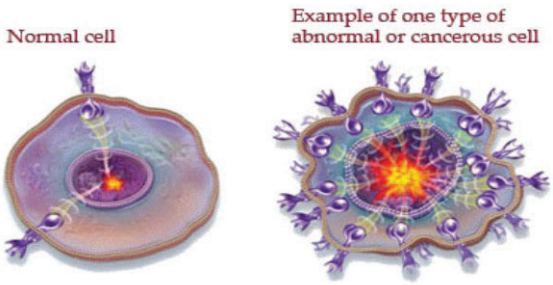
EDUCATION UPDATE

FUNDAMENTALS OF ONCOLOGY

February 19,2026



Allegheny Health Network Cancer Institute

Allegheny Health Network
Fundamentals of Oncology Course

The Fundamentals of Oncology Course is a 4-day introductory course intended for novice clinicians who practice in hematological-medical units, skilled nursing facilities, home care, hospice, radiation oncology and/or cellular transplant. This course may also be applicable to experienced oncology clinicians who require a basic review of oncology diseases and emergencies as well as complications surrounding these processes.

This course is designed to provide the oncology clinicians with basic oncology information and skills that would be applicable to any oncology patient population. The course NCPD can also be applied to the ILNA blueprint for ONCC certifications. Codes have been noted under each lecture. Please keep the course flyer for your ONCC renewal application process.

Course Faculty: This course uses a multidisciplinary approach from the knowledge and expertise of physicians, nurses, clinical nurse specialists, nurse practitioners, managers, genetic counselors, and social workers to provide a comprehensive overview of oncology.

Criteria for earning contact hours

Attendance: Participants are eligible for Nursing Continued Professional Development (NCPD) credits based on the sections they attend. Credits are only offered on the scheduled course dates attended.

Course Materials: Course materials will be distributed at the beginning of each course with additional handouts as necessary throughout the course. Materials include the course schedule, objectives, evaluation form, and content outlines. Post assessment will be provided at the end of each day, with a review conducted at beginning of next class day. Expectation is a passing score of 85%

Course Evaluation: Participants are requested to complete an evaluation for each speaker/lecture. The evaluations will be collected at the conclusion of each day. Feedback will be utilized for subsequent course evaluations.

Activity approval

West Penn Hospital is approved as a provider of nursing continuing professional development by Pennsylvania State Nurses Association, an accredited approver by the American Nurses Credentialing Center's Commission on Accreditation.

Allegheny General Hospital is accredited by the Accreditation Council for Continuing Medical Education to provide continuing education for physicians. Allegheny General Hospital designates this live activity for a maximum of 1.0 AMA PRA category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in this activity

Disclosure Statements

- The planners and presenters have no conflicts of interest to disclose for this activity except:
  - Shelbie O'Hara- Content Creator, Item writer-Oncology Nursing Society
  - Justin Engleka- Highmark Health, Pittsburgh Mobile Footcare
  - Katherine Chorik- Beautox Aesthetics
  - Cyrus Khan- Speakers Bureau – Roche; Beigene; AstraZeneca; AbbVie; BMS; Lily; Pfizer; Kite; ADC Therapeutics
- Any relevant conflicts have been mitigated
- There is no commercial support or sponsors for this educational activity.

Expiration date of enduring material (if applicable) After completion of the live course, enduring materials will be available until December 31, 2026.

Fundamentals of Oncology – Day 3

Thursday February 19, 2026

7:30 a.m. Registration & Review of take-home assessment
Mary E. Kern, MSN, RN, OCN, CHSE

8:00 a.m. Hematopoiesis/Myelosuppression
Tiffany Koss, DNP, CRNP

9:30 a.m. Break

9:45 a.m. Benign Heme + Coagulation
Arjun Lakshman, MD

10:30 a.m. Cellular Transplant
Ashley Button, RN

11:30 a.m. Clinical Trials
Samantha Cavolo

12:15 p.m. Lunch

1:00 p.m. Hematologic Malignancies
Cyrus Khan, MD

3:00 p.m. Wrap-up and Evaluations

Learning Outcomes

Upon conclusion of this conference, participants will be able to:

- Explore the genetic basis of inherited cancer syndromes
- Describe the genetic counseling process: referrals, genetic counseling, and genetic counseling
- Explain tumor nomenclature, molecular biology concepts, diagnosis, and treatment principles
- Distinguish the phases and components of clinical research trials
- Recognize Diversity, Equity, and Inclusion (DEI) and how it relates in oncology
- Discuss management of various vascular access devices available for use in patients with cancer
- Summarize care of medical, surgical, hematological, and radiation oncology patients including the common side effects, complications, and management related to treatment modalities
- Examine basic pathophysiology, assessment, diagnosis and treatment interventions of solid tumor, hematologic malignancies, and benign heme disorders
- Review rationale for the use of various blood products and components
- Identify the basic process of autologous, allogenic, haplo, and cord blood transplantation
- Recall radiation terminology and safety principles
- Explain the different radiation treatment modalities: External Beam Therapy, Brachytherapy
- Give examples of radiation disciplines coordinating patient care and treatment
- State principles of radiation treatment planning and process
- Differentiate the various oncologic emergencies and complications that may arise in the immunocompromised oncology patient
- Summarize nutritional issues impacting patients with cancer
- Examine survivorship issues associated with cancer diagnosis and various treatment modalities
- Assess fertility and sexuality issues related to cancer diagnosis and treatment modalities
- Differentiate between hospice and palliative care programs
- Distinguish the treatment modalities for acute , chronic, and oncologic pain
- Integrate coping strategies for clinicians when caring for patients with cancer
- Recommend oncology rehab strategies contributing to survivorship outcomes and quality of life
- Recognize various psycho-social issues pertinent to patients with cancer throughout the continuum of care
- Relate knowledge from course to clinical practice

Hematopoiesis & Immunosuppression

Presented by:
Tiffany S. Koss DNP, CRNP
Lead Advance Practice Provider
AHN Cancer Screening Program
Tiffany.koss@ahn.org

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Objectives

- Describe the process of hematopoiesis
- Differentiate the types of myeloid & lymphoid cell lines
- Interpret lab results
- Understand the management of neutropenia

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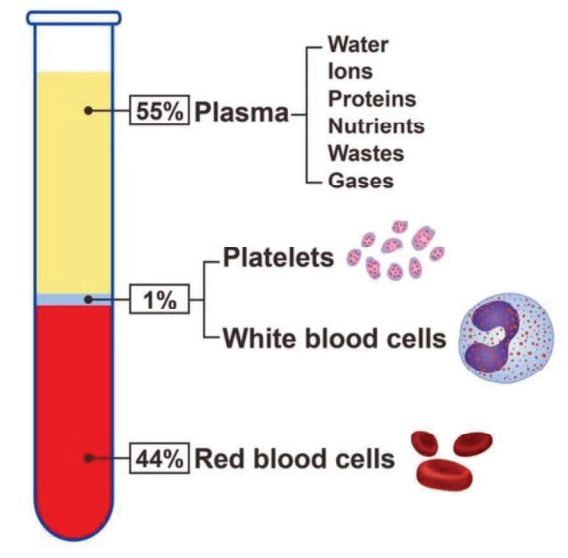
Components of Blood



Hematopoiesis

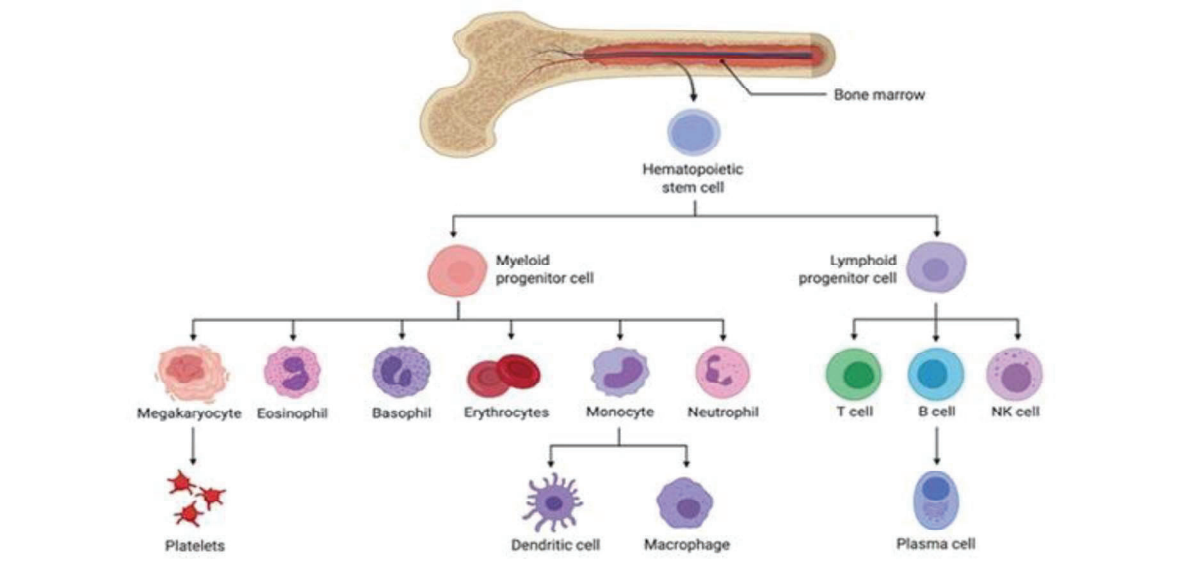
The process of blood cell formation

Occurs in the bone marrow, liver and spleen

Pluripotent cell (stem cell) originates in the bone marrow

- Responsible for production of all hematopoietic cells
- Capable of self-replication, proliferation & differentiation into myeloid & lymphoid stem cells

Hematopoiesis



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Pluripotent Differentiation

Myeloid Progenitor Cell

- Monocytes
- Macrophages
- Dendritic cells
- Granulocytes
  - Neutrophils
  - Basophils
  - Eosinophils
  - Mast cells
- Erythrocytes
- Platelets

***All part of innate immune response**

Lymphoid Progenitor Cell

- B-cell lymphocytes (activate immune system)
  - Memory B cells
  - Plasma cells
- T-cell
  - T helper cells (TH)/CD4
  - Cytotoxic T cells (Tc)/CD8
  - T regulatory (Treg)/suppressor cells
  - Memory T cells/secondary cell-mediated response
- Dendritic cells

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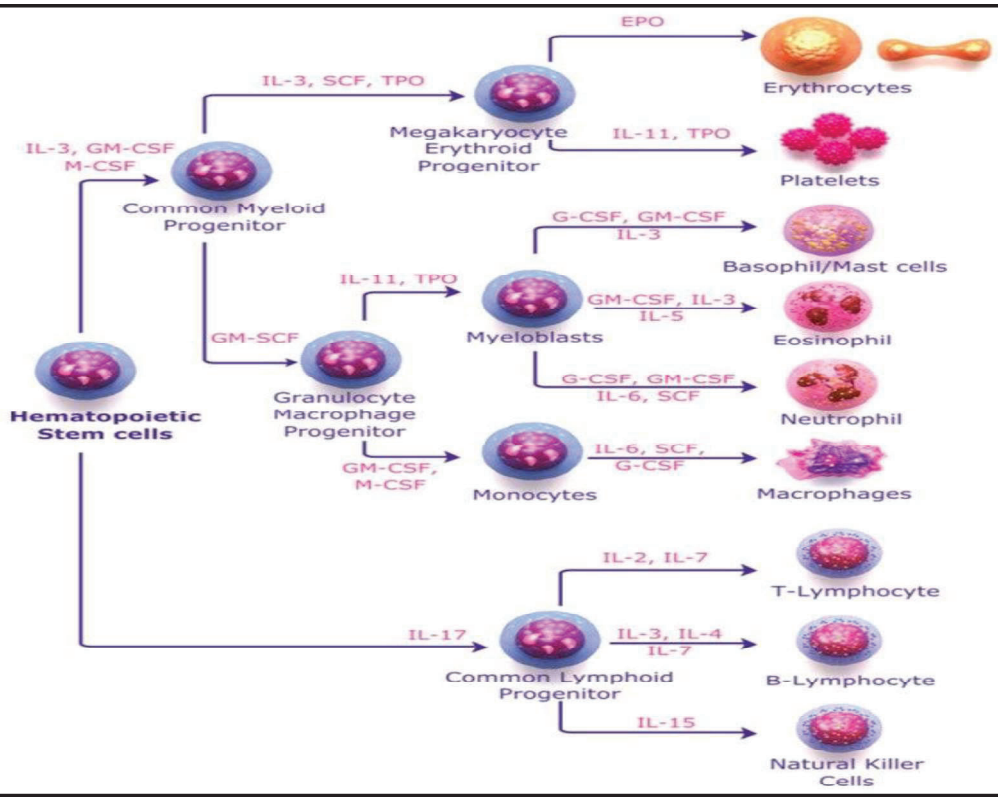
G-CSF: Granulocyte colony-stimulating factor
GM-CSF: Granulocyte-macrophage colony-stimulating factor
M-CSF: Macrophage colony-stimulating factor
EPO: Erythropoietin
TPO: Thrombopoietin
SCF: Stem Cell Factor
Interleukins: group of cytokines that regulate hematopoiesis



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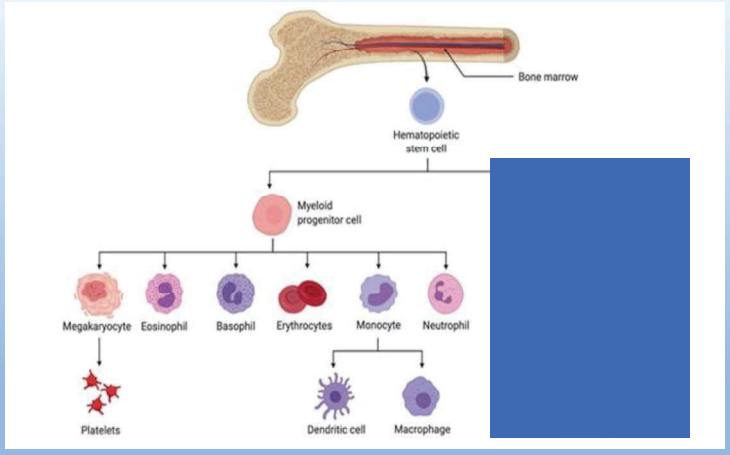
Myeloid

Myeloid Stem Cell Differentiation:

Agranulocytes
- **Monocytes**
- **Macrophages**

Granulocytes
- **Neutrophils**
- **Basophils**
- **Eosinophils**
- **Mast Cells**

Dendritic Cells
Erythrocytes
Platelets
***Part of the innate immune response**



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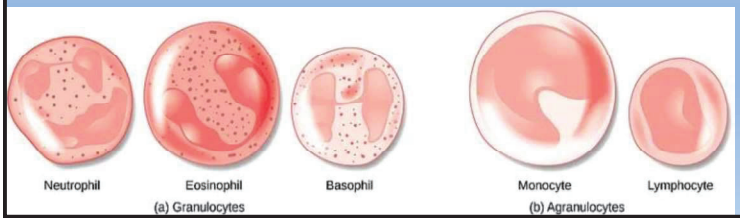
WBC Terminology

- Agranulocytes and granulocytes are two types of leukocytes (WBCs)
- **Agranulocytes** do not have granules
  - Work as phagocytes inside the tissues
  - Two types:
    - Lymphocytes
    - Monocytes/macrophages
- **Granulocytes** contain granules in their cytoplasm
  - Help to digest invading microbes
  - Work as phagocytes only in circulation
  - Also called polymorphonuclear leukocytes (PMN, PML or PMNL)
  - Four types
    - Neutrophils
    - Eosinophils
    - Basophils
    - Mast Cells



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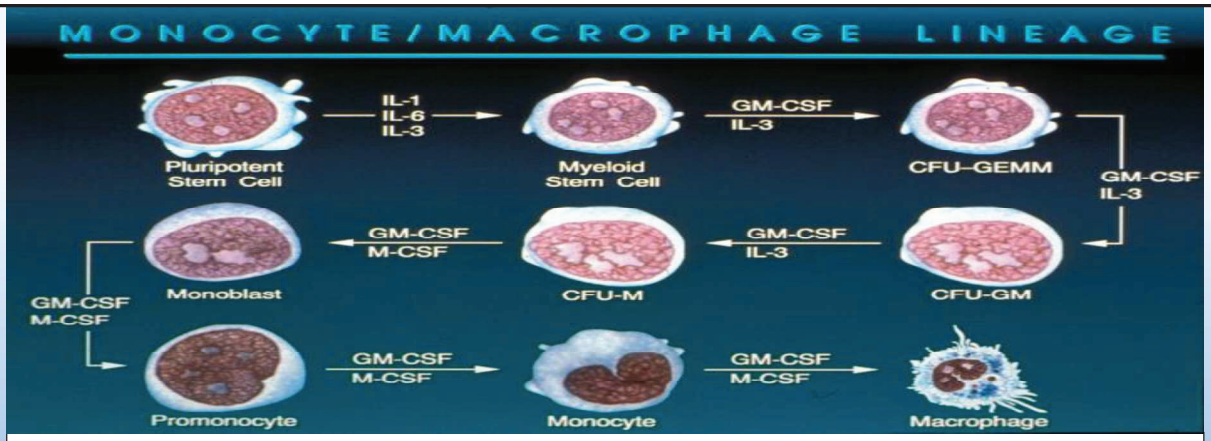

Agranulocytes
Initiate Immune Response/Phagocytosis

-recognize variety of microorganisms (infection and inflammation) esp. gram-negative bacteria
-activated monocytes turn into macrophages that can engulf and destroy microorganisms in the **tissues**
-macrophages (Antigen Presenting Cells- APC) seize foreign materials and present antigens to the B and T cells

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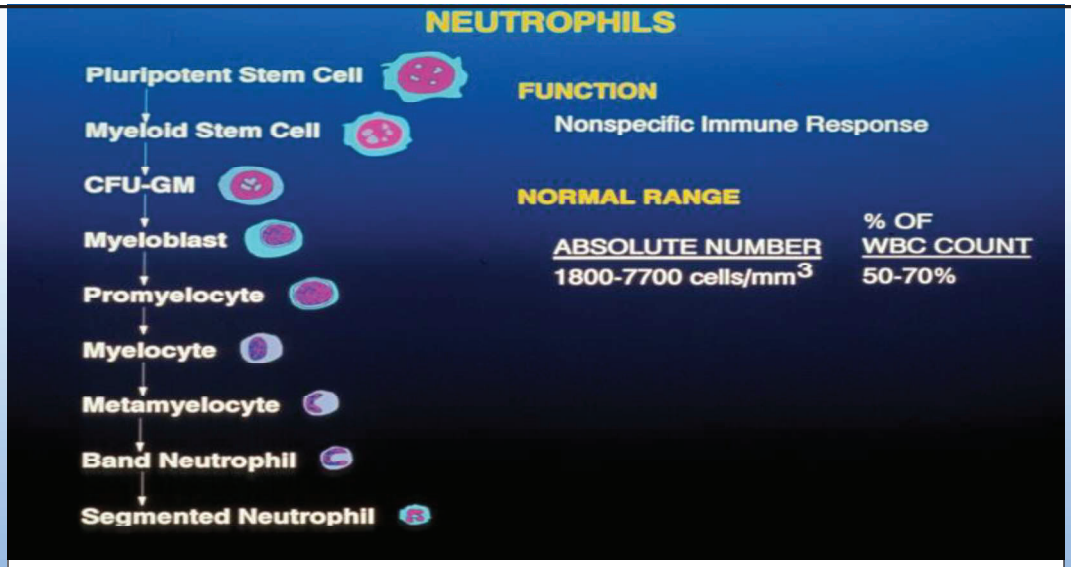
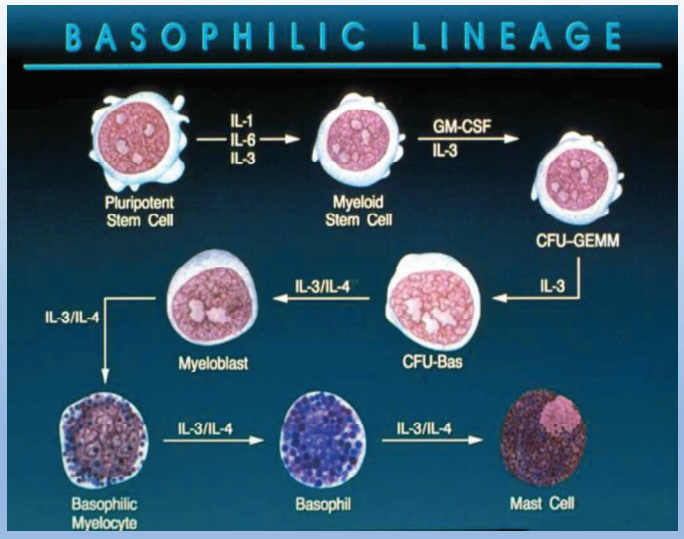
Granulocytes: Types of Myeloid Immune Cells

- **Neutrophils** (engulf)
  - Contribute to acute inflammatory response
- **Basophils** (in blood)
  - IgE receptros for allergic responses
  - Inflammatory mediators
    - Histamine
    - Prostaglandins
    - Serotonin
- **Mast Cells** (found in loose connective tissue)
- **Eosinophils**
  - Attack parasites
  - Secrete leukotrienes, prostaglandins & other cytokines



Granulocytes

***35-76%circulating WBCs with a poly-morphonuclear nucleus and 1st line of defense in blood**
***live 12 hours when healthy and only 2-3 hours when under stress**
***produce 2.5 million cells per hour**



Generates Inflammation Allergic Responses

-release substances that cause vasoconstriction, smooth muscle contraction, and increased permeability of small blood vessels
-basophils are stimulated by allergens

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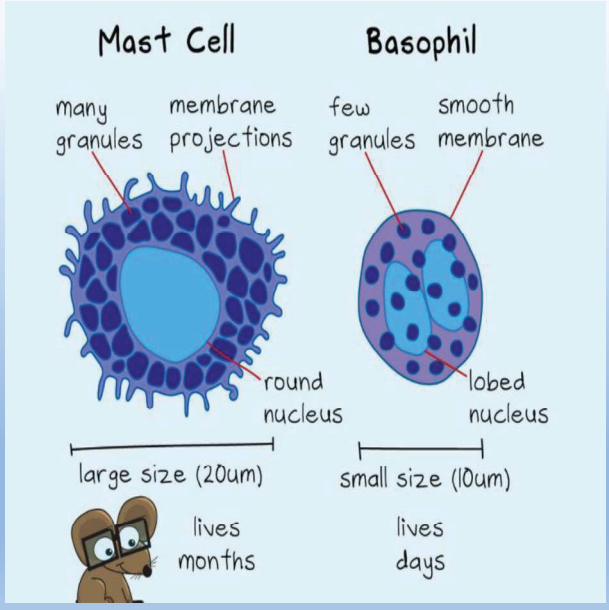

Mast Cells

- Granulocytes that have multiple mediators that produce inflammatory responses within tissues/vasoconstriction
- Located close to blood vessels in all tissues and often indistinguishable from basophils

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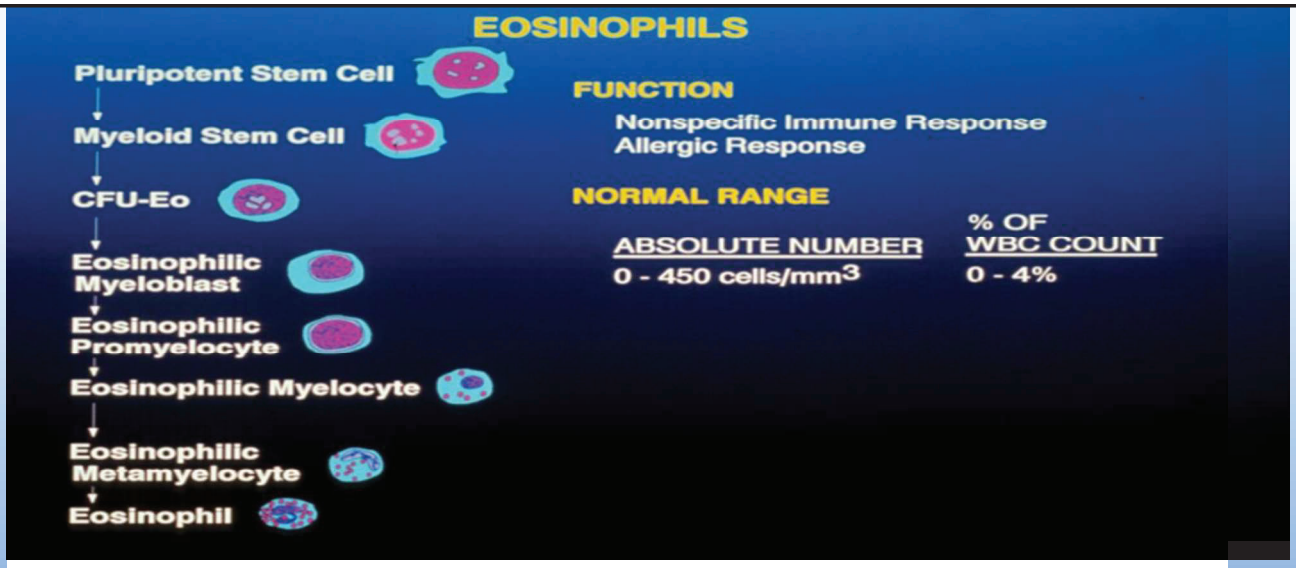

- non-specific immune responses
- eosinophils are stimulated by parasites and some bacteria
- increased with infections, NHL, leukemia
- secrete leukotrienes, prostaglandins, and other cytokines

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Neutropenia
Absolute Neutrophil Count (ANC)

Determining the risk of infection

To find your neutropenic patient's risk of infection, use this table, which is adapted from the National Cancer Institute's toxicity scale.

