Benign White Blood Cell Disorders

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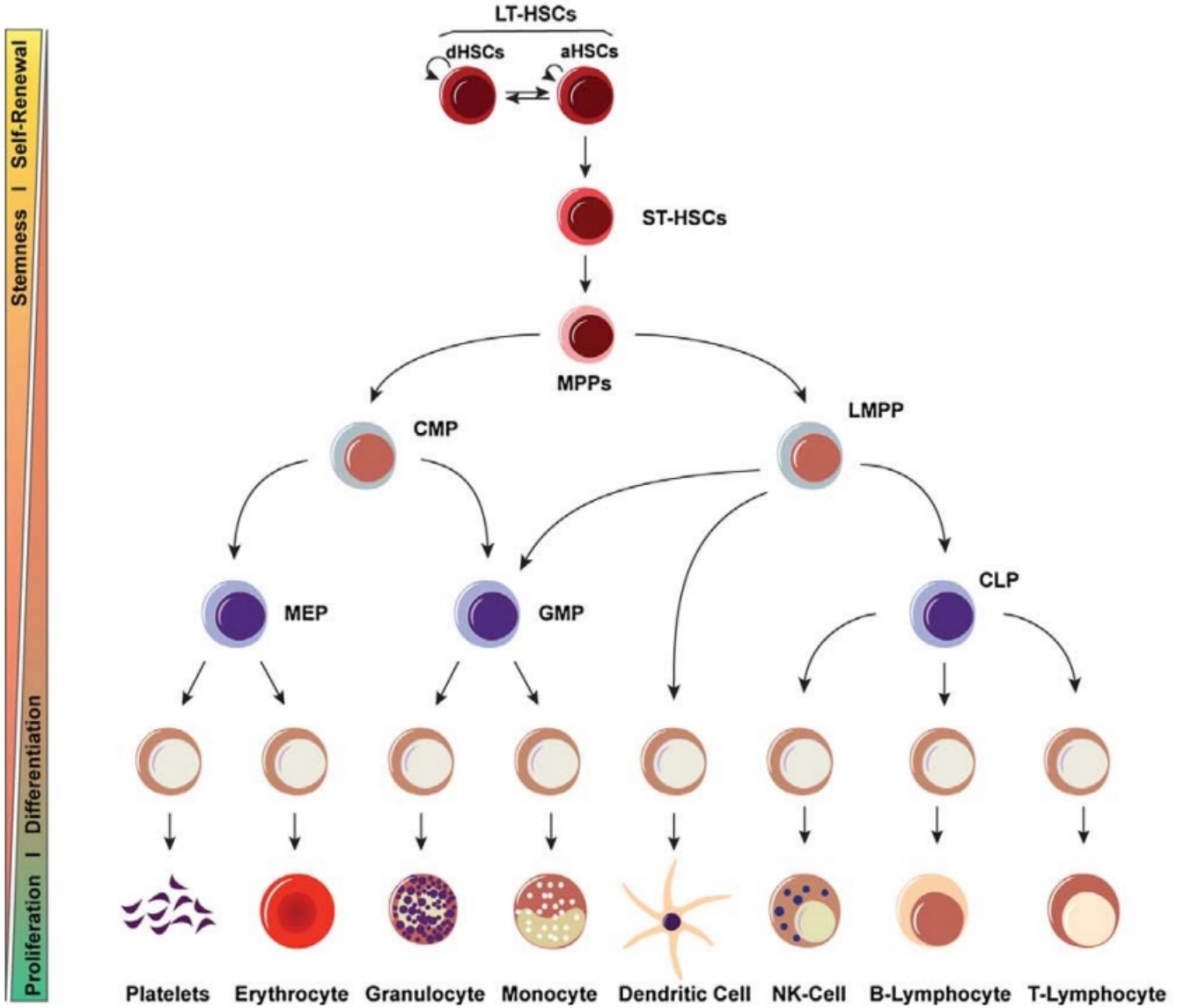
10.10.25

Hematopoiesis



Objectives

- Differentiate benign white blood cell disorders from malignant hematologic conditions
- Describe the pathophysiology and common causes of benign leukopenia, neutropenia, lymphocytosis, monocytosis, eosinophilia, and basophilia
- Interpret basic laboratory data (CBC with differential, peripheral smear) and know how to work up a patient to appropriately evaluate for etiologies of benign WBC disorders
- Recognize the clinical relevance and management strategies for common benign WBC abnormalities

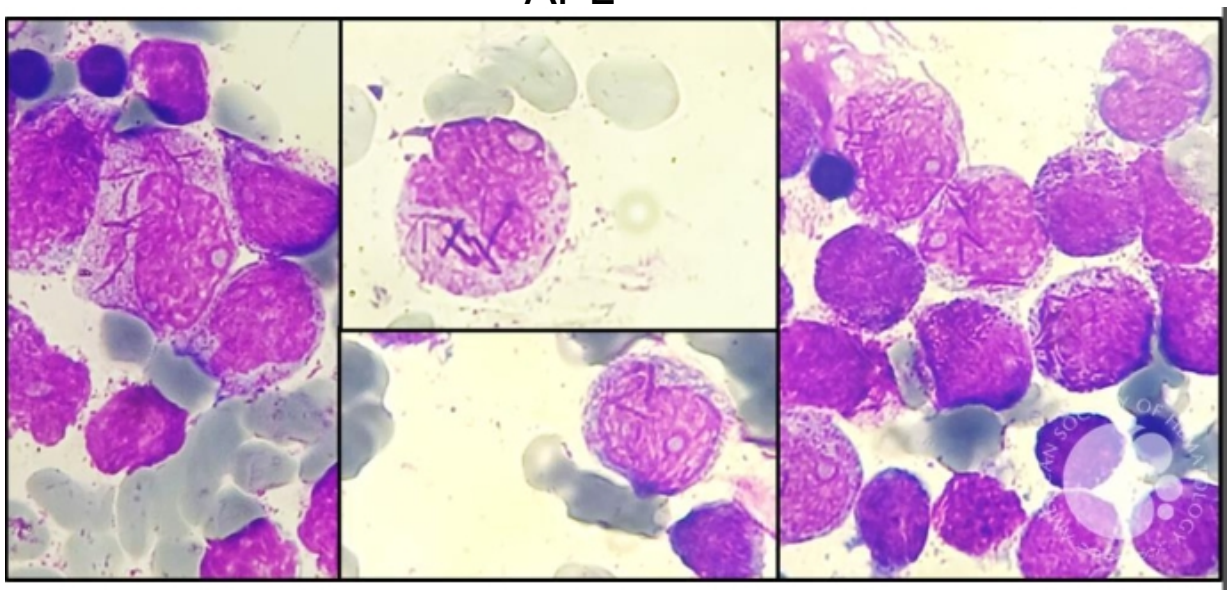
White Blood Cells: What's the Diff?

