Acute Myeloid Leukemia

Chapter 109 | Harrison's 22e

KEY CLINICAL POINTS

1. AML is the most common acute leukemia in older adults (median age 69 years) with a 5-year survival rate of only 32%.
2. Clonal hematopoiesis of indeterminate potential (CHIP) increases AML risk 10-fold compared to non-CHIP individuals.
3. Germline mutations in CEBPA, DDX41, TP53, RUNX1, and GATA2 are associated with myeloid neoplasms.
4. Diagnosis requires ≥20% blasts in bone marrow or peripheral blood; Auer rods are pathognomonic for AML and distinguish it from lymphoid leukemias.
5. Treatment is stratified by age: intensive chemotherapy (7+3) for patients <60 years; hypomethylating agents or low-intensity therapy for patients >60 years.
6. Acute Promyelocytic Leukemia (APL) is treated with tretinoin and arsenic trioxide based regimens.
7. Risk stratification (Favorable, Intermediate, Adverse) determines consolidation options such as high-dose cytarabine or allogeneic HCT.

1. DEFINITION & CLASSIFICATION

- **Definition:** Acute myeloid leukemia (AML) is a clonal hematopoietic malignancy characterized by proliferation of immature myeloid blasts.
- **Diagnostic Requirement:** ≥20% blasts in bone marrow or peripheral blood.
- **WHO 2022 Classification (Table 109-2):**
- **Defined by genetic abnormalities:**
- Acute promyelocytic leukemia with PML::RARA fusion
- AML with RUNX1::RUNX1T1, CBFB::MYH11, DEK::NUP214, RBM15::MRTFA, or BCR::ABL1 fusions
- AML with KMT2A, MECOM, or NUP98 rearrangements
- AML with NPM1 mutation or CEBPA mutation
- AML, myelodysplasia-related
- AML with other defined genetic alterations
- **Defined by differentiation:**
- Minimal differentiation
- Without maturation
- With maturation
- Basophilic leukemia
- Myelomonocytic leukemia
- Monocytic leukemia
- Erythroid leukemia

- Megakaryoblastic leukemia

2. EPIDEMIOLOGY

- **Incidence:** Increases exponentially after age 60; it is the most common acute leukemia in older adults.
- **Statistics (2023):** 20,380 new cases in the US (1% of all cancers, 31% of acute leukemias).
- **Mortality:** Causes 62% of leukemic deaths; median age at diagnosis is 69 years.
- **Survival:** Only 32% of patients survive 5 years.

3. ETIOLOGY & PATHOPHYSIOLOGY

- **Somatic Mutations:** Most cases arise from somatic mutations accumulating with age.
- **Clonal Hematopoiesis (CHIP):**
- Found in 5-6% of individuals over 70.
- Increases AML risk 10-fold compared to non-CHIP individuals.
- Associated genes: DNMT3A, TET2, and ASXL1.
- **Germline Predisposition (Table 109-1):**
- **Without preexisting disorders:** CE18PA-associated familial AML, DDX41, TP53 (Li-Fraumeni syndrome).
- **With preexisting platelet disorder:** RUNX1 (familial platelet disorder with associated thrombocytopenia), ANKRD26 (thrombocytopenia 2), ETV6 (thrombocytopenia 5).
- **With potential organ dysfunction:** GATA2 deficiency, Bone marrow failure syndromes (SCN, SDS, FA), Telomere biology disorders (e.g., Dyskeratosis congenita), RASopathies (NF1, CBL, Noonan syndrome), SAMD9/SAMD9L (MIRAGE/ataxia pancytopenia), and BLM (Bloom syndrome).

4. CLINICAL FEATURES

- **Symptoms (Table 109-4):**
- Anemia: Increasing fatigue or decreased exercise tolerance.
- Thrombocytopenia: Excess bleeding or bleeding from unusual sites (DIC).
- Neutropenia: Fevers or recurrent infections.
- CNS involvement: Headache, vision changes, nonfocal neurologic abnormalities.
- Splenomegaly: Early satiety.
- **Physical Examination (Table 109-4):**
- General: Performance status, fever, tachycardia.
- Localized signs: Ecchymosis/oozing from IV sites (possible APL), gum hypertrophy (monocytic leukemia), skin infiltration or nodules.
- Specific findings: Papilledema, retinal infiltrates (CNS leukemia); back pain, lower extremity weakness (spinal granulocytic sarcoma, common in t[8;21] patients).