Absolute neutrophil count	Risk rating	Risk of infection
Within normal limits	0	No risk
≥ 1,500 to < 2,000/mm³	1	No significant risk
≥ 1,000 to < 1,500/mm³	2	Minimal risk
≥ 500 to < 1,000/mm³	3	Moderate risk
< 500/mm³	4	Severe risk

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Calculating ANC

- WBC can be measured:
  - 2.3 k/mcL
  - 2300 mm^3
- If measured 2.3 k/mcL you need to multiply by 1000 to obtain the total WBC as 2300 mm^3

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Multiple Ways to Calculate ANC

Example: **WBC = 2700 mm3, or 2.7 K/mcL**
Neutrophils = 40%, Bands = 2%

(%neutrophils + %bands) x WBC/100
(40+2) x 2700 mm3/100 = 1134

(%neutrophils + %bands) x WBC mm3
(40+2)/100 x 2700 mm3 = 1134

(%neutrophils + %bands) xWBC k/mcL
(40+2) x 2.7 k/mcL x 10 = 1134

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Let's Practice:

1. CBC shows WBC 9.2 k/mcL, 33% neutrophils, 1% bands

ANC = 9.2 x (33+1) x 10

ANC = 9.2 x 34 x 10

ANC = 3,128 Normal

2. CBC shows WBC 1.0 k/mcL, 11% neutrophils, platelets 125k

ANC = 1.0 x 11 x 10

ANC = 110 Severe Neutropenia

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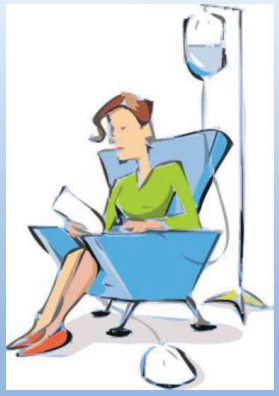
Risk Factors for Neutropenia

- Hematologic malignancy
- Splenectomy
- High-dose corticosteroid therapy
- Chemotherapy/Targeted therapy
- Radiation therapy
  - Sternum
  - Long bones
  - Iliac crest



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Assessment of Patient

System	Signs/Symptoms
Vitals	Fever (or chills); Hypotension; Tachycardia
Neurological	Mental status changes; Decreased LOC; Neck/back pain
Cardiac/Vascular	Edema; New murmurs Access devices – Redness, Swelling, Drainage, Integrity of dressing
Respiratory	Dyspnea; Cough; Sputum; Rhonchi/crackles; Hypoxia
GI	Oral mucosa – Erythema; Ulcers Difficulty swallowing Abdomen – Pain; Stiffness; Guarding Diarrhea
GU	Cloudy urine; Hesitancy; Urgency; Pain; Discharge
Integumentary	Any impaired skin integrity should be monitored for: Redness; Swelling; Drainage; Warmth Will have delayed wound healing

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Remember...

FEVER may be the ONLY sign of infection in neutropenic patient!!!

Neutropenic fever is when there is a single oral temperature greater than or equal to 101 F (38.3 C)

or

Temperature greater than or equal to 100.4 F

(38 C) for at least an hour, with an Absolute

Neutrophil count (ANC) of less than 1500 cells/microliter

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Fever in a Neutropenic Patient, What Next?

FEVER = >38.3 ° C

- Obtain full set of vital signs
- Notify MD immediately
- Obtain blood/urine/stool cultures
- Start antibiotics
  - Gold standard to be given within 30 – 60 minutes after onset of fever
  - Treat these as your "code drugs" in oncology
- If patient continues to remain febrile after 24 hours, consider fungal source – start fungal coverage
- If patient continues to remain febrile after 48 – 72 hours, consider viral source – start viral coverage

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Evidence-Based Interventions for Neutropenia

MOST LIKELY TO BE EFFECTIVE:

- Hand hygiene
- Growth factor for all patients with greater than 20% risk of febrile neutropenia
- Influenza vaccine (unless contraindicated)
- PneumoVax (unless contraindicated)
- Anti-infective prophylaxis
  - Bactrim – prevention of *Pneumocystis carinii* pneumonia
  - Nystatin – prevention of oral candidiasis
  - Fluconazole
  - Acyclovir – prevention of HSV and CMV
- No visitors with symptoms of respiratory infection
- Keep windows closed
- High-efficiency particulate air (HEPA) filters
- Contact precautions for resistant organism colonization

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Evidence-Based Interventions for Neutropenia

LIKELY TO BE EFFECTIVE	Private rooms Plant and flower restrictions Avoid animals and waste
EFFECTIVENESS NOT ESTABLISHED	Protective isolation
EFFECTIVENESS UNLIKELY	Low microbial diet for neutropenic patients
NOT RECOMMENDED FOR PRACTICE	Live attenuated vaccines

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Nadir

- After chemotherapy, the point at which the lowest blood cell county is reached
- Usually 7 – 14 days after day 1 chemotherapy
- WBC and platelet count are usually the first to drop
- Recovery dependent on:
  - ❑ Type of treatment
  - ❑ Length of treatment
  - ❑ Cycles of treatment
  - ❑ Disease

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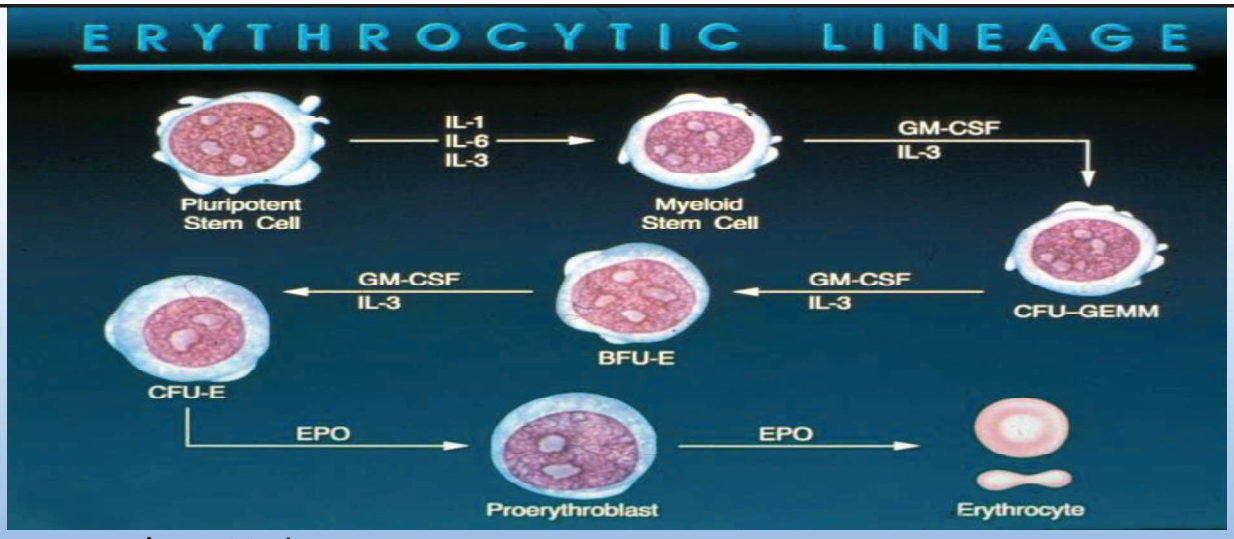

- Live 120 days
- No nucleus
- O2/CO2 transport and exchange
- Acid-base balance

- Reticulocyte
- Pre-rbc
- Increased = hemorrhage
- Decreased = folate deficiency

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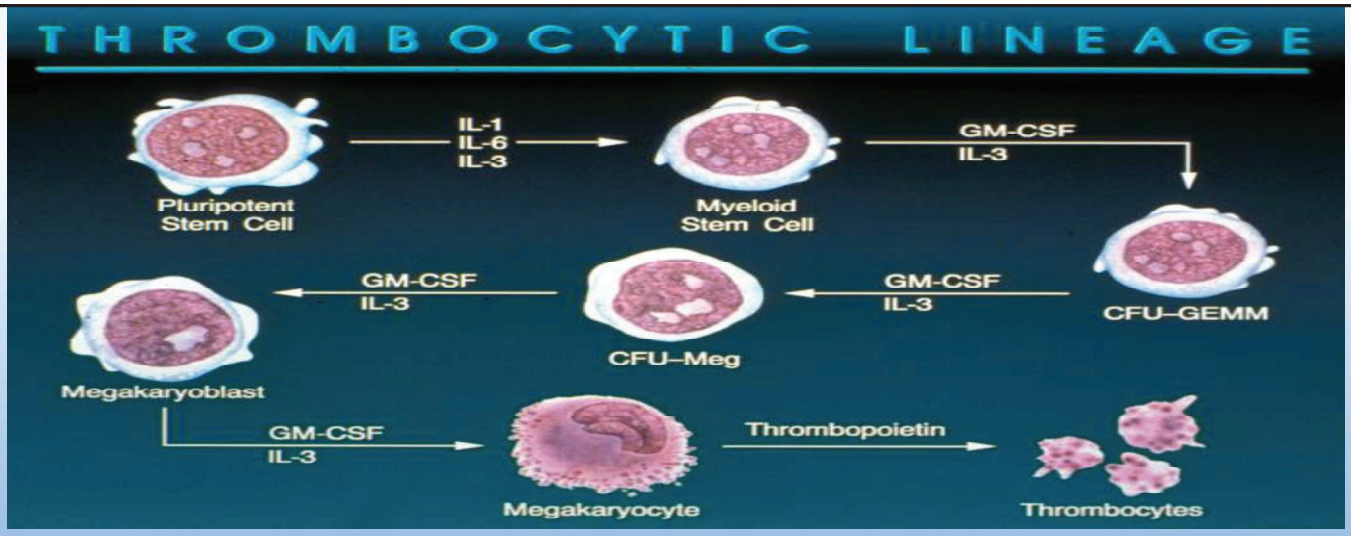

- Blood clotting
- Lifespan 10-14 days

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Medical Terminology

"ia" ⟷ "cytosis"

- Leukopenia – ↓ WBCs
- Neutropenia – ↓ Neutrophils
- Anemia – ↓ RBCs
- Thrombocytopenia - ↓ platelets

- Leukocytosis – Increased
- Erythrocytosis
- Thrombocytosis

** Increase risk of clots, stroke, HTN**

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Myelosuppression

- Reduction in the function of the bone marrow
  - Bone marrow suppression
- Pancytopenia
  - Leukopenia - ↓ WBC's
  - Neutropenia - ↓ neutrophils
  - Anemia - ↓ RBC's leading to ↓ Hgb/Hct
  - Thrombocytopenia - ↓ platelets
- Most common dose-limiting toxicity of cancer treatment
- Major cause of morbidity/mortality & poor quality of life in the oncology patient

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Colony Stimulating Factors (CSFs)

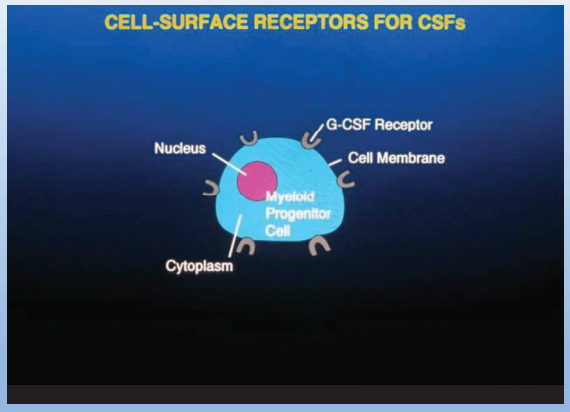
Cytokine

- any of a number of substances, such as interferon, interleukin, and growth factors, that are secreted by certain cells of the immune system and have an effect on other cells

Regulate Hematopoiesis

- proliferation
- differentiation
- maturation

Regulate functional activity of mature cells



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Hematopoietic Growth Factors (HGFs)

WBCs

Short Acting

1. Filgrastim (Neupogen) G-CSF
2. Tbo-filgrastim (Granix)
3. Filgrastim-sndz (Zarxio)*
4. Filgrastim-aafi (Nivestym)*
5. Sargramostim (Leukine) GM-CSF

Long Acting

1. Pegfilgrastim (Neulasta, Neulasta Onpro on-body injector)
2. Pegfilgrastim-ubqv (Udenyca)*
3. Pegfilgrastim-jmdb (Fulphila)*
4. Eflapegrastim-xnst (Rolvedon)*
5. Efbemalenograstim alfa-vuxw (Ryzneuta)*

RBCs

Epoetin alfa *(Procrit)*
Darbepoetin alfa *(Aranesp)*
Epoetin alfa-epbx *(Retacrit)**

Thrombopoietin Receptor Antagonists

Eltromopag
(Promacta)
Romiplostim
(N-Plate)

*biosimilar

Glycosylated proteins that function to regulate cell reproduction, cell maturation, and cell function of blood cells

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Granulocyte Colony-Stimulating Factors (G-CSFs)

- Used with myelosuppressive chemotherapy to shorten time to neutropenic recovery
- Benefits
  - Prevention of neutropenic fever
  - Ability to adhere to chemotherapy schedule
  - Decrease in hospital admission rates
- VERY COSTLY, but benefits outweigh the cost

Side effects

- Bone pain (Claritin/anti-histamine)
- Fever
- Leukocytosis
- Headache
- Nausea
- Vomiting
- Rash

Adverse effects

- Splenic rupture
- Hypersensitivity/allergic reaction
  - History of sensitivity to *E. coli*
- Acute respiratory distress syndrome (ARDS)
- Alveolar hemorrhage
- Sickle cell crisis – avoid with sickle cell patients

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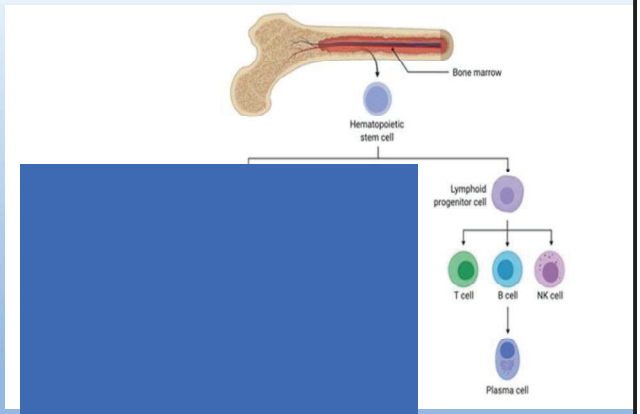
Lymphoid Immune Cells

B-cells

- Develop in BM
- Plasma and memory cells
- Surface markers
  - CD19
  - CD20
  - CD21
  - CD22
  - CD23
  - CD24
  - CD40
  - CD72
  - CD79a and b

T-Cells

- Leave the BM
- Enter bloodstream
- Migrate to thymus to mature
  (after puberty, the thymus shrinks and T cell production declines and there is no thymus T cell differentiation in kids)
- Th cells = helper
- Tc cells = cytotoxic
- Treg cells = regulatory
- Tm cells = memory
- NK cells



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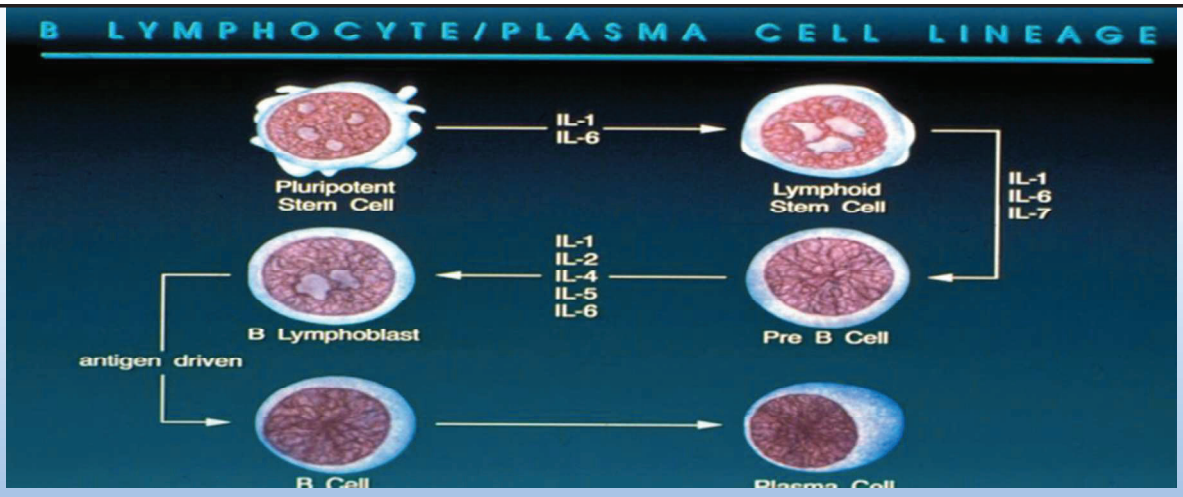

- **Produce Antibodies and Mediate Humoral Immunity**
  B cell produces a single species of antibody, each with a unique antigen-binding site (immunoglobulins). When a naïve or memory B cell is activated by antigen (presented by the helper T cell), it proliferates and differentiates into an antibody-secreting effector cell (plasma cell)

  Some stimulated B-cells become plasma cells, which secrete antibodies. Others become long-lived memory B-cells which can be stimulated later to differentiate into plasma cells. B cells can recognize the surface antigens of bacteria and viruses

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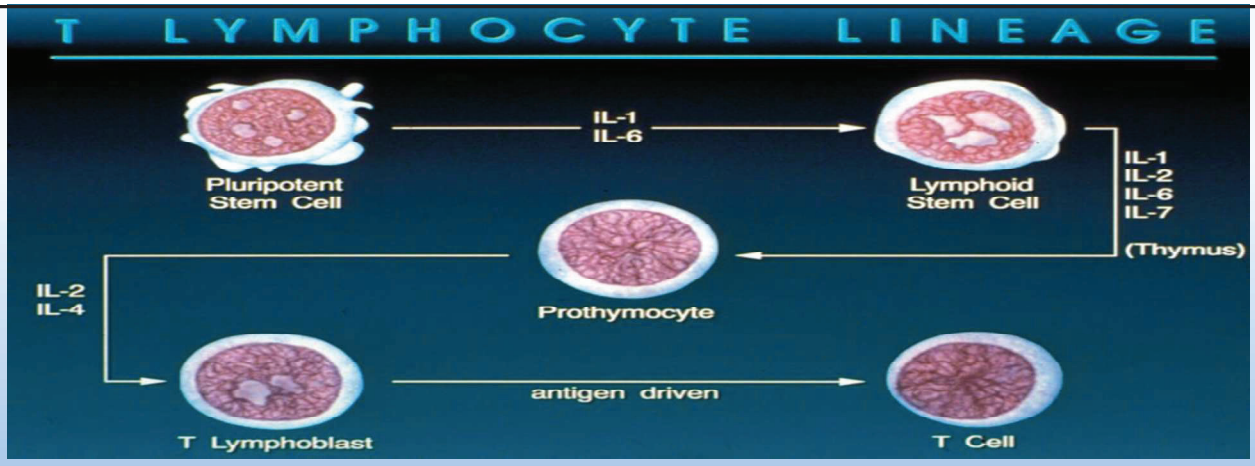

Mediate Cellular Immunity

*T cells can only recognize viral antigens outside the infected cells
*Once activated they divide rapidly and secrete cytokines that assist in immune response
*T cells require the action of APCs (usually dendritic cells, but also macrophages, B cells, fibroblasts and epithelial cells) to recognize a specific antigen
*CD4+ Helper Cells. CD4+ helper cells help in the maturation of B cells into plasma cells and memory B cells.
*CD8+ Cytotoxic Cells. CD8+ cytotoxic cells cause lysis of virus-infected and tumor cells
*Memory T Cells
*Natural Killer T Cells

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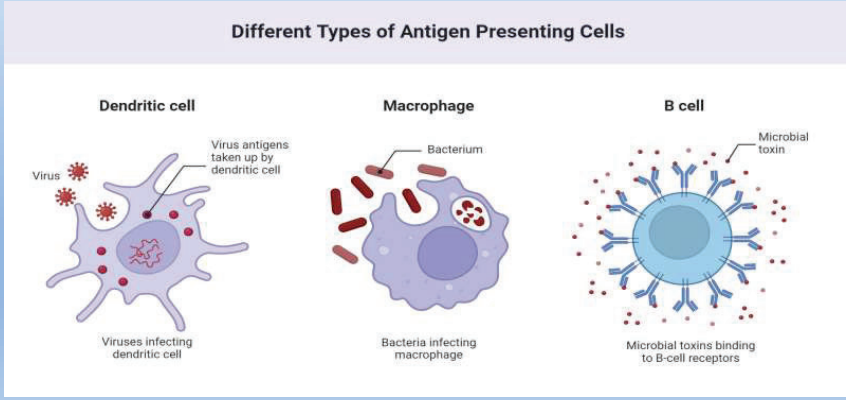
Antigen Presenting Cells (APCs)

- Seek out and present antigen to the T-cell to destroy the pathogen
- Serve to ensure adaptive immune responses are initiated to invading microorganisms



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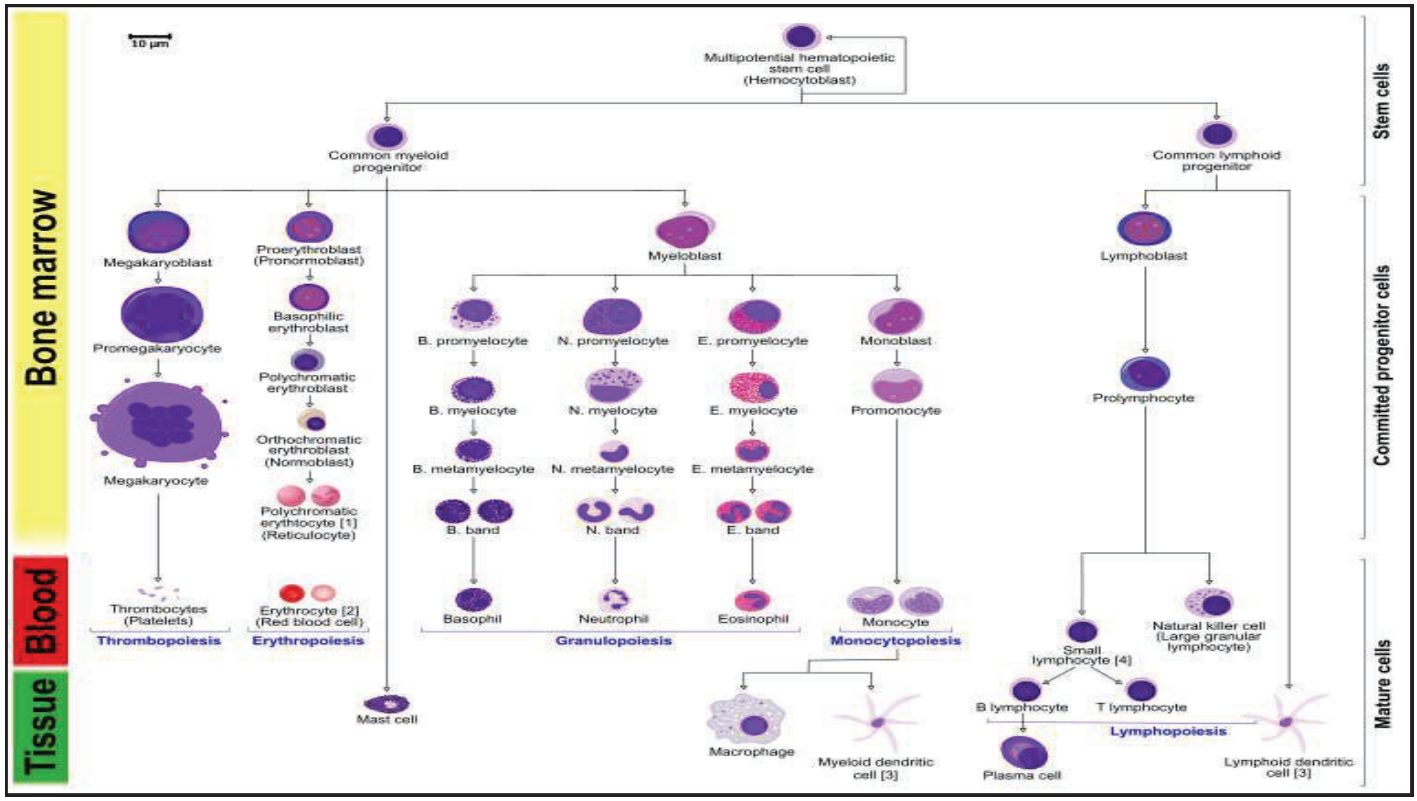

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Summary of Key Points

- Hematopoiesis is the process of blood cell formation
- The Pluripotent stem cell is capable of self-replication, proliferation, and differentiation into myeloid and lymphoid stem cells
- Myeloid:
  - •Myelosuppression - reduction in the function of the bone marrow
  - •Pancytopenia – leukopenia, neutropenia, anemia, thrombocytopenia
  - •Absolute Neutrophil Count (ANC) – k/mcL or mm^3
  - •Assessments – head to toe, fever greater than 38.3C
  - •Colony Stimulating Factors (CSFs)– cytokines that regulate hematopoiesis, proliferation, differentiation, maturation, and functional activity of mature cells.
    - •Most common adverse effect is bone pain

Lymphoid:

- •B cells - produce antibodies and mediate humoral immunity
- •T cells - mediate cellular immunity

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Thank you…

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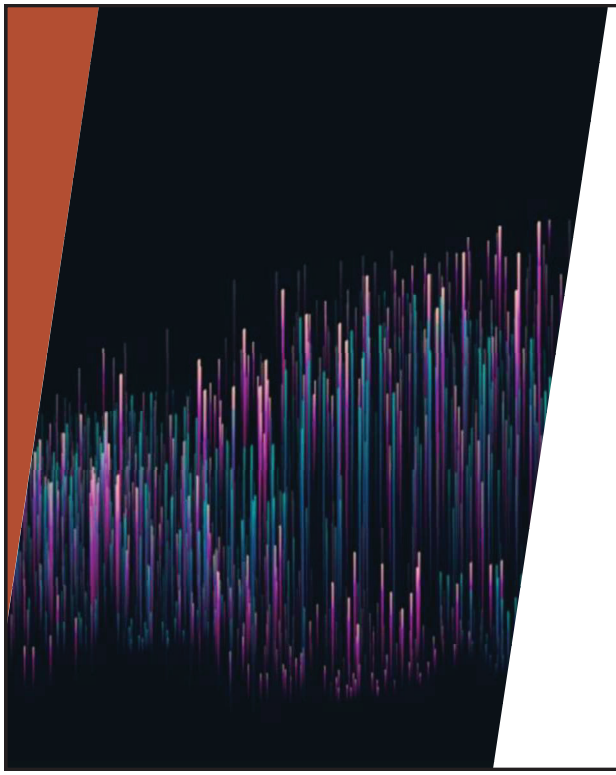

Defects of Coagulation

Developed by:
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Presented by:
Arjun Lakshman, MD
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1

Coagulation Disorders

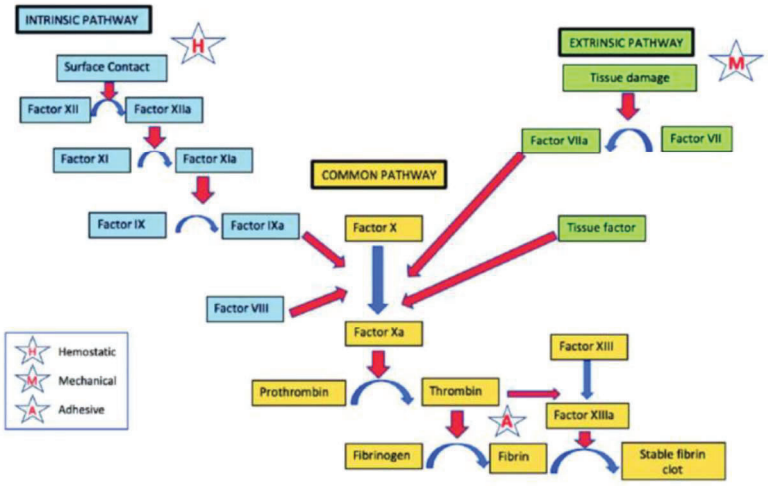
Affect the blood's clotting activities

Can result in bleeding disorders or thrombosis

Examples:

