CLL diagnosis

Initial consultation of suspected CLL

Includes best practice sharing by
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Diagnosis of CLL

The World Health Organization classification of haematopoietic neoplasias describes CLL as *"leukaemic, lymphocytic lymphoma and distinguishable from SLL by its leukaemic appearance"*.[1,4] It is important to distinguish CLL from other lymphoproliferative diseases that can mimic CLL by investigating the:[5]

- Blood smear
- Immunophenotype
- Genetic features*

Symptoms of CLL[1–3]

Symptoms vary and may take years to appear:

- Fatigue/ night sweats
- Weight loss
- Lymphadenopathy or splenomegaly
- Pallor
- Repeated infections
- Bleeding

Investigations

If CLL is suspected, the following should be carried out during the initial consultation:[2,6]

Routine

- **Medical history: Infections and B symptoms[2,6]**
- **Family history: Lymphoid malignancy[2]**
- **ECOG Performance Status[6]**
- **Physical examination: Measurement of size of liver, spleen and palpable lymph nodes[6†]**
- **CBC with differential and peripheral blood film[5,6]**
- **Comprehensive metabolic panel, including LDH[6]**
- **Immunophenotype[9]**

Additional investigations (as required):[6]

- Quantitative immunoglobulins[6]
- Reticulocyte count, haptoglobin, and direct antiglobulin test (Coombs)[6]
- Neck/chest/abdominal/pelvic CT with contrast[6]
- β2-microglobulin[6]
- Uric acid[12]
- Bone marrow aspirate and biopsy[6]
- Hepatitis B and C testing[6]
- MUGA scan/ECG (if anthracycline-based regimen is indicated)[13]
- Pregnancy testing in females of childbearing age (if systemic therapy or RT is required)[13]
- PET/CT scan to direct nodal biopsy (if histologic transformation is suspected)

Distinguishing CLL from SLL[1,5–8]

	CLL	SLL
Location	· Mainly in blood and bone marrow	· Primarily affects the lymph nodes
Diagnosis	· Diagnosis requires the presence of ≥5000 B lymphocytes/μL in the peripheral blood for at least 3 months · The clonality of the circulating B lymphocytes requires confirmation by flow cytometry · The leukaemia cells found in the blood smear are characteristically small, mature lymphocytes with a narrow border of cytoplasm, and a dense nucleus lacking discernible nucleoli and partially aggregated chromatin · Gumprecht nuclear shadows, or smudge cells, found as cellular debris, are additional morphological features commonly associated with CLL	· Diagnosis requires the number of B lymphocytes in the peripheral blood to not exceed 5000/μL · Where possible, diagnosis should be confirmed by histopathological evaluation of a lymph node biopsy · Some patients may present with enlarged lymph nodes that are not suspicious for solid tumours, and with peripheral blood B lymphocytes <5 × 10⁹/L that carry a typical CLL immunophenotype · In these cases, a tissue or lymph node biopsy to establish the diagnosis of SLL can be omitted as it may have limited clinical consequences

Recommended CLL scoring system[10,11]

The table is a recommended minimum panel of monoclonal antibodies and scoring system for the diagnosis of CLL.

The scoring system allocates one point each for the expression of weak surface membrane immunoglobulins **CD5** and **CD23**, and absent or low expression of **CD22, CD79B, FMC7** and **SmIg**.

Marker	Score 1	Score 0
SmIg	Weak	Strong
CD5	Positive	Negative
CD23	Positive	Negative
FMC7	Negative	Positive
CD22 or CD79B	Weak	Strong

Scores >3 suggestive of CLL; scores <3 suggestive of other B-cell malignancy

In the diagnosis of CLL, essential markers are **CD5, CD19, CD20, CD23,** and surface or cytoplasmic kappa and lambda light chains[5]

CD10, CD43, CD79B, CD81, CD200 and **ROR1** are additional targets useful in the differential diagnosis from other small B-cell lymphomas/leukaemias[5]

