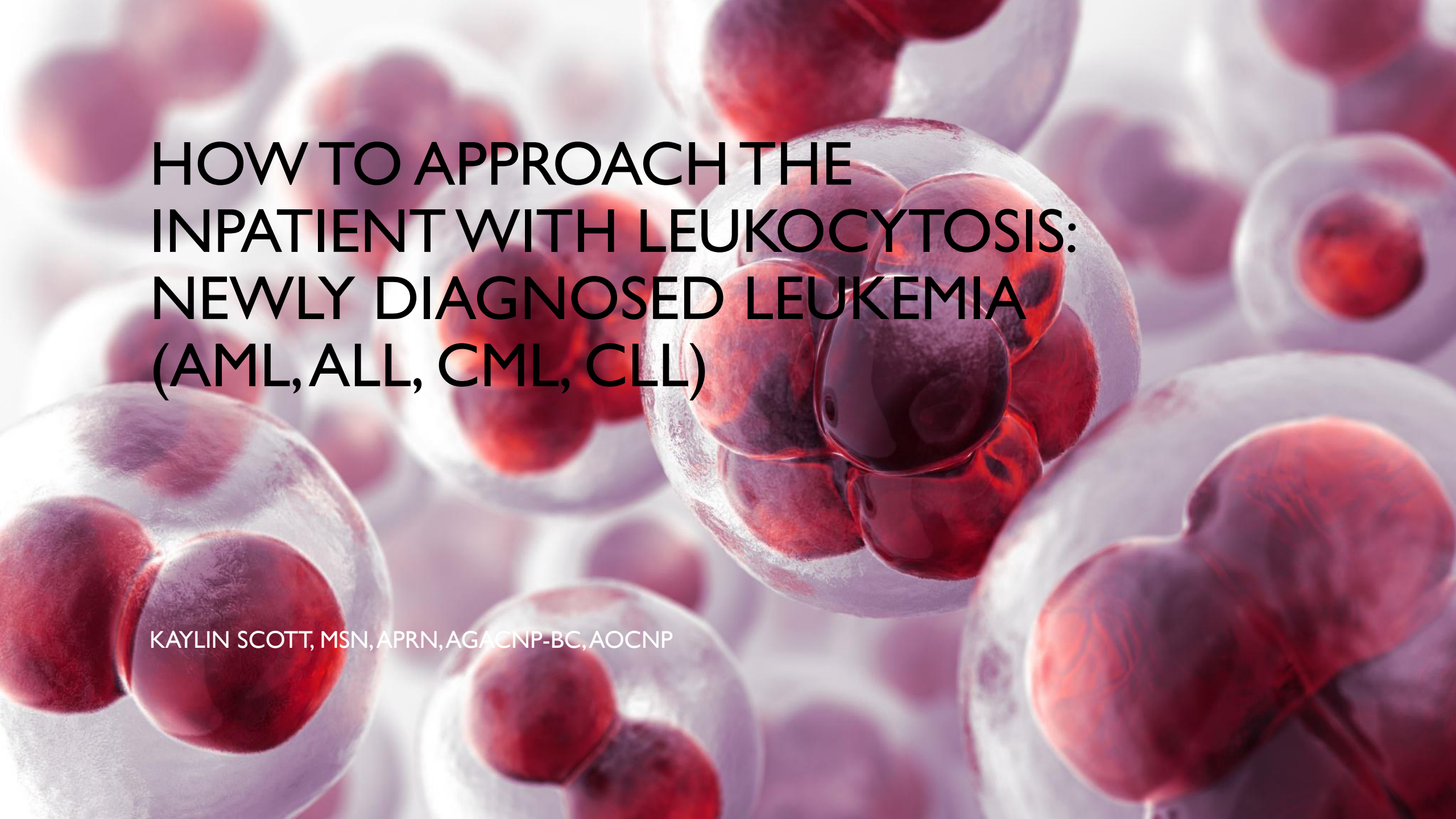
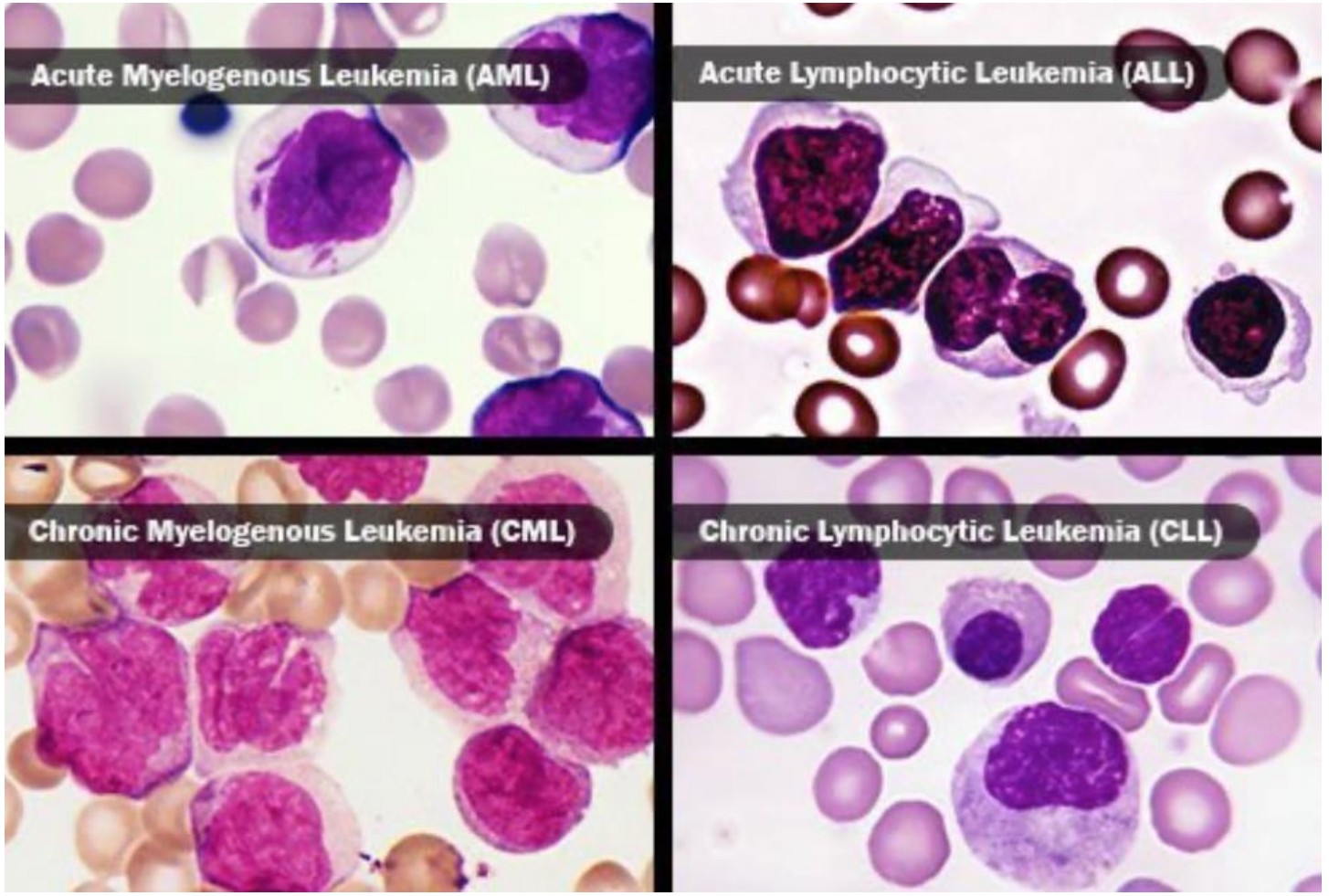


HOW TO APPROACH THE INPATIENT WITH LEUKOCYTOSIS: NEWLY DIAGNOSED LEUKEMIA (AML, ALL, CML, CLL)

KAYLIN SCOTT, MSN, APRN, AGACNP-BC, AOCNP

WHAT WE WILL DISCUSS

- Leukocytosis, specifically in the context of hematologic malignancies.
- Initial ”work up” in patient presenting with leukocytosis.
- Diagnosis and treatment of acute and chronic leukemias.



