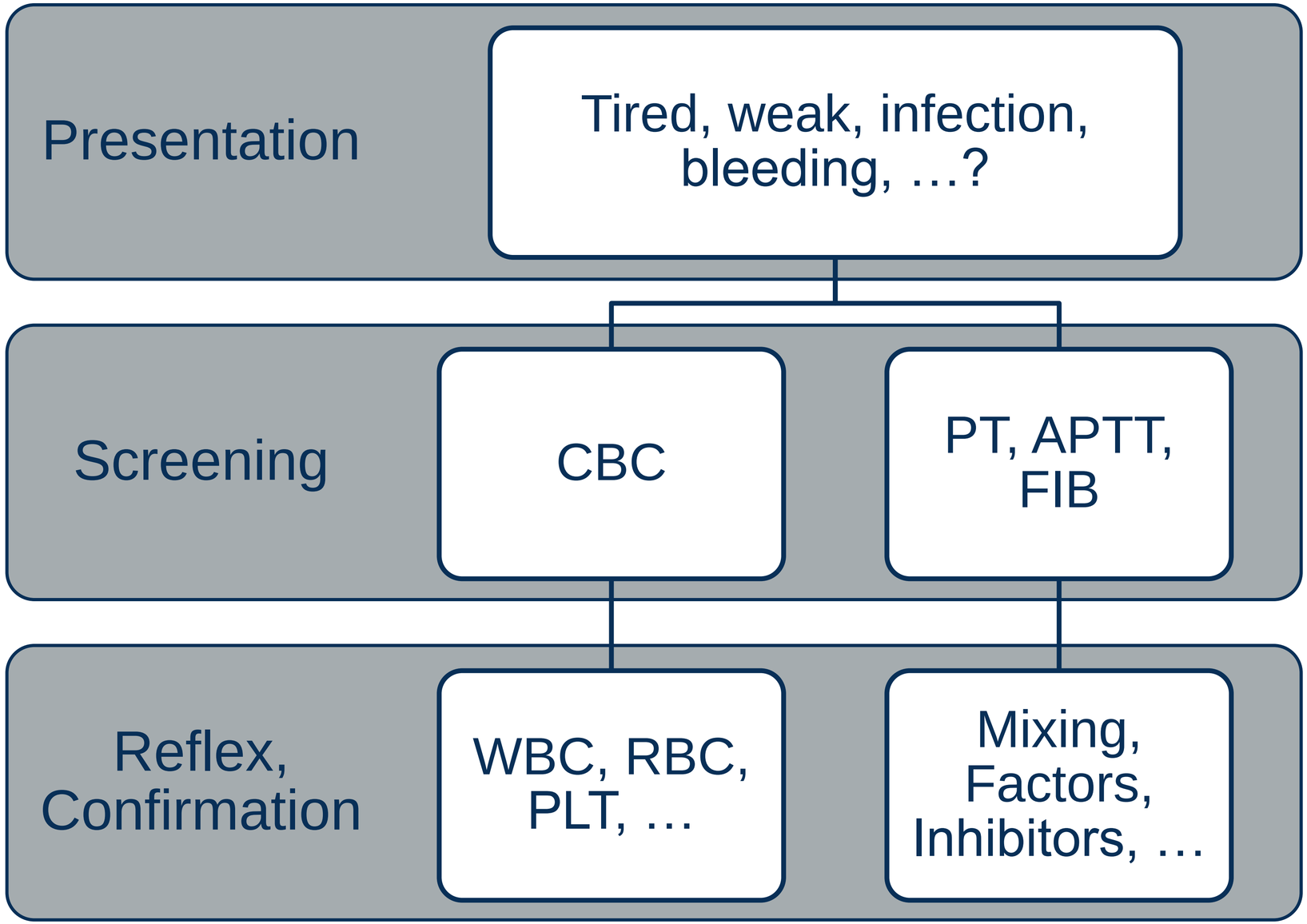
Clinical Hematology Review

General Hematology Flow



Erythrocytes Review

Anemia

Microcytic

- **Iron deficiency**
- **Chronic inflammation**
- **Sideroblastic**
- **Thalassemia**

Normocytic

- **Hereditary hemolytic**
- **Acquired hemolytic**
- **Hypoproliferative**
- **Acute hemorrhage**

Macrocytic

- **Megaloblastic**
- **Non-megaloblastic**

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Symptoms: Weakness/fatigue, tachycardia, circulatory collapse, shock, headache, vertigo, dyspnea, hematuria/emesis, bloody/black stools

Physical: Pale skin, hypotension, organomegaly (hepato-/sleno-megaly), koilonychia, smooth tongue, jaundice, dark urine, bone deformities, neurologic dysfunction

Screening Tests

Cell counts

- RBC indices, reticulocytes (%, corrected, RPI)

Differential and morphology evaluation

Iron studies

- Serum iron, ferritin, transferrin (TIBC)

Reflex Tests

Hemoglobin identification

- Solubility, HPLC, electrophoresis

Hemolytic indicators

- Haptoglobin, hemopexin, hemosiderinuria, lactate dehydrogenase

Other

- ESR, G6PD, Heinz body, Prussian blue, Kleihauer-Betke, bone marrow, flow cytometry, etc.

