

Chapter 2

Non-Invasive Office Screening Methods



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Office Base Screening

Small intestinal bleeding accounts for 5–10% of patients who present with gastrointestinal bleeding and remains a relatively uncommon cause [1]. As has previously been defined occult gastrointestinal bleeding is not visible to either the patient or the physician and is detected by either by fecal occult blood testing (FOBT), or iron deficiency anemia with or without a positive FOBT [1–3]. Unfortunately there are no guidelines or recommendations on screening this population. As a result non-invasive office base screening is based on the recommendations for accessing iron deficiency anemia as well as colorectal cancer screening. This is in addition to obtaining a thorough history and physical.

Anemia

The World Health Organization (WHO) defines anemia, as a condition in which the number of red cells or their oxygen carrying capacity is not sufficient to meet physiologic needs [4]. The WHO estimates the global burden of disease for anemia is about 30% of the world population [5–7]. The diagnosis is often made on laboratory full blood count testing for screening or the evaluation of another condition [4]. Anemia is associated with significant morbidity and mortality. A decrease in quality of life, cognitive function and work productivity have been reported [5, 7, 8].

The most common anemia is iron deficiency anemia (IDA) representing about 50% of all anemias' worldwide. Total body iron ranges from three to four grams

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with a net daily loss of one to two milligrams [9]. This is usually balanced through dietary iron. Iron deficiency anemia has a high prevalence in women [8]. The WHO reported in 1992 that 37% of all women were anemic and in the United States 12% of reproductive age women had iron deficiency. In addition 4% of women 20–49 years of age and 3% of women 50–69 years of age had iron deficiency anemia [5, 8, 9]. In addition iron deficiency is the most common nutritional deficiency worldwide. Despite this and IDA being so prevalent there are no consistent guidelines on the screening for IDA.

Guidelines

In the United States the Center for Disease Control and Prevention (CDC) recommends screening females of childbearing age every five to ten years and more frequently if clinically indicated [10]. In addition they recommend screening pregnant women at the first prenatal visit [10]. This contrasts the United States preventive Services Task Force (USPSTF) who finding insufficient evidence to recommend routine screening [11].

Making the Diagnosis of Iron Deficiency Anemia

Commonly the evaluation for anemia is initiated from findings picked up on history and physical. The diagnosis can be difficult to make in some cases where there are co-contaminant inflammatory states. Some findings have been associated with all anemias such as conjunctival pallor, nail-bed pallor, absence of nail bed blanching and palmar crease pallor [7, 12]. Other findings are specific for IDA (see Table 2.1). For example some of the symptoms associated with IDA include paleness, fatigue (in iron deficiency with or without anemia), dyspnea, headache, restless leg syndrome, and pica symptoms [5, 7, 8]. Physical findings commonly seen include alopecia, atrophic glossitis, dry skin [7]. In addition IDA anemia should be suspected in patients who are undergoing hemodialysis, middle age obese individuals, and obesity at any age [6]. Certain medications have also been associated with IDA such as Antacids, H2 blockers, Proton pump inhibitors, Nonsteroidal anti-inflammatory drugs (NSAIDs), aspirin, Zinc, and manganese supplements [8].

Once IDA is suspected and a complete blood count (CBC) confirms the presence of anemia several red blood cells indices help suggest IDA. A mean corpuscular volume (MCV) below 80 fL has a reported sensitivity of 97.6% for IDA; however IDA can present with normocytic anemia 40% of the time [8]. In addition the MCV may be low in other conditions such as thalassemia. The Mentzer index, which is the ratio of MCV to red blood cell count, can be used to help distinguish between IDA and Thalassemia trait [13]. A value greater than 13 suggests IDA. The red

Table 2.1 Signs and Symptoms of Iron Deficiency Anemia

Signs	Symptoms
Pallor	Fatigue
Alopecia	Dyspnea
Atrophic glossitis	Restless leg syndrome
Angular stomatitis	Headache
Defects of the nail bed (koilonychia and Mees lines)	Pica symptoms
Dry skin	Neurocognitive dysfunction
Dry and damaged hair	Angina pectoris
Cardiac murmur	Vertigo
Tachycardia	Tinnitus
Syncope	Taste disturbance
Hemodynamic instability	
Plummer-Vinson syndrome	

Table 2.2 Test for the diagnosis of iron deficiency anemia

Test	Limitations
Serum Iron/TIBC	Diurnal variations
Percent transferrin saturation	Not diagnostic by itself
Ferritin	Increased during inflammatory states independently of iron studies
Reticulocyte count	Not diagnostic
Soluble transferrin receptor (sTFRC)	Lacks standardization among different immune assays
Serum hepcidin	Not readily available in many laboratories
Reticulocyte hemoglobin concentration	Iron availability can be influenced by multiple factors

blood cell distribution width (RDW) may be elevated in patients with IDA and normal in patients with thalassemia [8].

