Leukemias

Overview of Leukemias

Leukemia is a group of hematologic malignancies characterized by the uncontrolled proliferation of abnormal leukocytes in the bone marrow, peripheral blood, or lymphoid tissues, leading to impaired hematopoiesis and clinical manifestations such as anemia, infections, and bleeding. Leukemias are classified based on the cell lineage (myeloid or lymphoid) and the disease course (acute or chronic). The main types include Acute Lymphoblastic Leukemia (ALL), Acute Myeloid Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), and Chronic Myeloid Leukemia (CML), with additional rare subtypes like Hairy Cell Leukemia (HCL). This guide provides a comprehensive overview of leukemia types, clinical presentation, emergencies, diagnostic workup, hospital management, statistics, and when to consult hematology, with tables and clinical scenarios for practical application.

Types of Leukemias and Clinical Presentation

Acute Lymphoblastic Leukemia (ALL):

- Overview: A malignancy of lymphoid precursors (lymphoblasts), ALL is the most common leukemia in children (80% of pediatric leukemias) but also affects adults (20% of adult acute leukemias). It progresses rapidly, requiring urgent treatment.
- Clinical Presentation:
  - Fatigue, pallor (anemia).
  - Fever, infections (neutropenia).
  - Easy bruising, petechiae, mucosal bleeding (thrombocytopenia).
  - Bone pain, joint pain (blast infiltration).
  - Lymphadenopathy, hepatosplenomegaly (50% of adults).
  - **CNS involvement (5-8%):** Headache, seizures, cranial nerve deficits.

Acute Myeloid Leukemia (AML):

- Overview:
- The most common acute leukemia in adults, AML involves the clonal expansion of myeloid blasts (>20% in bone marrow or peripheral blood). It is aggressive, with subtypes like Acute Promyelocytic Leukemia (APL) requiring specific management.

- Clinical Presentation:
  - Fatigue, weakness, pallor (anemia).
  - Fever, infections (neutropenia).
  - Bleeding, bruising, petechiae (thrombocytopenia).
  - **Less common:** Hepatosplenomegaly, lymphadenopathy.
  - **APL-specific:** Disseminated Intravascular Coagulation (DIC), bleeding risk (Auer rods on smear).

Chronic Lymphocytic Leukemia (CLL):

- Overview:
  - A slow-growing leukemia of mature B-lymphocytes (CD5+, CD23+), CLL is the most common leukemia in adults, typically affecting those aged 60-70. Many patients are asymptomatic at diagnosis.
- Clinical Presentation:
  - Often asymptomatic (50% incidental diagnosis via CBC).
  - Fatigue, weight loss, night sweats (15% have B-symptoms).
  - Lymphadenopathy, hepatosplenomegaly (common).
  - Recurrent infections (hypogammaglobulinemia).
  - **Autoimmune phenomena:** Hemolytic anemia, immune thrombocytopenia.

Chronic Myeloid Leukemia (CML):

- Overview:
  - A myeloproliferative neoplasm driven by the BCR-ABL fusion gene (t(9;22), Philadelphia chromosome), CML affects adults (median age 50-60). It progresses through chronic, accelerated, and blast phases.
- Clinical Presentation:
  - Often asymptomatic (20% incidental diagnosis).
  - Fatigue, weight loss, night sweats (30% have B-symptoms).
  - Splenomegaly (75%, often palpable).
  - **Less common:** Bleeding, infections (unless in blast crisis).

Hairy Cell Leukemia (HCL):

- Overview:
  - A rare subtype of CLL, HCL involves B-lymphocytes with "hairy" cytoplasmic projections. It progresses slowly and affects adults (median age 50-60).
- Clinical Presentation:
  - Fatigue, weakness (anemia).

- Recurrent infections (neutropenia).
- Splenomegaly (common, often massive).
- **Less common:** Lymphadenopathy, bleeding.

When to Expect Emergencies

Leukemic Emergencies:

