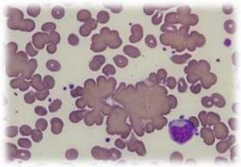

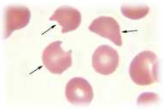

Rapid-fire hematology cases: anemia

Alfred Ian Lee, M.D., Ph.D.
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Professor of Medicine, Section of Hematology
Yale School of Medicine

Disclosures

None

Anemia is common in hospitalized patients

- In single-institution series, ~40-70% of hospitalized patients are anemic
  - ~5-15% have severe anemia
  - Iron deficiency, anemia of inflammation/chronic inflammatory conditions, and anemia of renal disease are common
- Among ICU patients, only 9% of hematology consultations are for anemia
  - Some level of comfort in evaluating and treating anemia is expected among hospitalists

(Randi ML et al *J Clin Med* 2020;9:950; Allen C et al, *Blood* 2023;142(Suppl_1):232; Soraci L et al, *Sci Rep* 2024;14:19721)

Categorization of anemia based on RBC size

Microcytic
- Iron deficiency
- Anemia of inflammation
- Thalassemia
- Sideroblastic anemia

Macrocytic

Megaloblastic
- B12 deficiency
- Folate deficiency

Nonmegaloblastic
- Liver disease
- Alcohol
- Hypothyroidism
- Reticulocytosis
- Monoclonal gammopathy
- Bone marrow problem (can be megaloblastic or nonmegaloblastic)

Normocytic
- Anemia of inflammation
- Acute blood loss
- Hemolytic anemia
- Anemia of renal disease

Categorization of anemia based on RBC size

Microcytic

- Iron deficiency
- Anemia of inflammation
- Thalassemia
- Sideroblastic anemia

	Iron deficiency	Anemia of inflammation
Iron	↓	↓
Total iron binding capacity (TIBC)	↑	↓
Ferritin	↓	↑

Categorization of anemia based on RBC size

Microcytic

- Iron deficiency
- Anemia of inflammation
- Thalassemia
- Sideroblastic anemia

Mentzer index
MCV/RBC ratio

- < 13: thalassemia
- > 13: iron deficiency

Categorization of anemia based on RBC size

Microcytic

- Iron deficiency
- Anemia of inflammation
- Thalassemia
- Sideroblastic anemia

Macrocytic

Megaloblastic

- B12 deficiency
- Folate deficiency

Nonmegaloblastic

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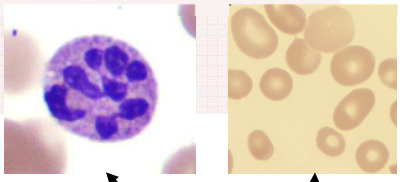
Normocytic

- Anemia of inflammation
- Acute blood loss
- Hemolytic anemia
- Anemia of renal disease

Categorization of anemia based on RBC size

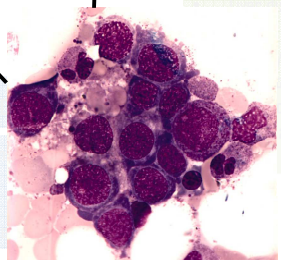
Hypersegmented neutrophils & macroovalocyte RBCs in blood



Macrocytic

Megaloblastic

- B12 deficiency
- Folate deficiency



Megaloblastic erythroid precursors in marrow

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Categorization of anemia based on reticulocyte response

Hypoproliferative

Absolute reticulocyte count < 100,000/mcL
Reticulocyte production index < 2

- Iron, B12, folate deficiency
- Anemia of inflammation
- Anemia of renal disease
- Infections
- Medications (myelosuppression)
- Bone marrow problem

Hyperproliferative

Absolute reticulocyte count > 100,000/mcL
Reticulocyte production index > 3

- Hemolytic anemia
- Acute blood loss

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Case 1: B.C.

B.C. is a 32 year-old woman with menorrhagia due to uterine fibroids. She has had longstanding iron deficiency and has tried taking iron pills in the past but has had difficulty tolerating them due to constipation. She presents to the emergency department with fatigue and dyspnea and is admitted after being discovered to have severe microcytic anemia. Her labs on admission show the following:

Lab parameter	Value	Reference range	Units
WBC	6,600	4-10,000	per mcL
Hemoglobin	8.2	12-15	g/dL
Platelets	475,000	150-350,000	per mcL
Mean corpuscular volume (MCV)	71	80-100	fL
RBC count	2.5	4.2-5.4	million/mcL
Iron	30	60-170	mcg/dL
TIBC	520	240-450	mcg/dL
Ferritin	5	20-150	ng/mL

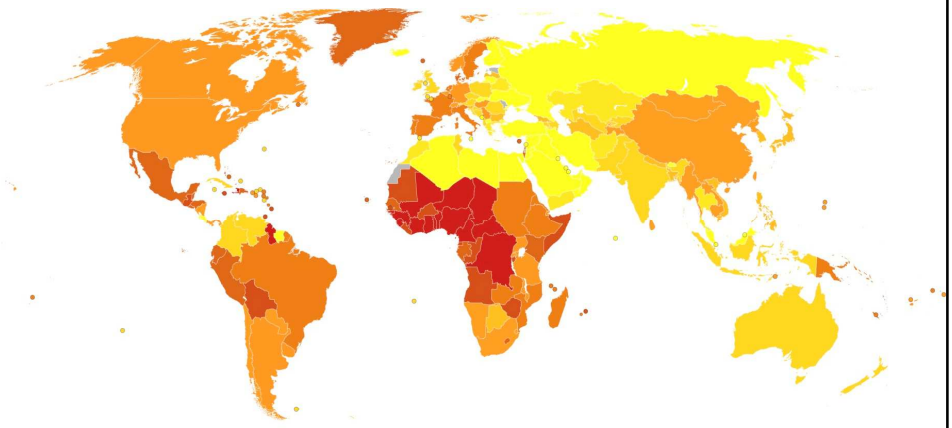
What is the most appropriate next step in treating her microcytic anemia?

1. PO iron every other day
2. PO iron daily
3. PO iron twice-daily
4. IV iron
5. RBC transfusion

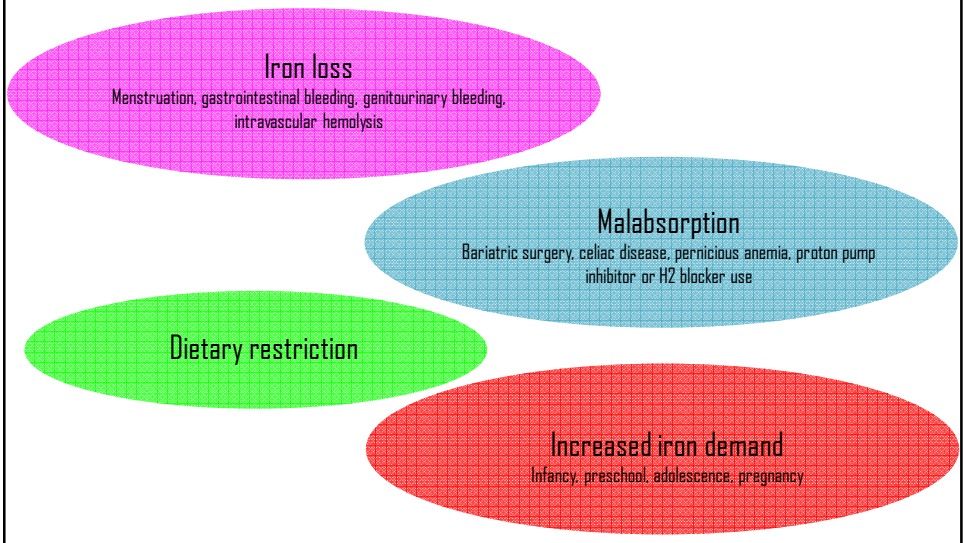
Clinical pearl

IV iron is a safe and effective treatment for patients with iron deficiency anemia who are intolerant of or poorly responsive to PO iron

