Blood Day for Primary Care

How I work up undifferentiated anemia

Ryan Zarychanski MD MSc FRCPC
Donald Houston MD PhD FRCPC

Department of Medical Oncology & Haematology, CancerCare Manitoba
Dept. Internal Medicine, Section of Hematology/ Medical Oncology, University of Manitoba
Disclosures

1. No shares
2. No grants
3. No speaking fees
4. No advisory boards
5. No dinners
Disclosures

RYAN ZARYCHANSKI

Grants/Research Support: None relevant to presentation
Speaker bureau/Honoraria amounts: None relevant to presentation
Consulting fees: None relevant to presentation
Other: None relevant to presentation
Objectives

1. Direct the investigation of anemia with reference to a practical algorithm that starts from the full set of data in the complete blood count

2. Employ appropriate additional testing including blood film, reticulocyte count, iron studies, and ancillary biochemical tests in the further characterization of anemia

3. Communicate effectively to make optimal use of the consultant hematologist
A case

- A 17 year old woman is referred for anemia (note at age 17, consult goes to adult service)
<table>
<thead>
<tr>
<th>TO CONSULT</th>
<th>Defined</th>
<th>DATE</th>
<th>Dec 4/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>TO TAKE OVER</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOR INFORMATION</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**USE THIS AREA WHEN REFERRING TO AMBULATORY CARE**

<table>
<thead>
<tr>
<th>FROM</th>
<th>AREA/CLINIC</th>
<th>CENTRE</th>
</tr>
</thead>
<tbody>
<tr>
<td>TO</td>
<td>CLINIC-APPT. DATE</td>
<td></td>
</tr>
<tr>
<td>PATIENT'S PHONE NUMBER</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Doctor and/or Service**

Proctology

Date: 6/12/14

**Your opinion is sought regarding:**

Chronic Anal MD

Evidence of Ca. Cause

Signed Dr.

**CONSULTANT'S REPORT**

To Doctor: 11:30 a.m. Hour

Date: Dec 4/14
A case

- No additional data provided with referral
- Looked up in e-Chart blood work from 6 mo. earlier:
  - WBC 5.6
  - Hb 91
  - MCV 66.6fL, MCHC 282g/L, MCH 18.8pg
  - RDW 18.5%
  - Platelets 338
A case

What investigation is most appropriate in work-up of this patient at this time?

1. Serum iron and TIBC
2. Reticulocyte count
3. LDH, haptoglobin, direct & total bilirubin
4. Serum ferritin
5. Hemoglobin electrophoresis
A case

- Result: serum ferritin 3ug/L
General Points

• Anemia is very common
• Anemia is often more important as an objective indicator of illness than a problem for the patient in itself
• Every case of anemia warrants thought; investigation should be undertaken if the cause of anemia is not apparent
• Most cases can be sorted out by generalists
First: Four Practical Rules

1. If your laboratory doesn’t automatically supply them, always order WBC and differential, red cell indices, and platelet count, when you order a hemoglobin (i.e. complete blood count, or CBC)

2. Look at prior CBC results, if available.
   • Trends are as informative as point values

3. If the abnormality is minor / unexpected: repeat it before embarking on extensive investigation

4. In formulating an investigation plan and establishing a diagnosis, take account of everything you know about the patient
START

Low Hb identified

WBC or Platelets also abnormal?

