

## **Anemia**

We are seeking an author or author group to write an edition of *FP Essentials* that will update family physicians on anemia. This edition will cover four topics:

1. Evaluation of the patient with suspected anemia
2. Microcytic anemia
3. Macrocytic anemia
4. Normocytic anemia

The main text of the manuscript should be approximately 10,000 words in length, divided into four sections of approximately 2,500 words each, plus an abstract of approximately 200 words for each section. In addition, there should be key practice recommendations, a maximum of 15 tables/figures total, suggested readings, and up to 200 references to provide support for all recommendations and factual statements in the manuscript.

This edition should focus on what is new in each topic and should answer the key questions listed for each section. Each section should begin with an illustrative case, similar to the examples provided, with modifications to emphasize key points; each case should have a conclusion that demonstrates resolution of the clinical situation. The references provided here include information that should be considered in preparation of this edition of *FP Essentials*. However, these should be used only as a starting point in identifying the most current guidelines and references to include in the edition.

**Needs Assessment:** Anemia is a common condition that family physicians manage in ambulatory and inpatient settings. Screening guidelines exist to detect anemia in the asymptomatic phase. There are also guidelines concerning the transfusion of blood and blood products, the use of intravenous iron, and management of anemia associated with chronic kidney disease. Family physicians need to be familiar with all of these guidelines. Furthermore, in a needs assessment survey by the American Academy of Family Physicians (AAFP), members reported that their greatest educational need pertaining to anemia was related to diagnosis, followed by management. This *FP Essentials* edition will address those needs by providing readers with information related to diagnosis and management of anemia.

## Section 1: Evaluation of the Patient With Suspected Anemia

**Example case:** *LK is a 58-year-old woman with a history of hypertension, dyslipidemia, and osteoarthritis who is seeing you for symptoms of increased fatigue. You compare today's complete blood cell count results with those from the appointment last year. Today's hemoglobin is 9 g/dL. Last year's was 12 g/dL.*

### Key questions to consider:

- What is the definition of anemia? How does it vary depending on different populations, including various ethnic groups; children, adults, and older adults; and in pregnant women? How common is anemia in these different populations
- What are the most common (and the most important uncommon) causes of anemia, and how prevalent are each of them?
- How does the presence of anemia affect health outcomes of individuals with chronic diseases (eg, heart failure, chronic kidney disease)? How does it affect the growth and development of children? How are pregnancy outcomes affected by anemia?
- What signs and symptoms suggest anemia? Are any presentations more sensitive or specific for anemia in particular circumstances or populations?
- Are there general risk factors for anemia (please note that this question can be more fully answered in the subsequent sections)? What medical conditions and drugs increase the risk of developing anemia?
- What physical examination findings suggest a patient might have anemia? Are they sufficiently sensitive and specific to rely on them? Does this vary based on different populations?
- What are the recommended guidelines from U.S. Preventive Services Task Force (USPSTF), American Academy of Family Physicians (AAFP), American Academy of Pediatrics (AAP), and American College of Obstetricians and Gynecologists (ACOG) regarding screening asymptomatic individuals for anemia? How do these guidelines differ? Should asymptomatic, nonpregnant adults be screened for anemia in the absence of known risk factors?
- What initial testing is indicated for individuals with suspected anemia? If positive, what additional testing is recommended (please note that this question can be more fully answered in the subsequent sections)?
- What are the definitions and practice implications of the various red blood cell indices?
- What conditions are associated with false-negative and false-positive testing for anemia?

### Initial references to consider:

- Sklarz T, Italiano A, Menon N, et al. Impact of correcting nutritional deficiency anemias in the elderly on hospitalizations, falls, and mortalities. *J Hematol.* 2021;10(6):233-245.
- Savaliya K, Sharma N, Surani R, Dhakar V, Gupta A. Multigravida women with moderate to severe anaemia in third trimester: fetomaternal outcomes. *Cureus.* 2021;13(12):e20493.