Iron deficiency anemia is the most common cause of anemia worldwide



Major etiologies for iron deficiency



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(Camaschella C, *Blood* 2019;133:30)

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Treatment of iron deficiency

PO iron

- Once-daily is better than more than once-daily
- Every other day may be better than once-daily

IV iron

- Indicated for patients intolerant of or inadequately responsive to PO iron

Ganzoni equation for calculating iron deficit for IV iron

MD+CALC

Weight	Norm: 2 - 330	lbs ⇆
Target hemoglobin	Norm: 12 - 17	g/dL ⇆
Actual hemoglobin	Norm: 12 - 17	g/dL ⇆
Iron stores Use 500 mg for adults and children ≥35 kg; use 15 mg/kg if <35 kg	500	mg

Most patients who require IV iron have an iron deficit of ~1000 mg

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(Koch TA et al, *Anemia* 2015:2015:763576; Moretti D et al, *Blood* 2015;126:1981; Stoffel NU et al, *Lancet* 2017;4:E524; Camaschella C, *Blood* 2019;133:30)

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Treatment of iron deficiency

PO iron

- Once-daily is better than more than once-daily
- Every other day may be better than once-daily

IV iron

- Indicated for patients intolerant of or inadequately responsive to PO iron

IV iron formulations

IV iron formulation	Trade name	Dosing	Adverse effects
Iron dextran	INFeD	1000 mg	Hypersensitivity
Iron isomaltoside	Monoferric	1000 mg	
Ferumoxytol	Feraheme	510 mg	
Ferric carboxymaltose	Injectafer	750 mg	Hypersensitivity Hypophosphatemia
Iron sucrose	Venofer	Mostly 100-200 mg	Hypersensitivity
Ferric gluconate	Ferrlecit	125 mg	

(Camaschella C, *Blood* 2019;133:30)

Treatment of iron deficiency

PO iron

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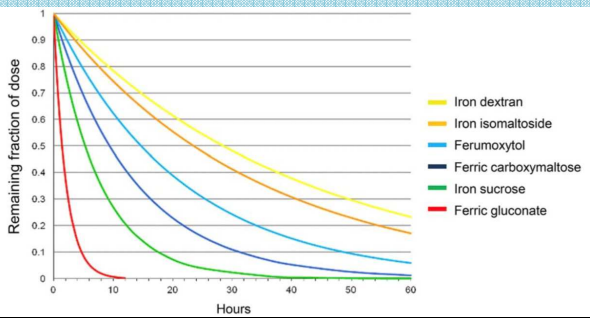
- Every other day may be better than once-daily

IV iron

- Indicated for patients intolerant of or inadequately responsive to PO iron

Different IV iron formulations have different elimination kinetics



(Auerbach M and Macdougall I, *Hemodial Int* 2017;21 Suppl 1:S83)

Treatment of iron deficiency

PO iron

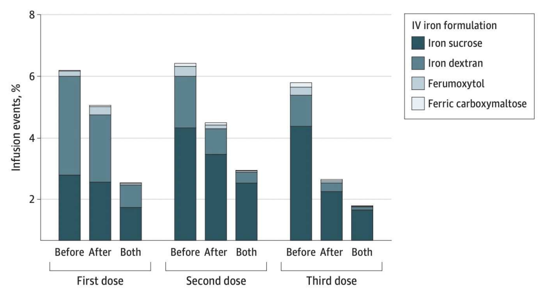
- Once-daily is better than more than once-daily
- Every other day may be better than once-daily

IV iron

- Indicated for patients intolerant of or inadequately responsive to PO iron

Risk of hypersensitivity from IV iron is generally low

	Intravenous iron group	Comparator group	Risk ratio (95% CI)	p value
All severe adverse events				
All iron studies	444/10 390 (4·3%)	440/8863 (5·0%)	1·04 (0·93–1·17)	0·41
Severe adverse events by compound				
Ferric carboxymaltose	127/2922 (4·3%)	91/2098 (4·3%)	0·82 (0·64–1·06)	0·16
Ferric gluconate	244/2132 (11·4%)	216/2128 (10·2%)	1·12(0·96–1·30)	0·12
Ferumoxytol	61/1648 (3·7%)	40/1099 (3·6%)	1·04 (0·71–1·53)	0·83
Iron dextran	51/832 (6·1%)	51/576 (8·9%)	1·05 (0·77–1·45)	0·66
Iron isomaltose or iron polymaltose	12/656 (1·8%)	8/424 (1·9%)	1·09 (0·43–2·80)	0·83
Iron sucrose	73/2899 (2·5%)	48/2536 (1·9%)	1·33 (0·96–1·83)	0·14
Severe adverse events by system				
Infections	25/5168 (0·5%)	27/4462 (0·6%)	0·96 (0·63–1·46)	0·7
Gastrointestinal	14/1460 (1·0%)	8/1545 (0·5%)	1·05 (0·63–1·77)	0·84
Cardiovascular	61/4069 (1·5%)	40/3341 (1·2%)	0·94 (0·60–1·46)	0·76
Thromboembolic	16/2798 (0·6%)	15/2439 (0·6%)	0·99 (0·52–1·86)	0·99
Respiratory	3/3461 (0·1%)	4/2788 (0·1%)	0·91 (0·27–3·86)	0·78
Neurological	15/5985 (0·3%)	5/4438 (0·1%)	1·05 (0·47–2·36)	0·47
Other severe adverse events				
Infusion reactions	35/9223 (0·4%)	4/7569 (0·1%)	2·47 (1·43–4·28)	0·0002
Mortality	91/6459 (1·4%)	85/5440 (1·6%)	1·06 (0·81–1·39)	0·87



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(Auerbach M et al. *Lancet Haematol* 2020;7:e342; Arastu AH et al. *JAMA Netw Open* 2022;5:e224488)

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Case 1: B.C.

B.C. is a 32 year-old woman with menorrhagia due to uterine fibroids. She has had longstanding iron deficiency and has tried taking iron pills in the past but has had difficulty tolerating them due to constipation. She presents to the emergency department with fatigue and dyspnea and is admitted after being discovered to have severe microcytic anemia. Her labs on admission show the following:

Lab parameter	Value	Reference range	Units
WBC	6,600	4-10,000	per mcL
Hemoglobin	8.2	12-15	g/dL
Platelets	475,000	150-350,000	per mcL
Mean corpuscular volume (MCV)	71	80-100	fL
RBC count	2.5	4.2-5.4	million/mcL
Iron	30	60-170	mcg/dL
TIBC	520	240-450	mcg/dL
Ferritin	5	20-150	ng/mL

What is the most appropriate next step in treating her microcytic anemia?

1. PO iron every other day
2. PO iron daily
3. PO iron twice-daily
4. IV iron
5. RBC transfusion

Due to prior intolerance to PO iron, she is recommended for IV iron. Her iron deficit is calculated to be ~900 mg. She is administered 1000 mg of IV iron dextran, which she tolerates well.

Case 2: A.D.

A.D. is a 56-year-old man who is hospitalized for progressive fatigue, exertional dyspnea, and mental fogginess. His past medical history is remarkable for rheumatoid arthritis, which is very active and debilitating, and which is being treated with etanercept, with poor control. His labs show the following:

Lab parameter	Value	Reference range	Units
WBC	9,200	4-10,000	per mcL
Hemoglobin	7.9	12-15	g/dL
Platelets	420,000	150-350,000	per mcL
MCV	83	80-100	fL
Reticulocyte count	1.6	-	%
Iron	65	60-170	mcg/dL
TIBC	380	240-450	mcg/dL
Ferritin	89	20-150	ng/mL

Which of the following is the most appropriate intervention to treat this patient's anemia?

