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Review Article

Anaemia as a problem, GP approach

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Short Title: Anaemia in the primary care settings

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Abstract

**Background:** Anaemia is a presentation of an underlying disease or deficiency. As stated by the World Health Organization, anaemia is defined as hemoglobin (Hb) levels <12.0 g/dl in women and <13.0 g/dl in men. This review of clinical practice aimed to determine diagnostic approach to anaemia in primary care patients.

**Summary:** The nutritional deficiencies, medications, chronic inflammatory conditions, malignancy, renal dysfunction, bone marrow and inherent disorders contribute to anaemia development. Anaemia is classified and diagnosed by the values of hematological parameters, the underlying pathological mechanism and patient history. The diagnostic approach of anaemia in primary care settings is focused on history, physical examination, laboratory findings including complete blood cell count, reticulocyte count and peripheral smear examination, fecal occult blood test and ultrasound findings.

**Key Messages:** Anemia is the most common haematological disorder that represents a major health burden worldwide. Hemoglobin levels alter with gender, ethnicity and physiological status. Anaemia is often multifactorial. The evaluation of a patient with anaemia in primary care includes clinical history, physical examination, laboratory findings with fecal occult blood test and abdominal ultrasound. The wide variations in general practice in European countries are based on different health care systems, but also knowledge of GPs that reflect educational and research policy.

Introduction

Anaemia is the most common hematological disorder that represents a major health burden worldwide affecting more than 2 billion people [1, 2]. It is a presentation of an underlying condition, defined as a reduction in the proportion of the red blood cells (RBC) [1, 2, 3]. A wide variety of factors contribute to the development of anaemia including nutritional deficiencies, chronic disorders, inflammatory process, medications, malignancy, renal dysfunction, hereditary diseases and bone marrow disorders [1,3]. Also, a higher prevalence of anaemia has been associated with a number of medical conditions such as essential hypertension, congestive heart failure and coronary artery disease, hypothyroidism and rheumatologic diseases [1].

According to the World Health Organization (WHO), anaemia is determined by hemoglobin (Hb) levels lower than 13g/dl in adult males and 12g/dl in females [4]. Nevertheless, Hb levels also alter with ethnicity and physiological status [1,2,3]. Due to the ageing of the population, an increase of anaemia has been registered in elderly people and recently defined by hemoglobin levels less than 12g/dl in both genders [2, 3]. As stated by the WHO in 2016, the estimated prevalence of anaemia in women of childbearing age was at 30.2% worldwide, while in Europe was at 20.2% [5]. Reduction of hemoglobin levels in pregnancy as a result of physiological hemodilution is defined as pseudoanæmia, maximal during 20-24 weeks of gestation [3, 5]. Furthermore, increased odds of having anaemia were determined in African-Americans and Hispanic race compared to Caucasians [1,2].

Apart from age, gender and racial differences, anaemia is recognized as an important risk factor to morbid mortality with serious impact on decreased quality of life, physical and mental capacities, psychiatric disorders and susceptibility to infections [6-9]. Although the majority cases of anaemia are diagnosed by general practitioners (GPs), studies about anaemia management in primary care settings are still scarce across different European countries [10, 11]. The wide variations in primary
care units in European countries are based on different health care systems, but also knowledge and awareness of GPs that reflect educational and research policy [10, 11].

Main Text

Classification and diagnosis of anaemia

The direct management of anaemia depends on the underlying cause. The etiology based approach is important in preventing, diagnosing and treating anaemia [2, 12]. While acute anaemia occurs predominantly due to acute blood loss or acute hemolysis, chronic anaemia is more frequent and secondary to various causes [12].

Using a kinetic approach, anaemias are classified based on the responsible pathophysiological mechanism including decreased red blood cell (RBC) production, increased RBC destruction and blood loss (shown in Figure 1) [13]. The reticulocyte count is used to estimate the degree of effective erythropoiesis with corrected reticulocyte count less than 2% in hypoproliferative anaemia and more than 2% in hyperproliferative anaemia [2]. According to morphologic approach, anaemias are categorized based on the size of RBC measured by mean corpuscular volume (MCV) into microcytic anaemia (MCV<80 fl), normocytic anaemia (MCV 80-100 fl) and macrocytic anaemia (MCV>100 fl) (shown in Figure 2) [13].

The most common cause of anemia still remains iron deficiency (ID)[2, 6]. The aetiology of iron deficiency anaemia (IDA) is variable and associated to a number of factors decreasing iron intake and absorption or increasing demand and loss. Various aetiologies of IDA include a number of disorders including Helicobacter pylori infection, celiac disease, inflammatory bowel disease, atrophic gastritis due to long-term use of proton pump inhibitors (PPIs), intoxication with heavy metals or parasitic disease [6, 9, 10].