Bone marrow aspiration and Perl’s staining is the gold standard for the diagnosis of iron deficiency (ID), as it shows an absence of stainable iron in the bone marrow [6]. However other test are available which can reliably diagnose IDA. These test include serum iron, total iron binding capacity (TIBC), percent transferrin saturation (TSAT), serum ferritin, reticulocyte count, soluble (serum) transferrin receptor levels, serum hepcidin, and reticulocyte hemoglobin concentration (CHr) (see Table 2.2) [5, 6]. A peripheral blood smears can also give valuable information in diagnosing ID (Fig. 2.1).

Serum Iron/TIBC

Serum iron represents the amount of iron bound to transferrin. This allows iron to be incorporated into hemoglobin in developing erythroblast. The transferrin bound iron pool has a high turnover that can be up to six times a day. This in conjunction

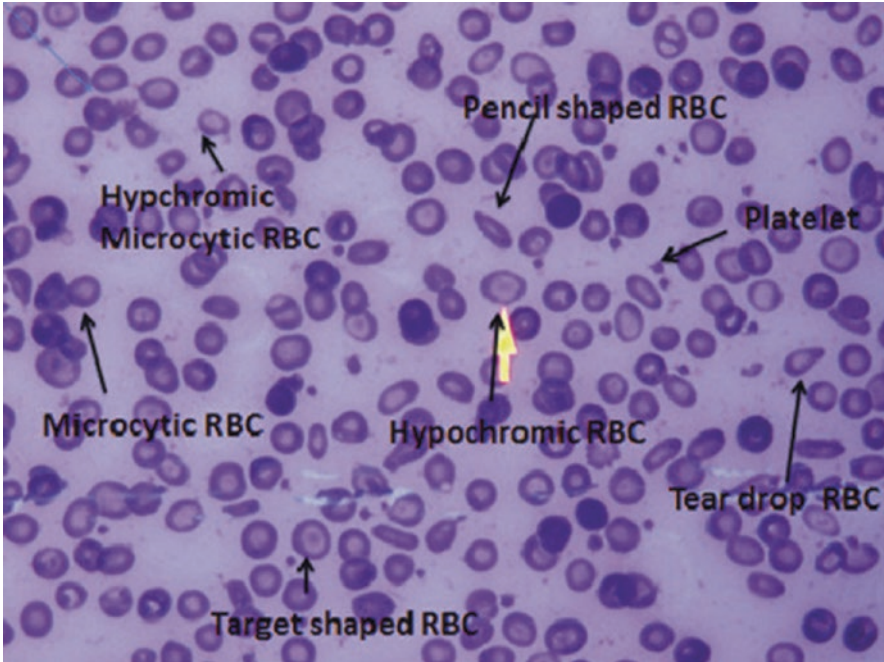


Fig. 2.1 Peripheral blood film with changes attributed to iron deficiency anemia [32]. (Copyright © 2012, Springer Nature)

with diurnal variation, and external factors make serum iron unreliable in diagnosing ID [5]. TIBC (expressed in micrograms/deciliter) is a functional measure of the level of transferrin circulating; an elevated TIBC is consistent with IDA [5, 8, 14].

Percent Transferrin Saturation

The TSAT is calculated by using the formula $(\text{Iron} \times 100) / \text{TIBC}$ and is expressed as a percent [8]. A very low TSAT usually less than 10–15% is consistent with IDA however it is not diagnostic by itself [5, 8].

Ferritin

In the absence of inflammation, ferritin (microgram/Liter) correlates with total body iron stores. A ferritin level of less than 15 microgram/L in patients older than five years old is diagnostic for ID and has a sensitivity of 59% and a specificity of 99% [7, 9]. The American Gastroenterology Association (AGA) gastrointestinal evaluation of iron deficiency anemia recommend using a ferritin threshold of less than 45 microgram/L to diagnose iron deficiency [9]. At this level the sensitivity of

ferritin is 85% and the specificity is 92%. Unfortunately ferritin levels increase during inflammatory states independently of iron stores [5, 7]. In acute and chronic inflammatory disorders such as malignant disease, liver or kidney disease ferritin levels of 50 micrograms/L or higher may still have ID. As such cut off of 100 micrograms/L and 200 micrograms/L have been suggested in patients with chronic kidney disease and hemodialysis respectively [7]. The AGA suggest using adjuvant testing to help establish the diagnosis of iron deficiency such as serum iron, transferrin saturation, or C-reactive protein [9].