1. RBC transfusion
2. PO iron
3. IV iron
4. Erythropoiesis stimulating agent

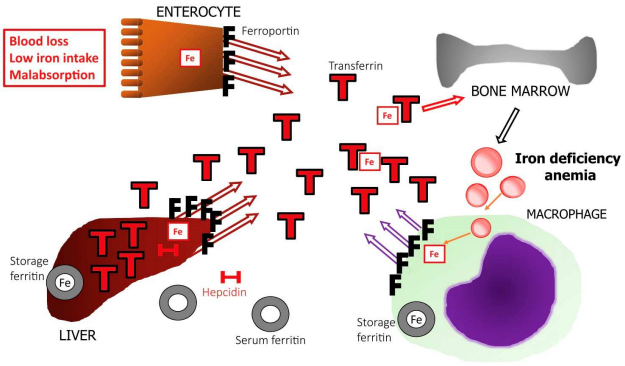
Clinical pearl

In patients with chronic inflammatory conditions (CIC), iron deficiency anemia can be discerned on the basis of an iron saturation < 20% and ferritin < 200 ng/mL

Iron deficiency anemia: low hepcidin state

Low hepcidin state

Iron	↓
TIBC	↑
Iron saturation	↓
Ferritin	↓



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(Fertrin KY. *Hematology Am Soc Hematol Educ Program* 2020;2020:478)

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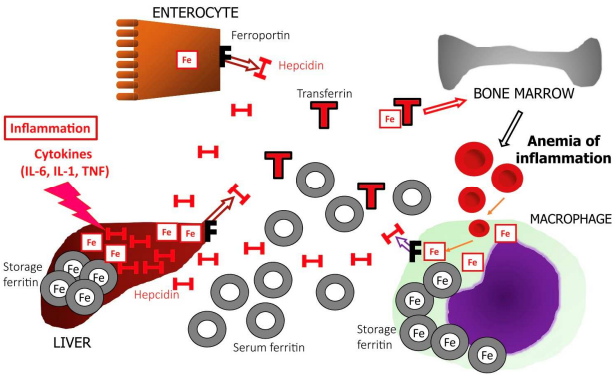
Anemia of CIC

High hepcidin state leading to iron-restricted erythropoiesis



Iron	↓
TIBC	↓
Iron saturation	↓
Ferritin	↑

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(Fertrin KY. *Hematology Am Soc Hematol Educ Program* 2020;2020:478)

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Soluble transferrin receptor (sTfR) in evaluating iron deficiency in CIC

Compared to bone marrow evaluation, sTfR has high yield in diagnosing iron deficiency in CIC

CIC				Rheumatoid arthritis			
Parameter	Sensitivity (%)	Specificity (%)	Efficiency (%)	Parameter	Sensitivity (%)	Specificity (%)	Efficiency (%)
sTfR >3.3 mg/l	86	69	75	sTfR >3.3 mg/l	75	100	94
Ferritin <12 µg/l	0	100	65	Ferritin <12 µg/l	0	100	78
MCV <77 fl	14	85	60	MCV <77 fl	25	100	83
MCH <27 pg	43	69	60	MCH <27 pg	25	100	83
Serum iron <12 µmol/l	57	46	50	Serum iron <12 µmol/l	75	21	33
TIBC >75 µmol/l	14	92	65	TIBC >75 µmol/l	0	100	78
Transferrin saturation <15%	29	69	55	Transferrin saturation <15%	50	57	56

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(Baillie FJ et al. *Clin Lab Haematol* 2003;25:353)

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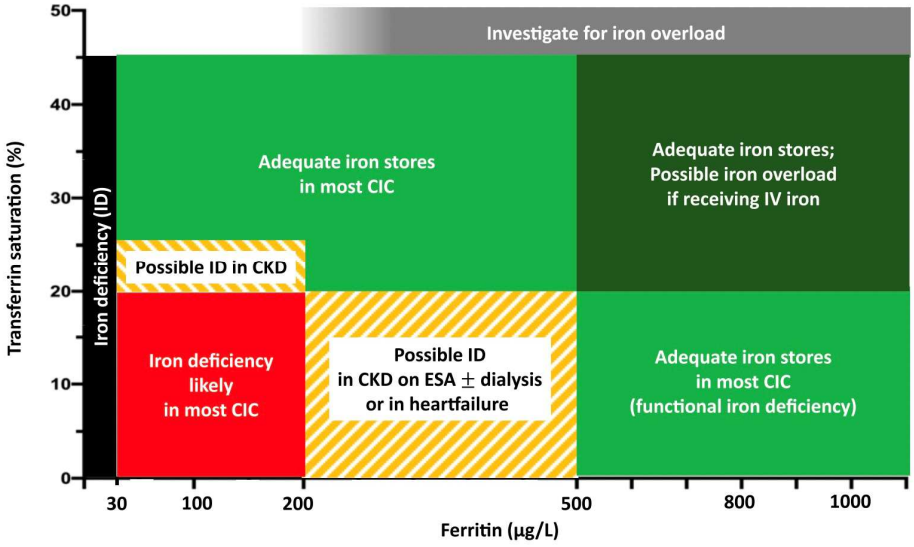
Iron indices in anemia of CIC



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(Fertrin KY. *Hematology Am Soc Hematol Educ Program* 2020;2020:478)

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Evaluating and treating anemia of CIC

- In all patients with anemia and an active inflammatory state:
  - Iron saturation < 20% and ferritin < 200 ng/mL suggests iron deficiency
  - Consider checking sTfR
- If iron deficiency is present with CIC and symptomatic anemia:
  - Consider treating with IV iron

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(Fertrin KY. *Hematology Am Soc Hematol Educ Program* 2020;2020:478)

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Case 2: A.D.

A.D. is a 56-year-old man who is hospitalized for progressive fatigue, exertional dyspnea, and mental fogginess. His past medical history is remarkable for rheumatoid arthritis, which is very active and debilitating, and which is being treated with etanercept, with poor control. His labs show the following:

Lab parameter	Value	Reference range	Units
Hemoglobin	7.9	12-15	g/dL
MCV	83	80-100	fL
Iron	65	60-170	mcg/dL
Ferritin	89	20-150	ng/mL

Which of the following is the most appropriate intervention to treat this patient's anemia?

1. RBC transfusion
2. PO iron
3. IV iron
4. Erythropoiesis stimulating agent

The iron saturation of < 20% with ferritin < 200 ng/mL in the setting of active rheumatoid arthritis suggests iron deficiency in the presence of CIC. As he is symptomatic from his anemia, he is treated with iron dextran 1000 mg IV.

Case 3: B.E.

B.E. is a 30-year-old man who is hospitalized for fatigue due to severe anemia. He has not had diarrhea, abnormal stools, melena, hematochezia, hematuria, or any bleeding manifestations. His dietary intake has been broad. He has no other health problems.

Lab parameter	Value	Reference range	Units
WBC	4,400	4-10,000	per mcL
Hemoglobin	6.3	12-15	g/dL
Platelets	197,000	150-350,000	per mcL
MCV	62	80-100	fL
RBC count	2.3	4.2-5.4	million/mcL
Reticulocyte count	1	-	%
Iron	15	60-170	mcg/dL
TIBC	475	240-450	mcg/dL
Ferritin	4	20-150	ng/mL
H. pylori breath test	Negative	Negative	-
Fecal occult blood test	Negative	Negative	-

What is (are) the most appropriate next step(s) in evaluating the etiology of his iron deficiency anemia?

