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CLINICAL AUDIT

Diagnosis and management of Vitamin B_{12} deficiency in primary care – are we following the guidelines?

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ABSTRACT

Background: Vitamin B_{12} deficiency is common in primary care but its treatment practices vary across centres. One important cause of B_{12} deficiency is pernicious anaemia (identified by intrinsic factor antibodies), which is a risk factor for developing gastric carcinoma, and should be excluded. Additionally, recent evidence has suggested that some patients have been continued on B_{12} injections with no clear clinical indication. Recently, guidelines were produced to improve the investigation and management of B_{12} deficiency. Hence, this audit studied the investigation and management of B_{12} deficiency and adherence to clinical guidelines in a general practice (GP) in north-west England.

Aim: To evaluate the appropriate diagnosis and management of vitamin B_{12} deficiency in our primary care centre against recognized standards.

Methods: Clinical data of patients currently on oral cyanocobalamin and/or intramuscular hydroxocobalamin injections over a 1-year period were audited.

Results: Thirty-eight patients (66% females, 34% males) receiving treatment for B_{12} deficiency were identified. Of these, 55% (21/38) had intrinsic factor antibodies checked and 52% (13/25) were managed according to the guidelines. 100% (8/8) of patients with dietary B_{12} deficiency (non-vegans) and 75% (3/4) of B_{12}-deficient patients on long-term metformin have had follow-up serum B_{12} monitoring.

Discussion: There is a need to improve the investigation for B_{12} deficiency, adherence to clinical guidelines, and documentation of patients' diagnoses, treatment plans, dietary statuses, and required monitoring. We anticipate that adhering to guidelines when appropriate, with clear documentation, will improve the diagnosis and management of vitamin B_{12} deficiency so that safe prescribing and potential cost savings can be achieved.

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Introduction

Vitamin B_{12} deficiency is commonly encountered in primary care, particularly among the elderly.[1] Although most clinicians are familiar with this condition, the approach to its diagnosis and treatment varies across practices, with the administration of oral, intramuscular, or other preparations of vitamin B_{12} being debated extensively.[2]

Moreover, it is controversial whether all patients who begin treatment for low serum B_{12} levels need to be on replacement therapy for life, as it has been argued that some patients continue to receive B_{12} replacement despite normal post-treatment serum B_{12} levels (defined as levels between 150–900 ng/L). Recently, the Manchester Anaemia Guide[3] was published, with reference to the NICE Clinical Knowledge Summaries (CKS),[4] to provide clinical guidance on these issues. It emphasised that, as part of the diagnostic process for every patient with suspected B12 deficiency, pernicious anaemia (PA), should be excluded by checking for intrinsic factor antibodies, as affected patients have an increased risk of developing gastric carcinoma.[5] Moreover, PA is associated with many other autoimmune conditions (e.g. Graves' disease and vitiligo).[6] Hence, identifying these patients would inform the need for further work-up or referral to a specialist for evaluation in the presence of any significant clinical finding that suggests an underlying gastric carcinoma or autoimmune condition.
In view of these issues, we conducted an audit to address them.

Aims and standards

Aims

1. Assess whether patients with vitamin B_{12} deficiency have been appropriately diagnosed, managed, and followed up according to the Manchester Anaemia Guide at a GP practice in northwest England.
2. Review our patients for the need of specialist referrals (e.g. to gastroenterology, haematology, or neurology) for further evaluation.

Standards

1. 100% of patients who have been diagnosed as being B_{12}-deficient (by normal serum B_{12} range: 150–900 ng/L) have had intrinsic factor antibodies (IFA) checked.
90% (to allow for patient choice and contraindications) of B_{12}-deficient patients:
2. Are managed appropriately according to the Manchester Anaemia Guide[3] (Figures 1a and 1b).
3. Have serum B_{12} levels checked every 6 months if their B_{12} deficiency results are from either:
    a. A dietary cause (non-vegans), where the deficiency has been fully corrected and appropriate dietary advice has been given; or
    b. Long-term use of metformin (PA excluded), where treatment has been initiated.

