

# Acute myeloid leukemia

**Acute Myeloid Leukemia (AML)** is a malignant clonal disease of hematopoiesis, characterized by the proliferation and accumulation of immature myeloid precursors (blasts) in the bone marrow and mostly in the peripheral blood. As a result, hematopoietic failure occurs - neutropenia, anemia, and thrombocytopenia. It is the most common acute leukemia in adults, with an incidence of 15/100,000 inhabitants per year. It is rarer in children, with an incidence of about 2-3/100,000 per year. The median age at diagnosis of AML is 65 years.

## Classification

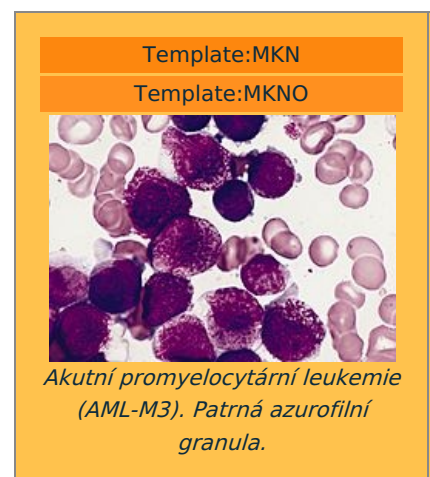
The classification according to WHO (2016) is based on a multiparametric approach that integrates clinical, morphological, immunophenotypic, cytogenetic, and molecular genetic features:

- **AML with recurrent genetic abnormalities** [1] ([https://www.who.int/medical\\_devices/diagnostics/selection\\_in-vitro/selection\\_in-vitro-meetings/00035\\_07\\_WHO\\_2391.full.pdf](https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/00035_07_WHO_2391.full.pdf))
- **AML with myelodysplastic changes**
- **AML due to prior therapy**
- **AML not elsewhere classified (NOS)** - FAB classification
  - AML with minimal differentiation
  - AML without maturation
  - AML with maturation
  - acute myelomonocytic leukemia
  - acute monoblastic and monocytic leukemia
  - pure erythroid leukemia
  - acute megakaryoblastic leukemia
  - acute basophilic leukemia
  - acute panmyelosis with myelofibrosis
- **Myeloid sarcoma**
- **Myeloid proliferation in Down syndrome**

## Causes

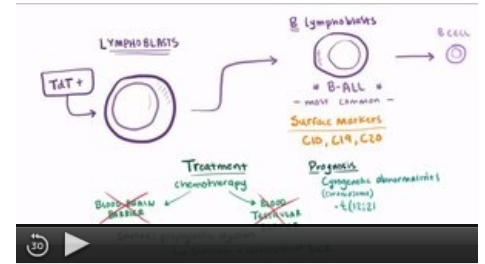
AML arises from the malignant transformation of a hematopoietic stem cell that differentiates into myeloid or myelomonocytic blasts, rarely into erythroid or megakaryocytic blasts. The etiology is multifactorial, the inducers include ionizing radiation and carcinogenic chemicals (including cytostatics) – benzene, herbicides, pesticides, alkylating cytostatics, and topoisomerase II inhibitors. There is an increased incidence in Fanconi anemia, Kostmann syndrome, Wiskott-Aldrich syndrome, Down syndrome, and Klinefelter syndrome. Acquired chromosomal rearrangements and mutations are of fundamental importance, as is the importance of changes in epigenetic regulation.

## Signs



The disease has a sudden onset and the condition deteriorates rapidly. Clinical signs are caused by a combination of anemia, neutropenia, and thrombocytopenia:

- malaise, fatigue and a feeling of exhaustion, paleness of the mucous membranes and skin, in elderly patients there may be ischemic chest pain or ischemic stroke in extreme cases,
- infection, often with an aggressive course,
- sub febrile to febrile without demonstrable infection,
- petechiae, ecchymoses, bleeding from the nose and gums,
- sometimes gingival hyperplasia,
- rarely skin infiltrates or soft tissue infiltration,
- manifestations of leukostasis in hyperleukocytosis - shortness of breath, visual disturbances, various neurological symptoms.