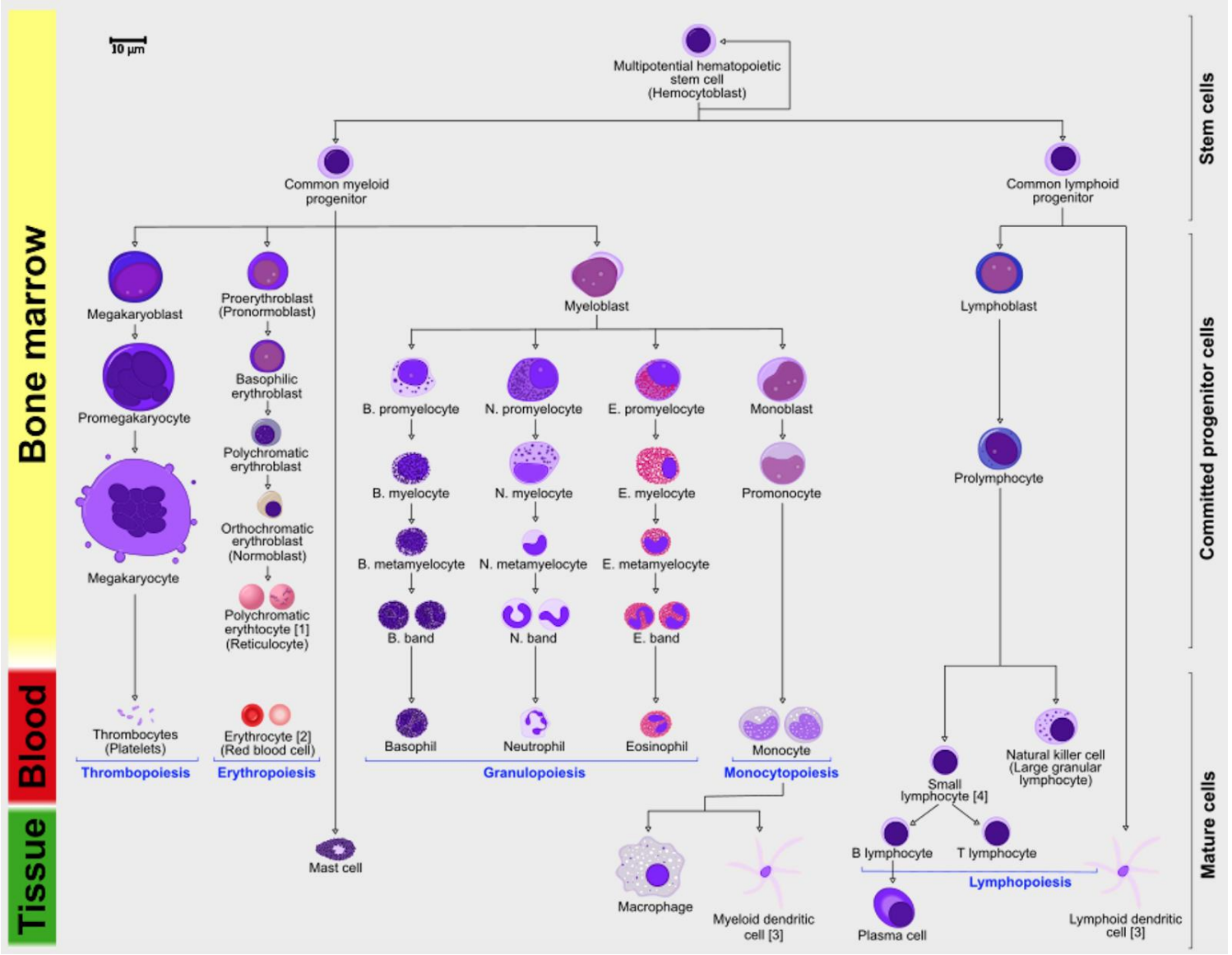
WHAT IS LEUKOCYTOSIS?

- Leukocytosis is defined as a total WBC count greater than 11,000 per mm^3
- WBC count > 100,000 per mm^3 is considered a medical emergency due to the potential for leukostasis (an occlusion of small vessels resulting in ischemia, such as MI or stroke) or coagulopathy (bleeding).
- Leukostasis occurs most commonly with AML and very rarely occurs with ALL or chronic leukemias.
- Leukostasis is treated by prompt cytoreduction with leukopharesis or chemotherapy (Cytarabine).

- Causes of Leukocytosis
  - Infection or Inflammation
  - Physical or Emotional Stress
  - Medications: Steroids
  - Primary Bone Marrow Disorders: Acute Leukemia, Chronic Leukemia, Myeloproliferative Disorders (CML, PV, ET, MF)
- In bone marrow disorders, leukocytosis is often accompanied by anemia and/or thrombocytopenia (though not always).
- Please note that acute leukemias may also present with pancytopenia, including a low WBC count.

HEMATOPOIESIS

- Normal process of maturation of hematopoietic stem cells into mature blood cells.
- Alterations in the growth and maturation of cells along this pathway results in hematologic malignancies.



DIFFERENTIAL

- Laboratory study that distinguishes or differentiates different types of WBCs: neutrophils, lymphocytes, monocytes, eosinophils, and basophils.
- May be performed manually or automated.

	Normal WBC Percentage (%)	Normal Absolute Count
Neutrophils	30-70%	1500-8000
Lymphocytes	20-45%	1000-4500
Monocytes	0-10%	0-800
Eosinophils	0-6%	0-600
Basophils	0-2%	0-200

HOW TO INTERPRET A DIFFERENTIAL

When do you consider hematologic malignancy?

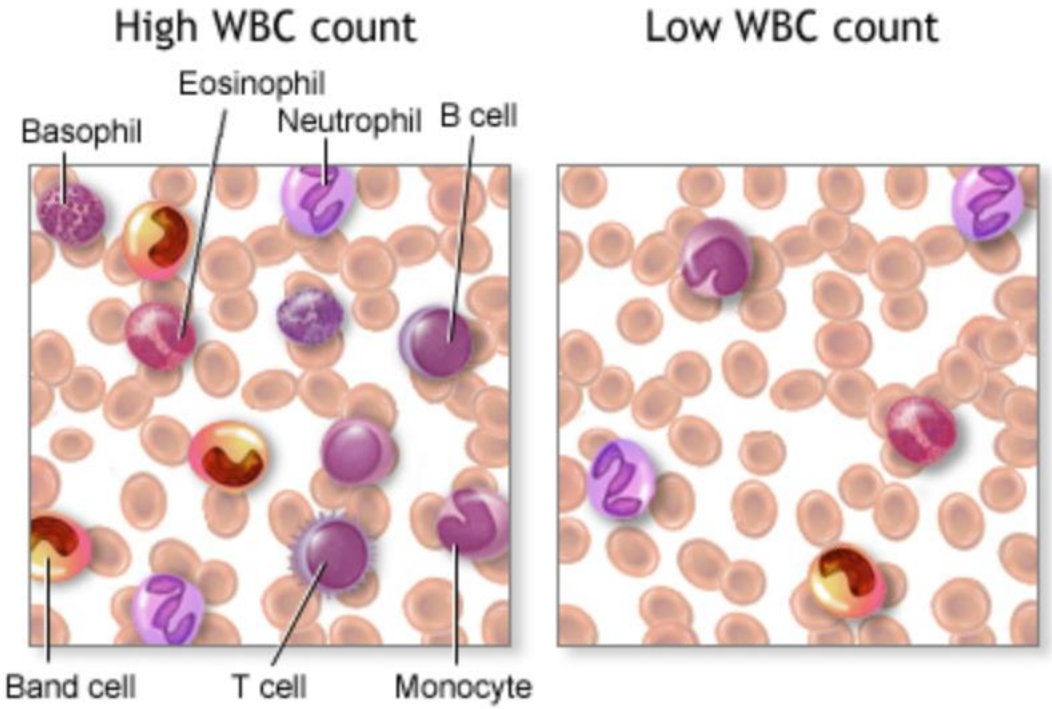
- Patients with acute leukemia may present with leukocytosis, normal WBC count, or leukopenia with associated neutropenia (ANC<1.5 x 10^9/L).
  - Lymphocytosis is most commonly associated with ALL and CLL.
  - Eosinophilia and basophilia are most commonly associated with CML.
  - Neutrophilia is most commonly associated with CML and MPN.
- Abnormal WBC count is most often accompanied by anemia and thrombocytopenia.
- Most importantly, the presence of blast cells (immature, leukemic cells) in the differential is indicative of acute leukemia.
- Proceed with hematologic malignancy work up. Consult Hematology/Oncology.

When do you consider other causes of leukocytosis?

- Leukocytosis with normal differential and without anemia or thrombocytopenia, likely not leukemia.
- Consider other causes, such as infection, inflammation, autoimmune diseases (lupus, RA, vasculitis), solid tumor neoplasms, pregnancy, medications, or smoking.
- Proceed with infectious, autoimmune/inflammatory, or solid tumor work up. Consult Infectious Disease, Rheumatology, or Hematology/Oncology.

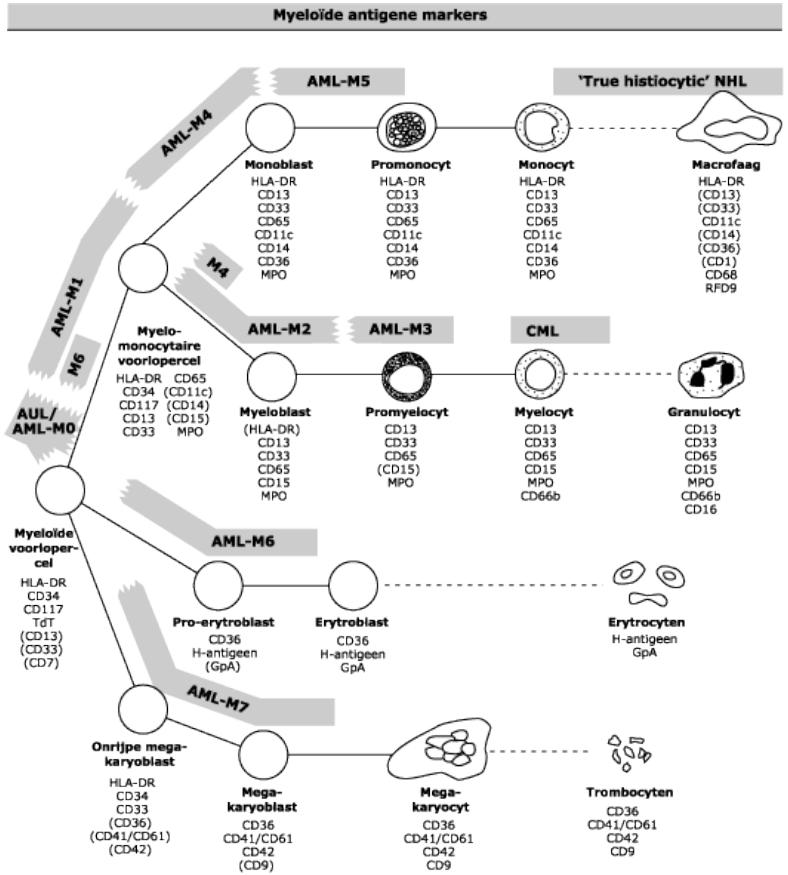
LEUKOCYTOSIS WORK UP: HEMATOLOGIC MALIGNANCY