Methodology

The inclusion criteria used in the selection of patients were as follows:

1) All patients on vitamin B_{12} replacement (in the form of oral cyanocobalamin tablets or intramuscular hydroxocobalamin) between 1 April 2013 and 1 April 2014 were identified through our clinical database (Emis Web).
2) From this group, clinical data was obtained (from Emis Web and Docman) and audited retrospectively.

Results

A total of 38 patients (66% female, 34% male) on B_{12} replacement were identified (figures 2 and 3), of which 4 (11%) presented with neurological symptoms associated with B_{12} deficiency (where other causes have been excluded) whereas the remaining 34 patients (89%) did not present with any neurological features (figure 2). The mean age of the patients is 62 years (range 23–93). Our patients with B_{12} deficiency-associated neurological symptoms were not referred for any specialist neurology evaluation as they were otherwise clinically stable.

The causes of their B_{12} deficiencies were categorized into the following: dietary only (6/38; 16%), non-dietary (11/38; 29%), multiple (8/38; 21%), and unascertained (13/38; 34%). Of those with an unascertained cause, 11 have not had an IFA test done, 1 had an inconclusive IFA test result, and the remaining patient is currently awaiting diagnosis (figure 3A).

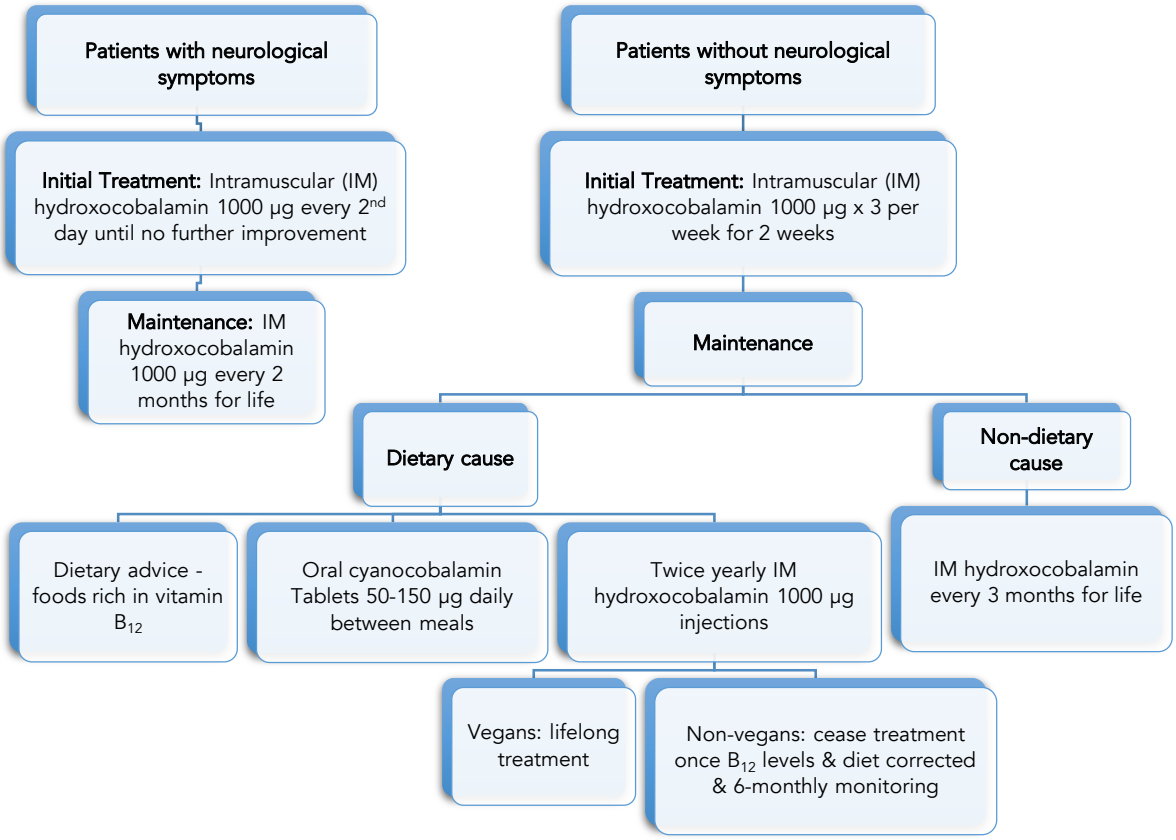

Figure 1a. Management of vitamin B_{12} deficiency in patients with/without neurological symptoms. Adapted from ref. 3

