Interpreting the CBC
And Other Helpful Tips

April 6, 2019
Texas Children’s Hospital
Advanced Practice Provider Conference
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Objectives

• Review the complete blood count (CBC) parameters
• Understand the normal ranges within the CBC and limitations of testing
• Examine common abnormalities of the CBC and formulate a differential diagnosis based on results
• Understand the iron panel and limitations of testing
• Identify abnormalities that require evaluation by a specialist
• Review common peripheral smear findings and clinical significance
Interpreting the CBC

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>5.98</td>
</tr>
<tr>
<td>RBC</td>
<td>4.59</td>
</tr>
<tr>
<td>HGB</td>
<td>10.1 (L)</td>
</tr>
<tr>
<td>HCT</td>
<td>31.4 (L)</td>
</tr>
<tr>
<td>MCV</td>
<td></td>
</tr>
<tr>
<td>MCH</td>
<td>Yada</td>
</tr>
<tr>
<td>MCHC</td>
<td>Yada</td>
</tr>
<tr>
<td>RDWCV</td>
<td>Yada</td>
</tr>
<tr>
<td>RDWSD</td>
<td></td>
</tr>
<tr>
<td>Platelets</td>
<td>220</td>
</tr>
<tr>
<td>ANC</td>
<td>2100</td>
</tr>
</tbody>
</table>
# Elements of the CBC

<table>
<thead>
<tr>
<th>Element</th>
<th>Differential:</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>RBC</td>
<td>Lymphocytes</td>
</tr>
<tr>
<td>HGB</td>
<td>Monocytes</td>
</tr>
<tr>
<td>HCT</td>
<td>Eosinophils</td>
</tr>
<tr>
<td>MCV</td>
<td>Basophils</td>
</tr>
<tr>
<td>MCH</td>
<td></td>
</tr>
<tr>
<td>MCHC</td>
<td></td>
</tr>
<tr>
<td>RDW</td>
<td></td>
</tr>
<tr>
<td>Platelet</td>
<td></td>
</tr>
<tr>
<td>MPV</td>
<td></td>
</tr>
</tbody>
</table>
CBC: The Basics of Red Cells

- **Red blood cells (RBC):** total number of erythrocytes per microliter
- **Hematocrit** or packed cell volume (hct, PCV): indirect measure of RBC mass, percentage of volume of packed RBCs in whole blood
- **Hemoglobin** (hb or hgb): concentration of hemoglobin grams per deciliter of blood – directly proportional to oxygen-combining capacity of the blood
- **Mean corpuscular volume (MCV):** average volume of one erythrocyte in femtoliters
  - Low MCV indicates routinely small RBCs – microcytosis
  - High MCV indicates routinely large RBCs – macrocytosis
  - Normal MCV indicates normal RBCs – normocytic OR could indicate a mixture of small and large RBCs
CBC: The Basics of Red Cells

• Mean corpuscular hemoglobin: the average weight of hgb per RBC
  • How much hemoglobin is carried in each RBC
  • If someone is iron deficient they will have low MCH because there is not enough hemoglobin (O2 carrying capacity) in the cells

• Mean corpuscular hemoglobin concentration: ratio of hemoglobin concentration to volume of erythrocytes
  • This is how much hemoglobin is carried in each RBC compared to its size
  • If someone is mildly iron deficient, they have a low MCH but the RBCs are also microcytic – therefore the concentration of hemoglobin may still be normal
CBC: The Basics of Red Cells

• Red cell size distribution width: degree of variation in erythrocyte size, a coefficient of variation
  • A high RDW indicates a large variation in size of RBCs
    If the MCV is normal and the RDW is high, there is a mixture of large and small RBCs
    If the RDW is normal and the MCV is high, the RBCs are likely all macrocytic
    If the MCV and RDW are both normal, the RBCs are likely all about the same normal size
CBC: The Basics of Red Cells

• The only DIRECT measurements on a CBC (with regard to erythrocytes) are RBC and Hb (and sometimes MCV) – everything else is determined based on one of these measurements.

