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Improving Outcomes in Geriatric Anemia

A Guide to the Differential Diagnosis of Treatable Causes

Brian Koffman, MDCM
Medical Director, CLL Society Inc.
Partner, St. Jude Heritage Medical Group
Diamond Bar, CA
Clinical Professor (Retired)
Department of Family Medicine
Keck School of Medicine, USC Family Practice
Los Angeles, CA

David P. Steensma, MD, FACP
Senior Physician, Dana-Farber Cancer Institute
Associate Professor of Medicine
Harvard Medical School
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Free Accompanying Mobile App!

A free anemia algorithm mobile app is available that covers concepts in this presentation

- The App icon is included on slides where the app would be especially useful
- **To download go to the Google Play store (Android phone/tablet users) or iTunes store (iPhone, iPad users)**

ANDROID APP ON Google play

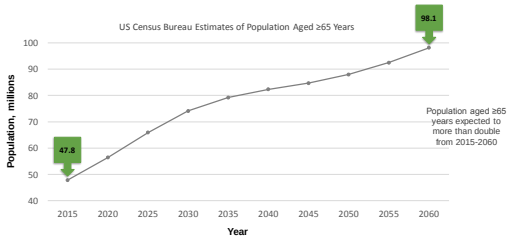
Available in the iPhone App Store

CLARITY COMMUNICATIONS

Anemia Best Practices

- **Anemia should not be considered a normal part of the aging process** and should be evaluated further
  - A cause can often be determined, and treatment may alter outcomes and improve quality of life (QOL)
- **Use mean cell volume (MCV)** to narrow differential diagnosis of geriatric anemia and determine initial tests
  - Microcytosis, MCV <80 fL
  - Normocytosis, MCV 80-100 fL
  - Macrocytosis, MCV >100 fL
- **Referral to hematologist** for possible bone marrow examination should be carefully considered in patients **with unexplained macrocytic anemia**

Who Are We Talking About?



US Census Bureau. *Projections of the Population by Sex and Selected Age Groups for the United States: 2015 to 2060 (Table 3)* http://www.census.gov/population/projections/data/national/2014/summarytables.html.

In 2016

- The life expectancy of a 65-year-old US male is:

  17 years

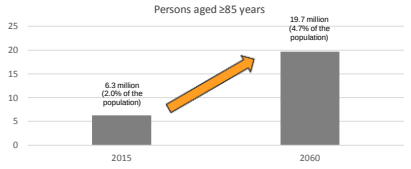
- The life expectancy of a 65-year-old US female is:

  19 years

Social Security Administration. Life Tables for the US Social Security Area 1900-2100. http://www.ssa.gov/oact/NOTES/as120/LifeTables_Body.html

Who Are We Talking About?

According to US Census Bureau projections persons **aged ≥85 years** are the **fastest growing segment** of the population



US Census Bureau. *Projections of the Population by Sex and Selected Age Groups for the United States: 2015 to 2060 (Table 3)* http://www.census.gov/population/projections/data/national/2014/summarytables.html.

Prevalence of Anemia

The oldest old persons, aged 85 years or older, are not only the fastest growing segment of the US population, they also have the highest prevalence of anemia

20% for women **26% for men**

Guralnik JM, et al. *Blood*. 2004;104:2263-2268.
Guralnik JM, et al. *Hematology*. 2005:528-532.

What is a "Normal" Hemoglobin?

App

Lower Limits of Normal Hemoglobin (g/dL) in Adults

Population	WHO (1968)	NHANES III (1994)* (20-59 years)	NHANES III (1994)* (>60 years)	Scripps-Kaiser (2006)*	Mayo Clinic CCL (2007)
White men	13	13.8	12.8	13.7	13.5
Black men	NRS	12.8	11.8	12.9	NRS
White women	12 (11 if pregnant)	12.2	12.0	12.2	12.0
Black women	NRS	11.3	11.3	11.5	NRS

*5% threshold in Gaussian distribution
NRS, not reported separately

Ethnic background, altitude of residence, smoking status, and **physiologic fluctuations of plasma volume** can influence hemoglobin

WHO. *World Health Organ Tech Rep Ser*. 1968;405:5-37.
Guralnik JM, et al. *Blood*. 2004;104:2263-2268.
Beutler E, et al. *Blood*. 2006;107:1747-1750.
Steensma DP, et al. *Mayo Clin Proc*. 2007;82:958-966.