no

Step 2

MCV

Macrocytic

Normocytic

Microcytic

Reticulocyte Count

Step 3

Hypoproliferative

Hyperproliferative

Hemolytic

Macrocytic

Blood smear

Schistocytes

Blasts

NRBCs

Dysplasia

Immature WBCs

Smear normal and other cytopenias not severe

Marrow infiltration

Myelodysplasia

Acute Leukemia

Bone marrow

Serum B12

B12 deficiency

Retic. count

Antimetabolites

Alcoholism

Potential folate deficiency

Liver disease

LFTs & enzymes

LFTs & enzymes

Liver disease

Bone marrow

Myelodysplasia

Step 1

Step 3a

Ferritin

normal, with signs of inflammation

low

Consider trial of iron therapy

Iron Deficiency

Acute blood loss or hemolysis

High

Step 3b

Drug history

Marrow toxins

Renal failure

Creatinine

Active inflammation? ESP, CRP

Chronic disease

Combined anemia

Ferritin, B12

Liver disease

LFTs & enzymes

Hypothyroidism & testosterone

Endocrine tests

Myeloma

SPEP & FLCR

Marrow infiltration

Bone marrow

Spleenomegaly

Microangiopathic Mechanical

Spherocytes

G-6-PD, PK screens

Enzymopathy

Normal

Coombs test

Schistocytosis

Autoimmune

Yellow area: Hematology consultation recommended

*Alteration in MCV is modest, and MCV is often within normal range

**Uncommon to cause more than mild anemia; test according to clinical context

Key:

Tests

Diagnoses

Classifications

© Donald S. Houston MD 2014
Notes about the Algorithm

- It starts with data provided for free by the automated analyzer (WBC and platelet count, and MCV)

- Disclaimer: No algorithm can address every possible patient; in particular it is common for patients to have more than one process contributing to their anemia

- Make use of all the data available to you!
Notes about the Algorithm

- Yellow area indicates when referral to Hematologist is warranted

- *Note about blood smears: if the automated hematology analyzer flags a significant abnormality, a blood smear will likely be done even if you haven’t requested it. Look for the result*
Refer to Dr. Moltzan’s algorithm on pancytopenia

Schistocytes in conjunction with thrombocytopenia: TTP/HUS or DIC – Emergent referral
Blasts – Urgent referral
Immature WBCs: more than 2% promyelocytes or myelocytes
Dysplasia: hypogranular neutrophils or platelets, Pelger-Huet
Low Hb identified → Step 1

WBC or Platelets also abnormal?

- no → Step 2
  - MCV
    - Microcytic
    - Normocytic
    - Macrocytic

*Alteration in MCV is modest, and MCV is often within normal range

**Uncommon to cause more than mild anemia; test according to clinical context

Yellow area: Hematology consultation recommended

Drughistory

Bone marrow infiltration, Myelodysplasia

Spherocytes

Enzymopathy

Autoimmune

Microangiopathic

Mechanical

Acute bloodloss or hemolysis

LDH, bilirubin, haptoglobin

Blood smear, Coombstest

G-6-PD, PK screens

Ferritin, Hbelectrophoresis

ACTIVE inflammation? if needed check ESR, CRP

LFTs & enzymes

Consider trial of iron therapy

Low Hb identified

Retic.count

Medication and alcohol history

Bonemarrow

Creatinine

Renal failure

Ferritin, B12 LFTs & enzymes

SPEP & FLCR

Endocrine tests

Schistocytes

Normal

High

Spherocytes

Step 1

Step 2

Step 3

Step 3a

Step 3b

Multiple Cytopenias
Anemia Algorithm

**START** Low Hb identified

- **Low Hb identified**
  - **Step 1**: WBC or Platelets also abnormal?
    - **Yes**: Blood smear
      - Schistocytes
      - Blasts
      - NRBCs
      - Immature WBCs
    - **No**: MCV
      - **Step 2**: MCV
        - **Step 2a**: MCV
          - **Microcytic**
            - Iron Deficiency
              - Ferritin
                - Low
          - **Normocytic**
            - Reticulocyte Count
              - **Step 3a**: Retic. count
                - N or Low
                - High
            - **Step 3b**: Hyperproliferative
              - Hemolytic
                - LDH, bilirubin, haptoglobin
          - **Macrocytic**
            - Serum B12
              - B12 deficiency

- **Multiple Cytophenias**
  - TTP, HUS
  - Bone marrow
  - Marrow infiltration, Myelodysplasia
  - Acute Leukemia

- **Step 3**
  - **Step 3a**: Retic. count
    - N or Low
    - High
  - **Step 3b**: Hyperproliferative
    - Hemolytic
      - Schistocytes
      - Dysplasia
      - Immature WBCs
      - LDH, bilirubin, haptoglobin
    - Recovery from nutriment deficiency, toxic exposure, or acute blood loss
  - **Low Hb identified**
    - **Step 3a**: Retic. count
      - Norm
      - Abn
    - **Step 3b**: Hyperproliferative
      - Schistocytes
      - Dysplasia
      - Immature WBCs
      - LDH, bilirubin, haptoglobin
    - **Multiple Cytophenias**
      - TTP, HUS
      - Bone marrow
      - Marrow infiltration, Myelodysplasia
      - Acute Leukemia