• Hematocrit vs Hemoglobin
  • Blood is centrifuged and the height of the packed cells as a percentage of total amount of blood in tube to determine hematocrit.
  • Say you have RBC 4.0 x 10^{12}/L
    If your RBCs are small and microcytic they will pack down to a smaller volume, causing a lower hct.
    If your RBCs are large and macrocytic they will pack down to a larger volume, causing a higher hct.
  Hemoglobin should be reliable no matter the MCV or RBC because it is a direct measure of O_2 carrying capacity of the blood.
Another way to see it
General Approach to a Cytopenia

The patient is either...

1. Not making it
   - Bone marrow suppression/failure

2. Destroying it
   - Immune destruction, iatrogenic

3. Losing it
   - Bleeding, abnormal storage
Anemia

- Anemia is defined by a decrease in erythrocytes, typically given in terms of hemoglobin or hematocrit.
- Reticulocyte count is the measure of circulating new red blood cells, usually RBCs 24-48 hours after leaving the bone marrow.

<table>
<thead>
<tr>
<th>Microcytic</th>
<th>Normocytic</th>
<th>Macrocytic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron deficiency</td>
<td>Acute/Chronic inflammation or infection</td>
<td>Reticulocytosis</td>
</tr>
<tr>
<td>Lead poisoning</td>
<td>Bone marrow suppression</td>
<td>Vitamin B12 or Folate deficiency</td>
</tr>
<tr>
<td>Thalassemias</td>
<td>Congenital/Acquired hemolytic anemias</td>
<td>Diamond Blackfan Anemia</td>
</tr>
<tr>
<td>Sideroblastic anemias</td>
<td>Acute/Subacute blood loss</td>
<td>Bone marrow failure</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>Hypersplenism/Splenic sequestration</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Hypoproteinemia</td>
<td>Transient erythroblastopenia of childhood (TEC)</td>
<td>Hypothyroid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Iatrogenic</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Normal newborn</td>
</tr>
</tbody>
</table>

Taken from *The Bethesda Handbook of Clinical Hematology*
Iron Deficiency

• Majority of iron is contained in hemoglobin
• Iron is recycled in the body when red blood cells naturally die
  • Most hemolytic anemias are NOT at risk of iron deficiency
• Transferrin brings iron to marrow to be utilized in synthesizing new erythrocytes
• Physiologic iron loss occurs in sloughed epithelial cells from skin and GI tract
  • About 1 mg of iron lost per day
  • Menstruating females average an additional 1 mg iron loss per day
Progression of iron deficiency

• Initially serum ferritin is utilized and becomes decreased
• Serum iron decreases
• Transferrin concentration increases as the body is trying to find all the iron possible
• Transferrin saturation decreases because there is nothing to saturate the transferrin
• Total iron binding capacity (TIBC) increases
  • Patient’s blood + iron ex vivo, then count how much iron binds – it will bind excessively because the blood is so hungry for iron and the transferrin is unsaturated
Progression of iron deficiency

• When there is not adequate iron, erythropoiesis suffers
  • fewer erythrocytes (decreased RBC count)
  • erythocytes with decreased hemoglobin concentration (hypochromia)
  • poorly made erythrocytes (microcytic ± poikilocytosis)
  • reticulocyte count is usually normal
Caveats to the Iron Panel

• Serum ferritin, transferrin and serum iron can be falsely elevated with underlying inflammation/infection
• Transferrin saturation is a calculated value (serum iron/TIBC)
• Serum iron fluctuates with iron ingestion
  • If you just ate a steak, it will be high even if you are iron deficient
High Risk Populations for Iron Deficiency

• Toddlers
  • Heavy milk drinkers, picky eaters
• Menstruating females
• Pregnant women
  • Infants are at risk of mother not properly treated or if exclusively breast fed
• Decreased iron absorption
  • Elderly, gastric bypass, PPI use, bowel inflammation, etc
If not high risk population...