Differential	Normal Ranges	Function
WBC	4500 to 11000 cells/μL	General immune system [reticulocytes/plt clumping can increase counts inaccurately]
Neutrophils	1500 to 8000 cells/μL (40-60% WBC)	Primary phagocytes for bacteria/fungi; first responders in acute inflammation/infection
Lymphocytes	1000 to 4000 cells/μL (20-40% WBC)	Mediators of adaptive immunity; B cells = antibodies; T-cells = regulate immune response; NK = target viral/tumor cells
Monocytes	200 to 1000 cells/μL (2-8% WBC)	Circulates and migrates to tissues to become macrophages or dendritic cells; primary phagocytosis; antigen-presenting cells
Eosinophils	0 to 500 cells/μL (0-4% WBC)	Modulates inflammatory responses (allergy, hypersensitivity rxn) and parasitic infections through release of cytotoxic granules/cytokines
Basophils	0 to 200 cells/μL (0.5-1% WBC)	Mediates allergic/inflammatory responses by releasing histamine/cytokines; role in Th2 immunity; parasites

Benign vs Malignant

- Symptoms: weight loss, fatigue, night sweats, fevers, unintentional weight loss
- Labs: >=2 cell line abnormalities, immature WBCs (blasts!)
  - **PERIPHERAL SMEAR**
- Duration: acute vs chronic
- Physical exam: lymphadenopathy, splenomegaly, abnormal bleeding/bruising, petechiae

APL



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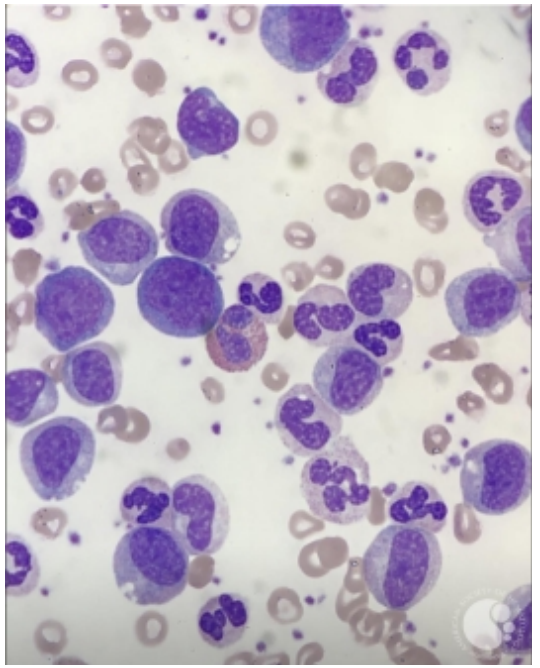
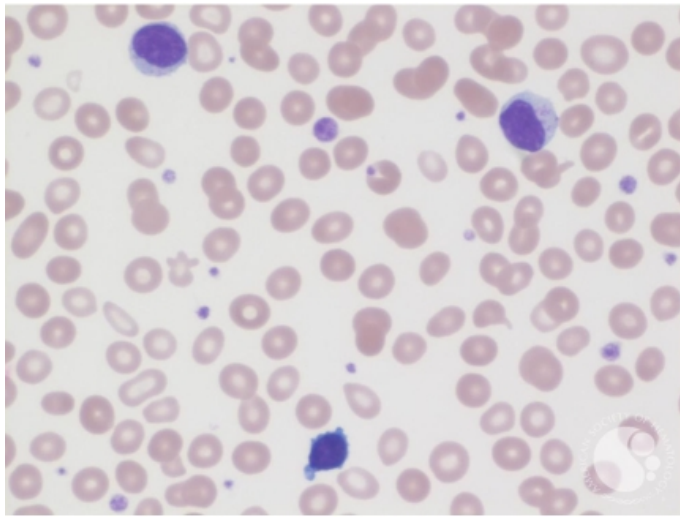


MDS



ASH IMAGE BANK
www.imagebank.hematology.org

Neutrophilia

- CC: smoking, obesity, pregnant, infection, steroids, autoimmune
- **Don't miss an infection!!**
  - Blood cultures, LP, TTE, TEE, UA
- Chronic idiopathic *neutrophilia* = diagnosis of exclusion with WBC 11 -40k; no increased risk of clinical disease on LTFU
- Malignancies: CNL, MPNs, CML, JMML

