Anemia in the Nursing Home Population

8th Annual Care By Design Long Term Care Conference

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Disclosures

• No conflicts of interest particularly relevant to this talk
• Scientific Advisory Boards
  • Celgene
  • Pfizer
  • AbbVie
• Co-/sub-investigator on a number therapeutic trials for various hematologic malignancies including leukemia, lymphoma, myeloma

• Off-label medication use:
  • Brief mention of erythropoietin stimulating agents for MDS
Lecture Objectives

By the end of this presentation, participants will be able to:

• 1. Formulate a differential diagnosis and work-up anemia in the nursing home patient population

• 2. Understand when interventions such as red cell transfusion and intravenous iron may be indicated

• 3. Know when patients may benefit from a Hematology referral
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• 1. Formulate a differential diagnosis and work-up anemia in the nursing home patient population

• 2. Understand when interventions such as red cell transfusion and intravenous iron may be indicated

• 3. Know when patients may benefit from a Hematology referral
Refresher - Normal Hematopoiesis

Bone marrow

Normal bone marrow
Refresher - Normal Hematopoiesis

A snapshot of blood production

Courtesy of Dr. Clinton Campbell, Hematopathology
Refresher - Normal Hematopoiesis

Bone marrow (factory and assembly line) → Peripheral blood (finished products)

- Organ of hematopoiesis in humans
  - Solid tissue
  - Functionally immature cells

- Circulating hematopoietic cells
  - Liquid tissue
  - Specified cell function

Maturation (increasing function / lineage specification)

Blast → Intermediate precursors → Neutrophil

Courtesy of Dr. Clinton Campbell, Hematopathology
Refresher- The Peripheral Blood Smear

- Look for morphological abnormalities that may explain the anemia

- Could be red cell or white cell (leukocyte abnormalities)

- Helps to direct next steps in the investigation

![Peripheral Blood Smear Image]

Courtesy of Dr. Clinton Campbell, Hematopathology
Refresher – The bone marrow

Normal bone marrow
## Refresher- CBC Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range*</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (White blood cells)</td>
<td>4.50-11.00</td>
<td>X 10^9 cells/L</td>
</tr>
<tr>
<td>RBC (Red blood cells)</td>
<td>4.50-6.50</td>
<td>X 10^{12} cells/L</td>
</tr>
<tr>
<td>Hgb (Hemoglobin)</td>
<td>140-180</td>
<td>g/L</td>
</tr>
<tr>
<td>Hct (Hematocrit)</td>
<td>0.420-0.540</td>
<td></td>
</tr>
<tr>
<td>MCV (Mean corpuscular volume)</td>
<td>80.0-97.0</td>
<td>fL</td>
</tr>
<tr>
<td>MCH (Mean corpuscular hemoglobin)</td>
<td>28.0-32.0</td>
<td>pg</td>
</tr>
<tr>
<td>MCHC (Mean corpuscular hgb concentration)</td>
<td>315-350</td>
<td>g/L</td>
</tr>
<tr>
<td>RDW (Red cell distribution width)</td>
<td>11.5-14.5</td>
<td>%</td>
</tr>
<tr>
<td>Plt (Platelet)</td>
<td>150-350</td>
<td>X 10^9 cells/L</td>
</tr>
<tr>
<td>MPV (Mean plateler volume)</td>
<td>9.0-12.5</td>
<td>fL</td>
</tr>
<tr>
<td>Reticulocyte count</td>
<td>28.80-94.0</td>
<td>X 10^9 cells/L</td>
</tr>
<tr>
<td>Reticulocyte percent</td>
<td>0.56-1.52</td>
<td>%</td>
</tr>
</tbody>
</table>
### Refresher – CBC Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal Range*</th>
<th>Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils (i.e. ANC, absolute neutrophil count)</td>
<td>2.00-7.50</td>
<td>X 10⁹ cells/L</td>
</tr>
<tr>
<td>Myelocytes*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Metamyelocytes*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Promyelocytes*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Blasts*</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>1.50-4.00</td>
<td>X 10⁹ cells/L</td>
</tr>
<tr>
<td>Monocytes</td>
<td>0.10-0.90</td>
<td>X 10⁹ cells/L</td>
</tr>
<tr>
<td>Eosinophils</td>
<td>0.00-0.50</td>
<td>X 10⁹ cells/L</td>
</tr>
<tr>
<td>Basophils</td>
<td>0.00-0.10</td>
<td>X 10⁹ cells/L</td>
</tr>
<tr>
<td>Immature granulocyte fraction (“IG”)</td>
<td>0.00-0.09</td>
<td>X 10⁹ cells/L</td>
</tr>
</tbody>
</table>

*Neutrophil precursors, will only be reported on manual differential (generally abnormal)

**KEY MESSAGE:** The absolute counts are more important/helpful than the percentage counts
Cytopenias – Conceptual Overview

Hematopoietic stem cells
Cytokines
Cellular differentiation program
Bone marrow microenvironment
Nutrients for cell proliferation

Environmental stimulus
(ex., bleeding, infection)
Destruction
Sequestration

Supply
Demand

Hematopoiesis

Inadequate supply
OR
Excessive demand

Cytopenia

Courtesy of Dr. Clinton Campbell,
Hematopathology
Cytopenias

• Conceptual definition:
  • Decreased **quantity** (absolute) of a given cell lineage due to the inability of body to support **effective hematopoiesis**
    • Imbalance of supply and demand

• Technical definition:
  • **Cell concentration** below reference range for age and gender
  • Generally measured in cells/L
Pancytopenia

<table>
<thead>
<tr>
<th>Cell type</th>
<th>Function</th>
<th>Lineage</th>
<th>Cytopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil</td>
<td>Fight infection</td>
<td>Myeloid</td>
<td>Neutropenia</td>
</tr>
<tr>
<td>Platelet</td>
<td>Primary hemostasis</td>
<td>Myeloid</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Growth factor production</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte (red cell)</td>
<td>Carry oxygen</td>
<td>Erythroid</td>
<td>Anemia</td>
</tr>
</tbody>
</table>