1. GI BLOOD LOSS
Treatment of IDA

• Fix underlying reason, if possible
  • Diet, blood loss, etc
• Encourage iron rich foods
• Supplement with oral iron
  • ~3 mg/kg/day dosed once daily
  • 65-130 mg daily for adults
  • Constipation and abdominal pain are common side effects
• IV iron is an option for refractory cases
Thalassemia Traits

• Typically causes a mild, microcytic anemia
  • Not responsive to iron and iron panel would be normal

• Alpha thalassemia trait
  • 4 genes encode for alpha globin
  • Multiple gene combinations (next slide)
  • Trait is typically only picked up on newborn screen (Bart’s Hemoglobin)

• Beta thalassemia trait
  • 2 genes encode for beta globin
  • Trait is never picked up on newborn screen
  • Hemoglobin profile reveals elevated hemoglobin A2
## Alpha Thalassemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Findings/Treatment</th>
<th>How to test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>αα/αα</td>
<td>Normal CBC</td>
</tr>
<tr>
<td>Silent Carrier</td>
<td>αα/α-</td>
<td>Normal CBC</td>
</tr>
<tr>
<td>Alpha thal trait</td>
<td>αα/- -&lt;br&gt;α -/α -</td>
<td>Mild microcytic anemia</td>
</tr>
<tr>
<td>Hemoglobin H</td>
<td>α -/- -</td>
<td>Moderate-severe microcytic anemia&lt;br&gt; +/- transfusions</td>
</tr>
<tr>
<td>Alpha thal major</td>
<td>- -/- -</td>
<td>Severe anemia in utero&lt;br&gt;In utero transfusions&lt;br&gt;Hydrops fetalis</td>
</tr>
</tbody>
</table>
Vitamin B12 and Folate Deficiencies

• Both can cause macrocytic anemia
• At risk populations
  • B12: Vegans, s/p gastric bypass, pernicious anemia, inborn errors of metabolism, IBD, parasites
  • Folate: Meat eaters, folate inhibiting medications, alcohol abuse
• Consequences of deficiency
  • B12: macrocytic anemia, pancytopenia, neurologic deficits
    • Elevated methylmalonic acid (MMA) +/- elevated homocysteine
  • Folate: neural tube defects (in pregnant women), early cardiovascular disease, malignancy
    • Elevated homocysteine
Bone Marrow Failure

• Acquired aplastic anemia (AA) vs Inherited bone marrow failure syndrome (IBMFS)
• AA usually presents with ≥2 cytopenias, often moderate to severe
• IBMFS may present with 1-3 cytopenias
  • Often macrocytosis is present even if anemia is not
  • Associated with short stature, skeletal abnormalities
• Cytopenias are typically progressive
• Most have an increased risk of acute myeloid leukemia (AML) and/or other cancers throughout lifetime
Fanconi Anemia

• Most common inherited bone marrow failure syndrome
• Inherited in an autosomal recessive pattern
• Abnormal skin coloration, short stature, abnormalities of thumbs, kidneys, reproductive organs
• Initial test for diagnosis is chromosome breakage
  • Follow up genetic testing for confirmation
Normal Red Cell Indices in Children

