The Workup and Management of Anemia in the Elderly: A Practical Approach for Improving Outcomes

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Free Accompanying Mobile App!

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

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Who Are We Talking About?


What is a “Normal” Hemoglobin?

WHO Recommendations for Hemoglobin Thresholds to Define Severity of Anemia (g/dL)

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Non-anemic (g/dL)</th>
<th>Mild (g/dL)</th>
<th>Moderate (g/dL)</th>
<th>Severe (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men aged ≥15 years</td>
<td>&gt;13.0</td>
<td>11.0–12.9</td>
<td>8.0–10.9</td>
<td>&lt;8.0</td>
</tr>
<tr>
<td>Women aged ≥15 years</td>
<td>&gt;12.0</td>
<td>11.0–11.9</td>
<td>8.0–10.9</td>
<td>&lt;8.0</td>
</tr>
<tr>
<td>Pregnant women</td>
<td>&gt;11.0&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.0–10.9</td>
<td>7.0–9.9</td>
<td>&lt;7.0</td>
</tr>
<tr>
<td>Children aged 6–59 months</td>
<td>&gt;11.0</td>
<td>10.0–10.9</td>
<td>7.0–9.9</td>
<td>&lt;7.0&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Children aged 5–11 years</td>
<td>&gt;11.5</td>
<td>11.0–11.4</td>
<td>8.0–10.9</td>
<td>&lt;8.0</td>
</tr>
<tr>
<td>Children aged 12–14 years</td>
<td>&gt;12.0</td>
<td>11.0–11.9</td>
<td>8.0–10.9</td>
<td>&lt;8.0</td>
</tr>
</tbody>
</table>

<sup>a</sup>Threshold is greater than 10.5 g/dL in the second trimester

<sup>b</sup>Generally, in settings with high malaria transmission, a hemoglobin concentration of 4 g/dL or less is an indication for blood transfusion, regardless of the clinical condition of the child; in settings with low malaria transmission, a threshold of 7 g/dL is recommended for blood transfusion.

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

Key Takeaway

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

*WHO criteria; Mean age=72.1 years
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

**Causes of Anemia**

- Inadequate RBC Production
  - Marrow Failure
  - Nutritional Deficiency
- Loss of RBCs
  - Bleeding (overt or occult)
- Premature RBC Destruction
  - Hemolysis (intrinsic or extrinsic)

Most useful inexpensive tests for determining etiology of anemia:
- red blood indices, peripheral blood smear, reticulocyte count

**Anemia Differential Diagnosis by MCV**

- MCV <80 fl
  - Microcytosis
  - Iron deficiency
  - Thalassemia
  - Anemia of chronic disease
  - Sideroblastic anemias
  - Hb C
  - Hb E
  - Unstable Hb
  - Vit C def.
  - Lead poison.
  - Paraneoplastic

- MCV >100 fl
  - Macrocytosis
  - B12 or folate deficiency
  - Alcohol abuse
  - Drugs (AZT, MTX, chemoRx, etc)
  - Marrow disorders (esp. MDS)
  - Reticulocytosis
  - Liver disease or hypothyroidism
  - Artifact

- Normocytosis
  - Anemia of chronic disease
  - Acute bleeding
  - Renal failure (low EPO)
  - Combined disorders
  - Early/mild iron deficiency
  - Hemolysis

Rarer causes

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Red Cell Distribution Width (RDW)

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

SD, standard deviation

- Anemia of chronic inflammation / renal disease
- Early iron, B₁₂, or folate deficiency
- Mixed anemia (eg, combined iron and B₁₂ deficiency)
- Acute blood loss or hemolysis
- Myelodysplastic syndrome
- Axle iron, B₁₂, or folate deficiency
- Chronic liver disease
- Antiviral / chemotherapy / alcohol
- Immune hemolytic anemia
- Cytotoxic chemotherapy
- Chronic liver disease
- Myelodysplastic syndrome
- Aplastic anemia
- Folate / vitamin B₁₂ deficiency

Reticulocytes

- Immature RBCs (typically ~1% of RBCs) containing ribosomal remnants that circulate in blood for about a day before fully developing into RBCs
- Marker of marrow RBC 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
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 B₁₂ (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%)

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Anemia of CKD

- Increased prevalence as renal function worsens
- Typically normocytic, normochromic, and hypoproliferative (i.e., low reticulocytes)
- EPO deficiency is the predominant cause
  - EPO production may be impaired out of proportion to drop in GFR
- 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; GFR = glomerular filtration rate

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Normocytic-Normochromic Anemias: Hemolytic Anemia

- A hemolytic process is indicated by: ↑ lactate dehydrogenase (marker of increased cell destruction), ↑ indirect bilirubin (marker of increased Hb catabolism), ↓ haptoglobin, and sometimes ↑ reticulocyte count (marker of bone marrow regenerative effort, if marrow normal)
- The urinary hemosiderin test can distinguish an intravascular (+ test) vs an extravascular (− test) process
- Evaluation of schistocytes or Coombs test can further guide the work-up (but up to 10% of healthy people have +Coombs)

Schistocytes on peripheral blood smear?