1. Colonoscopy and/or endoscopy
2. Serologic testing for celiac disease
3. Serologic testing for pernicious anemia
4. All of the above

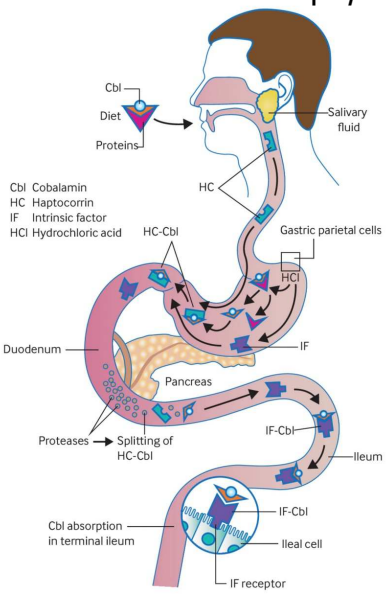
Clinical pearl

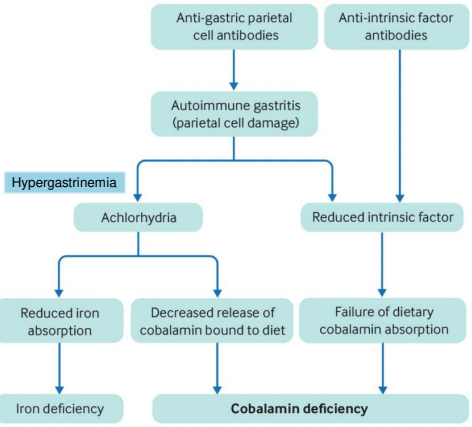
Patients with unexplained iron deficiency anemia should be evaluated for blood loss, H. pylori, celiac disease, & pernicious anemia

Blood loss, H. pylori & celiac disease make sense

Pernicious anemia as a cause of iron deficiency may be surprising

Vitamin B12 physiology & pernicious anemia





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(Mohamed M et al *BMJ* 2020;369:m1319)

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Iron deficiency is common in pernicious anemia

	Macrocytic	Normocytic	Microcytic
n	29	48	83
Mean age ± 1 SD, y	62 ± 15	58 ± 17	41 ± 15
Gender, M/F	17/12	18/30	18/65
Anemic, n (%)	18 (62)	19 (40)	83 (100)
Cobalamin deficiency, n (%)	29 (100)	44 (92)	38 (46)
Iron deficiency, n (%)	3 (10)	24 (50)	83 (100)
Thyroid disease, n (%)	3 (10)	14 (29)	15 (18)
Hypothyroid	3	12	12
Graves	0	1	2
Hashimoto	0	1	1
Intrinsic factor antibodies, %	20	40	38
Vitiligo	2	0	0
Diabetes mellitus, n (%)	1 (3)	4 (8)	7 (8)
Neurologic complications, n (%)	5 (17)	2 (4)	0 (0)
Gastric histology, n	13	24	32
Atrophic gastritis, n (%)	9 (69)	13 (54)	13 (41)
Chronic gastritis, n (%)	2 (15)	9 (38)	18 (56)
MALT, n (%)	1 (8)	1 (4)	0 (0)
GI neoplasia, n (%)	1 adeno Ca (8)	1 polyp (4)	1 polyp (3)

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(Hershko C and Camaschella C, *Blood* 2014;123:326)

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Testing for pernicious anemia

- Intrinsic factor antibody — Low sensitivity, High specificity
- Gastric parietal cell antibody — High sensitivity, Low specificity
- Fasting serum gastrin level — Variable sensitivity, Variable specificity

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(Snow CF, *Arch Intern Med* 1999;159:1289; Carmel R, *Blood* 2008;112:2214; Hershko C and Camaschella C, *Blood* 2014;123:326)

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Case 3: B.E.

B.E. is a 30-year-old man who is hospitalized for fatigue due to severe anemia. He has not had diarrhea, abnormal stools, melena, hematochezia, hematuria, or any bleeding manifestations. His dietary intake has been broad. He has no other health problems.

Lab parameter	Value	Reference range	Units
Hemoglobin	6.3	12-15	g/dL
MCV	62	80-100	fL
Reticulocyte count	1	-	%
TIBC	475	240-450	mcg/dL
H. pylori breath test	Negative	Negative	

What is (are) the most appropriate next step(s) in evaluating the etiology of his iron deficiency anemia?

1. Colonoscopy and/or endoscopy
2. Serologic testing for celiac disease
3. Serologic testing for pernicious anemia
4. All of the above

Serologic testing for celiac disease shows elevated transglutaminase IgA antibodies with a normal IgA level. Serologic testing for pernicious anemia shows a negative intrinsic factor antibody test with positive gastric parietal cell antibody and a high gastrin level. An upper endoscopy with gastric and duodenal biopsies confirms both pernicious anemia and celiac disease.

Case 4: F.T.

F.T. is a 40-year-old woman who is hospitalized for fatigue, with discovery of severe anemia. She has no other past medical history. Her menses are not heavy. Her dietary intake has been broad. She has had no melena or hematochezia. A colonoscopy is unrevealing.

Lab parameter	Value	Reference range	Units
WBC	4,400	4-10,000	per mcL
Hemoglobin	5.2	12-15	g/dL
Platelets	230,000	150-350,000	per mcL
MCV	119	80-100	fL
Vitamin B12	148	200-900	pg/mL
Intrinsic factor antibody	Positive	Negative	mcg/dL

Does she need an upper endoscopy?

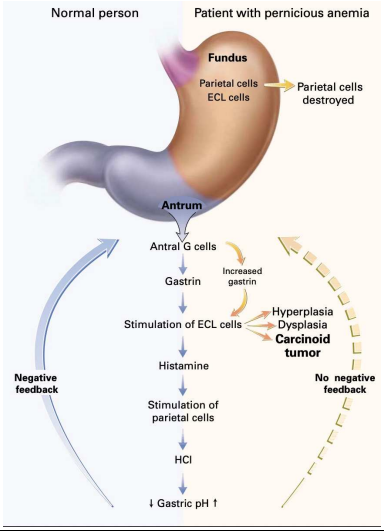
but not just to confirm a diagnosis of pernicious anemia…

1. Yes
2. No

Clinical pearl

Pernicious anemia is associated with gastric carcinoid and gastric adenocarcinoma

Hypergastrinemia drives development of gastric carcinoid in pernicious anemia



(*N Engl J Med* 1997;336:861)

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Pernicious anemia is associated with multiple GI and other cancers

Cancer type	Total	Individuals with pernicious anemia, %	OR (95% CI)[a]	*P*
Controls	100,000	1.5		
All cancers	1,138,390	1.5	1.07 (1.01–1.14)	.017
Lip	2340	1.5	1.07 (0.76–1.51)	.701
Tongue	4486	1.9	1.43 (1.15–1.79)	.002
Salivary gland	2482	1.7	1.06 (0.78–1.45)	.710
Floor of mouth	1412	1.7	1.39 (0.92–2.09)	.118
Gum and other mouth	3796	2.2	1.41 (1.12–1.77)	.003
Nasopharynx	779	1.9	1.63 (0.98–2.73)	.062
Tonsil	1583	2.1	2.00 (1.40–2.85)	.0001
Hypopharynx	1660	2	1.92 (1.35–2.73)	.0003
Esophagus	11,442	2	1.45 (1.25–1.68)	7.54×10^{-7}
Esophageal squamous cell carcinoma	4732	2.8	2.12 (1.76–2.55)	1.22×10^{-15}
Esophageal adenocarcinoma	5488	1.3	1.00 (0.79–1.28)	.98
Stomach	22,860	3.1	2.02 (1.84–2.22)	$<1.11 \times 10^{-16}$
Small intestine	3694	2.5	1.63 (1.32–2.02)	8.49×10^{-6}
Total colorectal	149,339	1.6	0.95 (0.89–1.02)	.190
Proximal colon	66,404	1.9	1.06 (0.98–1.15)	.170
Distal colon	40,862	1.4	0.89 (0.80–0.98)	.022
Total colon	112,777	1.7	1.00 (0.93–1.07)	.910
Rectum	36,562	1.2	0.82 (0.74–0.92)	.0004
Anus, anal canal, and anorectum	2633	1.6	1.02 (0.75–1.39)	.884
Liver	10,219	2	1.49 (1.28–1.73)	1.98×10^{-7}

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(Murphy G et al, *Clin Gastroenterol Hepatol* 2015;13:2282)

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All patients with pernicious anemia should undergo endoscopic evaluation to screen for gastric carcinoid and other gastric cancers

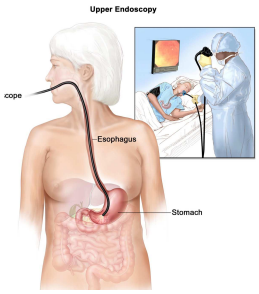
NIH NATIONAL CANCER INSTITUTE

Stomach Cancer Screening

Tests to screen for stomach cancer

Some people who have a higher risk of stomach cancer may benefit from screening with upper endoscopy, including:

- older people with chronic gastric atrophy or pernicious anemia
- people who have had
  - partial gastrectomy
  - a family history of stomach cancer
- people who have certain genetic syndromes
- people from countries where stomach cancer is more common



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Case 4: F.T.