<table>
<thead>
<tr>
<th>Age</th>
<th>HEMOGLOBIN (g/dL)</th>
<th>HEMATOCRIT (%)</th>
<th>RED CELL COUNT *(10^12/L)</th>
<th>MCV (fl)</th>
<th>MCH (pg)</th>
<th>MCHC (g/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth (cord blood)</td>
<td>16.5</td>
<td>51</td>
<td>4.7</td>
<td>108</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>1 to 3 days (capillary)</td>
<td>18.5</td>
<td>53</td>
<td>5.6</td>
<td>108</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>1 week</td>
<td>17.5</td>
<td>54</td>
<td>3.8</td>
<td>96</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>2 weeks</td>
<td>16.5</td>
<td>51</td>
<td>4.9</td>
<td>105</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>1 month</td>
<td>14.0</td>
<td>43</td>
<td>4.2</td>
<td>104</td>
<td>34</td>
<td>33</td>
</tr>
<tr>
<td>2 months</td>
<td>11.5</td>
<td>35</td>
<td>3.8</td>
<td>96</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>3 to 6 months</td>
<td>11.5</td>
<td>33</td>
<td>3.8</td>
<td>91</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>0.5 to 2 years</td>
<td>9.5</td>
<td>29</td>
<td>3.8</td>
<td>91</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>2 to 6 years</td>
<td>12.0</td>
<td>36</td>
<td>4.5</td>
<td>78</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>6 to 12 years</td>
<td>12.5</td>
<td>37</td>
<td>4.6</td>
<td>81</td>
<td>27</td>
<td>34</td>
</tr>
<tr>
<td>12 to 18 years</td>
<td>13.5</td>
<td>35</td>
<td>4.6</td>
<td>86</td>
<td>29</td>
<td>34</td>
</tr>
<tr>
<td>Female</td>
<td>14.0</td>
<td>41</td>
<td>4.6</td>
<td>90</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Male</td>
<td>14.5</td>
<td>43</td>
<td>4.9</td>
<td>88</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>18 to 49 years</td>
<td>14.0</td>
<td>41</td>
<td>4.6</td>
<td>90</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Female</td>
<td>15.5</td>
<td>47</td>
<td>5.2</td>
<td>90</td>
<td>30</td>
<td>34</td>
</tr>
<tr>
<td>Male</td>
<td>15.5</td>
<td>47</td>
<td>5.2</td>
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<td>30</td>
<td>34</td>
</tr>
</tbody>
</table>

*These data have been compiled from several sources. Emphasis is given to studies employing electronic counters and to the selection of populations that are likely to exclude individuals with iron deficiency. The mean ±2 SD can be expected to include 95% of the observations in a normal population.


LEUKOPENIA/NEUTROPENIA
Neutropenia

• Defined as an absolute neutrophil count (ANC) <1500/μL
• Typically referred to as
  • **Mild:** ANC 1000-1500
  • **Moderate:** ANC 500-1000
  • **Severe:** ANC <500
    Agranulocytosis: <200
What does a neutrophil do?

- *Primary* cell in immune response to pyogenic organisms and *predominate* cell in acute inflammatory infiltrates

- Neutropenia increases susceptibility to bacterial and fungal infections
  - Skin and oral cavity most commonly affected
  - Sepsis is a common complication resulting in morbidity and mortality
  - S/sx of infection may be altered with neutropenic patient
Common Causes of Neutropenia

• Infection/Viral suppression → #1 cause of transient neutropenia in kids
• Drug-induced (antibiotics, antiepileptic drugs, psychotropic agents)
• Autoimmune Neutropenia → #1 cause of chronic neutropenia in kids
• Ethnicity
• Immune dysfunction (autoimmunity, congenital immunodeficiencies, HIV)
• Neonatal causes (prematurity, alloimmune)
• Metabolic disorders
• Nutritional deficiencies
• Bone marrow failure/infiltration
Autoimmune Neutropenia (AIN)

• Primary
  • Isolated neutropenia, no other underlying condition causing neutropenia
  • Primarily in young children which is a self resolving condition
  • Neutropenia is out of proportion to infectious history (i.e. ANC <200 in an otherwise healthy child)
  • Anti-neutrophil antibody is helpful but not always diagnostic
  • Rarely requires use of G-CSF
  • Follows fever precautions

• Secondary
  • Broader immune or autoimmune disorder (DiGeorge, lupus, Sjogren’s)
  • Infection
  • Medications (hydralazine, procainamide)

Often followed by specialist to rule out other causes of neutropenia
Ethnic Neutropenia

• A BENIGN mild-moderate neutropenia found in certain ethnic groups
• Most common in those of African descent, also in certain Jewish and Arab populations
• Prevalence estimated at 10-30%
• Otherwise normal leukocytes
• No history of abnormal or recurrent infections
• NO INCREASED RISK OF LOCAL OR SYSTEMIC INFECTIONS
• Does not require specialist care

Approach to Neutropenia

• Age of patient
• Current status of patient (ill vs well)
• Why you got the ANC in the first place
• Previously normal ANCs
• Infectious history (or lack thereof)
• Severity of neutropenia
  • Particularly in relation to the current clinical status
• Family history
Approach to Neutropenia