Valvular prosthesis?

Yes

Yes

Microangiopathic, hemolytic anemia (MAHA) associated with defective valve

Valvular prosthesis?

No

Evaluate for disseminated intravascular coagulation (DIC) or other microangiopathic process such as hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP)

Coombs Test

Positive

Autoimmune hemolytic anemia (AIHA)

Osmotic fragility test to assess for spherocytes

Flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH)

RBC enzyme analysis, Hb electrophoresis

No

Negative

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

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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:** 22 ng/mL (normal range, 20-300 ng/mL)
- **Serum iron:** 50 mcg/dL (normal range: 60-170 mcg/dL)
- 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)

- **Predominant cause of microcytic anemia in the US**
  - **BUT** up to 40% of patients with IDA are normocytic
- Most common causes of IDA:
  - Heavy uterine bleeding (20%-30%)
  - GI bleeding due to long-term use of aspirin/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 of 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


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Key Takeaway

While a low ferritin is highly suggestive of IDA, an elevated ferritin does **NOT** exclude the diagnosis of IDA because it is also an acute phase reactant.

Oral Iron Therapy

- **Hb ↑ 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 (Fe\(^{2+}\)) salts are preferred because they are more readily absorbed than ferric (Fe\(^{3+}\)) salts
    - Vitamin C and an acidic stomach increase iron absorption in some patients

<table>
<thead>
<tr>
<th>Form</th>
<th>Formulation</th>
<th>Elemental Iron</th>
<th>Typical Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous fumarate</td>
<td>324-mg tablet</td>
<td>106 mg</td>
<td>One tablet twice per day</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>300-mg tablet</td>
<td>38 mg</td>
<td>1-3 tablets 2 or 3 times per day</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>325-mg tablet</td>
<td>65 mg</td>
<td>One tablet 3 times per day</td>
</tr>
</tbody>
</table>

- Adherence can be a challenge due to GI adverse events (epigastric discomfort, nausea, diarrhea, and constipation)
  - GI effects may be reduced when iron is taken with meals, but absorption may decrease by 40% with food
  - “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

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, gastroejunostomy, 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.

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

LMW, low molecular weight; HMW, high molecular weight.


Evaluation of Microcytic-hypochromic Anemias

Consider Hb analysis in patients from suspected ethnic groups with microcytic anemia, normal RDW and normal ferritin.

*Assays for serum hepcidin are in development. CRP = C-reactive protein; RBC = red blood cell; sTfR = soluble transferrin receptor; Hb = hemoglobin.

Microcytic-hypochromic Anemias: Thalassemia/Sickle Cell Disease

Consider Hb analysis to identify possible hemoglobinopathies in patients from suspected ethnic groups with microcytic anemia, normal RDW and normal ferritin.

<table>
<thead>
<tr>
<th>Test</th>
<th>α-thalassemia</th>
<th>β-thalassemia</th>
<th>Sickle-cell disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family History/ Ethnicity</td>
<td>SE Asian, Middle Eastern, Chinese, African</td>
<td>Chinese, other Asians, African Americans</td>
<td>Sub-Saharan Africa, Mediterranean basin, Middle Eastern, Indian</td>
</tr>
<tr>
<td>Hb electrophoresis / HPLC</td>
<td>Adults: normal*</td>
<td>↑HbA₂, ↓HbA, and probably ↑HbF</td>
<td>HbS±HbC</td>
</tr>
<tr>
<td>Genetics (typically recessive inheritance)</td>
<td>Deletion of HBA1 and HBA2 genes on chromosome 16</td>
<td>Mutations in the HBB gene on chromosome 11 (&gt;170 known)</td>
<td>Specific mutations in the 6th codon of HBB gene (HbS and or HbC)*</td>
</tr>
<tr>
<td>Determinants of disease severity</td>
<td>Number of affected alleles (1-4)</td>
<td>Number of affected alleles (1-2) and mutation type</td>
<td>Number of affected alleles (1-2), Hb variant and if thalassemia also present</td>
</tr>
<tr>
<td>Treatment</td>
<td>Trait: Asymptomaticc</td>
<td>Intermedia: Hemolysis which may need transfusions</td>
<td>Trait: Asymptomaticc</td>
</tr>
<tr>
<td></td>
<td>Major: Usually embryonic/newborn lethal</td>
<td>Major: Lifelong transfusions, chelation</td>
<td>Intermedia± transfusions</td>
</tr>
</tbody>
</table>

*HPLC, high-performance liquid chromatography

*Newborns: may have HbH or Hb Bart’s

*HbS=hemoglobin S (glu→val substitution at codon 6); HbC=hemoglobin C (glu→lys substitution at codon 6); HbSC=HbS/HbC compound heterozygote; HbSS=homozygous for HbS