Key Takeaway

The **cause of anemia** in the elderly, even if mild, **should be evaluated** for treatment to improve quality and quantity of life

Anemia Development is Predictive of Mortality in Older Persons

- During long-term follow-up (≤16 years) of the Cardiovascular Health Study (n=3,758), **anemia development*** (HR 1.39, 95% CI 1.15, 1.69) and **hemoglobin decline** (HR 1.11, 95% CI 1.04, 1.18 per 1 g/dL decrease) over 3 years **predicted subsequent mortality in men and women**
- Baseline increasing age, being African-American, and kidney disease predicted anemia development over 3 years
- Numerous other studies show similar results
- At-risk elderly individuals can be identified for early intervention to improve quality and quantity of life

*WHO criteria; Mean age=72.1 years
Zakai NA, et al. *Am J Hematol*. 2013;88:5-9.

Associations with a Low Hemoglobin Level in Older Persons

Increased

- Rates of **recurrent falls**
- Rates of **major depression**
- **Frailty** index
- Risk of **hospitalization** and longer duration in hospital

Decreased

- **Mobility**, **bone density**, skeletal **muscle mass**
- **Cognitive function**
- **Outcomes in specific diseases** (anemia as marker of disease severity – correlation ≠ causation)
  - Congestive heart failure (poorer hemodynamics, more symptoms, higher mortality)
  - Cancer (decreased survival)
  - HIV infection, independent of viral load

Steensma DP, et al. *Mayo Clin Proc*. 2007;82:958-966.

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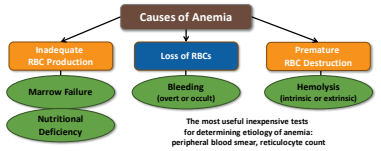
Anemia

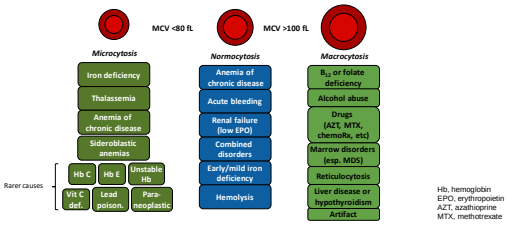
- Anemia is a sign of disease, **not a disease itself**
- Dozens of causes, many common
- Organized approach essential
- A specific cause can be found in almost all cases



Wolanskyj AP, et al. Hematology. In: Ficalora RD, ed. *Mayo Clinic Internal Medicine Board Review.* 10th ed. 2013;497-511.

Anemia Differential Diagnosis by MCV

App



Hb, hemoglobin
EPO, erythropoietin
AZT, azathioprine
MTX, methotrexate

Wolanskyj AP, et al. Hematology. In: Ficalora RD, ed. *Mayo Clinic Internal Medicine Board Review.* 10th ed. 2013;497-511.

Red Cell Distribution Width (RDW)

App

- RDW is the variation in RBC volume (reported as part of CBC)
- RDW= $\frac{SD\ of\ MCV}{MCV}$ X 100
- Normal RDW: 11%–15%
- Elevated RDW (>15%) known as anisocytosis
- RDW useful in identifying anemia of mixed causes

Low MCV Normal RDW	Low MCV Elevated RDW
• Anemia of chronic disease • Heterozygous thalassemia • Hemoglobin E trait	• Iron deficiency • β-thalassemia major
Normal MCV Normal RDW	**Normal MCV Elevated RDW**
• Anemia of chronic inflammation / renal disease • Acute blood loss or hemolysis	• Early iron, B_{12}, or folate deficiency • Mixed anemia (eg, combined iron and B_{12} deficiency) • Sickle cell disease
Elevated MCV Normal RDW	**Elevated MCV Elevated RDW**
• Aplastic anemia • Chronic liver disease • Antivirals / chemotherapy / alcohol	• Folate or vitamin B_{12} deficiency • Immune hemolytic anemia • Cytotoxic chemotherapy • Chronic liver disease • Myelodysplastic syndrome

SD, standard deviation

Marks PW, Glader B. Approach to Anemia in the Adult and Child. In: Hoffman F, et al. eds. *Hematology Basic Principles and Practice.* 5th. Philadelphia, PA: Churchill Livingstone/Elsevier;2009:439-446.