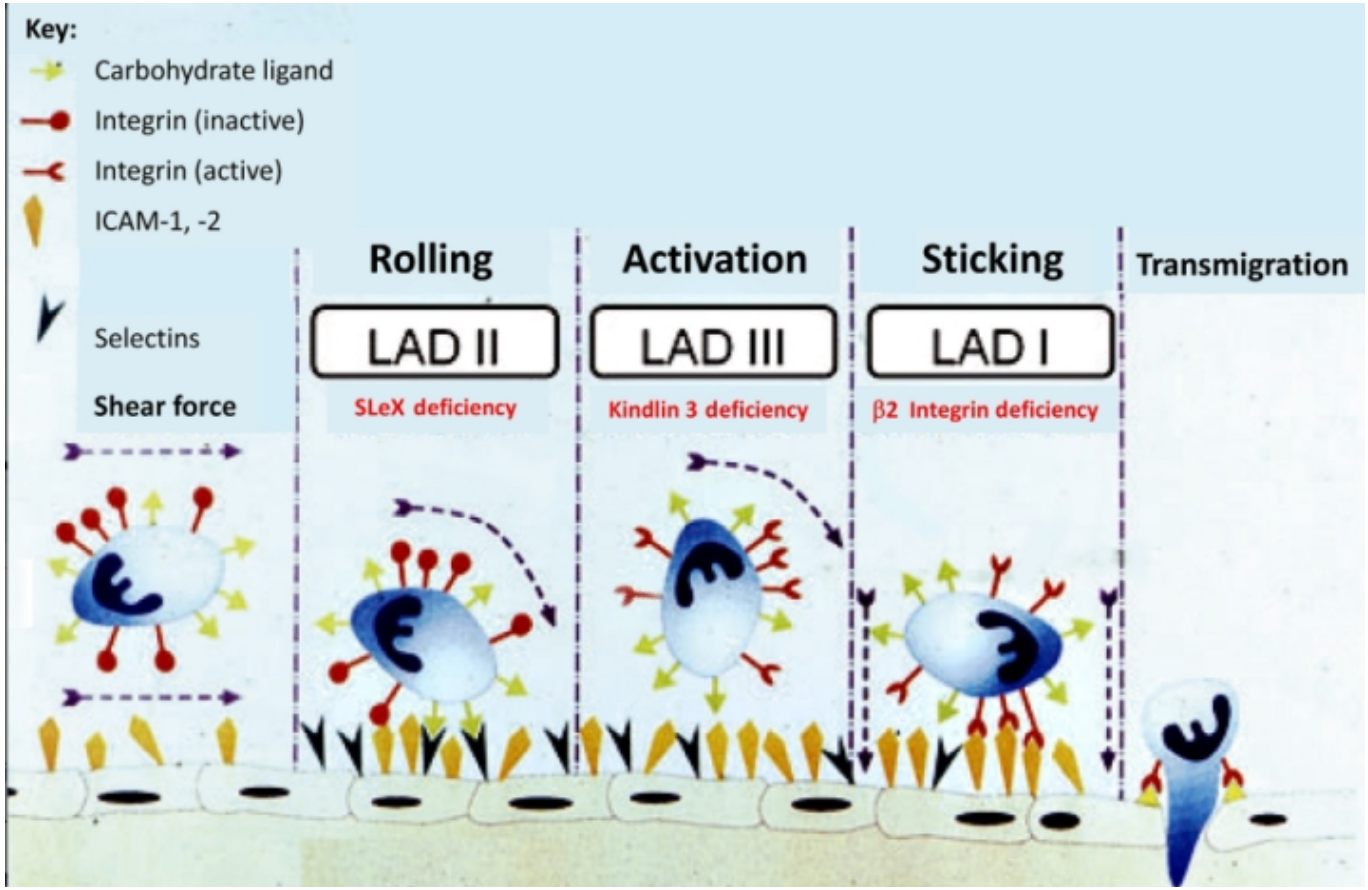
Table 3. Nonmalignant Causes of Neutrophilia

Cause	*Distinguishing features*	*Evaluation*
Patient characteristics	Pregnancy, obesity, race, age	Reference appropriate WBC count by age or pregnancy trimester Compare WBC count to recent baseline (if available)
Infection	Fever, system-specific symptoms Physical examination findings	Obtain system-specific cultures and imaging (e.g., sputum cultures, chest radiography) Consider empiric antibiotics Consider use of other biomarkers, such as CRP and procalcitonin
Reactive neutrophilia	Exercise, physical stress (e.g., postsurgical, febrile seizures), emotional stress (e.g., panic attacks), smoking	Confirm with history
Chronic inflammation	Rheumatic disease, inflammatory bowel disease, granulomatous disease, vasculitides, chronic hepatitis	Obtain personal and family medical history Consider erythrocyte sedimentation rate and CRP levels, specific rheumatology laboratories Consider subspecialist consultation (e.g., rheumatology, gastroenterology)
Medication induced	Corticosteroids, beta agonists, lithium, epinephrine, colony-stimulating factors	Confirm with history; consider discontinuation of medication, if warranted
Bone marrow stimulation	Hemolytic anemia, immune thrombocytopenia, bone marrow suppression recovery, colony-stimulating factors	Complete blood count differential; compare with baseline values (if available) Examine peripheral smear Consider reticulocyte and lactate dehydrogenase levels Consider flow cytometry, bone marrow examination, hematology/oncology consultation
Splenectomy	History of trauma or sickle cell disease	Confirm with history
Congenital	Hereditary/chronic idiopathic neutrophilia, Down syndrome, leukocyte adhesion deficiency	Obtain family, developmental history Consider hematology/oncology, genetics, and immunology consultations

Am Fam Physician. 2015;92(11):1004-1011

Leukocyte Adhesion Deficiency – Type I

- AR; Leukocytes (B/T cells) cannot escape blood to tissues for immune activation
- Type I = mutation in CD18 (*ITGB2 gene)* >> defective/deficient beta-2 integrin
  - Neutrophilia; delayed umbilical cord separation
  - No purulence; poor wound healing; recurrent infections (Staph, Pseudomonas), periodontitis
  - Mortality >50% by age 40yo
- Dx: flow cytometry for CD18, CD11; genetic sequencing
- Functional testing: *Nitroblue tetrazolium (NBT) test* (before and after stimulation with endotoxin) – should not change despite stimulation; [ddx CGD]
- Tx: BMT



Eur J Clin Invest. 2019 Feb;49(2):e13047. doi: 10.1111/eci.13047.

LAD – Type II & III [reference]

- Type II = mutation in *SLC35C1* >> absence of part of E-selectin (Sialyl Lewis X)
  - Less severe than LAD I
  - Recurrent skin infections, PNA, TB, bronchiectasis
  - Dx: flow cytometry CD15a
- Type III = mutation FERMT3 >> defect in kindlin-3 >> no integrin activation
  - Can result in hematologic abnormalities, such as BMF
  - Osteoporosis, omphalitis, bleeding complications

Neutropenia

*Vitamin deficiencies – copper, zinc, iron, B12, folate, vit C
*Endocrinopathies
*Radiation
*Chediak-Higashi Syndrome (LYST mutation; smear with giant granules)

TABLE 3 Neutropenia with normal BM reserve (adapted and updated from Ref [7])