- Peripheral blood smear
- Peripheral blood flow cytometry
- Anemia: Iron studies, B12, folate, ferritin, haptoglobin, reticulocyte count
- Cell Turn Over and Tumor Lysis: BMP, LDH, uric acid, electrolytes (Ca, K, Mg, Ph)
- Bone marrow biopsy and aspiration
  - Immunohistochemistry (IHC), Immunophenotype
  - Cytogenetics
  - Molecular Studies
- Imaging studies
  - Abdominal US: hepatosplenomegaly
  - CT W IV CO versus PET CT: lymphadenopathy

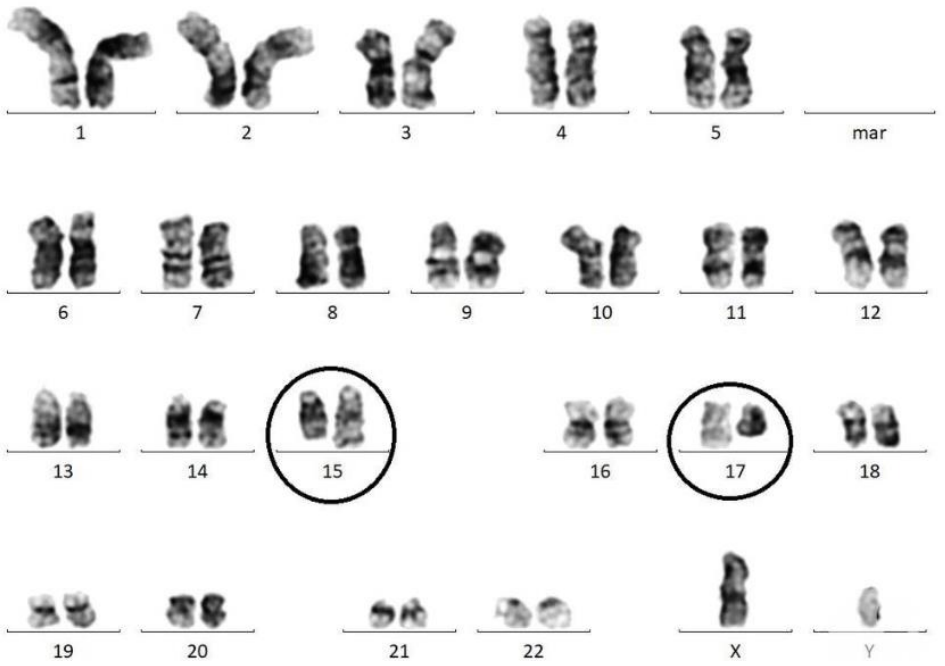


LEUKOCYTOSIS WORK UP

Immunophenotype



Cytogenetics: Karyotype



APL: t(15,17)

ACUTE LEUKEMIA

Acute Myeloid Leukemia (AML)

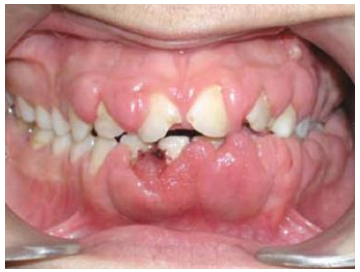
- AML is a heterogenous group of aggressive blood cell cancers that arise from clonal expansion of malignant hematopoetic precursor cells in the bone marrow involving the myeloid lineage. This overgrowth of abnormal cells interferes with the production of normal blood cells.
- Median Age: 68 years old
- American Cancer Society (ACS) estimates that in the United States in 2020:
  - About 19,940 new cases of acute myeloid leukemia (AML). Most will be in adults.
  - About 11,180 deaths from AML. Almost all will be in adults.
  - AML is one of the most common types of leukemia in adults. Still, AML is fairly rare overall, accounting for only about 1% of all cancers.

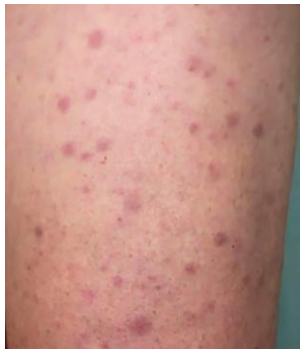
Acute Lymphocytic Leukemia (ALL)

- ALL is a hematologic malignancy caused by the overproduction of immature white blood cells, referred to as lymphoblasts. Classified as B-cell ALL or T-cell ALL depending on which cell lineage is affected. This overgrowth of abnormal cells interferes with the production of normal blood cells.
- Bimodal: Children/Young Adults (2-20 years old) and Older Adults (>50 years old)
- American Cancer Society (ACS) estimates that in the United States in 2021:
  - About 5,690 new cases of ALL (3,000 in males and 2,690 in females)
  - About 1,580 deaths from ALL (900 in males and 680 in females)
  - ALL is not a common cancer, accounting for less than 0.5% of all cancers in the United States.

ACUTE MYELOID LEUKEMIA (AML): DIAGNOSIS

- History & Physical
  - Fatigue, malaise
  - Weight loss and loss of appetite
  - Fever
  - Pallor
  - Dizziness or lightheadedness
  - Shortness of breath or dyspnea on exertion
  - Bleeding (nose, gums) or easy bruising
  - Gingival hyperplasia and/or thrush
  - Adenopathy (myeloid sarcoma)
  - Rash (leukemia cutis)
  - Neurological Changes: AMS, headaches, change in vision (leukemic meningitis vs cerebral hemorrhage)





- Laboratory Studies: CBC diff, CMP, uric acid, LDH, coagulation studies (PT, PTT, INR, fibrinogen)
- Peripheral blood smear
- Bone marrow biopsy/aspiration
  - Flow Cytometry/Immunohistochemistry (IHC) for Immunophenotype: CD34, CD117 (blast markers), CD13, CD14, CD15, CD33, MPO (myeloid markers)
  - Cytogenetics
  - Molecular studies
  - Note: These exams may be performed on peripheral blood in patients with leukocytosis or high blast counts or if delay in bone marrow biopsy is anticipated.

AML: DIAGNOSIS

- Imaging: CT Brain for hemorrhage, MRI Brain for leukemic meningitis, PET CT for extramedullary disease.
- Lumbar Puncture for leukemic meningitis if symptomatic or high risk.
  - Neurologic changes
  - WBC > 40,000 mm3 at time of presentation
  - Monocytic differentiation
  - Expression of CD56
  - LDH>700
- Echocardiogram with strain to evaluate baseline LVEF prior to anthracycline based chemotherapy.
- If anticipating need for allogeneic HSCT, may order HLA typing at time of diagnosis.
- If underlying infection is suspected, perform thorough infectious work up.
- Require central venous access for frequent blood sampling and chemotherapy. PICC line insertion preferable during induction phase.

AML: CLASSIFICATION

- AML is now best classified based upon molecular studies.
- Historically, patients with newly diagnosed AML that were deemed fit for intensive chemotherapy received "7+3" (Cytarabine + Daunorubicin). Now, in the era of targeted therapies, we often wait for results of cytogenetic and molecular testing to determine the best induction regimen for each patient.

Gene	Frequency	Effect
ASXL1	3%–5%	Associated with MDS, AML-MRC. Worse prognosis [19,29,42–44].
BCOR	4% CN-AML	Possible worse prognosis [45].
DNMT3A	20%	Possible worse prognosis. May respond to high dose anthracyclines [18,29].
IDH1	6%–9% adult 1% pediatric	Possible worse prognosis [29,46–49].
IDH2	8%–12% adult 1%–2% pediatric	Controversial. *IDH2* R140 mutation with *NPM1* associated with a favorable prognosis in one study [29,46–49].
MLL/KMT2A	4%–14%	*MLL* PTD shows worse prognosis in CN-AML [18,19,29–31].
NRAS	8%–13% adult and pediatric	No clear impact on prognosis [50,51].
KRAS	2% adult 9% pediatric	No clear impact on prognosis [52].
PHF6	2%–3%	Associated with adverse outcome [29].
RUNX1	5%–18%	Possibly poorer prognosis. May do better with allogeneic transplant [19,29,53].
TET2	7%–10% adult 1.5%–4% pediatric	Unclear, some studies show adverse outcome especially in intermediate risk AML with isolated *CEBPA* or *NPM1* [18,29,54,55].
TP53	2%–9% adult 1% pediatric	Unfavorable prognosis [18,19]. Mutations may be germline (Li-Fraumeni syndrome) and this possibility should be considered when testing especially in younger individuals.
WT1	4%–11%	Poorer outcome, especially in CN-AML [56,57].

MDS: myelodysplastic syndrome, AML-MRC: acute myeloid leukemia with myelodysplasia related changes, PTD: partial tandem duplication, CN-AML: cytogenetically normal acute myeloid leukemia.

AML: RISK STRATIFICATION

- Risk stratification is essential for determining overall treatment strategy, prognosis, and goals of care.
- Favorable risk are thought to be curable with intensive chemotherapy alone. Adverse risk are referred for allogeneic stem cell transplant, best performed in first remission.