Acute leukemia

## Leukostasis Syndrome

Hyperleukocytosis is a leukocyte count greater than 100,000/ $\mu$ l and is associated with higher morbidity and mortality. In patients with AML, symptoms of leukostasis can appear as early as 50,000/ $\mu$ l. A high number of leukocytes leads to an increase in blood viscosity, obstruction of capillaries, and subsequent hypoxia or bleeding when they rupture. This manifests itself in various neurological symptoms, visual impairment due to hemorrhage into the retina, shortness of breath, ischemia of other organs, or priapism. In patients with hyperleukocytosis and manifestations of leukostasis, we perform *leukapheresis and cytoreduction* (hydroxyurea) intending to prevent or reduce these symptoms and complications. In the beginning, sufficient hydration is necessary. This is a very acute situation that requires an immediate solution.

## Tumorlysis Syndrome

The breakdown of large numbers of cells leads to renal insufficiency, hyperkalemia, hyperphosphatemia, and hyperuricemia. It occurs at the start of treatment, or even spontaneously. Treatment is sufficient i.v. hydration, allopurinol, rasburicase, and possibly instrumental replacement of renal functions (hemodialysis).

## Disseminated Intravascular Coagulation (DIC)

It is a life-threatening condition characterized by extensive activation of the coagulation cascade, which leads to the formation of multiple thrombi. Organ ischemia occurs and subsequently increased bleeding (consumptive coagulopathy). It is most pronounced in acute promyelocytic leukemia and acute monocytic leukemia. Heparin and coagulation factors are administered.

## Diagnosis

In the blood count, anemia, and thrombocytopenia, the number of leukocytes can be increased, decreased, or even normal. The diagnosis is based on the finding of "20% myeloid blasts" in a bone marrow aspirate (myelogram) from a sternal puncture. In most cases, blasts are also detectable in peripheral blood. Typical *hiatus leukemic* (absence of intermediate stages of granulocyte development - promyelocytes, myelocytes, and metamyelocytes). The presence of Auer's rods (azurophilic elongated inclusions) is common, especially in acute promyelocytic leukemia, where there are large atypical promyelocytes with bundles of Auer's rods - the so-called *faggot cells*. The myeloid origin of the blasts is determined by flow cytometry of bone marrow aspirate or peripheral blood, or in foci of infiltrates by immunohistochemistry. Cytogenetic and molecular genetic examinations are necessary to determine the prognosis.

The laboratory examination may also show an elevation of lactate dehydrogenase (LD) and C-reactive protein (CRP), coagulopathy with prolongation of PT and aPTT, and an increased level of D-dimers.

AML is divided into prognostic groups according to cytogenetic and molecular biological findings according to ELN#7559139 ELN (2017) (<https://ashpublications.org/blood/article/129/4/424/36196/Diagnosis-and-management-of-AML-in-adults-2017->)

1. **Favorable**
2. **Medium**
3. **Unfavourable**

## Minimal Residual Disease

Minimal residual disease (MRD) is the name given to the minimal amount of leukemia cells left in the body after therapy. It is one of the main causes of relapses and an important prognostic factor. qRT-PCR quantification of transcripts of recurrent fusion genes is used for detection. If the patient does not have the fusion gene, flow cytometry is used.

## Treatment

Treatment of AML is based on intensive induction chemotherapy followed by postremission chemotherapy or allogeneic hematopoietic cell transplantation. However, transplantation has significant peritransplantation mortality (20–30%). Patients under the age of 65 are usually treated with curative intent, in the elderly, it is appropriate to consider comorbidities, the ability to tolerate intensive chemotherapy, and prognostic factors.

### Intensive treatment (patients under 65 without comorbidities)

- Induction treatment – a combination of 3 days of daunorubicin and 7 days of cytarabine ("3+7" regimen).

In patients with CD33-positive AML in the favorable or intermediate risk group, **gemtuzumab ozogamicin** (anti-CD33 monoclonal antibody conjugated with cytotoxic calicheamicin) is added.

In patients with FLT3 mutations, midostaurin (FLT3 inhibitor) is added.

