Approach to the abnormal CBC

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General Considerations

- Always repeat counts to establish validity of abnormality, and its trend
- Interval of repetition (and number of repetitions) are determined by severity of abnormality and clinical circumstances
Straight to bone marrow

- Blasts in the blood
- Nucleated red cells in a patient with an intact spleen
- Marrow should include cytogenetics and flow cytometry
Pancytopenia
(White count, platelet count, hematocrit all low)

- Think drugs
- Infection, especially viral
- Hypersplenism
- Evaluation is either bone marrow examination or observation
- Parvovirus PCR worth obtaining in immunocompromised
- B12 deficiency is great imitator
Erythrocytosis
(Elevated hemoglobin or hematocrit)

1. Artifact vs. polycythemia: RBC volume UNLESS Hgb consistently > 20 and no anasarca

2. P vera vs. secondary – JAK2 V617F

3. Physiologic secondary vs. non-physiologic – oxygen saturation, examination, scans, history
<table>
<thead>
<tr>
<th>WHO</th>
<th>ECP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
<td><strong>Pathologic Criteria</strong></td>
</tr>
<tr>
<td>A1. Hb &gt;18.5 g/dl male/16.5 g/dl female; or other evidence of increased RCM</td>
<td>P1. Marrow morphology</td>
</tr>
<tr>
<td>A2. Presence of JAK2 V617F or other functionally similar mutation</td>
<td>P2. Bone marrow EEC formation</td>
</tr>
<tr>
<td><strong>Minor Criteria</strong></td>
<td>P3. JAK2 V617F mutation</td>
</tr>
<tr>
<td>B1. Marrow morphology</td>
<td><strong>Clinical Criteria</strong></td>
</tr>
<tr>
<td>B2. Serum erythropoietin below reference range for normal</td>
<td>C1. Increased RCM (same as WHO A1)</td>
</tr>
<tr>
<td>B3. EEC colony formation in vitro</td>
<td>C2. Hematocrit 0.45–0.51 male 0.43–0.46 female</td>
</tr>
<tr>
<td>Marrow morphology: Hypercellular marrow with trilineage hyperplasia; clustering of pleomorphic megakaryocytes; absent stainable iron; no major inflammatory features</td>
<td>C3. Low serum erythropoietin</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>C4. Persistent thrombocytosis</td>
</tr>
<tr>
<td>A1 + A2 + any one from B</td>
<td>Grade I: 400,000–1,500,000/μl;</td>
</tr>
<tr>
<td>A1 + any two from B</td>
<td>Grade II: &gt;1,500,000/μl</td>
</tr>
</tbody>
</table>

EEC, endogenous erythroid colony formation; Hb, hemoglobin; LAP, leukocyte alkaline phosphatase; PV, polycythemia vera; RCM, red cell mass.

*Wintrobe's Clinical Hematology (12th ed), 2009.*
Leukocytosis
(High white blood count)

- Clonal vs reactive
- Spleen present, or on steroids?
- Workup based on differential
  - Lymphocytosis – flow cytometry
  - Granulocytosis – PCR for \textit{bcr-\textit{abl}}; cytogenetics
    - \textit{JAK2} V617F if associated with thrombocytosis or erythrocytosis
  - Left shift without eos, basos, metamyelocytes – observation +/- LAP if clinically appropriate
Leukopenia  
(Low white blood count)

- Constitutional
- Drugs
- Virus (HIV, CMV, others)
- If mild, and patient asymptomatic, some course of observation may be appropriate
- ? Large Granular Lymphocyte syndromes ?
- Bone marrow examination
Thrombocytosis
(High platelet count)

- Myeloproliferative vs. reactive
  - Essential thrombocytosis
  - CML
  - P vera
  - MDS with thrombocytosis
Essential thrombocytosis