Clinical presentation and features of anemia

The manifestation of symptoms in patients depend on the etiology of anaemia, the severity of onset and presence of other comorbidities. According to conducted investigations, the majority of patients become symptomatic when hemoglobin values drop below 7.0 g/dL [2, 13, 14].

Obtaining a good history from a patient with anaemia is important for further diagnostic algorithm with questions addressing prior blood loss, duration of anaemia, associated features and comorbidities, use of PPIs, aspirin and nonsteroidal antiinflammatory drugs [15].

The evaluation of patient includes a physical examination, presence of common signs of anaemia such as pallor of the conjunctive and mucous membranes, fastigie, dizziness, dyspnoea, tachycardia and heart murmur [15, 16]. Also, significant signs of anaemia are cheliosis and glositis indicating malnutrition (e.g. vitamin deficiency), jaundice and dark colored urin due to hemolysis, hepatosplenomegaly and bleeding (maelena, haematuria, etc) [16, 17]. Patints with severe life-threatening anaemia can experience sweating, thirst, cold extremities, oedema of lower limbs, develop respiratory distress and shock [2, 17]. Nevertheless, very low hemoglobin levels may be tolerated in the settings of slowly progressing anaemia [18].

Laboratory assessment of anaemia

The initial array of laboratory evaluation encompass complete blood cell count with differential reticulocyte count, peripheral smear and biochemical tests including iron profile (iron, ferritin, TIBC), macrocytosis and hemolysis profile (vitamin B12, folate, methylmalonic acid, homocysteine; haptoglobin, indirect bilirubin, lactate dehydrogenase), serum creatinine, erythropoietin and estimated glomerular filtration rate, thyroid function tests and liver function tests, coagulation screen and hemoglobin electrophoresis [15, 18]. Iron deficiency anaemia is the most common, estimated to be present in up to 2% of the adult population and remaining one of the top five leading causes of years lived with disability in humans [19, 20]. Nevertheless, GPs have to be aware of overlapping conditions that can mask the macrocytosis expression of megaloblastic anaemia.

Approximately one third of anemic elderly individuals have a nutritional basis for anaemia with coexisting iron depletion and nutritional deficiency of folate or vitamin B12 [4, 14].

Fecal occult blood testing (FOBT) evaluates the presence of red blood cells in the faeces including guaiac FOBT (gFOBT) and fecal immunological tests (FIT) [21].
The first fecal test used in colorectal carcinoma (CRC) screening was gFOBT. Although previous studies stated that an annual gFOBT can reduce incidence of CRC, the accuracy of this test is questionable [21]. The test is based on heme detection in the feces, which reacts with a hydrogen peroxide-based developer reagent to oxidize guaiac and turns blue [21]. Nevertheless, moderate concentrations of heme are needed to acquire color change. Furthermore, gFOBT depends on pure oxidation process while influence of peroxidases in food can lead to false positive results [21, 22]. Also, administration of antioxidants such as vitamin C can result in false negativity of gFOBT [21]. Therefore, food restrictions including red meat, plants with peroxidases must be implemented before the gFOBT. Limitations of gFOBT test are shown in Table 1.

The fecal immunochemical testing assesses the quantity of hemoglobin in the feces. In recent years, FIT has been endorsed by the UK’s National Institute for Health and Care Excellence (NICE) guideline for CRC screening [21]. Also, the World Endoscopy Organization Expert Working Group recommended FIT as the preferred technology compared to gFOBT because there is no influence by other fecal constituents, including medication and dietary products [23]. According to recent data, FIT have greater values than gFOBT in detecting neoplasms in the lower gastrointestinal tract. Namely, three-sample FIT in high-risk patients could improve the specificity of FIT by 35% compared with a single test [21, 24].

Nevertheless, broad implementation of fecal occult blood testing in all low-risk symptomatic patients can lead to endoscopy capacity crisis due to patients with false positive results or delayed diagnosis for patients with false-negative tests [25]. According to NICE diagnostic guideline from 2017, fecal blood testing should be performed in patients without rectal bleeding who have unexplained symptoms, but do not meet criteria for suspected cancer [26]. Hopkins R et al. reported microcytosis as a predictor of underlying cancer even in cases when haemoglobin is normal, especially in males [27].