Anemia

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Normocytic

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Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Most common nutritional deficiency worldwide; koilonychia, glossitis, muscle dysfunction, pica syndrome

Screening Tests

CBC

- ↓ MCV, ↓ MCHC, ↑ RDW
- %/# retic normal to ↑, RPI < 2

Differential

- Target cells (SL-MOD), ellipt/ovalocytes (SL-MOD), teardrops (SL)

Iron studies

- ↓ serum fe, ↓ ferritin, ↑ TIBC

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- BM erythroid hyperplasia
  - ↓ M:E, ↓ Prussian blue, ↑ ZPP

Anemia

Microcytic

- Iron deficiency
- **Chronic inflammation**
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Second most common anemia (1/3 hospitalized); ↑ hepcidin, chronic infections, chronic inflammatory disorders, trauma, organ failure, neoplastic disorders

Screening Tests

CBC

- N MCV, N MCHC, N RDW
- %/# retic normal to ↑, RPI < 2

Differential

- RBC morphology normal

Iron studies

- ↓ serum fe, N-↑ ferritin, ↓-N TIBC

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- BM erythroid normoplasia
  - ↑ M:E, N-↑ Prussian blue, N ZPP

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- **Sideroblastic**
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Inherited or acquired mutation affecting formation of ALA (in heme synthesis pathway); associations are lead poisoning, alcoholism, ringed sideroblasts

Screening Tests

CBC

- ↓ MCV, ↓ MCHC, ↑ RDW (dimorphic)
- %/# retic normal to ↑, RPI < 2

Differential

- Target cells (SL-MOD), pappenheimer bodies, basophilic stippling

Iron studies

- ↑ serum fe, ↑ ferritin, ↓-N TIBC

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- BM erythroid hyperplasia
  - ↓ M:E, ↑ Prussian blue, ↑ ringed sideroblasts, N ZPP

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- **Thalassemia**

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Quantitative (synthesis) defects; common variants are α-thalassemias and β-thalassemias; note demographics (ie African blacks, Mediterranean basin and Southeast Asia); RBC normal or ↓, but ↑ relative to hgb/hct levels

Screening Tests

CBC (↑ RBC)

- ↓ MCV, ↓ MCHC, ↑ RDW
- %/# retic normal to ↑, RPI < 2

Differential

- Target cells (MOD-MK), basophilic stippling, nRBCs

Iron studies

- ↑ serum fe, ↑ ferritin, ↓-N TIBC

Reflex Tests

Hemoglobin Identification

- α-thal: Bart's (γ4), HbH (β4)
- β-thal: ↑ HbA_2
- HPFH: ↑ HbF (Kleihauer-Betke)

Hemolytic Indicators

- Normal

Other

- BM erythroid hyperplasia
  - ↓ M:E, N Prussian blue, N ZPP

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **Spherocytosis**
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

- **Erythrocytosis**

Relative

Absolute

Key Features

Membrane defect; defect in vertical cytoskeleton protein interactions; ↓ spectrin and ankyrin

Screening Tests

CBC

- N-↓ MCV, ↑ MCHC (>36), N RDW
- %/# retic normal to ↑, RPI < 2

Differential

- Spherocytes (MOD-MK)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- ↑ serum bilirubin, ↓ haptoglobin

Other

- = DAT, + osmotic fragility, + autohemolysis

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **Elliptocytosis**
- Acquired hemolytic
  - Hypoproliferative
  - Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

- **Erythrocytosis**
  - Relative
  - Absolute

Key Features

Membrane defect; defect in horizontal cytoskeleton protein interactions; ↓ formation of spectrin tetramers

Screening Tests

CBC

- N-↓ MCV, ↑ MCHC, N RDW
- %/# retic normal to ↑, RPI < 2

Differential

- Elliptocytes/ovalocytes (MOD-MK)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal to slightly abnormal

Other

- = DAT, N osmotic fragility, N autohemolysis

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **Pyropoikilocytosis**
- Acquired hemolytic
  - Hypoproliferative
  - Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Membrane defect; subvariant of hereditary elliptocytosis; two defects - ↓ spectrin plus mutant spectrin

Screening Tests

CBC

- N-↓ MCV, ↑ MCHC, N RDW
- %/# retic ↑, RPI > 2

Differential

- Severe poikilocytes (budding, fragments, microspherocytes, elliptocytes, triangulocytes, bizarre forms)

Iron studies

- ↓ serum fe, ↓ ferritin, ↑ TIBC

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- ↑ serum bilirubin, ↓ haptoglobin

Other

- + thermal sensitivity, = DAT, + osmotic fragility,
  + autohemolysis

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **Stomatocytosis**
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Membrane defect;
Overhydrated (OH) - ↑ intracellular Na+ and K+
Dehydrated (DH) - ↑ intracellular Na+, ↓ intracellular K+

Screening Tests

CBC

- OH: ↑ MCV, ↓ MCHC, N RDW
  DH: N-↑ MCV, ↑ MCHC, N RDW
- %/# retic normal to ↑, RPI < 2

Differential

- OH: Stomatocytes (MOD-MK)
  DH: Target cells (MOD-MK), echinocytes (SL-MOD)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal to slightly abnormal

Other

- = DAT, + autohemolysis
- OH: + osmotic fragility at ↑ [NaCl]
  DH: + osmotic fragility at ↓ [NaCl]

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **Acanthocytosis**
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

- **Erythrocytosis**

Relative

Absolute

Key Features

Membrane defect; abnormalities of lipid membrane – lipid imbalance; consider ratio of cholesterol to phospholipids

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
  %/# retic ↑, RPI > 2

Differential

- Acanthocytes (MOD-MK), target cells (SL-MOD), echinocytes (SL-MOD)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- ↑ serum bilirubin, ↓ haptoglobin

Other

- ↑ liver enzymes, = DAT, N osmotic fragility,
  + autohemolysis at 48 hrs

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **PNH**
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Membrane defect; Paroxysmal Nocturnal Hemoglobinuria (PNH) all cells abnormally sensitive to lysis by complement; ↓ CD55 and ↓ CD59

