Anaemia: A disease or symptom?

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ABSTRACT

Anaemia is a common diagnosis for clinicians. This mini-review summarises criteria for diagnosing the cause of anaemia. Within the microcytic anaemias, iron-deficient anaemia is most common. In addition, we would like to raise awareness of thalassaemia as a differential diagnosis. A normocytic anaemia, such as anaemia of chronic disease, is a diagnosis of exclusion. A macrocytic anaemia scheme is provided and differentiates based on reticulocyte count. We aim to provide the readers a clear overview of anaemia and when to refer to haematologists.

KEYWORDS

Anaemia, iron deficiency anaemia, thalassaemia, vitamin B12 deficiency

INTRODUCTION

Anaemia is a haematological abnormality commonly encountered by general practitioners and hospital physicians. Worldwide, anaemia is estimated to affect 1.6 billion people.[1] Anaemia is diagnosed using a patient's haemoglobin concentration; however, this information does not determine the causative underlying pathology of the anaemic state. Anaemia pathology can be divided into three broad categories: a decreased production of red cells, an increased destruction of red cells, or a loss of red cells through bleeding. However, anaemia pathology is often multifactorial and can present as the manifestation of an underlying disorder.

DEFINITION OF ANAEMIA

The World Health Organization defines anaemia as a condition in which the number of red cells or their oxygen-carrying capacity is insufficient to meet physiological requirements. The United Kingdom (UK) laboratory definition of anaemia is a haemoglobin level two standard deviations below the normal for age and sex. This correlates as the following:

- Men, over 15 years of age: Hb below 130 g/l
- Non-pregnant women, over 15 years of age: Hb below 120 g/l
- Children, aged 12-14 years: Hb below 120 g/l

During pregnancy, homeostatic changes occur that necessitate an alteration of anaemia definitions. The definition of anaemia during pregnancy is as follows:

- First trimester: Hb below 110 g/l
- Second and third trimesters: Hb below 105 g/l
- Postpartum: Hb below 100 g/l

The mean cell volume (MCV) can be used to categorise anaemia and therefore guide subsequent investigations. Using MCV, anaemia can be categorised accordingly:

- Microcytic anaemia: MCV < 80 fL
- Normocytic anaemia: MCV 80-95 fL
- Macrocytic anaemia: MCV > 95 fL

MICROCYTIC ANAEMIA

Microcytic anaemia is defined as anaemia with an MCV of < 80 fL. The most common cause of microcytic anaemia, and indeed the most common cause of anaemia worldwide, is iron deficiency. Iron deficiency anaemia remains a significant problem in developed countries, with an estimated prevalence of 2-5% among men and post-menopausal women.[2] Rates of iron deficiency anaemia in women of childbearing age exceed this due to menstruation and pregnancy-related blood loss.[3]

Other causes of microcytic anaemia include anaemia of chronic disease, haemoglobinopathies, and sideroblastic anaemias. Table 1 demonstrates the use of full blood count parameters and iron studies to help differentiate between the causes of microcytic anaemia.

Table 1. *The differential diagnosis of microcytic anaemia*

Investigation	Iron deficiency	Anaemia of chronic disease	Thalassaemia (α or β)
MCV	Low	Low/normal	Very low for degree of anaemia
Serum ferritin	Low	Normal/ raised	Normal
Serum TIBC	Raised	Low	Normal
Transferrin saturation	Low	Low	Normal
Serum Iron	Low	Low	Normal
Reticulocyte count	Low	Low/ normal	Normal/ raised

Note: When iron deficiency occurs in combination with an inflammatory state, the ferritin may be spuriously high. In these instances, it is advised to perform a zinc protoporphyrin level.
MCV = mean cell volume; TIBC = total iron binding capacity

IRON DEFICIENCY ANAEMIA

In developed countries, iron deficiency anaemia is most commonly caused by chronic blood loss, usually from the gastrointestinal tract or uterus. Poor diet is rarely the sole cause in patients with iron deficiency anaemia in Western Europe. Nonetheless, diet-related iron deficiency remains an important cause of iron deficiency anaemia in the developing world. Malabsorption, particularly related to gluten-induced enteropathy or atrophic gastritis, is an important cause to exclude when considering an alternative aetiology to chronic blood loss. Furthermore, in women displaying iron deficiency anaemia, it is crucial to ask questions pertaining to their menstruation pattern. Extensive vaginal blood loss can be regulated with anti-conceptive drugs. In the event that vaginal blood loss continues, in the presence of an anti-conceptive drug, un-diagnosed von Willebrand disease should be considered. These patients can benefit from the use of tranxenamic acid administration.