Hemophilia
Von Willebrand Disease
Clotting factor deficiencies
Hypercoagulable states

2



3

Hemophilia

- Inherited bleeding disorders
- Deficiency of coagulation factor VIII (hemophilia A), factor IX (hemophilia B), or factor XI (hemophilia C)
- Acquired factor deficiencies
  - Caused by an autoantibody
- Severity varies
- Increased in males
- Initial presentation often as infant
- Family hx of bleeding disorders
- Coag studies, Factor levels (VIII, IX, XI)

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Von Willebrand Disease

- Most common inherited bleeding disorder
- Three types:
  - Type I
    - Most common
    - Decreased von Willebrand factor
  - Type 2
    - Dysfunctional von Willebrand factor
    - Four subtypes
  - Type 3
    - Absent or undetectable von Willebrand factor
    - Rare

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Von Willebrand Disease

Presents with:

- Bruising, mucocutaneous bleeding, heavy menses, postpartum bleeding
- GI bleeding less common
- May have normal CBC and coagulation studies
- Family history
- Prolonged aPTT

Diagnosis:

- CBC
- Platelet count (may be mildly low)
- Coagulation studies
- Von Willebrand panel (VWF antigen, platelet-dependent VWF activity, factor VIII activity)

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Von Willebrand Disease-Treatment

- Goal is to raise von Willebrand factor (VWF) levels
- Major bleeding or Surgery
  - VWF concentrates (ristocetin cofactor)
  - Recombinant VWF
- DDAVP
  - 0.3 mcg/kg once 30-60 mins prior to procedure (max 20 mcg/dose)
  - Prevention of surgical bleeding for mild-moderate disease
- Cryoprecipitate can be used if NO VWF concentrate is available
- Platelet transfusions for thrombocytopenia <50k
- Antifibrinolytic agents as adjunct to VWF concentrates (aminocaproic acid, tranexamic acid)
- Topical agents used in combination with other therapies (Gelfoam)

Thrombophilia

- Hypercoagulable state defined as group of inherited or acquired conditions associated with a predisposition to venous thrombosis, arterial thrombosis, or both
- Normally diagnosed at time of first thrombotic event
- Provoked vs unprovoked
  - Determines length of treatment with anticoagulation

Patient Presentation

- Most patients present with venous thromboembolism (VTE)
  - Deep vein thrombosis (DVT)
  - Pulmonary embolism (PE)
  - Diagnosed with Doppler, CTA Chest
- Arterial thrombosis
  - CVA
  - Acute limb ischemia

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Provoked vs Unprovoked VTE

- Provoked VTE
  - Major surgical procedure
  - Trauma
  - Hospitalization
  - Infections (COVID-19), DIC
  - Pregnancy
  - Immobility
  - Medications (oral contraceptives, hormone replacement therapy)
  - Malignancy
- Unprovoked
  - NO preceding aggravating event

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Initial Treatment of Acute VTE

- Choice of Anticoagulant
- Heparin, enoxaparin, warfarin, fondaparinux, DOACs
- Testing for hypercoagulable state can normally be complete as outpatient
  - Should be recommended by Hematologist
  - Costly
  - Acute phase of VTE can affect certain hypercoag tests
  - Anticoagulants may affect testing results

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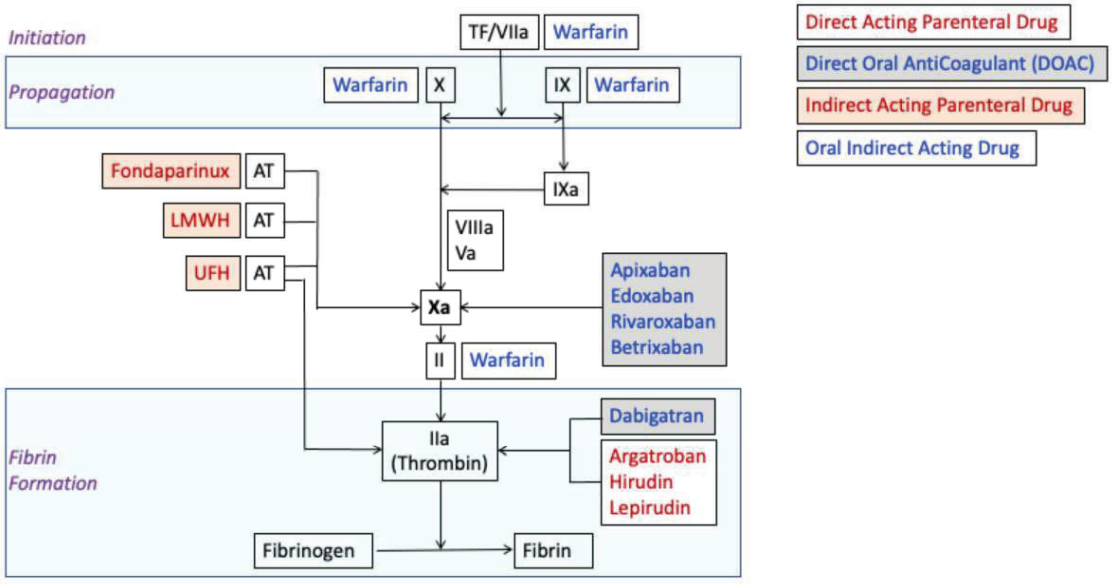
Coagulation Cascade



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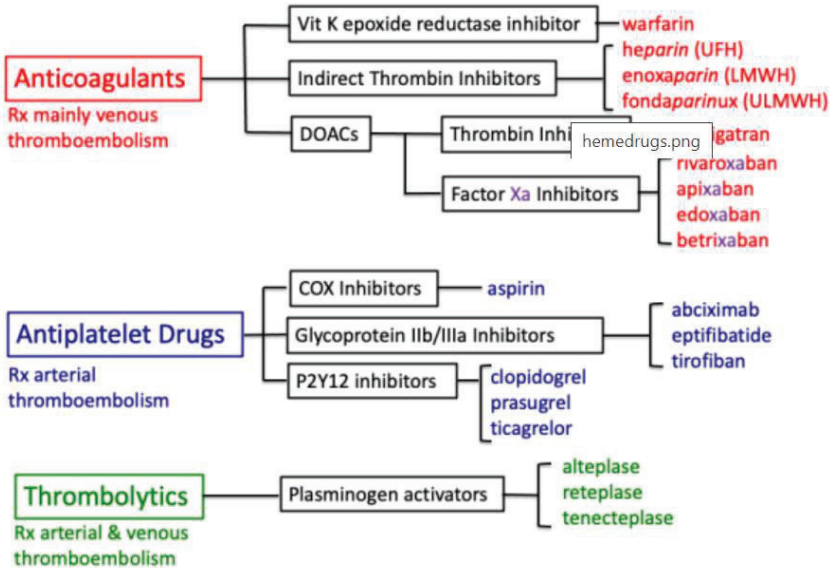
Drugs Used to Treat Clotting Disorders



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Who Should Have Hypercoagulable Workup?

- Unprovoked VTE
- VTE at young age (>45 years)
- Recurrent VTE
- VTE with family history
- Recurrent pregnancy/fetal loss
- Thrombosis in unusual vascular beds (portal, hepatic, mesenteric or cerebral veins)
- Strongly considered for patients with female relatives with known inherited hypercoagulable states

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Who Should NOT be Tested

- First episode of provoked VTE
- Active malignancy
- Inflammatory bowel disease
- Myeloproliferative disorders
- Heparin induced thrombocytopenia with thrombosis
- Retinal vein thrombosis

Hypercoagulable Workup

- Do not forget: Thorough physical examination and past medical history
- Common preliminary testing
  - CBC with differential
  - Coag studies (aPTT, PT, INR)
  - ESR/CRP
  - CMP
  - Imaging if needed
  - Hypercoag testing, preferable 2 weeks after discontinuation of anticoagulant

Inherited Thrombophilia

- Factor V Leiden mutation
- Prothrombin G20210A mutation
- Protein S deficiency
- Protein C deficiency
- Antithrombin deficiency

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Hypercoagulable Workup

- **Factor V Leiden Mutation**
- Inherited condition
- Single point mutation in the gene that codes for coagulation factor V
- Typical presentation as VTE or fetal loss

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Hypercoagulable Workup

- **Prothrombin Gene Mutation**
- Autosomal dominant mutation which results in over production of prothrombin
- If found incidentally, prophylactic anticoagulation not necessary
- More common in Caucasians
- Decision to continue anticoagulant beyond 6 months if unprovoked VTE
- DOACs can be used

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Hypercoagulable Workup

- **Antiphospholipid Syndrome**
- Two major subgroups of antiphospholipid antibodies:
  - Lupus anticoagulants
  - Anticardiolipin antibodies
- Can occur with autoimmune disorders (Systemic lupus erythematosus, Sjogren's syndrome, rheumatoid arthritis)
- Indefinite anticoagulation with warfarin
- Not a hereditary disorder
- Patients with arterial thrombosis

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Anticoagulation Treatment During Pregnancy

- Lovenox for most of pregnancy
- Heparin last few weeks of pregnancy
- Do not cross placenta

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Summary

- Defects in coagulation may present as VTE or bleeding episode
- Testing for hypercoagulable states should be recommended by Hematologist
- Timing of testing is important
- Average length of treatment with anticoagulation for first episode of VTE is at least 6 months.
- Interruptions in anticoagulation should be avoided in first 3 months of treatment

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The End

FUNDAMENTALS OF ONCOLOGY CELLULAR THERAPY

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1

AGENDA

1. Review of AHN Cellular Therapy Program
2. Sources of Stem Cells
3. Benefits and Drawbacks of Stem Cell Sources
4. Description of Stem Cell Transplants Phases
5. Types of Stem Cell Transplants

2

AHN CANCER INSTITUTE CELLULAR THERAPY PROGRAM

- One of only two adult stem cell transplant programs in Western Pennsylvania
- Only stem cell transplant program for AHN
- Services offered exclusively at West Penn Hospital

CTP PHYSICIANS

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Salman Fazal, MD – Director, Cell Transplant Program – Myeloid Diseases
Anna Koget, DO – Myeloid Diseases
Thomas Curley, MD –Myeloid Diseases
Cyrus Khan, MD - Lymphoma
Santhosh Sadashiv, MD – Myeloma, Plasma Cell Disorders
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TIL Coordinators
Lindsey Brown
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Heme Coordinators
Carlie Lorent
Kelly Polosky

Inpatient APPs
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Albert Bruckner
Madison Curran

Clinical Pharmacists
Devon Coffey
Samantha Maples
Kiersten Williams
Jaqueline Bronfman

Clinical Psychologists
Matthew Iwaniec
Chelsea Neill
Marissa Barash

Lab Quality
Paula Cockerham

Cell Processing Lab
Charlene Briedenbaugh – Manager
Rachael Cenname
Kim Schlieper
Samantha Sonnenberg
Tammy Tarosky
Carrie Travaglino

Navigation
Melissa Dunn
Anne King

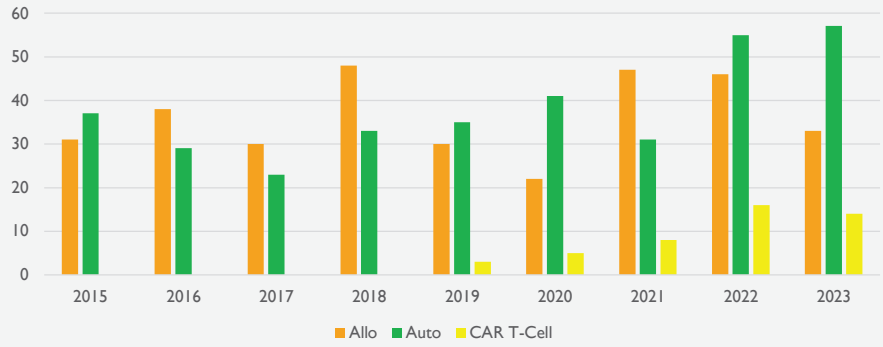
5

TYPES OF CELLULAR THERAPIES

- Autologous Stem Cell Transplant (AUTO)
  - Self
- Allogeneic Stem Cell Transplant (ALLO)
  - Unrelated (from NMDP)
  - Related
    - Fully Matched (sibling)
    - Haploidentical (half matched child/sibling/parent)
- CAR T-cell Therapy (Chimeric Antigen Receptor)
- TIL Therapy (Tumor Infiltrating Lymphocytes)

6

AHNCI TRANSPLANT VOLUME 2015-2023



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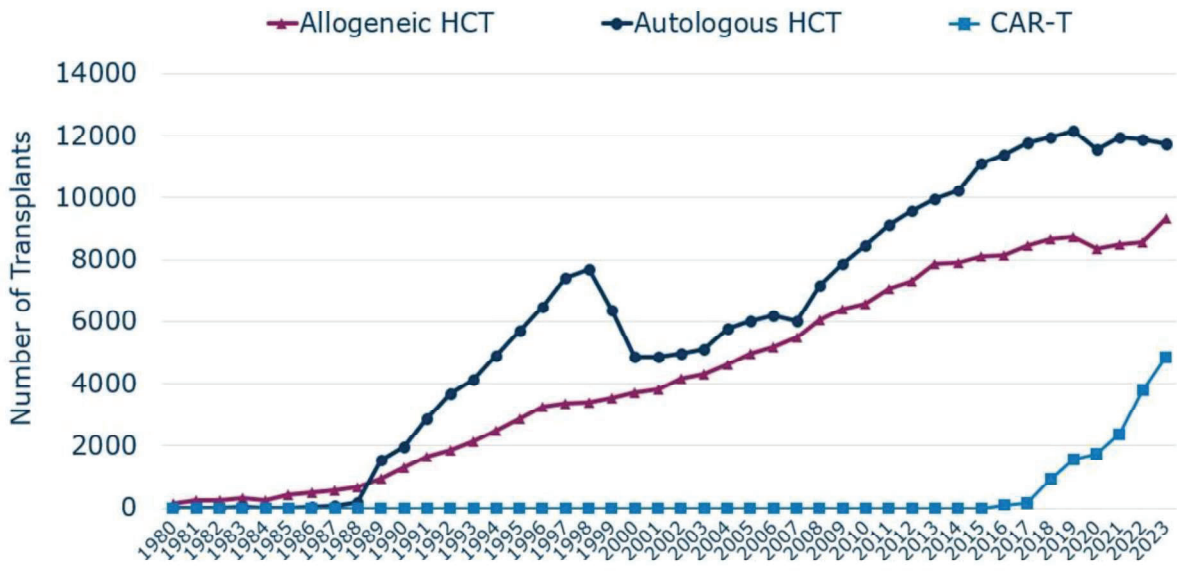
Number of 1st Cellular Therapies Reported to CIBMTR in the US



CIBMTR
A RESEARCH COLLABORATION BETWEEN THE MEDICAL COLLEGE OF WISCONSIN AND NMDP

CIBMTR.org 3

8

CELLULAR THERAPY PROCESS

- Referral – Physician refers potential recipient to transplant team
- Intake- CTP physician, CTP coordinator, financial coordinator, and psychologist meet with patient
- Pretesting Workup – includes physical exam, labs, dental clearance, HLA Typing (if allo transplant), bone marrow (if applicable), psychological evaluation, other disease specific tests
- *Auto Transplant – mobilization & collection
- *Allo Transplant – donor mobilization & collection
- *Car T-cell Therapy- MNC collection
- *TIL Therapy- Tumor harvest
- Admission for conditioning chemotherapy
- Transplant Day is Day 0
- Post-transplant care – daily monitoring of recipient for side effects and engraftment
- Post-transplant vaccinations

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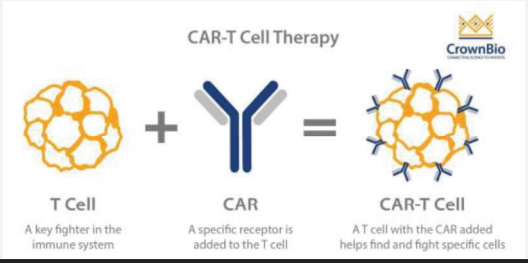
CAR T-CELL THERAPY

- **Treats:** B-cell Lymphomas, Mantle Cell Lymphoma, Follicular Lymphoma, B-cell ALL, r/r Multiple Myeloma
- **Process:**
  1. Pretesting
  2. Apheresis (MNC Collection- outpatient)
  3. Manufacturing (typically 3-4 weeks)
  4. Conditioning chemo (chemotherapy given prior to Car T-cell infusion)
  5. Infusion (Car T-cell product given via central line)
- **Goal:** Car T-cells continue replicating and finding/fighting cancer cells



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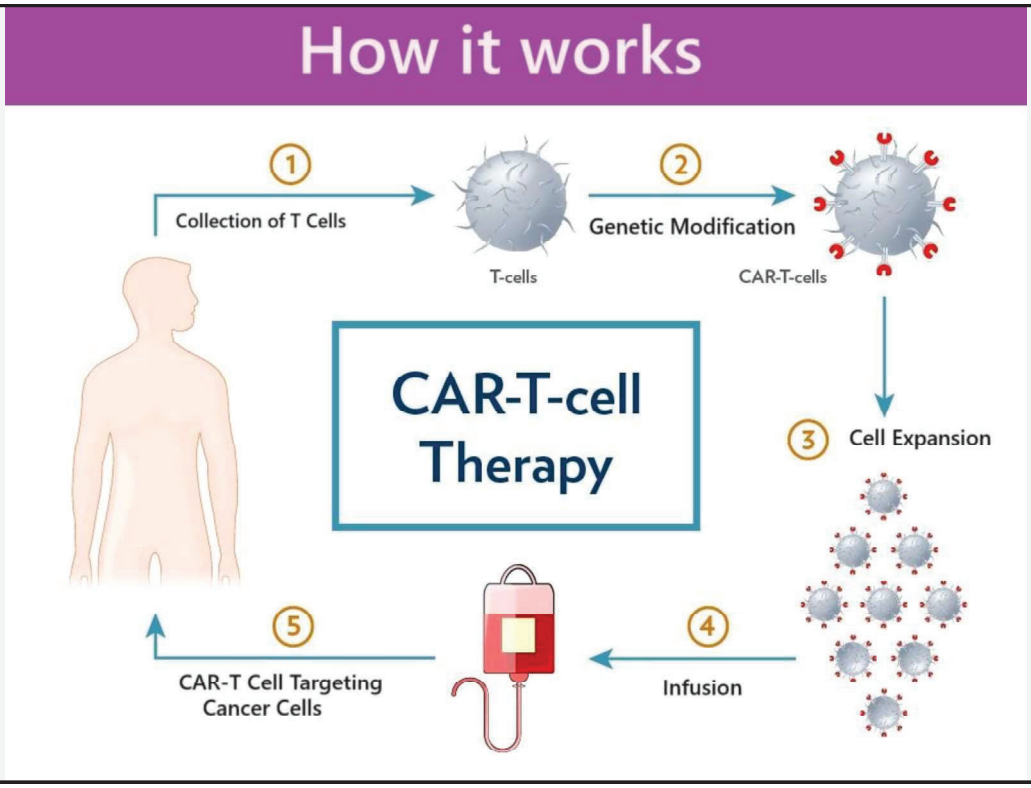

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TUMOR INFILTRATING LYMPHOCYTE (TIL) THERAPY

- **Treats:** Metastatic Melanoma (only current FDA approved indication, but many others are currently being studied)
- **Process:**
  1. Pretesting (including PET or CT scan to determine best site for tumor extraction
  2. Tumor Harvest (done in OR with surgical oncology)
  3. Manufacturing (typically 4-6 weeks)
  4. Conditioning chemo (chemotherapy given prior to TIL infusion)
  5. Infusion (TIL product given via central line)
- **Goal:** Increase the number of tumor infiltrating lymphocytes so they can fight the tumor more effectively

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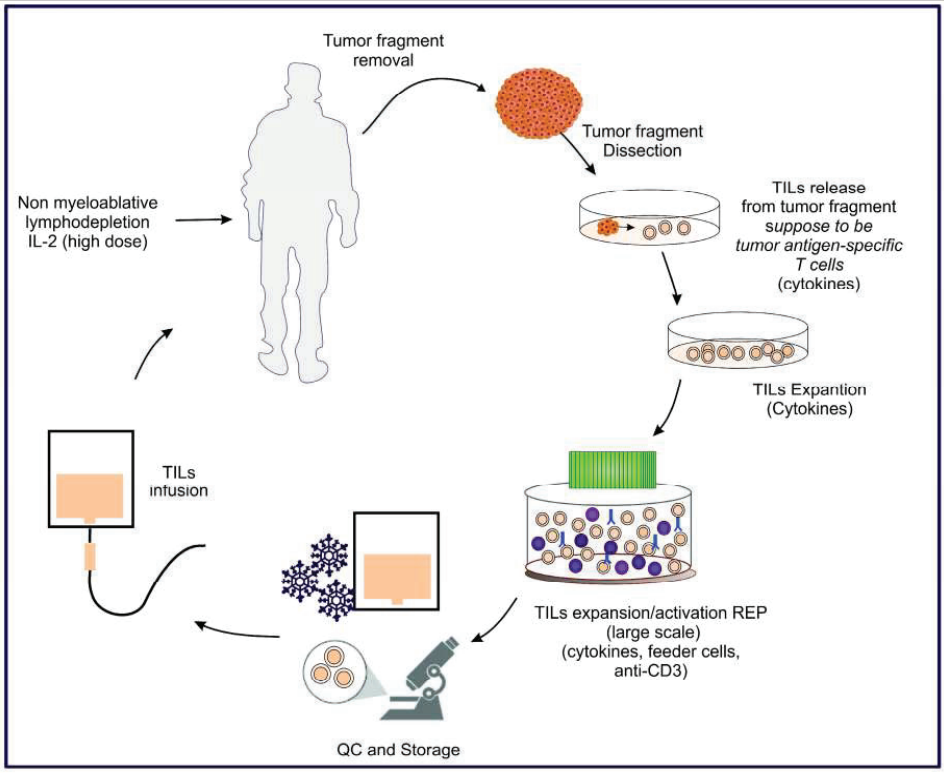

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STEM CELL TRANSPLANT GRAFT SOURCES

- Peripheral Blood (preferred)
- Bone Marrow
- Umbilical Cord Blood

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PERIPHERAL BLOOD

- Stem cells are mobilized from the bone marrow to the peripheral blood utilizing Granulocyte Colony-Stimulating Growth Factor (Neulasta/Neupogen/biosimilars) and, in some cases, chemotherapy
  - Outpatient procedure for donor called “apheresis”
  - Well tolerated procedure
  - No need for anesthesia/OR procedure
  - Preferred due to faster engraftment of ANC and platelets

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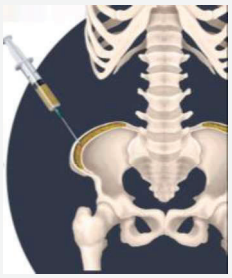
BONE MARROW

- Bone marrow collection/harvest was the only source of stem cells before the introduction of growth factors
- Donor given general anesthesia for OR procedure
- Normal for donor to experience discomfort at site for 48-72 hours after the procedure but usually well tolerated
- Collection is completed in 1-2 hours
- Risk for infections, bleeding, pain
- Longer duration until engraftment



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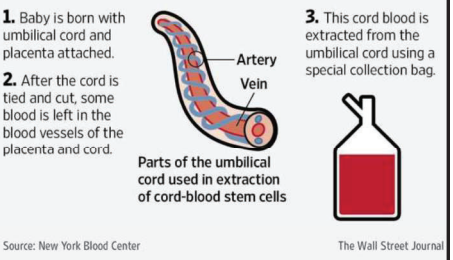
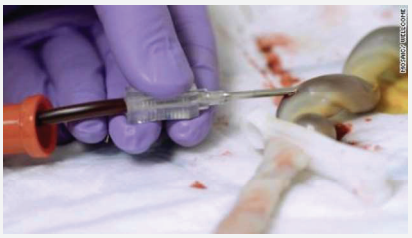
UMBILICAL CORD
(NOT TYPICALLY UTILIZED WITHIN OUR PROGRAM)

- Benefits
  - Quick & easy access
  - No harm to donor (mother/baby)
- Drawbacks
  - Limited number of cells in each cord- a large recipient would require multiple cords
  - Cannot request additional cells
  - Slower engraftment than peripheral blood or bone marrow
  - Increased risk for infections





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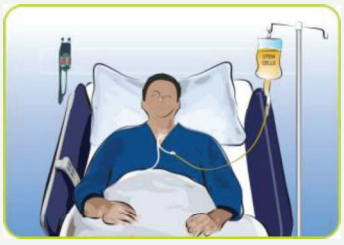
AUTOLOGOUS STEM CELL TRANSPLANT

- **Treats:** Myeloma, Lymphoma, and Amyloidosis
- **Process:**
  1. Pretesting
  2. Growth factor administration, possibly chemotherapy mobilization
  3. Apheresis (stem cell collection- done outpatient)
  4. Conditioning chemo (high-dose chemo- given inpatient prior to transplant)
  5. Transplant (cells administered via central line, no pump used- flows with gravity)
- **Goal:** rescue the bone marrow after it has been destroyed by the high-dose chemotherapy given prior to transplant



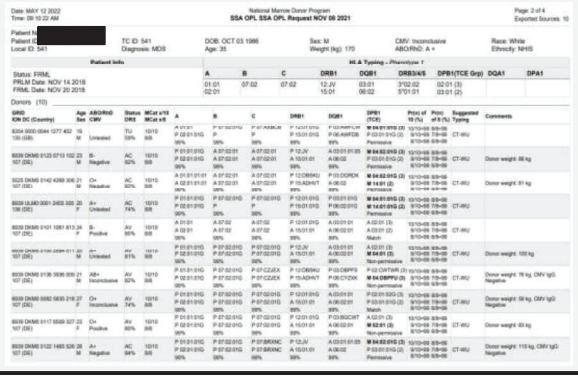
18

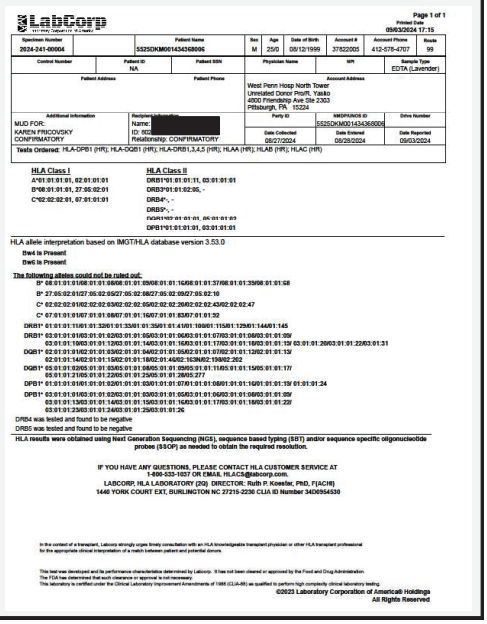
ALLOGENEIC STEM CELL TRANSPLANT

- **Treats:** leukemia, myelodysplastic syndromes and myeloproliferative neoplasms
- **Process:**
  1 Find a donor (buccal swabs for children/siblings, search the NMDP)
  2 Pretesting for patient & lab work/physical for donor
  3 Donor receives growth factor (typically Neupogen) & undergoes apheresis
  4 Patient admitted for chemotherapy
  5 Donor's healthy stem cells are infused into patient
- **Goal:** chemo given to irradicate cancerous cells from marrow, then the healthy stem cells from donor are infused to take over