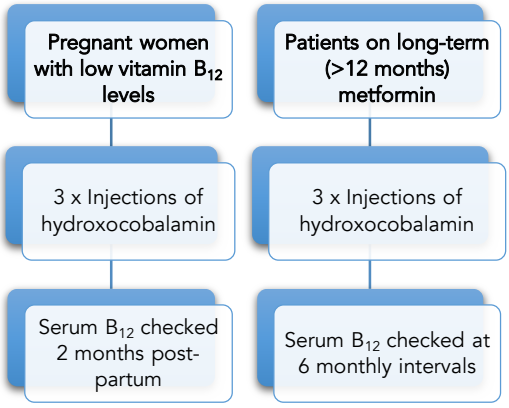

Figure 1b. Management of vitamin B_{12} deficiency in pregnant women & patients on long-term metformin

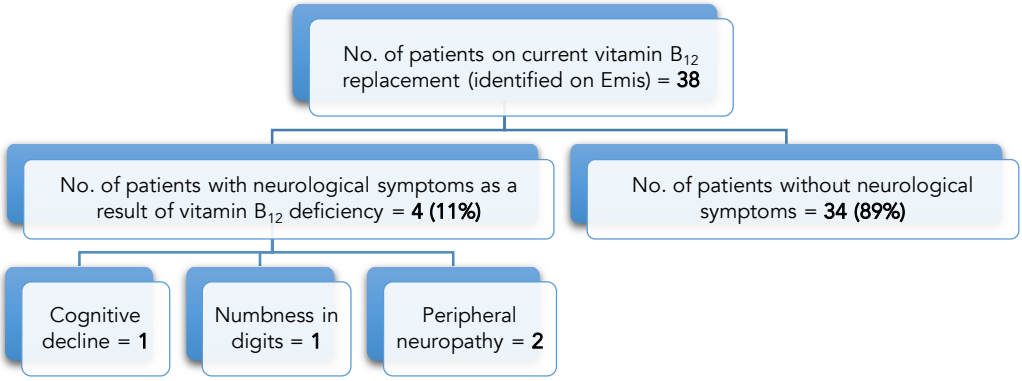

Figure 2. Classification of vitamin B_{12} deficient patients by neurological symptoms

