Welcome to the IBD Nurse Fellowship Program!

The program consists of 13 modules:

Module 1 – Ulcerative Colitis
Module 2 – Crohn's Disease
Module 3 – Ulcerative Colitis vs. Crohn's Disease
Module 4 – Management of Ulcerative Colitis
Module 5 – Management of Crohn's Disease
Module 6 – IBD and Surgery
Module 7 – Medication Adherence in IBD
Module 8 – Health Promotion and Maintenance in IBD
Module 9 – Nutrition and IBD
Module 10 – Extra-intestinal Manifestations of IBD
Module 11 – Anemia in IBD
Module 12 – Fatigue in IBD
Module 13 – Anxiety and Depression in IBD

Each module is divided into sections, all of which are listed in the Table of Contents. The Table of Contents allows you to click on the page numbers to navigate to each section. Each page has a Home Button on the bottom right-hand corner that will take you back to the Table of Contents.

The learning objectives are at the beginning and end of each module. Before completing the module, you will have the opportunity to take a self-directed quiz, which will test your knowledge on several of the key concepts and takeaways from the module. It is recommended that you take the quiz and accomplish all of the learning objectives before moving on to the next module.

This program is supported through an educational grant from janssen

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csgna
Canadian Society of Gastroenterology Nurses & Associates
Société canadienne des infirmières et infirmiers en gastroentérologie et travailleurs associés

CANIBD
Canadian Nurses IBD Group

Module 11

Anemia in IBD

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Learning objectives

After completing Module 11 you will be able to:

- Define anemia and describe the most common forms of anemia in patients with inflammatory bowel disease (IBD)
- Identify key contributing factors to the pathogenesis of anemia
- Explain the process of diagnosing anemia in patients with IBD
- Describe what procedures are involved in laboratory investigations of anemia
- Outline different treatment options for anemia, and the appropriate considerations for each type of treatment

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Section 1

Anemia in IBD

Prevalence and effects on the IBD Patient

- Anemia is the most common systemic complication and extra-intestinal manifestation of inflammatory bowel disease (IBD)
  - Iron deficiency occurs in about 60-80% of patients with IBD, and anemia manifests in approximately one-third of patients
  - Anemia is detected in up to 20% of outpatients and 70% of inpatients with IBD
- Consequences of iron deficiency can include fatigue, weakness, decreased work capacity, palpitations, pallor, and alterations in immune function
- Anemia in patients with IBD is associated with many consequences, including:
  - **Added complications:** including stomatitis and restless leg syndrome
  - **Economic burden:** The costs of care for patients with IBD with anemia are more than twice that of non-anemic patients
  - **Impaired quality of life:** Anemia is associated with frequent hospitalization, as well as loss of work productivity due to disease-associated fatigue

Stein and Dignass, 2012; Abhyankar et al., 2015; Guagnozzi et al., 2014.

Definition

- Anemia is defined by the WHO as a decline in blood hemoglobin (Hb) to a concentration of <12 g/dL (120 g/L) in women and <13 g/dL (130 g/L) in men, parameters which are equally applicable to patients with IBD
- Anemia with iron deficiency is characterized by a defect in Hb synthesis which results in red blood cells that are small and contain a reduced amount of Hb

Age or sex group	Hemoglobin		Hematocrit
	(g/dL)	(mmol/dL)	(%)
Children ½ to 5 years	11.0	6.83	33
Children 5 to 11 years	11.5	7.14	34
Children 12 to 13 years	12.0	7.45	36
Nonpregnant women	12.0	7.45	36
Pregnant women	11.0	6.83	33
Men	13.0	8.07	39

Minimum hemoglobin and hematocrit levels used to define anemia in people living at sea level

Normal Hb distributions vary with age and gender, at different stages of pregnancy, and with altitude and smoking.

IBD, inflammatory bowel disease; WHO, World Health Organization

Stein and Dignass, 2012; World Health Organization, 2001; Dignass et al., 2015.