*cPersons with trait are asymptomatic and require no treatment or long-term monitoring. They usually do not have IDA


Algorithm for Laboratory Evaluation of Macrocytic Anemias


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Vitamin B₁₂ Deficiency

- Most common cause of macrocytic anemia
- Increases risk of neurological complications and cardiovascular disease¹-⁴
- Can occur in vegetarians/vegans due to low intake of animal source foods¹,²
  - While dairy and eggs have vitamin B₁₂, many vegetarians/most vegans will eventually require supplements
- Pernicious anemia is a severe vitamin B₁₂ deficiency typically caused by autoimmune gastritis³,⁴
  - Requires lifelong vitamin B₁₂ therapy³
- Methodological problems can affect the sensitivity/specificity of current vitamin B₁₂ assays⁴
  - Vitamin B₁₂ deficiency may be confirmed by measurement of methylmalonic acid, homocysteine, or both
    - Elevated methylmalonic acid is more sensitive and specific for the diagnosis
    - If only homocysteine levels are elevated, then a folate deficiency may exist
- Daily high-dose oral vitamin B₁₂ tablets (1000 to 2000 μg) are as effective as monthly intramuscular injections in correcting blood and neurologic abnormalities³
- The natural bioidentical forms of vitamin B₁₂ – methylcobalamin, adenosylcobalamin and hydroxycobalamin – are preferred over the synthetic cyanocobalamin (better bioavailability/safety)⁵
  - Use the least-expensive natural form of B₁₂, such as methylcobalamin

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, B₁₂, 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
Key Features of Myelodysplastic Syndromes (MDS)

Patients
- Median age at diagnosis: ~70
- Prior chemotherapy (alkylators, topoisomerase II inhibitors) in 5%-10%
- Prior radiation: Exposure in <5%

Disease features
- >95% of patients have cytopenias, most commonly anemia; less than half have neutropenia or thrombocytopenia at diagnosis
- MDS Paradox: Bone marrow usually hypercellular but cytopenias present
- Cells look abnormal (“dysplastic”), blasts may be increased
- ~1/2 of patients have abnormal chromosomes on G-banded karyotyping, usually numeric anomalies; >90% have acquired gene mutations (point mutations) in one or more of ~40 genes

Clinical course
- "Preleukemia" Death from infection, bleeding, complications of anemia (50%)
- AML (25%)
- Death from other causes (25%)


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
Cytopenia 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 aged >70 years have detectable clonal mutations
- Unexplained cytopenias confer varying degrees of risk dependent on presence of clonal mutation(s) and/or dysplasia
  - Cytopenias + clonal mutations increase risk for a hematological neoplasm such as MDS

<table>
<thead>
<tr>
<th>State</th>
<th>Cytopenias</th>
<th>Clonal Mutation</th>
<th>Dysplasia</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal hematopoiesis</td>
<td>−</td>
<td>−</td>
<td>−</td>
<td>Healthy state</td>
</tr>
<tr>
<td>Idiopathic cytopenias of uncertain significance (ICUS)</td>
<td>+</td>
<td>−</td>
<td>−/+</td>
<td>Heterogeneous. May resolve over time or become MDS/other hematologic neoplasm</td>
</tr>
<tr>
<td>Clonal hematopoiesis of indeterminate potential (CHIP)</td>
<td>−/+</td>
<td>+ (single)†</td>
<td>−/+</td>
<td>Common in healthy aging population. Confers 0.5%-1.0% annual risk of progression. Increased all-cause mortality</td>
</tr>
<tr>
<td>Clonal cytopenias of undetermined significance (CCUS)</td>
<td>+</td>
<td>+ (≥2)‡</td>
<td>−/+</td>
<td>Can be considered a subset of CHIP but with higher risk of progression</td>
</tr>
<tr>
<td>MDS without blast increase</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>Specific mutation(s) may define MDS even in the absence of dysplasia</td>
</tr>
<tr>
<td>MDS with blast increase</td>
<td>+</td>
<td>+‡</td>
<td>+</td>
<td>Biologically similar to AML</td>
</tr>
</tbody>
</table>

†May be present in elderly; ‡<10% of cells per lineage; §Doesn’t meet WHO criteria for diagnosis of MDS or other neoplasm; †‡MDS specific

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

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)
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MDS is Worth Diagnosing Because Effective Therapies Are Available

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
<th>Indication</th>
<th>Efficacy in pivotal studies</th>
<th>Toxicities</th>
</tr>
</thead>
</table>
| Lenalidomide | 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 | 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)  
• Gastrointestinal side effects (diarrhea, nausea)  
• Aphthous ulcers of the mouth  
• Maculopapular skin rash |
| Decitabine  | 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 |                                                                                  |