Screening Tests

CBC (pancytopenia)

- N- ↑ MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- Normal

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- ↑ serum bilirubin, ↓ haptoglobin

Other

- = DAT, N osmotic fragility, + autohemolysis at 48 hrs, ↑ autohemolysis when add glucose, flow CD55 and CD59

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **G6PD Deficiency**
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Enzyme deficiency; most common enzyme deficiency; affects hexose monophosphate shunt – maintains levels of GSH to protect RBC from oxidant buildup; acute associations favism (fava beans, infection, drug-induced by primaquine)

Screening Tests

CBC

- N- ↑ MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- Bite cells (SL-MOD), blister cells (SL-MOD), spherocytes

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- ↑ serum bilirubin, ↓ haptoglobin

Other

- = DAT, supravital for Heinze bodies, G6PD activity 2-3 months post hemolytic episode

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- **Hereditary hemolytic**
  - **PK Deficiency**
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

- **Erythrocytosis**

Relative

Absolute

Key Features

Enzyme deficiency; Pyruvate Kinase (PK) second most common enzyme deficiency; affects rapoport-luebering shunt causing ↑ levels of 2-3-BPG and hemoglobin's O2 affinity; ↓ ATP production and membrane integrity (cell dehydration)

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- Echinocytes (SL-MOD), Target Cells (SL-MOD)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal to slightly abnormal

Other

- = DAT, RBCs incubated with PEP, LD, ADP, NADH – ↑ fluorescence indicates ↓ PK activity

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- **Acquired hemolytic**
  - **AIHA**
  - Hypoproliferative
  - Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

[Auto] immune defect; Autoimmune Hemolytic Anemia (AIHA); most cases warm
Warm (W) AIHA: optimal reactivity at 37°C, usually IgG to “Rh”; extravascular
Cold (C) AIHA: optimal reactivity < 37°C, usually IgM to I/i Ags; intravascular

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- nRBCs, schistocytes
  W: spherocytes (MOD-MK),
  C: RBC clump, spherocytes (SL)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- W: Normal to slightly abnormal
  C: ↑ serum bilirubin, ↓ haptoglobin

Other

- W: + DAT, + polyspecific,
  + anti-IgG
  C: + DAT, + polyspecific,
  + anti-C3

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- **Acquired hemolytic**
  - **PCH**
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

[Auto] immune defect; Paroxysmal Cold Hemoglobinuria (PCH); bi-phasic IgG antibody to P Ag, Donath-Landsteiner antibody; binds RBCs at < 20°C, activates complement, warm to 37°C, Ab detaches, RBC lysed by complement activation

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- nRBCs, schistocytes, spherocytes (SL)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- ↑ serum bilirubin, ↓ haptoglobin

Other

- + DAT, + polyspecific, + anti-IgG

Anemia

Microcytic
- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic
- Hereditary hemolytic
- **Acquired hemolytic**
  - **Transfusion Rxns**
- Hypoproliferative
- Acute hemorrhage

Macrocytic
- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies
- **Erythrocytosis**

Relative

Absolute

Key Features

[Allo] immune defect; patient's Abs react to foreign transfused RBCs
Immediate Rxn (IR): IgM Ab, occurs within 24 hrs, intravascular
Delayed Rxn (DR): IgG Ab, occurs 2-14 days post transfusion, extravascular

Screening Tests

CBC
- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential
- nRBCs
  IR: schistocytes (MOD-MK)
  DR: spherocytes (MOD-MK)

Iron studies
- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification
- Normal

Hemolytic Indicators
- IR: ↑ serum bilirubin, ↓ haptoglobin
  DR: Normal to slightly abnormal

Other
- IR: + DAT, + polyspecific,
  + anti-C3
  DR: + DAT, + polyspecific,
  + anti-IgG

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- **Acquired hemolytic**
  - **HDFN**
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

[Allo] immune defect; Hemolytic Disease of the Fetus and Newborn (HDFN); mother forms Abs to fetal RBCs
Rh: anti-D, more severe, immune IgG
ABO: anti-A and/or anti-B, more common, nonimmune IgG

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- nRBCs
  Rh: schist-/sphero-ocytes (SL)
  ABO: schist-/sphero-ocytes (MOD-MK)

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Rh: ↑ serum bilirubin, ↓ haptoglobin
  ABO: Normal to slightly abnormal

Other

- Rh: + DAT, + polyspecific, + anti-IgG
  ABO: weak + DAT

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- **Acquired hemolytic**
  - **HUS**
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

[MAHA] nonimmune defect; Microangiopathic Hemolytic Anemia (MAHA); Hemolytic Uremic Syndrome (HUS); most cases diarrhea-associated (D+) in children < 5; GI infection with E. coli

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- Schistocytes, helmet cells, spherocytes, echinocytes/burrs, WBC left shift, ↓ PLT

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal to slightly abnormal

Other

- ↑ D-dimer

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- **Acquired hemolytic**
  - **TTP**
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

[MAHA] nonimmune defect; Microangiopathic Hemolytic Anemia (MAHA); Thrombotic Thrombocytopenic Purpura (TTP); abnormal platelet aggregation on microvascular endothelium; deficiency of ADAMTS13 leads to ultra large vWF

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- Schistocytes, nRBCs
  WBC left shift, ↓ PLT

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal to slightly abnormal

Other

- N D-dimer

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- **Acquired hemolytic**
  - **DIC**
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