Etiology

- The two most frequent forms of anemia are iron deficiency anemia (IDA) and anemia of chronic disease (ACD), which are caused by negative effects of an activated immune system at different levels of erythropoiesis
  - IDA results from iron deficiency secondary to blood loss through the ulcerations of the intestinal mucosa, reduced iron absorption and intake, and ACD
  - ACD is characterized by normal or reduced mean corpuscular volume (MCV), reduced serum iron, reduced total iron binding capacity (TIBC), normal to elevated serum ferritin level, and reticuloendothelial system (RES) stores that are elevated relative to total body iron

Frequency	Etiology
Common	• Iron deficiency anemia • Anemia of chronic illness
Occasional	• Vitamin B12 deficiency • Folate deficiency • Drug-induced (sulfasalazine, thiopurine)
Exceptional	• Hemolysis • Myelodysplastic syndrome • Aplasia (often drug-induced) • Inborn hemoglobinopathies or disorder of erythropoiesis

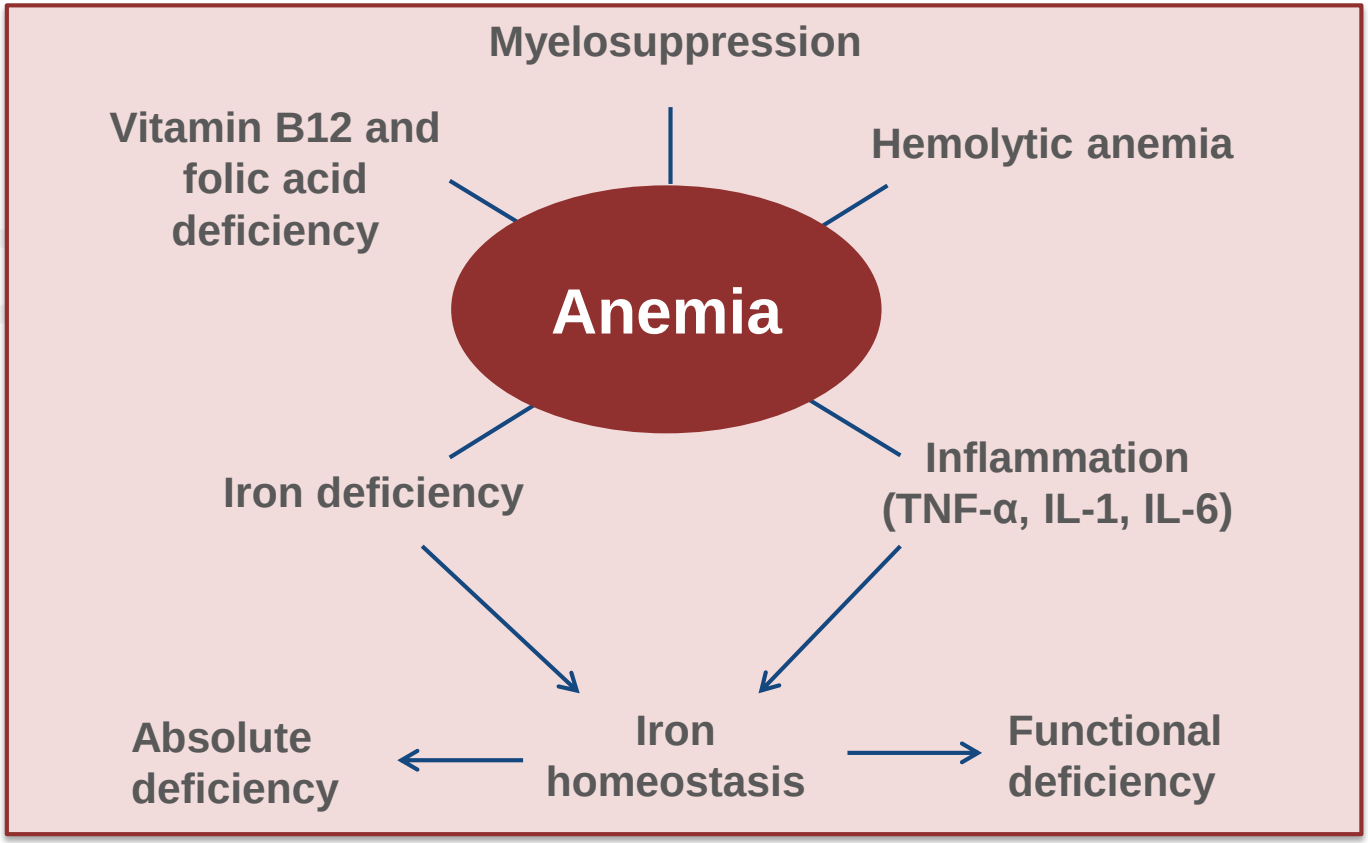
- Metabolic disturbances, vitamin deficiencies, and various drug therapies commonly used in IBD can also aggravate anemia in IBD patients

IBD, inflammatory bowel disease.