Reticulocytes

App

- **Immature RBCs** (typically ~1% of RBCs) containing ribosomal remnants that circulate in blood for about a day before fully developing into RBCs
- Serve as a **marker of marrow red cell production activity**
- Increase to compensate for severe loss of mature RBCs in conditions such as hemolytic anemia
  - Reticulocytosis = elevated number of reticulocytes in the blood
- Abnormally **low numbers indicate failure of erythropoiesis in marrow**
  - May indicate anemia of chronic inflammation, aplastic anemia, pernicious anemia, bone marrow malignancies, abnormal erythropoietin, vitamin or iron deficiencies, or chemotherapy

Brugnara C, et al. *Curr Opin Hematol.* 2013;20:222-230.

62-year-old Business Owner

- Seen for routine follow up of type 2 diabetes, no complaints
- Early retinopathy, neuropathy, and diabetic kidney disease
- Laboratory studies:
  - Hemoglobin: 10.2 g/dL; MCV: 90 fL
  - Fasting blood sugar: 146 mg/dL; HbA1c: 7.8%
  - Urine microalbumin screen: 100 mg/g creatinine (normal, <30)
  - BUN 42 mg/dL; creatinine 1.9 mg/dL; Estimated GFR: 35 mL/min/1.73 m2
  - Vitamin B_{12} (510 ng/L) and RBC folate within normal range

62-year-old Business Owner *CONTINUED*

- Iron studies
  - Serum ferritin: 58 ng/mL (normal range: 20-300 ng/mL)
  - Serum iron: 100 mcg/dL (normal range: 60-170 mcg/dL)
  - TIBC: 210 mcg/dL (normal range: 240-450 mcg/dL)
  - Transferrin saturation: 48% (normal range: 20%-50%)

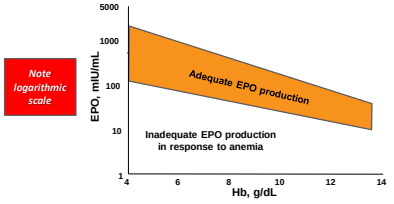
Anemia of CKD

- Increased prevalence as disease progresses; anemia is a risk factor for progression of ESRD
- Typically **normocytic, normochromic, and hypoproliferative** (i.e., low reticulocytes)
- **EPO deficiency** is the predominant cause
  - Relative EPO deficiency compared with similarly anemic patients with normal kidney function
- Associated with **disordered iron homeostasis**
  - Low serum transferrin saturation and normal to high serum ferritin with iron depletion in the bone marrow
  - Elevated hepcidin levels impair dietary iron absorption and iron mobilization from body stores
- Severity can be reduced by **correcting the iron deficiency** with iron supplementation
  - ESAs should be used after addressing all correctable causes of anemia

ESRD, end stage renal disease; CKD = chronic kidney disease; EPO = erythropoietin; ESA, erythropoiesis-stimulating agent

Babitt JL, et al. *J Am Soc Nephrol*. 2012;23:1631-1634.
KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. http://www.kdigo.org/clinical_practice_guidelines/pdf/KDIGO-Anemia%20GL.pdf

Relationship Between Serum EPO Level and Hb Level



Graphic shows the typical inverse relationship between erythropoietin levels and hemoglobin levels in anemia's not attributed to impaired erythropoietin production.
Cazzola M, et al. *Blood*. 1997;89(12):4248-4267.
Adapted with permission of American Society of Hematology from Use of Recombinant Human Erythropoietin Outside the Setting of Uremia, Cazzola, 89(12) 1997; permission conveyed through Copyright Clearance Center, Inc.

59-year-old Fitness Instructor

- Diagnosed with Crohn's disease at age 27
  - Symptoms have generally been mild to moderate and have responded to treatment with sulfasalazine, antibiotics, and budesonide in conjunction with nutritional therapy
- She now presents complaining of fatigue
- No bruising, bleeding, numbness, tingling or ataxia
- Other medications: NSAIDs for knee pain
- Surveillance colonoscopy performed 2 years ago was negative
- Physical examination:
  - Moderate pallor, some abdominal discomfort; otherwise unremarkable

59-year-old Fitness Instructor *CONTINUED*

- Complete blood count:
  - **Hemoglobin: 9.8 g/dL**
  - **MCV: 77 fl**
  - Hematocrit, RBC counts, and mean corpuscular hemoglobin all below normal ranges
  - Normal white blood count, differential and platelets
- **Ferritin 10 ng/mL** (normal range, 20-300 ng/mL)
- Transferrin saturation 9% (normal range 20%-50%)
- Erythrocyte sedimentation rate, albumin and C-reactive-protein levels within the normal ranges
- A stool sample tested positive for occult blood