Risk Group	Subsets
Favorable	t(8;21)(q22;q22); *RUNX1-RUNX1T1* inv(16)(p13.1q22)/ t(16;16)(p13.1;q22); *CBFB-MYH11* Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} Biallelic mutated *CEBPA* (normal karyotype)
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high} (normal karyotype) Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low} and no adverse genetic lesions t(9;11)(p21.3;q23.3); *MLLT3-KMT2A* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1); *DEK-NUP214* t(v;11q23.3); *KMT2A* rearranged t(9;22)(q34.1;q11.2); *BCR-ABL* inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2); *GATA2,MECOM(EVI1)* -5 or del(5q); -7; abn(17p) Complex karyotype, monosomal karyotype Wild-type *NPM1* and *FLT3*-ITD^{high} Mutated *RUNX1, ASXL1,* or *TP53*

Dohner H, et al. Blood. 2017;129:424-447.

AML: TREATMENT

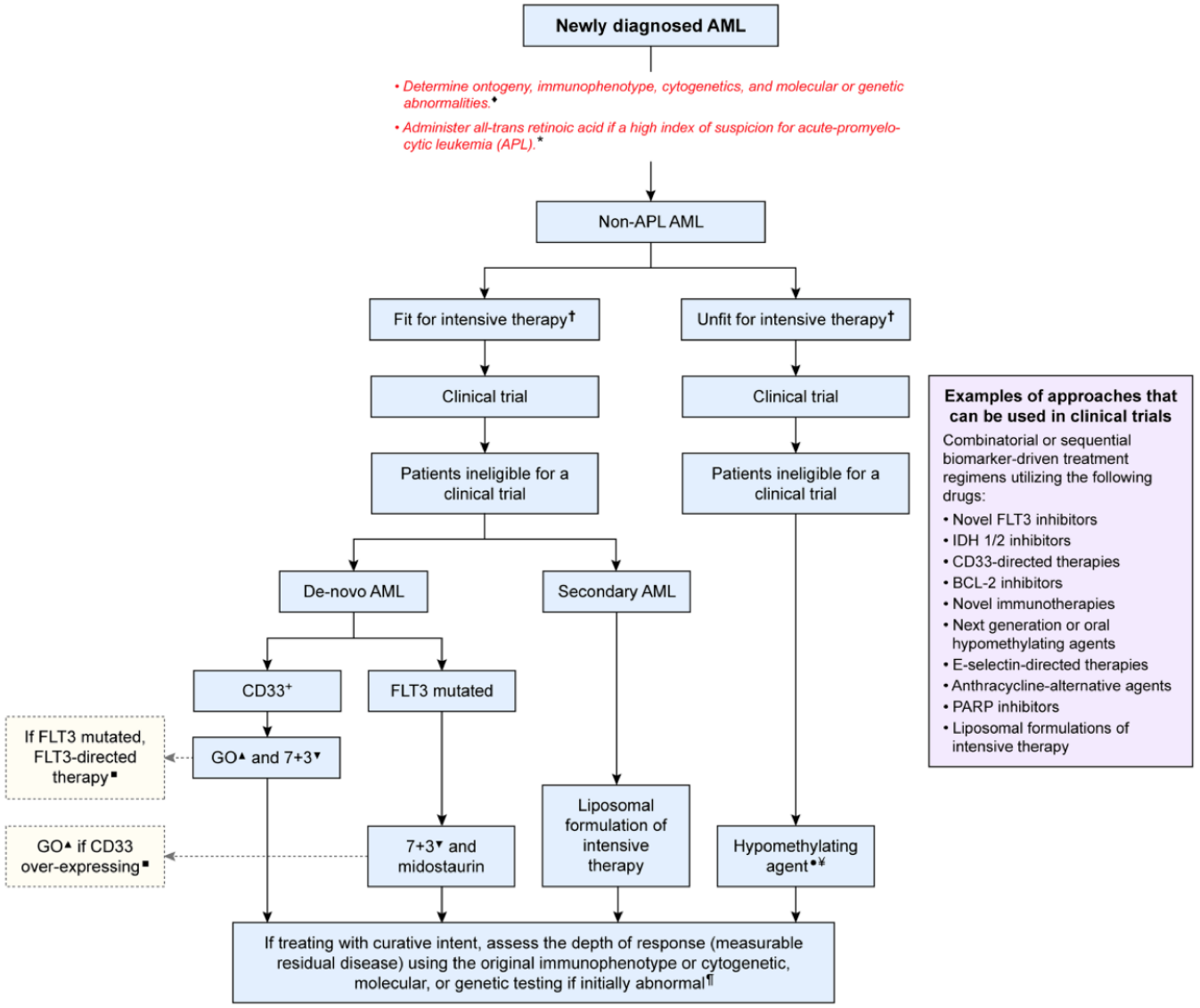
Determine "Goals of Care"

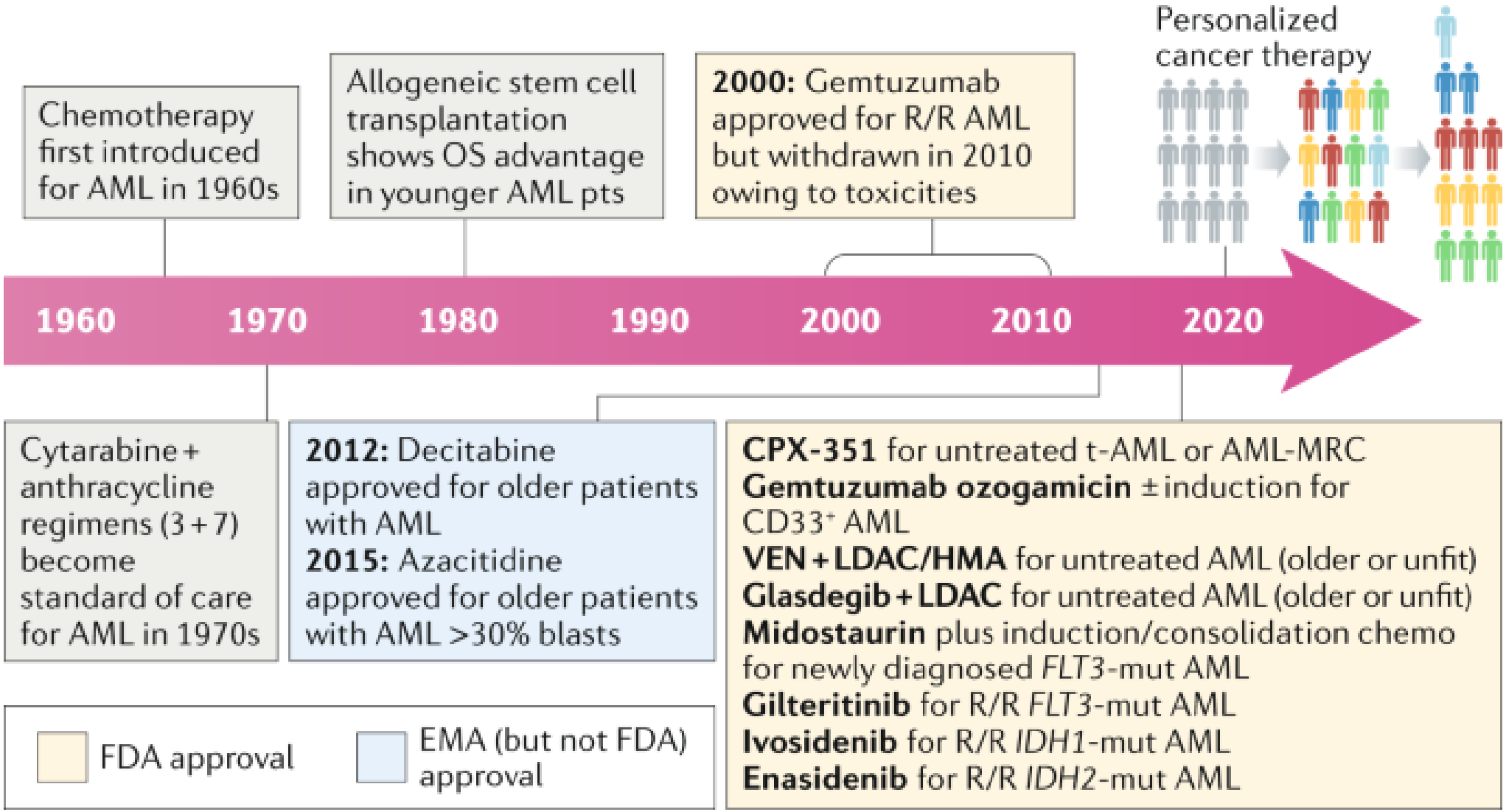
- Curative intent vs palliative intent vs hospice
- Consult Palliative Care and Psychology

Targeted Therapies

- Gemtuzumab: anti-CD33 antibody
- Midostaurin: FLT3 inhibitor
- Gilteritinib: FLT3 inhibitor
- Liposomal daunorubicin/cytarabine
- Enasidenib: IDH2 inhibitor
- Ivosidenib: IDH1 inhibitor
- Venetoclax: BCL2 inhibitor