Guagnozzi et al., 2014; Gasche et al., 2007; Stein and Dignass, 2012.

Pathogenesis

- The pathogenesis of IBD-associated anemia is multifactorial



IBD, inflammatory bowel disease.
Guagnozzi et al., 2014; Gasche et al., 2007.

Iron homeostasis regulation

- Hepcidin acts as the main regulator of systemic iron homeostasis
- Hepcidin acts to block iron efflux from various cell types by decreasing the expression of the iron transporter ferroportin (Fpn)
- Hepcidin is released into circulation by the liver, which:
  - **Increases** hepcidin production with higher circulating iron levels (transferrin-bound circulating iron [Fe-Tf]), or in an inflammatory state
  - **Decreases** production with increases in erythropoietic activity or low circulating iron levels (Fe-Tf])
- Hepcidin is measurable in urine, plasma, and serum

Hepcidin may play a significant role in the development of several iron-related disorders, such as anemia of chronic disease (ACD)

Tussing-Hunphreys et al., 2012.

Section 2

Evaluating and diagnosing anemia

Signs and symptoms

- Typical symptoms of iron deficiency with anemia include:
  - Reduced performance
  - Fatigue
  - Headache
  - Dizziness
  - Tachycardia
  - Exertional and even resting dyspnea
- Latent iron deficiency may result in non-hematological symptoms:
  - Hair loss
  - Stomatitis
  - Paresthesia of the hands and feet
  - Reduction in cognitive function
  - Restless legs syndrome
  - Pica (disorder characterized by persistent ingestion of non-food items)

Stein and Dignass, 2012.

Diagnosing anemia

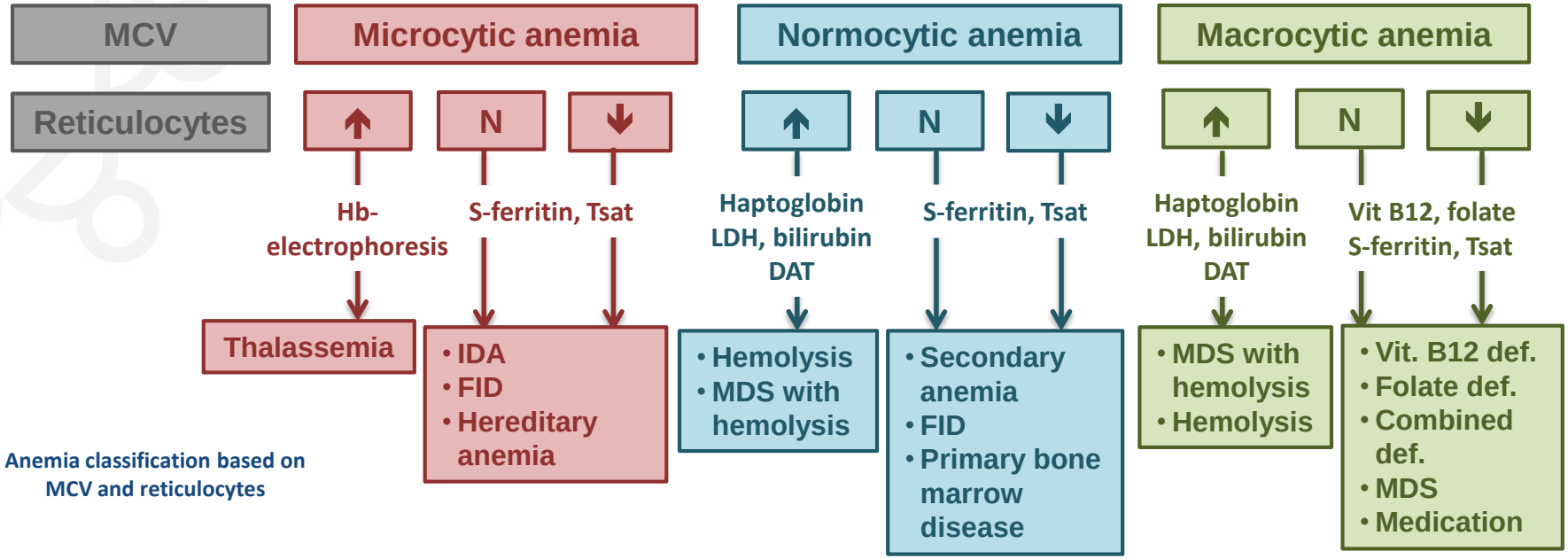
- Low mean corpuscular volume (MCV) and low mean corpuscular hemoglobin (MCH) are generally reliable indicators of iron deficiency
  - A normal MCV does not rule out iron deficiency as the cause of anemia
  - Low MCV does not necessarily indicate iron deficiency, as the presence of ACD can cause it to be normal or low
- All components of the body's iron metabolism can be monitored using routine laboratory methods
  - Iron stores: serum ferritin
  - Iron transport: transferrin saturation
  - Iron utilization: erythropoiesis (proportion of hypochromic erythrocytes or reticulocytes)

