

White Cell Disorders

Simon Mantha, MD, MPH

Memorial Sloan Kettering Cancer Center

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Focus

- **Clinical perspective:**

- **Neutrophils**

- Neutrophilia
- Neutropenia

- **Lymphocytes**

- Lymphocytosis
- Lymphopenia

→ **General approach to diagnosis**

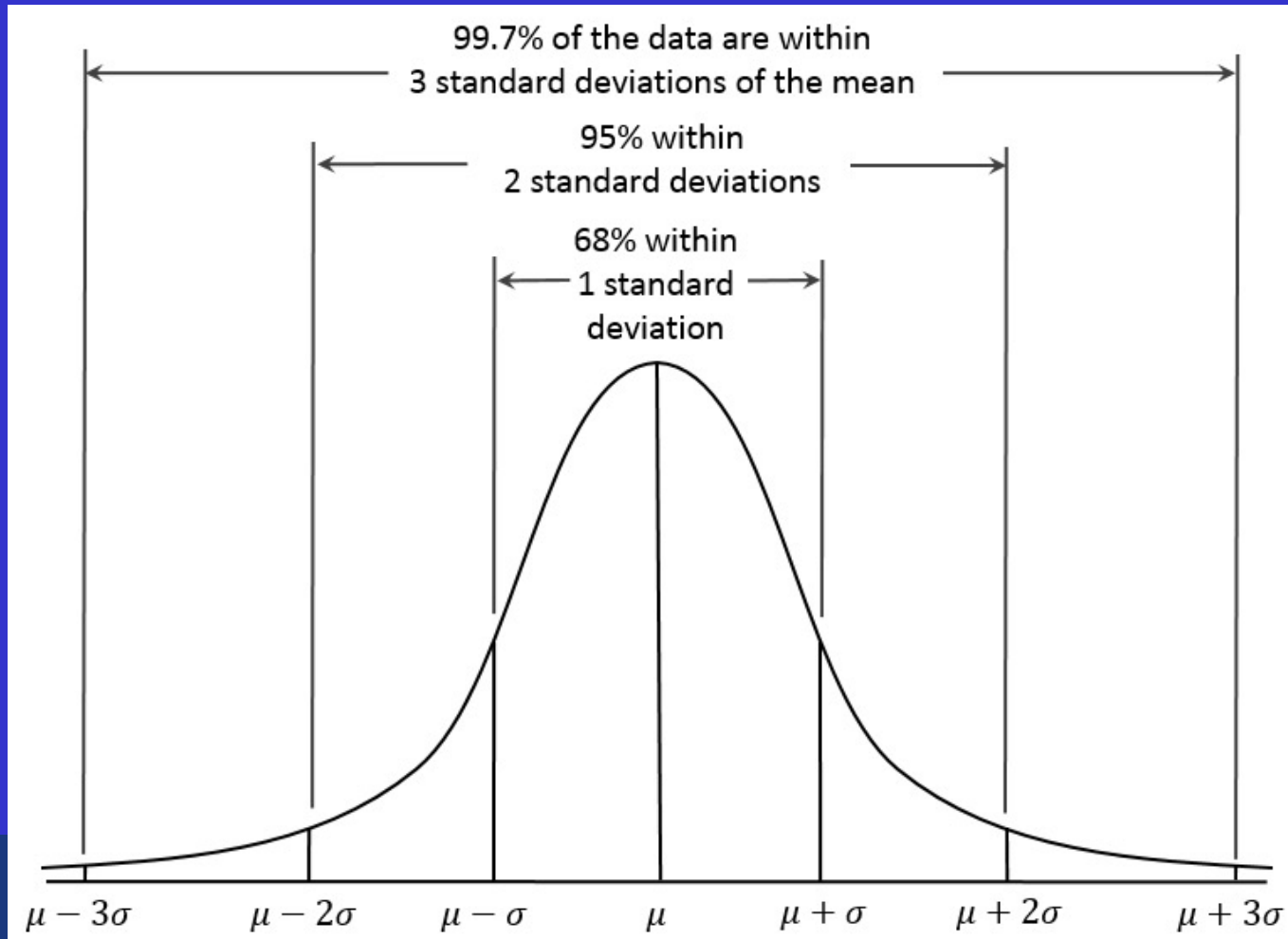


Pitfalls of the Total WBC

- **The total WBC provides aggregate information on:**
 - Neutrophils
 - Lymphocytes
 - Eosinophils
 - Basophils
 - Monocytes
- **The “normal” is defined as a result within 2 SD’s of the mean for the reference population.**



The Normal Distribution



Pitfalls of the Total WBC

- An “abnormal” total WBC does not necessarily imply any “abnormal” result for individual counts!
- A patient with a WBC lower than 97.5% of the population could be in either situation:
 - Have several individual counts at the lower end of the normal range.
 - Have isolated profound neutropenia.



