education

FROM THE JOURNALS Edited highlights of weekly research reviews on https://bit.ly/2PLtil8

Progesterone to prevent miscarriage

Underlying pregnancy there is a complex medley of hormones, so the theory that a hormone treatment would prevent miscarriage is appealing. Bleeding in early pregnancy suggests higher risk of loss of the pregnancy so it makes sense to target these women. A group of UK researchers randomised 4153 women with bleeding in early pregnancy to twice daily progesterone vaginal suppositories or placebo taken until week 16 of pregnancy. They found no difference in the live birth rate between groups. There was a suggestion of benefit in the subgroup of women with three or more previous miscarriages. But for everyone else, I think it's case closed for this therapy—it doesn't work.

N Engl J Med doi:10.1056/NEJMoa1813730

Ischaemic stroke and pulmonary embolism

A large French prospective cohort study looked for the presence of patent foramen ovale (PFO) on transthoracic echo and for presence of strokes on magnetic resonance imaging (silent or symptomatic) in 361 people who had acute pulmonary embolism. Of those with a PFO, 21.4% had recent ischaemic stroke. Of those with no PFO, 5.5% had recent ischaemic stroke. This suggests PFO are part of the mechanism of increased risk of stroke in people with pulmonary embolism.

Ann Intern Med doi:10.7326/M18-3485

Sunscreen screening

Matta et al applied sunscreen to 24 people (they were randomised to one of four types of sunscreen) and then tested their blood 30 times over seven days to look for the active ingredients, particularly avobenzone. For all four sunscreens, the participants' blood contained more than 0.5 ng/mL of avobenzone at day 1. This is still tiny but the significance is unknown. Given the widespread use of sunscreen in people of all age groups, one would hope the screening process for its safety is vigorous. And it probably is. These results simply highlight that additional testing is needed to determine the significance of the ingredients' absorption into the body as it is above the threshold for the FDA waiving the need for nonclinical toxicology studies.

JAMA doi:10.1001/jama.2019.5586

Alex Nowbar is a clinical research fellow at Imperial College London

Colorectal cancer screening and aspirin

Screening for colorectal cancer involves detecting blood in the faeces. Brenner et al randomised more than 2000 people to either aspirin or placebo to discover whether aspirin increased the ability to detect blood in the faeces, ie, to make the test more sensitive, leading to fewer missed cancer cases. The trial design is fascinating. To find enough cases of cancer to be able to detect a difference between groups, but without having to include an impractical number of people, they recruited people who were planned for a colonoscopy, although the indication for this could have been unrelated to rectal bleeding. This isn't the same as the population who receive colorectal cancer screening, but still seems valid for evaluating the hypothesis. Of the study population, 10.5% were found to have cancer. The sensitivity of the faecal occult blood test was no higher in the aspirin group than in the placebo group. However, the aspirin given was a one-off dose of 300 mg two days before the test. This may be quite different to the long term daily aspirin which many people undergoing screening will be taking. Aspirin might increase the sensitivity of the faecal occult blood test, but if it does, the effect size was too small for this study to detect, or the dose of aspirin used in this study was insufficient. Either way, there is no evidence to support the use of aspirin for this reason at the moment.

JAMA doi:10.1001/jama.2019.4755

Alcohol forecasts

We all like a good forecasting, and not just the royal baby name variety, but forecasts of health outcomes. Manthey et al looked at alcohol intake from 1990 to 2017 and model global alcohol exposure up to 2030. Half of all people are expected to be current drinkers by 2030, up from 43% in 1990 and from 47% in 2017. Some 23% are expected to be heavy episodic drinkers by 2030, up from 18.5% in 1990 and 20% in 2017. This shines a spotlight on the growing issue of alcohol exposure and the associated harms it brings.

Lancet doi:10.1016/S0140-6736(18)32744-2

NIHR | National Institute for Health Research

Does fluoxetine improve recovery after stroke?

There are around 100 000 strokes in the UK each year, and two thirds of stroke survivors leave hospital with a disability. Stroke is costly in terms of medical and social care, and in loss of earning potential.

The idea that a widely available inexpensive generic drug such as fluoxetine might improve function is attractive. However, research until now has been small scale, and a Cochrane review called for larger scale research to confirm or refute the theory.

This study was set up to find out whether patients diagnosed with stroke would have better functional outcomes when treated with fluoxetine for six months.

Researchers recruited 3127 adults with a clinical diagnosis of stroke, and no current depression or contraindications to fluoxetine, for the FOCUS double blind randomised controlled trial. They were prescribed either fluoxetine 20 mg (1564) or identical placebo (1563) for six months.

Functional status was measured after six months by postal questionnaire, followed up by telephone interview if the questionnaire was incomplete or not returned. The questionnaire used the modified Rankin scale, which categorises functionality from 0 (no symptoms) to 6 (dead), with scores of 3 and above indicating someone has moderate disability and is unable to live independently.

Researchers also looked at secondary outcomes, including incidence of depression after six months and adverse effects.

This large, multicentre trial was well conducted, and the results are likely to be reliable.

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What are the implications?

The findings of the study have clear implications: fluoxetine should not be added to stroke care as a routine treatment on the basis of the current evidence available.

This study was designed to give a definitive and statistically reliable answer to whether fluoxetine improves recovery after stroke, and was well conducted. The results are likely to be robust, and they support the current guidelines, which do not recommend routine use of fluoxetine.

STATE OF THE ART REVIEW

Sepsis associated acute kidney injury

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This article summarises the State of the Art review published on bmj.com.

State of the Art reviews are written with academic or specialist international and US readers in mind. This summary for non-specialists was created by *The BMJ* with input from the authors.

