# Anemia Introductory Lecture

# General Approach to Anemia

① Evaluate the CBC

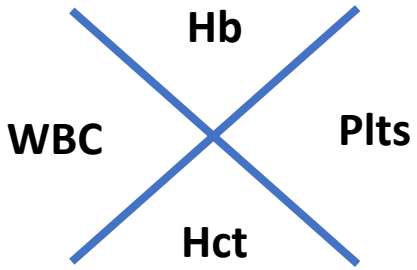
② Evaluate the MCV

③ Relevant History

④ Additional Labs

# General Approach to Anemia: Evaluating the CBC

## ① Evaluate the CBC




## Hemoglobin vs Hematocrit vs RBC Count

- **Hemoglobin (g/dL)** = concentration
  Normal natal women > 11/12
  Normal natal men > 13/14

- **Hematocrit (%)** = % volume of blood that is RBCs.
  often calculated RBC x MCV/10

- **RBC Count (#)** = # RBCs in X volume (cells [in millions]/uL)

# General Approach to Anemia: Evaluating the CBC

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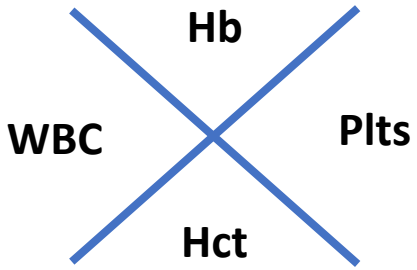


## Ensure Accuracy of CBC:

- Make sure the lab test makes sense in context of other labs and was drawn correctly
- If lab drawn incorrectly can be diluted → decrease in all blood counts
- Margin of error for Hb is approximately 1 g/dL . **Hb TREND** is what matters. A single value could always be spurious, a trend is reliable.

# General Approach to Anemia: Evaluating the CBC

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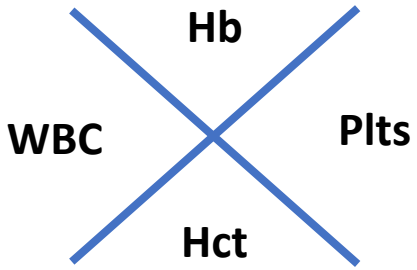



## Emergent vs Urgent vs Routine:

Emergency:

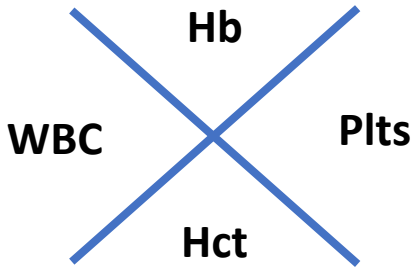
- If Hb <7 and signs/symptoms of hemodynamic instability
- Acute drop in hemoglobin is concerning
- Transfuse first and identify etiology later

Non-Urgent:

- Chronic low hemoglobin >7 is likely non-emergent

# General Approach to Anemia: Evaluating the CBC

## ① Evaluate the CBC




## Look at the Other Blood Counts:

Are the WBCs and/or platelets also low (or high)

**Isolated Anemia**

Suggests targeted issue with production or destruction of just RBCs

**Pancytopenia**

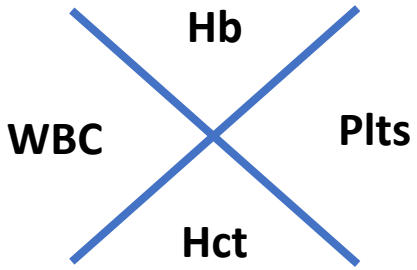
Suggests systemic issue with production (less likely destruction). Often related to bone marrow dysfunction

**Thrombocytosis**

Sign of iron deficiency anemia (IDA) or reactive inflammatory process

# General Approach to Anemia: Evaluating the CBC

## ① Evaluate the CBC




## Look at the Baseline Hemoglobin

Is this a new or old anemia? What is the baseline hemoglobin

**Acute Anemia**

acute process examples:

- IDA (GIB)
- Acute leukemia
- Drug toxicity

**Chronic Anemia**

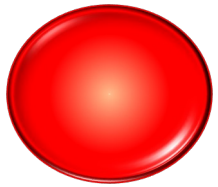
chronic process examples:

