Anaemia in gastroenterology

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Abstract

Anaemia related to the digestive system is mostly secondary to dietary deficiency, malabsorption, or chronic bleeding. We review the World Health Organization definition of anaemia and its morphological classification (microcytic, macrocytic and normocytic). We detail the importance of iron, vitamin B_{12} and folate deficiency anaemia; the interpretation of laboratory tests to differentiate between the causes of anaemia, especially anaemia of chronic disease; and the management options for patients with anaemia caused by gastrointestinal disease.

Keywords anaemia; anaemia of chronic disease; hepcidin; iron deficiency anaemia; vitamin B_{12} and folate

Introduction

Anaemia is a condition in which the number of blood cells (and consequently oxygen-carrying capacity) is insufficient to meet physiological needs. Relevant to gastroenterology, anaemia is usually related to bleeding (overt and occult) or malabsorption. The concept of chronic-disorder anaemia is a frequent cause of confusion and uncertainty, which will be discussed.

Anaemia is defined as a decrease in haemoglobin concentration from an individual baseline value. The World Health Organization (WHO) has defined a threshold for anaemia when the blood concentration of haemoglobin falls below 130 g/litre in men or 120 g/litre in women. This rule does not apply to infants, children and pregnant women, who have their own reference ranges that set lower limits of haemoglobin concentration. This article will deal only with anaemia in adults.

Classification of anaemia

In general, the differential diagnosis of anaemia can be substantially narrowed by subcategorization into 'microcytic', 'normocytic', and 'macrocytic' subtypes on the basis of mean corpuscular volume (MCV). However, such classification is a starting point and is not infallible.[1] Anaemia also can be classified according to the form of clinical presentation as acute (usually bleeding or haemolysis) or chronic.[2]

Microcytic anaemia

The most common cause of microcytic anaemia is iron deficiency. Other causes are listed in Table 1. As this article is focussing on anaemia in reference to the gastrointestinal tract, the following discussion will consider iron deficiency alone.

Iron deficiency anaemia

Iron deficiency anaemia (IDA) has a prevalence of 2–5% among adult men and post-menopausal women in the developed world and is a common cause of referral to gastroenterologists (4–13% of referrals). Whereas menstrual blood loss is the commonest cause of IDA in pre-menopausal women, blood loss from the gastrointestinal (GI) tract is the commonest cause in adult men and post-menopausal women[3] (Table 2).

Pathophysiology

Iron homeostasis is dependent on regulatory feedback between the body's iron requirements and intestinal iron absorption. Nearly all absorption of dietary iron occurs in the duodenum.[4] Here, dietary iron is reduced to the ferrous state, which is transported across the enterocyte by a specific transporter called a divalent metal transporter. Some of this iron is stored in enterocytes, from which it is subsequently excreted into the gut lumen when the mucosa denudes. However, most of the iron is transferred out of the enterocyte in to plasma by the basolateral transporter, ferroportin. Iron released into the circulation binds to transferrin and is transported to sites of use and storage.

Iron is mainly used in the production of haemoglobin by erythroid precursors. When senescent erythrocytes undergo phagocytosis by macrophages, iron is exported through the same ferroportin transporter back into the plasma. Hepatocytes serve as a storage reservoir for iron, taking up dietary iron from portal blood and, at times of increased demand, releasing iron into the circulation by way of ferroportin. The ferroportin-mediated release of iron from enterocytes, macrophages, and hepatocytes is recognized as an important determinant of iron homeostasis.

Hepcidin is a principal hormone in the liver and is now thought to play a central role in iron homeostasis. Hepcidin secreted into the circulation down-regulates the ferroportin-mediated release of iron from enterocytes, macrophages, and hepatocytes.[4] In the enterocyte, hepcidin decreases basolateral iron transfer and thus dietary iron absorption. In reticuloendothelial macrophages and hepatocytes, hepcidin causes a decrease in iron export and thus an increase in stored iron.

Diagnosis

The initial diagnosis of IDA is usually made with reference to haematological variables, such as haemoglobin, MCV and serum ferritin. However, serum ferritin is an acute phase protein that will be elevated in situations of inflammation, and this can mask iron deficiency. When there is doubt, measurement of iron, iron saturation and total iron-binding capacity (TIBC) is an adequate alternative.