- Hyperleukocytosis/Leukostasis:
  - **When:** WBC >100,000/μL (common in AML, ALL, CML blast crisis).
  - **Manifestations:** Neurologic (confusion, stroke), respiratory (dyspnea, infiltrates), cardiovascular (MI, limb ischemia).
  - **Action:** Urgent hematology consult, leukapheresis, hydroxyurea, fluids.
- Tumor Lysis Syndrome (TLS):
  - **When:** During induction chemotherapy (ALL, AML, high-burden CLL/CML).
  - **Manifestations:** Hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia; AKI, arrhythmias.
  - **Action:** Hydration (NS 3 L/m^2/day), allopurinol or rasburicase, monitor electrolytes q6h.
- Disseminated Intravascular Coagulation (DIC):
  - **When:** APL (AML subtype), high-risk AML/ALL.
  - **Manifestations:** Bleeding (mucosal, intracranial), thrombosis; labs show INR >1.5, fibrinogen <150 mg/dL, D-dimer ↑.
  - **Action:** Urgent hematology consult, ATRA for APL, FFP/platelets for bleeding.
- CNS Involvement:
  - **When:** ALL (5-8%), AML (rare unless hyperleukocytosis).
  - **Manifestations:** Headache, seizures, cranial nerve palsies.
  - **Action:** Lumbar puncture (LP), intrathecal chemotherapy, cranial radiation if severe.
- Infections:
  - **When:** Neutropenia (ANC <500/μL) in AML, ALL, or advanced CLL/CML.
  - **Manifestations:** Fever (>38°C), sepsis, pneumonia, fungal infections.
  - **Action:** Blood cultures, broad-spectrum antibiotics (e.g., piperacillin-tazobactam), antifungals if high risk.

Diagnosis and Labs

Initial Workup:

- Complete Blood Count (CBC) with Differential:
  - **Leukocytosis:** Common in CLL (>5,000/μL B-lymphocytes), CML (>20,000/μL), AML/ALL (variable, often >100,000/μL in hyperleukocytosis).
  - **Leukopenia:** AML/ALL may present with low WBC due to marrow replacement.
  - **Anemia:** Normocytic (Hgb <13 g/dL males, <12 g/dL females).
  - **Thrombocytopenia:** Platelets <150,000/μL.
- Peripheral Smear:
  - **Blasts:** >20% in AML/ALL (Auer rods in AML, especially APL).
  - **Lymphocytes:** Smudge cells in CLL, hairy cells in HCL.
  - **CML:** Left shift (increased myelocytes, basophils, eosinophils).
- Bone Marrow Aspiration/Biopsy:
  - **AML/ALL:** >20% blasts (confirmatory).
  - **CLL:** >30% lymphocytes, smudge cells.
  - **CML:** Hypercellular marrow, increased granulocyte precursors.
  - **HCL:** Hairy cells with cytoplasmic projections, dry tap (fibrosis).
- Immunophenotyping (Flow Cytometry):
  - **ALL:** TdT+, CD19+ (B-ALL), CD3+ (T-ALL).
  - **AML:** Myeloperoxidase+, CD33+, CD34+.
  - **CLL:** CD5+, CD23+, CD20+ (B-cell markers).
  - **HCL:** CD11c+, CD25+, CD103+.
- Cytogenetics/Molecular Testing:
  - **ALL:** t(12;21) (ETV6-RUNX1, pediatric), t(9;22) (Ph chromosome, poor prognosis).
  - **AML:** t(15;17) (APL), inv(16), t(8;21) (favorable); FLT3-ITD (poor prognosis).
  - **CML:** t(9;22) (BCR-ABL, diagnostic).
  - **CLL:** del(13q) (favorable), del(17p) (poor prognosis).
- Other Labs:
  - **CMP:** Hyperuricemia, hyperkalemia, hyperphosphatemia (TLS); elevated LDH.
  - **Coagulation:** INR, fibrinogen, D-dimer (DIC in APL).
  - **Cultures:** Blood, urine (febrile neutropenia).
  - **LP:** If CNS symptoms (ALL, AML).

When to Consult Hematology

- **Suspected Leukemia:** Any patient with unexplained leukocytosis (>20,000/μL), leukopenia with blasts, or pancytopenia (anemia + neutropenia + thrombocytopenia).
- **Emergencies:** Hyperleukocytosis, TLS, DIC, CNS involvement, or severe infections.
- **Diagnostic Confirmation:** Bone marrow biopsy, cytogenetics, or immunophenotyping needed.
- **Treatment Planning:** Induction chemotherapy, targeted therapies (e.g., ATRA, TKIs), or stem cell transplant (SCT) consideration.
- **Relapse/Refractory Disease:** For re-induction, clinical trials, or advanced therapies (e.g., CAR T-cell therapy).

Statistics

Incidence:

Total leukemia cases (2023): ~60,000 new cases in the U.S. (American Cancer Society).

ALL: ~6,500 cases; 75% in children <15 years, 20% in adults.

AML: 18% of leukemia cases; most common in adults (>65 years).

CLL: 25% of leukemia cases; ~20,000 cases annually, mostly adults >60 years.

CML: ~9,000 cases annually; median age 50-60 years.

HCL: ~700 cases annually; rare, median age 50-60 years.