**Key:**
- Tests
- Diagnoses
- Classifications

*Alteration in MCV is modest, and MCV is often within normal range
**Uncommon to cause more than mild anemia; test according to clinical context

Yellow area: Hematology consultation recommended
If iron deficiency is established or likely, evaluate for source of bleeding

Refer to Iron Deficiency algorithm
**Macrocytic**

<table>
<thead>
<tr>
<th>Step</th>
<th>Test/Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Serum B12</td>
</tr>
<tr>
<td>2.</td>
<td>Retic. count</td>
</tr>
<tr>
<td>3.</td>
<td>Medication and alcohol history</td>
</tr>
<tr>
<td>4.</td>
<td>LFTs &amp; enzymes</td>
</tr>
<tr>
<td>5.</td>
<td>Bone marrow</td>
</tr>
</tbody>
</table>

- **B12 deficiency**
- **Antimetabolites, alcoholism**
- **Potential folate deficiency**
- **Liver disease**
- **Myelodyplasia**
Anemia Algorithm

START
Low Hb identified

1. WBC or Platelets also abnormal?
   - yes
     - Blood smear
       - Schistocytes
       - Blasts
       - NRBCs
       - Dysplasia
       - Immature WBCs
     - Smear normal and other cytopenias not severe
   - no

2. MCV
   - Normocytic
     - Step 3a
       - Reticulocyte Count
         - Low or High
         - N or Low
       - Hypoproliferative
         - Hyperproliferative

   - Microcytic
     - Iron Deficiency
     - Low Ferritin
       - Consider trial of iron therapy
     - Chronic disease*
     - Thalassemia
     - Hb electrophoresis
     - Active inflammation?
       - If needed check ESR, CRP

   - Macrocytic
     - Serum B12
       - B12 deficiency
     - Marrow infiltration
       - Myelodysplasia

3. Reticulocyte Count
   - Step 3b
     - Hemolytic
       - LDH, bilirubin, haptoglobin
       - Recovery from nutrient deficiency, toxic exposure, or acute blood loss
       - Blood smear
       - Schistocytes
       - Spherocytes
       - Microangiopathic
       - Mechanical
       - Autoimmune
     - Coomb's test
       - G-6-PD, PK
       - Normal
       - Enzymopathy
     - Bone marrow
       - Myelodysplasia*

4. Step 2
   - MCV
     - Microcytic
     - Normocytic
     - Macrocytic

Key:
- Tests
- Diagnoses
- Classifications

*Alteration in MCV is modest, and MCV is often within normal range
**Uncommon to cause more than mild anemia; test according to clinical context

Yellow area: Hematology consultation recommended
Step 2
MCV

Normocytic

Step 3
Reticulocyte Count

Step 3a

Acute blood loss or hemolysis

N or Low
High

Hypoproliferative
Hyperproliferative
Notes about the Reticulocyte Count

• Retics should increase physiologically in response to anemia, but to do so requires:
  • Normal renal function (to produce erythropoietin)
  • Time (7 – 10 days from drop in hemoglobin)
  • Normal marrow function
• High reticulocyte can indicate
  • Compensation for hemolysis
  • Recovery from blood loss, nutritional anemia or marrow suppression
Notes about the Ancillary Tests

- It is expedient to order multiple investigations together at the outset of this diagnostic path:
  - Creatinine
  - Liver enzymes
  - LDH
  - Direct and total bilirubin
  - Serum ferritin and B12
  - TSH
  - Blood smear
To distinguish whether an elevated retic count reflects hemolysis, or recovery from blood loss or marrow suppression, order LDH, bilirubin direct/total, and haptoglobin.
Take Home Messages
HOW I WORK UP ANEMIA