CNS Involvement of AML




Personalized cancer therapy
Chemotherapy first introduced for AML in 1960s
Allogeneic stem cell transplantation shows OS advantage in younger AML pts
2000: Gemtuzumab approved for R/R AML but withdrawn in 2010 owing to toxicities
1960
1970
1980
1990
2000
2010
2020
Cytarabine + anthracycline regimens (3 + 7) become standard of care for AML in 1970s
2012: Decitabine approved for older patients with AML
2015: Azacitidine approved for older patients with AML >30% blasts
CPX-351 for untreated t-AML or AML-MRC
Gemtuzumab ozogamicin ± induction for CD33+ AML
VEN + LDAC/HMA for untreated AML (older or unfit)
Glasdegib + LDAC for untreated AML (older or unfit)
Midostaurin plus induction/consolidation chemo for newly diagnosed FLT3-mut AML
Gilteritinib for R/R FLT3-mut AML
Ivosidenib for R/R IDH1-mut AML
Enasidenib for R/R IDH2-mut AML
FDA approval
EMA (but not FDA) approval

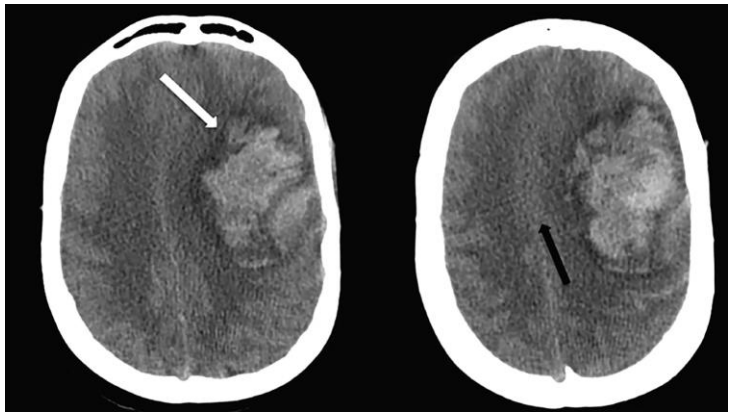
AML EMERGENCIES

Leukostasis

- WBC count > 100,000 per mm^3 is considered a medical emergency due to the potential for leukostasis (an occlusion of small vessels resulting in ischemia, such as MI or stroke).
- Leukostasis occurs most commonly with AML.
- Leukostasis is treated by prompt cytoreduction with leukopharesis or chemotherapy (Cytarabine 1-2g).
- If hyperleukocytosis without signs and symptoms of leukostasis, may initiate Hydrea for cytoreduction.

DIC, Bleeding

- Monitor CBC and coagulation studies frequently (q6h).
- Transfuse aggressively as needed (pRBCs, platelets, cryoprecipitate, FFP).
- Correction of coagulopathy (recombinant factor VIIa).
- Intervention if possible (Neurosurgery, GI, IVR).



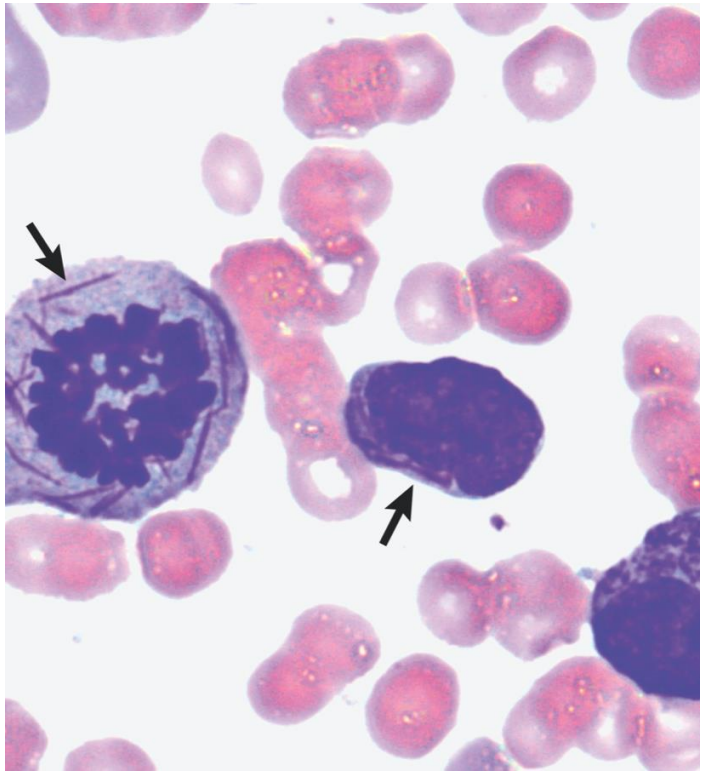
AML EMERGENCIES

Tumor Lysis Syndrome

- Elevated WBC count may result in autologous TLS (prior to initiation of cytotoxic therapy) resulting in renal failure, dysrhythmias, or seizures
- Signs of TLS
  - Uric acid >8 mg/dL
  - Potassium >6 mEq/L
  - Phosphorus >4.5 mg/dL
  - Calcium <7 mg/dL
  - Elevated creatinine
- Treatment
  - Aggressive hydration
  - Allopurinol
  - Rasburicase (may result in hemolytic anemia if G6PD deficient)
  - Avoid calcium replacement as this may worsen renal deposition and failure
  - Nephrology consultation

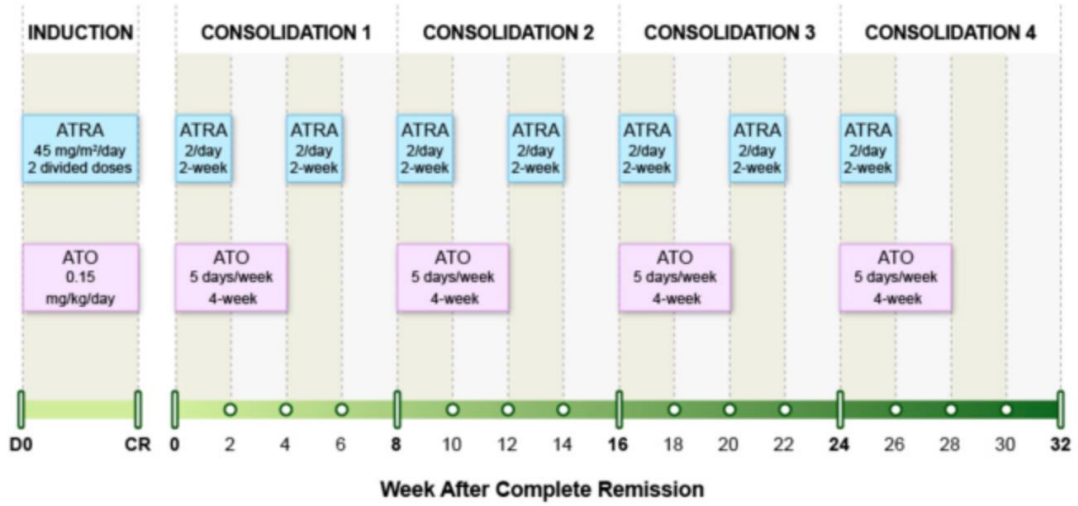
Degree of risk	Disease
High	• ALL with WBC ≥100,000 cells/μL or LDH >2x ULN • AML with WBC ≥50,000 cells/μL • Burkitt lymphoma/leukemia (stage III or IV) • Lymphoblastic lymphoma (stage III or IV) • Any intermediate risk patient with renal involvement or renal insufficiency • Any intermediate risk patient with LTLS
Intermediate	• ALL with WBC <100,000 cells/μL and LDH <2x ULN • AML with WBC 10,000-50,000 cells/μL • Bulky solid tumors • Burkitt lymphoma/leukemia (stage I or II) • Lymphoblastic lymphoma (stage I or II) • NHL with LDH >2× ULN
Low	• AML with WBC ≤10,000 cells/μL • CLL • CML • Hodgkin lymphoma • Indolent NHL • Multiple myeloma • NHL with LDH <2× ULN • Select solid tumors

ACUTE PROMYELOCYTIC LEUKEMIA (APL)



- Subclassification of AML characterized by t(15,17) or PML-RARA
  - May be determined by peripheral blood smear (Auer rods) and definitively by FISH
- Relatively rare, accounting for 10-15% of all newly diagnosed AML (approximately 800 patients/yr in US)
- Median Age: 40
- High curable (CR 92-100%) if patient survives initial onset without major bleeding (intracranial hemorrhage)
- Often presents with low WBC, low platelets, coagulopathy (low fibrinogen), spectrum of "bleeding to clotting"
- If there is any suspicion of APL, patient should be immediately started on all-trans retinoic acid (ATRA). Once diagnosis is confirmed, begin arsenic trioxide (ATO)
- Aggressive transfusion support to maintain platelets >50,000, fibrinogen >151 mg/dL, and INR<2.0