Accordingly, the investigation of iron deficiency anaemia should be guided by a thorough history and examination, particularly focusing on causes of blood loss. Table 2 summarises possible investigations for patients presenting with iron deficiency anaemia.

The management of iron deficiency anaemia consists of:
- Identification and treatment of the underlying cause of iron deficiency (e.g., treatment of peptic ulcer disease, treatment of extensive vaginal blood loss during menstruation)
- Correction of the iron deficiency by replacement with iron (oral or intravenous)

In the majority of patients, iron stores can be replenished through the use of oral iron supplements. Typical treatment regimens for iron deficiency anaemia advise 100-200 mg elemental iron per day in one dose (200 mg PO (orally) ferrous sulphate = 65 mg elemental iron).[4] For children and infants, a dose of 3-6 mg/kg (max. 200 mg) daily is advised.[5] However, current evidence would suggest

Table 2. *Investigation of iron deficiency anaemia*

1st line investigations	2nd line investigations	Additional investigations to consider
FBC	Coeliac serology	Zinc protoporphyrin (if normal/raised ferritin, but high suspicion of IDA)
MCV	Faecal occult blood	Blood film
Ferritin	Gastroscopy (upper GI symptoms)	Reticulocyte count
Serum TIBC	Colonoscopy or CT colography (lower GI symptoms)	
Serum iron		

Second-line investigations should be guided by the history and examination.
CT = computed tomography; FBC = full blood count; IDA = iron deficiency anaemia; GI =gastro-intestinal; MCV = mean cell volume; TIBC = total iron binding capacity

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that lower doses of iron may be as effective and better tolerated.[6] Haemoglobin should be re-checked after 2-4 weeks of iron supplementation. A haemoglobin rise of 20g/l over 3-4 weeks is indicative of a response. Once the haemoglobin and red cell indices have normalised, iron supplementation should be continued for three months. If faster repletion is required or if gastrointestinal absorption is impaired, intravenous (IV) iron can be an effective treatment modality. Nonetheless, it should be noted that IV iron supplementation requires administration by a healthcare professional and consequently, can increase the burden on healthcare resources. Furthermore, IV Iron therapy is associated with an increased risk of hypersensitivity reaction.[7]

THALASSAEMIAS

In patients with a microcytic anaemia and normal iron studies, a diagnosis of thalassaemia should be considered. Thalassaemia is often associated with a strong family history, and occurs predominately in patients of Mediterranean, Indian, South East Asian, or Chinese descent. Thalassaemias have a highly variable phenotype, ranging from asymptomatic patients to those who are transfusion dependant. Mehtzer's index (MCV/red blood count) can be used as a tool to differentiate between IDA and thalassaemia: - < 13 is suggestive of thalassaemia and > 14 is suggestive of IDA.[8] A recent meta-analysis has demonstrated that although this index is easy to calculate, it is associated with false positives and false negatives. Consequently, this index is best suited as a screening test in combination with other factors (e.g., ethnicity, age).[9] To accurately diagnose thalassaemia, a peripheral blood film and haemoglobin electrophoresis is required. In patients with a high index of suspicion of alpha thalassaemia trait (Chinese, South East Asian, and Indian descent) combined with low MCV and normal Hb electrophoresis, it is recommended that a DNA analysis is performed to detect the alpha thalassaemia gene. An alternative technique for detecting deletions in the haemoglobin alpha gene is multiplex ligation-dependent probe amplification (MLPA).[10] However, MPLA can only detect the seven most common alpha gene deletions. Therefore, if the suspicion of alpha thalassaemia persists and the MLPA testing is negative, further DNA analysis is warranted.

NORMOCYTIC ANAEMIA

A normochromic normocytic anaemia is frequently present in hospitalised patients. Sudden normochromic normocytic anaemia is often as a result of acute blood loss. Chronic normocytic anaemia is predominantly a manifestation of an underlying systemic disorder. This is either as the termed 'anaemia of chronic disease' (ACD) or secondary to another disorder such as renal failure, hypothyroidism, multiple myeloma. Assessment of patients with normocytic anaemia should include a focused analysis of these systemic disorders through a systematic approach including history, examination, and initial investigations (e.g., renal function, immunoglobulins and protein electrophoresis, and thyroid function tests, etc).