Iron Deficiency Anemia (IDA)

App

- **Predominant cause of microcytic anemia in the US**
  - *BUT* up to 40% of patients with IDA are normocytic
- Most common causes of IDA:
  - Abnormal uterine bleeding (20%-30%)
  - GI bleeding due to long-term use of aspirin or other NSAIDS (10%-15%)
  - Colorectal polyps/carcinoma (5%-10%)
- **Dietary IDA is rare in the US**, but may be seen in vegetarians/vegans
  - Plants contain non-heme iron, which is less well absorbed
- Diagnosis requires laboratory-confirmed evidence of anemia, as well as evidence of low iron stores (usually **low serum ferritin**, sometimes **elevated soluble transferrin receptor**)
- Once diagnosed, the **cause of IDA should be evaluated**

Total iron binding capacity (TIBC)

- Iron is bound to transferrin in the plasma
- TIBC is a direct measure of level of transferrin (i.e., capacity to bind iron)
- Transferrin levels are increased in IDA and reduced in inflammation

Soluble transferrin receptor (sTfR)

- Cell surface transferrin receptors internalize transferrin resulting in intracellular release or iron
- Expression of transferrin receptors increase in the absence of adequate iron stores
- sTfR levels closely reflect iron stores and is not affected by the inflammatory process
- Increased levels of sTfR are also found in conditions of increased red cell turnover

Short MW, et al. *Am Fam Physician*. 2013;87:98-104; Camaschella C. *N Engl J Med*. 2015;372:1832-1843.

Key Takeaway

Ferritin level is **NOT** a reliable measure of iron storage in the body, because it is a positive acute-phase reactant

Oral Iron Therapy

- **Hb increase of ≥1 g/dL after one month of treatment** defines an adequate response to treatment and confirms the diagnosis
  - Reticulocytes should increase after 1 week
- Ferrous (2+ valence) salts are preferred because they are more readily absorbed than ferric (3+)
  - Vitamin C and an acidic stomach increase iron absorption in some patients

Form	Formulation	Elemental Iron	Typical Dosage
Ferrous fumarate	324-mg tablet	106 mg	One tablet twice per day
Ferrous gluconate	300-mg tablet	38 mg	1-3 tablets 2 or 3 times per day
Ferrous sulfate	325-mg tablet	65 mg	One tablet 3 times per day

- Adherence can be a challenge due to GI adverse events (epigastric discomfort, nausea, diarrhea, and constipation)
  - These effects may be reduced when iron is taken with meals, but absorption may decrease by 40%
- **"Eating more red meat" is never enough**! (100 g ribeye steak = 1.94 mg iron = 254 kcal)
- Medications such as proton pump inhibitors may reduce absorption of dietary iron and iron tablets

Short MW, et al. *Am Fam Physician*. 2013;87:98-104.

Intravenous Iron Therapy

- Considered **better tolerated and more effective than oral iron** treatment in improving ferritin
- Can be used in patients who cannot tolerate/absorb oral iron, eg, those who have undergone gastrectomy, gastrojejunostomy, bariatric surgery, or other small bowel surgeries
- HMW iron dextran should be avoided (and is no longer marketed)
- Available as solutions for injection; dose based on weight and desired change in Hb
- Iron deficient patients usually need 1000 – 1500 mg to replete

Form	Elemental Iron	Typical single dose
LMW iron dextran (e.g. InFed®) – can give as total dose infusion	50 mg/mL	Up to TDI
Sodium ferric gluconate (Nulecit™)	12.5 mg/mL	62.5 or 125 mg
Iron sucrose (Venofer®)	20 mg/mL	100 mg
Ferumoxytol (Feraheme®)	30 mg/mL	510 mg
Ferric carboxymaltose (Injectafer®)	50 mg/mL	750 mg

LMW, low molecular weight; HMW, high molecular weight.
Short MW, et al. *Am Fam Physician*. 2013;87:98-104; Rodgers GM, et al. *J Am Soc Nephrol*. 2008;19:833-840.