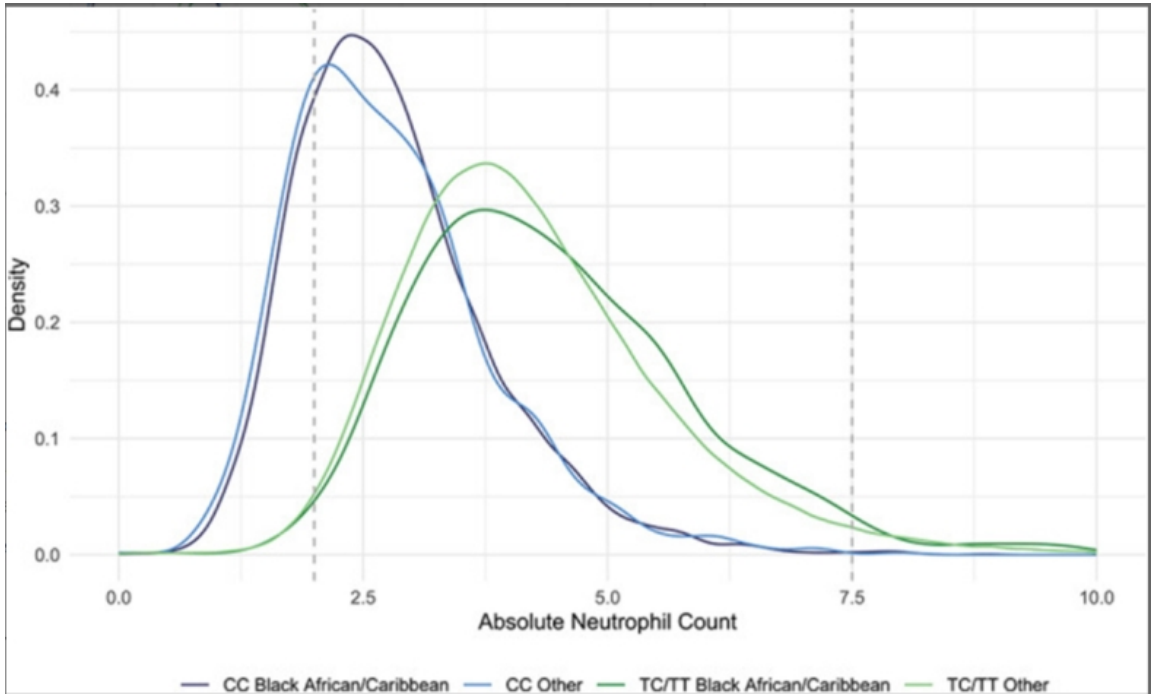
Disorder	Mechanism	Inheritance/frequency	Clinical characteristics	Diagnostic
Chronic benign neutropenia of infancy and childhood	Antineutrophil antibody	Common	90% detected before 14 mo of age; ANC usually < 500/mm^3; no risk of infection	BM—normal/increased myeloid elements
Nonimmune chronic benign neutropenia	Increased apoptosis	Not uncommon	Adults; incidental detection on CBC; ANC > 800-1000/mm^3	BM—hypoplasia of myeloid series
Ethnic or benign familial neutropenia	Unknown	AD Not uncommon	ANC 800-1400/mm3; no risk of infection; African Americans; Yemenite; Bedouins, Falasha Jews	Diagnosis of exclusion; similar findings in family member(s)
Autoimmune neutropenia	Antibody-related destruction; sequestration	Not uncommon	Associated with ITP, immune hemolytic anemia, SLE, Felty syndrome	BM—increased cellularity; (late) maturational arrest
Alloimmune neutropenia	Maternal alloimmunization	Not uncommon	Moderate/severe neutropenia in newborn; increased cutaneous infections	Resolves by 3-4 months of age
Drug-induced neutropenia	Antibody- or complement-mediated	3.4/million	Fever, sepsis, pneumonia; up to 25% mortality; 80% recover	Medication history; BM—late maturational arrest
Infection-related neutropenia	Virus-mediated antibody	Common	Clinical history of infection	Parvovirus B19 and HIV testing if indicated
Hypersplenism	Sequestration; destruction	Not uncommon	Mild neutropenia; associations—infection (malaria, TB), neoplasm, collagen vascular disease, hemolytic anemia	Peripheral blood smear-spherocytic red blood cells

Int J Lab Hematol. 2020 Jun:42 Suppl 1:121-132. doi: 10.1111/ijlh.13210.

- *ACKR1* = atypical chemokine receptor 1
- *DARC* = *D*uffy-associated receptor chemokine
- ADAN = ACKR1/DARC-associated Neutropenia
- DANC = Duffy null associated neutrophil count
- ~~BEN = benign ethnic neutropenia~~

"Duffy Null" = ACKR1/DARC–Associated Neutropenia

- Duffy Ag (Fy) on RBC for cellular signaling/chemotaxis
- Coded by *ACKR1* (formerly *DARC*) to make Fy(a) and Fy(b)
- 4 Phenotypes for Fy = (a+b-), (a-b+), (a+b+), and **(a-b-)**
- Neutropenia 2/2 increased migration/sequestration
- Associated with increased protection against P. vivax (uses Fy to enter RBC)
- West African, Middle Eastern and Yemenite Jewish decent; about 80% of patient with Sub-Saharan ancestry
- Not associated with increased bacterial infections or transformation into heme malignancy