- **Pancytopenia** = decrease below reference range (for age) of neutrophils, platelets, and erythrocytes
- Does not generally refer to lymphocytes, monocytes, other WBC lineages
A conceptual approach to pancytopenia

Think supply versus demand:

- Decreased blood cell production
  - Bone marrow hypoplasia / aplasia
    Aplastic anemia, paroxysmal nocturnal hemoglobinuria, congenital marrow failure syndrome, infection, iron, B12, folate, copper deficiency (nutritional deficiency), drugs, autoimmune
  - Bone marrow infiltration / replacement
    Leukemia, lymphoma, myeloma, infection, myelodysplasia, myelofibrosis, metastatic cancer

- Excessive demand for blood cell production or increased blood cell destruction
  - Infection
  - Chronic bleeding or hemolysis
    Hypersplenism, hepatomegaly
  - Sequestration
  - Myelodysplastic syndrome
    Premature destruction of hematopoietic precursors

Courtesy of Dr. Clinton Campbell, Hematopathology

Anemia in the Nursing Home Population - November 23, 2018
A conceptual approach to workup of pancytopenia

- Peripheral blood smear
- Bone marrow exam
- History and P/E

- Morphology
- Molecular biology
- Immunophenotyping
- History and P/E findings
- Additional testing as needed

- Differential diagnosis
- Patient age

Courtesy of Dr. Clinton Campbell, Hematopathology
Anemia in the Nursing Home Population

• Prevalence
  • Anemia is common in the elderly patient population
    • National Health and Nutrition Study (NHANES) III
      • Patients aged 65 or older
      • Anemia as per WHO: Hgb <130 g/L men, <120 g/L women
      • 11.0% of men, 10.0% of women
      • Anemia more common in men than women aged >75
  • Rates of anemia in nursing home population have been reported at ~10-50% in smaller studies

Guralnik et al. Blood 2004;104:2263
Anemia in the Nursing Home Population

• Prevalence
  • National Geriatrics Research Consortium
    • Chart Review of 5 skilled nursing home facilities
      • 900 patients with complete data
      • Mean age 79, median age 82
      • 87% of patients aged 65 or older; 63% female
      • 43% met WHO criteria for anemia at some point during 6 month review period
      • 6 month hospitalization rate 30% vs 15.8% anemic vs non-anemic
      • If hemoglobin <100 g/L up to 54.6% hospitalization rate

Anemia in the Nursing Home Population

• Etiology
  • NHANES III Study
    • 24% Blood Loss/Nutrition-related
      • 20% iron deficiency
      • 15% B12 and/or folate deficiency
    • 20% Anemia of Chronic Disease/Inflammation
    • 8% Anemia of Chronic Kidney Disease (low EPO)
    • 34% “Unexplained” Anemia

Guralnik et al. Blood 2004;104:2263
Anemia in the Nursing Home Population

• Etiology
  • 100 randomly selected patients (of 433 anemic patients) from NGRC study
  • 83 subjects eligible for inclusion in study
  • 60/83 patients subsequently confirmed to have anemia (74%)
    • Only 28/60 anemic patients had charted diagnosis of anemia (48%)
  • 14 patients with iron deficiency anemia (23%)
  • 8 patients with anemia of chronic disease (13%)
  • 6 patients with anemia of renal insufficiency (10%)
  • 3 patients with “presumed MDS” (other cytopenias)
  • 1 patient with hypothyroidism
  • 1 patient with hemoglobinopathy
  • 27 patients with no explanation for anemia (45%)
Anemia in the Nursing Home Population

- Etiology

Table 1. Mean Erythropoietin Levels and Related Parameters for Anemic Nursing Home Residents

<table>
<thead>
<tr>
<th>Type</th>
<th>Hemoglobin, g/dL*</th>
<th>Erythropoietin, mIU/mL †</th>
<th>Mean Corpuscular Volume, fL ‡</th>
<th>Ferritin, ng/mL §</th>
<th>Interleukin-6, pg/mL ‖</th>
<th>Albumin, g/dL*</th>
<th>C-Reactive Protein, mg/dL#</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency anemia</td>
<td>10.6 ± 1.1</td>
<td>29.0 ± 16.2</td>
<td>85.4 ± 7.0</td>
<td>22.5 ± 14.5</td>
<td>6.6 ± 2.7</td>
<td>3.7 ± 0.5</td>
<td>10.1 ± 15.4</td>
</tr>
<tr>
<td>(n = 14)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia of chronic disease</td>
<td>11.0 ± 1.5</td>
<td>20.3 ± 7.6</td>
<td>93.1 ± 3.4</td>
<td>167.4 ± 79.1</td>
<td>44.3 ± 72.4</td>
<td>3.6 ± 0.4</td>
<td>36.9 ± 35.5</td>
</tr>
<tr>
<td>(n = 8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic anemia</td>
<td>10.8 ± 1.0</td>
<td>14.6 ± 7.3</td>
<td>92.3 ± 5.9</td>
<td>201.6 ± 195.6</td>
<td>8.5 ± 7.8</td>
<td>3.6 ± 0.3</td>
<td>6.0 ± 5.0</td>
</tr>
<tr>
<td>(n = 27)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Other** (n = 5)</td>
<td>10.0 ± 1.2</td>
<td>13.4 ± 1.6</td>
<td>87.0 ± 9.3</td>
<td>356.0 ± 577.1</td>
<td>98.0 ± 106.8</td>
<td>3.6 ± 0.3</td>
<td>41.1 ± 68.7</td>
</tr>
<tr>
<td>Chronic renal insufficiency*</td>
<td>11.5 ± 0.8</td>
<td>12.5 ± 4.2</td>
<td>89.5 ± 6.5</td>
<td>177.8 ± 215.9</td>
<td>7.5 ± 1.4</td>
<td>3.9 ± 0.3</td>
<td>8.3 ± 5.6</td>
</tr>
<tr>
<td>(n = 6)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All (n = 60)</td>
<td>10.7 ± 1.1</td>
<td>18.6 ± 11.6</td>
<td>90.1 ± 6.7</td>
<td>166.9 ± 233.6</td>
<td>19.0 ± 41.0</td>
<td>3.7 ± 0.4</td>
<td>13.6 ± 25.7</td>
</tr>
</tbody>
</table>

Reference range: *11.5–15.0; †4.2–27.8; ‡80–98; §10–291; ‖0.447–9.96; *3.5–4.8; #0–4.9.
**No etiology of anemia uncovered.