APL: TREATMENT



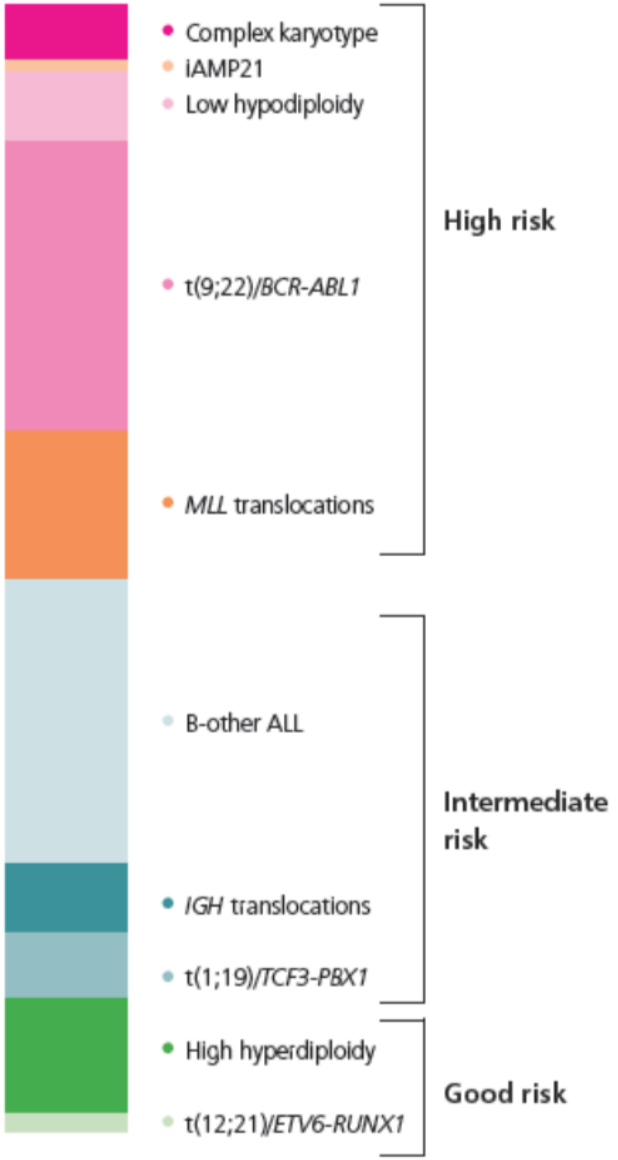
- Risk Stratification:
  - Low risk if WBC<10,000/mcL
  - High risk if WBC>10,000/mcL
- Induction Treatment
  - Low Risk: ATRA 22.5mg/m2 q12h + ATO 0.15mg/m2 QD d1-28
  - High Risk: Addition of gemtuzumab ozogamicin 6-9mg/m2 (single dose)
- Differentiation Syndrome:
  - Signs/Symptoms: fever, rising WBC, SOB, hypoxemia, pleural effusion, pericardial effusion
  - Prophylaxis (high risk): Prednisone 0.5mg/kg
  - Treatment: Dexamethasone 10mg q12h
- Monitor electrolytes closely (K>4.0 and Mg?2.0) and QTc interval weekly.
- If patient receives gemtuzumab ozogamicin, monitor closely for signs of veno-occlusive disease (VOD) and begin Ursodiol for VOD prophylaxis.

ACUTE LYMPHOCYTIC LEUKEMIA (ALL): DIAGNOSIS

- History & Physical
  - Fatigue, malaise
  - Weight loss
  - Fever, night sweats
  - Frequent infections
  - Bleeding, easy bruising
  - Pallor
  - Shortness of breath or dyspnea on exertion
  - Lymphadenopathy, mediastinal mass
  - Bone pain
  - Headache, change in vision (leukemic meningitis)
  - Testicular pain

- Laboratory Studies: CBC diff, CMP, uric acid, LDH, coagulation studies (PT, PTT, INR, fibrinogen)
- Peripheral blood smear
- Bone marrow biopsy/aspiration
  - Flow Cytometry/Immunohistochemistry (IHC) for Immunophenotype: CD10, CD19, CD20, CD22 (B-cell markers) or CD2, CD3, CD5, CD7 (T-cell markers)
  - Cytogenetics
  - Molecular studies
  - Note: These exams may be performed on peripheral blood in patients with leukocytosis or high blast counts or if delay in bone marrow biopsy is anticipated.

ALL: SUBTYPES AND RISK STRATIFICATION



- Types of ALL
  - B-cell ALLs (80%)
    - BCR-ABL positive
    - BCR-ABL negative
  - T-cell ALLs (20%)
    - Early T-cell precursor (ETP): lack CD1a, CD8 and express 1 or more myeloid marker
- Risk stratification is largely determined by presence of MRD (minimal residual disease) following induction chemotherapy.

ALL: TREATMENT

B-cell ALL

- BCR-ABL Positive
  - Young: Hyper-CVAD + TKI
  - Old: D-ABLA Protocol (Steroids + TKI with Blinatumomab consolidation)
- BCR-ABL Negative
  - Young: Pediatric-Inspired Regimen, Hyper-CVAD
  - Old: mini-CVD +/- Rituxan (CD20) +/- Inotuzumab (CD22)

T-cell ALL

- Pediatric-Inspired Regimens: COG AALL0434

Table. Principles of Pediatric-Type Adult ALL Regimens

- Mostly based on Berlin-Frankfurt-Münster backbone
- Multiple cycles of non–cross-resistant agents
- Early and frequent CNS prophylaxis
- Repeated doses of asparaginase
- Prolonged maintenance
- Less myelosuppression
- Higher cumulative doses of active agents

ALL = acute lymphoblastic leukemia; CNS = central nervous system.

Table. Principles of Pediatric-Type Adult ALL Regimens

ACUTE LEUKEMIAS: SUPPORTIVE CARE

Infection

- Patients with acute leukemia are severely immunocompromised and at high risk of infection.
- Infection Prophylaxis
  - Antiviral: Acyclovir
  - Antibacterial: Levofloxacin
  - Antifungal: Posaconazole (AML), Fluconazole (ALL), Micafungin (inpatient, IV only)
- Neutropenic Fever (Tmax > 38C)
  - Considered medical emergency
  - Comprehensive Infectious Work Up: blood cultures, urinalysis, urine culture, respiratory pathogens panel, CXR, further testing based on symptoms, ID consult
  - Empiric Antibiotics: Cefepime +/- Vancomycin, Merrem (hx of ESBL)

Tumor Lysis Syndrome

- Monitor CMP, uric acid, LDH closely with initiation of chemotherapy (q8h).
- Aggressive hydration.
- Allopurinol for prophylaxis.
- May require Rasburicase prior to initiation of chemotherapy.

Bleeding

- Monitor CBC and coags frequently with initiation of chemotherapy (q8h).
- Standing orders for transfusions to prevent delays.
- Platelet testing (HLA, antibody ID) in platelet refractory patients.

CHRONIC LEUKEMIAS

Chronic Myeloid Leukemia (CML)

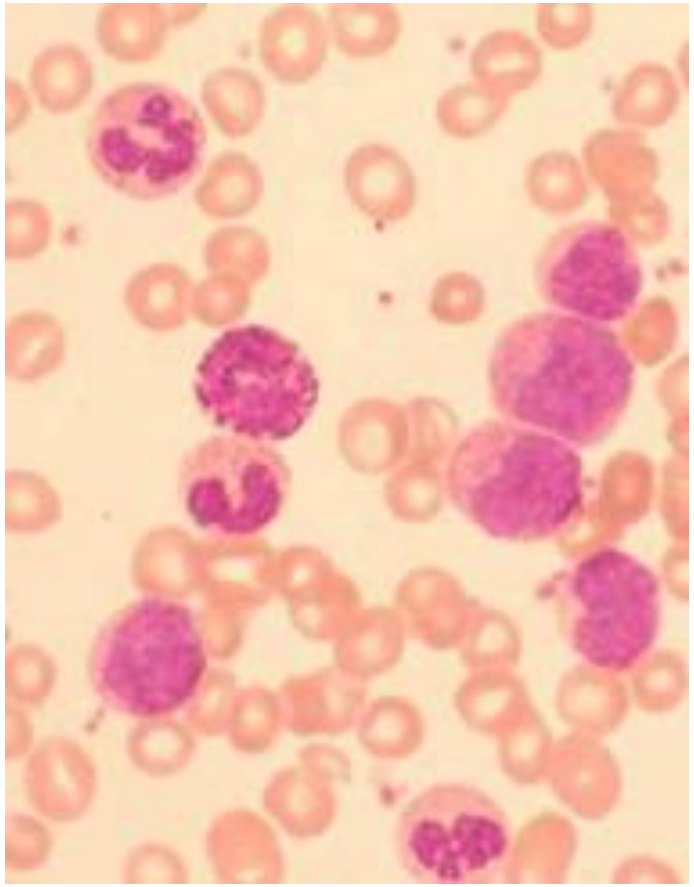
- Most commonly seen in middle aged adults (40-45 years old)
- Often asymptomatic and usually diagnosed incidentally on routine blood work demonstrating anemia and leukocytosis.
- Presence of Philadelphia chromosome (BCR-ABL or t(9,22))
- Three Phases of CML
  - Chronic Phase
  - Accelerated Phase
  - Blast Phase
- Treatment: TKIs

Chronic Lymphocytic Leukemia (CLL)