- Neuwirth AL, Boddapati V, Held MB, et al. Preoperative anemia is associated with 30-day morbidity in total knee arthroplasty. *Orthopedics*. 2022;45(2):e86-e90.
- Keel S, Geddis A. The clinical and laboratory evaluation of patients with suspected hypocellular marrow failure. *Hematology Am Soc Hematol Educ Program*. 2021;2021(1):134-142.
- Rajkomar A, McCulloch CE, Fang MC. Low diagnostic utility of rechecking hemoglobins within 24 hours in hospitalized patients. *Am J Med*. 2016;129(11):1194-1197.
- Siu AL; US Preventive Services Task Force. Screening for iron deficiency anemia in young children: USPSTF recommendation statement. *Pediatrics*. 2015;136(4):746-752.
- Cantor AG, Bougatsos C, Dana T, Blazina I, McDonagh M. Routine iron supplementation and screening for iron deficiency anemia in pregnancy: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med*. 2015;162(8):566-576.
- Jamwal M, Sharma P, Das R. Laboratory approach to hemolytic anemia. *Indian J Pediatr*. 2020;87(1):66-74.
- Lanier JB, Park JJ, Callahan RC. Anemia in older adults. *Am Fam Physician*. 2018;98(7):437-442.
- Goldman L, Schafer AI, eds. Chapter 149: Approach to the anemias. In: Goldman L, Schafer A, eds. *Goldman-Cecil Medicine*. 26th ed. Elsevier; 2019.
- Sîrbu O, Floria M, Dascalita P, et al. Anemia in heart failure—from guidelines to controversies and challenges. *Anatol J Cardiol*. 2018;20(1):52-59.
- Killick SB, Bown N, Cavenagh J, et al. Guidelines for the diagnosis and management of adult aplastic anaemia. *Br J Haematol*. 2016;172(2):187-207.
- Johansson K, Svensson PA, Söderling J, et al. Long-term risk of anaemia after bariatric surgery: results from the Swedish Obese Subjects study. *Lancet Diabetes Endocrinol*. 2021;9(8):515-524.
- Kelly AU, McSorley ST, Patel P, Talwar D. Interpreting iron studies. *BMJ*. 2017;357:j2513. Erratum in *BMJ*. 2017;357:j3175.
- Hoffmann JJ, 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(12):1883-1894.

## Section 2: Microcytic Anemia

**Example case:** *AN is a 33-year-old woman who delivered her first child 3 months ago. She reports difficulty with concentration and a lack of motivation to get things done. She denies feeling depressed, and the Patient Health Questionnaire-2 (PHQ-2) score is 0. You obtain a complete blood cell count, and the laboratory calls informing you of a critical hemoglobin level of 6 g/dL.*

### Key questions to consider:

- How is microcytic anemia defined based on red blood cell indices?
- What are the most common causes of microcytic anemia?
- In separate sections for iron deficiency anemia, thalassemia, sickle cell anemia, and sideroblastic anemia, address the following questions:
  - How common are they?
  - What are the risk factors for developing these anemias, including dietary choices?
  - What drugs are associated with each type of anemia?
  - Does level of physical activity influence the development of any of these forms of anemia?
  - Are there any clinical signs or symptoms that differentiate among these different types of anemia?
  - What are the differential diagnoses for these conditions?
  - What additional laboratory tests are recommended to confirm the diagnosis? What is the correlation among ferritin, transferrin saturation, and hemoglobin levels?
  - What additional investigative studies are needed to identify the cause of the anemia? When is genetic testing appropriate and which tests should be obtained? When should upper or lower endoscopy be considered?
  - Does management of the underlying conditions improve the anemia, and/or the laboratory values?
  - What is the preferred management of each type of anemia?
  - For iron deficiency anemia, what is the preferred oral replacement strategy? When is intravenous iron indicated? What are the side effects or contraindications to iron replacement? What are the indications for various oral and intravenous iron formulations? What strategies or formulations may improve gastrointestinal tolerability? What factors, including diet, can increase or decrease absorption of iron?
  - How long after management should the hemoglobin and red blood cell indices improve? When should symptoms improve?
  - How long should management be continued?
  - What are indications for referral to a hematologist?