- Congenital hemoglobinopathy (Thalassemia, Sickle Cell Disease)
- IDA (GIB, Menstrual Bleeding)
- MDS
- Chronic leukemia
- Malnutrition (B12/folate deficiency)
- Drug toxicity
- Chronic inflammatory disorder

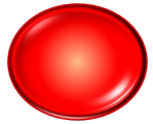
# General Approach to Anemia: Evaluating the MCV

## ② Evaluate the MCV:  Mean Corpuscular Volume

**Macrocytic** = **> 100 fL**



**Normocytic** = **80-100 fL**



**Microcytic** = **< 80 fL**

***Clinical Pearl:*** When evaluating a new anemia case the most important lab test I look at is the **MCV** and the **MCV Trend**

# Common Causes of Anemia by MCV

## Microcytosis
## MCV < 80 fL

**Acquired**
- IDA
- AOCD

**Hereditary**
- Thalassemia

## Normocytosis
## MCV 80-100 fL

**AOCD**
- CKD, CHF
- Infection/inflammation

**Microcytic Overlap**
- ex: IDA

**Macrocytic Overlap**
- ex: Multiple Myeloma

## Macrocytosis
## MCV > 100 fL

**Megaloblastic (DNA metabolism)**
- B12/Folate Deficiency
- Drugs, ETOH

**Immature Cells (Reticulocytosis)**
- Hemolysis

**Primary Bone Marrow Dysfunction**
- MDS, Leukemia, Myeloma

**Multifactorial (ex: Lipid Metabolism)**
- Liver disease
- Endocrinopathies (hypothyroidism)

***Clinical Pearl:*** Can have **mixed** microcytic and macrocytic anemia.
Often this corresponds to an increased **RDW (RBC distribution width)**.
Check MCV Trend to assess for developing micro or macrocytosis

# General Approach to Anemia: Relevant History

## ③ Relevant History

| | |
|---|---|
| **Medications** | Is the patient on any **blood thinners**? Anticoagulants or anti-platelet agents<br><br>Are they on any **myelotoxic medications**? Chemo, Bactrim |
| **Bleeding History** | **Melena, BRBPR, heavy or regular menses**<br><br>** Can have no history of GIB and/or negative guaiac and still have a GIB |
| **Systemic Illness** | **Signs/symptoms of systemic or chronic illness**<br><br>Ex: fevers and weight loss could indicate a malignant process<br>Ex: Chronic liver, kidney or heart disease |

# General Approach to Anemia: Additional Labs

## ④ Additional Labs

| | |
|---|---|
| **Iron Studies** | **Iron, TIBC or Transferrin, Ferritin** |
| **Hemolysis** | **Haptoglobin, Reticulocyte, LDH, Bilirubin (Total + Direct)** |
| **B12 +/- Folate** | **Folate:** Hard to be folate deficient.<br>Send if macrocytic anemia with history of malnutrition or hemolysis<br>**MMA** = high in B12 deficiency<br>**Homocysteine** = high in B12 and folate deficiency |
| **Multiple Myeloma** | **SPEP/UPEP, SIFE/UIFE, Free Kappa/Lambda** |

# Iron Studies

## Iron (Fe)

**Oxygen Binder ($$$)**
Hemoglobin: Heme + Globin
4 heme groups, each with iron that binds O2

## Transferrin/TIBC

**Fe Transport (wallet)**
Transferrin = protein transports iron in the blood
Total Iron Binding Capacity = Available transferrin
* TIBC is calculated from transferrin

***Transferrin***

***Ferry*** your iron

## Ferritin

**Fe Storage (bank)**
Predominantly intracellular protein that stores iron
acute phase reactant, increased in inflammatory states

***Ferritin***

Keep your iron in a ***Tin***

# Iron Studies

## Iron (Fe)

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## Transferrin Saturation

**Tsat = Fe/TIBC**

**Tsat < 20%**
= iron deficiency **likely**

**Tsat > 20%**
= iron deficiency **unlikely**

# Iron Studies

## Iron (Fe)

**Oxygen Binder ($$$)**
Hemoglobin: Heme + Globin
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## Ferritin

**Fe Storage (bank)**
Predominantly intracellular protein that stores iron
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**Iron Deficiency Anemia (IDA)**
**Fe: Low**
**TIBC: High** upregulated to transport Fe
**Ferritin Low** low Fe storage
**Tsat (Fe/TIBC) < 20%**
*Ferritin <40 is consistent with iron deficiency! Even if LLN in your lab is lower!