5. DIAGNOSTIC APPROACH

1. **Initial Clinical Evaluation (Table 109-4):**

- History: Assess for fatigue, bleeding, fever, CNS symptoms, family history of AML, and occupational exposures (radiation, benzene, petroleum products, paint, smoking, pesticides).
- Physical Exam: Evaluate performance status, signs of infection, and local infiltration.

2. **Laboratory and Radiologic Studies (Table 109-4):**
   - CBC with manual differential count.
   - Chemistry: Electrolytes, creatinine, BUN, calcium, phosphorus, uric acid, hepatic enzymes, bilirubin, LDH, amylase, lipase.
   - Coagulation: PT, PTT, fibrinogen, D-dimer.
   - Viral serologies: CMV, HSV-1, varicella-zoster.
   - RBC type and screen; HLA typing for potential allogeneic HCT.
   - Imaging: PA and lateral chest radiograph; MRI for suspected spinal involvement.
3. **Specialized Testing (Table 109-4):**
   - Bone marrow aspirate and biopsy: Morphology, cytogenetics, flow cytometry, molecular studies.
   - Cryopreservation of viable leukemia cells.
4. **Morphologic Confirmation:**
   - Requirement: ≥20% blasts in bone marrow or peripheral blood.
   - Key features:
   - Auer rods (pathognomonic for AML; distinguish from lymphoid leukemias).
   - Uniform primary cytoplasmic granules.
   - Nuclear budding and increased mitotic figures.
   - Peroxidase staining: Dark blue granules indicate myeloid lineage differentiation.

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6. MANAGEMENT & TREATMENT

1. **Initial Assessment:** Determine patient age, fitness, and risk stratification (Table 109-3).
2. **Induction Therapy Selection:**
   - Patients <60 years: Intensive induction with 7+3 regimen (Cytarabine 100–200 mg/m^2 /d + Daunorubicin 60–90 mg/m^2 /d; Idarubicin 12 mg/m^2 /d may replace Daunorubicin).
   - Patients >60 years: Hypomethylating agents (azacitidine, decitabine) or low-intensity therapy.
   - APL patients: Tretinoin and arsenic trioxide based regimens (with or without anthracyclines).
3. **Consolidation Therapy (if CR achieved):**
   - Based on risk stratification (Favorable, Intermediate, Adverse).
   - Options include high-dose cytarabine, allogeneic HCT, autologous HCT, or novel therapies.
4. **Salvage Treatment:**
   - For patients with myeloid induction failure: Myeloid-specific allogeneic HCT (if suitable donor available) → otherwise investigational therapy or HCT.
5. **Novel Therapies (Table 109-5):**
   - Kinase inhibitors: Midostaurin, Gilteritinib, Quizartinib (FLT3); Pemigatinib (FGFR1).
   - Other targeted agents: Menin inhibitors, IDH1/IDH2 inhibitors, Glasdegib (Hedgehog inhibitor).
   - Immunotherapies: Monoclonal antibodies (CD33, CD44, CD47, CD123, CLEC12A), CAR T cells, BiTEs.
6. **Supportive Care & Counseling:**
   - Dental evaluation for poor dentition.

- Lumbar puncture for CNS symptoms.
- Social work and counseling regarding genetic risks, sperm banking, menstrual suppression, financial support.

Decision Pathway for Treatment (Figure 109-2)

1. **Initial Diagnosis:** Identify AML.
2. **Status Check:** Determine if patient is "Previously untreated" or "Refractory/relapsed".
3. **Risk Stratification (for untreated):** Categorize as Favorable, Intermediate, or Adverse risk (Table 109-3).
4. **Induction Choice:**
   - Option A: Cytarabine-based regimen (Cytarabine 100–200 mg/m^2 /d + Daunorubicin 60–90 mg/m^2 /d; Idarubicin 12 mg/m^2 /d as alternative).
   - Option B: Investigational therapy (alone or in combination with lower intensity chemotherapy, e.g., venetoclax).
5. **Response Assessment:**
   - If CR achieved → Proceed to consolidation (Investigational therapy OR HCT based on risk).
   - If no CR → Investigational therapy, HCT, or other options.
6. **Salvage Pathway (Refractory/relapsed):**
   - If myeloid induction failure → Myeloid-specific allogeneic HCT (if suitable donor available).
   - If no myeloid-specific HCT → Investigational therapy, HCT, or other options.

