

Review Article

Acute Myelogenous Leukemia: Re-examining the Epidemiology, Etiology, Clinical Manifestations, Pathogenesis, Diagnosis, Prognosis and Treatment

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Abstract

Neoplastic myeloid diseases are clonal hematopoietic stem cell disorders characterized by abnormal proliferation, impaired differentiation, and accumulation of myeloid cells, resulting in disrupted normal hematopoiesis. Acute Myelogenous Leukemia (AML) is the most aggressive of these disorders and predominantly affects older adults, although it may occur at any age. Its development is driven by genetic and epigenetic alterations, environmental exposures, previous cytotoxic therapy, and antecedent hematologic diseases. Patients typically present with manifestations of bone marrow failure, including anemia, infections, bleeding, and constitutional symptoms. Diagnosis relies on complete blood count, peripheral blood smear, bone marrow examination, immunophenotyping, cytogenetic analysis, and molecular testing for prognostic mutations. Prognosis depends on age, cytogenetic and molecular risk profiles, treatment response, and measurable residual disease status. Management combines supportive care, intensive or low-intensity chemotherapy, targeted therapies, and allogeneic hematopoietic stem cell transplantation, with individualized treatment strategies improving survival and long-term outcomes.

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematological malignancy characterized by clonal expansion of immature myeloid cells in the bone marrow, blood, and occasionally extramedullary tissues. The accumulation of leukemic blasts disrupts normal hematopoiesis and can cause anemia, neutropenia, and thrombocytopenia, presenting clinically with fatigue, pallor, infections, fever, bruising, and bleeding [1–3]. AML is the most common acute leukemia in adults, although it can occur at any age. Contemporary classification and management increasingly integrate morphology, immunophenotype, cytogenetics, and molecular genetics to establish disease subtype, estimate risk, and guide treatment [1, 2, 4–6]. Advances in genomic characterization and targeted treatment have expanded therapeutic options, although relapse and treatment-related mortality remain important challenges [6, 7].

2. Epidemiology

AML incidence increases substantially with age, and the median age at diagnosis in many high-income settings is approximately 68–70 years [1, 8, 9]. It occurs somewhat more frequently in males, while population incidence and outcomes vary across countries because of differences in population age structure, exposure patterns, diagnostic capacity, access to specialist care, and treatment availability [8–10]. Global cancer estimates provide a broad picture of cancer burden, but country-level AML estimates should be interpreted in light of variation in cancer registration and diagnostic resources [8, 9]. Outcomes are generally poorer among older adults, in part because of adverse disease biology, comorbidities, and reduced tolerance of intensive therapy [1, 6, 10].

3. Etiology and risk factors

AML usually arises through the accumulation of somatic genetic and epigenetic alterations in hematopoietic stem or progenitor cells. Risk factors include increasing age, previous cytotoxic chemotherapy or radiotherapy, benzene and certain occupational exposures, ionizing radiation, tobacco smoking, inherited predisposition syndromes, and antecedent myeloid neoplasms [1, 6, 11–14]. Therapy-related AML and AML arising after myelodysplastic syndrome or another myeloid neoplasm may have distinct biological features and often carry adverse-risk characteristics [12–14]. Inherited conditions such as Down syndrome and Fanconi anemia can increase susceptibility to myeloid malignancy, although the magnitude and nature of risk differ by syndrome and age [11, 15]. No single exposure explains most AML cases. Rather, risk reflects interactions among age-related clonal evolution, inherited susceptibility, environmental exposures, and acquired mutations. Clonal hematopoiesis-associated mutations, including those involving DNMT3A, TET2, and ASXL1, can precede overt leukemia, but such clones do not inevitably progress to AML [16, 17]. Molecular studies have shown that AML is genetically diverse and may evolve through the acquisition of cooperating mutations over time [18–20].