F.T. is a 40-year-old woman who is hospitalized for fatigue, with discovery of severe anemia. She has no other past medical history. Her menses are not heavy. Her dietary intake has been broad. She has had no melena or hematochezia. A colonoscopy is unrevealing.

Lab parameter	Value	Reference range	Units
Hemoglobin	5.2	12-15	g/dL
MCV	119	80-100	fL
Intrinsic factor antibody	Positive	Negative	mcg/dL

but not just to confirm a diagnosis of pernicious anemia …

Does she need an upper endoscopy?

1. Yes
2. No

An upper endoscopy shows atrophic gastritis consistent with pernicious anemia, and a localized gastric carcinoid, which is followed thereafter by surveillance endoscopies.

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Case 5: K.P.

K.P. is a 71-year-old woman who is admitted for fatigue, which has been slowly evolving over the past year. She had a colonoscopy 5 years ago that showed no pathology, with normal blood counts and chemistries at that time. She has not seen a provider since then.

Lab parameter	Value	Reference range	Units
Creatinine	3.6	0.6-1.1	mg/dL
ALT	28	4-36	U/L
AST	24	8-33	U/L
Albumin	3.4	3.4-5.4	mg/dL
Globulin	4.2	2.0-3.5	mg/dL
WBC	9,100	4-10,000	per mcL
Hemoglobin	10.2	12-15	g/dL
Platelets	324,000	150-350,000	per mcL
MCV	104	80-100	fL
Absolute reticulocyte count	45,000	-	per mcL

What is the most important set of labs to check in this patient's case?

1. Iron, TIBC, ferritin
2. Vitamin B12, folate, methylmalonic acid, homocysteine
3. Serum protein electrophoresis, serum immunofixation, serum free light chains

Clinical pearl

A bone marrow problem may be suspected when anemia is accompanied by certain other laboratory features

- *Additional cytopenias*
- *Abnormal circulating cells/morphologies*
- *"CRAB" criteria +/- an elevated globulin level*

Anemia with other cytopenias

Malignant

- Leukemias
- Lymphoma and lymphoproliferative diseases
- Myelodysplastic syndromes
- Myeloproliferative neoplasms
- Aplastic anemia
- Bone marrow failure

Non-malignant

Micronutrient deficiency, medication/drug, infection, sepsis, critical illness, autoimmune, consumptive

Anemia with abnormal circulating cells/morphologies

Blasts

Raise concern for leukemia

Others that may sometimes be of concern

- Smudge cells … chronic lymphocytic leukemia
- Basophils … myeloproliferative neoplasms
- Plasma cells … plasma cell dyscrasias
- Monocytes (i.e., chronic monocytosis) … chronic myelomonocytic leukemia
- Nucleated red blood cells … myelofibrosis or myelophthisis
- Teardrop red cells … myelofibrosis or myelophthisis
- Schistocytes … thrombotic microangiopathies

Anemia with "CRAB" criteria +/- elevated globulin …

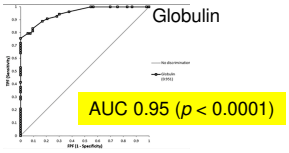
concern for multiple myeloma

CRAB criteria

- Hypercalcemia
- Renal impairment
- Anemia
- Bone lesions

Elevated globulin may be a screening tool for multiple myeloma

ROC for globulin to predict multiple myeloma



Screening tests for monoclonal gammopathies:

- Serum protein electrophoresis
- Serum immunofixation
- Serum free light chains (kappa/lambda)

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(Dispenzieri A et al, *Leukemia* 2009;23:215; O'Brien A et al, *Clin Biochem* 2023;116:13)

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Case 5: K.P.

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Lab parameter	Value	Reference range	Units
ALT	28	4-36	U/L
Albumin	3.4	3.4-5.4	mg/dL
WBC	9,100	4-10,000	per mcL
Platelets	324,000	150-350,000	per mcL
Absolute reticulocyte count	45,000	-	per mcL

What is the most important set of labs to check in this patient's case?

1. Iron, TIBC, ferritin
2. Vitamin B12, folate, methylmalonic acid, homocysteine
3. Serum protein electrophoresis, serum immunofixation, serum free light chains

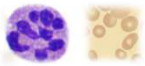
Based on the constellation of renal impairment and an elevated globulin, serum protein electrophoresis, serum immunofixation, and serum free light chains are obtained, which show IgG kappa monoclonal gammopathy. A bone marrow biopsy and aspirate are consistent with multiple myeloma.

Case 6: J.B.

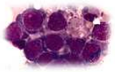
J.B. is a 46-year-old man who is admitted for profound fatigue of several months' duration. He has also had paresthesias in his hands & feet.

Lab parameter	Value	Reference range	Units
WBC	3,100	4-10,000	per mcL
Hemoglobin	3.3	12-15	g/dL
Platelets	28,000	150-350,000	per mcL
MCV	122	80-100	fL
Reticulocyte count	0.3	-	%
Vitamin B12	862	200-900	pg/mL
Lactate dehydrogenase (LDH)	4215	120-240	U/L
Haptoglobin	< 10	30-200	mg/dL
Direct antiglobulin (Coombs) test	Negative	Negative	-
Ferritin	140	20-150	ng/mL

A peripheral blood smear shows hypersegmented neutrophils and macro-ovalocyte RBCs.



A bone marrow biopsy and aspirate shows megaloblastic erythroid precursors & dysplasia.



What is the most appropriate next step in evaluating this patient?

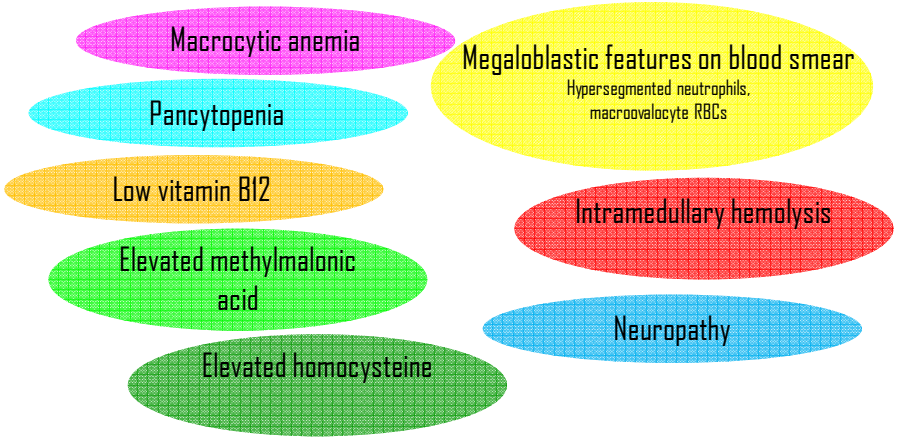
1. Check marrow karyotype
2. Check marrow next generation sequencing
3. Check HIV
4. Check methylmalonic acid & homocysteine