Artz et al. JAGS. 2004:52:423
Anemia

- Reticulocyte count
  - Elevated (destruction, blood loss)
  - Decreased, “abnormally normal” for degree of anemia
    - (decreased production)
- Reticulocyte index
  - Absolute reticulocyte count/maturation factor
    - Hct ≥ 0.35: 1.0
    - 0.35> Hct ≥ 0.25: 1.5
    - 0.25 > Hct ≥ 0.20: 2.0
    - 0.20 > Hct: 2.5
  - RI >0.02 = adequate marrow response; RI <0.02 = inadequate response
Anemia – Kinetic approach

Increased retics

Easy!
Bleeding or Hemolysis

• Source of bleeding?
• Hemolysis workup
  • LDH (increased)
  • Unconjugated Bilirubin (increased)
  • Haptoglobin (decreased)
  • DAT (autoimmune)
  • Peripheral smear
  • Specialized testing
    • Membrane defects
    • Hemoglobin electrophoresis
    • PNH screen (flow cytometry)

Decreased retics

More difficult...
Broader differential

• Morphologic approach
  • Size of cells (MCV)

Microcytic
Normocytic
Macrocytic
Anemia - Microcytosis

Iron status
- Ferritin*
- %sat
- (Reticulated hemoglobin)\(^1\)
- (Soluable transferrin receptor)\(^2\)

Iron deficiency anemia
- Other clues:
  - Increased RDW
  - Reactive thrombocytosis
  - Decreased MCV proportionate to degree of anemia
- Identify source

Anemia of chronic disease/inflammation (Hepcidin-mediated)
- Infection, inflammation

Acquired

Chronic

Thalassemias
- Normal or high RBC count
- Low MCV out of proportion to anemia

Heavy metal toxicity
(Lead, others – rare)

Chronic

Anemia in the Nursing Home Population - November 23, 2018

*Consider IDA if ferritin <100-200 particularly if concomitant inflammation
Anemia - Macrocytosis

Macrocytic

Rule out medication effect

B12, folate
(MMA, homocysteine if borderline)

If normal...

Mild increased MCV
(100-110 fL)

• "Round macrocytes"
  • Reticulocytosis
  • Liver disease
  • EtOH effect
  • Hypothyroidism
• "Oval macrocytes"
  • MDS

Apparent macrocytosis

• Clumps of cells
  • Agglutination
  • Rouleaux

• Monoclonal protein
  (SPEP)
• Inflammation/Infection

Marked increased MCV
(>110 fL)

• Myelodysplastic Syndrome (MDS)
• Other marrow disorders

- 6-MP/azathioprine
- Hydroxyurea
- Carbemazepine
- Metformin
- Isoniazid
- Zidovudane
- Trimethoprim
- Many others
  • reviewed in Hesdorffer NEJM; 2015;373:1649
Anemia- Normocytic

High retics

- Bleeding, hemolysis

Low/Normal retics

- Renal insufficiency? (high creatinine, low EPO)
- Early/concomitant B12/folate or iron deficiency?
- Hypothyroidism?

Anemia of inflammation/“chronic disease”

- Infection
  - Sepsis, HIV, HepB/C, parvovirus, EBV, CMV etc.
- Inflammatory disorders
- Malignancy
- Age?

Marrow failure

- (congenital)
- Myelodysplastic Syndrome (MDS)
- Aplastic anemia
- Pure red cell aplasia

Medication effect

Marrow infiltration

- Acute leukemia
- Myelofibrosis
- Lymphoma
- Myeloma
- Metastatic cancer
- Granulomatous diseases
- Storage diseases
- Fungal infection
Example Case # 1

• 80 year old woman presenting with fatigue x several months
  • Hgb 45 g/L => 105 g/L 1 year ago
  • MCV 59.0 fL => MCV 80.0 fL 1 year ago
  • Peripheral smear: “Severe microcytic, hypochromic anemia with pencil cells”
  • No history of overt GI bleeding/menorrhagia; normal diet; no other symptoms

• Likely diagnosis?:
  1. Iron deficiency
  2. Thalassemia trait
  3. Anemia of chronic disease
  4. Lead poisoning
Example Case # 1

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• Likely diagnosis?
  1. **Iron deficiency** – Ferritin 3
  2. Thalassemia trait
  3. Anemia of chronic disease
  4. Lead poisoning
Example Case #2

• Asymptomatic 87 year old woman presenting with anemia on routine CBC
  • Hgb 101 g/L  => 103 g/L 20 years ago
  • MCV 60.5 fL  => 61.7 g/L 10 years ago
  • RBC 5.6 x 10^{12} cells/L
  • Peripheral smear: “Mild anemia with severe microcytosis, target cells”

• Likely diagnosis?:
  • 1. Iron deficiency
  • 2. Thalassemia trait
  • 3. Anemia of chronic disease
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• Likely diagnosis?
  • 1. Iron deficiency
  2. Thalassemia trait
  • 3. Anemia of chronic disease
  • 4. Lead poisoning
Example case #3