ALLOGENEIC DONOR SEARCH

- HLA Typing
  - Human Leukocyte Antigen
    - Inherit two sets- one from mom & one from dad
    - Siblings have 25% chance of being a full match, unrelated potential donors with similar ethnic backgrounds/ancestry have greater chances of being a full match




LabCorp

Page 1 of 1
Printed Date
05/03/2024 17:15

Specimen Number	Patient Name	Sex	Age	Date of Birth	Account #	Account Phone	Route
2024-241-00004	5525DKM0014343G8006	M	25/0	08/12/1999	37822005	412-576-4707	99

Control Number	Patient ID	Patient SSN	Physician Name	NPI	Sample Type
	NA				EDTA (Lavender)

Patient Address: Patient Phone:

Account Address: West Penn Hosp North Tower, Unrelated Donor Prog/ft, Yasko, 4800 Friendship Ave Ste 2303, Pittsburgh, PA 15224

Additional Information: MUD FOR: KAREN FRICOVSKY CONFIRMATORY

Recipient Identifier: Name: [redacted] ID: 002 Relationship: CONFIRMATORY

Party ID: 5525DKM0014343G8006 | MMDP/DKMS ID: | Drive Number:

Date Collected: 05/27/2024 | Date Entered: 05/28/2024 | Date Reported: 05/03/2024

Tests Ordered: HLA-DPB1 (HR); HLA-DQB1 (HR); HLA-DRB1,3,4,5 (HR); HLA (HR); HLAB (HR); HLAC (HR)

HLA Class I
A*01:01:01:01, 02:01:01:01
B*08:01:01:01, 27:05:02:01
C*02:02:02:01, 07:01:01:01

HLA Class II
DRB1*01:01:01:11, 03:01:01:01
DRB3*01:01:02:05, -
DRB4*, -
DRB5*, -
DPB1*01:01:01:01, 03:01:01:01

HLA allele interpretation based on IMGT/HLA database version 3.53.0

Swi is Present
Swc is Present

The following alleles could not be ruled out:

B* 08:01:01:01/08:01:01:08/08:01:01:05/08:01:01:14/08:01:01:37/08:01:01:23/08:01:01:58
B* 27:05:02:01/27:05:02:03/27:05:02:08/27:05:02:09/27:05:02:10
C* 02:02:02:01/02:02:02:03/02:02:02:05/02:02:02:26/02:02:02:43/02:02:02:47
C* 07:01:01:01/07:01:01:08/07:01:01:16/07:01:01:83/07:01:01:32
DRB1* 01:01:01:11/01:01:33/01:01:33/01:01:35/01:01:41/01:10/01:11/01:12/01:14/01:145
DRB3* 03:01:01:01/02:01:01:02/03:01:01:05/03:01:01:06/03:01:01:07/02:01:01:08/03:01:01:09/03:01:01:10/03:01:01:12/03:01:01:14/03:01:01:16/03:01:01:17/02:01:01:18/03:01:01:13/ 03:01:01:20/03:01:01:22/03:01:01:31
DQB1* 02:01:01:01/02:01:01:03/02:01:01:04/02:01:01:05/02:01:01:07/02:01:01:12/02:01:01:13/ 02:01:01:14/02:01:01:15/02:01:01:18/02:01:01:40/02:163/M02:19/02:202
DQB1* 05:01:01:02/05:01:01:03/05:01:01:08/05:01:01:01/05:01:01:11/05:01:01:15/05:01:01:17/ 05:01:01:21/05:01:01:22/05:01:01:25/05:01:01:28/05:277
DPB1* 01:01:01:01/01:01:01:02/01:01:01:03/01:01:01:07/01:01:01:08/01:01:01:14/01:01:01:13/ 01:01:01:24
DPB1* 03:01:01:01/03:01:01:02/03:01:01:03/03:01:01:05/03:01:01:06/03:01:01:07/03:01:01:09/ 03:01:01:13/03:01:01:14/03:01:01:15/03:01:01:17/03:01:01:19/02:01:01:22/ 03:01:01:23/03:01:01:24/03:01:01:25/03:01:01:26
DRB4 was tested and found to be negative
DRB5 was tested and found to be negative

HLA results were obtained using Next Generation Sequencing (NGS), sequence based typing (SBT) and/or sequence specific oligonucleotide probes (SSOP) as needed to obtain the required resolution.

IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT HLA CUSTOMER SERVICE AT 1-800-533-1037 OR EMAIL HLACS@labcorp.com.
LABCORP, HLA LABORATORY (2G) DIRECTOR: Ruth P. Koesler, PhD, F(ACHI)
1440 YORK COURT EXT, BURLINGTON NC 27215-2230 CLIA ID Number 34D0954530

In the context of a transplant, Labcorp strongly urges timely consultation with an HLA knowledgeable transplant physician or other HLA transplant professional for the appropriate clinical interpretation of a match between patient and potential donors.

This test was developed and its performance characteristics determined by Labcorp. It has not been cleared or approved by the Food and Drug Administration. The FDA has determined that such clearance or approval is not necessary. This laboratory is certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA-88) as qualified to perform high complexity clinical laboratory testing.

POST TRANSPLANT VACCINATION SCHEDULE

CELL TRANSPLANTATION PROGRAM
ALLEGHENY HEALTH NETWORK
TOOL - VACCINATION SCHEDULE FOR IEC AND HSCT RECIPIENTS

VACCINE	TIME AFTER HEMATOPOIETIC STEM CELL TRANSPLANTATION		
	6 months	9 months	12 months
INACTIVATED VACCINES			
Diphtheria, Tetanus, Pertussis	Tdap-1	Tdap-2	Tdap-3
Inactivated Polio	IPV-1	IPV-2	IPV-3
13-valent Pneumococcal Conjugate (PCV13)	PCV13-1	PCV13-2	PCV13-3
Haemophilus Influenza type B conjugate	Hib-1	Hib-2	Hib-3
Hepatitis B	Hep B-1	Hep B-2	Hep B-3
Inactivated Influenza	Annually every fall, commencing 6 months after transplant		
Meningococcal vaccine	Recommended for patients at risk – 2 doses 5 years apart		
LIVE VACCINES and PPSV23	**24 months**		
Measles – Mumps – Rubella	Only to be administered to recipients without active GVHD and ≥ 1 year off all immunosuppressive therapy and ≥ 8 months out from any prior IVIG dose. Live vaccines to be administered no sooner than 24 months after transplant. *Second dose of Varicella vaccine is needed > 1 month after the first		
Varicella*			
23-valent Pneumococcal Conjugate (PPSV23)	For recipients off immunosuppression without active chronic GVHD administer PPSV23. For patients with active chronic GVHD consider giving a 4th dose of PCV13 instead of PPSV23.		
		Source: Centers for Disease Control	

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INTERESTED IN JOINING THE NMDP REGISTRY?

Ages 18-40

Step 1- Join online

Step 2- Buccal swab kit will get sent to your house

Step 3- Send it back & see if you're a match!

Scan QR code below or visit:

www.nmdp.org/get-involved/join-the-registry

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THANK YOU!

Please feel free to email us if you'd like to sit in on an intake and/or learn more about cellular therapy. ☺

ashley.button@ahn.org

candace.scanga@ahn.org

Allegheny Health Network

Clinical Research Overview

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OBJECTIVES

- Define “clinical trial”
- Review AHN clinical research activity
- Explore a brief history of clinical trials
- Examine the phases and components of clinical trials
- Discuss the conduct of clinical research at AHN

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What is a Clinical Trial?

The NIH defines a clinical trial as a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes

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What is a Clinical Trial?

- Clinical trials explore new approaches for <u>preventing</u>, <u>detecting</u> or <u>treating</u> disease, and may include:
  - New investigational drugs or new combinations of drugs
  - New medical devices, or new surgical or radiation procedures
  - New uses for existing therapies
  - Investigations into better prevention, diagnostic or screening methods
  - New behavioral methods (e.g. diet, physical activity, cognitive therapy) for improving health, or quality of life for those with acute or chronic illnesses
- Clinical trials determine whether these new interventions are <u>safe</u> and <u>effective</u>

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Clinical Trials: Why Do We Participate?

- To gain access to innovative and cutting edge therapies and technologies before they are widely available
- To participate in the advancement of the standard of care
- To contribute to the academic body of knowledge
- To attract new physicians and patients seeking access to clinical trials

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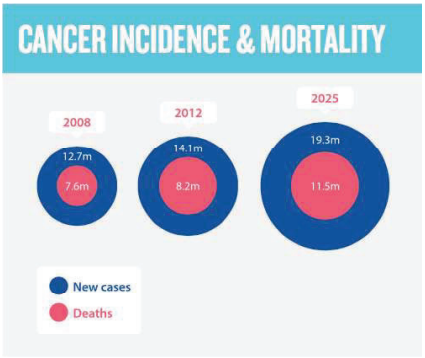
Why the Focus on Oncology?

Cancer is the second leading cause of death worldwide, with ~10 million fatalities each year
Globally, this is 1 in 6 deaths attributed to cancer
In 2024, just in the US, there are an estimated 2,002,000 new cancer cases and ~612,000 cancer deaths



**World Health Organization and American Cancer Society*

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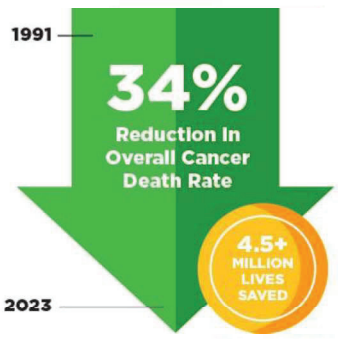
THE 2024 AACR CANCER PROGRESS REPORT



Between July 1, 2023, And June 30, 2024, FDA Approved:

- 15 **New anticancer therapeutics**, which are now benefiting patients with various types of cancer
- 15 **Previously approved anticancer therapeutics** for treating new types of cancer
- 1 **New imaging agent**
- 2 **Minimally invasive tests** for assessing inherited cancer risk or for early detection of cancer
- AI **Several artificial intelligence (AI)-based tools** to improve early detection and diagnosis of cancers

This steady progress is due to fewer people smoking, earlier detection for many types of cancer, and improved cancer treatments

Information discovered by conducting CLINICAL TRIALS

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https://cancerprogressreport.aacr.org/progress

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AHN CLINICAL TRIALS OVERVIEW

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AHN Clinical Research Activity

- The AHN Research Institute employs more than 200+ staff members
  - Oncology, CVI, Neurology, Surgery, Women's Health, Radiology etc.
  - 50 Clinical Research Coordinators and/or Research Nurses
- We offer new drug therapies, revolutionize surgical procedures, and offer innovative devices and wearable technology reducing the impact of chronic disease
- We partner with industry, government, academia, and health systems across the region to work toward one common goal:
  Develop the next "best practice" in medicine

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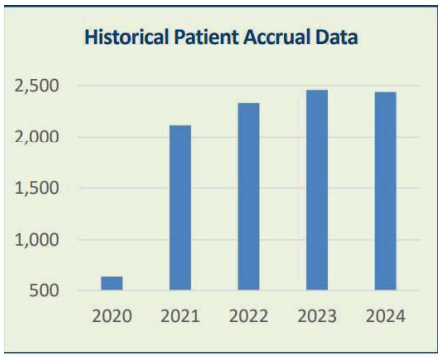
2024 Clinical Research Activity

- AHNRI offered 825 total clinical trials
- A total of 2439 Patient were recruited to trials
  - Non-interventional: 1223
  - Interventional: 1216

This number does not include the Moonshot Protocol



**2020 clinical trial activity and patient accruals were down due to COVID-19.*

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MOONSHOT

- AHN's Oncology Patient Biobank and Data Repository (MOONSHOT)
- Launched in 2020, under the direction of Dr. David Bartlett
- The purpose of this biobank and data repository is to maintain specimens and data for ongoing research of cancer and other disease conditions and to learn more about their causes and how to better treat patients
- Initially aimed to enroll 10,000 patients with [or likely] to have cancer treated at AHN that are 18-100 years old
  - Increased enrollment goal to 15,000 as of August 2025
  - **As of December 2025: 10,600 patients have been enrolled**
- Blood samples are collected across all AHN Cancer Institutes and some affiliated sites in Pennsylvania and stored within laboratory facilities across AHN
- Tissue will be acquired from any of the participants having qualified procedures at an AHN or AHN-affiliated Hospital

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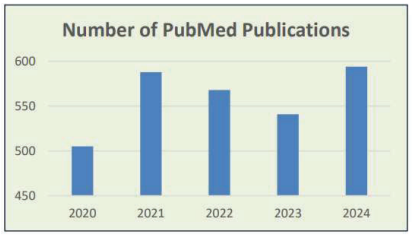
2024 CLINICAL RESEARCH ACTIVITY

- AHNRI investigators contributed to 594 PubMed-indexed publications
- AHNRI Office of Grants and Contracts assisted with 78 grant submissions that total more than $200 million
- AHNRI investigators were awarded nearly $12 million across 49 grants



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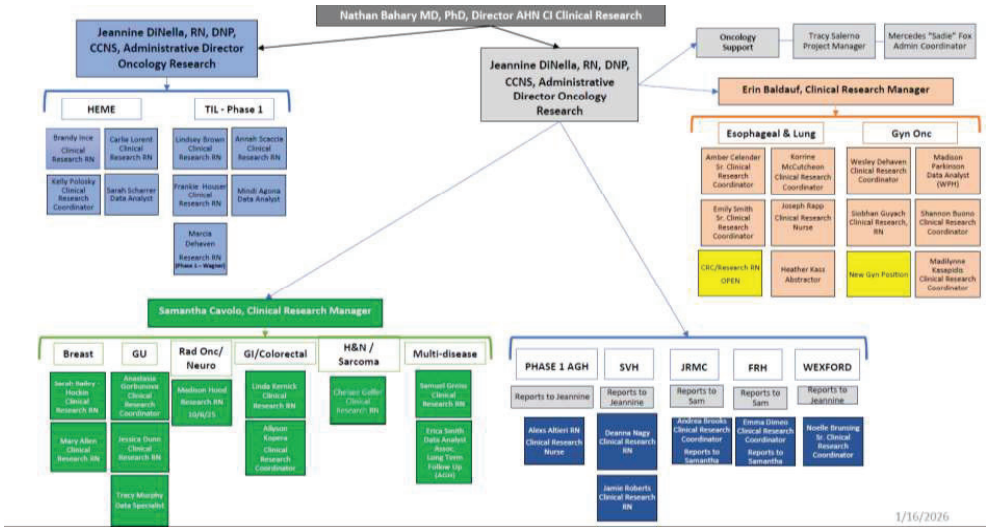
AHN Cancer Institute Research Organization



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Phase 1 Program

At Allegheny General Hospital

- Led by Medical Oncologist Dr. Ariel Lopez-Chavez
- The AHNCI's Precision Medicine and Developmental Therapeutics Clinic focuses on serving adults with metastatic solid tumors, and patients who may need second opinions or are seeking novel treatment options for rare, complex, or advanced-stage cancers
- Precision oncology focuses on matching the most effective and tailored cancer therapies to the individual cancer patient, based on the patient's unique profile, as well as genetic information from the cancer's molecular signatures
- TEMPUS TIME Program

At West Penn Hospital

- Introduced by Medical Oncologist Dr. Samhouri; continued efforts by Dr. Curley and Dr. Wagner
- Notable achievements with CAR T-cell therapy and TILs program
- CAR T-cell therapy involves taking blood from a patient and isolating the T-cells (disease-fighting immune cells). The patient's T-cells are then reengineered into "fighter" cells using a special machine on-site that reduces fighter cell production time. Having this technology on-site also means the fighter cells never have to be frozen before being infused back into the patient.
- TILs (tumor-infiltrating lymphocytes) are different than CAR T cells because they do not need to be genetically modified. The TILs process begins with a tumor biopsy, that biopsy is then taken to a clinical laboratory where the TILs are isolated, and then those TILs are infused, just like other cell therapy procedures, and then they begin their work to fight cancer

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THE HISTORY OF CLINICAL TRIALS

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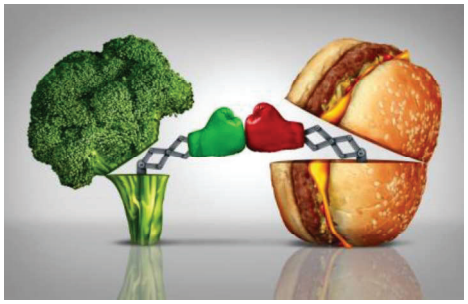
HISTORY OF CLINICAL TRIALS

The First Clinical Trial (562 BC)

- The world's first clinical trial is recorded in the "Book of Daniel" in The Bible
- Conducted by King Nebuchadnezzar, a resourceful military leader → Not a doctor
- During his rule in Babylon, Nebuchadnezzar ordered his people to eat only meat
- Several young men of royal blood, preferred to eat vegetables
- The king allowed these "rebels" to follow a diet of legumes and water — but only for 10 days



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History of Clinical Trials

The First Clinical Trial (562 BC)

- When Nebuchadnezzar's experiment ended, the vegetarians appeared better nourished than the meat-eaters, so the king permitted the legume lovers to continue their diet
- This was the one of the first times in evolution of human species that an open uncontrolled human experiment guided a decision about public health

Bhatt, Arun. "Evolution of clinical research: a history before and beyond james lind." *Perspectives in clinical research* vol. 1,1 (2010): 6-10.

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History of Clinical Trials

1747: James Lind and Scurvy Trial

- James Lind is considered the first physician to have conducted a controlled clinical trial of the modern era
- Dr. Lind (1716-94), while working as a surgeon on a ship, was appalled by the high mortality of scurvy amongst the sailors
- He planned a comparative trial of the most promising cure for scurvy

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History of Clinical Trials

1747: James Lind and Scurvy Trial

- He divided twelve sailors into six groups of two
- Each group all received the same diet plus:
  - Group 1 was given a quart of cider daily
  - Group 2 twenty-five drops of elixir of vitriol (sulfuric acid)
  - Group 3 three six spoonfuls of vinegar
  - Group 4 four half a pint of seawater
  - Group 5 received two oranges and one lemon
  - Group 6 a spicy paste plus a drink of barley water

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History of Clinical Trials

1747: James Lind and Scurvy Trial

- The treatment of group five stopped after six days when they ran out of fruit, but by that time one sailor was fit for duty while the other had almost recovered
- Apart from that, only group one also showed some effect of its treatment
- In 1753, he published *A treatise of the scurvy*
  (Which was virtually ignored)

  - Clinical Trials Day is celebrated annually on May 20, which commemorates the anniversary of James Lind's study

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History of Clinical Trials

The Syphilis Study at Tuskegee (1932-1972)

- Conducted by the US Public Health Service in Tuskegee, AL over a 40-year period to record the natural history of untreated syphilis
- Involved ~600 African-American men: ~400 with syphilis (cases) and ~200 without syphilis (controls)
- Subjects were recruited without informed consent and told that the medical procedures were special free treatments for "bad blood"
- In 1947, Penicillin was found to be effective in the treatment of syphilis but the study continued on until 1972, and the men were never provided with the known effective treatment

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History of Clinical Trials

The Syphilis Study at Tuskegee - Outcome

- By the end of the study, 28 had died from syphilis, 100 had died from related diseases, and 40 wives and 19 children had become infected with syphilis
- Public outrage led to a $10 million settlement for living participants and family members, and the passing of the National Research Act of 1974, which created The National Commission for the Protection of Human Subjects in Biomedical and Behavioral Research

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History of Clinical Trials

Nazi Medical War Crimes (1939-1945)

- "Medical experiments" were performed on thousands of concentration camp prisoners, and included procedures like exposure to deadly toxins to test antidotes, forms of torture to study effective treatments for the German military, and surgeries and transplants conducted without anesthesia
- From 1946-1949, the Nuremberg Trials tried Nazi officials for war crimes, including the Doctors Trial that indicted 23 Nazis for their willing participation in the systematic torture, mutilation, and murder of prisoners in experiments

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History of Clinical Trials

Nazi Medical War Crimes - Outcome

- The actions of the defendants were condemned as crimes against humanity
  - Corrupted the ethics of the medical and scientific professions
  - Repeatedly and deliberately violated the rights of the subjects
- 9 were imprisoned, 7 were sentenced to death
- The Nuremburg Code was developed in 1947, outlining 10 principles for ethical human experimentation, and later serving as the model for the 1964 Declaration of Helsinki

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HISTORY OF CLINICAL TRIALS

Nuremberg Code Principles *(summarized)*

1. Voluntary informed consent is essential.

2. Research should yield beneficial results for the good of society.

3. Research should be based on results of animal experimentation.

4. Avoid all unnecessary physical and mental suffering and injury.

5. No research should be conducted if there is reason to believe death or disabling injury will occur.

6. The risks should never exceed the anticipated benefits.

7. Proper preparations and adequate facilities should be provided to prevent possibilities of injury, disability, or death.

8. Research should be conducted only by scientifically qualified persons.

9. Subjects can withdraw from the research at any time.

10. Researchers must be able to terminate the study if there is a probable cause to believe that continuation of the experiment will cause injury, disability, or death.

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HISTORY OF CLINICAL TRIALS

Declaration of Helsinki - 1964

- Developed by the World Medical Association using the principles of the Nuremberg Code
- First generally accepted code of conduct governing the ethics of human research - *It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those involved in medical research*
- Outlines general principles for: Weighing risks and benefits; involving vulnerable groups; scientific requirements and protocols; ethics committees; privacy and confidentiality; informed consent; dissemination of results

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HUMAN RESEARCH REGULATION TODAY

FDA	Food and Drug Administration (USA)
EMA	European Medicines Agency
OHRP	Office of Human Research Protection
NCI	National Cancer Institute
IRB	Institutional Review Boards
CFR	Code of Federal Regulations

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THE TYPES AND PHASES OF CLINICAL TRIALS

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TYPES OF CLINICAL TRIALS

- Feasibility studies
  - They aim to find out things such as whether patients and doctors are happy to take part and how long it might take to collect and analyze the information
- Pilot studies
  - Small scale versions of the main study to help test that all the main parts of the study work together
- Prevention trials and Screening trials
  - Can be for the general population OR can be for a group of people who have a higher than normal risk of developing a certain disease
    - Example: Testing people for the early signs of cancer before they have any symptoms
- Treatment Trials
  - Performed in stages, called phases
- Multi-arm multi-stage (MAMS) trials
- Cross sectional studies
- Compassionate Use/Single Patient Exemption Trials
  - Single patient use of an unapproved but efficacious drug
  - Access to a new agent when a patient may not be eligible for a clinical trial using that agent

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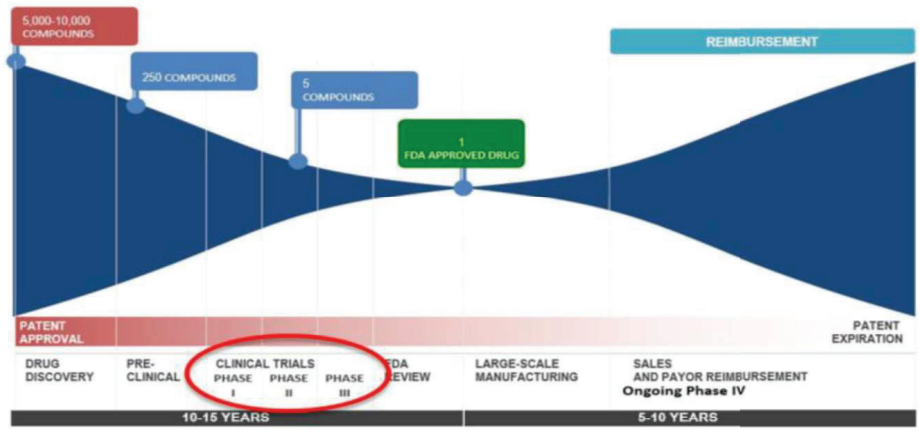
THE CLINICAL TRIAL PROCESS



Source: FDA

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PHASE I TRIALS

Objectives:

- Study drug metabolism and mechanism of action in humans
- Establish safe dosages of new drugs in humans (MTD)
- Assess a drug's effects in humans and establish the toxicity profile

❖ Small groups of participants (~15-30), often given investigational drugs in a dose-escalation fashion

❖ **Primary Focus: Safety**

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PHASE II TRIALS

Objectives:

- To evaluate the efficacy of a new drug for a particular indication
- Study the common short-term side effects

❖ Used in medium-sized groups of participants with the targeted disease (no more than a few hundred)

❖ Well controlled and closely monitored

❖ **Primary Focus: Efficacy and Side Effects (Safety)**

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PHASE III TRIALS

Objectives:

- Testing of a new drug against the current standard of care treatment
- Performed in a randomized setting

❖ Last phase of drug development prior to approval

❖ Used in large populations with the targeted disease (100s to 1000s of participants)

❖ **Primary Focus: Prove enhanced efficacy and/or safety over the current standard**

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PHASE IV TRIALS

POST-MARKETING SURVEILLANCE TRIALS

Objectives:

- Assess the long-term or rare side effects of a new treatment approved by the FDA (may be a condition of approval)
- Monitor long-term effectiveness or impact on QOL
- Compare newly approved drug to other marketed products, including cost-effectiveness

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Alternative Trials

Compassionate Use/ Single Patient Exemption Trials

Objectives:

- Single patient use of an unapproved but efficacious drug
- Access to a new agent when a patient may not be eligible for a clinical trial using that agent

Expanded Access Trials

Objectives:

- Treatment study that allows patients to receive a new therapy during the FDA submission process
- Collects additional data on efficacy and safety

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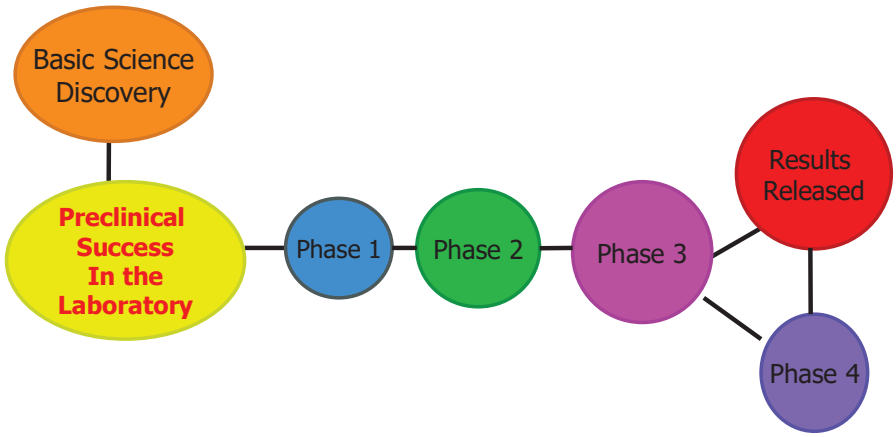
Visualizing the Phases



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THE CLINICAL TRIAL PROTOCOL

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THE CLINICAL TRIAL PROTOCOL

- Every clinical investigation begins with the development of a clinical protocol
- The protocol is a document that describes how a clinical trial will be conducted and ensures the safety of the trial subjects and integrity of the data collected

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THE CLINICAL TRIAL PROTOCOL

- **Objectives & Endpoints**

  Study Endpoints – Measureable outcomes that will answer the questions posed by a trial

  Endpoints to evaluate a cancer therapy's effectiveness may include:

  - Tumor response rate
  - Disease-free or Progression-free survival (PFS)
  - Overall survival (OS)

- **Background Information**
  - Prior non-clinical and clinical findings
  - Known potential risks and benefits
  - Justification for dosage, regimen, route of administration and treatment duration

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THE CLINICAL TRIAL PROTOCOL

- **Study Population**
  - Eligibility Criteria (Inclusion/Exclusion Criteria)
  - Withdrawal and replacement of subjects
- **Treatment of Subjects**
  - Drug dosing, route and schedule
  - Treatment and follow-up periods
  - Schedule of Events (screening, efficacy, safety procedures)
  - Dose modification and discontinuation guidelines
  - Methods for monitoring subject compliance
  - Statistical methods and data reporting, including safety events

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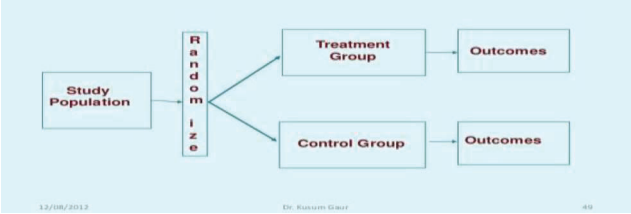
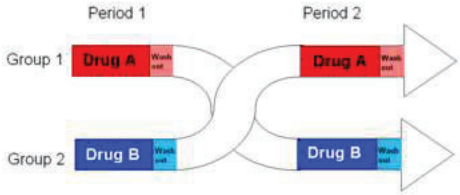
THE CLINICAL TRIAL PROTOCOL

- **Study Design**

PARALLEL



CROSSOVER



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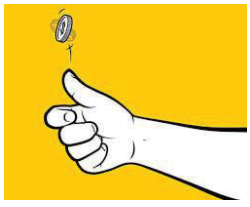
THE CLINICAL TRIAL PROTOCOL

- **Randomization**
  - Randomization is a process by which each participant has the same chance of being assigned to either intervention or control.
    - Example would be the toss of a coin, in which heads indicates intervention group and tails indicates control group
  - Neither trial participant nor investigator should know what the assignment will be before the participant's decision to enter the study.