Neutrophils



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Granulocyte Physiology

- **About 75% of neutrophils are in the bone marrow**
 - Mitotic and storage compartments
- **The remaining 25% is in the peripheral blood**
 - Half of those are marginated
 - Half-life is about 19 hours
- **The WBC measures only circulating neutrophils**



Granulocyte Maturation

myeloblast

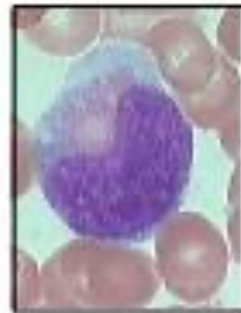
promyelocyte

myelocyte

metamyelocyte

band

neutrophil



MATURATION



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Causes of Neutrophilia

- **Infection**
- **Inflammation**
- **Physical stress**
- **Medications**
- **Asplenia**
- **Smoking**
- **Clonal**



Causes of Neutrophilia

- **Infection:**
 - Mostly bacterial (strep, staph, clostridium)
 - Usually source is obvious
 - Left shift, toxic granulations, Döhle bodies
 - Leukemoid reaction:
 - Very high level ($>50,000/\text{mcL}$, sometimes up to $100,000/\text{mcL}$)
 - Not dangerous in and by itself



Causes of Neutrophilia

- **Inflammation:**
 - Rheumatoid arthritis, Still's disease, Kawasaki, Crohn's, ulcerative colitis, ...
 - Usually mature neutrophils
 - Exacerbations of primary illness associated with an increase in the ANC



Causes of Neutrophilia

- **Physical stress:**
 - **Surgery, intense exercise, myocardial infarction, ...**
 - **Secondary in part to release of epinephrine**
 - **Fast (minutes)**
 - **Mediated by demargination**



Causes of Neutrophilia

- **Medications:**
 - **Epinephrine, corticosteroids, G-CSF, lithium, ATRA, plerixafor, ...**
 - **Various mechanisms**
 - **Stimulation of myelopoiesis**
 - **Release from the bone marrow**
 - **Demargination**
 - **Inflammation**
 - **Usually innocuous**



Causes of Neutrophilia

- **Asplenia:**
 - Following surgical removal or atrophy (e.g. in HbSS)
 - Likely due to loss of natural “reservoir”
 - Can lead to exaggerated leukocytosis with infection
 - Howell-Jolly bodies on the smear



Causes of Neutrophilia

- **Smoking:**
 - Common cause of neutrophilia in the otherwise healthy population
 - Mild
 - Unknown mechanism (inflammation?)
 - Can persist more than one year



Causes of Neutrophilia

- **Clonal:**
 - **Mature**
 - Chronic myeloid leukemia
 - Chronic myelomonocytic leukemia
 - Essential thrombocythemia
 - Polycythemia vera
 - Myelofibrosis
 - **Blasts**
 - Acute myeloid leukemia
 - Myelofibrosis (<5%)



Causes of Neutropenia

- **Medication**
- **Marrow replacement**
- **Constitutional neutropenia (“benign ethnic neutropenia”)**
- **Autoimmunity**
- **Infection**
- **Congenital disorder**



Causes of Neutropenia

- **Medication:**
 - **Dose-dependent (e.g. chemo) vs idiosyncratic (antibiotics, antiepileptics, antithyroid drugs, NSAID's, clozapine, rituximab, TKI's)**
 - **Inhibition of DNA synthesis:**
 - **Nadir usually between days #10 and 15**
 - **Pancytopenia is typical**
 - **Predictable incidence and recovery**
 - **Autoimmunity**
 - **Unpredictable**
 - **Difficult to treat and potentially lethal**



Causes of Neutropenia

- **Marrow replacement:**
 - From solid or liquid neoplasm
 - Usually pancytopenia but occasionally isolated neutropenia (LGL leukemia, hairy cell leukemia)
 - Initial chemo can be associated by prolonged nadir, followed by recovery



Causes of Neutropenia

- **Constitutional neutropenia (“benign ethnic neutropenia”):**
 - Patients of African ancestry have a different population distribution of their neutrophil count
 - ANC usually above 1,200/mcL
 - NO associated increase in infections
 - Unclear mechanism (decrease in Duffy Ag?)
 - Usually also found in siblings