ANAEMIA OF CHRONIC DISEASE

ACD is a diagnosis of exclusion that is characterised by functional iron deficiency. Worldwide, it is the second most common cause of anaemia, after iron deficiency anaemia, and is associated with a wide variety of inflammatory, infective and malignant diseases (see figure 1). These chronic inflammatory states cause anaemia to develop due to three pathophysiological mechanisms:
- Altered iron homeostasis due to excess hepcidin production[11,12]
- Reduced production of erythropoietin[13]
- Reduced red cell survival[14]

Anaemia of chronic disease should be considered in patients with a normal/raised ferritin, chronic inflammatory state, low haemoglobin and normal mean cell haemoglobin. It is important to rule out other causes of anaemia (e.g., iron deficiency, haematinic deficiency) before making a diagnosis of ACD.

Figure 1. *Conditions associated with anaemia of chronic disease*

Chronic infection
E.g., osteomyelitis, bacterial endocarditis, tuberculosis, abscesses, bronchiectasis, chronic urinary tract infections
Non-infective chronic inflammatory disorders
Rheumatoid arthritis
Polymyalgia rheumatica
Systemic lupus erythematosus
Inflammatory bowel disease
Malignant diseases
Most commonly metastatic disease
Other associations
Congestive cardiac failure
Ischaemic heart disease
Age > 85 years

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It is important to note that in elderly patients, anaemia is more frequent. The prevalence of anaemia in those > 85 years exceeds 20%. Furthermore, a lower haemoglobin (< 110 g/l) was independently associated with a greater mortality.[15] In addition to age, the severity of the anaemia can often correlate with the severity underlying disorder. Therefore, the successful treatment of the underlying disorder has been shown to improve the anaemia.[16,17] However, in some conditions (e.g., heart failure, incurable cancer) it may not be possible to reverse the underlying pathology. There is some evidence demonstrating that IV iron may be able to overcome hepcidin-associated reticuloendothelial blockade of iron. IV iron is not recommended for use in ACD associated with chronic infections, but may be a possible therapeutic option for ACD associated with malignancy or a chronic inflammatory disorder.

ANAEMIA ASSOCIATED WITH CHRONIC KIDNEY DISEASE

Normocytic anaemia is a common finding in patients with chronic kidney disease. This can be managed with erythropoietin stimulating agents (ESA), following consultation with a renal physician. Nonetheless, ESAs should be avoided if the benefits of improving the anaemia are negated by intractable co-morbidities or where the individual patient prognosis does not warrant such an approach.[18,19]

MACROCYTIC ANAEMIA

The causes of macrocytic anaemia are broadly divided into megaloblastic and non-megaloblastic anaemia. Megaloblastic anaemia is characterised by hypersegmented neutrophils and macro-ovalocytes on peripheral blood film, caused by defective RNA and DNA synthesis. These morphological abnormalities are not seen in non-megaloblastic anaemia.

Clinical history and examination are critical to help narrow down the differential diagnosis of macrocytic anaemia. Figure 2 lists the most common causes of macrocytic anaemia. Alcohol, liver disease, and anti-folate drugs (methotrexate) are common causes of macrocytic anaemia that can be identified through focused history taking. Figure 3 shows an algorithm for the further investigation for macrocytic anaemia. B12 and folate deficiency remain the most common reversible causes of macrocytic anaemia and should therefore be routinely screen for in any patient with a macrocytosis.

Figure 2. *Causes of macrocytic anaemia*

Megaloblastic
Vitamin B12 deficiency
Folate deficiency
Anti-folate drugs (e.g., methotrexate, anti-convulsants)
Drugs interfering with DNA synthesis (e.g., cytarabine, hydroxyurea, 6-mercaptopurine, azidothymidine (AZT))

Non-megaloblastic
Alcohol
Liver disease
Myelodysplastic syndrome (MDS)
Haemolysis
Hypothyroidism
Congenital bone marrow failure syndromes

