

Angioimmunoblastic T-cell lymphoma (AITL) is a rare and often fast-growing form of peripheral T-cell lymphoma (PTCL). It accounts for about 20-30% of PTCLs and is more common in older people (median age at diagnosis is 65 years), though it can affect young adults as well.

Symptoms of AITL include:

- Fatigue.
- High fever.
- Night sweats.
- Skin rash.
- *Autoimmune* disorders (group of diseases where the immune system attacks the body's own healthy tissues), such as autoimmune hemolytic anemia (AIHA; the body immune system attacks its own red blood cells) and immune thrombocytopenia (ITP; the body immune system attacks its own platelets).

Diagnosing AITL requires taking a *biopsy* (sample of the tumor tissue) and looking at the cells under a microscope. The cells are also analyzed by *flow cytometry* (a technique that uses a laser to detect and count the different types of blood cells, according to their size and number of small particles). Some patients may also require additional testing for specific genetic *mutations* (permanent changes) in the DNA (deoxyribonucleic acid, the molecule that carries the genetic information inside the cells). Other tests may be done to determine the extent, or stage (how much the disease has grown and the different locations in the body it affects) of the disease. These can include blood tests, a computed tomography (CT) scan (a procedure that uses X-rays to take detailed pictures of areas inside the body), a positron emission tomography (PET) scan (a procedure that uses a special dye to locate the cancer in the body), and a bone marrow (the spongy tissue inside the bones) biopsy. Rarely, a lumbar puncture (a needle is inserted into the lower back to collect a sample of the fluid that surrounds the brain and spinal cord) and a magnetic resonance imaging (MRI) scan (a procedure that takes detailed pictures of areas inside the body using a powerful magnet and radio waves) may also be recommended. Doctors may also check for active infection with Epstein-Barr virus (EBV, the virus that causes mononucleosis), which is present in some patients with AITL.

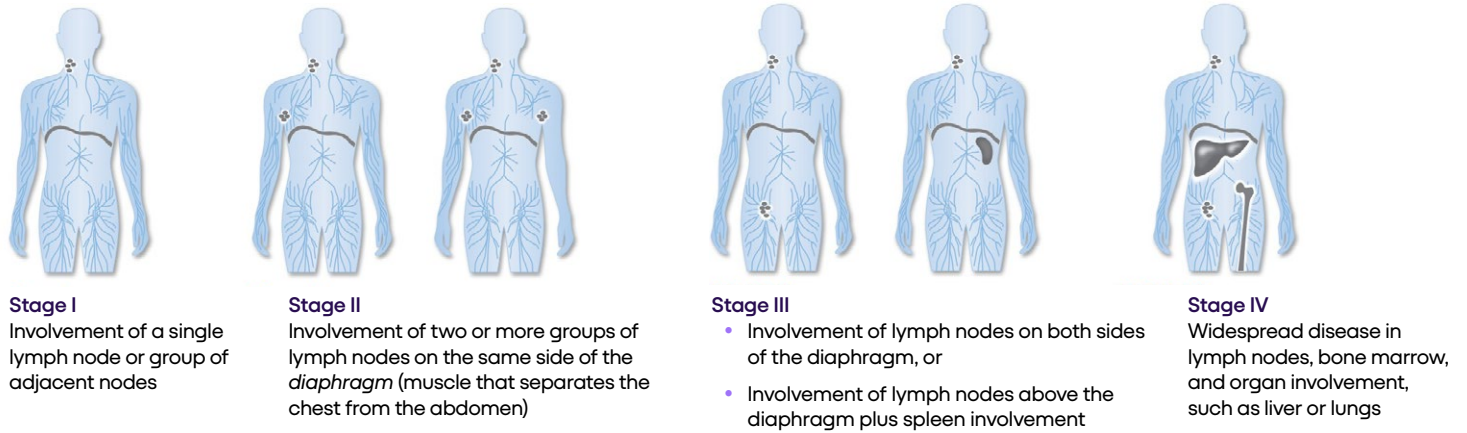
Most patients with AITL are diagnosed with advanced-stage disease (Stage III or Stage IV disease). This means that the disease has grown and/or affects many areas of the body (Figure 1) and requires treatment. Less-extensive disease, Stage I (localized disease that has not spread beyond one lymph node or other location) or Stage II (disease has spread only to nearby lymph nodes), is rare in AITL. In Stage III, affected lymph nodes are found both above and below the diaphragm (the muscle that separates the chest from the abdomen). In Stage IV, one or more organs beyond the lymph nodes are affected, such as the bone, bone marrow, skin, or liver.

For more information on AITL symptoms and diagnosis, please view the *Understanding Lymphoma and CLL Guide* on the Foundation's website (visit lymphoma.org/publications).

Prognosis

A new prognostic tool (predicts how well the patient will do) called the AITL Score was recently developed to predict the outcome in patients with AITL. The AITL Score categorizes patients by level of risk (low-, intermediate- and high-risk). The risk categories are determined by age, Eastern Cooperative Oncology Group (ECOG) performance status (a scale of 0 to 5 that describes the patient's ability to take care of themselves and perform daily activities, like walking or working), levels of C-reactive protein (CRP, a protein made in the liver in response to inflammation or tissue damage) and $\beta 2$ microglobulin (a protein that is increased in some types of cancer, like lymphoma).