ACD, anemia of chronic disease.

Stein and Dignass, 2012.

Anemia classification based on mean corpuscular volume and reticulocytes

- Mean corpuscular volume (MCV) reflects the size of red blood cells
  - Micro-, normo- and macrocytic anemias cover all forms of anemia
- The reticulocyte count tells whether the bone marrow can respond by increasing erythropoiesis
  - All deficiency states are excluded by increased reticulocytes



Anemia classification based on MCV and reticulocytes

DAT, direct antibody test; Def: deficiency; FID, functional iron deficiency; Hb, hemoglobin; IDA, iron deficiency anemia; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; MDS, myelodysplastic syndrome; N, normal; Retic, reticulocyte count; S-ferritin, serum ferritin; Tsat, transferrin saturation.

Dignass et al., 2015.

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Laboratory investigations

- The minimum workup should include:
  - Complete blood count (CBC) with MCV and reticulocytes
  - Serum ferritin: indicates total store of body iron
  - Transferrin saturation (TfS): evaluates available iron in the bone marrow
  - C-reactive protein (CRP): measures level of inflammation
- A more extensive workup to exclude potential hemolysis or renal disease may include:
  - Vitamin B12 (especially in patients with small disease or resection)
  - Folate
  - Haptoglobin
  - Differential white blood cell count
  - Creatinine
  - Urea
  - Bone marrow smear

For patients in remission or mild disease: CBC, CRP, serum ferritin measurements should be performed every 6 to 12 months

In outpatients with active disease CBC, CRP, serum ferritin should be performed at least every 3 months

MCV, mean corpuscular volume

Dignass et al., 2015; Reinisch et al., 2013.