Reticulocyte Count

A corrected reticulocyte count expressed as a percent of red blood cells can provide an estimate of appropriate bone marrow production compared to normal with an index greater than two being incompatible with IDA [5].

Soluble Transferrin Receptor (sTFRC)

Soluble transferrin receptor is cleaved by the membrane protease in the erythroid cells when not stabilized by diferric transferrin. In the presence of iron the TFRC mRNA is destabilized. In the absence of iron the mRNA becomes stable resulting in an up regulation of the TFRC [5, 6]. TRFC levels are not affected by inflammation and it has been suggested as a tool in differentiating IDA and anemia of chronic disease (ACD) [6]. It can also be used in identifying ID in patients with inflammatory conditions [5, 6]. Although it is not as sensitive and specific as a ferritin level of less the 30 microgram/L it does have a sensitivity and specificity of 86 and 75% respectively [6]. Unfortunately there is a lack of standardization among different immune assays. This results in difficulty comparing studies and translating into routine clinical practice.

Serum Hepcidin

Is a biomarker that is decreased in ID and are undetectable in severe IDA. As with TRFC there are different test available and it is not readily available in many laboratory. However studies have shown promise and this may be available in the future [6].

Reticulocyte Hemoglobin Concentration

The CHr measures recent iron availability and it has not been widely adopted due to the fact that iron availability can be influenced by a number of factors [5].

Stool Testing for Occult Blood

Occult gastrointestinal bleeding should be suspected in patients with positive stool testing for blood [1, 2]. In most cases these patients would have had testing done as an alternative for colorectal cancer screening (CRS). Colorectal cancer is the second leading cause of cancer death in the United States and the third leading cancer diagnosis [15, 16]. Colorectal cancer screening is recommended for average risk patients from the age of 50 to 75 by most society guidelines and expert groups [17–20]. The preferred modality is colonoscopy however fecal occult blood testing (FOBT) has been shown to be an effective screening tool and is an alternative for patients who do not wish to have a colonoscopy as the initial test. In some studies guaiac based or immunochemical have been shown to decrease colorectal cancer mortality by about 30% [21]. Screening can be done with sensitive guaiac-based fecal occult blood testing, fecal immunochemical testing (FIT), or multi-target stool DNA testing [18, 22]. These tests detect blood or shredded debris by polyps, adenomas or cancers [21]. Guidelines recommend high sensitivity guaiac based FOBT annually or biennially and, FIT annually (see Table 2.3) [21].

Sensitive Guaiac-Based Fecal Occult Blood Testing

Guaiac-based screening test (Hemoccult SENSAs, Beckman Coulter) have been shown to reduce CRC death [18, 23]. However they are less sensitive than FIT test. The reported sensitivity and specificity of these two tests are 62–70% and 87–96% respectively [18, 23]. In addition there has been concern about dietary restrictions when using guaiac based testing. Certain foods, vitamins, or medications can produce false positive and false negative so in general dietary restrictions are recommended [24]. The current recommendation is to obtain six stool samples from three bowel movements on three separate days. The sample should be returned to the lab within 14 days [25]. A single digital rectal exam sample is not sensitive for CRS

Table 2.3 Stool testing for occult blood

Test	Sensitivity	Specificity
Guaiac-based screening test (Hemoccult SENSAs, Beckman Coulter)	62–70%	87–96%
Fecal immunochemical testing (FIT)		
OC-light test using a cutoff of 10 microgram hemoglobin per gram of feces	79–88%	91–93%
OC FIT-CHEK family of tests using a cutoff of 20 microgram hemoglobin per gram of feces	73–75%	91–95%
Multi-target stool DNA testing (FIT-DNA)	92% (95% CI 84–97%)	84% (95% CI 84–85%)

Bibbins-Domingo et al. [33]

however a positive result would warrant further investigation. Another limitation of the test has been its low ability to detect polyps and its inability to determine clinically significant disease [24].