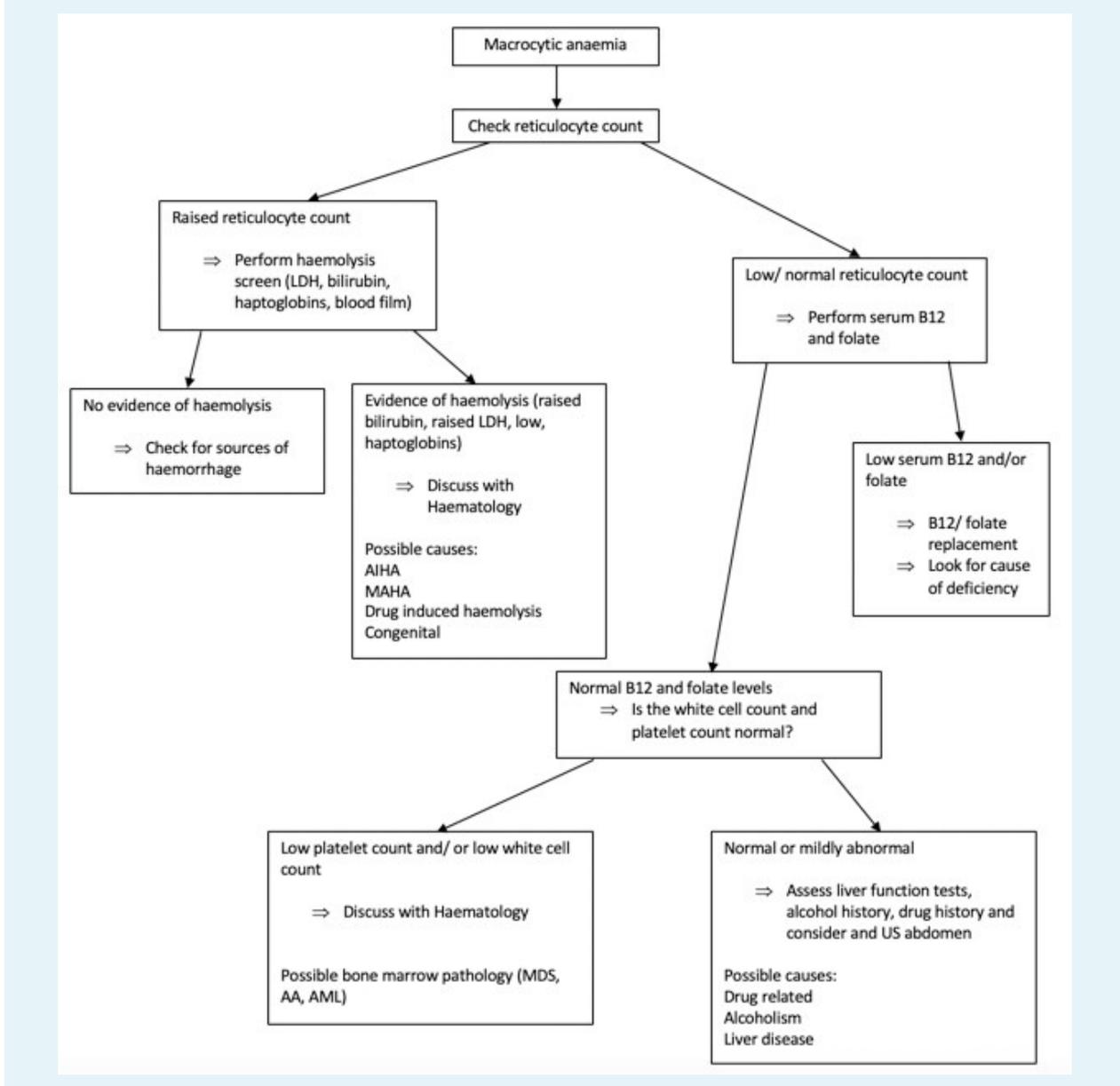As an initial evaluation of macrocytic anaemia, we recommend performing the following investigations:
- Serum vitamin B12 and folate
- Peripheral blood smear
  Red blood cell and white blood cell morphology can help establish the underlying cause (e.g., haematinic deficiency, MDS, haemolysis)
- Reticulocyte count
  Raised reticulocyte count indicates increased destruction of red cells (e.g., haemolysis) with an appropriate bone marrow response

VITAMIN B12 AND FOLATE DEFICIENCY

Vitamin B12 and folate deficiency remain the most common causes of megaloblastic anaemia worldwide. Vitamin B12 deficiency remains a common problem in developed countries, despite the fortification of some food groups. Those over the age of 60 years old are at particular risk, with deficiency or mild depletion found in > 20% of those > 60 years old in a United States (US) population-based study.[20]

Folate deficiency has become increasingly rare in countries where certain food groups have been supplemented with folate. Folate fortification of food in the US has reduced the prevalence of folate deficiency to < 1% of the population.[21] However, in countries where the supplementation of foods does not occur, folate deficiency is subsequently more frequent.[22] A 2015 report on a UK-based epidemiological study published serum folate levels below the WHO threshold for folate deficiency in 15.5% of men and 13.9% of women aged 19-64 years.[23]