CPD READING

0.5 HOURS

Definition and risk factors

Sepsis is defined as organ dysfunction resulting from the host's deleterious response to infection. One of the most common organs affected is the kidneys, and patients who meet consensus criteria for both sepsis and acute kidney injury (AKI) are deemed to have sepsis associated AKI (SA-AKI) or septic AKI.

Sepsis is associated with up to 50% of AKI, and up to 60% of patients with sepsis have AKI. Independent risk factors or clinical consequences of sepsis and AKI, such as hypovolaemia or exposure to nephrotoxic therapies, have confounded the relation between these entities. Although the pathophysiological mechanism is incompletely understood, the deleterious inflammatory cascade characteristic of sepsis also seems to contribute to the AKI.

Patients with sepsis complicated by AKI have a significantly increased mortality relative to patients without AKI. Also, patients with AKI associated with sepsis have significantly increased mortality relative to those with AKI of another cause.

Early detection

As both sepsis and AKI are independently associated with increased morbidity and mortality, length of stay, and cost of care, early detection is critical. Regardless of the cause and associated comorbidities, AKI remains a diagnosis based on increases in serum creatinine or decreases in urine output. Although useful, these measures have limitations that underscore the need for newer methods to detect AKI and SA-AKI.

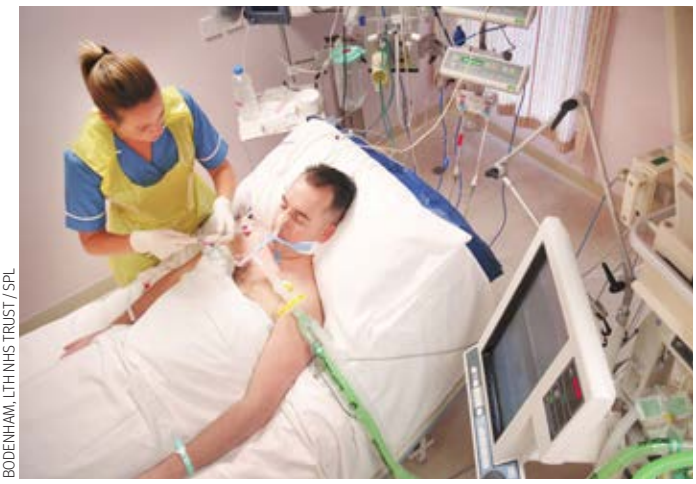
The initial limitation of a definition that relies on change in serum creatinine is establishing a baseline serum creatinine. No consensus method exists to establish pre-AKI baseline serum creatinine in the absence of previous values. Also, changes in serum creatinine are often delayed owing to renal reserve and the kinetics of AKI. Urine output is insensitive and is often measured accurately only in the intensive care setting.

Several alternative techniques to detect SA-AKI exist. These include urine analysis/urine microscopy, as well as novel serum and urine biomarkers of kidney injury. For example, proenkephalin and cystatin C are both highly associated with AKI and glomerular filtration rate and increase before serum creatinine does in critically ill patients with sepsis (table). Similarly, tissue inhibitor metalloproteinase-2 and insulin like growth factor binding protein-7 are elevated in the urine of patients at risk for severe SA-AKI 12-24 hours before a change in serum creatinine occurs.

Biomarkers used for detection of acute kidney injury (AKI)

Type of biomarker	Subclass of biomarker	Examples of biomarkers	Comments
Functional biomarker of AKI	Biochemical markers of glomerular filtration/function	Serum creatinine, serum cystatin c, proenkephalin, visible fluorescent injectates[69]	Serum creatinine remains the gold standard, but other novel markers of glomerular function have been shown to rise earlier and with the same accuracy as creatinine. Injectables may represent the future of GFR measurement, with the injection of small dextrans providing rapid determination of GFR at the bedside. May be elevated in the setting of CKD
	Global assessment of nephron function	Urine output	Urine output detects less severe AKI compared with creatinine and can be affected by diuretics and other drugs. Generally needs indwelling catheter for reliable measurement, with measurements being less frequent outside ICU
	Global assessment of nephron capacity	Furosemide stress test, renal reserve testing	These tests interrogate the kidney's capacity for increased function via protein loading (hyperfiltration) or diuretic responsiveness but are not validated in the setting of sepsis
Damage/injury biomarkers	Global assessment of nephron injury	Urine analysis	Urine analysis can detect injury along the entire nephron (from glomerulus to tubules); although scoring systems exist (box 2), none has been widely validated in any setting of AKI.
	Biochemical biomarkers of renal tubular injury	Urinary NGAL, urinary KIM-1, soluble FAS	These remain an area of intense AKI research but have yet to be widely validated in the setting of human AKI
AKI risk biomarkers	Biochemical biomarkers of AKI risk	TIMP2*IGFBP7, plasma NGAL	Increasingly available for clinical use, these markers quantify an individual patient's risk for impending AKI
	Biomarkers of AKI risk	Electronic alerts, electronic risk algorithms	Although not specific to SA-AKI, several alerts have shown their ability to predict the impending development of sepsis and AKI separately. Using these alerts in concert with biochemical biomarkers may help to enrich SA-AKI detection and risk stratification

CKD=chronic kidney disease; GFR=glomerular filtration rate; ICU=intensive care unit; IGFBP7=insulin like growth factor binding protein-7; KIM-1=kidney injury molecule-1; NGAL=neutrophil gelatinase associated lipocalin; SA-AKI=sepsis associated acute kidney injury; TIMP2=tissue inhibitor of metalloproteinase-2.