4. Pathogenesis

AML develops when genetic and epigenetic changes disrupt the balance between proliferation, differentiation, and programmed cell death in hematopoietic cells. Recurrent alterations affect transcription factors, signaling pathways, chromatin regulation, RNA processing, and tumor-suppressor function [18–21]. Commonly implicated genes include NPM1, FLT3, CEBPA, RUNX1, TP53, DNMT3A, IDH1, IDH2, and genes associated with spliceosome and chromatin regulation [18–22]. These mutations do not have equivalent biological or prognostic effects; their clinical significance depends on the specific alteration, co-occurring mutations, cytogenetic context, and treatment setting [2, 18, 22, 23]. For example, FLT3 alterations can activate proliferative signaling, whereas IDH1 and IDH2 mutations alter cellular metabolism and epigenetic regulation. Mutations in NPM1, CEBPA, TP53, and myelodysplasia-related genes help define biologically and clinically distinct AML subgroups [2, 18, 22–24]. Leukemic cells progressively impair normal erythropoiesis, granulopoiesis, and megakaryopoiesis, producing the cytopenias typical of marrow failure. Disease evolution is also influenced by clonal heterogeneity, the marrow microenvironment, immune interactions, and selection of resistant subclones during treatment [19, 20, 25].

5. Clinical presentation

Clinical manifestations often reflect bone marrow failure. Anemia can cause fatigue, weakness, pallor, dizziness, and exertional dyspnea. Neutropenia or dysfunctional leukocytes predispose patients to infections and persistent fever, while thrombocytopenia can cause petechiae, ecchymoses, epistaxis, gingival bleeding, and other mucosal or internal hemorrhage [1, 6, 26]. Some patients have bone pain, weight loss, night sweats, anorexia, or constitutional symptoms. Hepatosplenomegaly, lymphadenopathy, gingival hypertrophy, and leukemia cutis may occur, depending on the AML subtype [1, 26]. Hyperleukocytosis can produce leukostasis, particularly in the lungs and central nervous system, and may present with respiratory distress, confusion, focal neurological deficits, or other acute complications. Suspected acute promyelocytic leukemia (APL) is a medical emergency because of its association with severe coagulopathy and early hemorrhagic death; prompt recognition and immediate initiation of all-trans retinoic acid (ATRA) when APL is suspected are therefore essential [27, 28].

6. Classification

AML classification combines clinical history, morphology, immunophenotype, cytogenetics, and molecular findings. The fifth edition of the World Health Organization classification (WHO-HAEM5) and the International Consensus Classification (ICC) place substantial emphasis on genetically defined entities [3, 4, 29]. Important recurrent genetic abnormalities include PML::RARA, RUNX1::RUNX1T1, CBFB::MYH11, KMT2A rearrangements, DEK::NUP214, MECOM rearrangements, NUP98 rearrangements, NPM1 mutations, and CEBPA mutations [3, 4, 29, 30]. Both systems distinguish AML entities by biological features, but they differ in terminology, hierarchy, and blast-percentage requirements for some genetically defined categories [3, 4, 29]. The WHO-HAEM5 generally permits diagnosis of several genetically defined AML entities without a universal 20% blast threshold, whereas the ICC commonly applies a 10% blast threshold to many recurrent genetic categories, with specified exceptions. The systems also differ in how they define AML with myelodysplasia-related features and selected TP53-mutated or other molecular subgroups [3, 4, 29, 30]. These classifications are designed to improve diagnostic consistency and link disease biology with prognosis and treatment.

7. European LeukemiaNet risk classification

The 2022 European LeukemiaNet (ELN) recommendations stratify AML into favorable-, intermediate-, and adverse-risk groups using cytogenetic and molecular abnormalities, with clinical context and treatment response informing individual decisions [2, 31, 32]. Favorable-risk disease includes core-binding-factor AML, NPM1-mutated AML without FLT3-ITD in the appropriate genetic context, and AML with an in-frame bZIP CEBPA mutation. Intermediate-risk disease includes selected cases not meeting favorable- or adverse-risk criteria, including some FLT3-ITD and KMT2A-rearranged cases. Adverse-risk disease includes TP53-mutated AML, complex or monosomal

karyotypes, and specified adverse-risk genetic abnormalities [2, 31, 32]. The ELN category is a population-level prognostic framework rather than a deterministic prediction for an individual. Outcome also depends on age, fitness, treatment regimen, co-mutations, response depth, and availability of transplantation [2, 31–33]. Validation studies have examined the performance of ELN risk groups across different patient cohorts and treatment approaches, including lower-intensity regimens [32–34].