[MAHA] nonimmune defect; Microangiopathic Hemolytic Anemia (MAHA); Disseminated Intravascular Coagulation (DIC); abnormal activation of coagulation intravascularly; consumptive coagulopathy

Screening Tests

CBC

- N MCV, N MCHC, N-↑ RDW
- %/# retic ↑, RPI > 2

Differential

- Schistocytes,
  ↓ PLT

Iron studies

- Normal to slightly abnormal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal to slightly abnormal

Other

- Prolonged PT, APTT, TT
  ↑ D-dimer, FDPs
  ↓ fibrinogen

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- **Hypoproliferative**
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Aplastic Anemia; pancytopenia, BM “dry tap”; clinically associated with respective cytopenia (ie bleeding, petechia, anemia, infection); Hgb F can be ↑; EPO is often ↑; flow cytometry CD34+ [blasts] cells < 0.3%; differentiate from Renal Disease, Myelodysplastic Syndrome, Hypersplenism

Screening Tests

CBC (pancytopenia)

- N MCV, N MCHC, N-↑ RDW
- %/# retic normal, RPI < 2

Differential

- Relative lymphocytosis
  normal cell morphologies

Iron studies

- ↑ serum iron, > 50% saturation of transferrin

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- BM hypocellular (<25%) plus two of:

  Granulocyte <0.5 x109/L,
  PLT < 20 x109/L,
  Corrected Retic < 1%

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- **Acute hemorrhage**

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Rapid blood loss either internally (eg tissue damage) or externally (eg laceration)

Screening Tests

CBC

- N MCV, N MCHC, N RDW
- %/# retic normal, RPI < 2

Differential

- Normal

Iron studies

- Normal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- N/A

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- **Megaloblastic**
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Vitamin B12, Folic Acid, Folate Deficiencies, and Pernicious Anemia (absence of intrinsic factor); symptoms - lethargy, weakness, yellow or waxy pallor, neurological disturbances

Screening Tests

CBC (pancytopenia)

- ↑ MCV, N MCHC, N RDW
- %/# retic N-↓, RPI < 2

Differential

- Neutropenia w/ hypersegs
  ↓ PLT but > 100
  Macro-ovalocytes, HJ bodies, nRBCs

Iron studies

- Normal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- ↑ serum bilirubin, ↓ haptoglobin

Other

- B12, folate (serum vs RBC), MMA, Homocysteine, FIGLU
- BM erythroid hyperplasia
  ↑ M:E, megaloblastic cell morphologies

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- **Non-megaloblastic**

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Common causes are alcoholism (direct toxic effect on RBC precursors), reticulocytosis (hemolysis, GI bleed), and liver disease (RBC membrane changes); megaloblastic symptoms absent

Screening Tests

CBC

- N MCV, N MCHC, N RDW
- %/# retic N-↓, RPI < 2

Differential

- Round ovalocytes

Iron studies

- Normal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- Hepatic panel (liver enzymes, cholesterol, lipids)

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

Qualitative (structural) defects; common variants are Hgb S, Hgb E, Hgb C, Hgb D; note demographics (ie African blacks, Mediterranean basin and Southeast Asia); associations vaso-occlusive crisis, splenomegaly, dactylitis

Screening Tests

CBC

- N-↓ MCV, N-↓ MCHC, ↑ RDW
- ↑ %/# retic, RPI > 2

Differential (possible morphologies)

- Sickle cells (SL-MOD), target cells (MOD-MK), basophilic stippling, HJ bodies

Iron studies

- N serum fe, N ferritin, N TIBC

Reflex Tests

Hemoglobin Identification

- Solubility (+/=), HPLC and electrophoresis abnormal

Hemolytic Indicators

- Normal

Other

- BM erythroid hyperplasia
  - ↓ ME, N Prussian blue, N ZPP

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

No adverse effect on pulmonary gas exchange; associated with dehydration or an overall decrease in plasma volume relative to red cell mass (leading to high hematocrit)

Screening Tests

CBC

- N MCV, N MCHC, N RDW
  ↑ HCT
- N %/# retic, RPI < 2

Differential

- Normal

Iron studies

- Normal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- Normal

Anemia

Microcytic

- Iron deficiency
- Chronic inflammation
- Sideroblastic
- Thalassemia

Normocytic

- Hereditary hemolytic
- Acquired hemolytic
- Hypoproliferative
- Acute hemorrhage

Macrocytic

- Megaloblastic
- Non-megaloblastic

Hemoglobinopathies

Erythrocytosis

Relative

Absolute

Key Features

No adverse effect on pulmonary gas exchange; associated with benign causes, think body compensation Secondary Polycythemia Vera (SPV) (eg smoker, altitude, patients with renal disease receiving EPO) and malignant causes, think Myeloproliferative Neoplasm and Primary Polycythemia Vera (PPV)

Screening Tests

CBC

- N MCV, N MCHC, N RDW
  ↑ HCT
- N %/# retic, RPI < 2

Differential

- SPV: Normal
  PPV: ↑ WBC, ↑ PLT

Iron studies

- Normal

Reflex Tests

Hemoglobin Identification

- Normal

Hemolytic Indicators

- Normal

Other

- SPV: ↑ EPO, JAK2 =
  PPV: N EPO, JAK2 +

Leukocytes Review

Benign leukocyte disorders

- **Myeloid**
- **Lymphoid**

Myeloid neoplasia

- **Acute leukemia**
- **Myelodysplastic syndromes**
- **Myeloproliferative neoplasms**

Lymphoid neoplasia

- **Acute leukemia**
- **Chronic leukemia/lymphoma**
- **Plasma cell dyscrasias**