Individuals with positive FOBT must be referred for further investigations. According to conducted data, the availability of open access endoscopy ranged from 28% in Poland to over 80% in Holland, Czech and UK [10]. Also, 92% of Czech respondents, 52% in Spain, 45% in The Netherlands, 42% in Greece, 27% in UK and 21% in Poland reported open access to colonoscopy [10].

Rectal bleeding in general practice
The reported GP approach to patients with low risk rectal bleeding, below the age of 50 and presenting without alarm signals, include rectal and abdominal examination [10]. Nevertheless, patients with rectal bleeding associated with alarm signals were referred to endoscopic examination, with reported 95% of GPs in the UK and 70% in Poland using a special referral arrangement that provides a specialist appointment within 2 weeks [10]. While GPs from Spain, Holland, Poland and Czech would make a urgent referral in 30-50% of cases, up to 60% would arrange a colonoscopy [10]. Also, the awareness of national guideline for colorectal cancer risk differs between countries, from 29% in the Netherlands to 94% in the Czech Republic [10]. Colorectal cancer is often mistaken for hemorrhoids due to similarity of clinical manifestations, causing delayed diagnosis and ineffective treatments. The high awareness of CRC screening guidelines in some countries is based on established screening programmes in these countries. While Portugal and Spain, Belgium, the United Kingdom, the Netherlands, Denmark, Slovenia, Lithuania, Estonia and Finland have strong primary care system, relatively weak primary care organization is reported in countries of central and south-eastern Europe and Turkey [11].

Abdominal Ultrasound in anaemia diagnostics
In the primary care settings, ultrasound (US) of the abdomen as an essential non-invasive diagnostic approach can detect possible alterations such as abdominal masses that can address the possible etiology of detected anaemia. The US findings of liver, spleen, bowel, stomach, gynecologic or lymph nodes alterations can guide further investigation in patients with anaemia [28]. However, the role of abdominal ultrasound in evaluation of anemia is inferior to endoscopic examination including upper and lower gastrointestinal endoscopy.

According to Focused Assessment with Sonography for Trauma (FAST), rapid detection of free fluid can be suggestive for hemoperitoneum, hemothorax, and/or hemopericardium in patients with
anaemia due to acute blood loss [28]. The use of FAST has been reported to decrease the abdominal CT use by approximately 50% [28, 29]. The early detection of bleeding in non-traumatic cases is based on sonographic markers of hypovolemia including the diameter of the inferior cave vein and the thickness of the left ventricle [28].

The use of US in patients with anaemia due to intestinal diseases can be helpful. Namely, the European Crohn’s and Colitis Organisation (ECCO) guidelines highlighted ultrasonography as the imaging technique of choice for screening inflammatory bowel disease (IBD) patients [30]. While ultrasonographic signs of thickening, decreased compressibility and increased vascularisation of the bowel wall can be detected in IBD, “pseudo-kidney sign” (hypoechoic bowel wall thickening and irregular contour, loss of stratification of the wall layers and the absence of normal peristalsis) can be suggestive of CRC [28, 31]. Detection of liver lesions suggesting metastasis can indicate presence of malignancy [28, 31]. The US findings in lymphoproliferative disorders presented with anemia include splenomegaly and enlarged abdominal lymph nodes [28]. In patients with clinical signs of malnutrition and anaemia, US may identify the radiological signs of chronic pancreatitis (reduction in the size of the pancreas, irregular profiles, parenchymal calcifications, or dilated Wirsung duct with stones)[32].

**Conclusion**

General practitioners are the first contact of patient with the healthcare system. In addition to the limited research evidence from primary care units, the scarce recommendations for anaemia may also be driven by concerns about overwhelmed endoscopy services by referrals of patients or local priorities and beliefs about the costs and benefits of diagnostic testing.
Statements
All papers must contain the following statements after the main body of the text and before the reference list:

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Tamara Milovanovic wrote and designed the review article, Sanja Dragasevic wrote the article and performed the review of the literature, Andreja Nebojsa Nikolic, Milica Stojkovic Lalosevic and Dusan D Popovic analyzed current novelty data, Aleksandra Pavlovic-Markovic and Miodrag N Krstic provided guidance in this research.
References


**Figure Legends**

Fig. 1. Kinetic approach in classification of anemias
Fig. 2. Morphologic approach in classification of anemias
Figure 1: Kinetic approach in classification of anaemias
Figure 2: Morphologic approach in classification of anaemias
Table 1. Limitations of gFOBT

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<thead>
<tr>
<th>Exogenous peroxidase activity</th>
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<td>red meat</td>
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<td>Storage of slides</td>
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<td>uncooked fruits and vegetables (turnips, horseradish, broccoli...)</td>
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<td>Medications</td>
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