COLLEGE of AMERICAN PATHOLOGISTS

Initial Diagnostic Workup of Acute Leukemia Guideline

Statements and Strength of Recommendations

Summary of Recommendations

	Guideline Statement	Strength of Recommendation
1.	The treating clinician should provide relevant clinical data or ensure that this is readily accessible by the pathologist. Note: These data include, but are not limited to, the patient's age, gender, and ethnicity; history of any hematologic disorder or known predisposing conditions or syndromes; any prior malignancy; exposure to cytotoxic therapy, immunotherapy, radiotherapy, or other possibly toxic substances; and any additional clinical findings of diagnostic or prognostic importance. The treating clinician should also include any history of possibly confounding factors, such as recent growth factor therapy, transfusions, or other medications that might obscure or mimic the features of acute leukemia. The treating clinician should also obtain and provide information regarding any family history of any hematologic disorder or other malignancies.	Strong Recommendation
2.	The treating clinician should provide relevant physical examination and imaging findings or ensure that these are readily accessible by the pathologist. Note: This includes, but is not limited to, neurologic exam findings and the presence of tumor masses (eg, mediastinal), other tissue lesions (eg, cutaneous), and/or organomegaly.	Recommendation
3.	The pathologist should review recent or concurrent complete blood cell (CBC) counts and leukocyte differentials and evaluate a peripheral blood smear.	Strong Recommendation
4.	The treating clinician or pathologist should obtain a fresh bone marrow aspirate for all patients suspected of acute leukemia, a portion of which should be used to make bone marrow aspirate smears for morphologic evaluation. If performed, the pathologist should evaluate an adequate bone marrow trephine core biopsy, bone marrow trephine touch preparations, and/or marrow clots, in conjunction with the bone marrow aspirates. Note: If bone marrow aspirate material is inadequate or if there is compelling clinical reason to avoid bone marrow examination, peripheral blood may be used for diagnosis and ancillary studies if sufficient numbers of blasts are present. If a bone marrow aspirate is unobtainable, touch imprint preparations of a core biopsy should be prepared and evaluated, and an additional core biopsy may be submitted unfixed in tissue culture medium for disaggregation for flow and genetic studies. Optimally, the same physician should interpret the bone marrow aspirate smears and the core biopsy specimens, or the interpretations of these specimens should be correlated if performed by different physicians.	Strong Recommendation

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Summary of Recommendations continued

Guideline Statement		Strength of Recommendation
5.	In addition to morphologic assessment (blood and bone marrow), the pathologist or treating clinician should obtain sufficient samples and perform conventional cytogenetic analysis (ie, karyotype), appropriate molecular genetic and/or fluorescent in situ hybridization (FISH) testing, and flow cytometric immunophenotyping (FCI). The flow cytometry panel should be sufficient to distinguish acute myeloid leukemia (including acute promyelocytic leukemia), T-cell acute lymphoblastic leukemia (T-ALL) (including early T-cell precursor leukemias), B-cell precursor ALL (B-ALL), and acute leukemia of ambiguous lineage on all patients diagnosed with acute leukemia. Molecular genetic and/or FISH testing does not, however, replace conventional cytogenetic analysis. Note: If sufficient bone marrow aspirate or peripheral blood material is not available for FCI, immunohistochemical studies may be used as an alternative method for performing limited immunophenotyping. In addition, a second bone marrow core biopsy can be obtained and submitted unfixed in tissue culture media, for disaggregation for genetic studies and flow cytometry.	Strong Recommendation
6.	For patients with suspected or confirmed acute leukemia, the pathologist may request and evaluate cytochemical studies to assist in the diagnosis and classification of acute myeloid leukemia (AML).	Expert Consensus Opinion
7.	The treating clinician or pathologist may use cryopreserved cells or nucleic acid, formalin fixed, nondecalcified paraffin-embedded (FFPE) tissue, or unstained marrow aspirate or peripheral blood smears obtained and prepared from peripheral blood, bone marrow aspirate, or other involved tissues for molecular or genetic studies in which the use of such material has been validated. Such specimens must be properly identified and stored under appropriate conditions in a laboratory that is in compliance with regulatory and/or accreditation requirements.	Recommendation
8.	For patients with acute lymphoblastic leukemia (ALL) receiving intrathecal therapy, the treating clinician should obtain a cerebrospinal fluid (CSF) sample. The treating clinician or pathologist should ensure that a cell count is performed and that examination/enumeration of blasts on a cytocentrifuge preparation is performed and is reviewed by the pathologist.	Strong Recommendation
9.	For patients with acute leukemia other than those with ALL receiving intrathecal therapy, the treating clinician may, under certain circumstances, obtain a cerebrospinal fluid (CSF) sample when there is no clinical contraindication. The treating clinician or pathologist should ensure that a cell count is performed and that examination/enumeration of blasts on a cytocentrifuge preparation is performed and is reviewed by the pathologist.	Expert Consensus Opinion
10.	For patients with suspected or confirmed acute leukemia, the pathologist may use flow cytometry in the evaluation of CSF.	Recommendation
11.	For patients who present with extramedullary disease without bone marrow or blood involvement, the pathologist should evaluate a tissue biopsy and process it for morphologic, immunophenotypic, cytogenetic, and molecular genetic studies, as recommended for the bone marrow. Note: Additional biopsies may be indicated to obtain fresh material for ancillary testing.	Strong Recommendation