Hereditary anomalies

Key Features

Symptoms: bacterial infections, viral infections, bleeding, medication exposure

Physical: organomegaly

Screening Tests

Cell counts

- WBC, RBC, PLT concentrations

Differential and morphology evaluation

- Blast concentration

Reflex Tests

Special Stains

- MPO, SBB, SE, NSE, TdT, TB, PAS, LAP

Flow Cytometry Immunophenotyping

- CD Markers?
  Myeloid vs Lymphoid (T vs B)

Cytogenetics, Molecular

Other

Benign leukocyte disorders

Myeloid

NE

Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Neutrophil (NE) changes associated with *bacterial infections*, tissue damage or necrosis, injury, inflammation, leukoerythroblastic reaction

Screening Tests

Cell counts

- ↑ WBC (<50)

Differential and morphology evaluation

- ↑ % / # neutrophils with left shift, toxic changes – dohle bodies, toxic granulation, vacuolization

Reflex Tests

Special Stains

- ↑ LAP

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Benign leukocyte disorders

Myeloid

EO

Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Eosinophil (EO); associated with helminthic parasite infections

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- ↑ % / # eosinophils

Reflex Tests

Special Stains

- Normal

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Benign leukocyte disorders

Myeloid

BA

Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Basophil (BA); associated with hypersensitivity reactions and chronic myeloproliferative disorders (CML, PV, ET)

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- ↑ % / # basophils

Reflex Tests

Special Stains

- Normal

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Benign leukocyte disorders

Myeloid

MO

Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Monocytes (MO); associated with myeloid neoplasms (CML, CMML, some other acute leukemias)

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- ↑ % / # monocytes

Reflex Tests

Special Stains

- Normal

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Benign leukocyte disorders

- Myeloid
- **Lymphoid**

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Lymphocytosis (LY) associations are viral infections (eg infectious mononucleosis (IM), Bordetella pertussis, CMV)
Lymphopenia associations are HIV and inverted CD4:CD8, Wiskott-Aldrich syndrome, DiGeorge syndrome

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- Cytosis: ↑ % / # lymphocytes with ↑ % / # reactive lymphocytes
- Cytopenia: ↓ % / # lymphocytes

Reflex Tests

Special Stains

- Normal

Flow Cytometry Immunophenotyping

- Normal or evaluate CD4:CD8 ratios

Cytogenetics, Molecular

- Normal

Other

- IM only: + heterophile Ab

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- **Acute leukemia**
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Presence of blasts in PB and BM; common recurring cytogenetic abnormalities shown according to WHO; complication of APL is DIC; ↑ serum and urine muramidase associated with ↑↑↑ monos/monoblasts

Screening Tests

Cell counts

- ↓-N-↑ WBC
  ↓ PLT

Differential and morphology evaluation

- ↑ % Blasts, auer rods

BM Diff

- Hypercellular, >20% Blasts, auer rods

Reflex Tests

Special Stains

- [MPO, SBB]+, myeloid [SE]+, mono [NSE]+

Flow Cytometry Immunophenotyping

- Myeloblasts [CD34, CD13, CD33, HLA-DR]+
  Monoblasts [CD14, CD11b, CD11c]+
  APL abnormal “blast” promyelos [CD34]=

Cytogenetics, Molecular

- AML: t(8;21), RUNX1-RUNX1T1
  AMML(eo): t(16;16) or inv(16), CBFβ/MYH11
  APL: t(15;17), PML/RARα

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- **Myelodysplastic syndromes**
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Acquired proliferation of defective stem cell; associated with exposure to chemicals, radiation, viral infections, or therapy related (chemo/radiation)

Screening Tests

Cell counts

- ≥ 1 PB cytopenias

Differential and morphology evaluation

- Cell maturation abnormalities, anisopoikilocytosis

BM Diff

- <20% Blasts, auer rods, dysplasia, ringed sideroblasts

Reflex Tests

Special Stains

- Not necessary

Flow Cytometry Immunophenotyping

- Not necessary

Cytogenetics, Molecular

- Chromosome abnormalities of 5, 7, 8, 20, Y

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- **Myeloproliferative neoplasms**
  - **CML**

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Chronic Myelogenous Leukemia (CML); most common MPN; most often seen in elderly (> 50 years)

Screening Tests

Cell counts

- ↑↑↑ WBC, ↑↑↑ PLT

Differential and morphology evaluation

- ↑↑↑ myeloids left shift, ↑ eos, ↑ basos

BM Diff

- Hypercellular, <20% Blasts, ↑↑↑ M:E

Reflex Tests

Special Stains

- ↓ LAP

Flow Cytometry Immunophenotyping

- Not necessary

Cytogenetics, Molecular

- t(9;22), Ph +, BCR-ABL1

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- **Myeloproliferative neoplasms**
  - **PMF**

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Primary Myelofibrosis (PMF); Cytokine-mediated proliferation of fibroblasts and PDGF (platelet derived growth factor)

Screening Tests

Cell counts

- Pancytopenia

Differential and morphology evaluation

- Leukoerythroblastosis, teardrops, anisopoikilocytosis

BM Diff

- <20% Blasts, “dry tap”

Reflex Tests

Special Stains

- Not necessary

Flow Cytometry Immunophenotyping

- Not necessary

Cytogenetics, Molecular

- 50% JAK2 +

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- **Acute leukemia**
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