**Anemia of Chronic Disease (AOCD)**
Fe: Low (variable)
TIBC: Low (variable)
**Ferritin: High** (variable)

**Mixed IDA + AOCD**
Fe: Low-Normal (variable)
TIBC: High-Normal (variable)
**Ferritin: High-Normal** (variable)

* Soluble transferrin receptor is high in IDA. Can distinguish if there is IDA iso AOCD as this is not an acute phase reactant

# Hemolysis Labs

## LDH

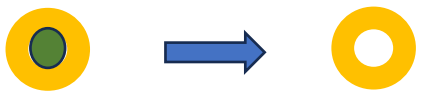
RBC lysis → intracellular LDH release


## Haptoglobin

Free heme binds haptoglobin →
Lowers haptoglobin


## Bilirubin

Heme breaks down → Bilirubin
Heme → Bilverdin → Unconjugated Bilirubin




## Reticulocytes

BM compensates for anemia by making
new RBCs = reticulocytes

↑ LDH

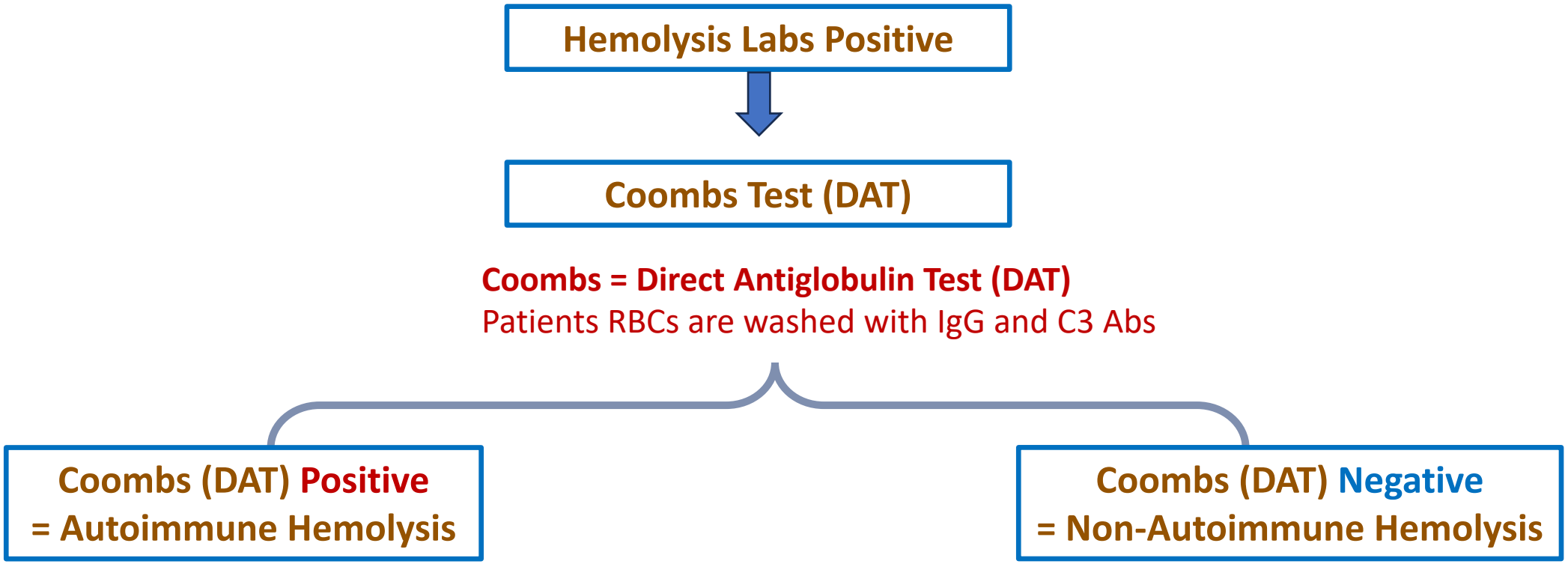
↓ Hapto

↑ Ind Bili

↑ Retics

***Clinical Pearl:*** specificity of **low haptoglobin** and **high LDH** is high (>90%)

# Coombs Test


Hemolysis Labs Positive
Coombs Test (DAT)
Coombs = Direct Antiglobulin Test (DAT)
Patients RBCs are washed with IgG and C3 Abs
Coombs (DAT) Positive
= Autoimmune Hemolysis
Coombs (DAT) Negative
= Non-Autoimmune Hemolysis

# Coombs Test

## Coombs (DAT) Positive = Autoimmune Hemolysis

**Coombs = Direct Antiglobulin Test (DAT)**
Patients RBCs are washed with IgG and C3 Abs
**Spherocytes can be present on peripheral smear**