Causes of Neutropenia

- **Autoimmunity:**
 - “autoimmune neutropenia”:
 - Ab-mediated
 - Usually benign, i.e. no infections
 - **Aplastic anemia:**
 - T-cell mediated
 - Pancytopenia
 - Potentially life-threatening
 - **Rheumatological syndromes**
 - Lupus, rheumatoid arthritis



Causes of Neutropenia

- **Infection:**
 - **Bacterial (in sepsis)**
 - From peripheral migration
 - **Rickettsial**
 - Anaplasmosis (HGA)
 - **Viral**
 - HIV, EBV, hepatitis
 - **Parasitic**
 - Malaria, leishmaniasis



Causes of Neutropenia

- **Congenital disorder:**
 - Numerous, rare syndromes
 - “severe congenital neutropenia”:
 - ELANE mutation in most cases
 - Life-threatening, onset at birth
 - Cyclic neutropenia
 - ELANE mutation
 - Waxing and waning neutropenia
 - 3-week cycles
 - Mild to moderate infectious manifestations



Lymphocytes



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Development of Lymphocytes

- **Primary lymphoid tissues:**
 - Bone marrow
 - Thymus
- **Secondary lymphoid tissues:**
 - Lymph nodes
 - Spleen
 - Tonsils
 - GI/respiratory tracts



Distribution of Lymphocytes

- **B cells: follicles**
- **T cells: inter-follicular area, tissues**
- **They transit in the peripheral blood and the bone marrow in small numbers**



Causes of Lymphocytosis

- **Infection**
- **Physical stress**
- **Drug reaction**
- **Clonal**



Causes of Lymphocytosis

- **Infection:**
 - **EBV is typical (i.e. infectious mononucleosis)**
 - “atypical” lymphocytes in the peripheral blood
 - **Pertussis (i.e. whooping cough)**
 - Typical convoluted nucleus
 - **CMV, HIV, mumps, rubella, measles, influenza, ...**



Causes of Lymphocytosis

- **Drug reaction:**
 - **Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)**
 - Usually occurs 2-6 weeks after offending drug intake
 - Eosinophilia and lymphocytosis are a feature
 - Also morbilliform rash, fever and lymphadenopathy
 - Allopurinol, anti-epileptics, dapsone, NSAID's have been implicated



Causes of Lymphocytosis

- **Clonal:**
 - **Mature**
 - Chronic lymphocytic leukemia
 - Large granular lymphocyte leukemia
 - Hairy cell leukemia
 - NHL with “leukemic” phase (FL, MCL, SMZ lymphoma, Sézary syndrome)
 - **Blasts**
 - Acute lymphoblastic leukemia



Causes of Lymphopenia

- **Medication**
 - Cytotoxic chemotherapy (fludarabine, cladribine)
 - Corticosteroids
 - Monoclonal antibodies (e.g. rituximab)
- **Radiation therapy**
- **“systemic disease”**
 - Bacterial/viral/fungal infection
 - Cancer
 - Post-op state



Causes of Lymphopenia

- **HIV infection**
 - Tropism for CD4+ T-cells
 - <200 cell/mcL is one defining criterion for AIDS
 - Discuss HIV risk factors and have low threshold for testing
- **Inherited**
 - SCID
- **Idiopathic**



Evaluation of WBC Disorders

- **Assess if process primary (i.e. clonal) vs secondary**
 - **Reactive elevations of WBC rarely require treatment other than the cause**
 - **Missing a cancer diagnosis can have serious consequences**
- **Assess the infectious risk**



Evaluation of WBC Disorders

- **WBC differential:**
 - **Blasts=red flag!**
 - **>50,000 myeloblasts/mcL can cause leukostasis**
 - **Febrile neutropenia (<500/mcL) is an emergency**
- **History (meds, smoking, splenectomy, B symptoms)**
- **Physical exam (fever, lymphadenopathy, infectious foci)**



Evaluation of WBC Disorders

- **Flow cytometry (for lymphocytosis)**
 - Light-chain restriction strongly suggests clonality
 - Aberrant Ag expression is key in establishing diagnosis of lymphoma
- **FISH and karyotype**
 - t(9:22), t(15:17), t(8:14)



Evaluation of WBC Disorders

- **HEME-IMPACT** or targeted genetic testing to help rule-out clonal processes
 - Use carefully
- **Bone marrow biopsy (when a neoplasm is suspected)**



Summary

- **WBC disorders are common and range from totally benign to medical emergency**
- **Know the red flags**
 - Blasts
 - Neutropenia $<500/\text{mcL}$
- **The total WBC can be misleading**
 - Always examine the absolute numbers in the differential
- **Focus on determining whether process is clonal vs not**





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