### Initial references to consider:

- Dela-Pena JC, King MA, Brown J, Nachar VR. Incorporation of novel therapies for the management of sickle cell disease: a pharmacist's perspective. *J Oncol Pharm Pract.* 2022;28(3):646-663.
- Ghoz H, Bryant M, Fritz H, et al. Endoscopic sleeve gastroplasty and postprocedural nutritional deficiencies: results from a single center exploratory study. *Eur J Gastroenterol Hepatol.* 2021;33(1S Suppl 1):e1039-e1041.
- Arshad S, Arif A, Ahmed N. Serum hepcidin response as a marker of iron deficiency during second trimester of pregnancy: a multicenter cohort study in Lahore. *Pak J Pharm Sci.* 2021;34(6 [Supplementary]):2347-2355.
- Detlefs SE, Jochum MD, Salmanian B, McKinney JR, Aagaard KM. The impact of response to iron therapy on maternal and neonatal outcomes among pregnant women with anemia. *Am J Obstet Gynecol MFM.* 2022;4(2):100569.
- Tanous O, Levin C, Suchdev PS, Luo H, Rinawi F. Resolution of iron deficiency following successful eradication of Helicobacter pylori in children. *Acta Paediatr.* 2022;111(5):1075-1082.
- Alnuwaysir RIS, Hoes MF, van Veldhuisen DJ, van der Meer P, Beverborg NG. Iron deficiency in heart failure: mechanisms and pathophysiology. *J Clin Med.* 2021;11(1):125.
- Samson KLI, Fischer JA, Roche ML. Iron status, anemia, and iron interventions and their associations with cognitive and academic performance in adolescents: a systematic review. *Nutrients.* 2022;14(1):224.
- Kumar A, Sharma E, Marley A, Samaan MA, Brookes MJ. Iron deficiency anaemia: pathophysiology, assessment, practical management. *BMJ Open Gastroenterol.* 2022;9(1):e000759.
- Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. *Int J Hematol.* 2018;107(1):16-30.
- Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J. UK guidelines on the management of iron deficiency in pregnancy. *Br J Haematol.* 2020;188(6):819-830.
- Kato GJ, Piel FB, Reid CD, et al. Sickle cell disease. *Nat Rev Dis Primers.* 2018;4:18010.
- Frangoul H, Altshuler D, Cappellini MD, et al. CRISPR-Cas9 gene editing for sickle cell disease and  $\beta$ -thalassemia. *N Engl J Med.* 2021;384(3):252-260.
- Langer AL, Esrick EB.  $\beta$ -thalassemia: evolving treatment options beyond transfusion and iron chelation. *Hematology Am Soc Hematol Educ Program.* 2021;2021(1):600-606.
- Shirk SK, Manolis SA, Lambers DS, Smith KL. Delayed clamping vs milking of umbilical cord in preterm infants: a randomized controlled trial. *Am J Obstet Gynecol.* 2019;220(5):482.e1-482.e8.
- Markowitz M. Lead poisoning: an update. *Pediatr Rev.* 2021;42(6):302-315.
- Zanetti R, Feldman B, Porea T. Microcytic anemia. *Pediatr Rev.* 2021;42(1):41-43.

- Damian MT, Vulturar R, Login CC, Damian L, Chis A, Bojan A. Anemia in sports: a narrative review. *Life (Basel)*. 2021;11(9):987.
- Ponorac N, Popović M, Karaba-Jakovljević D, et al. Professional female athletes are at a heightened risk of iron-deficient erythropoiesis compared with nonathletes. *Int J Sport Nutr Exerc Metab*. 2020;30(1):48-53.

### Section 3: Macrocytic Anemia

**Example case:** *ZT is a 53-year-old man with type 2 diabetes for the past 10 years. With metformin and lifestyle modification, ZT has achieved good glycemic control. Today, he reports symptoms of fatigue and poor focus. A review of recent laboratory test results shows a hemoglobin of 8 g/dL and elevated mean corpuscular volume (MCV) and mean corpuscular hemoglobin (MCH).*

#### Key questions to consider:

- How is macrocytic anemia defined based on red blood cell indices?
- In separate sections for megaloblastic anemia (vitamin B<sub>12</sub> deficiency and folate deficiency) and nonmegaloblastic anemia (liver dysfunction, hypothyroidism, alcohol use disorder, and myelodysplastic disorders), address the following questions:
  - How common are they?
  - What are the risk factors for developing these anemias, including dietary choices?
  - What drugs are associated with each type of anemia?
  - Are there any clinical signs or symptoms that differentiate among these different types of anemia?
  - What are the differential diagnoses and causes of these conditions?
  - What additional laboratory tests are recommended to confirm the diagnosis?
  - What additional investigative studies are needed to identify the cause of the anemia? Does management of the underlying conditions improve the anemia?
  - What is the preferred management of each type of anemia? When should sublingual versus parenteral vitamin B<sub>12</sub> preparations be used? What is the recommended replacement protocol for severe B<sub>12</sub> deficiency anemia?
  - When should the hemoglobin and red blood cell indices improve after management (and do all indices normalize)? When should symptoms improve?
  - How long should management be continued? How often should laboratory tests be repeated to monitor for response to management and recurrence?
  - What are indications for referral to a hematologist?

#### Initial references to consider:

- Torrez M, Chabot-Richards D, Babu D, Lockhart E, Foucar K. How I investigate acquired megaloblastic anemia. *Int J Lab Hematol.* 2022;44(2):236-247.
- Nasrin NN, Shanmugasundaram S, Kartikayan RK. The value of duodenal biopsies in the evaluation of megaloblastic anemia. *J Lab Physicians.* 2021;13(4):291-295.
- Kim J, Ahn CW, Fang S, Lee HS, Park JS. Association between metformin dose and vitamin B<sub>12</sub> deficiency in patients with type 2 diabetes. *Medicine (Baltimore).* 2019;98(46):e17918.