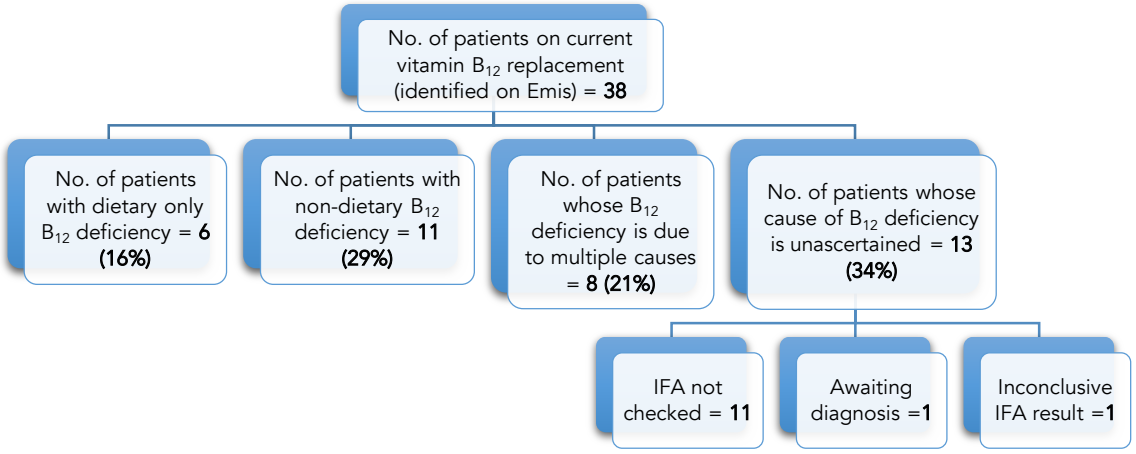

Figure 3A. Causes of vitamin B_{12} deficiency

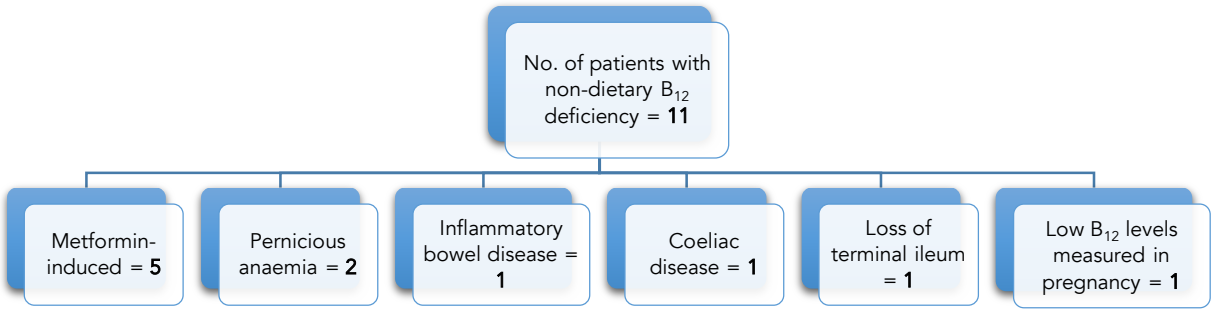

Figure 3B. Non-dietary causes of vitamin B_{12} deficiency – results of patients

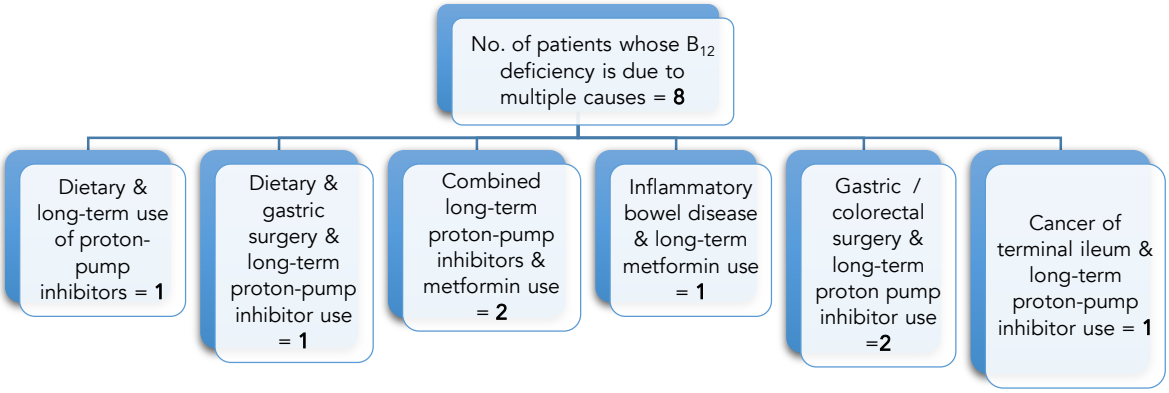

Figure 3C. Results of patients whose vitamin B_{12} deficiency is attributed to multiple aetiologies

In those with non-dietary causes, long-term (>12 months) metformin use (5/38; 13%), PA (2/38; 5%), inflammatory bowel disease (1/38; 3%), coeliac disease (1/38; 3%), loss of terminal ileum (1/38; 3%), and low levels of serum vitamin B_{12} measured in pregnancy (1/38; 3%) were identified (figure 3B).

In patients with multiple causes, other contributing factors such as long-term use (>12 months) of proton pump inhibitors (PPIs) (e.g. omeprazole), previous gastric/colorectal surgery (e.g. gastric bypasses, Nissen's fundoplication), and terminal ileum carcinoma have been identified (figure 3C).

Results of Standard 1 (figure 4): IFA tests were performed in 21 patients (55%). Of these, 2 were positive for IFA whereas 17 were not, and the remaining 2 patients had an inconclusive result due to insufficient samples. Seventeen patients (45%) did not have an IFA test. All patients who had tested positive for IFA did not need to be referred to the appropriate specialists for further evaluation as they were clinically stable and responsive to vitamin B_{12} replacement.