- Normal Hct with adequate iron stores, MCV-rules out P vera, also Fe deficiency
- Normal cytogenetics – rules out CML
- Usually has + JAK2 V617F mutation
- No reactive processes
<table>
<thead>
<tr>
<th>Causes (%)</th>
<th>&gt; 900K</th>
<th>&gt; 500K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>7.8</td>
<td>23.9</td>
</tr>
<tr>
<td>Postop</td>
<td>1.4</td>
<td>18.5</td>
</tr>
<tr>
<td>Solid tumor</td>
<td>5.8</td>
<td>9.1</td>
</tr>
<tr>
<td>Bleeding</td>
<td>0</td>
<td>8.9</td>
</tr>
<tr>
<td>Fe def</td>
<td>0</td>
<td>7.8</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>22</td>
<td>2.4</td>
</tr>
<tr>
<td>MPD</td>
<td>33</td>
<td>1.6</td>
</tr>
</tbody>
</table>
Thrombocytopenia
(Low platelets)

- Artifact – “satellitism”
- Drugs
- Virus (same as low WBC)
- Hypersplenism
- Increased destruction vs. decreased production
Approach to low platelets

- Peripheral smear – artifact, TTP
- PT/PTT – DIC, liver disease
  - Factor IX, VIII distinguish these
  - Liver disease VIII ↑ or ↔; DIC VIII ↓; IX low in liver disease
- Don’t forget HIT/HITT
  - PF4, serotonin release
- If only low platelets, most likely ITP
  - Antiplatelet antibodies detected 50% of time
If presumed ITP, some would suggest treatment is not necessary with plts > 60K

In presumed ITP patients who do not respond to steroids, or younger patients in whom observation is planned, bone marrow examination with cytogenetics is reasonable
Pathogenetic categories

- Red Cell Loss
  - bleeding or hemolysis

- Marrow Failure
  - toxic agents, clonal disorders, immune marrow

- Deficiency State
  - iron, B12, folate, endocrine, erythropoietin

- Combination
  - Anemia of chronic disease
Anemia Case Study -1

- 73 yo WM referred for chronic anemia. Treated empirically with B12, iron 6 wks ago without result
- PMH – Hemicolecotmy for polyps 2 years ago; HTN, Type II DM
- Exam – VS normal; 80 kg. Guiac negative. Otherwise normal
- Initial lab: Hct/Hgb 30.0/10.7; MCV 86 fL; WBC, Plts normal. Na 137, K 4.9; Cl 113; CO2 19; Gluc 123; Cr 2.2; (all are his chronic values); Panel 2 normal
Anemia Case Study -2

- Serum iron 100 µg/dL (60 - 140 µg/dL)
- Serum transferrin 207 µg/dL (200 - 400 µg/dL)
- Serum ferritin 205 µg/L (35 - 300 µg/L)
- Retics 1.8%
Scenario

- On a CBC ordered for another purpose, unsuspected anemia is found;

- OR -

- Based on clinical symptomatology or physical findings, you suspect that anemia is present;
- Confirm abnormal CBC
  - Include differential, manual slide review if available, reticulocyte count

- Obtain further studies which will let you evaluate anemia etiology:
  - Chemistry panel: should include creatinine, total bilirubin, total protein, and albumin
  - PT/PTT if platelets are low
  - Fe, TIBC/Transferrin, B12/Folate
What’s useful in the History?

- Bleeding
- Jaundice
- Chronic disease, including renal problems
- “Pancytopenia problems”
- Weight loss
- ? Family history
- Degree of symptomatology may reflect volume
What’s useful on the Physical?

- Stool guiac
- Telangectasias
- Splenomegaly/Lymph nodes
- Jaundice
- Purpura
- Thrush
- Hypovolemia
Other general lab

- Creatinine (estimated CCr most important)
- LDH
- Total Bilirubin
Hemolysis

- If Bilirubin/LDH elevated, think hemolysis
- Labs- retics, Coombs test, blood smear
- Autoimmune, hemoglobinopathy, microangiopathic, RBC structural defects, metabolic problems
- AIHA may be a clue to underlying disease
Red Cell Indices

- **MCV (mean corpuscular hemoglobin)**
  - Low MCV – decreased cellular hemoglobin synthesis
  - High MCV – nuclear/cytoplasmic dysynchrony

- **MCH (mean corpuscular hemoglobin)**

- **MCHC (mean corpuscular hemoglobin concentration)**
  - “Hypochromia”

- **RDW (Caveat - unless you are in Pediatrics)**
  - Normal RDW in Microcytosis favors thalassemia
RDW – Many sources of variation