- Miranti EH, Stolzenberg-Solomon R, Weinstein SJ, et al. Low vitamin B<sub>12</sub> increases risk of gastric cancer: a prospective study of one-carbon metabolism nutrients and risk of upper gastrointestinal tract cancer. *Int J Cancer*. 2017;141(6):1120-1129.
- Dangour AD, Allen E, Clarke R, et al. Effects of vitamin B-12 supplementation on neurologic and cognitive function in older people: a randomized controlled trial. *Am J Clin Nutr*. 2015;102(3):639-647.
- Wang H, Li L, Qin LL, Song Y, Vidal-Alaball J, Liu TH. Oral vitamin B<sub>12</sub> versus intramuscular vitamin B<sub>12</sub> for vitamin B<sub>12</sub> deficiency. *Cochrane Database Syst Rev*. 2018;3(3):CD004655.
- Nagao T, Hirokawa M. Diagnosis and treatment of macrocytic anemias in adults. *J Gen Fam Med*. 2017;18(5):200-204.
- Sukumar N, Saravanan P. Investigating vitamin B12 deficiency. *BMJ*. 2019;365:11865.
- Mohamed M, Thio J, Thomas RS, Phillips J. Pernicious anaemia. *BMJ*. 2020;369:m1319.

## Section 4: Normocytic Anemia

**Example case:** *AD is a 62-year-old man with stage 4 hypertensive chronic kidney disease. You referred him to a nephrologist for a discussion about future treatment options. Today, AD tells you that the nephrologist discussed the need for “a shot” to increase blood cell count, but AD does not understand what the shot is or when it needs to be started.*

### Key questions to consider:

- How is normocytic anemia defined based on red blood cell indices?
- What are the most common causes of normocytic anemia? Can iron deficiency cause normocytic anemia?
- In separate sections for each of those causes (including at a minimum, anemia of inflammation, hemolytic anemia, chronic kidney disease, acute blood loss, and aplastic anemia) address the following questions:
  - How common are they?
  - What are the risk factors for developing these anemias?
  - What drugs are associated with each type of anemia?
  - Are there any clinical signs or symptoms that differentiate among these different types of anemia?
  - What are the differential diagnoses for these conditions?
  - What additional laboratory tests are recommended to confirm the diagnosis?
  - What additional investigative studies are needed to identify the cause of the anemia? Does management of the underlying conditions improve the anemia?
  - What is the preferred management of each type of anemia?
  - For acute blood loss, what are the indications for blood transfusion? What are the different types of blood transfusions? What is the recommended approach to patients who do not wish to receive blood transfusions? How are transfusion reactions prevented and treated?
  - For anemia of chronic kidney disease, what are the indications for erythropoietin management? What are the contraindications? What is the goal hemoglobin level? Does administration require a hematologist? What other reasons for anemia besides erythropoietin deficiency should be considered in patients with chronic kidney disease?
  - When should the hemoglobin and red blood cell indices improve after management? When should symptoms improve?
  - How long should management be continued?
  - What are the indications for referral to a hematologist?

### Initial references to consider:

- Helmer P, Hottenrott S, Steinisch A, et al. Avoidable blood loss in critical care and patient blood management: scoping review of diagnostic blood loss. *J Clin Med.* 2022;11(2):320.
- Finkenthal TA, Aldaher Z, Ahmed S, DiValentin L. Autoimmune hemolytic anemia exacerbation associated with covid-19 infection and markedly elevated inflammatory markers. *Cureus.* 2021;13(12):e20416.
- Geneen LJ, Kimber C, Doree C, Stanworth S, Shah A. Efficacy and safety of intravenous iron therapy for treating anaemia in critically ill adults: a rapid systematic review with meta-analysis. *Transfus Med Rev.* 2021:S0887-7963(21)00068-7.
- Scheinberg P. A new standard immunosuppression regimen in severe aplastic anemia. *N Engl J Med.* 2022;386(1):89-90.
- Carson JL, Stanworth SJ, Dennis JA, et al. Transfusion thresholds for guiding red blood cell transfusion. *Cochrane Database Syst Rev.* 2021;(12):CD002042.
- Kalfa TA. Diagnosis and clinical management of red cell membrane disorders. *Hematology Am Soc Hematol Educ Program.* 2021;2021(1):331-340.
- Ganz T. Anemia of inflammation. *N Engl J Med.* 2019;381(12):1148-1157.
- Hill A, Hill QA. Autoimmune hemolytic anemia. *Hematology Am Soc Hematol Educ Program.* 2018;2018(1):382-389.
- Portolés J, Martín L, Broseta JJ, Cases A. Anemia in chronic kidney disease: from pathophysiology and current treatments, to future agents. *Front Med (Lausanne).* 2021;8:642296.
- Ho JCL, Chan AKC, Lau KK, Chan HHW. Iron deficiency as a common treatable cause of chronic normocytic anemia. *Blood.* 2014;124(21):4032.