Results of Standard 2 (figure 5): 13 patients (34%) were managed according to the guidelines (i.e. they were put on the most appropriate treatment regime

based on the cause of their deficiency and the presence of neurological symptoms). Of these, 3 needed an initial IFA test and 1 needed a repeat test (despite an established cause) due to previously inconclusive results. Twelve patients (32%) were not managed according to the guidelines and the remaining 13 patients (34%) were excluded from the results due as the causes of their deficiencies were unascertained. Hence, after correction, 52% (13/25) of patients with an established cause of B_{12} deficiency had been managed according to guidelines.

Results of Standard 3a (figure 6): In total 9 patients had dietary B_{12} deficiency (in isolation or in combination with other factors). All 9 patients had their B_{12} levels corrected with replacement therapy between 1 April 2013 and 1 April 2014 (which was subsequently stopped) and with improved diet, after which follow-up monitoring was commenced. Of these, 8 patients (89%) had their follow-up B_{12} serum levels checked, but 4 of these 8 patients had the tests performed after the 6-month interval (to account for certain unavoidable factors that can result in a patient not being followed up within 6 months, we considered a follow-up blood test performed more than 1 year from the discontinuation of treatment to be late). One other patient (11%) was not yet due for follow-up and hence, was excluded from the results. In summary, 100% of patients (8/8) had their follow-up B_{12} levels monitored but only 50% (4/8) of patients had this within the appropriate time interval.

Results of Standard 3b (figure 7): In total, 8 patients had B_{12} deficiency as a result of long-term metformin use (in isolation or in combination with other factors). Of these, 3 patients (37.5%) had their follow-up B_{12} test done but 2 of them had the tests beyond the 6-month interval (>1 year late). Four patients were not yet due for follow-up (hence were excluded) and 1 remaining patient has not had any follow-up. In summary, 75% of patients (3/4) had their follow-up B_{12} levels monitored but only 25% (1/4) of patients had this within the appropriate time interval.

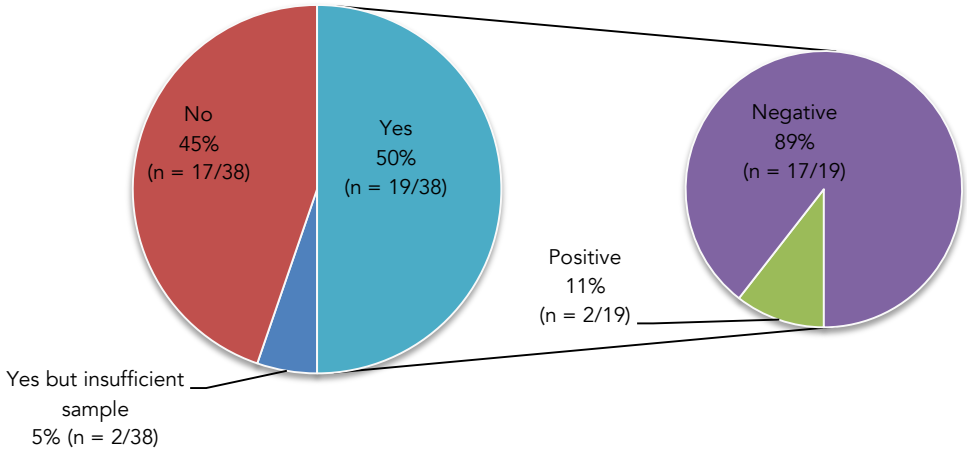

Figure 4. Results of Standard 1: intrinsic factor antibodies checked? (n=38)

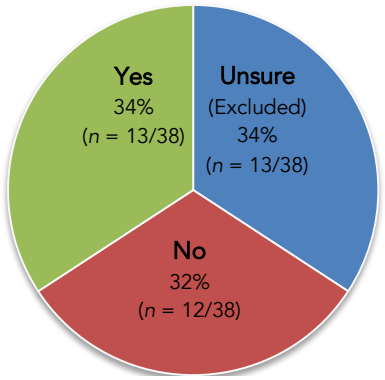

Figure 5. Results of Standard 2: Managed according to guidelines? (n=38)