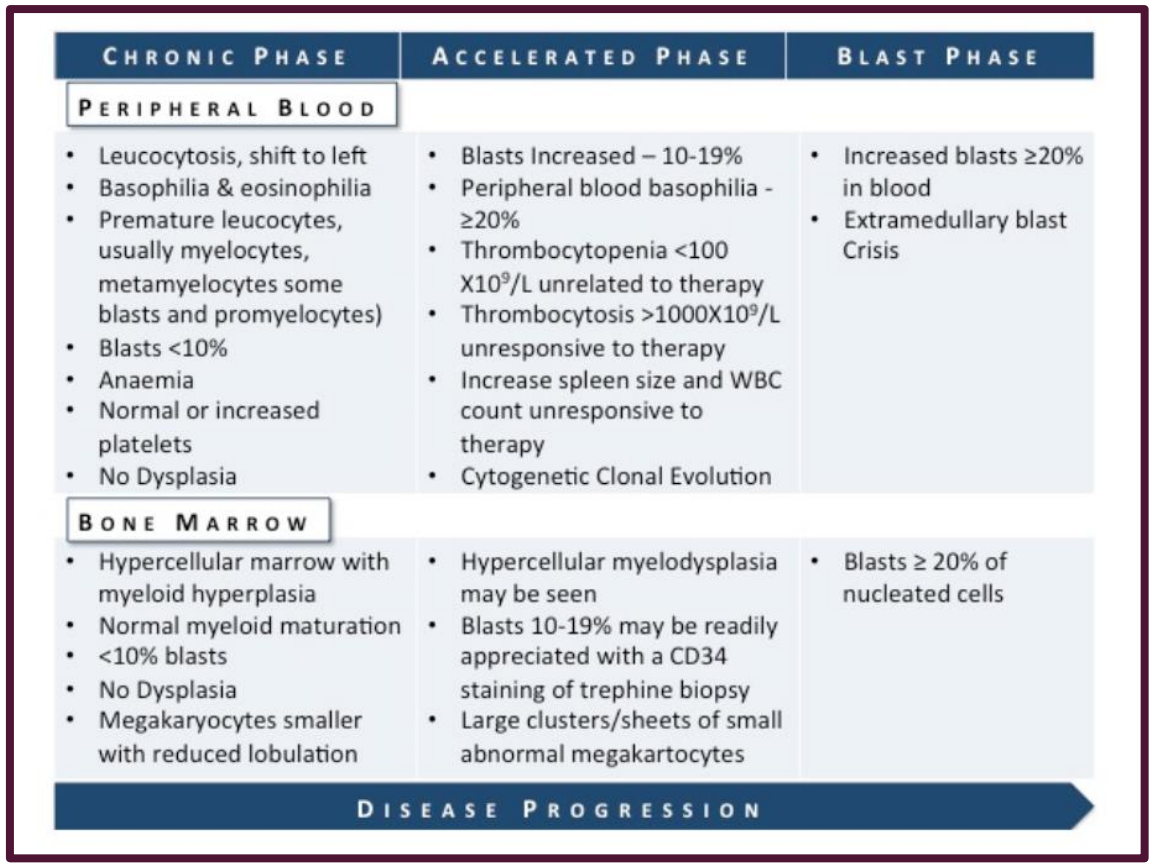
- Most commonly seen in older adults (60 years old)
- Often does not require treatment and a "watch and wait" approach is taken unless indications for treatment are present.

CHRONIC MYELOID LEUKEMIA (CML): DIAGNOSIS

- History & Physical
  - May be asymptomatic
  - Fatigue
  - Weight loss
  - Fever, night sweats
  - Abdominal pain or fullness, early satiety related to hepatosplenomegaly
- Laboratory Studies: CBC diff, CMP, uric acid, LDH
  - Chronic Phase: anemia and leukocytosis +/- thrombocytosis
  - Blast Phase: worsening anemia, leukocytosis with blasts, thrombocytopenia
- Peripheral blood flow cytometry to evaluate for accelerated or blast phase
- Bone marrow biopsy/aspiration for morphology, cytogenetics for t(9,22), and molecular studies for BCR-ABL
- Quantitative PCR for BCR-ABL (peripheral blood and marrow)
- Abdominal Imaging: US or CT to quantify splenomegaly
- Hepatitis Panel: If Hep B core ab positive, prophylaxis with tenofovir for prevention reactivation with rituximab



CML: PHASES AND TREATMENT



Chronic Phase	Accelerated Phase	Blast Phase
Peripheral Blood		
• Leucocytosis, shift to left • Basophilia & eosinophilia • Premature leucocytes, usually myelocytes, metamyelocytes some blasts and promyelocytes) • Blasts <10% • Anaemia • Normal or increased platelets • No Dysplasia	• Blasts Increased – 10-19% • Peripheral blood basophilia - ≥20% • Thrombocytopenia <100 $X10^9$/L unrelated to therapy • Thrombocytosis >1000$X10^9$/L unresponsive to therapy • Increase spleen size and WBC count unresponsive to therapy • Cytogenetic Clonal Evolution	• Increased blasts ≥20% in blood • Extramedullary blast Crisis
Bone Marrow		
• Hypercellular marrow with myeloid hyperplasia • Normal myeloid maturation • <10% blasts • No Dysplasia • Megakaryocytes smaller with reduced lobulation	• Hypercellular myelodysplasia may be seen • Blasts 10-19% may be readily appreciated with a CD34 staining of trephine biopsy • Large clusters/sheets of small abnormal megakartocytes	• Blasts ≥ 20% of nucleated cells
Disease Progression		

Chronic Phase

- Hydroxyurea for cytoreduction until confirmation of diagnosis
- Tyrosine Kinase Inhibitors (TKIs)
  - First Line
    - Imatinib
    - Dasatinib
    - Nilotinib
  - Second Line
    - Ponatinib (T315I mutation)
    - Bosutinib

Accelerated/Blast Phase

- Tyrosine Kinase Inhibitors (TKIs) at higher doses
- Treated like B-ALL

CHRONIC LYMPHOCYTIC LEUKEMIA (CLL): DIAGNOSIS AND STAGING

Diagnosis

- Immunophenotype: CD5, CD19, CD20, CD23
- Cytogenetics: del(13q), del(11q), del(17p), add(12)
- Molecular Studies: tp53, IGVH mutation
- Beta 2 microgloublin
  - Del(17p)/tp53, unmutated IGVH, ZAP-70, CD38 and beta 2 > 3.5 mg/L re associated with poor prognosis
- Immunoglobulins: If IgG<400, replace with IVIG.
- Abdominal imaging to evaluate for hepatosplenomegaly
- PET CT to evaluate for lymphadenopathy.
- May transform to an aggressive large B-cell lymphoma (Richter transformation).
- Associated with AIHA and ITP.

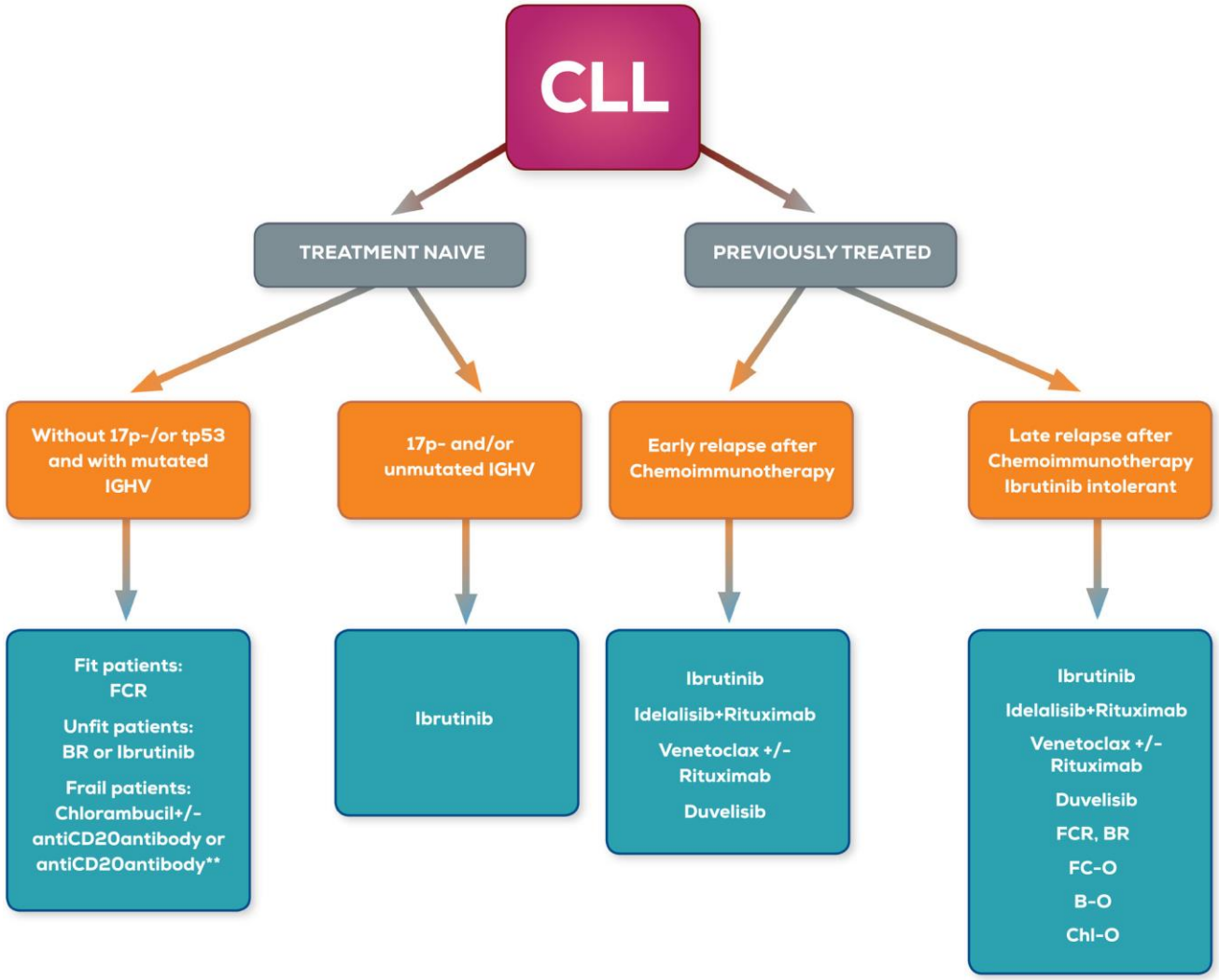
Staging: Rai and Benet

Risk Stratification	Rai Stage	Binet Stage
Low risk	0: Lymphocytosis only	A: <3 Lymphadenopathies
Intermediate risk	I: Lymphadenopathy	B: >3 Lymphadenopathies
	II: Organomegaly (splenomegaly/hepatomegaly)	
High risk	III: Anemia (hemoglobin <11 g/dL)	C: Hemoglobin <10 g/dL and/or platelets <100 × 10^9/L
	IV: Thrombocytopenia (platelets <100 × 10^9/L)	