8. Diagnosis

The diagnostic work-up integrates clinical assessment with laboratory and genetic investigations. A complete blood count and peripheral blood film may reveal cytopenias, circulating blasts, and abnormal cell morphology. Bone marrow aspirate and biopsy are generally central to diagnosis, enabling blast quantification, morphological assessment, and evaluation of marrow architecture [1, 2, 35]. Cytochemistry, including myeloperoxidase staining, can support myeloid lineage assignment, while multiparameter flow cytometry identifies lineage and characterizes the leukemic immunophenotype using markers such as CD13, CD33, CD117, myeloperoxidase, and HLA-DR [35–37]. Conventional karyotyping and fluorescence in situ hybridization detect chromosomal abnormalities, while molecular assays identify gene mutations and fusions with diagnostic, prognostic, and therapeutic relevance [2, 35, 38]. Testing commonly includes relevant alterations in NPM1, FLT3, CEBPA, TP53, RUNX1, IDH1/2, and recurrent fusion genes, selected according to the clinical presentation and diagnostic algorithm [2, 35, 38]. Rapid testing for PML::RARA is especially important when APL is suspected because treatment should begin before molecular confirmation if clinical and morphological findings support the diagnosis [27, 28]. Measurable residual disease (MRD) assessment uses multiparameter flow cytometry and/or molecular methods to detect disease below the threshold of conventional morphology. MRD results can refine relapse-risk assessment and support post-remission planning, but interpretation depends on the molecular target, assay sensitivity, sample timing, and treatment context [39–42]. The ELN MRD Working Party has published recommendations on assay performance, reporting, and clinically meaningful assessment time points [39]. MRD should be interpreted alongside clinical status and genetic risk rather than as an isolated result [39–42].

9. Prognosis

AML prognosis is heterogeneous and depends on patient characteristics, leukemia genetics, treatment response, and access to effective therapy. Age, performance status, comorbidities, and treatment tolerance influence the feasibility and outcomes of intensive treatment. Cytogenetic and molecular abnormalities remain major prognostic determinants, and the ELN system provides a widely used framework for risk grouping [2, 31–34]. TP53 mutations, complex karyotypes, and myelodysplasia-related abnormalities are generally associated with poorer outcomes, whereas selected genetically defined entities have more favorable outcomes when treated appropriately [2, 31, 32]. Achievement of complete remission is important, but it does not necessarily mean that all leukemic cells have been eradicated. Persistent or recurrent MRD is associated with increased relapse risk and poorer survival in many AML settings [39–42]. A systematic review and meta-analysis found a strong association between MRD status and survival outcomes, although the magnitude of prognostic effect varies by assay, disease subtype, treatment, and assessment time point [40]. For patients undergoing allogeneic hematopoietic stem-cell transplantation, pre-transplant disease status and MRD can help refine relapse-risk assessment [41, 43]. Prognosis should therefore be updated over time as genetic information, response assessments, MRD results, and treatment options become available [2, 39, 43].