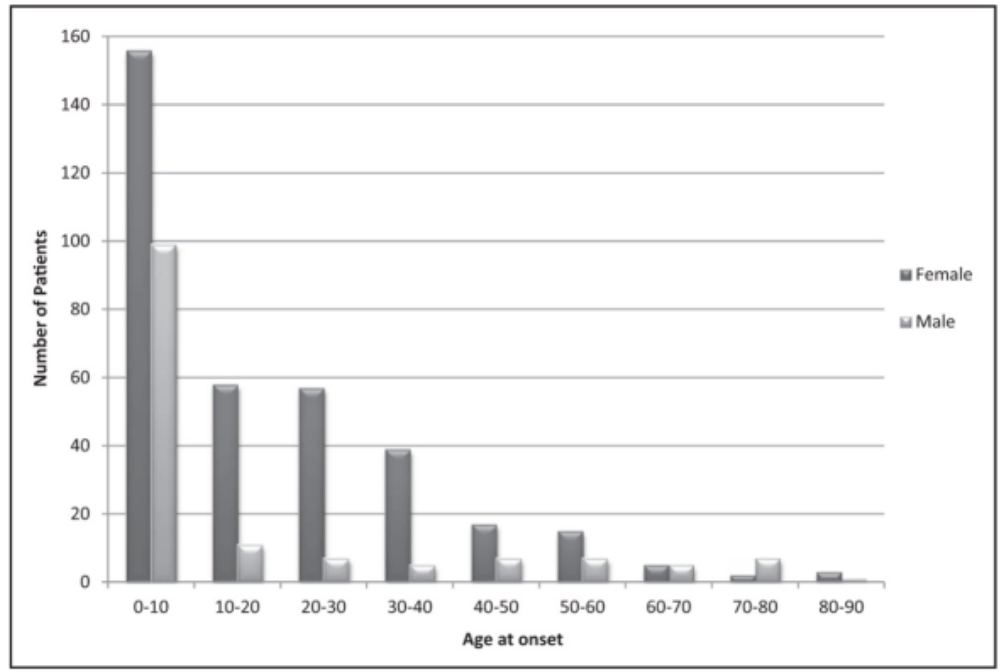


Duffy null mean ANC of 2.82×10^9/L (SD = 1.02)
Non-Duffy null mean ANC 4.43×10^9/L (SD = 1.41)

Br J Haematol. 2025 Sep;207(3):737-749. doi: 10.1111/bjh.20258.

Chronic Idiopathic Neutropenia & Autoimmune Neutropenia

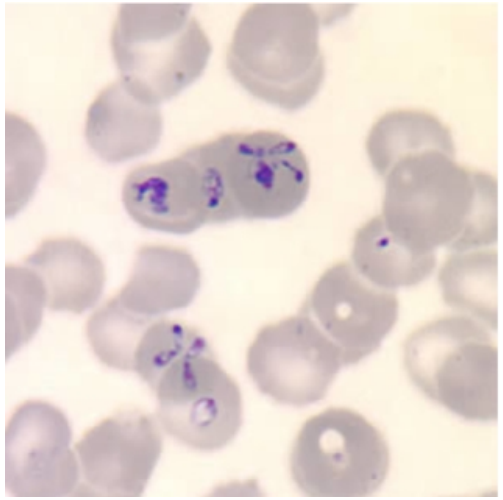
- ANC <1500 x 3 months and not attributable to other causes
  - Severe = ANC <500
- CIN & AIN overlap because we do not have enough testing to check every auto-Ab (anti-HNA)
- Most common cause of chronic neutropenia in adults/children
  - Female predominance
  - In children, can resolve
- Other WBC usually within normal range; Hb/plt usually normal to mildly low
- GCSF is effective for ANC <500 (use in fever, inflammatory syndromes, infections)
- Little data that GCSF use increases risk for myeloid malignancies



Onset of neutropenia. The figure shows the number of male and female patients with the diagnosis of chronic idiopathic or chronic autoimmune, by age groups, enrolled in the Severe Chronic Neutropenia International Registry.

Curr Opin Hematol. 2017 Jan;24(1):46-53. doi: 10.1097/MOH.0000000000000030

Lymphocytosis



- Monoclonal B-cell lymphocytosis [MBL]
  - < 5 × 10^9/L monoclonal B cells for >= 3 months
  - Rate of progression to CLL 1-2% in those with 0.5-5.0 × 10^9/L monoclonal B cells; otherwise same as gen pop (~7% normal blood donors)
- Congenital B cell lymphocytosis
  - Heterozygous missense mutation CARD11
  - Progress to CLL by 4th decade of life