CBC, complete blood count; CD, cluster of differentiation; CLL, chronic lymphocytic leukaemia; CT, computed tomography; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; MUGA, multigated acquisition; PET, positron emission tomography; RT, radiation therapy; SLL, small lymphocytic lymphoma

*The genetic features of the circulating lymphoid cell in some cases;† †Lymphadenopathy/splenomegaly/hepatomegaly

1. Hallek M, Al-Sawaf O. Am J Hematol 2021;96:1679–1705; 2. CLL Support. About CLL/SLL. https://www.cllsupport.org.uk/information-support/about-cll/. Accessed 9 January 2023; 3. Cancer Research UK. Symptoms of chronic lymphocytic leukaemia (CLL). https://www.cancerresearchuk.org/about-cancer/chronic-lymphocytic-leukaemia-cll/symptoms. Accessed 15 February 2023; 4. CLL Society. Diagnosis of chronic lymphocytic leukemia. March 2016. https://cllsociety.org/2016/03/diagnosis-chronic-lymphocytic-leukemia/. Accessed 9 January 2023; 5. Hallek M, et al. Blood 2018;131:2745–60; 6. Eichhorst B, et al. Ann Oncol 2021;32:23–33; 7. National Comprehensive Cancer Network®. Distress during cancer care. 2020. <https://www.nccn.org/patients/guidelines/content/PDF/distress-patient.pdf. Accessed 9 January 2023>; 8. Hallek M, et al. Blood .2008;111:5446–56 9. Alaggio R, et al. Leukemia 2022;36:1720–48; 10. Kay NE, et al. Hematology Am Soc Hematol Educ Program 2002;2002:193–213; 11. RM Partners. Pan-London Haemato-Oncology Clinical Guidelines. https://rmpartners.nhs.uk/wp-content/uploads/2020/01/Pan-London-CLL-Guidelines-Jan-2020.pdf. Accessed 9 January 2023; 12. Macmillan Cancer Support. FCR Chemotherapy. https://www.macmillan.org.uk/cancer-information-and-support/treatments-and-drugs/fcr. Accessed 9 January 2023; 13. Personal communication from Dr Ali Risman

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CLL diagnosis

A guide to diagnosing CLL

Includes best practice sharing by
Dr Ali Rismani, consultant haematologist,
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Diagnosis of CLL[1]

The diagnosis of CLL is established by blood counts, blood smears, and immunophenotyping of circulating B lymphocytes, which identify a clonal B-cell population carrying the CD5 antigen, as well as typical B-cell markers.

Baseline investigations of patients with CLL[2]

Diagnostic assessment	Details
Assessments to establish diagnosis	
· CBC and differential count	Always
· Immunophenotyping of peripheral blood lymphocytes	Always
Assessments before treatment	
· History and physical performance status	Always
· CBC and differential count	Always
· Marrow aspirate and biopsy	WCI*
· Serum chemistry, serum immunoglobulin, and direct antiglobulin assessment	Always
· Chest radiograph	Always
· Infectious disease status	Always
Assessments to establish diagnosis	
· CBC and differential count	Always
· Immunophenotyping of peripheral blood lymphocytes	Always
Additional assessments before treatment	
· Molecular cytogenetics (FISH) for del(13q), del(11q), del(17p), add(12) in peripheral blood lymphocytes	Always
· Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation)	NGI†
· *TP53* mutation	Always
· *IGHV* mutational status	Always
· Serum β2-microglobulin	Des
· CT scan of chest, abdomen, and pelvis	NGI
· MRI and PET scans	NGI
· Abdominal ultrasound¶¶	Poss

Biomarker testing in CLL[3]

Biomarker testing results are prognostic and may be predictive for informing treatment decisions for individual patients

Critical results from interphase FISH testing for del(17p), del(11q), del(13q) and trisomy 12, and sequencing for mutations in *TP53* and *IGHV* somatic hypermutation status inform a patient's risk stratification and their potential response to CLL therapies