Mortality:

Total leukemia deaths (2023): ~24,000 in the U.S.

ALL: 5-year survival ~90% in children, 30-40% in adults.

AML: 5-year survival ~30% (higher with favorable genetics, e.g., t(8;21)).

CLL/CML: 5-year survival >80% with modern therapies.

Demographics:

ALL: Higher incidence in Hispanic populations (ARID5B gene polymorphisms).

CLL/CML: More common in males and Whites; incidence increases with age.

AML: Risk increases after age 65; associated with prior chemotherapy/radiation.

Hospital Management

General Principles:

- Supportive Care:
  - **Transfusions:** PRBCs for Hgb <7 g/dL, platelets for <10,000/μL or bleeding.
  - **Infection prophylaxis:** Antibiotics (e.g., levofloxacin), antifungals (e.g., fluconazole), antivirals (e.g., acyclovir) if neutropenic.
  - **Hydration:** NS 3 L/m^2/day to prevent TLS.
  - **Allopurinol/rasburicase:** For TLS prevention/treatment.
- Monitoring:
  - **CBC daily:** Assess for cytopenias, blasts.
  - **CMP q6-12h:** Monitor for TLS (uric acid, K+, phosphate, Ca2+).
  - **Coagulation:** INR, fibrinogen, D-dimer (DIC).
  - **Cultures:** Blood, urine, sputum if febrile.

Specific Management by Type:

- ALL:
  - **Induction Chemotherapy:** Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone).
  - **CNS Prophylaxis:** Intrathecal methotrexate, especially if Ph+ or high-risk.
  - **Targeted Therapy:** Ponatinib for Ph+ ALL (improves survival to 80% without SCT).
  - **SCT:** Consider in high-risk or relapsed cases.
- AML:
  - **Induction Chemotherapy:** 7+3 regimen (cytarabine + daunorubicin).
  - **APL-Specific:** ATRA + arsenic trioxide (ATO); manage DIC with FFP/platelets.
  - **SCT:** Standard for high-risk AML (e.g., FLT3-ITD, secondary AML).
  - **Monitoring:** ECG/ECHO (anthracycline cardiotoxicity), TLS labs.
- CLL:
  - **Observation:** If asymptomatic (Rai stage 0-I).
  - **Treatment:** Chemoimmunotherapy (e.g., bendamustine + rituximab) or targeted therapy (e.g., ibrutinib) for symptomatic disease (Rai stage III-IV).

    - **Supportive Care:** IVIG for recurrent infections, treat autoimmune complications.
- CML:
    - **Tyrosine Kinase Inhibitors (TKIs):** Imatinib 400 mg PO daily (first-line); dasatinib or nilotinib if resistant.
    - **Monitoring:** BCR-ABL PCR q3 months; goal is major molecular response (MMR).
    - **SCT:** For accelerated/blast phase or TKI failure.
- HCL:
    - **Observation:** If asymptomatic.
    - **Treatment:** Cladribine 0.1 mg/kg IV daily x 7 days (first-line); rituximab if relapsed.
    - **Supportive Care:** Transfusions, infection management.

Management of Emergencies:

Hyperleukocytosis: Leukapheresis, hydroxyurea 50-100 mg/kg/day, fluids.

TLS: Rasburicase 0.2 mg/kg IV, dialysis if AKI (Cr >3x baseline).

DIC: ATRA for APL, FFP (10-15 mL/kg), cryoprecipitate (fibrinogen <100 mg/dL).

Infections: Empiric antibiotics (e.g., piperacillin-tazobactam 4.5 g IV q6h + vancomycin 15 mg/kg IV q12h), antifungals (e.g., micafungin 100 mg IV daily) if persistent fever.

Table: Characteristics of Major Leukemia Types

Leukemia Type	Cell Line	Typical Age	Key Features	Common Labs	Emergencies
ALL	Lymphoid (B/T lymphoblasts)	Children (peak 2-5 yrs), adults	Fatigue, fever, bruising, bone pain, lymphadenopathy	Blasts >20%, anemia, thrombocytopenia, TdT+	Hyperleukocytosis, CNS involvement, TLS
AML	Myeloid (myeloblasts)	Adults (>65 yrs)	Fatigue, fever, bleeding, APL: DIC	Blasts >20%, Auer rods (APL), myeloperoxidase+	Hyperleukocytosis, TLS, DIC (APL)
CLL	Lymphoid (mature B-cells)	Adults (60-70 yrs)	Asymptomatic, lymphadenopathy, infections	Lymphocytosis (>5,000/μL), CD5+, smudge cells	Infections, autoimmune cytopenias
CML	Myeloid (granulocytes)	Adults (50-60 yrs)	Splenomegaly, fatigue, often asymptomatic	Leukocytosis, left shift, t(9;22) (BCR-ABL)	Blast crisis, hyperleukocytosis