### WARM AIHA

**Dx: IgG+, C3+/-**

**Causes**: Autoimmune, infections, lymphoproliferative disorders, drugs, immunosuppression, transfusions

### COLD AIHA

**Dx: C3+, IgG-**

**Causes:** Cold Agglutinin Disease, Paroxysmal Cold Hemoglobinuria

## Coombs (DAT) Negative = Non-Autoimmune Hemolysis

### Microangiopathic

**Schistocytes on peripheral smear**

**MAHA = Microangiopathic HA**
ex: Mechanical heart valve

**TMA = Thrombotic Microangiopathy**
**= MAHA + Thrombocytopenia**
ex: DIC, TTP, HUS

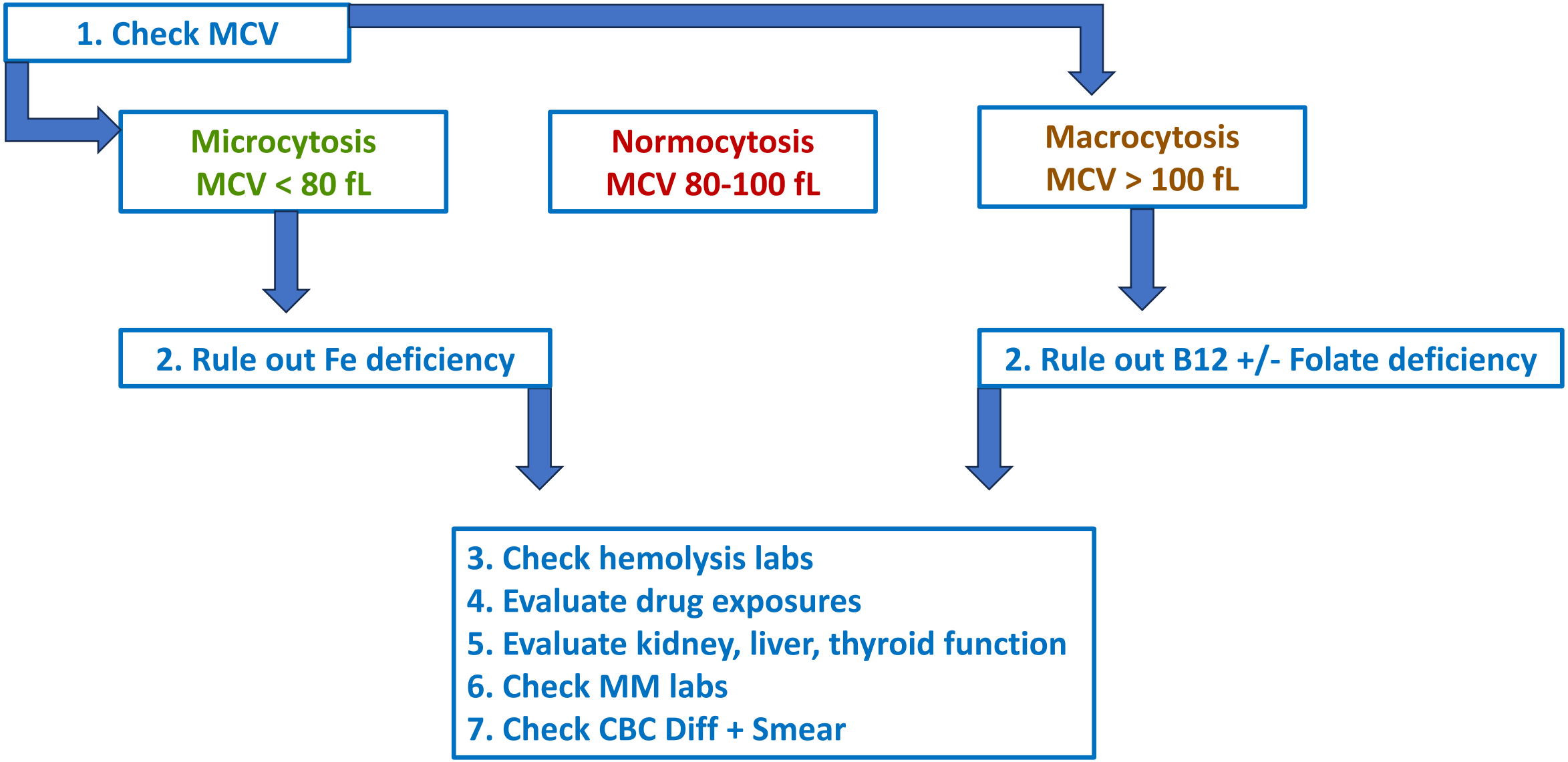
### Macroangiopathic

**Hemoglobinopathies**
ex: Sickle cell, Thalassemia