~80–85% of cases of childhood ALL is B-cell

Screening Tests

Cell counts

- ↓-N-↑ WBC
  ↓ PLT

Differential and morphology evaluation

- ↑ % Blasts

BM Diff

- Hypercellular, >20% Blasts

Reflex Tests

Special Stains

- Lymphoblasts [TdT] +
  B-blasts [PAS, AP] =
  T-blasts [PAS, AP] +

Flow Cytometry Immunophenotyping

- B-blasts [CD34, 10, 19, 20, 22] +
  T-blasts [CD34, 2, 3, 5, 7, 8] +

Cytogenetics, Molecular

- ~25% cases t(12;21), ETV6-RUNX1

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- **Chronic leukemia/lymphoma**
  - **CLL/SLL**
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Chronic Lymphocytic Leukemia (CLL) presents with PB lymphocytosis vs Small Lymphocytic Lymphoma (SLL) presents with lymphadenopathy

Screening Tests

Cell counts

- ↑ WBC

Differential and morphology evaluation

- ↑↑ %/# lymphs, turtle shell nucleus ↑↑ smudge cells

BM Diff

- Hypercellular

Reflex Tests

Special Stains

- Not necessary

Flow Cytometry Immunophenotyping

- B-cell [CD5, CD19] +, κ or λ clonality

Cytogenetics, Molecular

- None

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- **Chronic leukemia/lymphoma**
  - **HCL**
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Hairy Cell Leukemia (HCL)

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- ↑ %/# lymphs, "Hairy cells"

BM Diff

- “Dry tap”, “Fried-egg” appearance

Reflex Tests

Special Stains

- TRAP+

Flow Cytometry Immunophenotyping

- [CD19, 20, 22, 11c, 25, 103, sIg intense] +

Cytogenetics, Molecular

- None

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- **Chronic leukemia/lymphoma**
  - **BL**
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Burkitt Lymphoma (BL); EBV virus thought to play a role in pathogenesis

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- ↑ %/# lymphs, “blast” have deep blue basophilic cytoplasm with vacuoles

BM Diff

- “starry sky”

Reflex Tests

Special Stains

- TRAP+

Flow Cytometry Immunophenotyping

- [CD19, CD10, sIg]+ [CD5]=

Cytogenetics, Molecular

- t(8;14) (MYC and IGH gene rearrangement)

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- **Chronic leukemia/lymphoma**
  - **LGL**
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Large Granular Lymphocytic Leukemia (LGL); composed of mature T cells; must be differentiated from Reactive lymphocytosis and NK neoplasms

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- ↑ %/# lymphs, abundant pale cytoplasm, azurophilic granules

BM Diff

- None

Reflex Tests

Special Stains

- None

Flow Cytometry Immunophenotyping

- [CD4]=, [CD2, 3, 5, 7, 8, 16] + usually CD56=, CD57+

Cytogenetics, Molecular

- None

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- **Chronic leukemia/lymphoma**
  - **Sezary**
- Plasma cell dyscrasias

Hereditary anomalies

Key Features

Sezary's Syndrome; neoplasm of mature T-cells in skin, LN, PB; must be differentiated from mycosis fungoides (cutaneous T-cell lymphoma)

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- ↑ %/# lymphs, Convoluted (cerebriform) nuclei

BM Diff

- None

Reflex Tests

Special Stains

- None

Flow Cytometry Immunophenotyping

- [Cd7]=, [CD3, 4]+ CD4:CD8 > 10

Cytogenetics, Molecular

- None

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- **Plasma cell dyscrasias**
  - **WM**

Hereditary anomalies

Key Features

Waldenstrom's Macroglobulinemia (WM); combination of Lymphoplasmacytic Lymphoma with BM involvement and increase of IgM monoclonal paraprotein

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- rouleaux

BM Diff

- diffuse infiltrate of neoplastic lymphocytes and plasma cells

Reflex Tests

Special Stains

- None

Flow Cytometry Immunophenotyping

- None

Cytogenetics, Molecular

- None

Other

- Serum monoclonal heavy chain IgM, Monoclonal light chain cIg (κ or λ)

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma

Plasma cell dyscrasias

PCM

Hereditary anomalies

Key Features

Plasma Cell Myeloma (PCM) or Multiple Myeloma (MM); Ig-secreting cells in absence of neoplastic B lymphocytes; S/UPEP show M (monoclonal) spike

Screening Tests

Cell counts

- N-↑ WBC

Differential and morphology evaluation

- rouleaux

BM Diff

- Lytic bone lesions, Plasma cells

Reflex Tests

Special Stains

- None

Flow Cytometry Immunophenotyping

- None

Cytogenetics, Molecular

- None

Other

- Serum monoclonal heavy chain IgG, Monoclonal light chain cIg (κ or λ, in urine as Bence-Jones)

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

- **Pelger Huet**

Key Features

Cells function normally; decrease segmentation (hyposegments) of all granulocytes; maturation/texture of nucleus does not align with shape of nucleus and maturation of cytoplasm; homozygotes round/oval nuclei; heterozygotes bilobed

Screening Tests

Cell counts

- N WBC

Differential and morphology evaluation

- Automated and manual count show morphological left shift,
  no toxic changes

Reflex Tests

Special Stains

- Normal

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

- **Alder Reilly**

Key Features

Cells function normally; known as Hunter's or Hurler's syndrome; aggregate of incomplete mucopolysaccharides degradation

Screening Tests

Cell counts

- N WBC

Differential and morphology evaluation

- Large, purplish granules in cytoplasm of all WBCs

Reflex Tests

Special Stains

- + TB

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

- **Chediak Higashi**

Key Features

Cells dysfunctional – decreased bactericidal effect; fusion of primary + secondary granules in NEs and LYs