• 85 year old male presenting with fatigue, back pain, confusion
• Hgb 88 g/L
• MCV 104 g/L
• Serum total protein 130 g/L (ULN 83)
• Creatinine 117 umol/L
• Calcium 3.5 mmol/L (ULN 2.60)
• Peripheral smear: “Rouleaux present”

• Likely diagnosis?
  1. B12 deficiency
  2. Liver disease
  3. Myeloma
  4. Myelodysplastic syndrome
Example case #3

- 85 year old male presenting with fatigue, back pain, confusion
- Hgb 88 g/L
- MCV 104 g/L
- Serum total protein 130 g/L (ULN 83)
- Creatinine 117 umol/L
- Calcium 3.5 mmol/L (ULN 2.60)
- Peripheral smear: “Rouleaux present”

**Likely diagnosis?**

1. B12 deficiency
2. Liver disease
3. **Myeloma** => IgG 98 g/L, SPEP- monoclonal IgG kappa, marrow:50% plasma cells, skeletal survey => large lytic lesion left iliac bone
Example case #4

- 84 year old woman, increased fatigue, shortness of breath
  - Hgb 62 g/L (91 g/L six months ago)
  - MCV 112 fL (108 fL six months ago)
  - Absolute Neutrophil count 0.7 x 10^9/L (1.4 x 10^9/L six months ago)
  - Platelets 56 x 10^9/L (110 x 10^9/L six months ago)
  - Normal B12, folate, TSH, no offending medications
  - Peripheral smear: “Pancytopenia with macrocytosis of the red cells. Hypogranular neutrophils with abnormal lobation. Thrombocytopenia. Rare blast cell”

- Likely diagnosis?:
  1. Anemia of chronic disease
  2. Myelodysplastic syndrome (MDS)
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• Likely diagnosis?:
  1. Anemia of chronic disease
  2. Myelodysplastic syndrome (MDS)
  3. Iron deficiency
  4. Anemia of liver disease
Myelodysplastic Syndromes

• “Pre-leukemia”
• Malignant clonal stem cell disorders
• Dysplastic and ineffective blood cell production
  • Cytopenias (low cell counts)
  • Cells don’t work properly
• Risks
  • Progressive bone marrow failure
  • Progression to Acute Myeloid Leukemia
MDS- Clinical Features and Diagnosis

• Clinical features
  • Complications of Cytopenias
    • Infections, symptoms of anemia, bleeding

• Diagnosis
  • Peripheral Blood
  • Bone Marrow Biopsy
  • Cytogenetics
  • Molecular Testing
MDS - Epidemiology

- Incidence increases with age:
  - Cases per 100000
    - Age <50 – 0.5
    - Age 50-59 – 5.3
    - Age 60-69 – 15
    - Age 70-79 – 49
    - Age >80 – 89

- Diagnosed in 5-15% of elderly patients undergoing bone marrow evaluation for unexplained anemia

- Study of 124 patients older than age 75 with unexplained macrocytosis (MCV >95**)
  - 5% diagnosed with MDS
  - Another 15% with dysplastic features not completely fulfilling diagnosis of MDS

**probably a bit of a low cut-off for “macrocytosis”

Williamson et al BJH. 1994:87:743
MDS - Survival

- Revised IPSS Risk stratification

MDS- Treatment

• Supportive care
  • Transfusions, antibiotics

• Growth factors
  • Erythropoietin*, G-CSF

• Hypomethylating therapy (decitabine, azacitidine)

• Lenalidomide (for “5q minus syndrome”)

• AML-like intensive chemotherapy

• Stem cell transplant

• Investigational treatments (clinical trial)

*technically off-label, but approved/funded for MDS indication in NS if requiring >2 units PRBC
Lecture Objectives

By the end of this presentation, participants will be able to:

• 1. Formulate a differential diagnosis and work-up anemia in the nursing home patient population

• 2. Understand when interventions such as red cell transfusion and intravenous iron may be indicated

• 3. Know when patients may benefit from a Hematology referral
Iron deficiency management

• Iron replacement is preferred treatment for iron deficiency anemia
  • And investigate for causes of iron loss, as appropriate

• Cochrane Reviews:

  • “Iron therapy in anaemic adults without chronic kidney disease”
    • 4745 patients in 21 randomized trials (generally low/very low quality)
    • Different oral preparations vs parenteral iron vs inactive controls compared
    • Iron supplementation reduces risk of blood transfusion
    • No formulation of oral iron favoured
    • IV iron more efficacious at increasing hemoglobin than oral (unclear clinical benefit)

  • “Systematic review and meta-analysis of iron therapy in anaemic adults without chronic kidney disease: updated and abridged Cochrane review”
    • Both oral and IV iron decrease need for transfusion, no clear mortality benefit
<table>
<thead>
<tr>
<th>Route</th>
<th>Iron salt</th>
<th>Formulation (elemental iron)</th>
<th>Adult dose</th>
<th>Incidence of side effects</th>
<th>Approximate medication cost for adults / month*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Ferrous sulfate</td>
<td>Tablets 300 mg (60 mg)</td>
<td>1 tablet 3-times a day</td>
<td>+++</td>
<td>$2-3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sustained release tablets 160 mg (50 mg)</td>
<td>1-4 tablets once a day</td>
<td>+</td>
<td>$25 (at max dose)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension 75 mg/mL (15 mg/mL)*</td>
<td>4 mL 3-times daily</td>
<td>++</td>
<td>$100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Syrup 30 mg/mL (6 mg/mL)*</td>
<td>10 mL 3-times daily</td>
<td>++</td>
<td>$50</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>Tablet 300 mg (35 mg)</td>
<td>1-3 tablets 2-3 times a day</td>
<td>++</td>
<td>$3-5</td>
<td></td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>Tablet 300 mg (90mg)</td>
<td>1 tablet 2-times a day</td>
<td>++</td>
<td>$2-20</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Suspension 300 mg/5mL (20 mg/mL)*</td>
<td>3 mL 3-times daily</td>
<td>++</td>
<td>$35</td>
</tr>
<tr>
<td>Polysaccharide iron</td>
<td>Polysaccharide iron capsules 150 mg (150 mg)</td>
<td>1 capsule once a day</td>
<td>+</td>
<td>$24</td>
<td></td>
</tr>
<tr>
<td>Intravenous</td>
<td>Iron sucrose</td>
<td>Suspension (20 mg elemental iron/mL)</td>
<td>Multi-dose infusions to a total 1000 mg elemental iron**</td>
<td>+</td>
<td>$375 / 1000 mg (full course) + facility cost</td>
</tr>
<tr>
<td></td>
<td>Iron dextran complex*</td>
<td>Suspension (50 mg elemental iron/mL)</td>
<td>Usually 1000 mg elemental iron as a single infusion; depends on body wt and Hb; test dose required</td>
<td>+++</td>
<td>$280/ 1000 mg (full course)* + facility cost</td>
</tr>
</tbody>
</table>