- Aniso/poikilocytosis
- Inflammation *(Arch Pathol Lab Med 2009;133:638-42)*
- Renal insufficiency *(Scand J Lab Clin Invest 2009;68:745-8)*
- Mortality *(Arch Int Med 2009;169:588-94)*

In hospitalized anemic patients, these associations appear to fall out: an association persists with soluble transferrin receptor which is independent of parameters of iron status

*(Unpublished data – Means)*
Differential Diagnosis of Anemia

- **Low MCV**
  - Iron deficiency; ACD (20%); Hemoglobinopathy/thalassemia

- **Normal MCV**
  - ACD (80%); Early iron deficiency; Blood loss/hemolysis; Renal insufficiency; Mixed B12/Folate and Iron deficiency; Androgen deficiency; Primary marrow failure/MDS; Plasma cell dyscrasia; Sickle cell anemia

- **High MCV**
  - B12/Folate deficiency; Liver disease; Hypothyroidism; Primary marrow failure/MDS; Plasma cell dyscrasia with rouleaux; Artifact of inflammation or reticulocytosis
Reticulocyte counts

- Expressed in a variety of ways
  - Percentage, “corrected” percentage, RPI, absolute count
- Is non-invasive and now automated
- Typically low in adult anemias
- Discriminating power is greatest when elevated or VERY low (< 0.2%)
  - Elevated – rules out underproduction
  - Very low – indicates need for marrow (PRCA, aplastic anemia)
Iron deficiency

- Suspect with history of bleeding (GI or menses), pregnancy with inadequate iron supplements, MCV with low MCHC
  - Most common etiology of anemia – consider in all anemic patients
- Diagnosis: Serum ferritin, serum iron, serum TIBC/Transferrin
  - Ferritin < 25-30 µg/L
  - Elevated TIBC/transferrin with % saturation < 10%
    - % Saturation = (Iron ÷ TIBC/Transferrin) x 100
Iron deficiency

- **Factors confusing studies**
  - Ferritin rises with inflammation; iron, TIBC fall with inflammation
  - Oral iron or hemolysis artifactually elevate serum iron
  - Inflammation may cause RBC clumping, falsely elevating MCV

- **Other tests**
  - Soluble transferrin receptor (sTfR) – elevated in iron deficiency
    - Becoming more obtainable
    - Most specific as ratio with ferritin
  - Bone marrow examination
    - Usually requires consultation
    - Patient comfort/convenience issues
Iron deficiency

- **Management**
  - Oral Iron salts/saccharates
    - FeSO₄ 325 mg TID
    - Others work, need to dose ≥150 mg elemental iron/day
  - Intravenous iron
    - Generally requires referral

- **A sign of disease, not a disease itself**
  - GI endoscopy on all males, females after menopause
Table 2. Endoscopic Findings in 100 Patients with Iron-Deficiency Anemia.*

<table>
<thead>
<tr>
<th>Procedure and Lesion</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colonoscopy</td>
<td></td>
</tr>
<tr>
<td>Colon cancer</td>
<td>11</td>
</tr>
<tr>
<td>Polyp†</td>
<td>5</td>
</tr>
<tr>
<td>Vascular ectasia</td>
<td>5</td>
</tr>
<tr>
<td>Colitis</td>
<td>2</td>
</tr>
<tr>
<td>Cecal ulcer</td>
<td>2</td>
</tr>
<tr>
<td>Parasitic infestation</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
</tr>
<tr>
<td>Esophagogastrroduodenoscopy</td>
<td></td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>11</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>6</td>
</tr>
<tr>
<td>Gastritis</td>
<td>6</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>5</td>
</tr>
<tr>
<td>Vascular ectasia</td>
<td>3</td>
</tr>
<tr>
<td>Anastomotic ulcer</td>
<td>3</td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>1</td>
</tr>
<tr>
<td>Other‡</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
</tr>
</tbody>
</table>

*One patient had two lesions (gastritis and a colonic polyp).

Thirty-eight patients had no detectable lesions.

†Two patients had two polyps each.