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Figure 3. *Algorithm for the investigation of macrocytic anaemia*

AA = aplastic anaemia; AIHI = autoimmune haemolytic anaemia; AML = acute myeloid leukaemia;
LDH = Lactate dehydrogenase; MAHA = microangiopathic haemolytic anaemia; MDS = myelodysplastic syndrome

The underlying aetiology of B12 and folate deficiency is outlined in table 3. Although serum folate and serum B12 (cobalamin levels) are readily available and easy to perform tests, they are both associated with significant false-negative rates. Therefore, in instances where the clinical suspicion of B12 deficiency and serum B12 levels are borderline, it is recommended to perform methylmalonic acid levels or Holotranscobalain levels.[24] Similarly, in the presence of strong clinical suspicion of folate deficiency, but a persistently normal serum folate level (and B12 level), a red cell folate assay may be undertaken. Importantly, this assay is not available in all laboratories and is less cost effective.[25]

HAEMOLYTIC ANAEMIA

The term haemolytic anaemia encompasses anaemias caused by increased red cell turnover, due to abnormal breakdown of red blood cells. This broad category of anaemias includes microangiopathic haemolytic anaemias, autoimmune haemolytic anaemia, haemolysis-associated

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Table 3. *Summary of the aetiology of vitamin B12 and folate deficiency*

Patient population	Vitamin B12 deficiency	Folate deficiency

All age groups	**Inadequate dietary intake**
	   Strict vegan diet at increased risk
	Malabsorption
	   Pernicious anaemia
	Medical conditions
	   Gastric resection
	   Bariatric surgery
	   Coeliac disease
	   Upper GI tract inflammation (e.g., Crohn's disease)
	Infective cause
	   Helicobacter pylori, giardia
		Inadequate dietary intake
		Malabsorption
		   Coeliac disease
		   Upper GI tract inflammation (e.g., Crohn's disease)

Infants and children	**Congenital disorder**
	   Transcobalamin deficiency
	   Cobalamin mutations
	Inadequate dietary intake
		Congenital disorder
		   Mutations in the SLC46A1 gene (proton-coupled folate transporter deficiency)

Older persons	**Malabsorption**
	   Proton pump inhibitors (achlorhydia)
	   Gastritis
		Malabsorption
		   Poor bioavailability

Table 3 summarises the most common causes of B12 and folate deficiencies in the relevant population groups.[24] GI = gastrointestinal

inherited red cell disorders, transfusion-related haemolysis, and haemolysis as a result of drugs, infections, or burns. An elevated reticulocyte count indicates increased red cell turnover and should raise the possibility of haemolysis. Other laboratory markers of haemolysis are:

- Raised lactate dehydrogenase
- Raised bilirubin
- Low haptoglobins
- Peripheral blood smear: spherocytes, bite cells, schistocytes (dependent upon the cause of the haemolytic anaemia)

Patients presenting with features of haemolytic anaemia should be discussed with a haematologist for further advice on investigation, management, and potential referral.

OTHER CAUSES OF MACROCYTIC ANAEMIA

Alcohol and liver disease remain important causes of macrocytosis and macrocytic anaemias. A full medical, drug, and social history should be included in the initial work-up of macrocytic anaemia. Alcoholism is a common cause of macrocytosis in the UK, and alcohol-induced anaemia may persist even after months of abstinence. A history of liver disease or stigmata of chronic liver disease on examination should prompt consideration of liver disease-related anaemia.

Myelodysplastic syndrome and other bone marrow failure syndromes are also important causes of anaemia. In bone marrow pathologies, normocytic or macrocytic anaemia often occurs in combination with thrombocytopenia and/or leucopenia. Peripheral blood film should be performed to look for distinctive morphological abnormalities (e.g., Pseudo Pelget Huet cells, immature granulocytes), which can help guide whether a patient requires further investigation with a bone marrow biopsy.

DISCLOSURES

REFERENCES

1. De Benoist B, et al. Worldwide prevalence of anaemia 1993-2005. WHO Global Database of Anaemia, World Health OrganiZation, 2008.