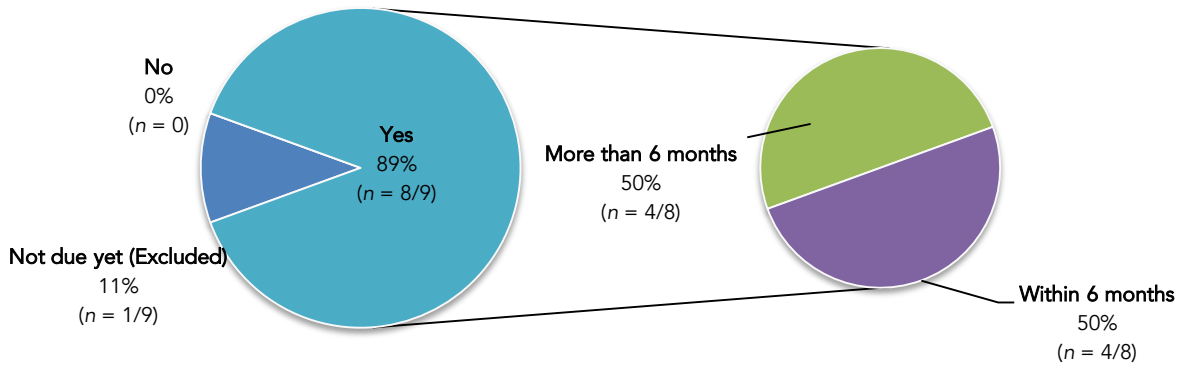

Figure 6. Results of Standard 3a: 6-Monthly follow-up serum B12 checked? (Patients with dietary B12 deficiency) (n = 9)

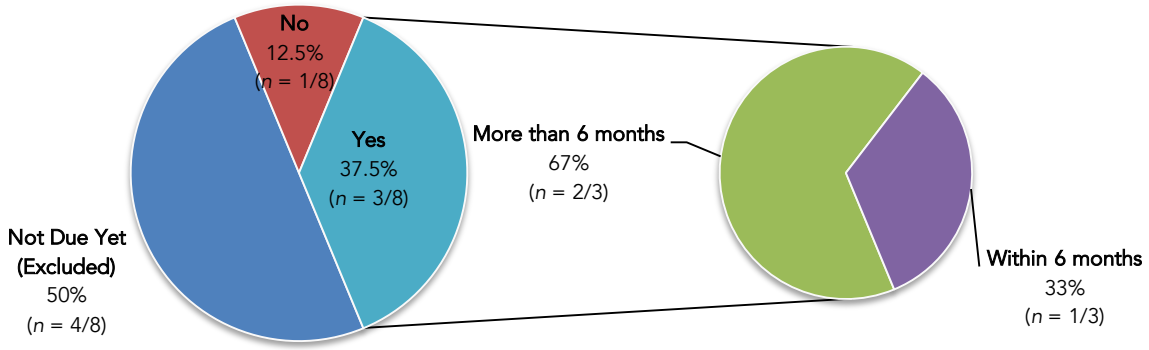

Figure 7. Results of Standard 3b: 6-monthly follow-up serum B12 checked? (Patients on long-term metformin) (n =8)

Table 1 summarizes the results of the audit.

Table 1. Summary of audit results	
Standards	**Compliance to standard**
1) **100%** of patients who have been diagnosed as vitamin B_{12} deficient (by serum B_{12}) have had intrinsic factor antibodies checked.	**55% (21/38)** No patients were excluded
2) **90%** of patients with established vitamin B_{12} deficiency were managed appropriately according to the Manchester Anaemia Guide.	**52% (13/25)** 13 patients excluded due to unascertained diagnosis.
3a) **90%** of patients with established vitamin B_{12} deficiency from a dietary cause (non-vegans) that has been fully corrected and who have had been given appropriate dietary advice have their serum B_{12} levels checked every 6 months.	**50% (4/8) – within 6-month intervals** 50%(4/8) – exceeded 6-month intervals 1 excluded – not yet due for test.
3b) **90%** of patients with established vitamin B_{12} deficiency from long-term use of metformin (PA excluded) who have been treated have their serum B_{12} levels checked every 6 months.	**25% (1/4) – within 6-month intervals** 50% (2/4) – exceeded 6-month intervals 4 excluded – not yet due for test .