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7. KEY PEARLS & HIGH-YIELD POINTS

- **Auer rods** are pathognomonic for AML and distinguish it from lymphoid leukemias.
- **Age is a primary driver** of treatment intensity: <60 years (intensive) vs. >60 years (hypomethylating agents).
- **Risk stratification** (Table 109-3) is critical for determining the necessity of consolidation like high-dose cytarabine or HCT.
- **CHIP** significantly increases the risk of AML in older patients.
- **Rapid identification** of APL is essential due to specific treatment with tretinoin and arsenic trioxide.

REFERENCE TABLES

TABLE 109-1

World Health Organization 2022, Subtypes of Myeloid Neoplasms Associated with Germline Predisposition Myeloid neoplasms...

- Myeloid neoplasms with germline predisposition without a preexisting platelet disorder or organ dysfunction • Germline CEBPA P/LP variant (CEBPA-associated familial AML) • Germline DDX41 P/LP varianta • Germline TP53 P/LP varianta (Li-Fraumeni syndrome) Myeloid neoplasms with germline predisposition and preexisting platelet disorder • Germline RUNX1 P/LP varianta (familial platelet disorder with associated myeloid malignancy [FPD-MM]) • Germline ANKRD26 P/LP varianta (thrombocytopenia 2) • Germline ETV6 P/LP varianta (thrombocytopenia 5) Myeloid neoplasms with germline predisposition and potential organ dysfunction • Germline GATA2 P/LP variant (GATA2 deficiency) • Bone marrow failure syndromes • Severe congenital neutropenia (SCN) • Shwachman-Diamond syndrome (SDS) • Fanconi anemia (FA) • Telomere biology disorders •

RASopathies (neurofibromatosis type 1, CBL syndrome, Noonan syndrome or Noonan syndrome-like disordersa) • Down syndromea • Germline SAMD9 P/LP variant (MIRAGE syndrome) • Germline SAMD9L P/LP variant (SAMD9L-related ataxia pancytopenia syndrome)b • Biallelic germline BLM P/LP variant (Bloom syndrome)

TABLE 109-2

World Health Organization 2022 Classification of Acute Myeloid Leukemia Acute myeloid leukemia with defining genetic...

- Acute myeloid leukemia with defining genetic abnormalities Acute promyelocytic leukemia with PML::RARA fusion Acute myeloid leukemia with RUNX1::RUNX1T1 fusion Acute myeloid leukemia with CBFB::MYH11 fusion Acute myeloid leukemia with DEK::NUP214 fusion Acute myeloid leukemia with RBM15::MRTFA fusion Acute myeloid leukemia with BCR::ABL1 fusiona Acute myeloid leukemia with KMT2A rearrangement Acute myeloid leukemia with MECOM rearrangement Acute myeloid leukemia with NUP98 rearrangementb Acute myeloid leukemia with NPM1 mutation Acute myeloid leukemia with CEBPA mutationa,c Acute myeloid leukemia, myelodysplasia-relateda,d Acute myeloid leukemia with other defined genetic alterationsa Acute myeloid leukemia, defined by differentiation Acute myeloid leukemia with minimal differentiation Acute myeloid leukemia without maturation Acute myeloid leukemia with maturation Acute basophilic leukemia Acute myelomonocytic leukemia Acute monocytic leukemia Acute erythroid leukemia Acute megakaryoblastic leukemia

TABLE 109-3

2022 European LeukemiaNet Risk Classification of Acute Myeloid Leukemia (AML) by Genetics at Initial Diagnosis a

RISK CATEGORY	GENETIC ABNORMALITY
Favorable	• t(8;21)(q22;q22.1)/RUNX1::RUNX1T1b,c • inv(16)(p13.1q22) or t(16;16)(p13.1;q22)/CBFB::MYH11b,c • Mutated NPM1b,d without FLT3-ITD • bZIP in-frame mutated CEBPAe
Adverse	• t(6;9)(p23.3;q34.1)/DEK::NUP214 • t(v;11q23.3)/KMT2A-rearrangedg • t(9;22)(q34.1;q11.2)/BCR::ABL1 • t(8;16)(p11.2;p13.3)/KAT6A::CREBBP • inv(3)(q21.3q26.2) or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1) • t(3q26.2;v)/MECOM(EVI1)-rearranged • −5 or del(5q); −7; −17/abn(17p) • Complex karyotype,h monosomal karyotypei • Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, and/or ZRSR2j • Mutated TP53k

TABLE 109-4

Initial Diagnostic Evaluation and Management of Adult Patients with AML History Increasing fatigue or decreased...