In case of failure to achieve **complete remission**, the 2nd cycle is given. Patients who do not achieve remission after the 2nd cycle usually have a poor prognosis. We consider complete remission to be a condition when the number of blasts in the bone marrow is below 5% and the number of neutrophils is above  $1 \times 10^9/l$ , and there is no need to administer blood transfusions.

- Post-remission treatment - depends on the prognostic group according to cytogenetic and molecular biological risk:
  1. Favorable – 2-3 cycles of consolidation chemotherapy. In case of relapse or persistent minimal residual disease, allogeneic hematopoietic stem cell transplantation is.
  2. Moderate – Allogeneic hematopoietic stem cell transplant or consolidation chemotherapy, 1-2 cycles of consolidation chemotherapy may be required during donor search.
  3. Unfavorable – allogeneic transplantation of hematopoietic stem cells, possibly 1-2 cycles of consolidation chemotherapy during the search for a donor.

### Palliative and symptomatic treatment (patients over 65 or with comorbidities)

- low-dose cytarabine
- 5-azacytidine
- decitabine
- venetoclax
- glasdegib
- symptomatic therapy in patients in a generally poor condition

Supportive treatment includes prophylaxis with antibiotics and antifungals (immunodeficiency), the substitution of erythrocytes and platelets, hormonal cessation of menstruation, and ovarian protection (risk of severe bleeding and sterility after chemotherapy).

### Treatment of Relapsed or Refractory Disease

Salvage chemotherapy regimens (FLAG, FLAG-IDA or MEC), gilteritinib and quizartinib for *FLT3* mutations, ivosiednib for *IDH1* mutations, enasidenib for *IDH2* mutations, new drugs in clinical trials. Allogeneic hematopoietic stem cell transplantation must always be performed, otherwise, the probability of maintaining remission is low.

## Differential diagnosis

Identical or similar symptoms may have:

- acute lymphoblastic leukemia
- myelodysplastic syndrome (number of blasts up to 20%)
- aplastic anemia
- other leukemias and lymphomas
- primary myelofibrosis
- bone marrow infiltration by cancer cells
- drug-induced bone marrow damage
- infectious mononucleosis

## Prognosis

The prognosis is variable and dependent on cytogenetic-molecular changes and clinical factors (age, response to chemotherapy, initial condition). Patients under the age of 60 achieve complete remission in 60-80% and the overall 5-year survival is around 50%. In older patients, complete remission is 50%, and overall 5-year survival is only 20%. After the use of allogeneic transplantation, the 3-year survival rate is greater than 50%. Patients only survive a few weeks to months on symptomatic treatment.

## Links

### Related Articles

- Leukemia
- Acute lymphoblastic leukemia
- Acute promyelocytic leukemia
- Chronic myeloid leukemia
- Chronic lymphocytic leukemia
- Hairy cell leukemia

## References

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- DOUBEK, Michael, MAYER, Jiří (Eds.). *Treatment procedures in Hematology 2020. Recommendation of the Czech Hematology Society of the Czech Medical Society of Jan Evangelista Purkyně*. 1st ed. 2020. ISBN 978-80-270-8240-7. ([http://www.hematology.cz/doporuceni/klinika-files/Doporuceni\\_CHS\\_CLS\\_JEP-Cervena\\_kniha.pdf](http://www.hematology.cz/doporuceni/klinika-files/Doporuceni_CHS_CLS_JEP-Cervena_kniha.pdf))
- 'Acute myeloid leukemia: a comprehensive review and 2016 update' (<https://www.ncbi.nlm.nih.gov/pmc/article/PMC5030376/>)
- Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5291965/>)
- The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia ([https://www.who.int/medical\\_devices/diagnostics/selection\\_in-vitro/selection\\_in-vitro-meetings/00035\\_07\\_WHO\\_2391.full.pdf](https://www.who.int/medical_devices/diagnostics/selection_in-vitro/selection_in-vitro-meetings/00035_07_WHO_2391.full.pdf))
- <https://www.sciencedirect.com/science/article/pii/S0268960X12000045?via=ihub>

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