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Summary of Recommendations continued

Guideline Statement		Strength of Recommendation
12.	For patients with suspected or confirmed acute leukemia, the pathologist or treating clinician should ensure that flow cytometry analysis or molecular characterization is comprehensive enough to allow subsequent detection of minimal residual disease (MRD).	Strong Recommendation
13.	For pediatric patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(12;21)(p13.2;q22.1); *ETV6-RUNX1*, t(9;22)(q34.1;q11.2); *BCR-ABL1, KMT2A(MLL)* translocation, iAMP 21, and trisomy 4 and 10 is performed.	Strong Recommendation
14.	For adult patients with suspected or confirmed B-ALL, the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2) ; *BCR-ABL1* is performed. In addition, testing for *KMT2A (MLL)* translocations may be performed.	Strong Recommendation for testing for t(9;22)(q34.1;q11.2) and *BCR-ABL1*; Recommendation for testing for *KMT2A (MLL)* translocations
15.	For patients with suspected or confirmed ALL, the pathologist or treating clinician may order appropriate mutational analysis for selected genes that influence diagnosis, prognosis, and/or therapeutic management that includes, but is not limited to, *PAX5, JAK1, JAK2,* and/or *IKZF1* for B-ALL and *NOTCH1* and/or *FBXW7* for T-ALL. Testing for overexpression of *CRLF2* may also be performed for B-ALL.	Recommendation
16.	For pediatric and adult patients with suspected or confirmed acute myeloid leukemia (AML) of any type, the pathologist or treating clinician should ensure that testing for *FLT3*-ITD is performed. The pathologist or treating clinician may order mutational analysis that includes, but is not limited to: *IDH1, IDH2, TET2, WT1, DNMT3A*, and/or *TP53* for prognostic and/or therapeutic purposes.	Strong recommendation for testing for *FLT3*-ITD; Recommendation for testing for other mutational analysis
17.	For adult patients with confirmed core binding factor (CBF) AML (AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* or inv(16)(p13.1q22) /t(16;16)(p13.1;q22); *CBFB-MYH11*), the pathologist or treating clinician should ensure that appropriate mutational analysis for *KIT* is performed. For pediatric patients with confirmed core binding factor AML (AML with t(8;21)(q22;q22.1); *RUNX1-RUNX1T1* or inv(16)(p13.1q22) /t(16;16)(p13.1;q22); *CBFB-MYH11*), the pathologist or treating clinician may ensure that appropriate mutational analysis for *KIT* is performed.	Strong Recommendation for testing for *KIT* mutation in adult patients with CBF AML; Expert Consensus Opinion for testing for *KIT* mutation in pediatric patients with CBF AML
18.	For patients with suspected acute promyelocytic leukemia (APL), the pathologist or treating physician should also ensure that rapid detection of *PML-RARA* is performed. The treating physician should also order appropriate coagulation studies to evaluate for disseminated intravascular coagulation (DIC).	Strong Recommendation
19.	For patients other than those with confirmed core binding factor AML, APL, or AML with myelodysplasia-related cytogenetic abnormalities, the pathologist or treating clinician should also ensure that mutational analysis for *NPM1*, *CEBPA*, and *RUNX1* is also performed.	Strong Recommendation

Summary of Recommendations continued

	Guideline Statement	Strength of Recommendation
20.	For patients with confirmed acute leukemia, no recommendation is made for or against the use of global/gene specific methylation, micro RNA (miRNA) expression, or gene expression analysis for diagnosis or prognosis.	No Recommendation
21.	For patients with confirmed mixed phenotype acute leukemia (MPAL), the pathologist or treating clinician should ensure that testing for t(9;22)(q34.1;q11.2); *BCR-ABL1*, and *KMT2A* (MLL) translocations is performed.	Strong Recommendation
22.	All laboratory testing performed for the initial workup and diagnosis of a patient with acute leukemia must be performed in a laboratory that is in compliance with regulatory and/or accreditation requirements.	Strong Recommendation
23.	If after examination of a peripheral blood smear, it is determined that the patient will require immediate referral to another institution with expertise in the management of acute leukemia for treatment, the initial institution should, whenever possible, defer invasive procedures, including bone marrow aspiration and biopsies, to the treatment center to avoid duplicate procedures, associated patient discomfort, and additional costs.	Strong Recommendation
24.	If a patient is referred to another institution for treatment, the primary institution should provide the treatment center with all laboratory results, pathology slides, flow cytometry data, cytogenetic information, and a list of pending tests at the time of the referral. Pending test results should be forwarded as they become available.	Strong Recommendation
25.	In the initial report, the pathologist should include laboratory, morphologic, immunophenotypic, and, if performed, cytochemical data, on which the diagnosis is based, along with a list of any pending tests. The pathologist should issue addenda/amended reports when the results of additional tests become available.	Strong Recommendation
26.	The pathologist and treating clinician should coordinate and ensure that all tests performed for classification, management, predicting prognosis, and disease monitoring are entered into the patient's medical records. Note: This information should include the sample source, adequacy, and collection information, as applicable.	Strong Recommendation
27.	Treating physicians and pathologists should use the current World Health Organization (WHO) terminology for the final diagnosis and classification of acute leukemia.	Strong Recommendation

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