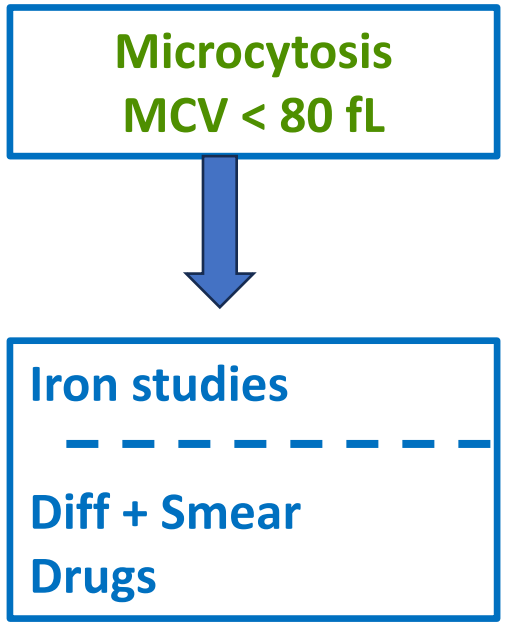
**Enzymopathies**
ex: G6PD Deficiency

**RBC Membrane Disorders**
ex: Hereditary Spherocytosis

# MCV-Based General Diagnostic Approach



# Common Differential Diagnosis




## Acquired: Iron Deficiency Anemia (IDA)

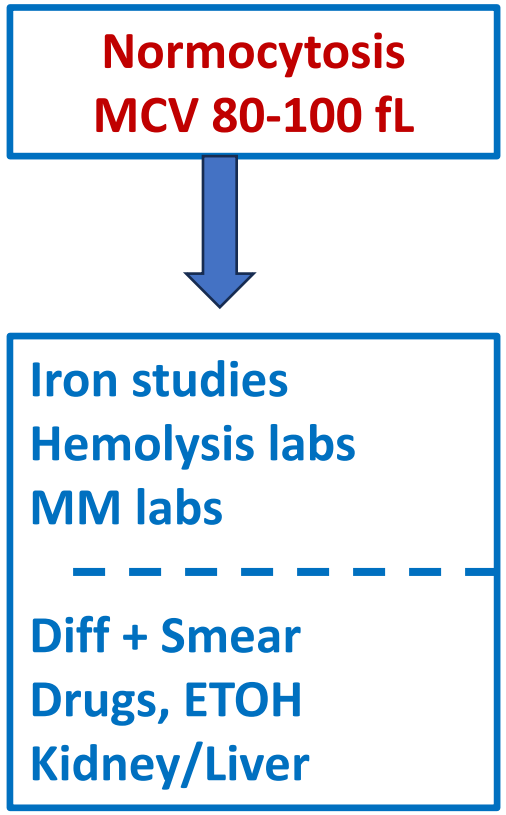
- Often down-trending MCV
- History of bleeding (GI, menstrual). Very common in menstruating women! ~ 20%
- Iron studies: Low Fe, High TIBC, Low Ferritin, Tsat <20%, elevated RDW. Ferritin < 40 = IDA
- Smear: Microcytic, hypochromic RBCs
- Plts: Can have thrombocytosis
- Drugs: History of anticoagulants or anti-plts