Leukemia Type	Cell Line	Typical Age	Key Features	Common Labs	Emergencies
HCL	Lymphoid (mature B-cells)	Adults (50-60 yrs)	Splenomegaly, infections, fatigue	Hairy cells, pancytopenia, CD11c+	Infections, severe cytopenias

Table: Diagnostic Workup for Leukemias

Test	ALL	AML	CLL	CML	HCL
CBC/Smear	Blasts >20%, anemia, thrombocytopenia	Blasts >20%, Auer rods (APL)	Lymphocytosis, smudge cells	Leukocytosis, left shift	Pancytopenia, hairy cells
Flow Cytometry	TdT+, CD19+ (B-ALL), CD3+ (T-ALL)	Myeloperoxidase+, CD33+	CD5+, CD23+, CD20+	Myeloid markers, basophilia	CD11c+, CD25+, CD103+
Cytogenetics	t(12;21), t(9;22)	t(15;17) (APL), FLT3-ITD	del(13q), del(17p)	t(9;22) (BCR-ABL)	BRAF V60E mutation
Bone Marrow	>20% lymphoblasts	>20% myeloblasts	>30% lymphocytes	Hypercellular, granulocyte precursors	Hairy cells, fibrosis

Clinical Scenarios

Scenario 1: Young Adult with ALL and CNS Involvement

- Presentation: A 25-year-old male presents with 2 weeks of fatigue, fever, bruising, and a new-onset seizure. Exam shows T 38.5°C, BP 110/70 mmHg, HR 100 bpm, pallor, petechiae, lymphadenopathy, and GCS 14 (confusion).
- Labs/Studies: WBC 50,000/µL (blasts 60%), Hgb 8 g/dL, platelets 20,000/µL, peripheral smear: lymphoblasts, flow cytometry: TdT+, CD19+, LP: lymphoblasts in CSF, cytogenetics: t(9;22) (Ph+).
- Diagnosis: ALL (Ph+ B-ALL) with CNS involvement → Blasts >20%, TdT+, CNS findings.
- Management: Admit to ICU (seizure, infection risk). Start induction chemotherapy (hyper-CVAD), ponatinib (Ph+ ALL), intrathecal methotrexate for CNS prophylaxis. Prophylaxis: Levofloxacin, fluconazole, acyclovir. Monitor TLS (uric acid 8 mg/dL, treated with rasburicase). Consult hematology: Plan for SCT (high-risk). After 4 weeks, blasts <5%, remission achieved.

Scenario 2: Elderly Male with AML (APL) and DIC

- Presentation: A 70-year-old male presents with 1 week of fever, epistaxis, and fatigue. Exam shows T 38°C, BP 100/60 mmHg, HR 110 bpm, gingival bleeding, ecchymosis.
- Labs/Studies: WBC 30,000/μL (blasts 40%), Hgb 7 g/dL, platelets 15,000/μL, smear: Auer rods, INR 2.0, fibrinogen 100 mg/dL, D-dimer elevated, flow cytometry: myeloperoxidase+, t(15;17).
- Diagnosis: AML (APL) with DIC → Blasts >20%, Auer rods, t(15;17), coagulopathy.
- Management: Admit to ICU (DIC, bleeding risk). Start ATRA + ATO immediately. Supportive care: FFP 15 mL/kg, cryoprecipitate (fibrinogen <100 mg/dL), transfuse PRBCs/platelets. Prophylaxis: Antibiotics, antifungals. Consult hematology: Monitor TLS, plan consolidation therapy. After 1 week, DIC resolves, blasts <5%.

Scenario 3: Elderly Female with Asymptomatic CLL

- Presentation: A 65-year-old female presents for routine checkup with no symptoms. Exam shows T 37°C, BP 130/80 mmHg, HR 80 bpm, cervical lymphadenopathy, splenomegaly.
- Labs/Studies: WBC 40,000/μL (lymphocytes 80%), Hgb 12 g/dL, platelets 150,000/μL, smear: smudge cells, flow cytometry: CD5+, CD23+, cytogenetics: del(13q).
- Diagnosis: CLL (Rai stage I) → Lymphocytosis, CD5+, asymptomatic.
- Management: Observation (asymptomatic, Rai I). Monitor CBC q3 months. Educate on infection risk (vaccinations, avoid crowds). Consult hematology: Plan for ibrutinib if symptomatic progression. After 6 months, remains stable, no treatment needed.