Clinical pearls

Vitamin B12 deficiency can be very difficult to diagnose as no single test is entirely adequate

Patients with vitamin B12 deficiency can have completely normal measured vitamin B12 levels, especially in pernicious anemia

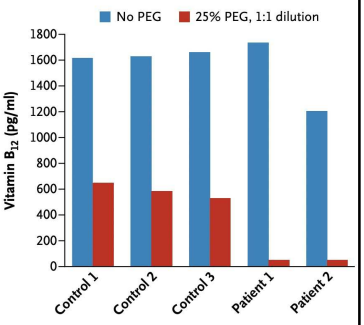
Pathologic & laboratory features of vitamin B12 deficiency



Any of these, alone or in combination, can be seen in vitamin B12 deficiency

Intrinsic factor antibodies may interfere with vitamin B12 measurements

Serum Sample No.	Anti–Intrinsic Factor Anti-bodies	Radioisotope-Dilution Assay	Competitive-Binding Luminescence Assay			Cause of Cobalamin Deficiency
			No. 1†	No. 2‡	No. 3§	
			cobalamin level — ng/liter			
1	Negative	0	56	94	86	Pernicious anemia
2	Negative	10	65	106	114	Malabsorption of cobalamin in food¶
3	Negative	13	75	72	116	Pernicious anemia
4	Negative	23	20	87	116	Veganism¶
5	Negative	25	0	60	105	Pernicious anemia
6	Negative	25	30	83	106	Postgastrectomy state¶
7	Negative	60	97	167	173	Pernicious anemia
8	Negative	149	155	215	200	Pernicious anemia
9	Positive	0	29	88	103	Pernicious anemia
10	Positive	3	0	57	97	Pernicious anemia
11	Positive	12	239	71	181	Pernicious anemia
12	Positive	17	2	66	129	Pernicious anemia
13	Positive	53	92	141	288	Pernicious anemia
14	Positive	64	123	158	170	Pernicious anemia
15	Positive	88	258	352	313	Pernicious anemia
16	Positive	97	126	185	161	Pernicious anemia
17	Positive	120	126	186	175	Pernicious anemia
18	Positive	127	118	202	206	Pernicious anemia
19	Positive	151	247	234	270	Pernicious anemia
20	Positive	158	268	263	303	Pernicious anemia
21	Positive	162	259	322	306	Pernicious anemia
22	Positive	165	147	216	219	Pernicious anemia
23	Positive	172	188	234	269	Pernicious anemia
Reference interval		190–1016	180–914	223–925	200–700‖	



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(Yang DT and Cook RJ, *N Engl J Med* 2012;366:1742; Carmel R et al, *N Engl J Med* 2012;367:385)

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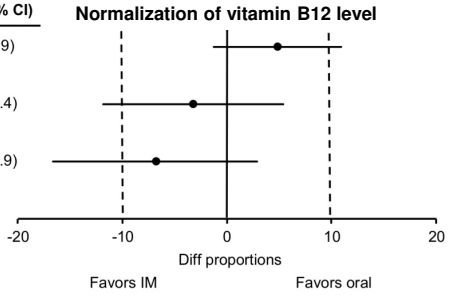
PO and IM vitamin B12 replacement may be equivalent in vitamin B12 deficiency…

Visit	Oral route n/N (%)	IM route n/N (%)	Difference in proportions (95% CI)
Week 8	133/140 (95.0)	129/143 (90.2)	4.8 (-1.3 to 10.9)
Week 26	115/140 (82.1)	122/143 (85.3)	-3.2 (-11.8 to 5.4)
Week 52	103/140 (73.6)	115/143 (80.4)	-6.8 (-16.6 to 2.9)



	Oral route		IM route			
At least one altered sign (glossitis and/or altered vibration sensitivity and/or altered position sensitivity)						
Visit	**N**	**n (%)**	**N**	**n (%)**	**P value**	**Proportion difference (95% CI)**
Baseline	140	16 (11.4)	143	21 (14.7)	0.416	–3.3 (–11.1 to 4.6)
Week 8	135	15 (11.1)	130	13 (10.0)	0.769	1.1 (–6.3 to 8.5)
Week 26	131	14 (10.7)	122	12 (9.8)	0.824	0.9 (–6.6 to 8.3)
Week 52	122	14 (12.5)	117	9 (7.7)	0.226	3.8 (–3.7 to 11.2)

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(Sanz-Questa T et al, *BMJ Open* 2020;10:e033687)

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PO and IM vitamin B12 replacement may be equivalent in vitamin B12 deficiency…

… But by convention, a lot of patients and providers still favor IM over PO vitamin B12 particularly in elderly patients with pernicious anemia and neurological manifestations

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(Green R, *Blood* 2017;129:2603)

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Case 6: J.B.

J.B. is a 46-year-old man who is admitted for profound fatigue of several months' duration. He has also had paresthesias in his hands & feet.

Lab parameter	Value	Reference range	Units
Hemoglobin	3.3	12-15	g/dL
MCV	122	80-100	fL
Vitamin B12	862	200-900	pg/mL
Haptoglobin	< 10	30-200	mg/dL
Ferritin	140	20-150	ng/mL

A peripheral blood smear shows hypersegmented neutrophils and macro-ovalocyte RBCs.

A bone marrow biopsy and aspirate shows megaloblastic erythroid precursors & dysplasia.

What is the most appropriate next step in evaluating this patient?

1. Check marrow karyotype
2. Check marrow next generation sequencing
3. Check HIV
4. Check methylmalonic acid & homocysteine

Measurements of methylmalonic acid and homocysteine are both high, suggesting vitamin B12 deficiency. Serologic testing is positive for intrinsic factor antibodies with an elevated gastrin level. An upper endoscopy shows atrophic gastritis, consistent with pernicious anemia. He is treated with IM vitamin B12 1000 mcg daily for 7 days, then weekly for 4 weeks, then monthly thereafter.

Case 7: T.R.

T.R. is an 88-year-old woman who is admitted for gastrointestinal bleeding. She is discovered to have a gastric ulcer, which is treated endoscopically with epinephrine. Her course is complicated by NSTEMI, attributed to demand ischemia due to severe anemia.

Lab parameter	Value	Reference range	Units
WBC	9,400	4-10,000	per mcL
Hemoglobin	5.3	12-15	g/dL
Platelets	350,000	150-350,000	per mcL
Troponin T	0.39	0-0.04	ng/mL

What is her optimal hemoglobin target for RBC transfusion?

1. 7 g/dL
2. 10 g/dL
3. Not sure

Clinical pearl

Most RBC transfusion studies favor a restrictive rather than a liberal strategy, except in myocardial infarction, where the literature is conflicting

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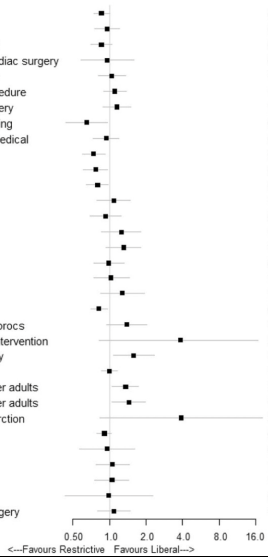
Summary of major RBC transfusion trials