Fecal Immunochemical Testing (FIT)

In the United States there are multiple FITs from different manufacturers with different test methods and performance characteristics [23]. The OC FIT-CHEK family of FITs has the highest sensitivity and specificity. The OC-Light test using a cutoff of 10 microgram hemoglobin per gram of feces to detect CRC has sensitivity and specificity of 79–88% and 91–93%, respectively; For the OC FIT-CHEK family of tests using a cutoff of 20 microgram hemoglobin per gram of feces it ranges from 73% to 75% and 91% to 95%, respectively as reported by Lin et al. [23]. Dickerson et al. reported a sensitivity of 79% and specificity of 94% for available FIT test for the detection of CRC [25]. A study performed by Goede et al. comparing guaiac fecal occult blood to FIT testing in Ontario, Canada showed that switching to FIT testing at a high cut-off increased health benefits without increasing colonoscopy demands [26]. The test provides several advantages including only requiring one sample and does not require dietary modifications [18].

Multi-Target Stool DNA Testing (FIT-DNA)

Multi-target stool DNA testing has increased single test sensitivity however it is less specific than FIT alone. The test characteristics of the only FIT-DNA test available in the United States (Cologuard; Exact Sciences) were studied and the sensitivity and specificity to detect colorectal cancer was 92% and 84% respectively. Its sensitivity to detect advanced precancerous lesions was 42%, and its specificity to detect “all non-advanced findings” was 87% [18, 27]. Although sensitivity is the most important aspect of cancer screening test, specificity is also important as it limits the amount of false positive results and hence unnecessary interventions [27].

Other Considerations

Celiac Disease

Celiac disease, which is also known as gluten-sensitivity enteropathy, is a systemic disorder that affects about 1% of Americans [28]. Celiac disease results in a T-Cell-mediated immune response to gluten. This immune response in people whom have

the genetic predisposition results in the malabsorption of nutrients due to damage to the small intestine [28]. Celiac disease is often under diagnosed and in the United States estimates 10–15% of persons with this condition are diagnosed [28]. Undiagnosed celiac disease is a significant cause of IDA and in general screening for it is recommended in patients presenting with IDA [4]. Screening usually involves serum IgA antibodies to tissue transglutaminase (tTG) or Transglutaminase 2 (TG2) [28]. In addition four biopsies from the second part of the duodenum are recommended during endoscopy have been recommended [4]. However the AGA recommends against routine small bowel biopsy unless serologic testing is positive [9]. Other indications for celiac disease screening as well as genetic modalities are beyond the scope of this chapter.

Infectious Diseases

Infectious diseases, particularly parasitic diseases lead to extracorporeal iron losses and anemia of inflammation [29]. The World Health Organization has classified a severe health problem in over 60 developing countries for children under five as well as pregnant women. One of the main reasons is extracorporeal iron loss [29]. Hookworm is the most important parasitic disease in humans and the burden is mainly due to extra-corporeal blood loss [29]. Other parasites include Schistosomiasis and less commonly Trichuris. In the right setting such as in returning travelers or recent immigrants from high-risk areas testing stool examination for ova and parasite can be performed. More advanced testing such as polymerase chain reaction (PCR), serology or antigen testing is beyond the scope of this chapter.

Helicobacter pylori (*H. pylori*) is a common chronic bacterial infection which has been associated with peptic ulcer disease and gastric cancer which can result in iron deficiency in addition plays a role in unexplained IDA. Both the American College of Gastroenterology (ACG) and the AGA recommend screening patients with unexplained ID for *H. Pylori* [9, 30]. The AGA goes further and recommends noninvasive testing for *H. Pylori* with treatment if positive over no testing [9]. This is preferred over routine gastric biopsy in patients with unremarkable endoscopies. An approach of urea breath testing after a negative endoscopy was noted to have significant cost savings when compared with routine gastric biopsy at the time of the endoscopy [9]. This resulted in minimal harm from the short term delay in diagnosis from false-negative noninvasive testing. Other available noninvasive test for *H. Pylori* include stool antigen testing and serology. However a recent Cochrane database review found that for most people urea breath tests had a high diagnostic accuracy when compared to serology and stool antigen testing in the diagnosis of *H. Pylori* [31].

Conclusion

There are no guidelines regarding non-invasive office screening methods for occult gastrointestinal bleeding. The findings of occult gastrointestinal bleeding in the office are often incidental and found as a result of recommended screening for other conditions such as iron deficiency anemia and colorectal cancer screening. In addition if symptoms of anemia develop the search for the etiology may lead to the diagnosis of occult gastrointestinal bleeding. Once the diagnosis of IDA is made screening for celiac disease and when appropriate infectious etiology should be undertaken.

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