2. WHO (2015) The global prevalence of anemia in 2011. World Health Organization; https://www.who.int/nutrition/publications/micronutrients/global_prevalence_anaemia_2011/en/

3. Hoffbrand AV, Moss PAH. (2016). Essential Haematology. Wiley Blackwell.

4. Stoffel NU, Cercamondi CI, Brittenham G, et al. Iron absorption from oral iron supplements given on consecutive versus alternate days and as single morning doses versus twice-daily split dosing in iron-depleted women: two open-label, randomised controlled trials. Lancet Haematol. 2017;4;e524-e53.

5. NICE CKS. Anaemia- Iron deficiency. September 2018. https://cks.nice.org.uk/anaemia-iron-deficiency.

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6. Joosten E, Vander-Elst B, Billen J. Small-dose iron absorption testing anemia and non-anemic elderly hospitalised patients. Eur J Haematol. 1997;58:99-103.

7. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant. 2006;21:378-82.

8. Mentzer WC Jr. Differentiation of iron deficiency from thalassaemia trait. Lancet. 1973;1:882.

9. Hoffmann J, Urrechaga E, Aguirre U. Discriminant indices for distinguishing thalassemia and iron deficiency in patients with microcytic anemia: a meta-analysis. Clin Chem Lab Med. 2015;53:1883-94.

10. Sabath DE. Molecular Diagnosis of Thalassemias and Hemoglobinopathies: An ACLPS Critical Review. Am J Clin Pathol. 2017;148:6-15.

11. Sharma S, Nemeth E, Chen YH, et al. Involvement of hepcidin in the anemia of multiple myeloma. Clin Cancer Res. 2008;14:3262-7.

12. de Mast Q, van Dongen-Lases EC, Swinkels DW, et al. Mild increases in serum hepcidin and interleukin-6 concentrations impair iron incorporation in haemoglobin during an experimental human malaria infection. Br J Haematol. 2009;145:657-64.

13. Miller CB, Jones RJ, Piantados S, Abeloff MD, Spivak JL. Decreased erythropoietin response in patients with the anemia of cancer. N Engl J Med. 1990;322:1689-92.

14. Mitlyng BL, Singh JA, Furne JK, Ruddy J, Levitt MD. Use of breath carbon monoxide measurements to assess erythrocyte survival in subjects with chronic diseases. Am J Hematol. 2006;81:432-8.

15. Goodnough LT, Schrier SL. Evaluation and management of anemia in the elderly. Am J Hematol. 2014;89:88-96.

16. Vreugdenhil G, Wognum AW, van Eijk HG, Swaak AJ. Anaemia in rheumatoid arthritis: the role of iron, vitamin B12, and folic acid deficiency, and erythropoietin responsiveness. Ann Rheum Dis. 1990;49:93-8.

17. Bergamaschi, G, Di Sabatino A, Albertini R, et al. Prevalence and pathogenesis of anemia in inflammatory bowel disease. Influence of anti-tumor necrosis factor-alpha treatment. Haematologica. 2010;95:199-205.

18. Pfeffer MA, Burdmann EA, Chen CY, et al. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med. 2009;361:2019-32.

19. National Institute for Health and Care Excellence (NICE) guideline NG8. Chronic kidney disease: managing anaemia. June 2015. https://www.nice.org.uk/guidance/ng8.

20. Pfeiffer CM, Johnson CL, Jain RB, et al. Trends in blood folate and vitamin B-12 concentrations in the United States, 1988-2004. Am J Clin Nutr. 2007;86:718-27.

21. Pfeiffer CM, Hughes JP, Lacher DA, et al. Estimation of trends in serum and RBC folate in the U.S. population from pre- to postfortification using assay-adjusted data from the NHANES 1988-2010. J Nutr. 2012;142:886-93.

22. Bailey RL, West Jr. KP, Black RE. The Epidemiology of Global Micronutrient Deficiencies. Ann Nutr Metab. 2015;66:22-33.

23. PHE (Public Health England) (2015) National Diet and Nutrition Survey Rolling Programme Supplementary report: blood folate results for the UK as a whole, Scotland, Northern Ireland (Years 1 to 4 combined) and Wales (Years 2 to 5 combined). Available at: https://www.gov.uk/government/statistics/national-diet-and- nutrition-survey-supplementary-report-blood-folate.

24. Devalia V, Hamilton MS, Molley AM. Guidelines for the diagnosis and treatment of cobalamin and folate disorders. Br J Haematol. 2014;166:496-513.

25. Farrell CJ, Kirsch SH, Herrmann M. Red cell or serum folate: what to do in clinical practice? Clin Chem Lab Med. 2013;51:555-69.

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