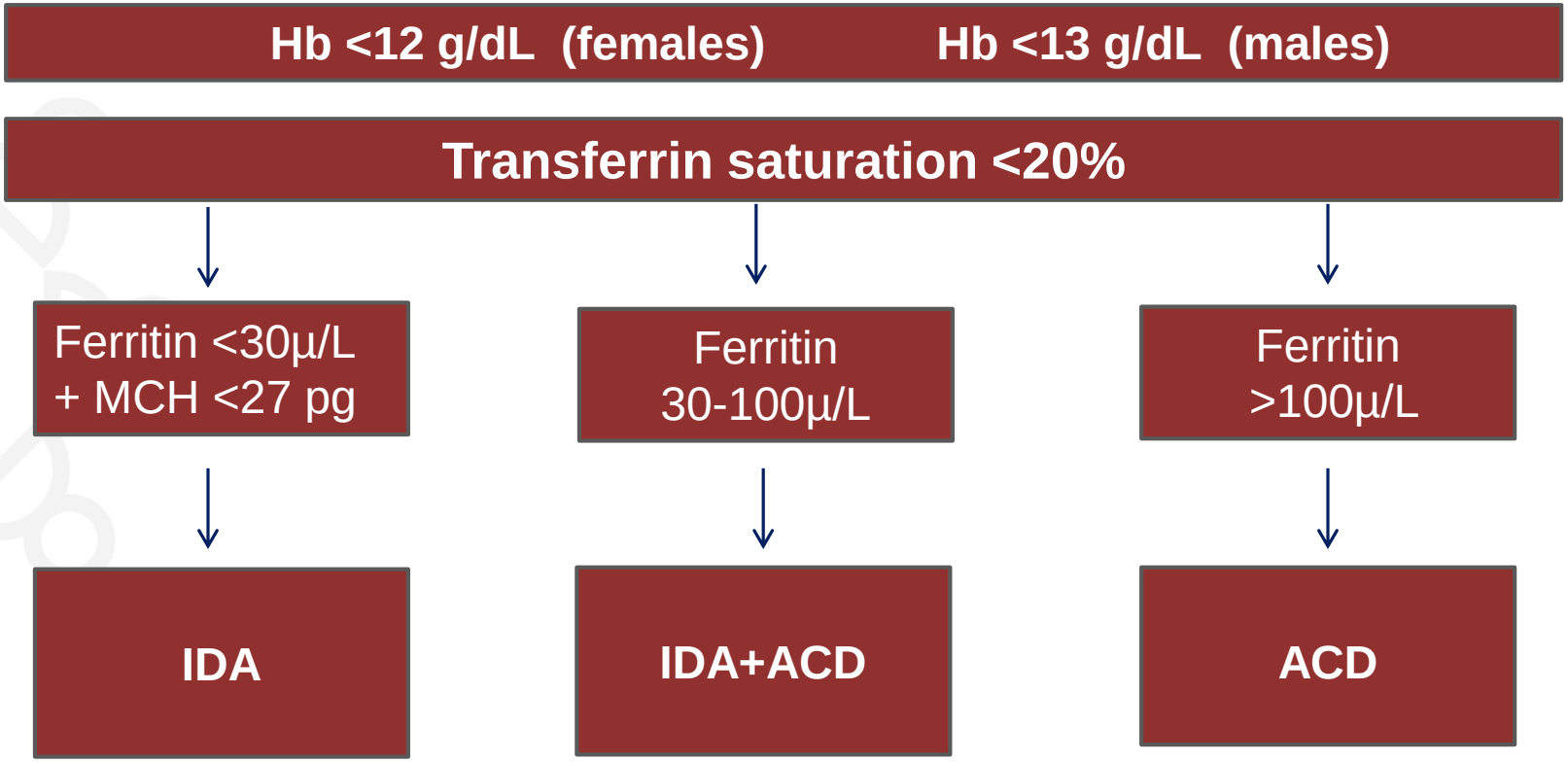
Basic laboratory workup in anemia

- There is no single biomarker to diagnose iron deficiency
- Assessment of iron status involves simple measurements and allows in most cases the differentiation between iron deficiency anemia (IDA), anemia of chronic disease (ACD), and the combination of the two

Laboratory measure	IDA	ACD	IDA and ACD
Hemoglobin	↓	↓	↓
CRP	Normal	↑	↑
Serum ferritin	↓	↑	↑ or normal
Transferrin saturation	↓	↓	↓

CRP, C-reactive protein
Reinisch et al., 2013.

Algorithm for diagnosis of anemia in IBD



ACD, anemia of chronic disease; Hb, hemoglobin; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; MCH, mean corpuscular hemoglobin.

Reinisch et al., 2013

Section 3

Treatment of anemia in IBD patients

Treatment of iron deficiency anemia

- Correcting iron deficiency anemia improves quality of life in IBD
- Iron supplementation should be considered in all iron-deficient patients with IBD and initiated in those in whom Hb concentrations are below normal
- **Oral iron** may be used in patients with mild anemia, whose disease is clinically inactive, and who have not been previously intolerant to oral iron
- **Intravenous iron** should be considered in patients with clinically active IBD, with previous intolerance to oral iron, with hemoglobin below 10 g/dL, and in patients who need erythropoiesis-stimulating agents