BODENHAM, LTH NHS TRUST / SPL

Box 1 | Summary of management strategies for sepsis associated acute kidney injury (SA-AKI)

Screening and diagnosis

- Closely monitor both urine output and serum creatinine in patients with sepsis
- Given limitations of urine output and serum creatinine, consider adoption of emerging risk scoring systems or serum biomarkers

Supportive care

- Use best practice strategies for patients with sepsis
  - Early administration of appropriate antibiotics
  - Achieve control or removal of source of infection
  - Adequate resuscitation with intravenous fluids while avoiding over-resuscitation
  - Use norepinephrine, vasopressin, or both as initial vasoactive drug(s)

Avoid further kidney injury

- Avoid potentially nephrotoxic drugs when possible
- Avoid potentially nephrotoxic contrast loads when possible
- Do not use hydroxyethyl starches

Treatment of SA-AKI

- Early initiation of renal replacement therapy (RRT) has not been shown to be superior to conventional timing of initiation of RRT
- The delivered dose of continuous RRT (CRRT) should be 20-25 mL/kg/h, which often requires dosing CRRT at 30-35 mL/kg/h
- Higher dose RRT (70-85 mL/kg/h) has not been shown to be superior to lower dose RRT (35-50 mL/kg/h)

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

A 62 year old man with a previous history of postoperative sepsis associated acute kidney injury (SA-AKI) who had a hospital limited course of renal replacement therapy four years ago with the subsequent development of post-AKI chronic kidney disease accepted an invitation to review the manuscript as a patient reviewer for *The BMJ*. He reviewed the paper in its entirety, providing suggestions on which sections were most and least relevant to his personal history. As a result of this input, we emphasised the effect of SA-AKI on the potential development of chronic kidney disease as well as the limited treatment options in the setting of AKI. The patient asked us to emphasise the importance of continuing to work to discover and validate treatment options in the setting of acute kidney injury (and chronic kidney disease) and to remind people of the importance of nephrology care in the setting of kidney disease.

Management

Box 1 summarises management strategies for SA-AKI. Prompt resuscitation with intravenous fluids is a key component of sepsis management.However, excessive administration and accumulation of fluids in an attempt to treat hypotension or oliguria after AKI is common and harmful.

A randomised trial in 1000 patients with acute respiratory distress syndrome found that the patients given a conservative fluid strategy had significantly more ventilator-free and intensive care-free days. Other studies of fluid management have also shown the harms of excess fluid during and after the development of AKI. Possible reasons for this observation include cardiac overload with falling cardiac output, resultant renal venous hypertension, increasing resistance, and decreased renal perfusion pressures. In addition to the volume of fluids given, the type of resuscitation fluid may affect outcomes of sepsis and SA-AKI. The most definitive and consistent finding relates to the use of hyperoncotic starch solutions, which should be avoided in sepsis and in all other patients at risk for AKI.

High quality evidence also shows no advantage to albumin containing regimens, so their use cannot be recommended over less costly crystalloid solutions. More recent studies have compared outcomes between balanced and hyperchloraemic crystalloid solutions, with some but not all suggesting that hyperchloraemic solutions may be associated with increased AKI and mortality

The selection of the ideal vasopressor in the setting of shock (regardless of AKI status) has been studied in several large scale multicentre trials. In the setting of SA-AKI, traditional agents such as noradrenaline (norepinephrine), adrenaline, vasopressin, and dopamine and more novel agents such as angiotensin II and levosimendan, have been investigated. Based on this evidence, the consensus is that noradrenaline and vasopressin should be first line agents for the treatment of septic shock, although treatment should be tailored to the individual patient.

Critically ill patients with sepsis and septic shock often need mechanical ventilation with positive pressure to provide support with oxygenation, ventilation, and airway protection in the setting of organ failure. Positive pressure ventilation has potentially deleterious effects on kidney perfusion and function; however, mechanical ventilation is unavoidable in many patients, and the ventilation strategy is largely dictated by the effect on oxygenation and overall survival. Whether a given strategy would potentially protect the kidney independent of and without sacrificing the support of the respiratory system is not clear.

Several trials have assessed the timing, dose, and modality of renal replacement therapy in patients with SA-AKI. The results of these trials are summarised in the box.

Despite aggressive screening of patients at risk and early intervention, SA-AKI will remain a highly morbid complication of a common critical illness. Novel translational animal models, the wealth of data available in modern electronic health records, and novel clinical biomarkers may allow us to set a new course for prevention, treatment, and renal recovery.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following interests: JLK has received consulting fees from Astute Medical, Baxter, Sphingotec, and Pfizer and research fees from Astute Medical, Bioporto, NxStage Medical, and Satellite Healthcare for work in biomarkers of AKI, not specific to SA-AKI.

Cite this as: *BMJ* 2019;365:k4891

Find the full version with references at http://dx.doi.org/10.1136/bmj.k4891

Investigating vitamin B12 deficiency

CPD READING
0.5 HOURS

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor of medicine, Weill Cornell Medical College Qatar; and Eric Kilpatrick, Division Chief, Clinical Chemistry, Sidra Medical and Research Center, Qatar; honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School.

A 44 year old woman attends her general practitioner with a two year history of lethargy, which has resulted in her being unable to continue her job as a primary school teacher. She had a history of anaemia a few years ago and was not taking any regular medication, except for the combined contraceptive pill. Her mother has hypothyroidism, for which she takes levothyroxine; there is no other family history of note. Physical examination was unremarkable. Recent blood tests showed haemoglobin 110 g/L (reference range 115-160) and mean corpuscular volume 102 fL (range 80-100). Blood tests for vitamin B12 and folate were requested, which showed vitamin B12 138 pmol/L (reference range 148-600) and folate 40.5 nmol/L (4.5-45).