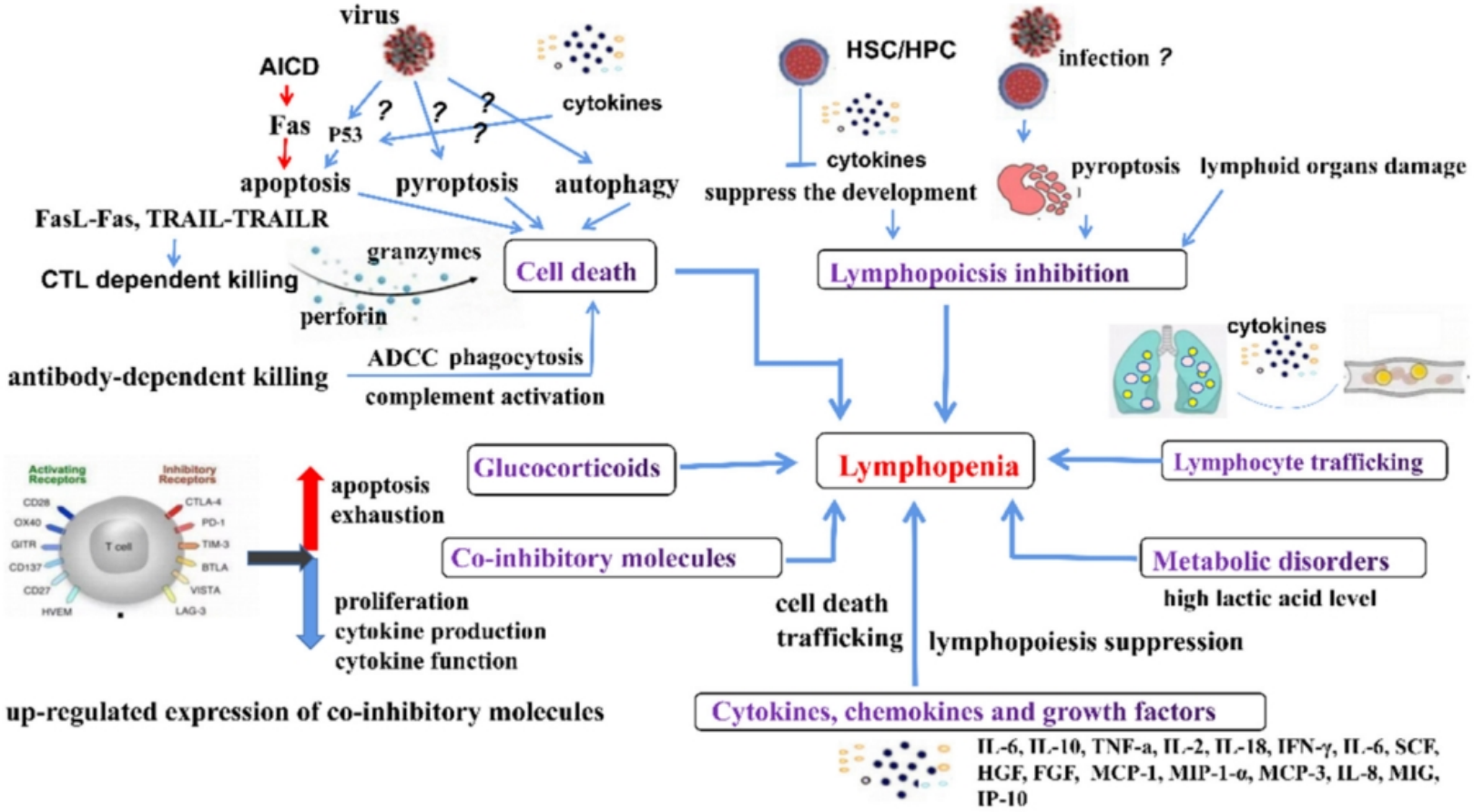
Other Secondary Causes

- **Viral** – CMV, EBV, HIV, HTLV1, HCV, HBV, MMR, VZV, HSV, influenza, adenovirus
- Bacterial – pertussis, rickettsial, TB, syphilis, brucellosis, bartonella
- Parasites – toxoplasma, babesia
- Drugs – BTKi can transiently cause increase in lymphocytes; DRESS
- Stress
- Asplenia
- Serum sickness
- Persistent B-cell polyclonal B-Lymphocytosis

Hematology Am Soc Hematol Edu Program. 2015:2015:106-10.
Hamad H, Mangla A. Lymphocytosis. [Updated 2023 Jul 17]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www-ncbi-nlm-nih-gov.offcampus.lib.washington.edu/books/NBK549819/
Zimmer AJ, Simonsen KA. Babesiosis. [Updated 2023 Jul 31]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430715/

Lymphopenia

- Infections (viral) – EBV, CMV, HIV, VZV,
- Vitamin/nutrient deficiencies
- Autoimmune diseases
- Drugs – chemoimmunotherapies, immunosuppressants, DMARDs, clonazapine, carbamazepine
- Splenic sequestration
- Radiation
- Endocrinopathies (cortisol/catecholamines)
- Idiopathic



Viruses **2021**, *13*, 1876.
https://doi.org/10.3390/v13091876

Monocytosis / Eosinophilia / Basophilia

- Always consider evaluating for a heme malignancy in adults
- Flow cytometry + peripheral smear
- Most increases in basophils >> malignancy
- Eos = *FIP1L1-PDGFRA* fusion, PDGF1-beta, FGFR1, PCM-JAK2, BCR/AB
- Baso/Mono = JAK2 V617F, CALR, MPL, BCR/ABL, myeloid NGS panel
- Idiopathic Hypereosinophilic Syndrome (iHES) = dx of exclusion
  - AEC ≥1.5 x 10^9/L on ≥2 occasions at least two weeks apart + organ damage
  - Tx = high dose steroids, mepolizumab, [ivermectin], HU, imatinib, vincristine