Microcytic-hypochromic Anemias (Common Causes)

App

Cause	Clinical/lab clues	Next test
Iron deficiency	▪ Low ferritin ▪ Low iron with high TIBC = low TfSat ▪ High sTfR ▪ High RDW ▪ High platelets ▪ Low hepcidin*	▪ GI evaluation, unless bleeding source obvious ▪ Consider celiac disease (antigliadin Ab)
Anemia of chronic disease/inflammation	▪ Normal or high ferritin ▪ Low iron/low TIBC ▪ Low sTfR ▪ RDW variable ▪ High hepcidin*	▪ ESR, CRP to confirm inflammation ▪ Specific immunological evaluation ▪ Serum EPO level

*Assays for serum hepcidin are in development

sTfR, soluble transferrin receptor. sTfR is not a positive acute-phase reactant that may be used to complement ferritin. In vitro diagnostic (IVD) assays for sTfR are available

TfSat, transferrin saturation; TIBC, total iron-binding capacity

Camaschella C. *N Engl J Med*. 2015;372:1832-1843.

Microcytic-hypochromic Anemias (Thalassemia Syndromes/Sickle Cell Disease)

App

Test	Iron deficiency	β-thalassemia	α-thalassemia	Sickle-cell disease
Family History/ Ethnicity	–	Chinese, other Asians, African Americans	SE Asian, Middle Eastern, Chinese, African	African descent; rare but still possible in others
MCV (<80 fL in adults*)	Low	Low	Low	Normal; low if thalassemia also present
RDW	High	Normal; occasionally high	Normal	Normal to high
Ferritin	Low	Normal	Normal	Normal to high
Hemoglobin electrophoresis / HPLC	Normal (may have reduced HbA_2)	Increased HbA_{2}, reduced HbA, and probably increased HbF	Adults: normal Newborns: may have HbH or Hb Bart's	$HbS^{\dagger}$ ± another abnormal Hb
Treatment	GI evaluation, unless bleeding source obvious	Trait: Asymptomatic[‡] Intermedia: ± transfusions Major: Lifelong transfusions, chelation	Trait: Asymptomatic[‡] Intermedia: Hemolysis which may need transfusions Major: Usually embryonic/ newborn lethal	Trait: Asymptomatic[‡] $HbSS^{\dagger}$: Transfusions to reduce HbS levels, chelation, hydroxyurea for painful venoocclusive crises, BMT $HbSC^{\dagger}$: Less severe than HbSS

HPLC, high-performance liquid chromatography
*<70 fl in children 6 months to 6 years of age; and <75 fl in children 7 to 12 years of age
†HbS=hemoglobin S (caused by a b-chain mutation); HbC=hemoglobin C; HbSC=compound heterozygote for HbS and HbC; HbSS=homozygous for HbS
‡Persons with trait are asymptomatic and require no treatment or long-term monitoring. They usually do not have IDA.

Muncie HL, Campbell JS. *Am Fam Physician*. 2009;80:339-344. Yawn BP et al. *JAMA*. 2014;312(10):1033-1048.

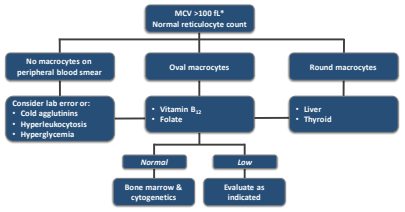
Microcytic-hypochromic Anemias (Rarer Causes)

App

Cause	Clinical/lab clues	Next test
Sideroblastic anemias	▪ High RDW/dimorphic picture	▪ Bone marrow exam
Vitamin C deficiency	▪ Petechiae, loose teeth; patient is typically alcoholic or malnourished	▪ Vitamin C level
Hemoglobin C	▪ African, chronic hemolysis	▪ Hemoglobin electrophoresis/HPLC
Hemoglobin E	▪ SE Asian, chronic hemolysis	▪ Hemoglobin electrophoresis/HPLC

RDW = red cell distribution width; SE = Southeast; HPLC = high performance liquid chromatography
Wolanskyj AP, et al. Hematology. In: Ficalora RD, ed. *Mayo Clinic Internal Medicine Board Review*. 10th ed. 2013;497-511.

Algorithm for Laboratory Workup of Macrocytic Anemias



*If MCV is ***very*** high (>110 fL), suspect: B_{12}/folate deficiency, RBC agglutination

Reprinted from *Med Clin North Am*, 76/3, Colon-Otero G, Hook C, Menke D. A practical approach to the differential diagnosis and evaluation of the adult patient with macrocytic anemia. 581-97, Copyright 1992, with permission from Elsevier.