Background

The prevalence of vitamin B12 (B12) deficiency is approximately 6-12% in adults under 60 years old and around 17% in all adults with macrocytic anaemia.[1-3] However, elderly people, pregnant women, and vegans are more susceptible to B12 deficiency, so have a higher index of suspicion in these populations in the presence of suggestive symptoms and signs (see box right). Some of the common causes, risk factors, and likely mechanisms of B12 deficiency are summarised in the table.

In this article, we discuss the key indications for B12 testing and the recommended tests along with some of the issues surrounding their interpretation.

Acquired causes of vitamin B12 deficiency (adapted from Herrmann et al[10])

Condition causing B12 deficiency	Mechanism of action
High risk groups—Vegetarians/vegans and their children, poverty, malnutrition, anorexia nervosa, alcoholism, old age	Restricted intake of B12
Pregnancy, lactation	Increased demands
Drugs:	
H_2 receptor antagonists, proton pump inhibitors	Changed gastrointestinal pH
Metformin	Inhibition of B12 absorption
Oral contraceptives	Reduced level of haptocorrin (R-protein, a B12-carrying protein)
Autoimmune conditions:	
Pernicious anaemia	Lack of intrinsic factor (IF, a B12-carrying protein) due to antibodies to parietal cells or IF
Age related atrophic gastritis or *H pylori* infection	Changed gastrointestinal pH
Malabsorptive conditions:	
Terminal ileal diseases, pancreatic insufficiency, ileal or gastric resection, coeliac disease, Crohn's disease	Interference with intestinal absorption
Small bowel bacterial overgrowth	Bacteria compete for and break down IF-B12 complex

Vitamin B12 deficiency in vulnerable populations[4-9]

Pregnant women

- B12 levels <150 pmol/L found in 20-30% of pregnant women worldwide
- May be physiological, so holotranscobalamin can be used as a marker of active B12
- Can have serious implications—association with higher risk of low birthweight babies and preterm labour[4 5]

Infants and young children

- The first two years of a child's life are critical for myelination of neurones, so adequate B12 stores are required for neurological development during this period
- Breastfed infants of B12-deficient mothers and young children whose diets are deficient in B12 are at risk of deficiency and associated complications[8]
- In young children at risk of B12 deficiency or those who display signs and symptoms attributable to low B12, we recommend a low threshold to initiating treatment

Elderly people

- Older people are at risk of a lack of B12 due to dietary deficiency, loss of gastric function leading to malabsorption, and higher incidence of pernicious anaemia
- B12 deficiency is linked to anaemia, dementia, and cognitive decline in this population
- Check and correct B12 deficiency before mandatory or voluntary fortification of folic acid as this can mask the haematological manifestations of B12 deficiency, leading to neuropsychiatric sequelae[9]

WHAT YOU NEED TO KNOW

- Vitamin B12 deficiency may present with non-specific symptoms, but it warrants urgent evaluation and treatment when haematological or neurological features are present
- B12 deficiency can have nutritional, drug induced, and gastrointestinal causes; autoimmune pernicious anaemia is relatively rare
- Consider specialist referral if there is no obvious cause for B12 deficiency, if it is refractory to treatment, or if neurological features or persistent macrocytic anaemia are present
- Parenteral B12 replacement is indicated if urgent treatment is required, if gastrointestinal malabsorption is suspected, and in elderly people
- Oral B12 replacement may be a suitable alternative in asymptomatic individuals with dietary B12 deficiency