Table from BC iron deficiency guidelines; adapted from Silverstein. J Pharm Pract 2008:21:431
Oral iron - dosing

• Optimal dosing schedule or formulation not clear
  • As per Cochrane no good quality evidence supporting one formulation over the other
  • Likely the best formulation is whichever one patient will tolerate

• Randomized trial of 60 iron deficient women (aged 18-40) to 120 mg elemental iron once daily vs split dose BID
  • No difference in absorption

• Randomized trial of 40 women to 60 mg elemental iron daily vs every other day (14 doses in each arm = same total dose)
  • Improved absorption in alternating day arm

• Small randomized trial of hospitalized patients age 80+ showed no difference in hemoglobin increase between elemental iron doses of 15 mg, 50 mg or 150 mg

Stoffel et al. Lancet Hematology 2017;4:e524
Intravenous Iron

• When to consider:
  • Failure of oral iron (should see reticulocytosis in ~ 1 week, 10-20 g/L rise by 2 months)
  • Unable to tolerate oral iron
  • Decreased oral absorption (celiac, IBD, gastric bypass, bowel resection)
  • Blood/iron loss exceeds ability to replete orally
  • More rapid repletion required (?more severe/symptomatic IDA, need to increase prior to surgery, etc)

• In Nova Scotia, generally iron sucrose used for most patients
  • Typically dose 200-300 mg IV q1-2 weeks
  • Various calculations for “iron deficit” exist
  • Practically speaking 3-5 doses/ ~1000 mg of iron adequate for most patients
Transfusion

• At what hemoglobin level should you transfuse?
Transfusion

• At what hemoglobin level should you transfuse?

“There are many wrong answers to this question and one right one”
Transfusion

• At what hemoglobin level should you transfuse?
  • Patient symptomatic due to anemia
    AND
  • Potential benefits of transfusion outweigh the potential risks
Transfusion

• Most patients tolerate hemoglobin of 90-100 g/L or greater
• Many patients symptomatic with hemoglobin <70-80 g/L
  • Some may tolerate levels lower than this surprisingly well, particularly if chronic
• Generally evidence shift towards favouring “restrictive” over “liberal” transfusion thresholds (i.e. <70-80 vs higher targets) – selected studies below

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>R vs L targets (g/L)</th>
<th>No. of patients</th>
<th>Mean Age</th>
<th>Mortality R vs L</th>
<th>Significant?</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRICC</td>
<td>ICU</td>
<td>70 vs 100</td>
<td>836</td>
<td>58</td>
<td>19 vs 23%</td>
<td>No</td>
</tr>
<tr>
<td>Villanueva et al.</td>
<td>UGIB</td>
<td>70 vs 90</td>
<td>921</td>
<td>65</td>
<td>5% vs 9%</td>
<td>Yes</td>
</tr>
<tr>
<td>FOCUS</td>
<td>Hip fracture</td>
<td>80 vs 100</td>
<td>2016</td>
<td>82</td>
<td>4% vs 5%</td>
<td>No</td>
</tr>
<tr>
<td>TRACS</td>
<td>CV surgery</td>
<td>Hct 0.24 vs 0.30</td>
<td>502</td>
<td>60</td>
<td>10% vs 11% (composite)</td>
<td>No</td>
</tr>
</tbody>
</table>
Transfusion

• Unanswered questions
  • Best target for chronically transfused patients?
    • Randomized trials in MDS patients currently looking at outcomes including QoL measures
      • Canadian trial “EnhanceRBC” (NCT02099669)
      • Hgb target 80-85 g/L vs 110-120 g/L
  • Our general trigger locally for outpatient hematology malignancy patients is to transfuse if hemoglobin <80 g/L; slightly higher targets 85-90 g/L for some patients
## Nova Scotia Transfusion Guideline 2017

<table>
<thead>
<tr>
<th>Hemoglobin Level</th>
<th>ADULT Recommendation and Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than or equal to 60 g/L or less than or equal to 70 g/L in pregnancy*</td>
<td>Transfuse 2 units and re-check patient symptoms and hemoglobin prior to transfusing a 3rd unit</td>
</tr>
<tr>
<td>Greater than 60 g/L and less than or equal to 70 g/L</td>
<td>Transfuse 1 unit and re-check patient symptoms and hemoglobin prior to transfusing a 2nd unit</td>
</tr>
<tr>
<td>Outpatient or a patient undergoing dialysis and hemoglobin less than or equal to 70 g/L</td>
<td>Transfuse as requested</td>
</tr>
<tr>
<td>Less than or equal to 80 g/L with one or more of the following:</td>
<td></td>
</tr>
<tr>
<td>- Pre-existing cardiovascular disease</td>
<td>Transfuse as requested</td>
</tr>
<tr>
<td>- Hematology/Oncology patient with chemotherapy-induced cytopenia</td>
<td></td>
</tr>
<tr>
<td>- Chronically transfused</td>
<td></td>
</tr>
<tr>
<td>- Undergoing orthopedic surgery or cardiac surgery</td>
<td></td>
</tr>
<tr>
<td>Patient is undergoing radiation therapy and hemoglobin less than or equal to 100 g/L</td>
<td>Transfuse as requested</td>
</tr>
<tr>
<td>Obstetrical patient with a high risk of postpartum hemorrhage and hemoglobin is between 80 g/L and 100 g/L</td>
<td>Discuss with Medical Director or designate on call. Requests for RBCs may be appropriate</td>
</tr>
</tbody>
</table>
### Risks Associated with Blood and Blood Components