Discussion

The standards set were not fully met. There are several possible explanations for this. For one, it is possible that not all of the primary care physicians were aware of the new updates in guidance before the audit period, which may have dampened

adherence to guidelines. Moreover, patients may not have been fully compliant with treatment, as the majority of our patients are receiving the B_{12} injections in a specialist nurse-based appointment, which may have been missed, hence disrupting treatment schedule.

A possible oversight of the clinician may result in IFA tests not being arranged. The test may also have been deemed unnecessary, as a definitive cause of patients' B_{12} deficiency may have already been identified on clinical evaluation.

With regard to follow-up monitoring, it is important to note that the 6-monthly monitoring interval for patients whose B_{12} deficiency is attributed to a dietary cause and/or long-term metformin use, as outlined in the Manchester Anaemia guide, serves only as a general guide. Currently, there is little evidence to guide monitoring in these groups, and regular monitoring has not been recommended in established guidelines, such as the NICE Clinical Knowledge Summaries.[4] Again, clinicians who are not familiar with the Manchester Anaemia Guide would not be aware of the monitoring suggestions in the guide and hence, may not have monitored their patients as suggested. The lack of a documented reminder for a clinical or prescription review may have resulted in patients continuing on unnecessary B_{12} injections or being put on the incorrect treatment regime.

In conducting this audit, we noted some limitations. Firstly, there may be patients who have not been included in our study due to a personal choice not to undergo testing or receive any treatment for their B_{12} deficiency. Also, lapses in medical record keeping could have arisen as patients may have had testing conducted outside primary care that were not recorded or communicated to their primary care physician.
Furthermore, not every patient could be allocated to a specific category for the management guidelines due to multiple or unascertained diagnoses. Hence, patients with an unascertained cause were excluded from tabulating the results of Standard 2. However, we will continue to monitor this group of patients. Lastly, the IFA test is highly specific (nearly 100%) but poorly sensitive (50-60%),[6-7] and this means that false-negative results could have occurred. In our study cohort, although 17 out of 19 patients tested negative for IFA, it is debatable whether a true diagnosis of PA can be excluded.

Furthermore, another important point to note is that vitamin B_{12} deficiency may arise in the absence of PA and positive IFA in *Helicobacter pylori*-associated pangastritis.[8] This is due to a reduction in gastric acid secretion and subsequent reduced release of cobalamin from haptocorrin to the intrinsic factor.[8] Hence, true cases of *H. pylori*-associated pangastritis may be missed in the presence of IFA.[9]

Although the issue of gastritis is not addressed in the Manchester Anaemia Guide, patients with vitamin B_{12} deficiency, with or without associated anaemia, should undergo gastroscopy with bioptic sampling of antral, corporal, and duodenal mucosa at least once during the diagnostic work-up to definitely exclude the presence of atrophic gastritis, *H. pylori*-associated pangastritis (which is highly reversible with *H. pylori* eradication treatment), or coeliac disease.[10]

Vitamin B_{12} may be administered effectively through oral, sublingual, intranasal, or parenteral (intramuscular or subcutaneous) routes.[11-12] Oral cyanocobalamin has been proposed to be a cheaper and equally effective option to intramuscular hydroxocobalamin.[2,13] However, parenteral therapy remains the most common[14] and this was observed in our audit population. Nyholm *et al.*[2] concluded that oral cyanocobalamin was an effective alternative to injections for B_{12} deficiency of most causes, but this is rarely used in the United Kingdom and is only available to vegans or patients with dietary B_{12} deficiency on an NHS prescription. Oral B_{12} also provides patients with an alternative choice, and helps reduce costs in primary care and the burden of work for nurses either at home or at the surgery in giving B_{12} injections. Moreover, it has been proposed that oral B_{12} can be used to treat B_{12} deficiency related to *H. pylori* infection.[9] However, patients with a rare condition known as tobacco amblyopia should remain on hydroxocobalamin injections as oral cyanocobalamin may worsen the condition.[15]

The option of oral tablets or other routes of therapy could be offered to patients, but determining the optimal dosage to administer may be difficult, especially for older patients who may need oral dosages of more than 500 µg/day for optimal absorption.[16]

At this point, screening is controversial and the evidence for it is scarce. There have been debates over the value of testing where there is an apparent aetiology (e.g. gastric surgery), as treatment is similar irrespective of the cause.[7] However, clinicians should identify patients at risk of developing B_{12} deficiency and consider testing for it.