• If an incidental finding in an otherwise well child, most likely can repeat in a few months
  • If persistently <1000, refer
• If ANC <500 in a febrile illness, send to ED
  • Minimum blood cultures, broad spectrum antibiotics
• If physical exam reveals lymphadenopathy, organomegaly, unintentional weight loss, etc, consult with hem/onc or send to ED
• If found due to history of recurrent/abnormal infections, refer
• If CBC also reveals anemia or thrombocytopenia, refer
Other Leukocytes: Eosinophils and Basophils

Non-phagocytic, de-granulate to fight infections
Particularly good at fighting multicellular organisms
Primary cells in atopic disorders

**Eosinophilia** (absolute eosinophil count >500):
Allergy, asthma, parasitic infections, malignancies, rheumatologic disorders, immunodeficiencies, hypereosinophilic syndrome

**Basophilia:**
Hypersensitivity reactions, anaphylaxis, infections, chronic myelogenous leukemia (CML)
Other Leukocytes

Lymphocytes (T cells, B cells, NK cells, NKT cells)
• Primary cell of specific immune recognition
• Differentiate self vs non-self
• Lymphocytosis - Infection (especially viral), leukemia
• Lymphopenia – rheumatologic diseases

Monocytes
• Multiple functions including phagocytosis and antigen presentation
• Typically first cell to repopulate with marrow recovery
• Monocytosis
  • Infections (subacute bacterial endocarditis, TB), malignancies, rheumatologic diseases, SCN
Approach to Leukopenia

• Determine which specific leukocyte is decreased
  • Refer if neutrophils or lymphocytes are severely decreased
• If no lines are significantly low, options include repeating labs, consulting with hem/onc or referral
  • WBC persistently <3.0K is more concerning than mild leukopenia
Thrombocytopenia

• Platelets are responsible for primary hemostasis and wound healing
  • Normal platelet count is 150,000/μL to 450,000/μL
• Bleeding due to thrombocytopenia is typically mucocutaneous
  • Oral, GI, GU, skin
• Moderate-severe bleeding typically occurs with counts <20,000/μL
Thrombocytopenia

• Newborn
  • Infection, infection, infection
  • Maternal factors (preeclampsia, medications, etc)
  • Neonatal alloimmune thrombocytopenia (NAIT)
• Immune thromobocytopenia (ITP)
• Autoimmune disease
• Inherited platelet/bone marrow disorders
• Iatrogenic
• Pseudothrombocytopenia/lab error
How to approach Thrombocytopenia

• If a mild, incidental finding in an otherwise well child, most likely can repeat in a few months
  • If persistently <100, refer
• If active or uncontrolled bleeding, send to ED
• If physical exam reveals lymphadenopathy, organomegaly, unintentional weight loss, etc, consult with hem/onc or send to ED
• If found due to history of recurrent/abnormal bleeding or bruising, refer
• If CBC also reveals neutropenia or thrombocytopenia, refer
Elevated Counts

• Erythrocytosis
  • Hypoxemia, smoking, some hemoglobin disorders, myeloproliferative neoplasms (MPN)
• Leukocytosis
  • Infection, inflammatory state, MPNs
• Thrombocytosis
  • Infection, inflammatory state, iron deficiency, MPNs
Peripheral Smear Cheat Sheet

• Anisocytosis – variation in size of RBCs
• Poikilocytosis – variation in shape of RBCs
• Polychromasia – increased reticulocytes (stain purple)
• Acanthocytes – aka spur cells, thorn-like projections
• Echinocytes – aka burr cells, similar to acanthocytes with more regularity in projections
• Howell Jolly bodies – small fragments of nuclear material in RBCs, usually cleared by spleen (asplenia)
• Target cells – excess membrane with relation to amount of hemoglobin (liver disease, hemoglobin C, asplenia)
• Drepanocytes – aka sickled erythrocytes
• Schistocytes – fragmented RBCs (looks like cut in half, concern for TTP)
• Basophilic stippling – ribosomal RNA in erythrocytes (lead poisoning, ineffective erythropoiesis)
• Blister cells – aka helmet cells, RBCs with vacuoles (G6PD deficiency)