#### Infectious Risks

<table>
<thead>
<tr>
<th>Virus</th>
<th>Approximate Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 8 million</td>
</tr>
<tr>
<td>HCV</td>
<td>1 in 6.7 million</td>
</tr>
<tr>
<td>HBV</td>
<td>1 in 1.7 million</td>
</tr>
<tr>
<td>HTLV</td>
<td>1 in 2.5 million</td>
</tr>
</tbody>
</table>

#### Non-Infectious Risks

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Associated Component</th>
<th>Approximate Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Allergic</td>
<td>RBCs, Platelets, Plasma</td>
<td>1 in 100</td>
</tr>
<tr>
<td>Febrile non-hemolytic transfusion reactions (FNHTR)</td>
<td>RBCs</td>
<td>1 in 500</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>1 in 200</td>
</tr>
<tr>
<td>Transfusion associated circulatory overload (TACO)</td>
<td>RBCs, Platelets, Plasma</td>
<td>1 in 700</td>
</tr>
<tr>
<td>Transfusion related acute lung injury (TRALI)</td>
<td>RBCs</td>
<td>1 in 5,000</td>
</tr>
<tr>
<td></td>
<td>Platelets, Plasma</td>
<td>1 in 1,200 – 5,000</td>
</tr>
<tr>
<td>Delayed hemolytic reactions</td>
<td>RBCs</td>
<td>1 in 7,000</td>
</tr>
<tr>
<td>Acute hemolytic reactions</td>
<td>RBCs</td>
<td>1 in 40,000</td>
</tr>
<tr>
<td></td>
<td>Platelets, Plasma</td>
<td>Rare</td>
</tr>
<tr>
<td>Bacterial Contamination</td>
<td>RBCs</td>
<td>1 in 50,000</td>
</tr>
<tr>
<td></td>
<td>Platelets</td>
<td>1 in 1,000</td>
</tr>
<tr>
<td></td>
<td>Plasma</td>
<td>Very rare</td>
</tr>
<tr>
<td>Hypotensive Reaction</td>
<td>RBCs, Platelets, Plasma</td>
<td>Unknown</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>RBCs, Platelets, Plasma</td>
<td>Rare</td>
</tr>
<tr>
<td>Post Transfusion Purpura (PTP)</td>
<td>RBCs, Platelets</td>
<td>Rare</td>
</tr>
<tr>
<td>Transfusion-related alloimmune thrombocytopenia</td>
<td>RCBs, Platelets, Plasma</td>
<td>Rare</td>
</tr>
<tr>
<td>Graft-versus-host disease (GVHD)</td>
<td>RBCs, Platelets</td>
<td>Rare</td>
</tr>
<tr>
<td>Iron Overload</td>
<td>RBCs</td>
<td>Rare (due to repeated RBC transfusion)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>RBCs</td>
<td>Dependent on clinical situation (seen in massive, rapid transfusion)</td>
</tr>
</tbody>
</table>

Lecture Objectives

By the end of this presentation, participants will be able to:

• 1. Formulate a differential diagnosis and work-up anemia in the nursing home patient population

• 2. Understand when interventions such as red cell transfusion and intravenous iron may be indicated

• 3. Know when patients may benefit from a Hematology referral
When should patients be referred to Hematology

• Unexplained cytopenias
  • Moderate to severe (pancytopenia/bicytopenia > single lineage)
    • Hgb < 80-100, Plt <50-100, ANC < 1.0
    • (Rapidly) progressing cytopenias
  • Concerning peripheral blood film abnormalities
    • Circulating blast cells
    • Red cell fragments/schistocytes, spherocytes (with hemolysis)
    • Abnormal lymphocytes
    • “Clinical hematology consultation recommended” comments

• If in keeping with patient goals of care
  • Life expectancy, comorbidities/frailty, desire for work-up/treatment
  • Age in itself not usually a barrier

• We are generally always happy to discuss a case if you are unsure
### Anemia in the Nursing Home Population

**November 23, 2018**

<table>
<thead>
<tr>
<th>Triage category</th>
<th>Examples (not all inclusive)</th>
<th>Process</th>
<th>Facilities</th>
</tr>
</thead>
</table>
| **Emergent C1** | - New diagnosis of acute leukemia  
- Severe thrombocytopenia (Platelets <20,000)  
- Severe anemia (Hgb <80)  
- Severe leukopenia (WBC <1,000)  
- Patients with a new diagnosis of DVT or PE should be referred directly to the Emergency Department | PHONE 902-473-2220  
AND FAX referral marked URGENT | Recent blood work  
Bone marrow report (if available) |
| **Urgent C2** | - New established diagnosis of Lymphoma or Hodgkin Lymphoma (if lymphoma is suspected, please arrange a biopsy to confirm BEFORE referral.) | Fax referral | Tissue biopsy (usually by a general surgeon) is generally required prior to appointment  
Recent blood work  
Bone marrow report (if available) |
| **Semi-Urgent C3** | - New diagnosis of myeloma  
- New diagnosis of chronic myeloid leukemia (CML), if patient stable  
- Moderate anemia <80  
- Moderate thrombocytopenia <50,000 | Fax referral | Recent blood work  
Bone marrow report (if available) |
| **Non-Urgent C4** | - Mild cytopenias  
- WBC <4.5  
- Hgb <120  
- Platelets <100,000  
- Duration of anticoagulation  
- Hemoglobinopathy (Hemochromatosis)  
- New diagnosis of chronic lymphocytic leukemia (CLL), if patient stable  
- Moderate leukopenia, anemia or thrombocytopenia  
- Personal or family history of anemia | Fax or mail referral | Data of surgery REQUIRED when patients are referred for perioperative management of anticoagulation  
Recent and previous CBC as well as other relevant blood tests are always appreciated |