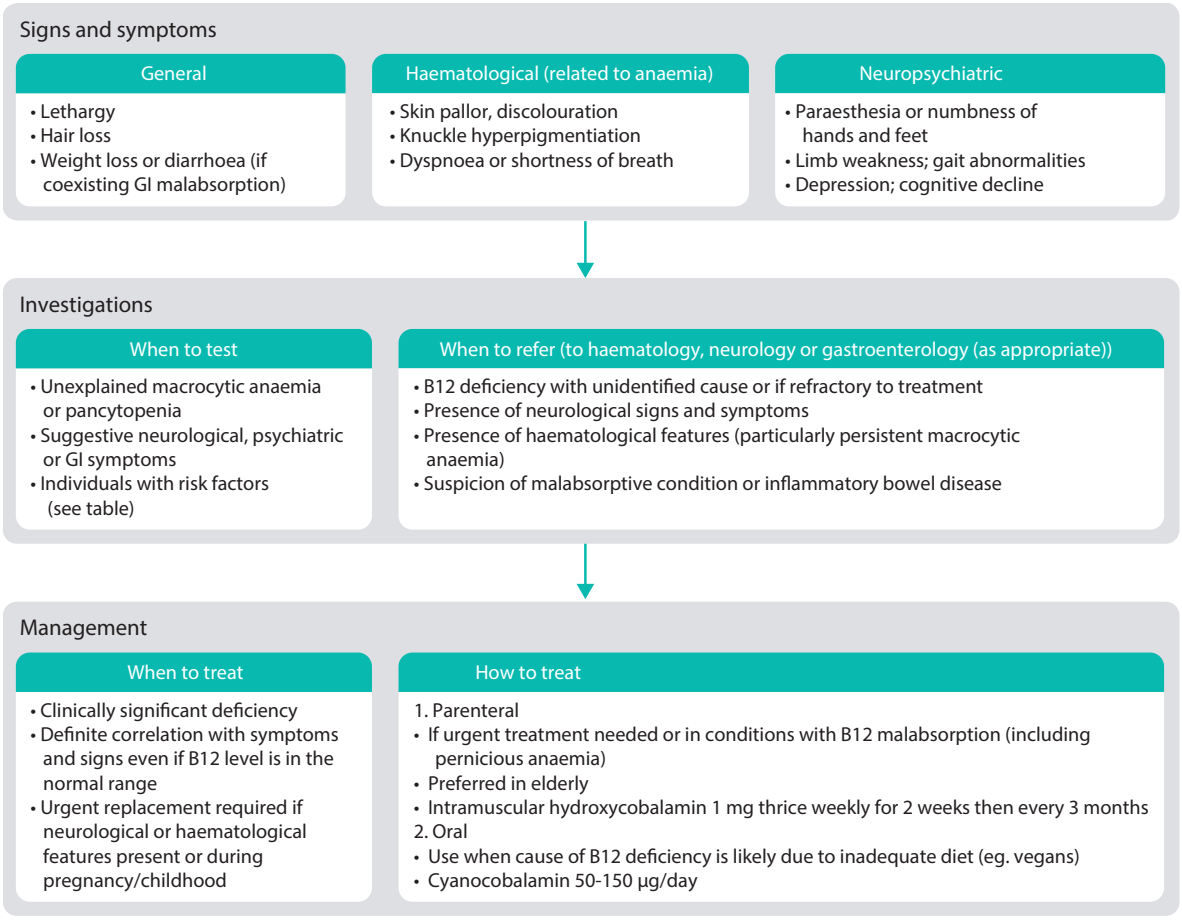


Fig 1 | Visual summary of investigation and management of vitamin B12 deficiency

Assessing the patient

When to suspect vitamin B12 deficiency

Suspect B12 deficiency in patients with suggestive symptoms and signs (such as neurocognitive symptoms, anaemia, or those listed in fig 1), particularly if they have risk factors such as those listed in the table. However, since neurological sequelae may occur in the absence of anaemia, measure B12 levels in any patient with early neurological signs and symptoms.

In the absence of specific features or definite risk factor, checking B12 levels routinely has limited clinical utility and can lead to dilemmas about treatment.

What to look for on physical examination

Perform a focused clinical examination looking for signs of anaemia and neuropsychiatric changes (fig 1). In the most severe form of B12 deficiency, subacute combined degeneration of the spinal cord can develop. This presents as slowly progressive symmetrical weakness and paraesthesia of the lower limbs (peripheral sensory neuropathy) accompanied by sensory ataxia. In the initial stages, this can be detected as impairment of proprioception or vibration sense.

What are the initial investigations?

The first line investigations to request in primary care when B12 deficiency is suspected are:

Serum vitamin B12

A level of <150 pmol/L has been conventionally used as the cut-off to define deficiency, but clinicians should also refer to the reference range provided by the local laboratory.[11] B12 levels can be requested on a non-fasting blood sample easily in primary care.

Full blood count to determine haemoglobin, mean corpuscular volume, haematocrit, and a blood film

The presence of anaemia, particularly if macrocytic (that is, mean corpuscular volume of red blood cells >100 fL) raises suspicion of B12 deficiency and requires prompt testing of B12 and folate levels.

One cause of macrocytic anaemia is megaloblastosis. This occurs exclusively in the presence of B12 or folate deficiency. Other haematological findings in B12 deficiency include mild leucopenia, thrombocytopenia, pancytopenia, and hypersegmented neutrophils.

It is important to remember that the mean corpuscular volume may be normal if there is concomitant microcytosis, such as due to iron deficiency or thalassaemia trait. Screen for these conditions if clinically indicated.

Serum folate

Folate acts synergistically with B12 for its cellular function, and so it should be checked and corrected

accordingly. B12 and folate deficiency can coexist, particularly in situations of malabsorption or severe nutritional deficiency.

When are specialist investigations needed?

Suspected pernicious anaemia

The prevalence of pernicious anaemia is approximately 4% in European countries and increases with age.[13] It is a form of atrophic gastritis with autoimmune destruction of gastric parietal cells and loss of intrinsic factor production, which leads to reduced B12 absorption (fig 2). There is an association with other autoimmune conditions, although it can occur in isolation.

From our clinical experience, we suggest that investigations for pernicious anaemia be considered in patients with features of clinical B12 deficiency (such as presence of haematological or neurological symptoms) regardless of their B12 levels, as well as in those with low serum B12 levels without any obvious cause or risk factors.[11]

Test for antibodies to intrinsic factor—These are highly specific for pernicious anaemia (95-100%), which means that false positives occur <5% of the time. However, the sensitivity of the test is only 50-60%, so a negative result does not rule out the disease.