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AHN
CLINICAL TRIAL PROCESS & REQUIREMENTS

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CLINICAL TRIALS TEAM MEMBERS

- Site Principal Investigator
- Associate and Sub-Investigators
- Study Coordinator/Research Nurse
- Regulatory Coordinator
- Data Manager
- Clinical Trial/IDS Pharmacist

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CLINICAL RESEARCH OVERSIGHT

Institutions are required to review research activities in order to protect the rights, safety and well-being of human subjects

Institutional Review Boards approve, require modifications, or disapprove all research before it may begin

- Oversee the informed consent process
- Monitor protocol deviations and safety hazards to subjects
- Report any issues to the appropriate regulatory agencies (FDA)
- Conduct continuing review of all research activities, at least annually

Institutional Biosafety Committees must review and approval all clinical trial research involving potentially hazardous biological agents before the trials can be initiated

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Clinical Trial Participation at AHN – Research Compliance

- Completion of Human Subject and GCP Training
  - NIH Human Subject Training
  - CITI Training Modules (Collaborative Institutional Training Initiative)
- Conflict of Interest Training & Registration
- Informed Consent Training
- Current Curriculum Vitae (signed & dated)
- Study-Specific Trainings
  - Addition to the Delegation of Authority Log
  - Addition to the Key Study Personnel form
  - Approval by sponsor and regulatory bodies

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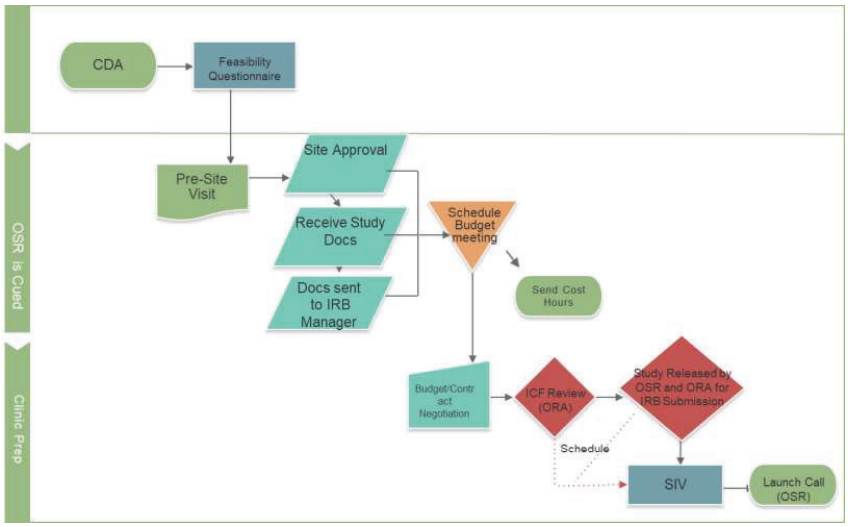
CLINICAL TRIAL IMPLEMENTATION



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CLINICAL TRIAL IMPLEMENTATION

- Clinical trial agreement is executed
- Site feasibility and a qualification visit are completed
- Office of Sponsored Research finalizes contract and budget negotiations with the Sponsor
- AHN IRB or a Centralized IRB approves the protocol, Informed Consent form and other required documents
- In-services and trainings with involved staff are implemented and documented
- Trial is opened to accrual

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Steps to Enrolling on a Clinical Trial

- Pre-Screening
- Informed Consent
- Screening
  - Registration/Randomization
- Treatment
- Follow up

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Pre-Screening

- Mechanism to identify, screen and/or recruit potential subjects prior to obtaining informed consent
- Contains no more than minimal harm or risk
- Request to perform pre-screening activities must first be approved by the IRB and must outline how the potential subjects' information will be accessed, utilized and protected

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INFORMED CONSENT

- Requirement established by the enactment of the National Research Act of 1974 in response to ethical concerns
- A mandatory and basic fundamental right of all subjects
- Title 45 – Code of Federal Regulations dictates the required elements to ensure adequate explanation in an understandable language, enforced by the IRB

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INFORMED CONSENT

BASIC REQUIRED ELEMENTS

- Explanation of the research involved
- Reasonably expected risks or benefits
- Disclosure of treatment alternatives
- Extent that confidentiality will be maintained
- Compensation in event of injury
- Contact info for questions regarding subject rights or a research-related injury
- Participation is voluntary

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INFORMED CONSENT

- An investigator may not involve a person in research without obtaining legally effective informed consent
- Must be signed and dated by the subject [or legally authorized representative] and consenting investigator, and a copy provided
- Must be obtained prior to any research procedures

**Exceptions may occur in emergent situations*

A study published in the Journal of Pharmacy & Pharmacognosy Research found that failure to obtain proper informed consent was the most common issue raised by FDA inspectors when inspecting clinical research organizations (published January 2024)

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SCREENING

Confirmation that subjects meet EVERY Eligibility Criteria for study entry by:

- Conducting all required tests (Imaging, Labs, Cardiology tests, Biopsies, etc) and ensuring results meet the protocol criteria
- Proper documentation in medical records to support diagnosis, current disease status, prior therapies, co-morbidities, performance status, etc

Eligible subjects are then enrolled into the trial and assigned a treatment

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Treatment and Follow-Up

The research protocol dictates an exact treatment plan

- Strict treatment and assessment structure to ensure all participants receive comparable care and are evaluable
- Response evaluations with requisite assessment criteria (such as RECIST for solid tumors)
- Toxicity (Adverse Event) evaluations and management

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Toxicities / Adverse Events

- *Adverse Event: Any untoward medical occurrence that develops or worsens during the course of a study, regardless of relationship to drug*
- Common Terminology Criteria for Adverse Events (CTCAE)
  - Nationally recognized grading system developed by the US Department of Health and Human Services
  - Provides consistent terminology and Grades of severity (1-5) throughout the research community
- Treatment modification or discontinuation is based upon evaluation and grading of side effects

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RESEARCH DATA DOCUMENTATION

- Accurate and thorough documentation is critical for collecting and reporting research data
- Good documentation demonstrates compliance to (or deviation from) the protocol treatment plan
- *Source documents* verify the validity of the reported data
  - Included but not limited to: MD/RN notes, medication records, test results (labs, scans, EKGs), pathology reports, and operative notes

- GCP mandates:
  Correct errors with a single line, initials and date
  NEVER use white out

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IMPLICATIONS OF NON-COMPLIANCE

- Patient risk and/or injury
- Audits resulting in suspension of research activity
- Reduced access to new clinical research due to previous unfavorable experiences
- Non-payment
- Litigation against the Investigator, Institution, etc.

Deviations from the protocol must be reported!

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AHN Data Safety Monitoring Committee

- Committee of clinical research experts who monitor the progress of a clinical trial and review patient safety and efficacy data
- Duties of the DSMC:
  - Review details of all internal SAEs and unanticipated events (such as protocol deviations) to monitor patient safety and study compliance
    - Monitor frequency and severity of adverse events
    - Obtain consensus regarding attribution to drug, risk to patient
    - Submit recommendations for corrective action to study PI, if necessary
  - Review significant errors or potential misconduct by any trial investigators or their research staff
  - Recommend continuation or termination of a study if changes to the anticipated risk/benefit ratio occur

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Final Thoughts and Conclusions

- If you have a patient interested in clinical trials, please refer them to the disease site research nurses & coordinators
- Also please be sure to let the research staff know if you need to schedule or change a protocol patient's appointment!
  (This may affect protocol compliance and/or coverage for that visit)

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FINAL THOUGHTS AND CONCLUSIONS

- Adhering to the clinical trial protocol is critical for ensuring the success of the trial, the validity and credibility of the results, and the protection of the subjects
- Clinical Research Trials are essential to promoting cutting edge treatments and patient care in our institutions
- **Clinical Research is a team effort and we are <u>all</u> part of the team!**

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ACCESSING CURRENT CLINICAL TRIALS AT AHN

www.ahn.org

- For Professionals
  - Research
    - Active clinical trials
      - Search by keyword, category, or hospital

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HEMATOLOGICAL MALIGNANCIES

**** estimated 186,400 diagnosed with blood cancer (10%)***
**** estimated 57, 750 deaths from blood cancers***
**** every 3 minutes someone is diagnosed***
****every 9 minutes someone dies***

**Data specified for "blood cancer" include leukemia, lymphoma and myeloma, and do not include data for myelodysplastic syndromes (MDS) or myeloproliferative neoplasms (MPNs)*

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Disclosures

Dr Khan is on the Speaker's Bureau for the following companies:

AstraZeneca
BMS
Beigene
Lilly
Pfizer
Roche
AbbVie
Kite
ADC Therapeutics

2

Learning Outcomes

- Examine the pathophysiology, assessment, diagnosis, and treatment interventions of basic hematologic malignancies.

Estimated New Cases (%) of Leukemia, Lymphoma and Myeloma, 2023

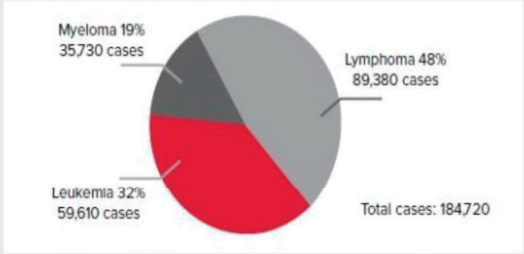


Figure 1. Source: *Cancer Facts & Figures 2023.* American Cancer Society; 2023.

5-Year Relative Survival Rates by Year of Diagnosis

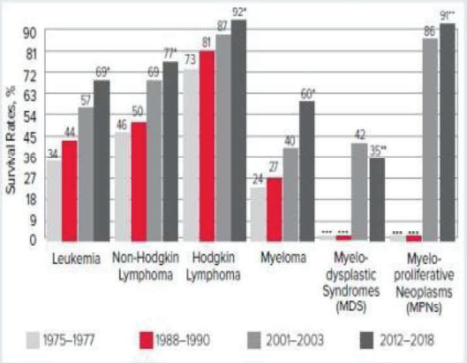


Figure 2. Source: Surveillance, Epidemiology, and End Results (SEER Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 8 Registries, Nov 2021 Sub (1975-2019) - Linked To County Attributes - Time Dependent (1990-2019) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2022, based on the November 2021 submission.

*The difference in rates between 1975-1977 and 2012-2018 is statistically significant ($P < .05$).

**The difference in rates between 2001-2003 and 2012-2018 is statistically significant ($P < .05$).

***Due to shorter reportability period, long-term survival statistics are not available.

Facts and Figures

LEUKEMIA	LYMPHOMA	MULTIPLE MYELOMA	MYELODYS-PLASTIC SYMDROME
• AML 20,380 new • 11,310 deaths • 32% 5 yr survival • ALL 6540 new • 1390 deaths • 71% 5 yr survival • CML 8930 new • 1310 deaths • 71% 5 yr survival • CLL 18,740 new • 4490 deaths • 88% 5 yr survival	• 89,380 new cases • 8,830 HL (900 deaths) • 159,867 HL in remission • 81, 560 NHL (20,180 deaths) • 702,631 NHL in remission	• 35,730 new cases • 157,561 in remission • 12,590 deaths	• 77,646 new cases • No death data at this time • 58,835 in remission • MDS not on SEER as cause of death

5

Physiology of Hematological System

- Hematopoiesis is process of blood cell formation
- Blood forming organs include bone marrow, liver, spleen
- Liver and spleen are primarily blood-forming organs in fetuses, but are capable of blood cell production in response to demand or disease processes in adults

- Normal bone marrow is essential to
  - Develop immunity
  - Maintain homeostasis
  - Transport hemoglobin, oxygen, carbon dioxide

6

Myeloproliferative Disorders/Neoplasm (MPNs)

- Abnormal proliferation of myeloid cells
  - **AML**
  - **MDS**
  - **CML**
  - **Myelofibrosis**
  - **Polycythemia Vera**
  - **Essential thrombocytosis**
  - Thrombocytopenia
  - Leukopenia - ↓ WBC's
  - Leukocytosis – increased WBCs > 10 x 10^9/L
  - Anemia
    - Iron deficiency
    - Hemolytic
    - Pernicious'
    - **Aplastic**
    - Anemia chronic disease

Lymphoproliferative Disorders

- Abnormal proliferations of lymphocytes
  - **CLL**
  - **ALL**
  - **Hairy cell leukemia**
  - **Lymphomas**
  - **Multiple Myeloma (MM)**
  - Autoimmune
    - lymphoproliferative syndrome (ALPS)
    - ITP
    - TTP

7

Diagnostic Tests - BM Biopsy

Aspirate

- Maturation
- Morphology
- Differential
- Iron staining

Biopsy

- Cellularity
  - (non-bony space with hematopoietic cells as opposed ot fat)
- Bone, vessels, stromal cells
- Infiltration pattern
- Megakaryocyte number

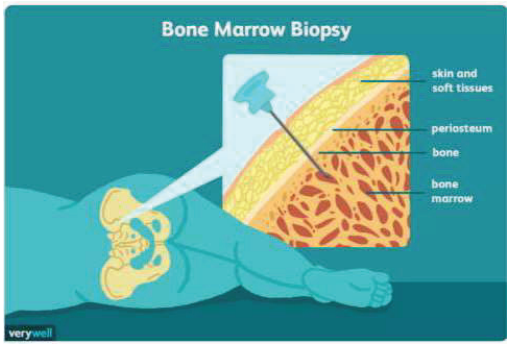
Hypocellular

- More fat than cells
- Aplastic anemia

Hypercellular

- 90% cellularity
- Dense and infiltrated
- MDS

https://www.google.com/search?q=bone+marrow+biopsy+piture&rlz=1C1GCEA_enUS952US952&source=lnms&tbm=isch&sa=X&ved=2ahUKEwjHnPL2k9DyAhVNEFkFHULnAJgQ_AUoAXoECAEQAw&biw=1280&bih=577#imgrc=EW75Bldb86VNlM



8

Types of Molecular Testing

- **Polymerase Chain Reaction (PCR)**
  - Analyzes DNA and RNA unique genetic codes and sequencing for 'red flags'
  - Technique used in molecular biology to **amplify** a single copy or a few copies of a selected segment of DNA genome across several orders of magnitude, generating thousands to millions of copies of a particular DNA sequence
  - 60% sensitivity – likelihood the test correctly identifies the disease as positive
  - 98% specificity – likelihood the test correctly identifies the disease as negative
    - Inversely related
      - A test with 95% sensitivity will correctly identify 95% of people with disease but incorrectly identifies 5% as negative
      - A test with 95% specificity will correctly identify 95% of people without the disease but incorrectly identifies 5% as positive

Advantages	Disadvantages
• More reliable and accurate • Amplification from a single copy of material • More sensitive and gold standard for detecting for measurable residual disease (MRD)	• Lengthy turnaround time (3-7 days) • Higher false positive rate • Only detects what's ordered for the test

https://www.google.com/search?q=PCR+you+tube+made+simple&safe=active&sca_esv=602485622&sxsrf=ACQVn09o7WIVgWZdGgHauH4NXzu49QP7mw%3A1706569440597&ei=4C64ZYT0I6us5NoPi9udiAM&ved=0ahUKEwiE5KnK2oOEAxUrFlkFHYttBzEQ4dUDCBA&uact=5&oq=PCR+you+tube+made+simple&gs_lp=Egxnd3Mtd2l6LXNlcnAaAhgDIhhQQ1IgeW91IHR1YmUgbWFkZSBzaW1wbGUyChAhGAoYoAEYiwMyChAhGAoYoAEYiwMyCBAhGKsCGIsDMggQIRirAhiLA0i8M1C5BVjyMXAGeACQAQCYAccBoAHZF6oBBDAuMjC4AQPIAQD4AQHCAg4QABiABBiKBRiGAxiwA8ICBBAjGCfCAgsQABiABBiKBRiRAsICCBAAGBYYHhgKwgIKEAAYFhgeGA8YCsICCxAAGIAEGIoFGIYDwgIGEAAYFhgewgIIEAAYCBgeGA3CAggQABiABBiiBMICBRAhGKsCwgIHECEYChigAeIDBBgBIEGIBgGQBgE&sclient=gws-wiz-serp#fpstate=ive&vld=cid:277d963e,vid:3XPAp6dgl14,st:0

9

Types of Molecular Testing

- **Fluorescence In Situ Hybridization (FISH)**
  - Molecular cytogenetic technique that uses fluorescent probes that bind to only those parts of the chromosome with a high degree of sequence complementarity (specific nucleotide sequences)
  - Fluorescent probes identify specific DNA or RNA sequences or chromosomes in cells and tissues
  - Maps genetic materials in cells specific to portion of genes

Advantages	Disadvantages
• Detects gene fusions • Highly sensitive and specific • Detects genomic abnormalities in non-viable and non-dividing tissues	• Less sensitive detecting for measurable residual disease (MRD) • Targeted test with only limited number of probes used at once • Only specific locus or gene tested • Cannot see which gene is fused

https://www.youtube.com/watch?v=KXn533DTrsM

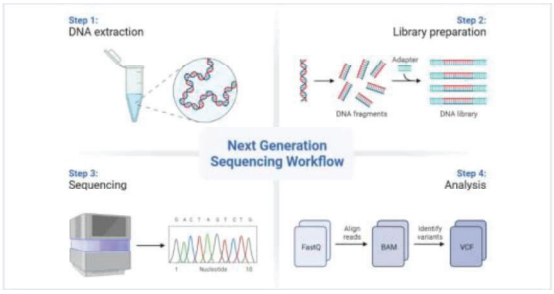
https://www.google.com/search?q=youe+tube+FISH+cytogenetics#fpstate=ive&vld=cid:96a1cb57,vid:qcSxdTKpMzg,st:0

10

Types of Molecular Testing

- **Next generation sequencing**
  - High-throughput sequencing results in 1 day
  - Can sequence hundreds and thousands of genes or whole genome in 1 assay
  - Technology that determines the order of nucleotides in DNA or RNA by sequencing millions of small fragments simultaneously

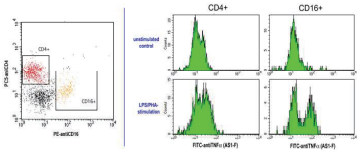
Advantages	Disadvantages
• Sequences more fragments at once • Can detect rare variants and transcripts • More sensitive and specific detection MRD	• More complex • Cost • Data storage



https://microbenotes.com/next-generation-sequencing-ngs/

Types of Molecular Testing

- **Flow Cytometry**
  - Laser-based cell surface antigens
  - Analyzes characteristics of cells or particles
  - Detects, identifies, and counts specific cells
  - Measures DNA in cells
  - Identifies portions of the cell in different parts of the cellular cycle
  - Clusters of Differentiation (CDs)



Advantages	Disadvantages
• High throughput analyzing millions of cells at once • Simultaneously measures multiple markers • Qualitative and quantitative analysis • Superior to immunohistochemistry (IHC) for detecting antigens in low amounts	• Cost and time • May cause cell damage due to high pressures

https://www.youtube.com/watch?v=B2zreF2dnWk

Types of Molecular Testing

- **Immunohistochemistry (IHC)**
  - Sees overexpression of cellular proteins and gene fusions (ie. PD-L) but can only see 1 cell at a time
  - Uses antibodies to detect antigens in a tissue sample
  - Diagnostic technique that involves analyzing a patients biopsy tissue sample
  - Pathology uses modified antibodies to stain specific proteins in the tissues to identify certain types and subtypes of a disease
  - Also used to identify protein markers (identifies surface markers)

Advantages	Disadvantages
• Cornerstone for diagnostic pathology • Can use fresh or frozen tissue samples • inexpensive	• IHC stains not standardized worldwide • Lacks high resolution imaging • Difficult to quantify results

https://www.youtube.com/watch?v=B2zreF2dnWk

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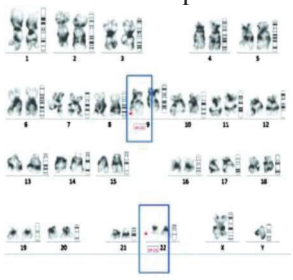
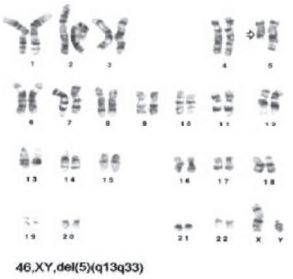
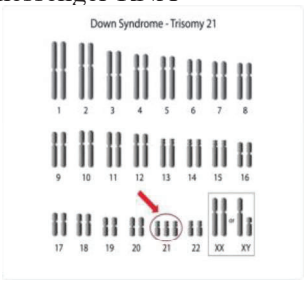
Types of Molecular Testing

A series of cellular and/or genetic alterations or translocations, chromosomal abnormalities

- Translocations (ie: **t**9;22 – **t**15;17)
- Deletions (ie: **q**5 with MDS)
- Inversions (ie: **i**16 with leukemia)
- Amplifications (more copies of DNA sequence)
- Aneuploidy (abnormal number chromosomes)
- Transcription errors of DNA when transcribed into messenger RNA







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14

Philadelphia Chromosome (t9;22)

CML

- Ph chromosome is present in the bone marrow cells of almost all people with CML
- It is the result of a genetic accident that occurs in a blood-forming stem cell in the bone marrow, where pieces of chromosomes 9 and 22 break off and trade places
- This fusion creates a new gene called BCR-ABL, which tells blood cells to produce too much of a protein called tyrosine kinase
- Tyrosine kinase promotes cancer by allowing certain blood cells to grow out of control, resulting in a slow-growing leukemia that causes the bone marrow to overproduce white blood cells

ALL

- The Ph chromosome is seen in about 20–30% of adults diagnosed with ALL
- It is associated with a poorer prognosis than Ph-negative ALL
- The Ph chromosome causes a protein to be present in the body that acts like a switch, signaling cells to divide uncontrollably, which can lead to cancer

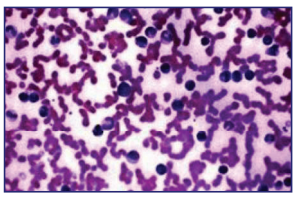
15

LEUKEMIA

ACUTE

AML

ALL

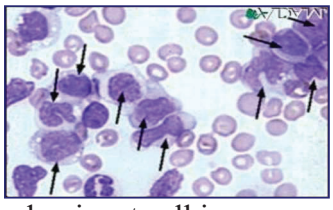


- undifferentiated or immature (blast) cells
- abrupt and rapid
- 1-5 months

CHRONIC

CML

CLL



- predominant cell is more mature in appearance but does not function normally
- prolonged clinical course with longer survival time
- 2-5 years