### Average Wait Times for Referring Physicians

- Cardiology
- Clinical Dermatology & Cutaneous Science
- Digestive Care & Endoscopy
- Endocrinology & Metabolism
- General Internal Medicine
- Geriatric Medicine
- Hematology
- Infectious Diseases
- Medical Oncology
- Nephrology
- Neurology
- Palliative Medicine
- Physical Medicine & Rehabilitation
- Respiratory Medicine
- Rheumatology

#### Hematology wait times

<table>
<thead>
<tr>
<th>Triage category</th>
<th>Standard wait time</th>
<th>Average wait time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergent C1</strong></td>
<td>2 days</td>
<td>1.4 days</td>
</tr>
<tr>
<td><strong>Urgent C2</strong></td>
<td>14 days</td>
<td>12.6 days</td>
</tr>
<tr>
<td><strong>Semi-Urgent C3</strong></td>
<td>42 days</td>
<td>28.3 days</td>
</tr>
<tr>
<td><strong>Non-Urgent C4</strong></td>
<td>60 days</td>
<td>77.6 days</td>
</tr>
</tbody>
</table>

*Posted January 30, 2019*
Thrombocytopenia

**Increased consumption/destruction**
- ITP
  - Primary
  - Secondary
- Drug-induced
  - Quinine
  - Antibiotics
  - GP IIb/IIIa inhibitors
  - Heparin (HITT)
- Thrombotic microangiopathies (schistocytes, hemolysis +/- abN coags)
  - TTP/HUS
  - DIC
  - HELLP syndrome
  - Others

**Decreased production**
- EtOH, other drugs
- Liver disease
- B12, folate deficiencies
- Infection
  - HIV, HepB/C
  - EBV, CMV
  - H. pylori
  - Sepsis
- Marrow problem
  - MDS, aplastic anemia
  - Leukemia, lymphoma, other marrow infiltration
- Inherited disorder

**“Other”**
- Splenic sequestration
  - Cirrhosis/portal HTN
  - Other causes of splenomegaly
- Pseudothrombocytopenia
  - Platelet clumping
  - EDTA artifact
  - Send in citrate tube
  - Send fresh draw, glass tube, no tourniquet etc.

*Interpreting an Abnormal CBC – April 11, 2018*
Thrombocytopenia

• Platelet thresholds
  • >100 => neurosurgery, other very high bleeding risk surgeries
  • >50 => most other surgical procedures
  • <20-30 => increased risk of spontaneous bleeding, would consider treatment for ITP patients
  • <10 => increased risk of spontaneous bleeding, would consider platelet transfusion even in absence of bleeding
    • Transfusion may not be effective in ITP; ?possible harm in TTP (however would still consider if actively bleeding)
Neutropenia

• ANC of 1.0 - 1.5 x 10^9 in absence of other cytopenias/findings may warrant investigation non-urgently. Reassuring if chronic/stable/isolated
• ANC of 0.5 - 1.0 x 10^9 more concerning, particularly if recurrent infections
• ANC of < 0.5 x 10^9 should be evaluated urgently particularly if new onset
  • If febrile treat as febrile neutropenia with broad spectrum (often IV) antibiotics (medical emergency)
Neutropenia

• Congenital
  • Cyclical, inherited marrow failure syndromes
  • “Benign ethnic neutropenia” – normal variant

• Medications (non-exhaustive list)
  • Many culprits- most chemotherapies, rituximab, other monoclonal antibody therapies, antibiotics (macrolides, vanco, semi-synthetic penicillins, cephalosporins, TMP-SMX, others), anticonvulsants, 5-ASA, NSAIDs, methimazole, PTU, anti-arrythymics, clozapine, cocaine (levamisole), EtOH
  • B12, folate deficiency, ?iron deficiency
  • Infections- viral, sepsis
  • Inflammation- trauma/ICU, rheumatoid arthritis (Felty syndrome), autoimmune
Neutropenia

• Lymphoproliferative disorders
  • Any secondary to marrow infiltration (usually pancytopenic)
  • T-LGL leukemia and hairy cell leukemia in particular (can be isolated)

• Myeloid neoplasms
  • Acute myeloid leukemia
  • MDS
  • Myelofibrosis

• Other marrow failure syndromes
  • Aplastic anemia, PNH

• Other marrow infiltrative processes (usually with pancytopenia)
  • Metastatic cancer, granulomatous diseases, storage diseases
<table>
<thead>
<tr>
<th>Disease</th>
<th>Oversimplified definition</th>
<th>Detailed Description</th>
</tr>
</thead>
</table>
| Leukemia                | Cancer of the white blood cells           | • Acute (immature cells = “blasts”)  
• Chronic (mature cells)  
• Myeloid (AML, CML)  
• Lymphoid (ALL, CLL)  
• Can also be in nodes, spleen, marrow |
| Lymphoma                | Cancer of the lymphocytes                 | • Hodgkin Lymphoma  
• B cell Non Hodgkin Lymphoma  
• T cell Non Hodgkin Lymphoma  
• Mostly mature cells  
• Can also be in blood, marrow, spleen, skin, and other organs |
| Multiple Myeloma        | Cancer of the bone and marrow             | • Involves the most differentiated form of lymphocytes (plasma cells)  
• Usually makes abnormal antibody protein (monoclonal protein) |
| Myeloproliferative      | Proliferation of other blood cells        | Overproduction of:  
• Platelets -- Essential thrombocytosis  
• Red Blood Cells -- Polycythemia Vera |
| neoplasms               |                                           |                                                                                                                                                      |
| Myelodysplastic         | Faulty differentiation of 1 or more       | • Abnormal production of blood cells  
• Bad cells accumulate in marrow |
| syndrome (MDS)          | blood cell line                           |                                                                                                                                                      |
Interpreting an Abnormal CBC – April 11, 2018