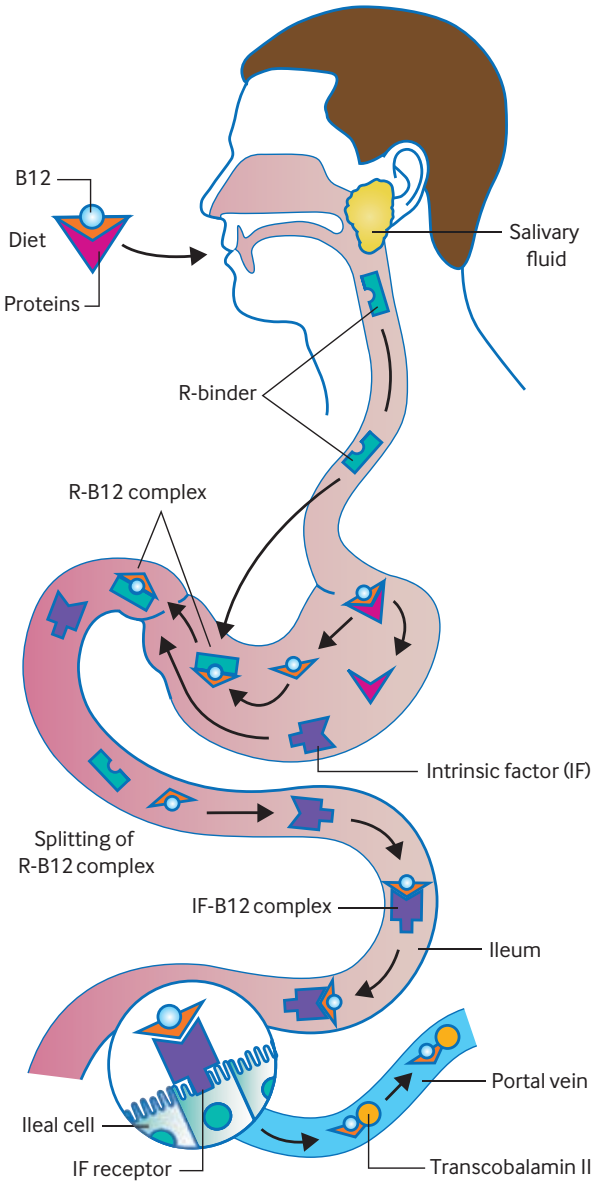


Fig 2 | Absorption of vitamin B12. Dietary B12 is released from food in the stomach and binds to R-protein (haptocorrin, this complex is stable in the gastric acidic environment). The R-B12 complex then travels to the duodenum, where B12 binds to intrinsic factor (IF, secreted by gastric parietal cells and therefore lost in pernicious anaemia). This B12-IF complex is carried down the small intestine until the terminal ileum, where it attaches to IF receptors and is absorbed into the bloodstream bound to transcobalamin. Over 95% of dietary B12 is absorbed through the IF pathway

Malabsorptive conditions

Investigate patients in whom gastrointestinal malabsorption is suspected (see table) and consider referral to gastroenterology as appropriate.

Other specialist investigations

The following investigations are best conducted in secondary care because of limitations in sample collection and storage and uncertainties in interpretation of results.

- *Holotranscobalamin*—This is the functional form of B12 that is taken up and used by tissues. It generally correlates well with total B12 levels, as measured by standard B12 assays.
- *Methylmalonic acid*—This has been recommended as a second line test to diagnose B12 deficiency, although its availability in clinical practice is limited.[11]
- *Homocysteine*—Levels can be elevated in coexistent folate or vitamin B6 deficiency, hypothyroidism, and renal failure, so it is less specific than methylmalonic acid for the diagnosis of B12 deficiency.

Elevation of methylmalonic acid and homocysteine levels can occur as B12 levels fall below 400 pmol/L, which is higher than the threshold associated with adverse clinical outcomes, and may be particularly associated with accelerated cognitive decline (fig 3).[15]

How should I interpret the test results?

The clinical presentation of the patient along with any risk factors, if present, will be the most important factors in determining the importance of the test results because there is no single test among those described above that define B12 deficiency. In patients where deficiency is strongly suspected, serum B12 levels of <150 pmol/L can be used to guide treatment, but if the B12 levels are above this the patient can be referred to secondary care for consideration of the specialist investigations described above.[11] Do not delay treatment in such situations, however, particularly if there is concern about neurological damage. However, in patients with non-specific symptoms and signs and no anaemia, test results for B12 levels may be falsely low, and so should be repeated before further investigations or starting treatment.[11]

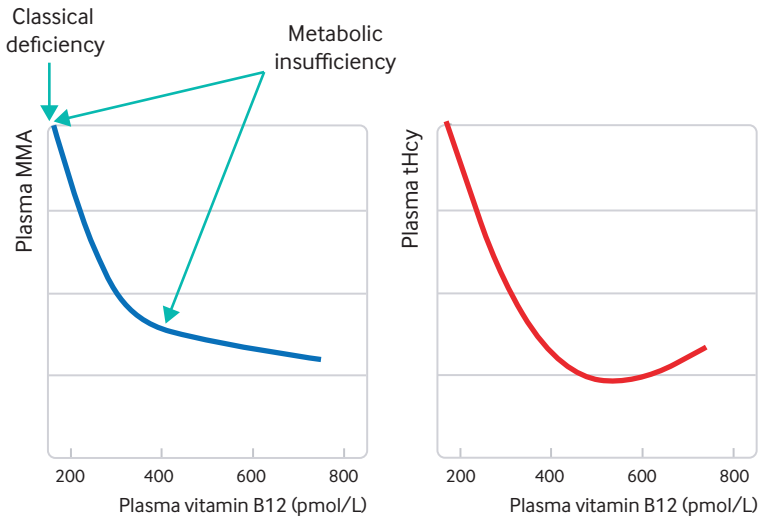


Fig 3 | Relation between plasma vitamin B12 and plasma total homocysteine (tHcy) or methylmalonic acid (MMA) in 3262 community-dwelling people aged 71-74 years in Norway (adapted with permission from Smith et al[15])

VOLKER STEGER / SPL

Management

Consider treatment with vitamin B12 with the primary aim of relieving symptoms and signs caused by B12 deficiency. We recommend following the British Society of Haematology guidelines on management of patients with suspected B12 deficiency, which is further divided into patients with definite clinical signs and those with non-specific symptoms.[11]

Briefly, the modalities of B12 replacement available are:

- *Parenteral B12 (intramuscular or deep subcutaneous injection of hydroxycobalamin)*—The *British National Formulary* suggests 1 mg three times per week for two weeks and then once every three months. However, if neurological features are present, the initial treatment should be given on alternate days until there is no improvement in symptoms, followed by maintenance treatment once every two months.[16] The duration of treatment will depend on reversibility of any underlying cause and may be life long, particularly in cases of pernicious anaemia.
  - Order a full blood count at 7-10 days and at eight weeks after treatment if anaemia or macrocytosis is present. Monitoring B12 levels is usually not necessary, but they can be checked one or two months after starting parenteral treatment if there is no clinical improvement.[17]
- *Oral B12*—Oral cyanocobalamin 50-150 µg daily can be tried in asymptomatic individuals who have no evidence of malabsorption or for maintenance treatment after correction of their signs or symptoms with parenteral B12, except in cases of pernicious anaemia.[11-19]
  - We recommend that patients taking oral B12 replacement have serum B12 levels measured every 6-12 months: if patients show a good response, together with reversal of any underlying risk factors, a trial without B12 supplements may be carried out.