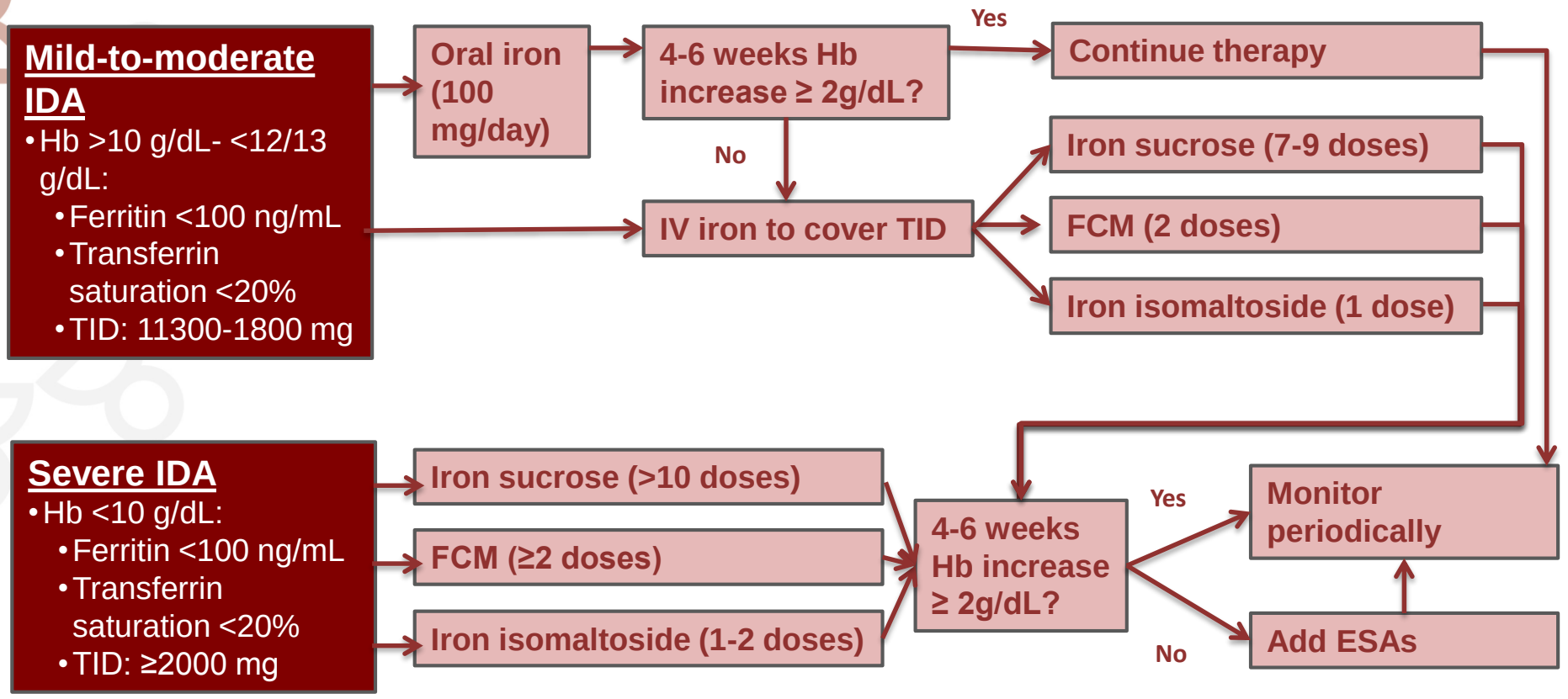
The goal of iron supplementation is to normalize hemoglobin levels and iron stores

Due to its low cost and non-invasive method of administration, oral iron therapy is the conventional approach in patients with mild to moderate anemia

Hb, hemoglobin; IBD, inflammatory bowel disease.
Dignass et al., 2015; Reinisch et al., 2013.

Treatment algorithm for iron deficiency anemia

Oral iron should be the first line of treatment for anemia, but IV iron replacement may be required in some cases



IDA, iron deficiency anemia; FCM, ferric carboxymaltose; Hb, hemoglobin; LMWID, low molecular weight iron dextran; ESA, erythropoiesis stimulating agent; TID, total iron deficit.

Reinisch et al., 2013.

Oral iron

- Oral iron compounds are mostly available as inorganic ferrous salts, sometimes combined with vitamin C which enhances iron absorption
- Oral iron at a daily dose between 50 mg and 200 mg is recommended for patients with mild to moderate anemia (Hb ≥10 g/dL, ferritin 30 µg/L)
- A maximum of 10-20 mg of oral iron can be absorbed per day
  - **Ferrous fumarate:** 106 mg elemental iron/tablet
  - **Ferrous sulfate:** 65 mg elemental iron/tablet
  - **Ferrous gluconate:** 28-36 mg iron/tablet
  - **Ferrous sulfate Elixir:** 44 mg/5 mL (used if intolerant to oral iron tablets)
- The recommended maximum daily dose is up to 100 mg elemental iron per day, as higher doses do not increase its absorption and efficacy, and the side effects of oral iron are dose-related