Study	Timepoint	Setting or Subgroup	Risk Ratio (95% CI)	GRADE
Holst 2015	Mixed	Mixed specialties	0.86 (0.74, 1.01)	High
Shehata 2018	≤30-day	Cardiac surgery	0.96 (0.76, 1.21)	Moderate
Melchor 2016	Mixed	Critical care and ACS	0.86 (0.70, 1.05)	Moderate
Docherty 2016	30-day	CVD-stratified, no cardiac surgery	0.96 (0.58, 1.59)	Moderate
Cortes Puch 2018	≤30-day	CVD, cardiac surgery	1.04 (0.81, 1.35)	Moderate
Cortes Puch 2018	≤30-day	CVD, no cardiac procedure	1.11 (0.90, 1.37)	Moderate
Docherty 2016	30-day	CVD, no cardiac surgery	1.15 (0.88, 1.50)	Moderate
Odutayo 2017	Mixed	Gastrointestinal bleeding	0.65 (0.44, 0.97)	Moderate
Hovaguimian 2016	≤30-day	Acute care surgical/medical	0.94 (0.73, 1.20)	Moderate
Salpeter 2014	Hospital	Mixed specialties	0.74 (0.60, 0.92)	Moderate
Salpeter 2014	30 day	Mixed specialties	0.77 (0.61, 0.96)	Moderate
Salpeter 2014	Mixed	Mixed specialties	0.80 (0.65, 0.98)	Moderate
Brunskill 2015	30-day	Orthopaedic surgery	1.09 (0.79, 1.49)	Moderate
Brunskill 2015	60-day	Orthopaedic surgery	0.93 (0.69, 1.25)	Moderate
Brunskill 2015	90-day	Orthopaedic surgery	1.25 (0.86, 1.82)	Moderate
Chong 2018	30-day	Perioperative	1.31 (0.94, 1.82)†	Moderate
Carson 2018	30-day	Cardiac surgery	0.99 (0.74, 1.33)	Low
Kheiri 2018	≤30-day	Cardiac surgery	1.03 (0.74, 1.45)	Low
Patel 2015	30-day	Cardiac surgery	1.28 (0.85, 1.94)*†	Low
Chong 2018	30-day	Critical care	0.82 (0.70, 0.97)†	Low
Hovaguimian 2016	≤30-day	CVD, cardiovascular procs	1.39 (0.95, 2.04)	Low
Cortes Puch 2018	≤30-day	CVD, percutaneous intervention	3.85 (0.82, 16.67)	Low
Luo 2018	60-day	Haematology/oncology	1.58 (1.08, 2.33)†	Low
Carson 2018	30-day	Mixed specialties	1.00 (0.86, 1.16)	Low
Simon 2017	30-day	Mixed specialties, older adults	1.36 (1.05, 1.74)	Low
Simon 2017	90-day	Mixed specialties, older adults	1.45 (1.05, 1.98)	Low
Carson 2018	30-day	Acute myocardial Infarction	3.88 (0.83, 18.13)	Low
Patel 2015	30-day	Non-cardiac surgery	0.91 (0.79, 1.04)†	Low
Gu 2018	30-day	Orthopaedic surgery	0.96 (0.57, 1.62)	Low
Mao 2017	30-day	Orthopaedic surgery	1.06 (0.78, 1.45)	Low
Mitchell 2017	ND	Orthopaedic surgery	1.05 (0.76, 1.44)	Low
Muller 2018	30-day	Orthopaedic surgery	0.98 (0.43, 2.27)	Low
Hovaguimian 2016	≤30-day	CVD, orthopaedic surgery	1.09 (0.80, 1.49)	Low



(Trentino KM et al, *BMC Med* 2020;18:154)

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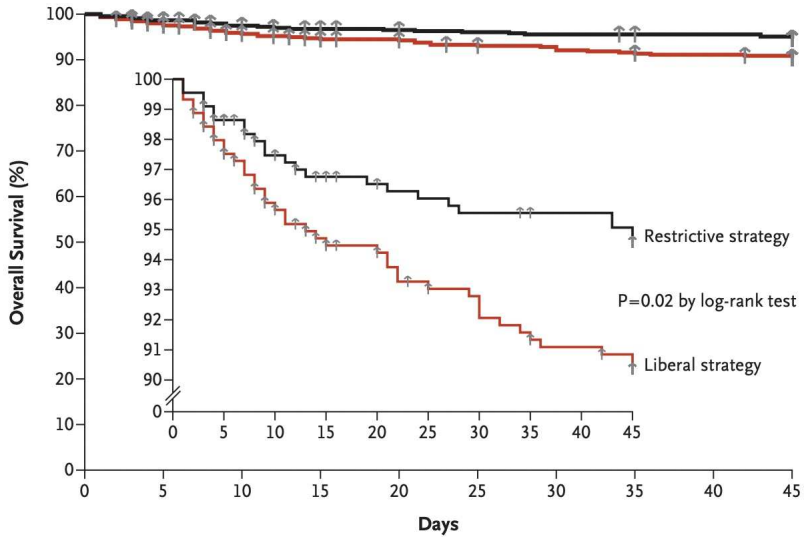
RBC transfusions in GI bleeding



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(Villanueva C et al, *N Engl J Med* 2013;368:11)

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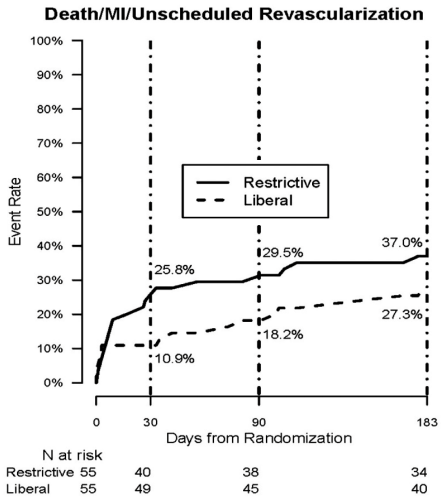
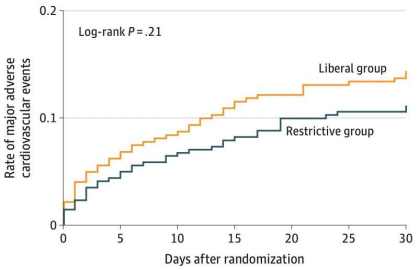
RBC transfusions in myocardial infarction





No. of patients at risk

Liberal group	324	301	293	285	281	278	275
Restrictive group	342	326	319	314	307	305	305

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(Carson JL et al, *Am Heart J* 2013;165:964; Ducrocq G et al, *JAMA* 2021;325:552)

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Case 7: T.R.

T.R. is an 88-year-old woman who is admitted for gastrointestinal bleeding. She is discovered to have a gastric ulcer, which is treated endoscopically with epinephrine. Her course is complicated by NSTEMI, attributed to demand ischemia due to severe anemia.

Lab parameter	Value	Reference range	Units
Hemoglobin	5.3	12-15	g/dL
Troponin T	0.39	0-0.04	ng/mL

What is her optimal hemoglobin target for RBC transfusion?

1. 7 g/dL
2. 10 g/dL
3. Not sure

Following extensive multidisciplinary discussion amongst the cardiology, gastroenterology, hematology, and hospitalist services, the patient is transfused RBC according to a restrictive strategy with a hemoglobin target of 7 g/dL.

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Case 8: E.J.

E.J. is a 53-year-old man with a history of DVT/PE, on long-term anticoagulation with reduced-dose rivaroxaban. He is a Jehovah's witness and declines all human blood product transfusions. He is admitted after a motor vehicle accident, with development of hemoperitoneum, which is treated non-operatively with administration of 4-factor prothrombin complex concentrate and cessation of rivaroxaban.

Lab parameter	Value	Reference range	Units
WBC	10,000	4-10,000	per mcL
Hemoglobin	5.8	12-15	g/dL
Platelets	410,000	150-350,000	per mcL

Which of the following is (are) appropriate in managing this patient's anemia?

