monitoring of people being treated with vitamin B12 or folic acid is generally considered unnecessary (unless a lack of compliance with folate treatment is suspected, or anaemia recurs).

BMJ4:
Cobalamin and Holotranscobalamin levels are not helpful because they increase with vitamin 12 influx regardless of the effectiveness of treatment,24 and retesting is not usually required.

High serum levels of B12

BCSH9:
Although there is little evidence that more frequent dosing is harmful, specific objective studies demonstrating clinical benefit are absent, and the GWG cannot make specific recommendations.

Shichting Tekort
Treatment with high dose vitamin B12 been shown to be safe for more than 50 years.

Injections for PA are for life

BMJ7:

In irreversible cases, for example, pernicious anaemia, the treatment should be continued for life. For temporary causes, such as pregnancy, the treatment can be reviewed when the patient is fully replete and the causative agent removed.

Can B12 supplements interfere with the anti-IF antibody test?

This is not a simple question. Over the years there have been many assays for these antibodies. The original Radioimmunoassay (RIA) from the early 1980s required a gap of up to 3 weeks between an injection and testing. The later RIA in the late 1980s required a gap of two days (or maybe two weeks). About 10 years ago an Enzyme Linked ImmunoSorbent Assay (ELISA) was developed that suffers no interference from B12 in the blood.

The problem is that you won't know which assay is being used. Nor is your doctor likely to know.

Many thanks to Laura5 who helped dig through the available info and came up with this reference to the EILSA assay which says that the previous assays suffered interference that the new assay does not.

http://www.accessdata.fda.gov/cdrh_docs/reviews/K071346.pdf

Investigations

BMJ6:
Table 1.

Guide to annotations:

BCSH:
1 & 2: Summary of key recommendations. P2
3 & 4: Cobalamin deficiency. P3
5 & 6: (b) Serum cobalamin. P4
7: (a) Anti-intrinsic factor antibody. P7
8 & 9: C. Treatment of cobalamin deficiency. P8

BMJ:
1: Summary points. P2
2: What are the clinical features of B12 deficiency? P2
3: Neurological features. P3
4: How is response to treatment assessed? P4
5: Box 4 Who to refer for specialist care? P5
6: Investigations to assess vitamin B12 deficiency. P7
7: Parenteral Treatment. P4

NICE:
1: Checking for anti-intrinsic factor antibodies. P2
2: When should I refer a person with vitamin B12 or folate deficiency anaemia? P3
3: How should I treat a person with vitamin B12 deficiency anaemia? P4
4: What if a person is still symptomatic despite vitamin B12 treatment? P6
5: Basis for recommendation. P6
6: What monitoring of vitamin B12 or folate deficiency treatment is recommended? P8

Stichting Tekort:
Whole article.