Screening Tests

Cell counts

- N WBC

Differential and morphology evaluation

- Giant green-gray bodies

Reflex Tests

Special Stains

- Normal

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Benign leukocyte disorders

- Myeloid
- Lymphoid

Myeloid neoplasia

- Acute leukemia
- Myelodysplastic syndromes
- Myeloproliferative neoplasms

Lymphoid neoplasia

- Acute leukemia
- Chronic leukemia/lymphoma
- Plasma cell dyscrasias

Hereditary anomalies

- **May Hegglin**

Key Features

Cells function normally; cytoplasmic inclusions of RNA from RER

Screening Tests

Cell counts

- N WBC

Differential and morphology evaluation

- Blue, large, and round Dohle-like bodies in all granulocytes
  Giant platelets

Reflex Tests

Special Stains

- Normal

Flow Cytometry Immunophenotyping

- Normal

Cytogenetics, Molecular

- Normal

Other

- N/A

Hemostasis Review

Platelets

Quantitative abnormalities

- **Thrombocytopenia**
  - **Increased destruction**
  - **Decreased production**
  - **Pseudothrombocytopenia**
- **Thrombocytosis**

Qualitative defects

- **von Willebrand disease**
- **Bernard-Soulier syndrome**
- **Glanzmann thrombasthenia**

Disease States

Coagulation factor deficiencies

- **Acquired**
- **Hereditary**

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Platelet and vWF disorders: superficial skin or mucous membrane bleeding (nose, gums), petechia, purpura, ecchymoses
Coagulation factor disorders: hematoma, deep tissue/joint bleeding
Thrombosis disorders: DVT, PE, neurological, cerebral/myocardial infarction
Age of initial presentation can aid in differentiating hereditary vs acquired disorder

Screening Tests

Platelet

- CBC count
- Morphology evaluation

Hemostasis

- PT/INR/APTT
  Fibrinogen

Therapy Monitoring

Reflex Tests

Platelet

- Function (PFA)
- Aggregation Studies

Hemostasis

- D-dimer, Thrombin Time, Mixing study, inhibitor screen
- Factor assay, vWF assay
- aPL, Protein C/S, HIT
- FV Leiden, PT20210

Platelets

Quantitative abnormalities

Thrombocytopenia

Increased destruction

ITP

Decreased production

Pseudothrombocytopenia

Thrombocytosis

Qualitative defects

von Willebrand disease

Bernard-Soulier syndrome

Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

Acquired

Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Immune Thrombocytopenia (ITP); Most common form of thrombocytopenia; associated with children 5-6 yrs following a viral infection; autoreactive antibodies to GPIIb/IIIa or GPI/IX

Screening Tests

Platelet

- ↓ PLT
- Morphology normal

Hemostasis

- Normal

Reflex Tests

Platelet

- Function normal

Hemostasis

- Normal

Platelets

Quantitative abnormalities

Thrombocytopenia

Increased destruction

HIT

Decreased production

Pseudothrombocytopenia

Thrombocytosis

Qualitative defects

von Willebrand disease

Bernard-Soulier syndrome

Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

Acquired

Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Heparin-Induced Thrombocytopenia (HIT); immune-mediated destruction of platelets via heparin-dependent platelet activating IgG antibodies; complication is activation of platelets leading to thrombosis

Screening Tests

Platelet

- PLT trend ↓ after heparin initiation
- Morphology normal

Hemostasis

- Normal

Therapy Monitoring

- APTT or anti-Xa

Reflex Tests

Platelet

- Function normal

Hemostasis

- Normal

Platelets

Quantitative abnormalities

Thrombocytopenia

Increased destruction

Decreased production

Pseudothrombocytopenia

Thrombocytosis

Qualitative defects

von Willebrand disease

Bernard-Soulier syndrome

Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

Acquired

Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

See Aplastic Anemia (AA) and Myelodysplastic Syndrome (MDS)

Screening Tests

Platelet

- ↓ PLT
- Morphology normal in AA, abnormal in MDS

Hemostasis

- Normal

Reflex Tests

Platelet

- Function normal

Hemostasis

- Normal

Platelets

Quantitative abnormalities

- **Thrombocytopenia**
  - Increased destruction
  - Decreased production
  - **Pseudothrombocytopenia**
- Thrombocytosis

Qualitative defects

- von Willebrand disease
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

In vitro artifact of automated cell counting – “low” automated platelet count; usually autoantibody (GPIIb/IIIa) – recognizes EDTA-induced cryptic epitopes on platelets

Screening Tests

Platelet

- ↓ PLT
- PLT clumping, satellitosis

Hemostasis

- Normal

Reflex Tests

Platelet

- Function normal

Hemostasis

- Normal

Platelets

Quantitative abnormalities

- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- **Thrombocytosis**

Qualitative defects

- von Willebrand disease
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Primary association is ↑ production (eg MPNs); secondary associated with reactive process (eg acute hemorrhage, post splenectomy, surgery); transient thrombocytosis associated with vigorous exercise and childbirth

Screening Tests

Platelet

- ↑ PLT
- Morphology normal

Hemostasis

- Normal

Therapy Monitoring (if thrombosis occurs)

- APTT or anti-Xa

Reflex Tests

Platelet

- Function normal

Hemostasis

- Normal or D-dimer if thrombosis occurs

Platelets

Quantitative abnormalities
- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects
- **von Willebrand disease**
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies
- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Most common hereditary bleeding disorder; main role in primary hemostasis – mediates platelet adhesion via GPIb/IX/V and collagen; main role in secondary hemostasis – complexes with and stabilizes FVIII; Type 1 vWD is quantitative, Type 2 is qualitative

Screening Tests

Platelet
- N PLT
- Morphology normal

Hemostasis
- N-↑ APTT,
  N PT/INR

Reflex Tests

Platelet
- ↑ PFA
- N ADP, collagen, epinephrine, ristocetin w vWF
  ABN ristocetin