## Acquired: AOCD

- Can be more chronic
- Can be normocytic
- Often elevated ferritin (acute phase reactant)

## Hereditary: Thalassemia

- Chronic anemia (congenital)
- MCV often quite low (< 65-75), out of proportion to degree of anemia
- Iron studies and RDW normal




# Common Differential Diagnosis

## AOCD

- Many causes: CKD, CHF, Infection/inflammation
- Fe studies can be confusing, ferritin often high
- Can have mixed AOCD with IDA

## Microcytic Overlap

- ex: IDA

## Macrocytic Overlap

- ex: Multiple Myeloma

**Macrocytosis**
**MCV > 100 fL**

**B12 +/- folate**
**Hemolysis labs**
**MM labs**
**TSH**
**Iron studies (ferritin)**

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**Diff + Smear**
**Drugs, ETOH**
**Kidney/Liver**

# Common Differential Diagnosis

## Megaloblastic (DNA metabolism)

- B12/Folate Deficiency
- Drugs, ETOH (low retics iso BM suppression)

## Immature Cells (Reticulocytosis)

- Hemolysis (low hapto, high LDH, high indirect bili, high retics)

## Primary Bone Marrow Dysfunction

- MDS, Leukemia, Myeloma
- Smear: Immature cells (ex: blasts in leukemia)

## Multifactorial (ex: Lipid Metabolism)

- Liver disease (acanthocytes/spur cells present, abnormal LFTs)
- Endocrinopathies (hypothyroidism)

# Anemia Reference Handout

## CBC Evaluation

1. Accurate vs. Inaccurate
2. Urgent vs. Non-urgent
3. Acute vs. Chronic
4. Anemia vs. Pancytopenia or Thrombocytosis
5. MCV & MCV Trend

## Other Labs

| | |
|---|---|
| Iron Studies | Iron, TIBC or Transferrin, Ferritin<br>IDA: Fe $^{low}$ TIBC $^{high}$ Ferritin $^{low}$ Tsat <20%<br>AOCD: Ferritin $^{high}$ |
| Hemolysis | Haptoglobin $^{low}$ LDH $^{high}$ Ibili $^{high}$<br>Reticulocyte $^{low}$ |
| B12 +/- Folate | Folate<br>MMA $^{B12}$<br>Homocysteine $^{B12 + Folate}$ |
| Multiple Myeloma | SPEP/UPEP, SIFE/UIFE, Free Kappa/Lambda |

## Anemia Eval by MCV

**Microcytosis**
**MCV < 80 fL**

**2. Rule out Fe deficiency**

**Normocytosis**
**MCV 80-100 fL**

**Macrocytosis**
**MCV > 100 fL**

**2. Rule out B12 +/- Folate deficiency**

3. Check hemolysis labs
4. Evaluate drug exposures
5. Evaluate kidney, liver, thyroid function
6. Check MM labs
7. Check CBC Diff + Smear

## Hemolytic Anemia

**Coombs (DAT) Positive**
**= Autoimmune Hemolysis**

Spherocytes can be present on peripheral smear

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**Dx: IgG+, C3+/-**

**Causes**: Autoimmune, infections, lymphoproliferative disorders, drugs, immunosuppression, transfusions

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