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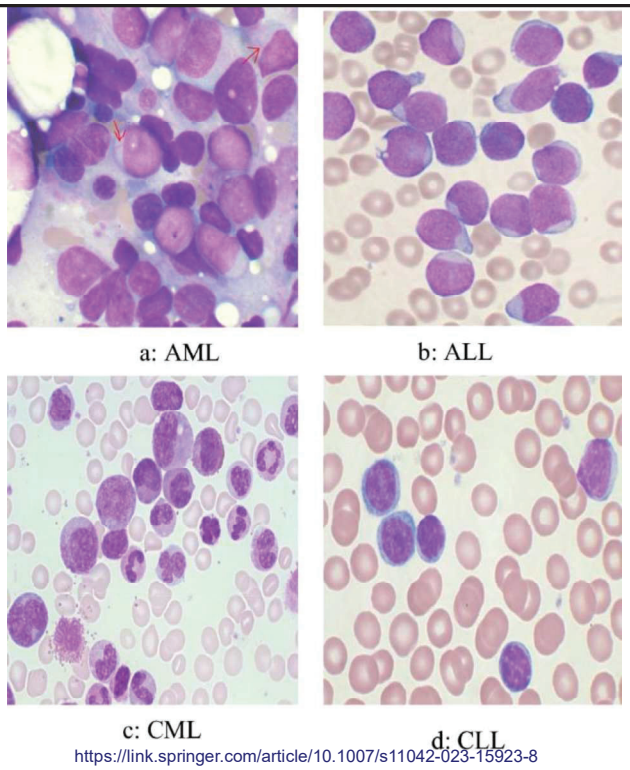

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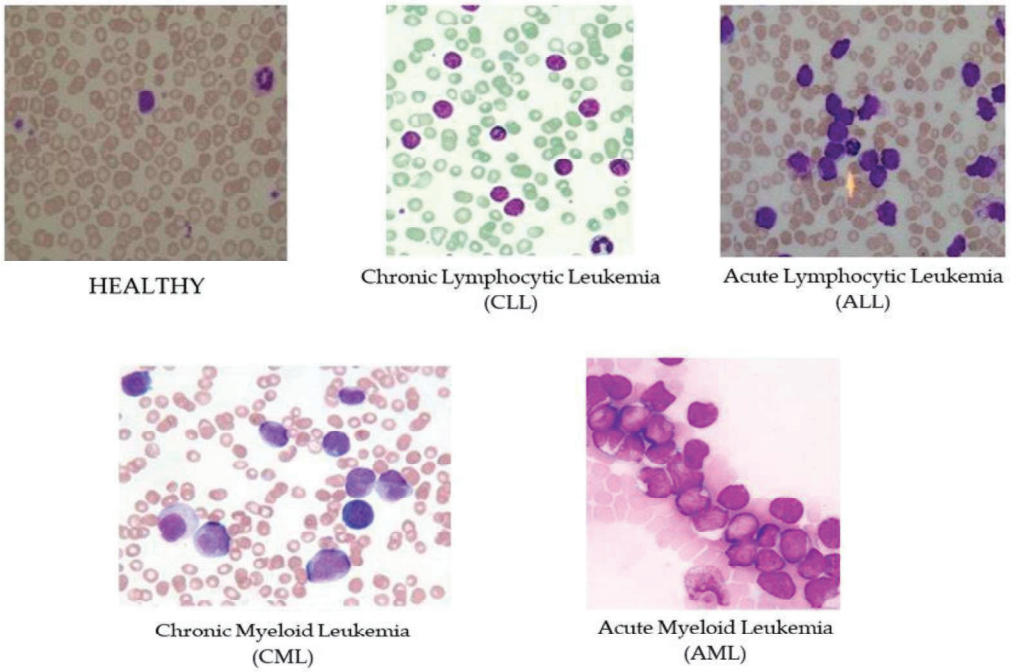
17



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LEUKEMIA

- The leukemias are a heterogeneous group of disorders which are characterized by a neoplastic transformation and abnormal differentiation of the hematopoietic progenitor cells
- The immature cells proliferate and accumulate primarily in the bone marrow, peripheral blood and organs, resulting in the inhibition of normal hematopoiesis

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LEUKEMIA – Risk Factors

- Sex:
  - Males increased risk over females
  - Minority males have a 50% higher risk than females in all racial/ethnic groups
- Race/Ethnicity:
  - Increased risk in Caucasians of European descent
  - Increased risk in African Americans of European descent than of African descent
  - Decreased risk in Chinese, Japanese and Korean descent

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LEUKEMIA – Risk Factors

- Increasing age:
  - Each decade of life increases the overall risk
- Maternal exposures during peak periods of fetal cellular growth and/or division - germ line predisposition
- Familial predisposition:
  - Chronic Lymphocytic Leukemia
- Genetic predisposition
- Previous cancer chemotherapy
- Electromagnetic field exposures
- Ionizing radiation exposure:
  - Previous cancer radiotherapy and chemotherapy (alkylating agents and topoisomerase II inhibitors)
  - Work related exposures
  - Hiroshima and Chernobyl survivors

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LEUKEMIA – Risk Factors

- Viruses:
  - Human T-Lymphotropic Virus I (HTLV-I)
  - Human T-Lymphotropic Virus II (HTLV-II)
  - Retroviruses
- Occupational exposures:
  - Benzene
  - Agricultural chemicals
  - Organic solvents used in dry cleaning, printing, industrial cleaning agents and plastic production

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LEUKEMIA – Risk Factors

- Leukemic transformation from other bone marrow diseases:
  - Polycythemia Vera (P Vera)
  - Aplastic Anemia (AA)
  - Myelodysplastic Syndrome (MDS)
  - Agnogenetic Myeloid Metaplasia (AMM)
  - Paroxysmal Nocturnal Hemoglobinuria (PNH)
  - Fanconi Anemia (FA)

LEUKEMIA - Diagnosis

- Leukemia is a clonal disorder that arises in an early hematopoietic stem cell (acquired mutation)
  - the accumulation results in a hypofunctional bone marrow
- As a result, there is a varying degrees of neutropenia, anemia, and thrombocytopenia with corresponding clinical sequelae

LEUKEMIA – Signs and Symptoms

- Roughly 20% of patients are asymptomatic
- Roughly 25% of all leukemia's are found during routine physical examinations and screenings
- When symptoms do appear, they vary from minor to severe in nature
- Sanctuary site infiltration:
  - Skin nodules → leukemic cutis
  - Swollen, tender testes
  - Gingival infiltration
  - Headaches, confusion or seizures

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LEUKEMIA – Signs and Symptoms

Abnormal white blood cell production

- Fever, chills or flu-like symptoms
- Pneumonia
- Swollen, tender lymph nodes or spleen
- Night sweats
- Bone or joint pain
- Poor wound healing

Abnormal red blood cell production

- Pallor
- Weakness, fatigue and activity intolerance
- Dyspnea
- Anorexia and weight loss

Abnormal platelet production

- Petechiae and ecchymosis
- Spontaneous bleeding
- Heavy menses

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ACUTE LEUKEMIAS

AML:

- myeloid line >20% blasts in BM or peripheral blood
- Unregulated proliferation or undifferentiation myeloid progenitor cells in BM and periphery
- M0-M7
- WHO standards
- t(15;17); t(8;21) more favorable
- Inv(16)

ALL:

- lymphocytic
- 80% B cell lineage
- 20% T cell lineage
- Develop sanctuary sites and more infiltration noted into other organs
- Based or morphology
- Burkitts
- t(12,21) –good prognosis
- t(9,22) – poor prognosis

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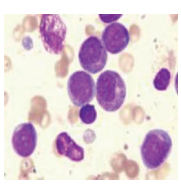
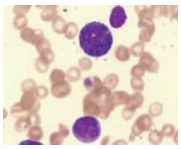
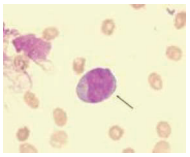
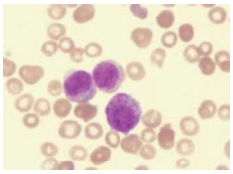




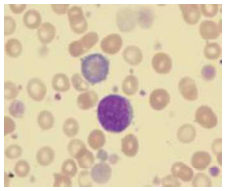
Variations M2



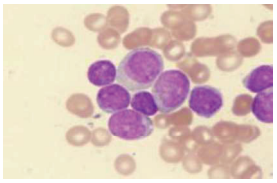


M3

AML FAB Morphology



M7



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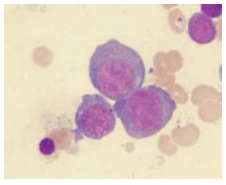
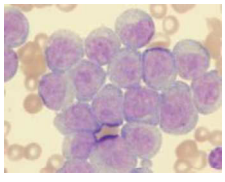


M6



M5

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AML – Pathogenesis and Molecular Biology

***more than 23 genes commonly mutated and multiple mutations**

- FLT3
  - 30% mutated on stem cell with normal cytogenetics
  - Aggressive disease
- NPM1
  - 50% incidence
  - Common with FLT3
  - Favorable outcome if NPM1 (mut)/FLT3ITD (neg)
- DNMT3A
- NRAS
- CEBPA
- TET2
- WT1

- IDH1
- IDH2
- KIT
- RUNX1
- MLL-PTD
- ASXL1
- PHF8
- KRAS
- PTEN
- TP53

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WHO 2022 AML Classifications

Acute myeloid leukaemia with defining genetic abnormalities
Acute promyelocytic leukaemia with *PML*::*RARA* fusion
Acute myeloid leukaemia with *RUNX1*::*RUNX1T1* fusion
Acute myeloid leukaemia with *CBFB*::*MYH11* fusion
Acute myeloid leukaemia with *DEK*::*NUP214* fusion
Acute myeloid leukaemia with *RBM15*::*MRTFA* fusion
Acute myeloid leukaemia with *BCR*::*ABL1* fusion
Acute myeloid leukaemia with *KMT2A* rearrangement
Acute myeloid leukaemia with *MECOM* rearrangement
Acute myeloid leukaemia with *NUP98* rearrangement
Acute myeloid leukaemia with *NPM1* mutation
Acute myeloid leukaemia with *CEBPA* mutation
Acute myeloid leukaemia, myelodysplasia-related
Acute myeloid leukaemia with other defined genetic alterations
Acute myeloid leukaemia, defined by differentiation
Acute myeloid leukaemia with minimal differentiation
Acute myeloid leukaemia without maturation
Acute myeloid leukaemia with maturation
Acute basophilic leukaemia
Acute myelomonocytic leukaemia
Acute monocytic leukaemia
Acute erythroid leukaemia
Acute megakaryoblastic leukaemia

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AML - Diagnostic Criteria

Criteria 1

- Blasts 20% of total cells in BM

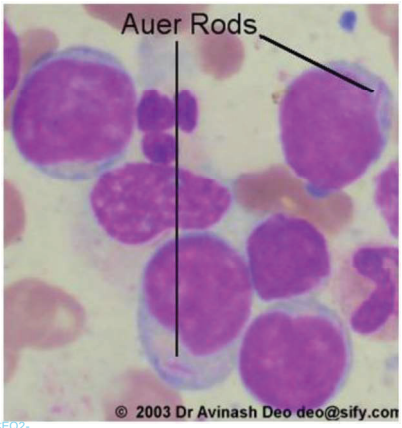
OR

- Blasts 20% total cells peripheral

Note: t(8;21); inv(16); t(15;17) supersedes the 20% requirement

Criteria 2

- Myeloid descent
- Auer rods or myeloid/monocytic markers



https://www.google.com/search?q=auer+rods&tbm=isch&ved=2ahUKEwilyquK7ePnAhWHBVkKHZRvCCEQ2-cCegQIABAA&oq=auer+rods&gs_l=img.3..0i67j0l9.314933.317593..317713...1.0..0.253.1052.5j3j1.....0....1..gws-wiz-img.......0i131j0i10j0i5i30j0i8i30j0i10i24.XBAIWUYUtMw&ei=-G5QXqXuLIeL5AKU36GIAg&bih=611&biw=1280&rlz=1C1GCEA_enUS841US841#imgrc=r4kvm2knU2C7VM

AML- Risk Stratification Examples

Favorable (60%)

- **t(8;21); q(22;q22); RUNX1-RUNX1T1**
- **Inv(16); (p13;1q22); t(16;18);CBFB-MYH11**
- **Mutated NPM1 without FLT3**
- **Mutated CEBPA**

Intermediate (40%)

- **Mutated NPM1 and FLT3 (high) – normal karyotype**
- **Wild-type NPM1 without FLT3**
- **t(9;11); MLLT3-MLL**

Adverse (15-20%)

- **Inv(3); t(3;3); GATA2**
- **t(6;9); DEKNUP214**
- **DEK-NUP214**
- **KMT2A**
- **Monosomy 5 or 5q**
- **Monosomy 7**
- **-17p**
- **KIT**

Also need to consider
Age
Comorbidity
Performance Status (PS)

AML – Treatment (Induction)

- Cytarabine + anthracycline (7+3)
- Daunorubicin 60-90 mg/m2/d or idarubicin 12 mg/m2/d x 3
  - Cytarabine 100-200 mg/m2/d x 7 continuous infusion
- Vyxeos (liposomal daunorubicin and cytarabine)
- FLT3 positive AML
  - Midostaurin (Rydapt)
  - Gilteritinib (Xospota)
- Gemtuzumab ozogamicin (Mylotarg) - CD33+ AML
- Ivosidenib or Enasidenib
- Onureg (oral Azadactine)
- Venetoclax (Venclexa) + Azacitidine or Decitabine
- Glasdegib (Daurismo) + LDAC)

* Making progress over 9 new drug since 2017

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AML - Treatment (Consolidation)

***younger or fit older patients

- ❑ HIDAC (High dose Cytarabine)
- ❑ Allogeneic SCT

***older or younger with comorbidities

<u>Hypomethylating Agents</u>

- ❑ Decitabine (must receive if TP53 mutation)
- ❑ Azacitidine
- ❑ Venetoclax

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Acute Promyelocytic Leukemia (APL) - M3

- 10% all acute myeloid
- Distinct morphology and clinical features than others
- DIC secondary to consumption of fibrinogen and platelets
- Exacerbated with cytotoxic agents
- 10-30% die from hemorrhage during induction
- Hyperleukocytosis
- Reciprocal translocations between long arms on chromosomes (t15;17)
- Results in fusion of PML gene on 15 to RARa gene on 17 (PML/RARa)
- Arrests myeloid maturation at promyelocytic stage

Treatment

ATRA

Arsenic

Differentiation Syndrome

- Fever; elevated WBC; hypoxia; SOB; effusions
- Dexamethasone
- Temporary discontinue ATRA

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ALL Clinical Presentation

- Cytopenias
- Bone marrow failure
- Adenopathy of LN
- Mediastinal mass (t cell)
- Hepatosplenomegaly
- CNS
- Fatigue
- Fevers
- Sweats
- Weight loss
- Bone pain

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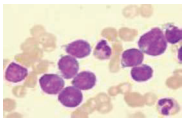
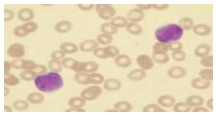
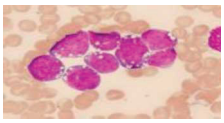
ALL –Classifications





- Precursor B-cell ALL
- Precursor T-cell ALL
- Burkitt-type ALL
- Philadelphia chromosome positive (*BCR-ABL* fusion) ALL



  - Children ALL >80%
  - Adults ALL 30-40%

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ALL - Classification

- Defined as Lymphoblastic Lymphoma (LBL) if there is a mass in the mediastinum or elsewhere and BM blasts less than 25%

- Defined as Acute Lymphoblastic Leukemia (ALL) if there are more than 25% blasts in the bone marrow with or without a mass

Morphology – no granules in the cytoplasm

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ALL
Cytogenetics and Immunophenotype

- Cytogenetics
  - Favorable
    - Hyperdiploidy
    - TEL-AML1
    - t(12;21)
    - t(5;14); t(1;19)
  - Unfavorable
    - Hypodiploidy
    - t(9;22); Ph+
    - COMPLEX
- Immunophenotype (favorable)
  - Pre-B cell
    - CD10; CD 22; CD20
  - Mature B cell
    - CD20; PanB markers
  - Tcell
    - CD3; CD1a; CD7; CD52
  - Burkitts
    - T(8;14); t(8;2); t(8;22); 14q; t(14;18)

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ALL - Prognostic Factors

- Age
- WBC
- Ph Chromosome t(9;22)
  - PH+ worse prognosis than PH-
  - 1/3 + and increases with age
- Sanctuary sites (CT, LP; MRI)
  - CNS
  - Testicles
  - LNs

*50% adults relapse regardless of age

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ALL – Treatment

Diagnosis	Treatment	Cure
Burkitt	**HCVAD-R EPOCH**	**80-90%**
Ph-Positive ALL	**HCVAD +TKI; TKI Allo SCT in CR1**	**50%**
T-ALL	**HD CTX HD Cytarabine Asp + Nelarabine**	**50-60%**
CD20 ALL	**ALL chemo Rx +Rituximab**	**40-50%**
AYA	**Augmented BFM HCVAD**	**60%**
Elderly	**HCVD + blincyto**	

*****MUST use Dexamethasone not Prednisone because Dex penetrates the CNS**
Ph Chromosome + add a TKI – (Imatinib or Dasatinib)
Relapsed/Refractory
- **Blinatumomab (Blincyto)**
- **Inotuzumab ozogamicin (Besponsa)**
- **CAR-T**

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Case Study #1

Patient Background:
- 66 year old male
- Retired Navy Seal and school bus driver
- Current Volunteer at Veteran's Affairs Hospital in Louisville, KY
- Lives with wife of 45 years
- Type II diabetic, controlled
- Left Transtibial Amputation secondary to diabetic ulcer
- Previous physical therapy in acute, rehabilitation, and outpatient settings following surgery

Chief Complaint:
Patient presents to outpatient physical therapy clinic (2 months post discharge), with desire for further prosthetic training.

Patient's prior outpatient PT included gait training and stair training with use of cane.

Now, patient desires more independence without assistive device and further training to accommodate his increased activity level in the community with his volunteer work.

Patient notes that he feels increasingly tired after a day of volunteering, therefore he wants more endurance training with his prosthetic.

https://www.physio-pedia.com/Acute_Myeloid_Leukemia_Case_Study

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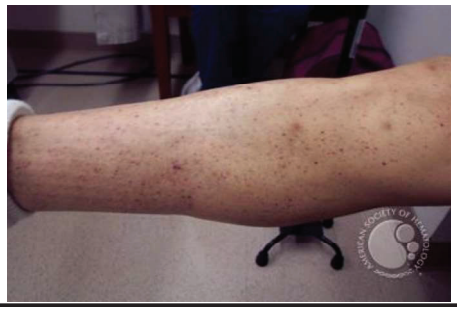
Case Study #1 (con't)

Medical History:
• Previous history of smoking, 30 pack years
• Quit smoking at age 48, when he was diagnosed with Type II diabetes
• Diabetic ulcer on L heel, led to transtibial amputation approximately 1 year ago
• Patient reports history of anemia while in hospital post-op
•Recent onset of headaches, 3 out of 10 on pain scale[1]
•Patient reports shortness of breath with increased activity[1]
•1 year post-operation from amputation
• Discharged from outpatient physical therapy 2 months prior to current visit

https://www.physio-pedia.com/Acute_Myeloid_Leukemia_Case_Study

OBJECTIVE:
Vital Signs:
• Blood Pressure 110/75 mmHg
• Heart Rate 64bpm
• Respiratory Rate 18bpm(at rest)
• Temperature 99.4°F

•Petechaie and bruising noted on patients R lower leg and ankle, also minor spots noted on residual limb (example in the picture below)



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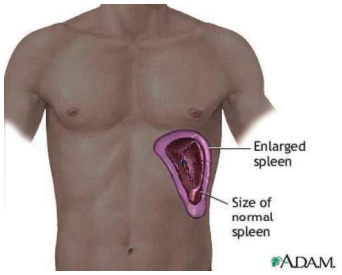
Case Study # 1 (con't)

Due to fever, palpation of abdomen revealed enlarged spleen and tenderness (example of enlarged spleen (splenomegaly) in the picture below)



What are the risk factors in this scenario?

What are the signs and symptoms?

https://www.physio-pedia.com/Acute_Myeloid_Leukemia_Case_Study

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Case Study # 1 (con't)

Risk Factors for AML Noted in Clinical Presentation

- Age (greater than 63 y/o increases risk for AML; 80% of AML cases occur in adults)
- Male
- History of Smoking Diabetes
- History of Anemia

Signs and Symptoms

- Petechiae
- Fatigue
- Headache
- Proximal muscle weakness
- Enlarged spleen
- Signs of possible infection (low grade fever, adventitious breath sounds)

The clinical impression of this patient is that the proximal muscle weakness and increased fatigue are consistent with presentation of acute myeloid leukemia

The patient will be referred back to his primary care physician. The patient would benefit from physical therapy to strengthen proximal muscles and increase cardiovascular endurance

https://www.physio-pedia.com/Acute_Myeloid_Leukemia_Case_Study

Case Study #2

A 41-year-old man consulted for left side frontal headache and mild fever, headache increase when laying forward.

Medical history:

- HTN
- no family history for blood disorder

Physical exam:

- normal except frontal and maxillary sinuses tender
- **peripheral blood was normal/abnormal?**
- chemistry panel was normal

Patient was given Augmentin, after sinusitis diagnosed.

Lab view	15/11/2018
General Hematology	
WBC	5.3
RBC	H 6.0
Hgb	17.0
Htc	48.6
MCV	L 81.3
MCH	28.4
MCHC	H 35.0
RDW-CV	12.2
Platelet	253
MPV	
Absolute Neutrophil count Auto #(ANC)	9.2
Lymphocyte Auto #	10.5
Monocyte Auto #	2.05
Eosinophil Auto #	2.62
Basophil Auto #	0.41
Neutrophil Auto %	0.21
Lymphocyte Auto %	0.04
Monocyte Auto %	38.4
Eosinophil Auto %	49.2
Basophil Auto %	7.7

Figure 1 : first visit laboratory test ; normal

https://www.hematology.org/education/trainees/fellows/case-studies/female-with-new-onset-aml-and-leukostasis
https://mecsj.com/uplode/images/photo/ACUTE_LYMPHOCYTIC_LEUKEMIA,_CASE_REPORT.pdf

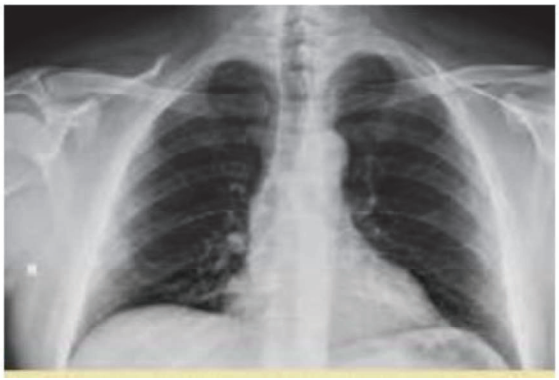
Case Study #2

Patient came back after one week with, cough produced white sputum, mild fever, general fatigue

Chest auscultation: diffuse wheezes, prolonged expiratory phase accompanied with crackles

Chest X-ray show increased Broncho vascular marking

Patient treated as bronchitis



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Case Study #2

One-week later patient presented with persistent night fever, sweating, significant lose weight (5 Kg, last month)

Urgent CBC test shows ????

Lab view	19/11/2018
General Hematology	
WBC	L 3.8
RBC	L 3.9
Hgb	L 11.1
Htc	L 32.7
MCV	84.1
MCH	28.5
MCHC	33.9
RDW-CV	H 14.8
Platelet	*L 69
MPV	
Absolute Neutrophil count Auto	10.4
Lymphocyte Auto #	
Monocyte Auto #	*C 0.2
Eosinophil Auto #	1.7
Basophil Auto #	H 1.8
Neutrophil Auto %	0.0
Lymphocyte Auto %	L 0.09
Monocyte Auto %	6.1
Eosinophil Auto %	44.5
Basophil Auto %	46.7

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Acute Leukemia

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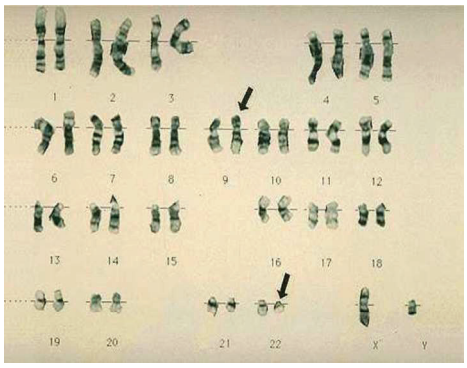
https://www.google.com/search?q=key+point+summary+&safe=active&sca_esv=4d8d0b367783d084&sca_upv=1&udm=2&biw=1280&bih=631&ei=kknCZtTbH8KtptQPopbYuAM&ved=0ahUKEwjU7P-4of-HAxXClokEHSILFjcQ4dUDCBA&uact=5&oq=key+point+summary+&gs_lp=Egxnd3Mtd2l6LXNlcnAiEmtleSBwb2ludCBzdW1tYXJ5IDIFEAAYgAQyBBAAGB5I9RJQnANYIQxwAXgAkAEAmAFroAGdCqoBBDEyLjK4AQPIAQD4AQGYAgGgAnKYAwDiAwUSATEgQIgGAZIHAzAuMaAH1AU&sclient=gws-wiz-serp#vhid=4C2cE8DVw-d-DM&vssid=mosaic

Chronic Myeloid Leukemia

CML (granulocytic)

- Myeloid
- Characterized by marked splenomegaly and increased production of granulocytes esp. neutrophils
- Philadelphia chromosome (90%)
  - Translocation 9;22
  - Forms oncoprotein BCR/ABL which activates tyrosine kinase (TK)
- Neoplastic expansion
- Massive leukocytosis
- Use Sokol score for risk stratification

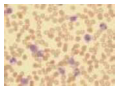


Myeloproliferative neoplasm (MPN) characterized by the dysregulated production and uncontrolled proliferation of mature and maturing granulocytes with fairly normal differentiation characterized by the presence of the Philadelphia Chromosome (BCR-ABL – 9;22)

Chronic Myeloid Leukemia Phases

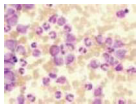
Chronic: (25+ years)

- Excessive proliferation and accumulation of granulocytes
- No lymphadenopathy
- + splenomegaly
- 95% with + Ph



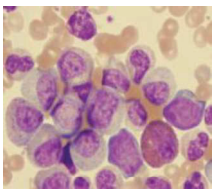
Acclerated: (4-5 years)

- Progressive leukocytosis
- Increased myeloid cursors and basophils
- Wt. loss and weakness
- Progressive chromosomal abnormalities
- Splenomegaly
- >15% peripheral blasts



Blast Crisis: (6-12 months)

- 20% blasts or promyelocytes in BM
- Leukocytosis
- Microvascular occlusion of CNS or lungs
- Myeloblastic transformation more common than lymphoblastic



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CML – Treatment

Tyrosine Kinases

- Imatinib
  - Edema; fluid retention; myalgia; GI; hypophosphatemia
- Bosutinib
  - GI; rash; pleural effusion
- Dasatinib
  - Pleural/pericardial effusions; bleeding
- Nilotinib
  - Increased pancreatic enzymes; QT prolongation; indirect hyperbilirubinemia
- Ponatinib
  - Increased pancreatic enzymes

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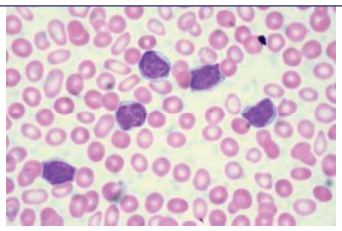
Chronic Lymphocytic Leukemia

- Most commonly diagnosed form leukemia in US
- 66% overall 5 year survival
- Peripheral blood lymphocytes
  - CLL – Primarily in blood with more than 5000
  - SLL – Primarily in nodes with less than 5000
- Incurable typically after indolent course
- Average age 70
- Many have at least one coexisting medical condition

- Clinical presentation
  - Many asymptomatic
  - Fevers
  - Night sweats
  - Weight loss
  - Weakness
  - Fatigue
  - Abdominal full ness
  - Anemia
  - Bleeding
  - Enlarged lymph nodes



https://www.lecturio.com/magazine/chronic-lymphocytic-leukemia/

CLL - Immunophenotype

- CD5; CD19; CD23; CD20
- Occasionally CD38

Prognostic Factors:

- 17q
- Trisomy 12
- 11q
- IgVH mutation

Revised Rai Staging System

Low risk (formerly stage 0)

- Lymphocytosis, lymphocytes in blood > 15,000/mcL, and > 40% lymphocytes in the bone marrow

Intermediate risk (formerly stages I and II)

- Lymphocytosis as in low risk with enlarged node(s) in any site, or splenomegaly or hepatomegaly or both

High risk (formerly stages III and IV)

- Lymphocytosis as in low risk and intermediate risk with disease-related anemia (hemoglobin level < 11.0 g/dL or hematocrit < 33%) or platelets < 100,000/mm^3

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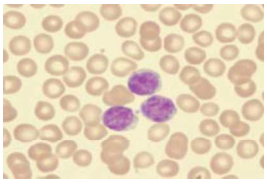
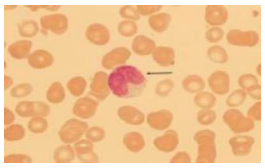
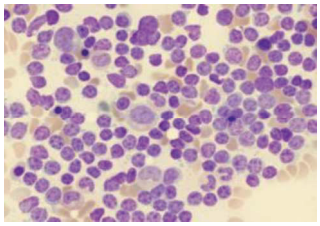


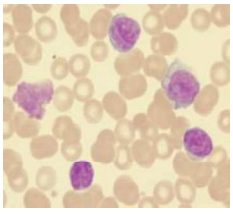
CLL B-Cell



CLL-large cleaved cells



CLL



CLL-Prolymphocytic transformation

www.healthsystem.virginia.edu/.../leukemias.cfm

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Chronic Lymphocytic Leukemia Treatment

- FCR (Fludarabine, Cytoxan; Rituximab)
- FR
- PCR
- R-Bendamustine
- Obinatuzumab
- Ofatumumab
- Ibrutinib/Acalabrutinib/Zanubrutinib/Pirtobrutinib
  - Hemorrhage; a-fib; cytopenias; TLS; GI; rash)
- Idelalisib/Duvelisib
  - Diarrhea; transaminase elevation; pneumonitis
- Venetoclax
  - GI; cytopenias; URIs
- Purine Analogues (Chlorambucil)
- CAT-T
- Allogeneic Transplant

Case Study # 3

A 70-year-old man presented to his primary care physician with 2 months of fatigue and 10-pound weight loss. He noted a general sense of malaise and feeling poor. On physical examination, the clinician was able to palpate the spleen 4 cm below the costal margin (splenomegaly) but noted no palpable lymphadenopathy. Family history was noncontributory.
Interpret the labs….