Hemostasis
- vWF assay

Platelets

Quantitative abnormalities
- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects
- von Willebrand disease
- **Bernard-Soulier syndrome**
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies
- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Dysfunctional/deficient GPIb/IX/V complex

Screening Tests

Platelet
- ↓ PLT
- Morphology giant

Hemostasis
- Normal

Reflex Tests

Platelet
- ↑ PFA
- N ADP, collagen, epinephrine
  ABN ristocetin, ristocetin w vWF

Hemostasis
- Normal

Other
- Flow shows ↓ or abnormal GPIb/IX (CD42b/CD42a)

Platelets

Quantitative abnormalities
- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects
- von Willebrand disease
- Bernard-Soulier syndrome
- **Glanzmann thrombasthenia**

Disease States

Coagulation factor deficiencies
- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Dysfunctional/deficient GPIIb/IIIa complex leading to platelets unable to link via fibrinogen/fibrin

Screening Tests

Platelet
- N PLT
- Morphology normal

Hemostasis
- Normal

Reflex Tests

Platelet
- ↑ PFA
- N ristocetin, ristocetin w vWF
  ABN ADP, collagen, epinephrine

Hemostasis
- Normal

Other
- Decreased GPIIb/IIIa by flow cytometry (CD41 and CD61)

Platelets

Quantitative abnormalities

- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects

- von Willebrand disease
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

- **Acquired**
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Commonly associated with DIC - consumptive coagulopathy, liver disease (LD) - primary organ of hemostasis protein production, Vitamin K Deficiency (VKD) - vitamin K dependent factors; onset is later in life
DIC associated with systemic bleeding; LD, VKD with deep bleeding

Screening Tests

Platelet

- DIC: ↓ PLT
  LD, VKD: N PLT
- Morphology normal

Hemostasis

- DIC, LD, VKD: ↑ APTT, PT/INR, ↓ FIB

Reflex Tests

Platelet

- Function and aggregation normal

Hemostasis

- Not indicated; treat underlying disorder

Platelets

Quantitative abnormalities

- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects

- von Willebrand disease
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

- Acquired
- **Hereditary**

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Order of prevalence – FVIII, FIX, FXI or Hemophilias A, B, C; associated with deep bleeding with an early age onset

Screening Tests

Platelet

- N PLT
- Morphology normal

Hemostasis

- ↑ APTT,
  N PT/INR, FIB

Reflex Tests

Platelet

- Function and aggregation normal

Hemostasis

- Mixing study corrects, inhibitor screen corrects
  Factor specific assays

Platelets

Quantitative abnormalities

- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects

- von Willebrand disease
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Factor specific inhibitors (FSI) acquired after receiving treatment
Antiphospholipid antibodies (aPL) associated with thrombosis presentation but bleeding indicated by hemostasis testing

Screening Tests

Platelet

- N PLT
- Morphology normal

Hemostasis

- FSI: ↑ APTT (for intrinsic factors),
  N PT/INR, FIB
  aPL: ↑ APTT,
  N PT/INR, FIB

Reflex Tests

Platelet

- Function and aggregation normal

Hemostasis

- FSI: Mixing study corrects, inhibitor screen prolongs; perform inhibitor titer
  aPL: Mixing study prolongs, inhibitor screen prolongs; perform further confirmation testing

Platelets

Quantitative abnormalities

- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects

- von Willebrand disease
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC

Key Features

Normally plasminogen activator (PA) converts plasminogen to plasmin; plasmin breaks down fibrin via fibrinolysis; PA is inhibited by plasminogen activator inhibitor (PAI), plasminogen is inhibited by thrombin-activatable fibrinolysis inhibitor, plasmin is inhibited by antiplasmin … leads to less fibrinolysis and more thrombosis

Screening Tests

Platelet

- N PLT
- Morphology normal

Hemostasis

- N APTT,
  N PT/INR, FIB

Reflex Tests

Platelet

- Function and aggregation normal

Hemostasis

- Excessive plasmin activation leads to more fibrinolysis and fibrinogenolysis leading to increased D-dimer and FDP concentrations; excessive plasmin without fibrin formation is primary fibrinogenolysis and only FDP is increased

Platelets

Quantitative abnormalities

- Thrombocytopenia
  - Increased destruction
  - Decreased production
  - Pseudothrombocytopenia
- Thrombocytosis

Qualitative defects

- von Willebrand disease
- Bernard-Soulier syndrome
- Glanzmann thrombasthenia

Disease States

Coagulation factor deficiencies

- Acquired
- Hereditary

Inhibitors

Fibrinolytic system

Hypercoagulable states

DIC (RBC Hemolytic Anemia)

Key Features

Arterial vs venous thrombi; ↓ in natural inhibitors of clotting - Antithrombin Deficiency, Protein C/S Deficiency; ↑ in procoagulant potential - FV Leiden, PT20210; Abnormalities of fibrinolysis - Fibrinolytic System Disorders; Inpatients receive anticoagulant heparin, outpatients receive anticoagulant coumadin

Screening Tests

Platelet

- N PLT
- Morphology normal

Hemostasis

- N APTT,
  N PT/INR, FIB

Therapy Monitoring (if thrombosis occurs)

- Inpatient: APTT or anti-Xa
  Outpatient: PT/INR

Reflex Tests

Platelet

- Function and aggregation normal

Hemostasis

- ↑ D-dimer
- Antithrombin, Protein C/S assays
- FV Leiden, PT20210 by PCR