Vitamin B_{12} / Folate Deficiency

- Low intake of **animal** source foods; may be seen in vegetarians/vegans[1,2]
  - While dairy and eggs have vitamin B_{12}, many vegetarians/most vegans will eventually require supplements
- Severe vitamin B_{12} deficiency most commonly caused by autoimmune gastritis (pernicious anemia)[3,4]
- Methodological problems may **compromise the sensitivity and specificity of current vitamin B_{12} assays**[4]
  - Vitamin B_{12} deficiency may be confirmed by measurement of methylmalonic acid, homocysteine, or both
  - An elevated level of methylmalonic acid is more sensitive and specific for the diagnosis
  - If only homocysteine levels are elevated, then a folate deficiency may exist
- **High-dose oral vitamin B_{12} tablets** (1000 to 2000 µg) taken daily are as effective as intramuscular monthly injections in correcting blood and neurologic abnormalities[3]
- Pernicious anemia / malabsorption require **lifelong vitamin B_{12} therapy**[3]

1. Gilsing AM et al. *Eur J Clin Nutr*. 2010;64(9):933-939. 2. Herrmann W et al. *Am J Clin Nutr*. 2003;78(1):131-6.
3. Kaferle J, Strzoda CE. *Am Fam Physician*. 2009;79:203-208. 4. Stabler SP. *New Engl J Med*. 2013;368:149-160.

68-year-old Retired Teacher

- Complains of reduced stamina and new dyspnea upon exertion, no chest pain
- Past medical history: breast cancer 6 years ago, treated with lumpectomy and adjuvant chemotherapy and radiotherapy, follow up exams all negative
- No significant alcohol use or smoking history
- Physical examination: lungs clear, mild sinus tachycardia (heart rate ~102/min.); exam otherwise unrevealing

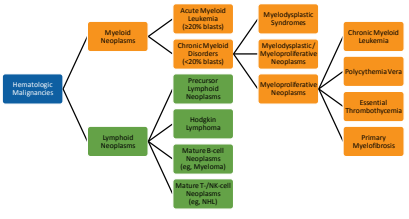
68-year-old Retired Teacher *CONTINUED*

- Laboratory studies:
  - Hemoglobin 9.6 g/dL, MCV 102 fL; rest of CBC within normal range
  - Folate, B_{12}, thyroid stimulating hormone (TSH), serum ferritin, serum iron, % iron saturation all within normal range
  - Fecal occult blood negative x 2
  - 2 years ago, screening colonoscopy was negative

Key Takeaway

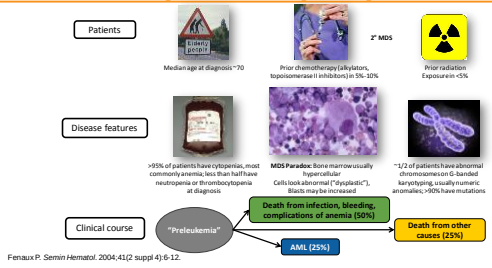
- Once gastrointestinal bleeding, nutritional cause, and renal failure have been ruled out, **evaluation of anemia should continue**
- A **bone marrow examination may be indicated** even if anemia is the only cytopenia

Classification of Hematologic Malignancies



Swerdlow SH, et al, eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*. Lyon, France: IARC Press; 2008.
Arber DA et al. *Blood*. 2016;127(20):2391-2405.

Key Features of Myelodysplastic Syndromes (MDS)



Fenaux P. *Semin Hematol*. 2004;41(2 suppl 4):6-12.

Key Takeaway

It is important to diagnose/rule out MDS and other chronic myeloid neoplasms because:

- Effective therapies are available
- Even if the cause of anemia is not due to MDS or another chronic myeloid neoplasm, the hematologist may be able to find a specific cause

Cytopenic and Clonal States and Their Relationship to MDS and Risk

- Molecular genetic testing for mutations can complicate diagnosis but is reasonable in elderly patients with unexplained anemia, especially if cytopenias exist
  - **≥10% of patients older than 70 years of age have detectable clonal mutations**
- Unexplained cytopenias have varying degrees of risk based on presence of clonal mutation(s) and/or dysplasia
  - Cytopenias in the presence of clonal mutations increase risk for a hematological neoplasm such as MDS