‡One patient had portal hypertensive gastropathy, and one had a gastric adenomatous polyp.
Anemia of chronic disease

- Suspect with moderate anemia in setting of an inflammatory syndrome, whether acute or chronic

- Diagnosis:
  - Low iron, usually low TIBC/transferrin, with high normal/elevated ferritin
  - Low iron with ferritin $> 200 \, \mu g/L$ essentially makes diagnosis
  - sTfR, sTfR ferritin ratio, normal
  - MCV occasionally as low as 78 fL, rarely ever lower
Anemia of chronic disease

- May be confused with iron deficiency due to low iron, occasional low MCV
  - Ferritin or Ferritin +sTfR will usually distinguish
  - Bone marrow rarely required
  - Serum erythropoietin usually relatively low
  - Often evidence of inflammation (high ESR, CRP)
  - Referral may be needed to confirm diagnosis

- Management:
  - Anemia usually moderate; specific management not required
  - Treat underlying disease
  - Administering iron not helpful
  - No need for colonoscopy/EGD to find blood loss site
  - Treatment with erythropoietin corrects anemia but not approved in US
B12/Folate deficiency

- Suspect with elevated MCV; in elderly, malnourished, institutionalized or heavy EtOH users; after gastric/upper small bowel surgery; in neuropathy

- Diagnosis: Serum B12 and serum folate – if you suspect one, check both
  - If MCV > 105, hypersegmented neutrophils, or neuropathy, B12 < 200-250 ng/L makes diagnosis of B12 deficiency
    - If clinical suspicion high but B12 normal, check methylmalonic acid level
  - Serum folate < 3.5-4.0 µg/L diagnostic of folate deficiency
    - If clinical suspicion high but serum folate normal, check RBC folate level
B12/Folate deficiency

- **Management: B12**
  - Evaluate for etiology: intrinsic factor antibodies, gastrin
  - Give 3-4 1000 µg SC injections cyanocobalamin over 1-3 weeks, then monthly for life
  - Follow Hct/Hgb for response, not B12 levels
  - Oral B12 works but requires 2000 µg/day forever

- **Management: Folate**
  - Folate 1mg po/day; can go up to 5 mg if poor response
  - Follow Hct/Hgb for response

- **No harm to treat with both until results come back**
Anemia of Renal Insufficiency

- Due to erythropoietin deficiency
- Suspect in patients with eGFR < 45 ml/min, or Cr > 2.0 AND no other etiology of anemia on evaluation
- Diagnosis:
  - Requires measured or estimated CFR/Creatinine clearance < 45 ml/min
  - Otherwise negative evaluation
  - Serum erythropoietin levels not usually necessary or helpful
Renal insufficiency

Predicted prevalence of hemoglobin level less than 11, less than 12, and less than 13 g/dL among men (A) and women (B) 20 years and older who participated in the Third National Health and Nutrition Examination Survey (1988-1994)

Anemia of Renal Insufficiency

Management

- If not symptomatic and hemoglobin consistently > 9-10 g/dL, no anemia treatment needed
- Otherwise can be treated with recombinant erythropoietin products
- Typically requires referral to either nephrologist or hematologist/oncologist
Thalassemia/Hemoglobinopathy Trait

- Suspect with microcytosis, minimal anemia, reticulocytosis greater than expected for anemia, and normal iron studies
  - Often MCV very low and out of proportion to degree of anemia
  - MCHC, RDW often normal

- Diagnosis:
  - Hemoglobin electropheresis – usually > 45% Hgb A
    - Abnormal hemoglobin – hemoglobinopathy trait
    - Elevated Hgb A2 and/or Hgb F – β thalassemia trait
    - No abnormal hemoglobin, A2, or F, but microcytosis – infer α thalassemia trait
      - Can confirm by showing family member in same situation
  - Blood smear
    - Microcytosis with or without target cells
Thalassemia/Hemoglobinopathy Trait

- **Management:**
  - No specific management required
  - Folate 1 mg po/day to support reticulocytosis

- May become anemic with minor infections due to suppression of increased reticulocytosis
  - Corrects rapidly when infection resolves

- Has somewhat higher risk of gallstones than age-matched controls

- May have total bilirubin at upper border of normal due to increased RBC turnover