CLL: INDICATIONS FOR TREATMENT

- Anemia (Hb <10 g/dL) or thrombocytopenia (platelet counts <100 × 10^9/L).
- Massive (ie, ≥6 cm below the left costal margin) or progressive or symptomatic splenomegaly.
- Massive nodes (ie, ≥10 cm in longest diameter) or progressive or symptomatic lymphadenopathy.
- Progressive lymphocytosis with an increase of ≥50% over a 2-month period, or lymphocyte doubling time (LDT) <6 months.
- Autoimmune complications including anemia (AIHA) or thrombocytopenia (ITP) poorly responsive to corticosteroids.
- Symptomatic or functional extranodal involvement (eg, skin, kidney, lung, spine).
- Disease-related symptoms as defined by any of the following:
  - Unintentional weight loss ≥10% within the previous 6 months.
  - Significant fatigue (ie, ECOG performance scale 2 or worse; cannot work or unable to perform usual activities).
  - Fevers ≥100.5°F or 38.0°C for 2 or more weeks without evidence of infection.
  - Night sweats for ≥1 month without evidence of infection.

CLL: TREATMENT



EXAMPLE 1

Lab View	08/28/2021 10:00 - 21:59 EDT	08/27/2021 22:00 - 9:59 EDT	08/27/2021 10:00 - 21:59 EDT	08/26/2021 22:00 - 9:59 EDT	08/26/2021 10:00 - 21:59 EDT	08/25/2021 22:00 - 9:59 EDT	08/25/2021 10:00 - 21:59 EDT
Blood Count							
Hemoglobin	7.7 (L)	8.4 (L)	8.1 (L)	8.3 (L)	8.8 (L)	8.4 (L) [2][(L	8.8 (L)
Hematocrit	21.8 (L)	24.2 (L)	23.0 (L)	23.1 (L)	24.9 (L)	23.4 (L) [2][	25.1 (L)
WBC	0.47 (!)	0.26 (!)	0.28 (!)	0.30 (!)			0.44 (!)
Platelet Count	65 (L)	46 (L)	35 (L)	23 * (!)			26 * (!)
RBC	2.33 (L)	2.56 (L)	2.43 (L)	2.47 (L)			2.69 (L)
MCV	93.6	94.5	94.7	93.5			93.3
Absolute Neutrophils	0.14 (L)		0.07 (L)	0.07 (L)			0.11 (L)
Absolute Neutrophils-Calculated		0.10 (L)					
Absolute Lymphocytes	0.28 (L)		0.19 (L)	0.21 (L)			0.29 (L)
Absolute Lymphocytes-Calculated		0.16 (L)					
Absolute Monocytes	0.03 (L)		0.02 (L)	0.02 (L)			0.03 (L)
Absolute Monocytes-Calculated		0.00 (L)					
Absolute Eosinophils	0.00		0.00	0.00			0.00
Routine Coagulation							
PT - INR (Prothrombin Time)	13.3	13.7	13.4	14.0	14.4	14.9	15.2
International Normalized Ratio	1.0 *	1.1 *	1.0 *	1.1 *	1.1 *	1.2 *	1.2 *
PTT (Partial Thromb Time)	23.7	25.1	25.2	26.7	25.4	26.4	22.4
Fibrinogen Level	208 (L)	198 (L)	223 (L)	230 (L)	214 (L)	195 (L)	228 (L)

EXAMPLE 2

Blood Count							
Hemoglobin	9.0 (L)	9.6 (L)	10.9 (L)	11.0 (L)	11.1 (L) [2][	11.8 (L)	13.4
Hematocrit	27.4 (L)	28.9 (L)	32.8 (L)	34.5 (L)	34.3 (L) [2][	37.3 (L)	40.9
WBC	13.38 (H)	22.17 (H)	26.06 (H)	32.60 (H)	40.72 (H) [2	40.82 (H)	85.18 * (!)
Platelet Count	40 (L)	29 * (!) [2][(	26 * (!)	37 (L)	51 (L) [2][(L)	60 * (L)	160
RBC	2.90 (L)	3.08 (L)	3.48 (L)	3.59 (L)	3.61 (L) [2][	3.86 (L)	4.30
MCV	94.5	93.8	94.3	96.1	95.0 [2]	96.6	95.1
Absolute Neutrophils-Calculated	10.97 (H)	14.63 (H)	11.47 (H)	16.95 (H)		15.10 (H)	12.78 (H)
Absolute Lymphocytes							
Absolute Lymphocytes-Calculated	0.40 (L)	0.89	2.35	1.96		2.86	0.00 (L)
Absolute Monocytes							
Absolute Monocytes-Calculated	1.47 (H)	3.55 (H)	7.82 (H)	7.50 (H)		8.57 (H)	42.59 (H)
Absolute Eosinophils							
Absolute Eosinophils-Calculated	0.00	0.00	0.00	0.00		0.00	0.00
Blasts	4 * (H)						84 * (!)
Other Cells		8	17 *	13 *		35 *	0 * (c)
Routine Coagulation							
PT - INR (Prothrombin Time)	16.2 (H)	16.3 (H)	16.6 (H)	18.3 (H)		18.1 (H)	
International Normalized Ratio	1.4 * (H)	1.4 * (H)	1.4 * (H)	1.6 * (H)		1.6 * (H)	
PTT (Partial Thromb Time)	38.9	39.4 (H)	38.5	43.3 (H)		51.0 (H)	
Fibrinogen Level	610 (H)	581 (H)	650 (H)	610 (H)		427	

EXAMPLE 3

Blood Count							
Hemoglobin	6.6 * (!)	7.1 (L) [3][(!	7.2 (L)	7.8 (L)	8.0 (L) [3][(!	4.3 * (!) [2][	
Hematocrit	19.3 * (!)	20.7 * (!) [3	21.2 (L)	22.8 (L)	23.9 (L) [3][	13.7 * (!) [2	
WBC	26.18 (H)	101.18 * (!)	72.53 * (!)		223.66 * (!)	389.46 * (!)	
Platelet Count	20 * (!)	56 (L) [2][(L]	15 * (!)		27 * (!) [2][(	34 (L) [2][(L]	
RBC	2.19 (L)	2.12 (L) [2][	2.38 (L)		2.69 (L) [2][	1.46 (L) [2][	
Absolute Neutrophils-Calculated			4.35		2.08	3.89 [2]	
Absolute Lymphocytes							
Absolute Lymphocytes-Calculated			10.88 (H)		31.20 (H)	0.00 (L) [2][	
Absolute Monocytes							
Absolute Monocytes-Calculated			0.00 (L)		0.00 (L)	0.00 (L) [2][	
Blasts			79 * (!)		84 * (!)	99 * (!) [2][(	
Routine Coagulation							
PT - INR (Prothrombin Time)	14.7		15.6 (H)		16.7 (H)		16.3 (H)
International Normalized Ratio	1.2 *		1.3 * (H)		1.4 * (H)		1.3 * (H)
PTT (Partial Thromb Time)	25.1		24.8		26.0		27.5
Fibrinogen Level	184 (L)		138 (L)		107 (L)		159 (L)

EXAMPLE 3, CONT.

Routine Chemistry						
Sodium on Blood	138	135 * (L)	138	136	139 [2]	137 [2][(L)]
Potassium on Blood	4.5	4.5	4.8	5.8 * (H)	5.3 * (H) [2]	5.4 * (H) [2]
Chloride on Blood	107	104	107	107	107 [2][(H)]	107 [2]
CO2 on Blood	28	24	24	22	23 [2]	22 [2]
Anion Gap	3	7	7	7	9 [2]	8 [2]
Creatinine	1.17	1.46 * (H)	1.36 * (H)	1.54 * (H)	1.59 * (H) [	1.52 * (H) [
BUN on Blood	29 * (H)	27 * (H)	28 * (H)	27 * (H)	29 * (H) [2]	31 * (H) [2]
BUN/Creatinine Ratio	24.8 (H)	18.5	20.6 (H)	17.5	18.2 [2]	20.4 (H) [2]
eGFR (CKD-EPI) if African Am	57 *	44 *	48 *	41 *	39 * [3]	42 * [2]
eGFR (CKD-EPI) NonAfrican Am	49 *	38 *	41 *	35 *	34 * [3]	36 * [2]
Calcium (Total)	6.4 * (L)	6.7 * (L)	6.5 * (L)	7.3 * (L)	8.1 * (L) [2]	8.2 * (L) [2]
Uric Acid Blood	2.9 [2]	8.1 * (H)	8.3 * (H)	10.8 * (H)	12.9 * (H)	15.9 * (!)
Phosphorus Level	3.8 [2]	4.1	4.3	4.3	4.0 [2][(H)]	
LDH	916 * (H) [2	1,032 * (H)	906 * (H)	1,126 * (H)	1,139 * (H)	1,438 * (H)

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