Recommendations

Table 2 summarizes the recommendations for change. We aim to re-audit this study in 2 years.

Table 2. Recommendations for change

Issue	Recommendation
1. Lack of awareness of the new guidelines	• Disseminate the diagnostic and management guideline algorithms to practice staff
2. Patients not managed according to the guidelines: • Some patients are put on long-term B_{12} injections inappropriately. • Some patients are put on a different type of B_{12} therapy (i.e. intramuscular instead of oral).	• Review the patients who are not managed according to guidelines – change regime as appropriate and review their B12 prescriptions. • Use oral supplements in patients who are B_{12} deficient from a dietary cause.
3. The causes of some patients' vitamin B_{12} deficiency are unknown.	• Review these patients, chase up results, and perform the necessary investigations (e.g. IFA test, anti-parietal cell antibodies test). • In all future diagnostic work-ups for suspected B_{12} deficiency, PA should first be excluded.
4. Patients did not have a follow-up monitoring of serum B_{12} levels.	• Check serum B_{12} levels for patients on long-term metformin and non-vegan patients with dietary B_{12} deficiency. Document this and arrange for 6-monthly monitoring. • Review these patients and cease B_{12} therapy if necessary.
5. Documentation issues: • Cause of B_{12} deficiency unclear. • Treatment plan unclear. • Dietary status of patients unclear.	• Future documentation to include: a. Cause of B_{12} deficiency. b. Appropriate B_{12} treatment regime plan. c. For patients with a dietary B_{12} deficiency: i. Dietary status (e.g. vegan or non-vegan), ii. Any dietary advice given. • Re-document all current patients with vitamin B_{12} deficiency.

Conclusion

Clearly, there needs to be improvements in performing IFA tests for patients with established vitamin B_{12} deficiency, as well as in documentation, assessing adherence to management and ensuring the implementation of monitoring guidelines. With these recommendations in place, we foresee that more patients with PA will be identified, thus rectifying any diagnostic doubts and allowing for the evaluation of the need for specialist referral or changes in treatment. These measures may result in safe prescriptions and potential cost savings, and improved documentation will allow clinicians to be aware of the patient's diagnosis and treatment plan and this, in turn, will improve follow-up monitoring.

What is known already:	What this study adds/ highlights:
• Vitamin B_{12} deficiency is usually treated with oral supplements or intramuscular injections. However, prescription practices may vary across Primary Care Centres due to the lack of clear guidelines in directing treatment. • If vitamin B_{12} deficiency is suspected, pernicious anaemia must be excluded first. • Some patients have been receiving long-term B_{12} replacement despite normal serum B_{12} levels.	• The Manchester Anaemia Guide (in conjunction with NICE Clinical Knowledge Summaries) has recently been published to guide the diagnosis and management of vitamin B_{12} deficiency. • The treatment regime of vitamin B_{12} deficiency varies according to its aetiology and whether patients have neurological symptoms. • The causes of vitamin B_{12} deficiency, particularly pernicious anaemia, have not been thoroughly excluded in some patients with established vitamin B_{12} deficiency. Hence, there is a need for the testing of intrinsic factor antibodies to be tighter and for each patient's cause(s) of vitamin B_{12} deficiency and dietary status to be well documented in order to initiate the appropriate treatment regime. • It has been recommended that patients on long-term metformin use and/or patients (non-vegans) whose vitamin B_{12} deficiencies have been corrected should have their serum B_{12} levels checked at regular 6-monthly intervals. • Clearly, there needs to be improvements in adhering to guidelines and documentation.

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