Test	Patient	Reference Range and Units
WBC	39 180	4000-10 400/cmm
RBC	4.37	4.36-5.78 M/cmm
Hemoglobin	13	13.8-17.3 g/dL
HCT	40	39.5-50.2%
MCV	92	81-95 fL
MCH	29.7	27.6-33.0 pg
MCHC	32.5	32.8-36.4 g/dL
RDW-CV	13.1	<14.2%
RDW-SD	43.4	<46.0 fL
PLT	216,000	141 000-377 000/cmm
MPV	11.2	9.5-12.7 fL

Differential Test	Patient	Reference Range and Units
Neutrophils	67	%
Bands	9	%
Lymphocytes	7	%
Monocytes	2	%
Eosinophils	3	%
Basophils	4	%
Metamyelocytes	5	%
Myelocytes	3	%
ABS neutrophils	26 240	2200-8850/cmm
ABS bands	3530	K/cmm
ABS lymphs	2740	1090-3300/cmm
ABS monocytes	780	100-800/cmm
ABS eosinophils	1180	30-610/cmm

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6902376/

Case Study # 3 (con't)

Interpretation of lab values:
The CBC reveals marked leukocytosis (elevated white blood cell [WBC] count) and mild normocytic anemia (decreased hemoglobin, with normal mean corpuscular volume). Platelets (PLTs) are within the normal range.

What Is the Differential of Leukocytosis, and How Does the Complete Blood Count Differential Help Narrow This Down?

Leukocytosis in general is a nonspecific finding that can have a variety of etiologies, ranging from benign to neoplastic conditions, including infection, autoimmune disease, allergy, drug reaction, acute and chronic inflammation, leukemia, and lymphoproliferative disorders.

The next step is to look at the CBC differential to identify what types of cells are causing the WBC increase, as each type of WBC will be listed as a percentage of the total and in absolute counts. Are mature WBCs (lymphocytes and/or neutrophils) causing the increase or are they immature (blasts, promyelocytes, myelocytes, metamyelocytes)?

Lymphocytosis may be caused by viral infection, hypersensitivity, leukemia, or lymphoma. Neutrophilia, on the other hand, may be caused by an acute inflammatory response to infection (usually bacterial), medication, bone marrow stimulation, or myeloproliferative disease. An increase in immature WBCs may be concerning for an underlying neoplasm.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6902376/

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Case Study # 3 (con't)

What Entities Should Be Considered in This Patient?

The patient has absolute neutrophilia, eosinophilia, and basophilia. There is also a "left shift," meaning there is an increase in immature myeloid cells (bands, metamyelocytes, myelocytes). Both of these findings suggest chronic myeloid leukemia (CML), a clonal disease of myeloid cells (cells that are made in the bone marrow), but are not specific.

In this age-group, acute leukemia must be considered with a presentation of leukocytosis and anemia. There are myeloid and lymphoid types of both chronic and acute leukemias depending on the lineage of the malignant cells, but in contrast to chronic leukemias, which are characterized by increases in mature cells, acute leukemias are characterized by increases in very immature cells (blasts).

Acute leukemias are more aggressive clinically, as the cells proliferate much more rapidly. There are many types of AMLs, but the CBC in AML often shows decreased mature WBCs and increased blasts (very immature WBCs). You would also expect pancytopenia (decrease in all 3 cell lines: mature WBCs, red blood cells, and PLTs) as the neoplastic cells take over the bone marrow.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6902376/

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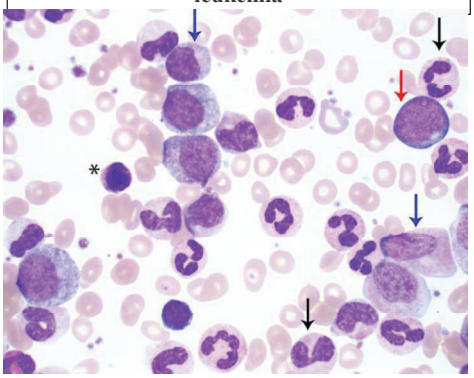
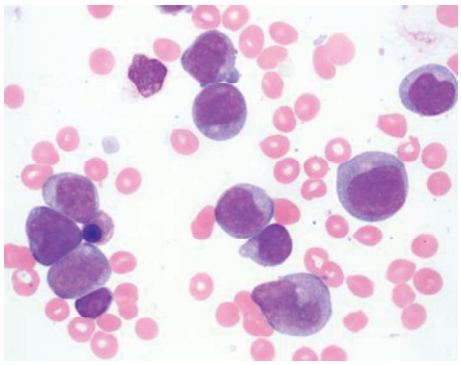
Case Study #3 (con't)

Note the spectrum of maturation within the myeloid cells, including immature forms (blast, red arrow), mid-stage myeloids (blue arrows), and late-stage myeloids (neutrophils and band forms, black arrows). A basophil is also present (star). These feature are typical of chronic myeloid leukemia



Acute myeloid leukemia (Wright-Giemsa, ×1000). The predominant cell type here is a blast, characterized by large rounded nucleus, smooth fine chromatin, prominent nucleoli, and scant cytoplasm with or without granules



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6902376/

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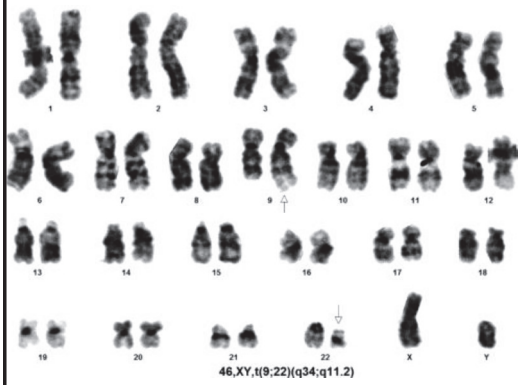
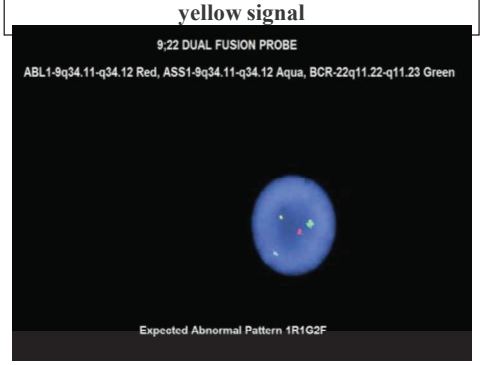
Case Study # 3 (con't)

Conventional karyotype showing the classic t(9;22) between the long arms of chromosomes 9 and 22 which characterizes chronic myeloid leukemia. Arrows represent the abnormal derivative chromosomes resulting from this apparently balanced translocation



Dual fusion fluorescence in situ hybridization in chronic myeloid leukemia (CML). The *ABL1* gene on chromosome 9 is marked in red, and the *BCR* gene on chromosome 22 is marked in green. A normal diploid cell should have 2 red signals and 2 green signals (2 copies of each gene). In CML, you typically see 1 red, 1 green, and 2 yellow signals, meaning that the 2 genes are close enough such that the red and green signals fuse into a yellow signal



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6902376/

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Case Study # 4

Initial Presentation

- A 67-year-old man presented to PCP with complaints of fatigue and night sweats
- PMH: patient takes OTC antacid tablets a few times a week for a "sensitive" stomach
- PE: Enlarged mobile lymph nodes bilaterally (~1.5 cm) in cervical chain, no palpable spleen or liver
- Laboratory findings:
  - WBC; 102,000
  - Lymphocytes; 79
  - Hbg; 11.4 g/dL
  - Platelets; 180,000
  - ANC; 1,900/mm3
  - LDH 1470 U/L
  - Cytogenetics; del(11q), IgVH-unmutated
  - beta2M, 3.0 mg/L

1. What is the probable diagnosis and why?
2. What Stage and why?
3. What would be the treatment and why?

https://www.targetedonc.com/view/case-presentation-a-67-year-old-man-with-chronic-lymphocytic-leukemia

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Case Study # 4 (con't)

- this case is a somewhat common presentation that we see, especially with a patient with these molecular abnormalities
- average age diagnosis of patients as a reminder is about 70 to 71 years of age, so the patient is well within that nice bell-shaped curve
- was relatively healthy, feeling well, up until very recently when these symptoms started

https://www.targetedonc.com/view/case-presentation-a-67-year-old-man-with-chronic-lymphocytic-leukemia

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Chronic Leukemia

shutterstock.com · 1826644598

https://www.google.com/search?q=key+point+summary+&safe=active&sca_esv=4d8d0b367783d084&sca_upv=1&udm=2&biw=1280&bih=631&ei=kknCZtTbH8KtptQPopbYuAM&ved=0ahUKEwjU7P-4of-HAxXClokEHSILFjcQ4dUDCBA&uact=5&oq=key+point+summary+&gs_lp=Egxnd3Mtd2I6LXNlcnAiEmtleSBwb2ludCBzdW1tYXJ5IDIFEAAYgAQyBBAAGB5I9RJQnANYIQxwAXgAkAEAmAFroAGdCqoBBDEyLjK4AQPIAQD4AQGYAgGgAnKYAwDiAwUSATEgQIgGAZIHAzAuMaAH1AU&sclient=gws-wiz-serp#vhid=4C2cE8DVw-d-DM&vssid=mosaic

Myelodysplastic Syndromes (MDS)

- Heterogenous clonal disorder characterized by hypercellular/plastic marrow, peripheral cytopenias, and cell function abnormalities
  - Impaired proliferation
  - Maturation of progenitor cells – ineffective hematopoiesis
- Bone marrow failure and defective stem cells clone over and over until overwhelm healthy cells and take over marrow
- Chromosome abnormalities on 50-75% at level of stem cell
  - 5,7,8,11,12,20
  - Chromosome 5 lost in MDS
- "smoldering leukemia" – evolution to AML = 25-30%

MDS vs. AML

Characteristic	MDS	AML
Apoptosis	Prominent in RA, RARS	Low
Differentiation	Normal at onset	Blocked at onset
Response to Ara-C	Poor	Excellent
Mean age at presentation	70 years	45-65 years
Lineage involvement	One or more with dysplasia	Lineage restricted with differentiation block
Clonality	Clonal	Clonal
Normal Hematopoiesis	Suppressed	At a growth disadvantage
Cytogentics Abnormalities	Deletion or loss of chromosome 5 and/or 7	Translocation t(8;21); inv 16; t(15;17)
Blast Count	<20%	>20%

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MDS

- Greatest risk factor = advancing age
  - (76 years is median age of diagnosis)
- From 2007-2011 73,888 new cases
- Previous cancer therapy
- Benzene exposure, pesticides, radiation
- Smoking
- Congenital disorders
- Male sex increased prevalence
- More common in Caucasians
- 35% 3 year survival

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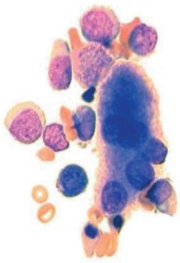
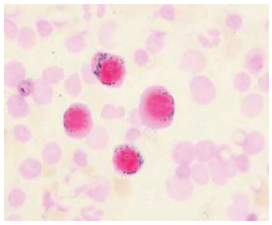
MDS Diagnostic Evaluation

- Peripheral blood counts
- Retic count
- BM biopsy and aspiration
- Iron saturation
- Ferritin
- B12 – Folate levels
- EPO level
- Sideroblast is an immature red blood cell with nuclei or centers surrounded by rings of iron.





https://www.ncbi.nlm.nih.gov/books/NBK537073/figure/article-17540.image.f2/

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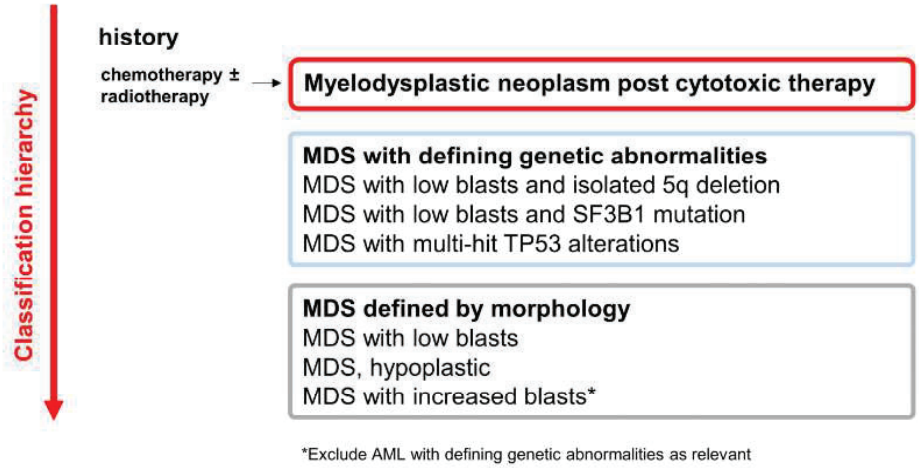
Myelodysplastic Neoplasm



https://www.mll.com/en/the-new-who-classification-2022#:~:text=Myelodysplastic%20Syndromes%20Are%20Now%20Myelodysplastic%20Neoplasia&text=MDS%20is%20further%20divided%20into,the%20number%20of%20entities%20reduced.

70

IPSS-R

https://www.mds-foundation.org/ipss-r-calculator/

Most commonly used system to score patients disease in terms of risk for life expectancy and chances of transformation to AML

Based on % BM blasts, Karyotype, Cytopenias

Table 2: The risk score IPSS-R (International prognostic scoring system - revised)

Characteristics	Score values						
	0	0.5	1	1.5	2	3	4
Cytogenetics	Very good	-	Good	-	Intermediate	Poor	Very poor
Blasts BM, %	≤2	-	>2 - <5	-	5-10	>10	-
Hb	≥10	-	8-<10	<8	-	-	-
Platelets	≥100	50-<100	<50	-	-	-	-
Neutrophils	≥0.8	<0.8	-	-	-	-	-

Risk groups	
Very low	≤1.5
Low	>1.5 – 3
Intermediate	>3 – 4.5
High	>4.5 - 6
Very high	>6

Cytogenetic risk groups			
Prognostic subgroup	Cytogenetic Aberration	Median survival, yrs	Median AML-evolution 25%, yrs
Very good	-Y, del(11q)	5.4	NR
Good	Normal, del (5q), del (12p), del (20q), double including del (5q)	4.8	9.4
Intermediate	del (7q), +8, +19, i(17q), any other single or double independent clones	2.7	2.5
Poor	-7, inv(3)/t(3q)/del(3q), double including -7/del(7q), complex: 3 abnormalities	1.5	1.7
Very poor	Complex: >3 abnormalities	0.7	0.7

www.ipss-r.com/ *Greenberg P et al., Blood, 2012*

Table 3: IPSS-R – survival related to age

Age groups, y	IPSS-Risk categories				
	Very low	Low	Inter-mediate	High	Very high
All	8.8	5.3	3.0	1.6	0.8
≤60	NR	8.8	5.2	2.1	0.9
>60-70	10.2	6.1	3.3	1.6	0.8
>70-80	7.0	4.7	2.7	1.5	0.7
>80	5.2	3.2	1.8	1.5	0.7

Survival (Median, years)

www.ipss-r.com/ *Greenberg P et al., Blood, 2012*

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What is the IPSS-M?

- An international research team (The International Working Group for the Prognosis of MDS) analyzed 2,957 MDS patients and developed an improved prognostic score using the following parameters:
- Hemoglobin
- Platelet counts
- Bone marrow blasts
- IPSS-R cytogenetic risk category
- Molecular genetic information on 31 genes

- The following is needed in addition to the blood counts:
- Cytomorphology (bone marrow blast count)
- Cytogenetics/chromosome analysis
- The IPSS-M panel according to Bernard et al. in molecular genetics
- https://mds-risk-model.com/ The result of the IPSS-M is a number, which is classified into six risk categories: Very Low, Low, Moderate Low, Moderate High, High, Very High

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Treatment

- Supportive and Observation
  - Low risk and Int-1 with 5q- and non-5q-
    - Improve marrow function, decrease impact MDS on QOL, monitor plan
  - Int-2 and high risk
    - Stabilize marrow, lower risk to transform, move to definitive therapy
- BM Transplant
- Chemotherapy
  - Lenalidomide with 5q deletion
  - Azacitidine – splices methyl groups on DNA
  - Decitabine
  - Delay time to progression
- INFECTION is main cause of death
- May treat when MDS converts to a leukemia using standard treatment for the leukemia

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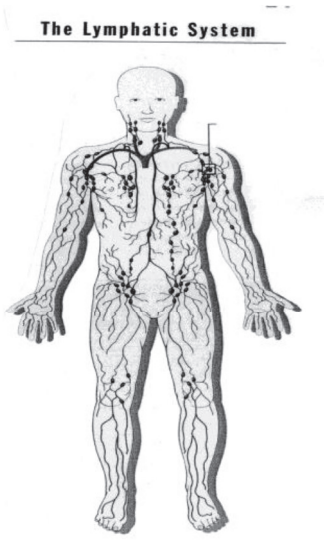
LYMPHOMA



HODGKIN

NHL

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LYMPHOMA

- Primary lymphoid tissues are in bone marrow and the thymus
  - T-cells, B-cells, monocytes in peripheral blood, macrophages in tissues, reticular supporting system forming LN structure, dendritic cells in skin and LN
- Lymphocytes develop from committed lymphoid stem cells in bone marrow
  - A portion migrates to the **thymus**, proliferates and matures into **T-cells** (adults continue to proliferate continually)
  - Lymphocytes maturing in **bone marrow** become **B-cells** (plasma cells, produce immune globulins)

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LYMPHOMA

<u>Secondary Lymphoid Tissues</u>

- LN, spleen, Waldeyers (oropharyngeal lymphoid tissue)
- Peyers patches in gut
- Lymphoid cells in epithelium of gut and respiratory tract (mucosa-associated lymphoid tissue = MALT)

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Lymphoma – Classifications

- Hodgkin Lymphoma
  - **Lymphocyte predominant (5%)**
  - **Nodular sclerosis (75%)**
  - **Mixed cellularity (20%)**
  - **Lymphocyte depleted (<1%)**
- B Cell Indolent NHL
  - **CLL/SLL (blood or LN)**
  - **Lymphoplasmacytic (Waldenstroms)**
  - **Follicular (grade 1-2)**
  - **Hairy Cell Leukemia**
  - **Marginal Zone (Nodal; MALT; Splenic)**
  - **Mantle Cell**
- B Cell Aggressive NHL
  - **DLBCL**
  - **Follicular (grade 3-4)**
- T Cell Lymphoma
  - **Agressive**

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Lymphoma Signs and Symptoms

- Lymphadenopathy (90%)
- Most common are cervical and supraclavicular (75%)
- Mediastinal Mass (60%)
- "B" Symptoms (30%)
  - Fever, night sweats, weight loss
- Hepatosplenomegaly (25%)
- BM (5%)

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Ann Arbor Lymphoma Staging

- I - involvement of single node or organ
- II - involvement of 2 or 3 nodes close to each other (neck, chest, abdomen) – same side of diaphragm
- III - involvement of several node regions in neck, chest, & abdomen (usually above & below diaphragm)
- IV -widespread involvement of nodes or other organs (lung, liver, bones, spleen)

- CBC;ESR; LFT; CMP
- CT TAP; PET; BM
- PFTs; ECHO/MUGA
- HIV if risk factors present
- Excisional biopsy (FNA not adequate)
- Immunophenotyping (CD)
- Cytogentic rearrangements (14;18)
- Overexpression bcl-2 oncogene which is known to prevent cell apoptosis which leads to over accumulation of B-cells = (poorer outcomes)

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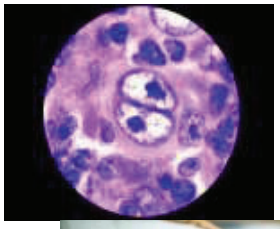
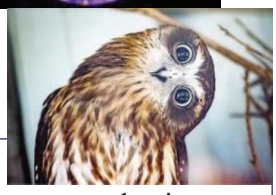
HODGKIN LYMPHOMA

- Malignant cell is Reed-Sternberg cell
- Epidemiology
  - Unknown
  - EBV
- Peak ages 15-34 and then >55 years
- Estimated 7880 new cases and 1330 deaths
- Slightly more men than women
- "A" exhibit no symptoms
- "B" symptoms include >10% weight loss within 6 months, night sweats, fevers, and increased ESR & LDH, lymphadenopathy, splenomegaly
- Diagnosis with excisional biopsy, CT TAP, BM Bx, liver profile, ESR levels





Classical

- Lymphocyte predominant (5%)
- Nodular sclerosis (75%)
- Mixed cellularity (20%)
- Lymphocyte depleted (<1%)

Nodular lymphocyte predominant

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Hodgkin - Treatment

- Early stage disease has 10 year 90% survival rate
- Radiosensitive – XRT
- Chemo
  - ABVD → AVD + Brentuximab Vedotin
  - BEACOPP
  - ICE
  - RICE
  - DHAP
- BMT/PBSCT
- Monitor for tumor lysis, SVC, and tamponade

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Non-Hodgkin Lymphoma (NHL)

Malignancy of T-cells (15%) & B-cell (85%) lymphocytes
Average age is mid-60's
5th most common cancer
Overall incidence increases annually

- Viral/Bacterial
  - H. Pylori- Gastric MALT NHL
  - EBV- Burkitts (Africa)
  - Hep C- some indolent lymphomas (lymphoplasmacytic, Marginal zone)
  - HTLV-1 (Adult T Cell Leukemia/lymphoma- Japan)
- Environmental/Occupational
  - Pesticide/Herbicide exposure
  - Dark Hair Dyes?
- Autoimmune Diseases
  - RA, Sjorgens syndrome, ataxia telangiectasia, etc

- Decreased Immune system
  - Immunosuppressive drugs- organ or bone marrow transplantation
  - Prior chemo and/or irradiation
  - HIV/AIDS
- Hereditary
  - ? Environmental vs. truly hereditary factors
- Dietary
  - Low vegetable intake- increased NHL
  - Red meat- slight increase in NHL

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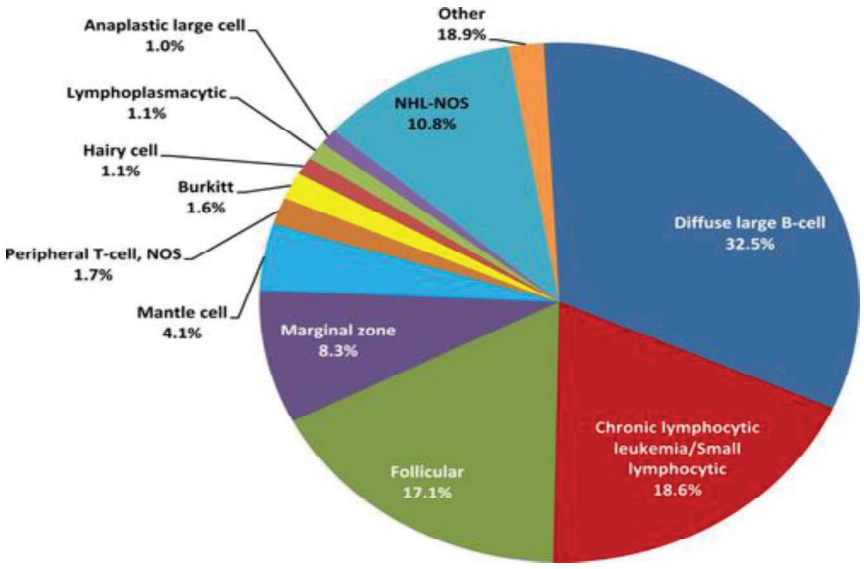
Most Common Subtypes of NHL



https://onlinelibrary.wiley.com/doi/10.1002/ajh.24086

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- Approximately 40 subtypes of NHL with varying clinical behavior patterns
- Most common is diffuse B-cell (typically responds well to rx)
- 2nd most common is follicular (respond well initially but not long term)