- History
- Increasing fatigue or decreased exercise tolerance (anemia)
- Excess bleeding or bleeding from unusual sites (DIC, thrombocytopenia)
- Fevers or recurrent infections (neutropenia)

- Headache, vision changes, nonfocal neurologic abnormalities (CNS leukemia or bleed)
- Early satiety (splenomegaly)
- Family history of AML (Fanconi, Bloom, or Kostmann syndromes or ataxia-telangiectasia)
- History of cancer (exposure to alkylating agents, radiation, topoisomerase II inhibitors)
- Occupational exposures (radiation, benzene, petroleum products, paint, smoking, pesticides)
- Physical Examination
- Performance status (prognostic factor)
- Ecchymosis and oozing from IV sites (DIC, possible acute promyelocytic leukemia)
- Fever and tachycardia (signs of infection)
- Papilledema, retinal infiltrates, cranial nerve abnormalities (CNS leukemia)
- Poor dentition, dental abscesses
- Gum hypertrophy (leukemic infiltration, most common in monocytic leukemia)
- Skin infiltration or nodules (leukemia infiltration, most common in monocytic leukemia)
- Lymphadenopathy, splenomegaly, hepatomegaly
- Back pain, lower extremity weakness (spinal granulocytic sarcoma, most likely in t[8;21] patients)
- Laboratory and Radiologic Studies
- CBC with manual differential cell count
- Chemistry tests (electrolytes, creatinine, BUN, calcium, phosphorus, uric acid, hepatic enzymes, bilirubin, LDH, amylase, lipase)
- Clotting studies (prothrombin time, partial thromboplastin time, fibrinogen, d-dimer)
- Viral serologies (CMV, HSV-1, varicella-zoster)
- RBC type and screen
- HLA typing for potential allogeneic HCT
- Bone marrow aspirate and biopsy (morphology, cytogenetics, flow cytometry, molecular studies)
- Cryopreservation of viable leukemia cells
- Myocardial function (echocardiogram or MUGA scan)
- PA and lateral chest radiograph
- Placement of central venous access device
- Interventions for Specific Patients
- Dental evaluation (for those with poor dentition)
- Lumbar puncture (for those with symptoms of CNS involvement)
- Screening spine MRI (for patients with back pain, lower extremity weakness, paresthesias)
- Social work referral for patient and family psychosocial support
- Counseling for All Patients
- Provide patients with information regarding their disease and genetic risks, sperm banking or menstrual suppression, financial counseling, support group contact, and consent for tissue banking of leukemic cells

TABLE 109-5

Novel Therapies in Clinical Development in Acute Myeloid Leukemia (AML)

	UNDER INVESTIGATION	APPROVED BY FOOD AND DRUG ADMINISTRATION SINCE 2017
Kinase inhibitors/ cell signaling	FLT3 inhibitors IRAK-4 inhibitors KIT inhibitors PI3K/AKT/mTOR inhibitors Aurora and polo-like kinase inhibitors, CDK4/6 inhibitors, CDK9 inhibitors, CHK1, WEE1, CSFR1, and MPS1 inhibitors SRC and HCK inhibitors Syk inhibitors	Midostaurin (FLT3) Gilteritinib (FLT3) Quizartinib (FLT3) Pemigatinib (FGFR1)
	Menin inhibitors, other spliceosome modulators DNA methyltransferase inhibitors Histone methylation or acetylation modulators Other spliceosome modulators IDH1 and IDH2 inhibitors DOT1L inhibitors BET-bromodomain inhibitors	
Chemotherapeutic agents	Liposomal preparations Nucleoside analogues	CPX-351 (liposomal cytarabine and daunorubicin) Oral azacitidine
	BH3 mimetics; Bcl-2, Bcl-xL, and Mcl-1 inhibitors Caseinolytic protease inhibitors	
Therapies targeting oncogenic proteins	Fusion transcript targeting EVI1 targeting NPM1 targeting Hedgehog inhibitors	Glasdegib (hedgehog)
	Monoclonal antibodies against CD33, CD44, CD47, CD123, CLEC12A Immunoconjugates Bispecific T-cell engagers (BiTEs) and dual-affinity retargeting molecules (DARTs) for CD33, CD123, others Trispecific T-cell or NK-cell engagers Chimeric antigen receptor (CAR) T cells, genetically engineered T-cell receptor (TCR) T cells, CAR-NK cells Immune checkpoint inhibitors (PD-1/PD-L1, CTLA-4, LAG-3, LILRB4) Vaccines	
Therapies targeting AML environment	CXCR4 and CXCL12 antagonists Antiangiogenic therapies	