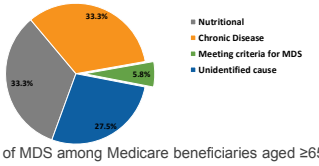
State	Cytopenias	Clonal Mutation	Dyspalsia	Comment
Normal hematopoiesis	–	–	–[a]	Healthy state
Idiopathic cytopenias of uncertain significance (ICUS)	+	–	–/+[b]	Heterogeneous. May resolve with time or become MDS/other hematologic neoplasm
Clonal hematopoiesis of indeterminate potential (CHIP)	–/+	+ (single)[c]	–/+[b]	Common in healthy aging population. Confers 0.5%-1.0% annual risk of progression. Increased all-cause mortality
Clonal cytopenias of undetermined significance (CCUS)	+	+ (≥2)[c]	–/+	Can be considered a subset of CHIP but with higher risk of progression
MDS without blast increase	+	+[d]	+	Specific mutation(s) may define MDS even in the absence of dyplasia
MDS with blast increase	+	+[d]	+	Biologically similar to AML

Risk to patient

[a]May be present in elderly; [b]<10% of cells per lineage; [c]Doesn't meet WHO criteria for diagnosis of MDS or other neoplasm; [d]MDS specific

Pursuit of Unexplained Anemia in the Elderly – How Common is MDS?

- In the NHANES III ~6% of the total anemic population (~17% of those with unexplained anemia) met ≥1 diagnostic criteria for MDS[1]

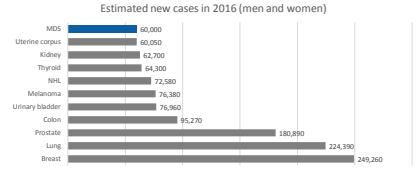


- Annual incidence of MDS among Medicare beneficiaries aged ≥65 years: 75 per 100,000[2]

[1] Guralnik JM, et al. *Blood*. 2004;104:2263-2268.
[2] Cogle CR, et al. *Blood*. 2011;117:7121-7125. (Using an algorithm that required one or more MDS claims and accounted for recommended diagnostic services during the year before the first claim; 2005 data)

If there are ~60,000 new MDS cases per year then....

- MDS is the 2nd most common hematological malignancy after Non-Hodgkin Lymphoma (NHL) and a top 10 cancer in frequency



Comparison: 18,960 new cases of chronic lymphocytic leukemia and 8720 new cases of testicular cancer in 2016

Cancer Facts and Figures 2016. American Cancer Society. http://www.cancer.org/acs/groups/content/@research/documents/document/acspc-047079.pdf.

Commonly Employed Treatments for MDS: Evolution in the Last 15 Years

2001

- Hematopoietic growth factors, especially ESAs*
- Danazol*/androgens
- Low-dose cytarabine
- Hematopoietic stem cell transplant in <5% of patients

2016

- ESAs* used less
- Oral iron chelation (deferasirox is FDA approved for iron overload associated with transfusions and non-transfusion-dependent thalassemia (NTDT); see black box warning about hepatic/renal failure)
- G-CSF*/GM-CSF*, pegfilgrastim*, TPO receptor agonists*
- Immunosuppressive therapy (IST)*
- Decitabine (injectable; FDA approved 2006)†
- Azacitidine (injectable; FDA approved 2004)†
- Lenalidomide (oral; FDA approved 2005)
- Hematopoietic allogeneic stem cell transplant in up to 20% of patients (RIC, URD, umbilical cord for adults, etc.)
- Investigational immunotherapies including PD-1 checkpoint inhibitors combined with azacitidine, CAR T-cell therapy

CAR, chimeric antigen receptor; ESA, erythropoiesis-stimulating agent, G-CSF, granulocyte-colony stimulating factor, GM-CSF, granulocyte-macrophage-colony stimulating factor; PD-1, Programmed cell death protein 1; RIC, reduced intensity conditioning; TPO, thrombopoietin; URD, unrelated donor.

*Not FDA approved for MDS; †Oral formulation in development.

Steensma DP. *Hematol Oncol Clin North Am*. 2010;24:423-441. †Garcia-Manero G, et al. *J Clin Oncol*. 2011;29:2521-2527.