LYMPHOPROLIFERATIVE
- HL
- NHL
- MM
- CLL
- ALL

MYELOPROLIFERATIVE
- AML
- CML
- PV
- ET
- PMF

MYELODYSPlastic
- MDS
  - MDS-SLD
  - MDS-RS
  - MDS-MLD
  - MDS-EB
  - 5q minus

(See abbreviation slide at end of presentation)
Classification of Lymphoid Malignancies

Lymphoid Malignancies

- Lymphoma
- Myeloma
- Leukemia
  - Acute Lymphocytic Leukemia
  - Chronic Lymphocytic Leukemia
Too many cells - Thrombocytosis

- Always consider reactive causes first
  - Iron deficiency
  - Trauma, burns, surgery
  - Infection
  - Malignancy
  - Post-splenectomy
- Myeloproliferative disorders
  - Essential thrombocytosis
  - Polycythemia vera
  - Primary myelofibrosis
  - Chronic myeloid leukemia (can occasionally present with isolated thrombocytosis)
Too many cells - Erythrocytosis

• Appropriately increased EPO
  • Smoking
  • Chronic pulmonary disease
  • OSA
  • Obesity/hypoventilation syndrome
  • Cardiac shunts
  • Altitude

• Inappropriately increased EPO
  • Renal cell carcinoma
  • Hepatocellular carcinoma
  • Pheochromocytoma
  • Fibroids
Too many cells - Erythrocytosis

- Apparent increased RBCs
  - Plasma volume contraction due to diuretics, other causes
- Medications
  - Erythropoeitin-stimulating agenets
  - Testosterone, androgeneic/anabolic steroids
- Acquired bone marrow disorders
  - Polycythemia vera (Jak2 v617F mutation positive in 90-95%)
  - Myelofibrosis
  - CML
- Inherited
  - EPOR mutations, certain hemoglobinopathies, other mutations
Too many cells - Erythrocytosis

• When to be concerned:
  • Men: Hgb >165 (especially if >180)
  • Women: Hgb >160

• Suggested workup:
  • Evaluate for secondary causes, medications etc.
  • Consider EPO level (usually low in PV)
  • Consider peripheral blood molecular testing for JAK2 V617F
Too many cells – WBCs (Neutrophils)

• Secondary
  • Smoking
  • Physical stress
  • Infection
  • Heatstroke
  • Medications
    • Glucocorticoids, G-CSF therapy
    • Lithium, other medications
  • Solid organ malignancies
  • Post-splenectomy/Asplenia
Too many cells – WBCs (Neutrophilia)

• Primary
  • Myeloproliferative disorders
    • Chronic Myeloid leukemia (BCR-ABL testing is diagnostic, can be ordered on peripheral blood)
      • “left-shifted” granulocytes, basophilia, eosinophilia
    • Chronic neutrophilic leukemia
    • Myelofibrosis, polycythemia vera > essential thrombocytosis
      • JAK2 V617F, calreticulin, MPL mutations
  • Inherited disorders
    • Down syndrome
Too many cells- WBC (lymphocytosis)

- Secondary/Reactive:
  - Smoking (especially younger women)
  - Infections
    - Viral – EBV, CMV, HIV, others
    - Bacterial – Pertussis, TB, syphilis, bartonella, rickettsial
  - Drug-induced
  - Trauma/physical stress
  - Thymoma, rheumatoid arthritis
  - Hyperthyroidism
  - Non-hematologic malignancy
  - Post-splenectomy
Too many cells- WBC (lymphocytosis)

• Lymphoproliferative disorders
  • Monoclonal B cell lymphocytosis (pre-CLL)
  • Chronic lymphocytic leukemia
• Other B cell NHLs
  • Mantle cell, splenic marginal zone lymphoma, follicular lymphoma, others
• Acute lymphoblastic leukemia (usually would be reported as blasts)
• T cell neoplasms
  • Mycosis fungoides/Sezary syndrome
  • T-LGL leukemia
  • Others
Lymphocytosis- when to evaluate?

- Mild lymphocytosis <7-10 x 10^9 cells/L in absence of cytopenias, adenopathy, splenomegaly, etc
  - Can repeat CBC in 6-8 weeks to confirm persistence, then consider evaluation or referral
- Lymphocytosis with ALC 7-10^9 cells/L, or persistent lymphocytosis without a clear cause (or fevers/sweats/wt. loss/adenopathy/splenomegaly)
  - Reasonable to send hematology referral
  - Could send peripheral blood flow cytometry screen to evaluate for monotypic lymphoid population while awaiting consultation
    - Polytypic = unlikely a lymphoproliferative disorder
    - Lymph node biopsy can be helpful if adenopathy
Chronic Lymphocytic Leukemia – a few comments

• Indolent (for many) mature B cell neoplasms
• Analogous to Small Lymphocytic Lymphoma in the lymph nodes
• Generally incurable (outside of allogeneic stem cell transplant)
• **Lymphocyte count by itself generally not concerning**
  - Many patients with WBC ~100+, personal record WBC >600 before requiring treatment  
  - Lymphocyte-doubling time of <6 months soft-indication for treatment  
    - Rarely treat based on this alone  
    - Lymphocyte count commonly goes up with infection, surgery, etc.
• Indications for treatment/re-evaluation include progressive cytopenias, symptomatic adenopathy or splenomegaly, “B Symptoms”, fatigue related to CLL