Histiocyte

Small Cells	Intermediate Cells	Large Cells
 Small round (Lymphocyte)	 Lymphoblast (Convoluted Lymphoblast)	 Large non-cleaved (Centroblast)
 Small cleaved (Centrocyte)	 Small non-cleaved (Burkitt's lymphoblast)	 Immunoblast (Immunoblast)
 Plasmacytoid small lymph (Immunocyte)		
 Monocytoid small lymph (Monocytoid lymph)		

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NHL – Classifications

- Indolent
  - Disseminated
  - Predominately nodal (liver/spleen/BM)
  - Long median survival
  - Incurable with conventional therapy
  - Relentless relapse after therapy
  - CD19;CD20; CD10; CD5; CD23; Cyclin D1
  - 13q;trisomy 12; 11q;17p
  - IgVH mutation
    - ZAP70
    - CD38
    - Beta 2 microglobulin

- Aggressive
  - May appear localized at diagnosis
  - Minority extranodal
  - Short median survival without treatment
  - Long disease-free survival possible

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NHL – B-Cell Classifications

Indolent

- CLL/SLL
  - blood or LN
- Lymphoplasmacytic (Waldenstroms)
  - Plasmactic differentiation; IgM; CD20; CD19; cyclin D1 neg; MYD88 mutated
- Follicular (grade 1-2)
  - CD20; CD10; BCL6; BCL2; CD5
  - t(14;18) -80-90%
- Hairy Cell Leukemia
  - TRAP +; CD19; CD20; CD25; CD103; CD123; CD200; BRAF
- Marginal Zone (Nodal; MALT; Splenic)
  - H. Pylori; Hep C; t(11;18); 3q; q21;q21
- Mantle Cell
  - t(11;14); overexpression cyclin D1

Aggressive

- DLBCL
  - Nodal or extranodal; CD20; BCL2;BCL6
- Follicular (grade 3-4)

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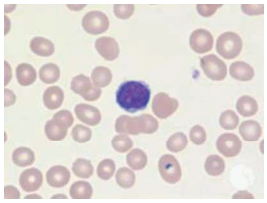
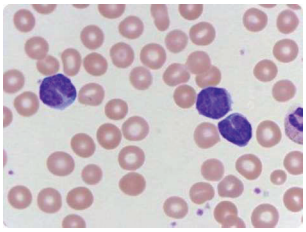
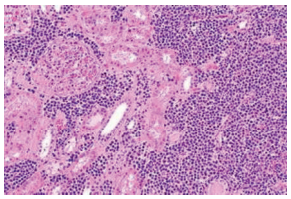


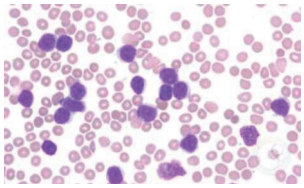
Mantle Cell



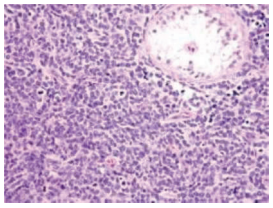
Diffuse Large B-Cell



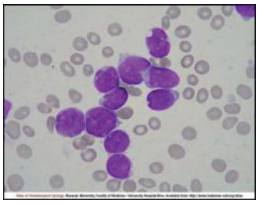
Marginal Zone



Follicular Cell



T-Cell Lymphoblastic



B-Cell Lymphoblastic

http://imagebank.hematology.org/image/61761/mantle-cell-lymphomablood
https://www.keepmeinformed.eu/Condition?conditionGuid=27c2ab95-a41d-4f15-bd14-06b38a5eef41
https://basicmedicalkey.com/lymphoblastic-leukemialymphoma/
https://conquer-magazine.com/issues/2017/vol-3-no-6-december-2017/45-follicular-lymphoma
https://www.google.com/search?q=b+lymphoblastic+lymphoma&tbm=isch&ved=2ahUKEwjNrb_1ndDyAhUUGVkFHb8cB4MQ2-cCegQIABAA&oq=b+lymphoblastic+lymphoma&gs_lcp=CgNpbWcQAzIFCAAQgAQyBggAEAcQHjIICAAQBxAFEB4yBggAEAgQHjIECAAQGDIECAAQGDIECAAQGDoICAAQCBAHEB5QorgCWPy9AmDswgJoAHAAeACAAZgCiAGpA5IBBTAuMS4xmAEAoAEBqgELZ3dzLXdpei1pbWfAAQE&sclient=img&ei=Y1goY3wDJSy5NoPv7mcmAg&bih=577&biw=1280&rlz=1C1GCEA_enUS952US952#imgrc=OfAmLI76CERIYM
https://librepathology.org/wiki/Marginal_zone_lymphoma

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Prognostic Indicators

- IPI (DLBCL)
  - Age; PS; LDH; nodal sites; stage
- FLIPI (Follicular)
  - Age; Stage; Hemoglobin;LDH;# nodal sites
- MIPI (Mantle)
  - Age; PS; LDH; WBC

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NHL – Treatments

CLL/SLL	Follicular	Hairy Cell	Marginal Zone	Mantle Cell	Diffuse Large Cell B-Cell DLBCL
• FCR • BR • FR • PCR • Obinutuzu-mab + Chloram-bucil • BTK Inhibitors (Ibrutinib,Idelalisib, • Veneto-clax • CAR-T	• Watch and wait (grade 1-2) • R-CHOP • R-CVP • R-Benda-mustine • R-FND • Transplant • Bortezo-mib • Lenalido-mide • Bispecifics • CAR-T • Zanubrutinib	• Cladribine • BRAF inhibitors • Vemura-fenib • Dabra-fenib	• Fludara-bine • Rituxi-mab • R-Benda-mustine • BTK inhibitors	• R-CHOP • HCVAD • R-Benda-mustine • Transplant • CAR-T • BTK inhibitors	• R-CHOP • R-EPOCH • R-DHAP • RICE • R-ESHAP • CAR-T • Loncastuximab • Polatuzumab Vedotin • Bispecific T Cell Engagers • Tafasitamab

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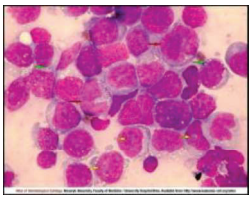
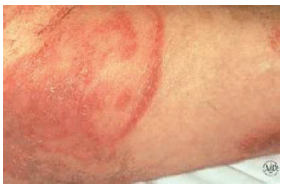
NHL – T-Cell Classifications

- Peripheral T-Cell Lymphoma- (PTCL)
  - Most common
  - Skin and GI extranodal
  - CHOP or CHOEP



- Primary CNS Lymphoma (PCNSL)
  - Rare less than 1%
  - HD MTX/ ARA-C given every 21 days



- Cutaneous T- Cell Lymphoma (CTCL)
  - Mycosis Fungoides
    - Mature T Cell lymphoma that Involves nodes, blood, skin
  - Sézary Syndrome
    - Erythrodermic CTCL, leukemic involvement of malignant T Cells
  - Treatment
    - ECP (Extracorporeal Photophoresis)
    - Romidepsin
    - Brentuximab Vedotin
    - Mogamulizumab
    - Low dose MTX

https://www.google.com/search?q=peripheral+t+cell+&tbm=isch&ved=2ahUKEwjC97nLn9DyAhX8E1kFHWEICOIQ2-cCegQIABAA&oq=peripheral+t+cell+&gs_lcp=CgNpbWcQAzoECAAQQzoLCAAQgAQQsQMQgwE6CAgAEIAEELEDOgUIABCABDoGCAAQChAYUOldEFiCIBBg9buQaABwAHgCgAGKBYgB9xeSAQw0LjExLjAuMS4xLjGYAQCgAQGqAQtnd3Mtd2l6LWItZ8ABAQ&sclient=img&ei=l1ooYYLaN_yn5NoP4cqgkA4&bih=577&biw=1280&rlz=1C1GCEA_enUS952US952#imgrc=5s6eJoTLQLC9kM
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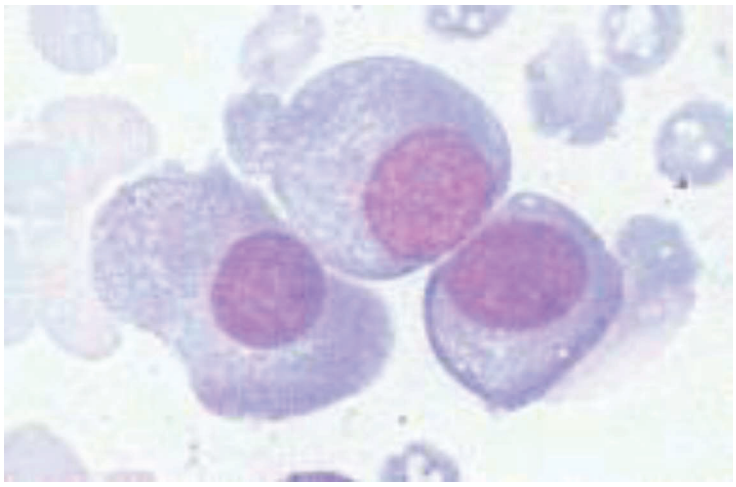
MULTIPLE MYELOMA



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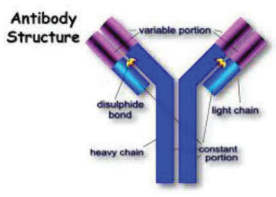
MULTIPLE MYELOMA

- Malignancy of plasma cell with plasma cell dyscrasia – 1% all malignancies
- Effects twice as many African Americans
- Median age 66
- Obesity
- Predisposing MGUS
- Etiology related to ionizing XRT, exposure to metals, hereditary, genetic

- Malignant neoplasm results from proliferation of plasma cells, which results in over production of an immunoglobulin
  - Immunnoglobulins are secretory products of plasma cells
  - Each immunoglobulin has molecule has 2 heavy and 2 light chains
    - Heavy = IgM, IgD, IgG, IgA, IgE
    - Light = Kappa and Lambda
  - /



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Immunoglobulins

- IgG = Found in blood, in many common antibodies that respond to bacteria and viruses
- IgA = found in serum and external body secretions such as saliva, tears, and sweat as well as GI, respiratory, and GU tracts
- IgM = Usually produced first in an immune response and later replaced by other types of antibodies
- IgD = found on surface of B cells (B lymphocytes) – little known about normal function
- IgE = includes antibodies elicited by an allergic substance (allergen) – the "E' stands for "erythema"

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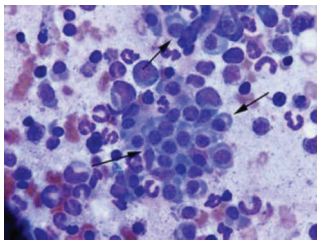
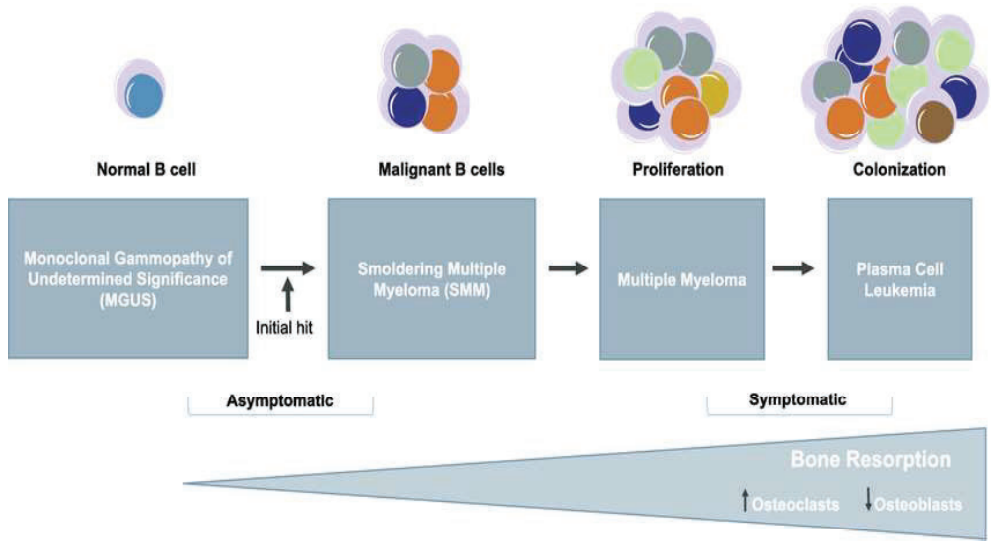
MULTIPLE MYELOMA

- Plasma cells scatter in skeletal and soft tissues
  - produce osteoclast activating factor which produces lytic bone lesions (pathologic fx) and increases bone resorption causing hypercalcemia
  - Osteoclasts erode old bone and resorb formed bone
  - Osteoblasts form new layers of bone
- B-cell differentiated to produce light chain of immunoglobulins
  - B cells are associated with humoral immunity
- (Bence-Jones cells hallmark sign) found in urine
- Proteins damage renal tubular cells



https://www.mspca.org/angell_services/diagnosis-of-multiple-myeloma-bence-jones-proteins/

94



https://www.google.com/search?q=mulitple+myeloma+progression+&tbm=isch&ved=2ahUKEwj0yfiD8OPnAhUBMd8KHTzKD6oQ2-cCegQIABAA&oq=mulitple+myeloma+progression+&gs_lcimg.3...1971140.1977153..1977398...0.0..2.506.5089.4j17j5j2j0j1.....0....1..gws-wiz-img.....0j0i131j0i67j0i10j0i10i24.-R7pfIX0w68&ei=EHJQXvSBJoHi_Aa8IL_QCg&bih=611&biw=1280&rlz=1C1GCEA_enUS841US841#imgrc=unWJEdfGHiX7hM

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Multiple Myeloma – Presentation

- elevated blood proteins or anemia
  (BM crowded by plasma cells with ↓ RBC production and ↑RBC destruction)
- bone pain or back pain secondary to lytic lesions
  (accumulation of plasma cells in bone marrow)
- renal insufficiency secondary to hypercalcemia, hyperviscosity, or deposited of amyloids or immunoglobulins
- M protein coats the RBC and platelets (sticky)
  (hemolysis and sludging of RBCs and platelets normal but abnormal function)

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Multiple Myeloma - Diagnostic Criteria

- bone marrow biopsy
- skeletal survey/bone scan
- lab results -complete chemistry and hematological panel)
- M protein in urine and blood (24 hour urine for electrophoresis)
- serum B-2 microglobulin
- serum calcium
- serum protein electrophoresis
- quantitative immunoglobulins
- serum free light chain assay
- t(4;14); t(14;16); 17p13q; t(11;14); 19q; 1 amplification
- CRAB

  *C: Calcium elevation (> 11.0 mg/L or ULN)
  R: Renal dysfunction (serum creatinine > 2 mg/dL, or CrCl<40)
  A: Anemia (Hb < 10 g/dL or 2 g < normal)
  B: Bone disease (lytic lesions or osteoporosis)

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Patient Criteria	MGUS	Smoldering Myeloma	Active Myeloma
M protein	< 3 g/dL spike	≥ 3 g/dL spike and/or	In serum and/or urine
Monoclonal plasma cells in bone marrow, %	< 10	≥ 10	≥ 10
End-organ damage	None	None	≥ 1 CRAB* criteria

Stage I:
- Indolent disease and stable
- Median survival 40-46 months
- Watch and treat when show progression with symptoms

Stage II :
- Chemo prolongs survival
- 35-40 months
- Monitor every 3 months

Stage III:
- More clinically symptomatic with increased symptoms
- Median survival 24-30 months

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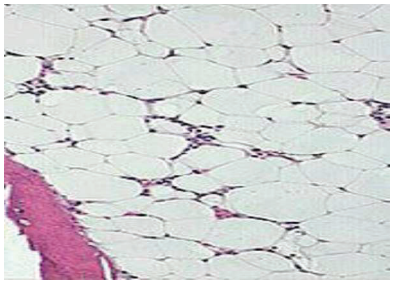
Multiple Myeloma – Treatment

- Allogeneic and autologous PBSCT
- Immunomodulatory Agents
  - Thalidomide; Lenalidomide; Pomalidomide
- Proteasome Inhibitors
  - Bortezomib
  - Carfilzomib
- Decadron
- Daratumumab
- Elotuzumab
- CAR-T
- Teclistamab/Talquetamab
- Assess for hypercalcemia, spinal cord compression, tumor lysis, anemia, renal failure
- Biphosphanates – bone health

- RVD- lenalidomide, bortezomib, dexamethasone
- DRD- daratumumab, lenalidomide dexamethasone
- IRD- Ixazomib, lenalidomide, dexamethasone
- D-RVD- Daratumumab , lenalidomide, bortezomib, dexamethasone
- CyBorD- Cytoxan, Bortezomib dexamethasone.
- KRD- Carfilzomib, lenalidomide dexamethasone
- E- Elotuzumab
- Isa- Isatuximab
- X- Selinexor

HEMTOLOGICAL MALIGNANCIES



APLASTIC ANEMIA

APLASTIC ANEMIA

- Failure or suppression of bone marrow to produce sufficient quantities of all hematopoietic lineages
- Hypoplastic bone marrow which is replaces normal cellular bone marrow with fat
- Most cases due to stem cell damage or lack of stem cells

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Aplastic Anemia

Diagnosis

- fatigue, pallor, petechiae, ecchymosis
- » anemia and thrombocytopenia
- BM Bx

Treatment

- severe cases are treated more aggressively and need PBSCT
- » best results are with sibling matched allogeneic transplant
- » also use immunosuppressive therapy (steroids, growth factors, Atgam or CSA)

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Fundamentals of Oncology Course Post-Assessment- Day 3
Version 1- (2026)

The purpose of this assessment is to verify minimal comprehension of basic oncology concepts and care of the patient with cancer by clinicians caring for oncology patients.

This assessment consists of 9 pages with 36 questions worth 46 points. Please check your booklet to make sure you have the correct number of pages in the proper sequence.

Section I (Multiple Choice)
The following items are multiple choice. There is only <u>one</u> correct answer for each question. Please select and circle the correct answer. (1 point each)

1. Neutrophils arise from which of the following stem cell lineages?
    a. Lymphoid stem cells
    b. Megakaryocyte stem cells
    c. Myeloid stem cells
    d. Epithelial stem cells

2. The most serious complication of chemotherapy that can be fatal in oncology patients is:
    a. anemia.
    b. thrombocytopenia.
    c. neutropenia.
    d. dysplasia.

3. The following bleeding precautions orders have been written for a client with a platelet count of 10,000/mm^3. Which of the following should the nurse question?
    a. Avoid using a blood pressure cuff or tourniquet
    b. Administer rectal acetaminophen for fever of 101F (38.3C)
    c. Apply firm pressure to venipuncture sites for 5 minutes
    d. Obtain an order for stool softener twice a day

4. Myelosuppression is defined as the reduction in bone marrow function that results in a reduced release of which cells into the peripheral circulation?

    a. RBC's, megakaryocytes, tumor necrosis factor
    b. WBC's, erythroblasts, colony-stimulating factors
    c. Platelets, RBC's, interleukin
    d. RBC's, WBC's, platelets

5. Which of the following is responsible for the production of hematopoietic cells?

    a. Myeloid cell
    b. Pluripotent cell
    c. Lymphoid cell
    d. Dendritic cell

6. Granulocytes collectively include:

    a. neutrophils, basophils, eosinophils.
    b. neutrophils, lymphocytes, basophils.
    c. monocytes, lymphocytes, eosinophils.
    d. lymphocytes, neutrophils, basophils.

7. Which of the following cells is capable of self-replication, proliferation, and differentiation?

    a. Pluripotent
    b. Myeloid
    c. Granulocyte
    d. Lymphoid

8. Which of the following cells generates allergic responses and inflammation?
    a. Erythrocytes
    b. Neutrophils
    c. Eosinophils
    d. Basophils

9. Which of the following cells mature into plasma cells?
    a. B-lymphocytes
    b. Memory T-cells
    c. B-cells
    d. T-Lymphocytes

10. The bone marrow aspirate determines which of the following?
    a. Morphology
    b. Infiltration pattern
    c. Cellularity
    d. Stromal cells

11. A patient referred to a hematologist with a tentative diagnosis of AML. The client's only complaint was fatigue. Which of the following diagnostic tests would the hematologist most likely order first?
    a. LFT's
    b. Lumbar puncture with CSF analysis
    c. Uric acid
    d. Bone marrow aspirate and biopsy

12. A patient presents with complaints of fatigue and unintentional weight loss over six months. Labs were WBCs: 43,000/ mm^3, Hemoglobin: 8.3 g/dL, Platelets: 185,000/mm^3. Fluorescent in situ hybridization (FISH) reveals an abnormality on chromosome 9;22. What is the likely diagnosis of this patient?

    a. AML
    b. CML
    c. ALL
    d. CLL

13. Which type of leukemia presents with disseminating intravascular coagulation (DIC)?

    a. Acute promonocytic leukemia
    b. Chronic myeloid leukemia
    c. Acute promyelocytic leukemia
    d. Chronic lymphocytic leukemia

14. Which of the following diseases are characterized by proliferation and accumulation of small, abnormal mature lymphocytes?

    a. AML
    b. CML
    c. ALL
    d. CLL

15. Leukemia cell types are more differentiated in which type of leukemia?

    a. Acute
    b. Chronic

16. A patient diagnosed with ALL complains of new onset of nausea and headaches. It is suspected this patient may be experiencing:

    a. radiation side effects.

    b. chemotherapy side effects.

    c. meningeal irritation.

    d. migraines.

17. A patient's bloods smear shows blast cells with Auer rods. The patient is most likely diagnosed with:

    a. ALL

    b. CLL

    c. AML

    d. CML

18. Which of the following statements best explains why ongoing monitoring of asymptomatic patients with MDS is important?

    a. T-cell abnormalities increase the risk of opportunistic infections

    b. Compliance with the prescribed treatment delays and/or prevents the onset of symptoms

    c. All patients with MDS eventually develop acute leukemia

    d. Patients eventually develop life threatening anemias, thrombocytopenias, and/or neutropenias

19. The Reed-Sternberg cell is the determinant factor for the diagnoses of:

    a. Hodgkin lymphoma.

    b. Non-Hodgkin lymphoma.

    c. Multiple Myeloma

    d. Myelodysplastic Syndrome

20. Which of the following is an example of indolent lymphoma?

    a. Hodgkin
    b. Follicular grade 3-4
    c. Mantle cell
    d. Diffuse large b-cell

21. Which type of cancer produces Bence Jones proteins and damaging casts that result in renal dysfunction, often requiring hemodialysis?

    a. Multiple myeloma
    b. Testicular cancer
    c. Cervical cancer
    d. Myelodysplastic Syndrome

22. Multiple myeloma is a cancer of the following cells:

    a. platelets
    b. red
    c. renal
    d. plasma

23. Which of the following absolute granulocyte count places a client with cancer at greatest risk for developing septic shock? Less than:

    a. $500/mm^3$.
    b. $1000/mm^3$.
    c. $1500/mm^3$.
    d. $2500/ mm^3$.

24. Patients with high WBCs are monitored for complications associated with leukostasis. The most common and lethal complication of leukostasis is:

    a. disseminated intravascular coagulation.
    b. blast crisis.
    c. cerebellar toxicity.
    d. intracerebral hemorrhage.

25. RBC transfusions are indicated for a client with:

    a. platelet count of 90,000, without symptoms.
    b. hbg of 6.7g/dl, without symptoms.
    c. platelet count of 20,000, with no known etiology.
    d. hbg of 9.8 g/dl, experiencing fatigue.

26. A patient six months post stem cell transplant requires a PRBCs transfusion due to Hg 7.4 g/dl with symptoms of increased dyspnea with exertion. Which order is appropriate for this patient?

    a. One unit PRBCs, Leukoreduced, CMV safe
    b. Two-units PRBCs, Irradiated, CMV negative
    c. One unit PRBCs, Leukoreduced, Irradiated, CMV negative
    d. Two units PRBCs, Leukoreduced, CMV negative

27. A patient is hospitalized with pneumonia, and new onset anemia. Labs show Hbg 8.5 g/dl. What additional testing is required?

    a. LDH, CMP, Haptoglobin
    b. Platelet morphology, PT/aPTT, LDH
    c. CMP, EPO, Coombs
    d. Pathology review of peripheral smear, PT/INR, LFT's

28. In which type of transplant is the collection of stem cells from the patient performed with the intent of reinfusing the cells later?

    a. Autologous

    b. Syngeneic

    c. Allogenic

    d. Umbilical cord

29. Which of the following stem cell sources result in the quickest engraftment time post-transplant?

    a. Bone marrow

    b. PBSCT (larger number of PBSC)

    c. UCB

    d. Bone/joint

30. Which of the following cytogenetic abnormalities is associated with an aggressive and poorer prognosis in patients with AML?

    a. RAS

    b. FLT 3 and IDH 1

    c. Translocation 9;22

    d. Deletion 15;17

31. The most effective evidence-based interventions for neutropenia include which of the following?

    a. Low microbial neutropenic diet

    b. Protective isolation

    c. Colony stimulating factors

    d. Live viruses

32. The most common side effects associated with granulocyte-colony stimulating factors includes which if the following?

    a. Splenic rupture
    b. Bone pain
    c. Stroke
    d. QT Prolongation

33. Clinical trials are important in determining if a new treatment is:

    a. profitable for healthcare settings.
    b. better than the current practice.
    c. good clinical practice.
    d. Affordable for patients.

34. Phase IV clinical trials assess:

    A. drug safety.
    B. ongoing side effects of a new treatment.
    C. drug efficacy.
    D. if current practice should be stopped.

Section II (Short answer/Fill in the Blank)
The following items are calculations. You may use formulas and calculators to complete this section. Please be sure to show any work. (1 point each)

35. Calculate the ANC

WBC 5800/uL
Diff:

Neutrophils =	40	Eos =	2
Bands =	4	Baso =	1
Lymph =	36	Atypical Lymphs =	1
Monos =	8	platelets = 85,000/uL	

ANC _____

36. Calculate the ANC

WBC 2900/uL
Diff:

Neutrophils =	5	Eos =	0
Bands =	4	Baso =	0
Lymph =	38	Monos =	5
Atypical lymphs =	1	Platelets = 195,000u/L	

ANC _____

Fundamentals of Oncology Day 3 Evaluation