Hb, hemoglobin.
Kaitha et al., 2015

Instructions for taking oral iron

- Oral iron should be started at a low dose after meals
  - If well tolerated, the dose can then be increased and should be taken on an empty stomach to increase absorption
- Iron should be given two hours before, or four hours after, ingestion of antacids, dairy products, caffeine and calcium
- A 250 mg ascorbic acid tablet or a half-glass of orange juice can be added at the time of iron administration to enhance the degree of iron absorption

Iron is best absorbed as the ferrous (Fe++) salt form in a mildly acidic medium

IBD, inflammatory bowel disease
Kaitha et al., 2015

Intravenous iron

- **Advantages**
  - Rapid reversal of IDA
  - Repletion of iron stores is unaffected by inflammation or intestinal resection
  - Relatively better tolerance and fewer side effects
  - Compliance can be monitored
  - Single dose is sufficient
- **Disadvantages**
  - Need for IV access and hospital staff for administration
  - Expensive
  - Inconvenience (travel, obtain IV access)
  - Iron dextran causes life-threatening anaphylactic reactions
- **Follow-up monitoring**
  - Patients with IBD should be monitored for recurrent iron deficiency every 3 months for at least one year after correction, and between 6 and 12 months thereafter

IBD, inflammatory bowel disease; IDA, iron deficiency anemia.

Dignass et al., 2015; Kaitha et al., 2015.

Intravenous iron dose calculation

- IV iron dose calculation based on Ganzoni's formula captures the total body iron deficit in milligrams

Total iron deficit
= body weight in kg x [target hemoglobin - actual hemoglobin in g/dL] x 0.24 + 500

This formula is inconvenient, prone to error, inconsistently used in clinical practice, and underestimates iron requirements

- However, the estimation of iron need based on baseline Hb and body weight is more effective for the treatment of IDA in IBD patients than individualized dosing based on the traditional Ganzoni's formula

Hemoglobin g/dL	Body weight <70 kg	Body weight ≥70 kg
10-12 (women)	1000 mg	1500 mg
10-13 (men)	1000 mg	1500 mg
7-10	1500 mg	2000 mg

IBD, inflammatory bowel disease; IV, intravenous.
Dignass et al., 2015.

Gastrointestinal iron absorption in IBD

- Absorption of iron from the gastrointestinal tract is limited, and unabsorbed iron exposed to the ulcerated intestinal surface may cause mucosal harm
  - Soy protein, dietary calcium, phytates (bran, oats, rye), cereals, tea, antacids such as H2 receptor blockers, and proton pump inhibitors prevent absorption of non-heme iron
- Studies in animal models of IBD indicate that luminal iron may exacerbate disease and alter intestinal microbiota
- The low bioavailability of oral iron is further compromised in patients with IBD due to an inflammation-driven blockade of intestinal absorption
- Side effects from oral iron are dose-dependent
- It may take two to three weeks for Hb concentrations to increase, up to two months to achieve normal values, and at least six months to replenish iron stores
  - The lower the baseline Hb, the longer the time to normalization of Hb
  - An increase in Hb of at least 2g/dL within 4 weeks of treatment is an acceptable speed of response

Hb, hemoglobin; IBD, inflammatory bowel disease

Dignass et al., 2015; Reinisch et al., 2013.

Section 4

Self-assessment quiz

Self-assessment quiz

- Now that you have reviewed the module content, you have the opportunity to test your knowledge and understanding of the material by completing a self-assessment
- The assessment consists of 5 multiple choice questions
- Please attempt each question before looking at the answer key, which is located on page 33
- The answer key provides the rationale for each answer and indicates where the correct answer can be found in the module

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Question 1

Which of the following definitions accurately describes anemia?

a) A decline in blood hemoglobin (Hb) to a concentration of <12 g/dL (120 g/L) in women and <13 g/dL (130 g/L) in men

b) A decline in Hb to a concentration of <13 g/dL (130 g/L) in women and <15 g/dL (150 g/L) in men

c) Anemia with iron deficiency is characterized by a defect in Hb synthesis which results in red blood cells that are small and contain a reduced amount of Hb

d) Both a) and c)

Question 2

Which of the following is categorized as an exceptional cause of anemia in IBD?