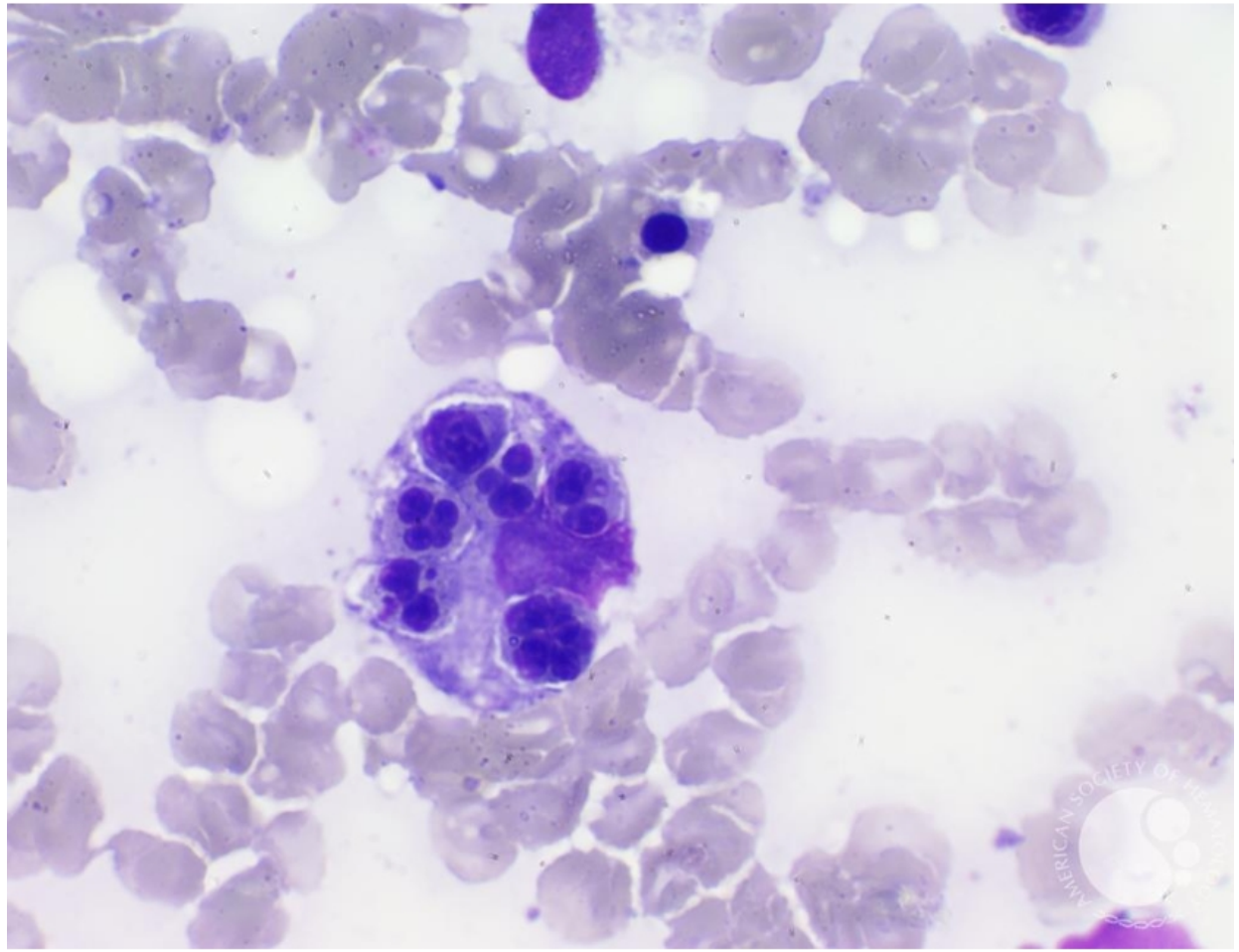
Other Secondary Causes

- Infection (esp Monos) -- fungal, parasitic (Eos – stronglyloides, toxoplasma)
- Autoimmune diseases- ex EGPA (Eos)
- Solid malignancies
- Acute inflammation(esp Monos)
- Pregnancy (Monos)
- MI (Eos)
- Allergy/atopy (Eos/Baso)
- Associated congenital disorders (Monos)
- Stress (Monos)
- Endocrinopathies

Curr Hematol Malig Rep. 2021 Jun;16(3):267-275.

Hemophagocytic lymphohistiocytosis

- Cytopenias >=2 lines
- Immune dysregulation, hyperinflammatory state, cytokine storm >> multiorgan dysfunction
- Primary (familial) vs secondary (commonly due to infection, autoimmune disease or malignancy; CART)
- Best treatment >> treat underlying cause
- HLH-2004 protocol = high dose dexamethasone, etoposide, CSA +/- IT MXT



Lancet Rheumatol. 2024 Jan;6(1):e51-e62. doi: 10.1016/S2665-9913(23)00273-4.

Infection **52**, 471–482 (2024). https://doi.org/10.1007/s15010-023-02104-w

Panel 3: HLH-2004 diagnostic criteria for HLH, adapted from Henter and colleagues[16]

HLH is diagnosed if criterion 1 or 2 has been fulfilled.

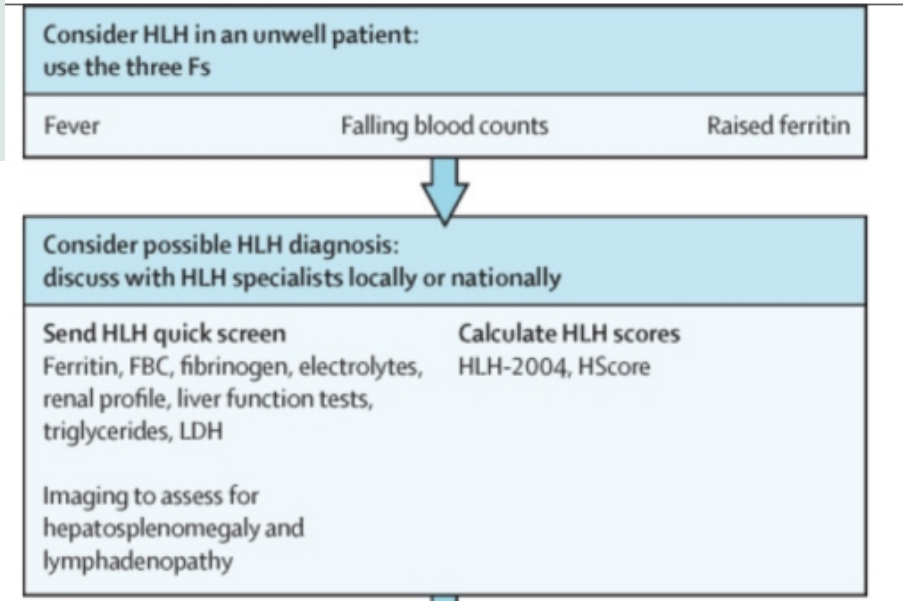
Criterion 1

Molecular diagnosis consistent with HLH.

Criterion 2

Diagnostic criteria for HLH fulfilled (five of eight):

- Fever
- Splenomegaly
- Cytopenia (affecting more than two of three lineages: haemoglobin <90 g/L, platelets <100 × 10^9/L, neutrophils <1·0 × 10^9/L)
- Hypertrigylceridemia or hypofibrinogenemia (or both; fasting triglycerides ≥3·0 mmol/L, fibrinogen ≤1·5 g/L)
- Haemophagocytosis in bone marrow, spleen, or lymph node
- Low or no natural killer cell activity
- High ferritin (≥500 µg/L)
- High soluble CD25 (≥2400 U/mL)