1. Clarify transfusion decisions with patient +/- church leaders
2. Minimize blood draws, using pediatric tubes
3. Administer IV iron
4. Administer vitamin B12 and folate
5. Start erythropoiesis stimulating agent
6. All of the above

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Clinical pearl

The care of patients with anemia who decline blood product transfusions is individualized, incorporating supportive measures while limiting blood draws

Bloodless medicine

Intervention	Comments
Iron	1000 mg IV total
Vitamin B12	1000 mcg IM single dose
Folic acid	1 mg PO daily
Epoetin alfa	Variable dosing regimens • 300 U/kg, or 20-30,000 U, daily for 3-15 days • 40,000 U SC weekly if hemoglobin > 7 g/dL
Restrict phlebotomy	• Minimize blood draws • Draw blood into pediatric tubes
Personal consultation	Review transfusion preferences with patient +/- family and advisors

(Resar LM and Frank SM, *Hematology Am Soc Hematol Educ Prog* 2014;2014:553; Shander A and Goodnough LT, *Am J Hematol* 2018;93:1183)

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4. Administer vitamin B12 and folate
5. Start erythropoiesis stimulating agent
6. All of the above

The patient is given iron dextran 1000 mg IV and vitamin B12 1000 mcg IM, started on folic acid 1 mg PO daily, and given epoetin alfa 20,000 U daily for 5 days. Lab draws are restricted to a CBC drawn in a pediatric tube every 3 days. A discussion with the patient and church elders confirms that he declines RBC, platelet, and plasma transfusions.

Case 9: N.R.

N.R. is a 34-year-old man who at age 21 sustained a splenic laceration requiring a splenectomy. He is admitted for one week of fever, fatigue, jaundice, and dark urine.

Lab parameter	Value	Reference range	Units
WBC	13,200	4-10,000	per mcL
Hemoglobin	4.4	12-15	g/dL
Platelets	288,000	150-350,000	per mcL
MCV	129	80-100	fL
Absolute reticulocyte count	350,000	-	per mcL
LDH	1531	120-240	U/L
Haptoglobin	< 10	30-200	mg/dL
Bilirubin	3.5	≤1.2	mg/dL
Direct antiglobulin (Coombs) test	Negative	Negative	-

What is the most appropriate next step in evaluating this patient?

1. Review peripheral blood smear
2. Check iron, TIBC, and ferritin
3. Check vitamin B12
4. Check folate

Clinical pearl

The peripheral blood smear is central to evaluation of hemolytic anemia

Approach to hemolytic anemia

Hemolytic anemia may be categorized according to whether the pathophysiology is autoimmune or non-immune

Autoimmune

Warm autoimmune hemolytic anemia

- IgG autoantibodies lead to extravascular hemolysis via splenic macrophages
- Direct antiglobulin (Coombs) test
  IgG+, C3-negative

Cold autoimmune hemolytic anemia

- IgM autoantibodies lead to intravascular hemolysis via complement activation
- Direct antiglobulin (Coombs) test
  IgG-negative, C3+

Non-immune

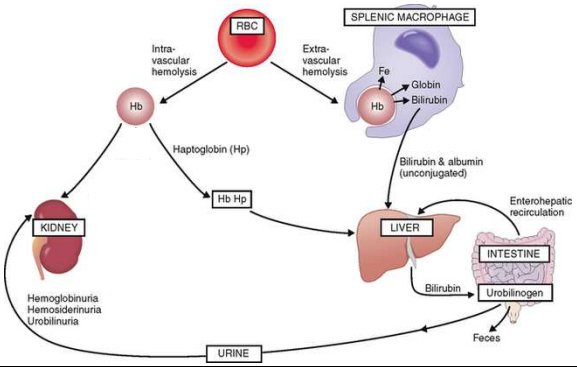
"Everything else"

Thrombotic microangiopathy
Disseminated intravascular coagulation
RBC parasites
Hereditary RBC disorders
Hemoglobin disorders

Approach to hemolytic anemia

Hemolytic anemia may be categorized according to site of RBC destruction

Intravascular: blood vessels	Extravascular: spleen



Approach to hemolytic anemia

Hemolytic anemia may be categorized according to site of RBC destruction

Intravascular: blood vessels	Extravascular: spleen
↑↑↑ LDH ↓↓↓ Haptoglobin ↑ Reticulocyte count ↑ Indirect bilirubin	↑ LDH ↓ Haptoglobin ↑ Reticulocyte count ↑↑↑ Indirect bilirubin
E.g.: cold autoimmune hemolytic anemia, microangiopathic hemolytic anemia, RBC parasites	E.g.: warm autoimmune hemolytic anemia, hereditary RBC disorders, hemoglobin disorders

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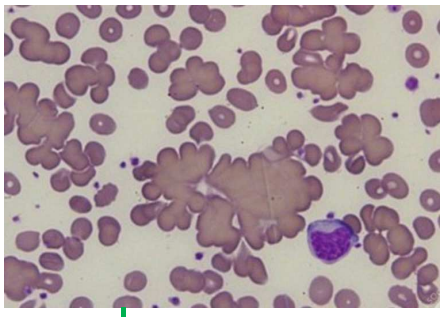
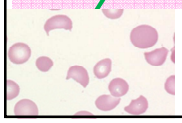
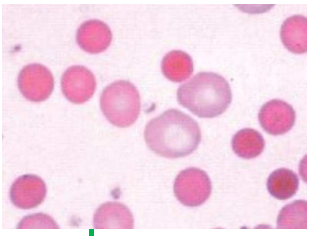
Approach to hemolytic anemia

Peripheral blood smear examples

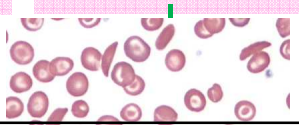


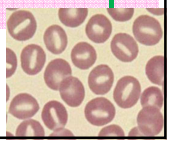
E.g.: cold autoimmune hemolytic anemia, microangiopathic hemolytic anemia, RBC parasites





E.g.: warm autoimmune hemolytic anemia, hereditary RBC disorders, hemoglobin disorders





Case 9: N.R.

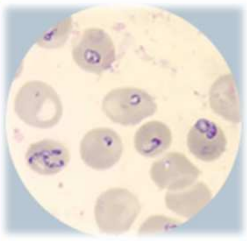
N.R. is a 34-year-old man who at age 21 sustained a splenic laceration requiring a splenectomy. He is admitted for one week of fever, fatigue, jaundice, and dark urine.

Lab parameter	Value	Reference range	Units
Hemoglobin	4.4	12-15	g/dL
MCV	129	80-100	fL
LDH	1531	120-240	U/L
Bilirubin	3.5	<1.2	mg/dL

What is the most appropriate next step in evaluating or managing this patient?

1. Review peripheral blood smear
2. Check iron, TIBC, and ferritin
3. Check vitamin B12
4. Check folate

The peripheral blood smear shows intracellular RBC forms consistent with Babesia. His parasite titre is 11%. He is diagnosed with severe Babesia infection in the setting of prior splenectomy and treated with antimicrobial therapy and RBC exchange transfusion.



Summary: anemia for hospitalists

Categorization of anemia based on RBC size & reticulocyte response

Evaluation of monoclonal gammopathy

Iron deficiency & administration of IV iron

RBC transfusion targets

Anemia of inflammation/CIC

Vitamin B12 deficiency (with hemolysis & pancytopenia)

Bloodless medicine

Pernicious anemia

Hemolytic anemia

Anemia with abnormal cells/morphologies (blasts, schistocytes, etc.)

Summary: anemia for hospitalists

- What are the basic labs to check when evaluating anemia?
  - Iron, TIBC, ferritin, vitamin B12, folate, methylmalonic acid, homocysteine, LDH, haptoglobin, reticulocyte count, smear
- What features of anemia warrant hematology consultation?
  - Severe anemia
  - Unexplained or puzzling anemia
  - Anemia with other cytopenias
  - Anemia with abnormal cell types
  - Anemia with CRAB criteria +/- elevated globulin
  - Hemolytic anemia
  - Anemia with schistocytes

Questions?