The value of testing has been increasingly recognised, with prognostic models and diagnostic guideline recommendations to include it when making treatment considerations

Prognosis and staging of CLL[1]

The clinical staging systems provide prognostic information by using the results of physical examination and blood counts

Various biological and genetic markers provide additional prognostic information

Deletions of the short arm of chromosome 17 (del[17p]) and/or mutations of the *TP53* gene predict resistance to chemoimmunotherapy and a shorter time to progression with most targeted therapies

The CLL-IPI integrates genetic, biological, and clinical variables to identify distinct risk groups of patients with CLL

There are two widely accepted clinical staging systems[1]

Binet staging[1,2]

Stage	Details
Based on the number of involved areas‡	
Areas of involvement are (1) head and neck, including the Waldeyer ring;§ (2) axillae;‖ (3) groins, including superficial femoral;¶ (4) palpable spleen; and (5) palpable liver#	
A	Hb ≥10g/dL + platelets ≥100 x 10^9/L + ≤2 of the above involved
B	Hb ≥10g/dL + platelets ≥100 x 10^9/L + organomegaly > stage A definition**
C	Hb <10g/dL and/or platelets <100 x 10^9/L

Rai staging[1,2]

Risk group	Details
Low	Patients who have lymphocytosis with leukaemia cells in the blood and/or marrow (lymphoid cells >30%)††
Intermediate	Patients with lymphocytosis, enlarged nodes in any site, and splenomegaly and/or hepatomegaly (lymph nodes being palpable or not)‡‡
High	Patients with disease-related anaemia (as defined by a Hb level <11g/dL)§§ or thrombocytopenia (as defined by a platelet count of <100 x 10^9/L)‖‖

Binet is most commonly used in the UK[4]

The different CLL-IPI categories:[1]

CLL-IPI category	OS at 5 years	Potential clinical consequence
Low risk	93.2%	Do not treat
Intermediate risk	79.3%	Do not treat except if the disease is really symptomatic
High risk	63.3%	Treatment is indicated except if the disease is asymptomatic
Very high risk	23.3%	If you need to treat, use targeted therapy or enrolment into a clinical trial

add, additional; CBC, complete blood count; CD, cluster of differentiation; CLL, chronic lymphocytic leukaemia; CT, computed tomography; del, chromosome deletion; Des, desirable; FISH, fluorescence in situ hybridisation; Hb, haemoglobin; *IGHV*, immunoglobulin heavy chain variable; IPI, International Prognostic Index; MRI, magnetic resonance imaging; NGI, not generally indicated; OS, overall survival; PET, positron emission tomography; Poss, possible; TP, tumour protein; WCI, when clinically indicated
*Unclear cytopenia; †Conventional karyotyping in peripheral blood lymphocytes (with specific stimulation) may be useful before therapy, if established methodology is available; ‡As defined by the presence of enlarged lymph nodes >1cm in diameter or organomegaly, and on whether there is anaemia or thrombocytopenia; §This counts as one area, even if more than one group of nodes is enlarged; ‖Involvement of both axillae counts as one area; ¶Involvement of both groins counts as one area; #Clinically enlarged; **Three or more areas of nodal or organ enlargement; ††Former Rai stage 0; ‡‡Former Rai stage I or II; §§Former Rai stage III; ‖‖Former Rai stage IV; ¶¶Used in some countries to monitor lymphadenopathy and organomegaly in some cases

1. Hallek M, Al-Sawaf O. Am J Hematol 2021;96:1679–1705; 2. Hallek M, et al. Blood 2018;131:2745–60; 3. Mato AR, et al. Clin Lymphoma Myeloma Leuk 2020;20:174–83.e3; 4. Macmillan Cancer Support. Stages of chronic lymphocytic leukaemia (CLL). https://www.macmillan.org.uk/cancer-information-and-support/leukaemia/chronic-lymphocytic-leukaemia-cll-stages. Accessed 15 February 2023

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