- Look at all the data from the CBC
- Most anemias also need a reticulocyte count
- Non-microcytic anemias need a blood smear
- Microcytic anemia: check ferritin first
- Other anemias: obtain a set of investigations including creatinine, liver enzymes, LDH, direct and total bilirubin, serum ferritin, serum B12, TSH
When to consider a referral to hematology

**HOW I WORK UP ANEMIA**

- Indication of bone marrow disorder
  - Pancytopenia
  - Blast cells on blood film
  - NRBCs and immature white cells
- Indication of hemolysis
  - Elevated retics, increased indirect bilirubin, increased LDH, decreased haptoglobin
- You’re stumped
Another case

Dr. Don Houston
Cancer Care Manitoba
Ph: 787-2336
Fax: 786-0621

Thanks for seeing Scott, a very pleasant older gent who has anaemia of unknown etiology. He originally was felt to be likely anemic because of a severe chronic gastritis and H.pylori infection. These have been treated and he is feeling good, but his hemoglobin has really not improved.

I have checked B12 and TSH, both seem normal enough not to be the culprit.

I have enclosed the rest of the bloodwork that was done originally.

His hemoglobin has fallen from 134 to 114 over the past year.

Your opinion and treatment as indicated would be much appreciated.

Thanks,
## Another case

<table>
<thead>
<tr>
<th></th>
<th>Dec 3</th>
<th>Nov 14</th>
<th>Jul 18</th>
<th>A year ago</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>6.4</td>
<td></td>
<td>6.0</td>
<td></td>
</tr>
<tr>
<td>Hb</td>
<td>114</td>
<td>119</td>
<td>115</td>
<td>134</td>
</tr>
<tr>
<td>MCV</td>
<td>95.1</td>
<td>93.5</td>
<td>95.2</td>
<td></td>
</tr>
<tr>
<td>platelets</td>
<td>180</td>
<td></td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>PMNs</td>
<td>2.8</td>
<td>2.3</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>Lymphs</td>
<td></td>
<td></td>
<td>1.9</td>
<td></td>
</tr>
<tr>
<td>Monos</td>
<td>1.2*</td>
<td>1.0*</td>
<td>1.0*</td>
<td></td>
</tr>
<tr>
<td>Eos</td>
<td>0.1</td>
<td>0.2</td>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>Basos</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>
Another case

Additional data provided:

- Serum B12 (N), serum ferritin (538)
- SPEP and UPEP (negative), total protein (60), albumin (39)
- TSH (N)
- ESR (35)
- AST, ALT, alk phos, GGT (N)
- LDH (153), total bilirubin (10.3)
- Creatinine (84)
Another case

Are there any other data you would like?
What should be done next?
**Low Hb identified**

- **Microcytic**
  - Iron Deficiency
  - Ferritin normal, with signs of inflammation?
  - Consider trial of iron therapy
- **Normocytic**
  - Acute blood loss or hemolysis
  - Active inflammation? ESR, CRP
  - Marrow toxins
  - Drug history
  - Renal failure
  - Creatinine
  - Chronic disease
  - Hb electrophoresis
- **Macrocytic**
  - Serum B12
  - B12 deficiency

**Step 2**
- MCV

**Step 3a**
- Reticulocyte Count
  - Low
  - Ferritin
  - Normal, with signs of inflammation?
  - Consider trial of iron therapy
  - Chronic disease
  - Thalassemia
  - Hb electrophoresis

**Step 3b**
- Hyperproliferative
  - LDH, bilirubin, haptoglobin
  - LFTs & enzymes
  - Recovery from nutrient deficiency, toxic exposure, or acute blood loss
  - Bone marrow

**Multiple Cytopenias**
- Blood smear
  - Schistocytes
  - Blasts
  - NRBCs
  - Dysplasia
  - Immature WBCs
  - Smear normal and other cytopenias not severe
- Bone marrow
  - Marrow infiltration, Myelodysplasia
  - Acute Leukemia

**Key:**
- Tests
- Diagnoses
- Classifications

*Alteration in MCV is modest, and MCV is often within normal range
**Uncommon to cause more than mild anemia; test according to clinical context

© Donald S. Houston MD 2014
Questions?

Ryan Zarychanski
rzarychanski@cancercare.mb.ca

Donald Houston
houston@cc.umanitoba.ca