Outcomes

In the case described, initial clinical examination and screening tests did not identify any obvious underlying cause of B12 deficiency. However, the patient was a strict vegan, so was likely to have lower than recommended dietary intake of B12. Her test for antibodies to intrinsic factor were negative. Her use of oral contraceptives may also have given falsely lower total B12 readings, but, in view of her symptoms and anaemia, it was decided to treat her with intramuscular hydroxycobalamin 1000 µg three times a week for two weeks. She responded well to this with an increase in serum B12 to 400 pmol/L and in haemoglobin to 133 g/L at three months as well as an improvement in her lethargy. She was then advised to take oral cyanocobalamin supplements indefinitely as maintenance to prevent further deficiency.

Competing interests: PS is partly supported by a project grant from MRC (Grant Ref: MR/J000094/1) which is designed to assess the impact of B12 levels in early pregnancy on gestational diabetes.

Cite this as: *BMJ* 2019;365:l1865

Find the full version with references at http://dx.doi.org/10.1136/bmj.l1865

RATIONAL TESTING INTO PRACTICE

- What is your current approach to treating patients with subclinical B12 deficiency (150-250 pmol/L) without an obvious cause?
- What proportion of patients in your practice have elevated levels of homocysteine and/or methylmalonic acid (when these have been checked) in the presence of B12 deficiency?
- In your practice, how effective is oral B12 supplementation in asymptomatic individuals without malabsorption?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

During the planning stage of this article, we did informal interviews with pregnant women diagnosed with vitamin B12 deficiency. They were anxious about their diagnosis as they were not aware of the implications of B12 deficiency and what all the different tests meant. These points were taken into consideration when writing the article

SPOT DIAGNOSIS

A neonate with bilious emesis

A newborn girl (gestational age 35+1 weeks, birth weight 2130 g) was admitted to the neonatal intensive care unit with bilious vomiting on the first day after her birth. She had a perinatal history of polyhydramnios. On physical examination, her abdomen was flat, soft, and non-tender and no mass was palpable. Digital rectal examination revealed that her anus was patent, but only intestinal mucus (instead of meconium) was found on the glove. There were no apparent visible dysmorphic features or other congenital malformations. A plain abdominal radiograph was taken (fig 1).

What is the diagnosis?

Submitted by Zhen-Lang Lin and Jiang-Hu Zhu

Parental consent obtained

Cite this as: *BMJ* 2019;365:l1351

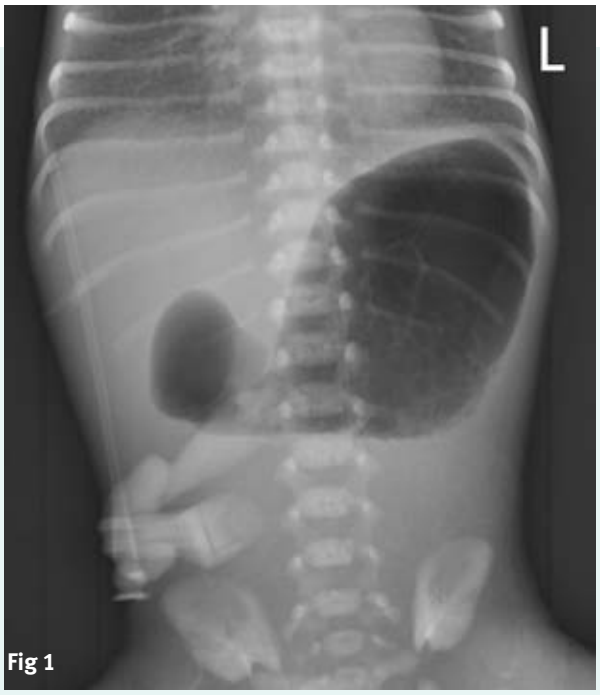


Fig 1

If you would like to write a Case Review or Spot Diagnosis for Endgames, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

answers

For extra material, including patient outcome, go to bmj.com/endgames

SPOT DIAGNOSIS

A neonate with bilious emesis

Congenital duodenal atresia (complete closure of the duodenum). Abdominal radiography is sufficient for diagnosis. Typically, no air is seen in the distal intestine and the characteristic "double-bubble" sign is present (stomach and proximal duodenum distention, separated by the pyloric sphincter) (fig 2). Incidence is approximately one in 6000-10 000 live births, with a slightly higher prevalence in baby boys than in girls. Around 25-30% of cases are associated with Down's syndrome. Anomalies—such as cardiovascular malformations, intestinal malrotation, oesophageal atresia, tracheoesophageal fistula, and renal anomalies—may coexist.

Medical management includes gastrointestinal decompression via a nasogastric or orogastric tube, withholding oral feeding, and the maintenance of fluid, electrolyte, and acid base balances. Definitive treatment is duodenoduodenostomy (via laparotomy or laparoscopy). Prognosis is generally good but is dependent on access to neonatologists and paediatric surgeons trained in duodenoduodenostomy.

LEARNING POINTS

- Perform abdominal radiography in neonates with bilious emesis.
- The "double-bubble" sign on abdominal radiography is characteristic of duodenal atresia.