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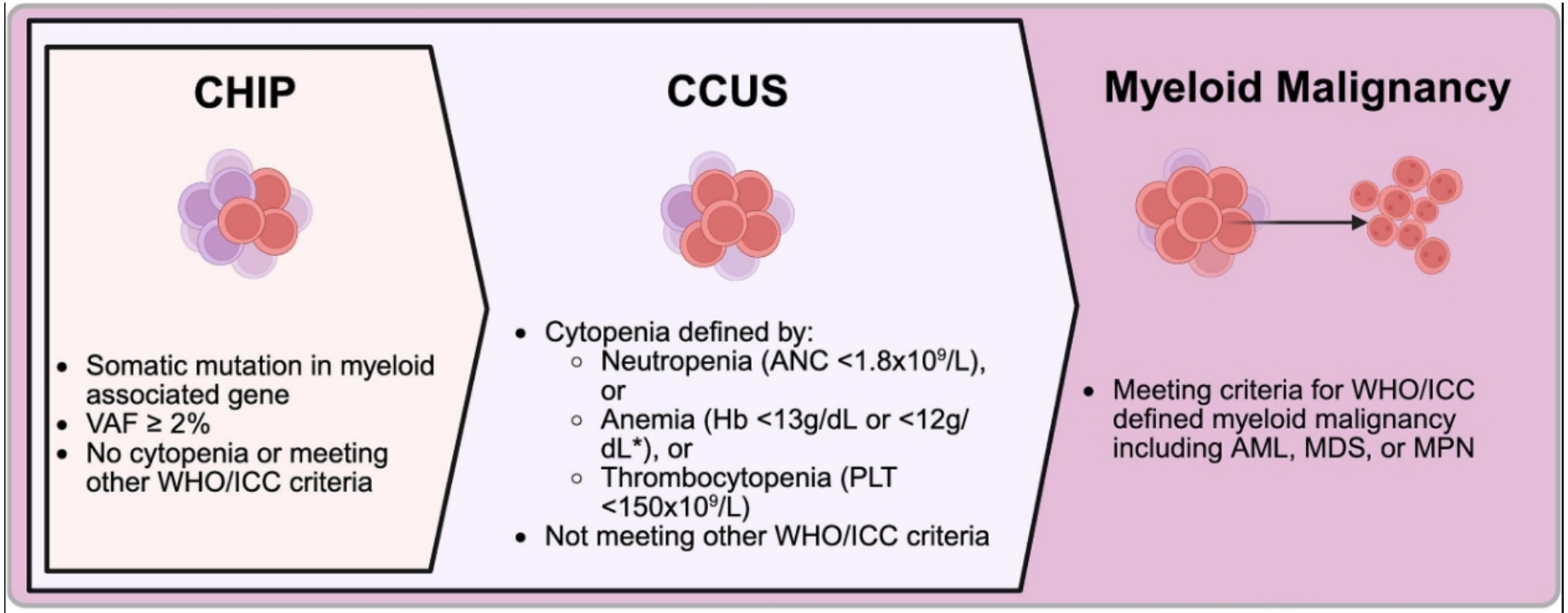
H-Score

Criteria	Extent	Value
Immunosuppression	no	0
	yes	18
Fever	<38.4°C	0
	38.4-39.4°C	33
	>39.4°C	49
Organomegaly	none	0
	liver or spleen	23
	liver and spleen	38
Cytopenia	0-1 lineages	0
	2 lineages	24
Hgb ≤ 92 g/l; WBC≤5/nl; Platelets≤110/nl	3 lineages	34
Ferritin	<2,000 ng/ml	0
	2,000–6,000 ng/ml	35
	>6,000 ng/ml	50
Triglycerides	<132.7 mg/dl	0
	132.7-354 mg/dl	44
	>354 mg/dl	64
Fibrinogen	>250 mg/dl	0
	≤250 mg/dl	30
AST	<30 U/l	0
	≥30 U/l	19
Hemophagocytosis	no	0
	yes	35

Calculation of HScore for the diagnosis of reactive hemophagocytic lymphohistiocytosis. The HScore is formed from the sum of the values of the individual criteria. *Hgb* hemoglobin, *WBC* white blood count, *AST* aspartate aminotransferase

Cytopenias of Undetermined Significance



Risk Prediction Tools

Clonal Hematopoiesis Risk Score (CHRS)
Weeks LD, et al. *NEJM Evidence* 2023

MN-Predict
Gu M, et al. *Nature Genetics* 2023

Clonal Cytopenia Risk Score (CCRS)
Xie Z, et al. *Blood* 2024

	Lower risk	Higher risk
	No cytopenia Age <65 Single *DNMT3A* mutation Normal RDW and MCV VAF <20%	Thrombocytopenia (PLT <100x10⁹/L) Age ≥65 Multiple mutations Splicing gene and adverse mutations Elevated RDW and MCV VAF ≥20%
Risk of progression to myeloid malignancy		
CHRS (5 years)	<1%	24%
CCRS (2 years)	6%	37%

Blood Rev. 2025 Jul 25:101323. doi: 10.1016/j.blre.2025.101323.

Case #1

A 34-year-old recent traveler to rural India has an absolute eosinophil count of 1,800/mm³. He denies allergies. Which of the following is the **most appropriate next step**?

A. Bone marrow biopsy
B. Begin corticosteroids
C. Peripheral blood smear and stool O&P exam
D. CT scan of chest and abdomen

Case #1 - Answer

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A. Bone marrow biopsy

B. Begin corticosteroids

C. **Peripheral blood smear and stool O&P exam**

D. CT scan of chest and abdomen

Case #2

A 30-year-old healthy African American man presents for a routine check-up. His CBC reveals a WBC count of 3.2 × 10^9/L and an absolute neutrophil count (ANC) of 1.1 × 10^9/L. He denies any symptoms and has no history of recurrent infections. Physical exam is unremarkable. Repeat labs are similar. Which of the following best explains this finding?

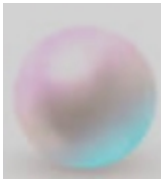
A. Early presentation of chronic neutrophilic leukemia
B. Viral suppression of the bone marrow
C. Drug-induced neutropenia
D. ADAN due to ACKR1 gene variant
E. Idiopathic aplastic anemia

Case #2 - Answer

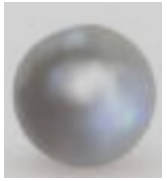
A 30-year-old healthy African American man presents for a routine check-up. His CBC reveals a WBC count of 3.2 × 10^9/L and an absolute neutrophil count (ANC) of 1.1 × 10^9/L. He denies any symptoms and has no history of recurrent infections. Physical exam is unremarkable. Repeat labs are similar. Which of the following best explains this finding?

A. Early presentation of chronic neutrophilic leukemia
B. Viral suppression of the bone marrow
C. Drug-induced neutropenia
D. **ADAN due to ACKR1 gene variant >> “DUFFY NULL”**
E. Idiopathic aplastic anemia

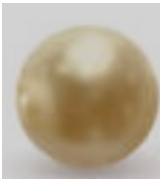
Pearls



- Be able to recognize the signs/symptoms of malignant vs benign WBC

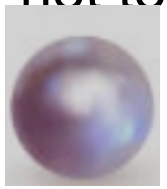


- Many of the common etiologies of WBC disorders are similar – evaluate for infections, autoimmune diseases, medications, solid malignancies, allergy/atopy



- Always order and look at the peripheral smear; know when ordering a peripheral flow cytometry will help with diagnosis

- Be able to recognize and treat potentially dangerous “benign” WBC disorders such as iHES & HLH, or when not to worry, such as in chronic idiopathic neutrophilia, CIN/AIN



- Basophilia is rarely normal!!

Thank you!