a) Vitamin B12 deficiency

b) Folate deficiency

c) Hemolysis

d) Drugs

Question 3

Latent iron deficiency may result in which of the following non-hematological symptoms?

a) Tachycardia

b) Headache

c) Fatigue

d) Paresthesia of the hands and feet

Question 4

Which laboratory measure may be reduced in iron deficiency anemia but elevated in anemia of chronic disease?

a) Hemoglobin

b) Serum ferritin

c) Transferrin saturation

d) C-reactive protein

Question 5

Which option can enhance the degree of oral iron absorption?

a) Orange juice

b) Milk

c) Coffee

d) All of the above

Answer key

1. **The correct answer is d.** Anemia is defined by the WHO as a decline in blood hemoglobin (Hb) to a concentration of <12 g/dL (120 g/L) in women and <13 g/dL (130 g/L) in men; and iron deficiency anemia is characterized by a defect in Hb synthesis which results in red blood cells that are small and contain a reduced amount of Hb. See page 7 for more information on this topic.

2. **The correct answer is c.** Hemolysis is an exceptional cause for anemia in IBD. See page 8 for more information on this topic.

3. **The correct answer is d.** Latent iron deficiency may result in paresthesia of the hands and feet, which is a non-hematological symptom. See page 12 for more information on this topic.

4. **The correct answer is b.** Serum ferritin may be reduced in iron deficiency anemia but elevated in anemia of chronic disease. See page 16 for more information on this topic.

5. **The correct answer is a.** A half-glass of orange juice can be added at the time of iron administration to enhance the degree of iron absorption. See page 22 for more information on this topic.

Congratulations!

You have completed the 11th module of the program.

Based on what you learned in Module 11, you should be able to:

- Define anemia and describe the most common forms of anemia in patients with inflammatory bowel disease (IBD)
- Identify key contributing factors to the pathogenesis of anemia
- Explain the process of diagnosing anemia in patients with IBD
- Describe what procedures are involved in laboratory investigations of anemia
- Outline different treatment options for anemia, and the appropriate considerations for each type of treatment

If you have answered the quiz questions correctly and achieved the learning objectives, you are ready to move on to Module 12, which will focus on fatigue in IBD.

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References

- Abhyankar A and Moss AC. (2015). Iron Replacement in Patients with Inflammatory Bowel Disease. *Inflammatory Bowel Diseases*, *Aug;21(8):1976-81.*
- Dignass AU, Gasche C, Bettenworth D, Birgegård G, Danese S, Gisbert JP, Gomollon F, Iqbal T, Katsanos K, Koutroubakis I, Magro F, Savoye G, Stein J, Vavricka S; European Crohn's and Colitis Organisation [ECCO].European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis. 2015 Mar;9(3):211-22.
- Gasche C, Waldhoer T, Feichtenschlager T, Male C, Mayer A, Mittermaier C, Petritsch W; Austrian Inflammatory Bowel Diseases Study Group. Prediction of response to iron sucrose in inflammatory bowel disease-associated anemia. Am J Gastroenterol. 2001 Aug;96(8):2382-7.
- Guagnozzi D, Lucendo AJ. Anemia in inflammatory bowel disease: a neglected issue with relevant effects. World J Gastroenterol. 2014 Apr 7;20(13):3542-51.
- Kaitha S, Bashir M, Ali T. Iron deficiency anemia in inflammatory bowel disease. World J Gastrointest Pathophysiol. 2015 Aug 15;6(3):62-72.
- Reinisch W, Staun M, Bhandari S, Muñoz M. State of the iron: how to diagnose and efficiently treat iron deficiency anemia in inflammatory bowel disease. J Crohns Colitis. 2013 Jul;7(6):429-40
- Stein J, Dignass AU. Management of iron deficiency anemia in inflammatory bowel disease - a practical approach. Ann Gastroenterol. 2013;26(2):104-113.
- Tussing-Humphreys L, Pusatcioglu C, Nemeth E, Braunschweig C. Rethinking iron regulation and assessment in iron deficiency, anemia of chronic disease, and obesity: introducing hepcidin. J Acad Nutr Diet. 2012 Mar;112(3):391-400.
- World Health Organization. (2001). Iron Deficiency Anaemia: Assessment, Prevention, and Control. A guide for programme managers. *World Health Organization*, 114. Accessed: http://doi.org/10.1136/pgmj.2009.089987

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