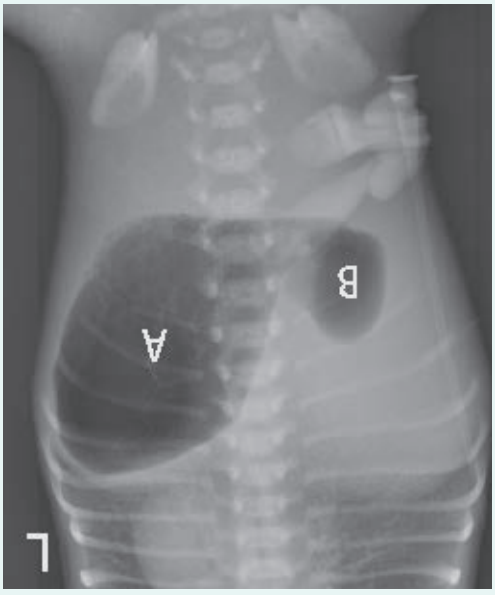


Fig 2 | The patient's plain abdominal radiograph showing a markedly dilated stomach (A) and proximal duodenum (B) (the double-bubble sign), with lack of air in the rest of the intestine

CPD READING
0.5 HOURS

You can record CPD points for reading any article. We suggest half an hour to read and reflect on each.

LEARNING MODULE

Articles with a "learning module" logo have a linked BMJ Learning module at http://learning.bmj.com.

Postoperative gas gangrene

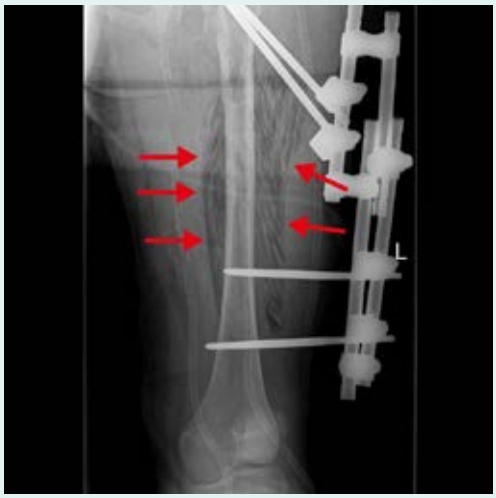
A 13 year old girl presented with two days of pyrexia, left groin and leg pain, crepitus in the left groin and abdominal wall, and a feathery pattern of extensive gas formation (figure, red arrows) on radiography. Three days before this presentation, she had received debridement, external fixation, suturing, vacuum sealing drainage, and antibiotic prophylaxis for an open left femoral neck fracture after being in a road traffic incident. Her latest symptoms were indicative of gas gangrene, which was treated with immediate radical debridement, aggressive antibiotic treatment, hyperbaric oxygen therapy, and left hip disarticulation.

Gas gangrene can occur despite antibiotic prophylaxis if the vacuum sealing drainage becomes obstructed by necrotic muscular tissue—the wound under the sealing polyurethane film becomes hypoxic, which encourages anaerobic *Clostridium* growth.

Jun-Song Yang; Wei Liu; Liang Yan; Ding-Jun Hao (dingjun.hao@qq.com), Honghui Hospital, Xi'an Jiaotong University, Xi'an, Shaanxi, China

Parental consent obtained.

Cite this as: *BMJ* 2019;365:l2054



If you would like to write a Minerva picture case, please see our author guidelines at http://bit.ly/29HCBAL and submit online at http://bit.ly/29yyGSx

Breakfast and heart disease

A recent systematic review in *The BMJ* failed to reach a definite conclusion about the value of eating breakfast for people wanting to lose weight. Although a large longitudinal study from the US throws no more light on this question, it did discover an association between breakfast and heart disease (*J Am Coll Cardiol*). People who never ate breakfast had double the cardiovascular mortality of those who ate breakfast every day. A direct causal link seems unlikely, but the observation might be useful in flagging up a high risk group.

Recognising sepsis

The problem with screening tools for sepsis is achieving adequate sensitivity while limiting the number of false positives. The quick sequential organ failure assessment (qSOFA) failed on both counts when a database of over a million hospitalised patients was used to evaluate its performance (*Chest*). Around a quarter of the patients had signs which made them qSOFA-positive on admission, but only one in six of these had a diagnosis of sepsis confirmed. Even worse, qSOFA was negative in a third of patients who did have sepsis.

Post-traumatic stress disorder

Follow-up of a series of cases presenting to an emergency department with life threatening conditions found that a quarter of the survivors described symptoms of post-traumatic stress disorder when questioned a month after discharge (*Intensive Care Med*). This was true even if they hadn't spent time in an intensive care unit. Those who recalled that their treatment had been delivered with kindness and compassion were less likely to report symptoms. Even leaving aside doubts about the reliability of this information, Minerva wonders whether anything useful can be concluded. Medical care should be given with sympathy regardless of circumstances or the possibility of a future health benefit.

Psoriatic arthritis

Early treatment with tumour necrosis factor inhibitors and other disease modifying drugs has substantially improved the long term outlook for people with rheumatoid arthritis. A small trial suggests that the same is likely to be true for psoriatic arthritis (*Ann Rheum Dis*). Among 51 patients with active disease, those randomised to golimumab and methotrexate were twice as likely to achieve remission by 6 months as those allocated to methotrexate alone.

Screen time and children's behaviour

A decade ago there was anxiety that young children watched too much television. These days the worry is that they are over-exposed to mobile devices and interactive media. A study from Canada reports that pre-school children who spend more than two hours in front of a screen each day are more likely to meet criteria for attention deficit/hyperactivity disorder and to have problems with behaviour and attention (*PLoS ONE*). But which came first, the behaviour or the electronic devices? Perhaps parents use screens to calm children down when they behave in a way that is hard to cope with?

Cite this as: *BMJ* 2019;365:l2096