The investigations required to clarify the cause of IDA will depend in part on the presentation. Investigations that may be required are as follows.

- Gastroscopy and colonoscopy are recommended for asymptomatic post-menopausal women and all men aged

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Causes of anaemia according to morphological classification

Microcytic (MCV <82 fl)	Normocytic (MCV 82–99 fl)	Macrocytic (MCV >100 fl)
Iron deficiency anaemia (IDA)	Acute blood loss	Haemolysis/reticulocytosis
Thalassaemia	Anaemia of chronic disease	Nutritional (B_{12} and folate deficiency)
Sideroblastic anaemia	Nutritional causes (mixed Fe, B_{12} &/or folate deficiency)	Alcohol
Lead poisoning	Renal failure	Drugs
	Hypothyroidism	Hypothyroidism
	Bone marrow failure (e.g. aplastic anaemia)	Splenectomy

MCV, mean corpuscular volume.

Table 1

50 years or older,[3] as age is the strongest predictor of malignant pathology in patients with IDA.[5]

- Coeliac serology, either anti-endomysial antibody (EMA) or anti-tissue transglutaminase antibody (tTG) should be taken at presentation.
- Virtual computed tomographic (CT) colonoscopy has similar rate of detection of significant pathology compared to colonoscopy, although not for more subtle pathology (e.g. polyps <1 cm).[6] This can be used as an alternative to colonoscopy where colonoscopy has failed or the risk of the procedure is too high (e.g. frail elderly). Because of this new technology, the barium enema examination is now performed much less frequently, and in due course will probably become redundant.
- Small bowel imaging (barium follow-through, magnetic resonance imaging (MRI), capsule endoscopy, and balloon enteroscopy) is reserved for transfusion-dependent patients or those with clear gastrointestinal symptoms, in whom gastroscopy and colonoscopy reveal no abnormality.
- A CT scan of the abdomen can be a helpful adjunct to the endoscopic work-up, and should be considered in all patients in whom there is a strong suspicion of pathology eluding detection.

Management of IDA

Treatment should aim to restore normal haemoglobin concentration and replenish the iron stores. Failure to achieve this should be a trigger to further evaluation.[1]

- Oral iron preparations are usually enough to achieve this goal but should be maintained for a minimum of 3 months to replete iron stores. Aim for ferrous sulphate 200 mg twice daily or equivalent.
- Ascorbic acid (250–500 mg twice daily with the iron preparation) may enhance iron absorption, and can be used as a supplement.
- Parenteral iron can be used for patients where there are problems with compliance, or intolerance to oral preparations.

Blood transfusions should be reserved for symptomatic patients, patients where ongoing bleeding is suspected and patients with, or at risk of, cardiovascular instability which includes acute coronary syndrome with ischaemia. Haemoglobulin concentrations should aim towards a safe range 80–100 g/litre in this high-risk group.

Normocytic anaemia

Normocytic anaemia can represent a decreased production of normal-sized red blood cells (e.g. anaemia of chronic disease, aplastic anaemia); an increased destruction or loss of red blood cells (e.g. haemolysis, post-haemorrhagic anaemia); an uncompensated increase in plasma volume (e.g. pregnancy, fluid overload); or a mixture of conditions producing microcytic and macrocytic anaemias.

The most common cause of normocytic anaemia is anaemia of chronic disease (ACD). Gastrointestinal causes mainly involve nutritional deficiencies, specifically a combination of iron and B_{12}/folate. Acute blood loss can also cause a normocytic anaemia, but this is usually evident from the patient's presentation, and investigation and management will be directed to the source of the bleeding.

Cause of iron deficiency anaemia[2]

Occult gastrointestinal (GI) blood loss	Malabsorption	Non-GI blood loss
GI tumours	Coeliac disease	Menstruation
Benign peptic ulceration	Infection (giardiasis, TB, helminths)	Other gynaecological pathology
Angiodysplasia	Immunodeficiency	Blood donation
Gastric ectasia ('watermelon' stomach)	Crohn's disease	
	Post-surgery (gastrectomy, vagotomy, bypass surgery (e.g. bariatric procedures))	
	Radiation enteritis	

Table 2