Many Patients With MDS Become Transfusion Dependent

- **Transfusions are needed in 39% (lower risk) to 79% (higher risk) of MDS patients**[1]
- Transfusion requirements are associated with significantly reduced OS[2]
- Issues with transfusions[3-4]
  - Temporary improvement
  - Risk of infection, reaction
  - Need for iron chelation after multiple transfusions
  - Impact on blood supply (MDS accounts for ~3% of transfusions)
  - Impact on QoL
  - Inconvenient
  - Costly (blood product processing, drugs/consumables, staff/overhead, management of complications and hospitalization)

[1] Brechignac S, et al. *Blood.* 2004;104:263b:Abstract 4716; [2] Cazzola M, et al. *N Engl J Med.* 2005;352:536-538; [3] Gupta P, et al. *Leuk Res.* 1999;23:953-959; [4] Hellström-Lindberg E, et al. *Br J Haematol.* 2003;120:1037-1046.

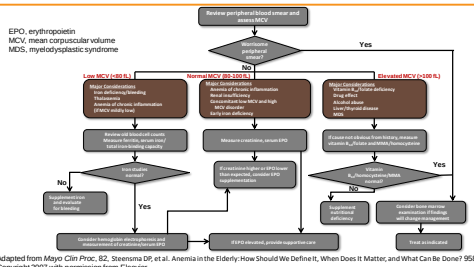
MDS is Worth Diagnosing Because Effective Therapies Are Available

Drug	MOA	Indication	Efficacy in pivotal studies	Toxicities
Lenalidomide[1,2]	Immunomodulatory (has effects on MDS cells, the bone marrow microenvironment, and host immunity)	Transfusion-dependent anemia due to low- or int-1-risk MDS associated with a del(5q) abnormality ± additional cytogenetic abnormalities	• 67% transfusion independence • Median Hb ↑ 5.4 g/dL • Median duration of response >2 years • 45% complete cytogenetic remission	• Cytopenias • Peripheral neuropathy • Concern about teratogenicity • Rash • VTE (rare when used as monotherapy as in MDS)
Azacitidine[3,4]	Hypomethylating agent (affects gene expression)	All MDS subtypes	• Significant 9.4 months improvement in OS vs control • 45% transfusion independent vs 11% for control	• Cytopenias • Febrile neutropenia, especially in first 2 cycles • Skin reactions (with subcutaneous azacitidine)
Decitabine[5-7]	Hypomethylating agent (affects gene expression)	All MDS subtypes including previously treated and untreated, de novo and secondary MDS	• 32% ORR • 51% overall improvement rate including 18% hematologic improvement • No OS benefit in EORTC study	• Gastrointestinal side effects (diarrhea, nausea) • Aphthous ulcers of the mouth • Maculopapular skin rash

1. List A, et al. *N Engl J Med.* 2006;355:1456-1465. 2. Revlimid® (lenalidomide) prescribing information. http://www.revlimid.com/wp-content/uploads/2013/11/PI.pdf. 3. Fenaux P, et al. *Lancet Oncol.* 2009;10:223-232. 4. Vidaza® (azacitidine) prescribing information. www.vidaza.com. 5. Steensma DP, et al. *J Clin Oncol.* 2009;27:3842-3848. 6. Lübbert M, et al. *J Clin Oncol.* 2011;29:1987-1996. 7. Dacogen® (decitabine) prescribing information. http://otsuka-us.com/products/Documents/DACOGEN.PI.pdf.

Proposed Algorithm for Evaluation of Low Hemoglobin in Older Patients

App



Adapted from *Mayo Clin Proc*, 82, Steensma DP, et al. Anemia in the Elderly: How Should We Define It, When Does It Matter, and What Can Be Done? 958-966, Copyright 2007 with permission from Elsevier.

Anemia Best Practices

- **Anemia should not be considered a normal part of the aging process** and should be evaluated
  - A cause can often be determined, and treatment may alter outcomes and improve quality of life (QOL)
- **Use mean cell volume (MCV)** to narrow differential diagnosis of geriatric anemia and determine initial tests
  - Microcytosis, MCV <80 fL
  - Normocytosis, MCV 80-100 fL
  - Macrocytosis, MCV >100 fL
- **Referral to hematologist** for possible bone marrow examination should be carefully considered in patients **with unexplained macrocytic anemia**

Free Accompanying Mobile App!

A free anemia algorithm mobile app is available that covers concepts in this presentation

- The App icon is included on slides where the app would be especially useful
- **To download go to the Google Play store (Android phone/tablet users) or iTunes store (iPhone, iPad users)**

ANDROID APP ON Google play

Available on the iPhone App Store

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Thank you!