10. Treatment

Treatment selection depends on AML subtype, molecular profile, ELN risk, age, fitness, comorbidities, patient goals, and availability of specialist care. APL is managed separately from other AML because differentiation therapy is highly effective and early hemorrhagic complications can be life-threatening. ATRA should be started immediately when APL is suspected; ATRA plus arsenic trioxide is a standard approach for non-high-risk APL, while high-risk disease generally requires additional cyto-reduction [27, 28, 44]. For patients fit for intensive therapy, induction commonly uses cytarabine plus an anthracycline, with consolidation based on disease risk, response, and transplant eligibility [2, 45, 46]. Allogeneic hematopoietic stem-cell transplantation may be recommended for patients whose predicted relapse risk justifies its potential benefits and risks; decisions should account for comorbidity, donor availability, patient preference, and treatment response [2, 43, 47]. Core-binding-factor AML and other favorable-risk subtypes may follow different post-remission strategies from adverse-risk disease [2, 31, 45]. Molecularly targeted therapies have expanded treatment options. FLT3 inhibitors are used in appropriate FLT3-mutated AML settings, including midostaurin with intensive chemotherapy in newly diagnosed disease and gilteritinib in relapsed or refractory disease; quizartinib is another option for selected FLT3-ITD AML [48–51]. IDH inhibitors are used for selected IDH1- or IDH2-mutated cases, depending on treatment line and clinical circumstances [52, 53]. Other agents, including gemtuzumab ozogamicin and liposomal daunorubicin-cytarabine (CPX-351), may be appropriate for selected disease subgroups [54, 55]. For older adults or patients unsuitable for intensive induction, hypomethylating agents combined with venetoclax are widely used, based on evidence of improved remission and survival outcomes compared with hypomethylating-agent monotherapy in relevant populations [56, 57]. Low-dose cytarabine plus venetoclax is another option in selected patients [58]. Oral azacitidine can be used as maintenance therapy for some patients who achieve remission after intensive chemotherapy but are not proceeding to transplantation [59]. Maintenance strategies and post-transplant approaches are individualized because benefits vary by disease biology and clinical context [2, 47, 59, 60]. Relapsed or refractory AML remains difficult to treat. Options include salvage chemotherapy, mutation-directed therapy, clinical trials, and allogeneic transplantation in eligible patients [2, 6, 61]. Menin inhibitors have emerged as a treatment approach for selected leukemias with KMT2A rearrangements or NPM1 mutations, reflecting continuing development of genotype-directed therapy [62]. Clinical-trial participation should be considered when feasible, particularly for high-risk or relapsed disease [6, 61, 62]. Supportive care is essential throughout treatment. It includes red-cell and platelet transfusions when indicated, prompt evaluation and treatment of febrile neutropenia, antimicrobial prophylaxis according to patient risk, tumor-lysis prevention, management of bleeding and coagulopathy, and monitoring for treatment toxicity [2, 10, 63–66]. Infection prevention and rapid treatment of suspected sepsis are particularly important during prolonged neutropenia [63, 64]. Transfusion decisions should be individualized to clinical status, bleeding risk, symptoms, and local protocols [65, 66]. Psychosocial support, clear communication, shared decision-making, and palliative-care involvement when appropriate are important components of comprehensive

AML care [6, 67].

11. Emerging directions and challenges

Current research is evaluating rational combinations of targeted agents, improved MRD-guided treatment strategies, cellular and immune-based approaches, and therapies designed to overcome resistance [6, 7, 62, 68]. The growing complexity of molecular testing creates a need for timely diagnostics, standardized interpretation, and equitable access to treatment. These needs can be particularly challenging in resource-limited settings, where molecular diagnostics, transfusion support, intensive care, and transplantation may be limited [8, 10, 67, 69]. Multidisciplinary pathways and locally adapted treatment protocols can help improve care while maintaining appropriate safety standards [2, 10, 69, 70].

12. Conclusion

Acute myeloid leukemia is a biologically diverse malignancy that requires prompt diagnosis, integrated genetic classification, risk-adapted treatment, and ongoing response monitoring. Progress in molecular diagnostics, targeted therapy, transplantation, and MRD assessment has broadened the options available to patients, but relapse, treatment toxicity, and inequities in access remain substantial challenges. Continued clinical research and coordinated multidisciplinary care are essential to improve survival and quality of life.

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