Figure 1: Staging of NHL according to the Lugano system. This system categorizes NHL from Stage I (limited disease) to IV (advanced disease), based on whether the cancer is restricted to a single group of lymph nodes, has spread to other lymph nodes, or has reached the bone marrow (the spongy tissue inside the bones) and/or other organs (like the liver or lungs).



Patients aged 60 years or older, with an ECOG performance status greater than 2, an elevated CRP and $\beta 2$ microglobulin have an increased risk of severe disease when compared to other patients. However, keep in mind that no two patients are alike and that statistics can only predict how a large group of patients will do (not what will happen to an individual patient). The doctor most familiar with the patient's situation is in the best position to interpret the increased risk, understand how it applies to a patient's particular situation, and respond to any questions you might have.

Treatment Options

Treatment types for AITL include:

- Chemotherapy (drugs that stop the growth of or kill cancer cells)
- Stem cell transplantation (SCT, the patient is treated with high-dose chemotherapy or radiation to remove their blood-forming cells or stem cells, and then receives healthy stem cells to restore the immune system and the bone marrow's ability to make new blood cells)

Patients with AITL are usually treated with combinations of chemotherapy drugs. Recommended frontline (initial) therapy for the treatment of AITL is either a clinical trial (a research study that evaluates the best dose, safety and efficacy of a new treatment in human patients) or a course of chemotherapy using a combination of drugs, such as:

- CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone).
- CHOEP (doxorubicin, vincristine, cyclophosphamide, etoposide, prednisone).
- BV-CHP (Brentuximab vedotin [Adcetris] in combination with cyclophosphamide, doxorubicin, and prednisone) is the standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts) for cancers that have the CD30 marker (a protein involved in cell growth and survival, found in increased amounts on some white blood cells), like in some cases of AITL.

The goal of such therapy is often to achieve *durable remission* (no signs and symptoms of cancer for a long time). In cases where the treatment goal is mostly to relieve symptoms, steroids may be used. Sometimes higher doses of chemotherapy, followed by SCT, may be added at the end of treatment with the multidrug chemotherapy. The aim is to increase the chance of the patient reaching durable remission. In some cases, patients may be treated with radiation therapy.

Disease *relapse* (returns after treatment) is common with this cancer. The treatment types used in relapsed or refractory (does not respond to treatment) AITL include:

- Targeted therapies (drugs that target molecules that cancer cells use to grow and spread). This includes belinostat (Beleodaq), a histone deacetylase (HDAC) inhibitor that blocks tumor cells from growing and dividing, causing cell death.
- Immunotherapy (drugs that use the body's immune system to fight cancer). This includes:
 - The antibody-drug conjugate (ADC, a monoclonal antibody attached to a chemotherapy drug) brentuximab vedotin (Adcetris). The monoclonal antibody in the ADC recognizes and binds to a protein called CD30 on the cancer cell surface. Once the ADC is inside the cell, the chemotherapy drug separates from the ADC and kills the cancer cell by targeting cell multiplication
 - Immunomodulatory drugs (a drug that works by increasing or reducing the immune response) such as lenalidomide (Revlimid).
 - Monoclonal antibodies (a protein made in the laboratory that binds to cancer cells and helps the immune system destroy them).
- Chemotherapy, such as pralatrexate (Folotyn), which works as a dihydrofolate reductase (DHFR) inhibitor and blocks the cells' ability to divide and multiply.

Treatments following relapse may include high-dose chemotherapy followed by an *autologous SCT* (patients receive their own stem cells) or an *allogeneic SCT* (patients receive stem cells from a donor). For additional information about stem cell transplantation, view the *Understanding Cellular Therapy* publication on the Lymphoma Research Foundation's website (visit lymphoma.org/publications).

Other Treatment Possibilities Lenalidomide (Revlimid) is an immunomodulatory drug that has been tested alone or in combination with current chemotherapy regimens and shows promise for the treatment of AITL. Some other drugs used in other types of lymphoma that may occasionally be considered for the treatment of patients with AITL include targeted therapies like romidepsin (Istodax), bortezomib (Velcade), and chemotherapies like gemcitabine (Gemzar), bendamustine (Treanda), and azacitidine (Vidaza). Immunosuppressive agents (drugs that prevent the body's immune system from attacking its own healthy cells and tissues by mistake) like cyclosporin can also be used in patients who have autoimmune disorders. Alemtuzumab (Campath) is a monoclonal antibody also occasionally considered, although it is no longer commercially available and is provided only through the Campath Distribution Program.

Treatments Under Investigation

Many treatments (also referred to as investigational drugs) are currently being tested in clinical trials in patients who are previously untreated and relapsed/refractory AITL. Results from these clinical trials may improve or change the current standard of care (the proper treatment that is widely used by healthcare professionals and accepted by medical experts). The table below lists some of these investigational drugs that can be accessed through a clinical trial.

It is important to remember that today's scientific research is always evolving. Treatment options may change as new treatments are discovered and current treatments are improved. Therefore, it is important that patients check with their physician or with the Foundation for any treatment updates that may have recently appeared. It is also very important that patients consult with a specialist to clear up any questions.

Clinical Trials

Clinical trials are crucial in identifying effective drugs and the best treatment doses for patients with AITL. Because AITL is a rare disease, clinical trial enrollment is critical for establishing more effective, less toxic treatments. The rarity of the disease also means that the new treatments are often available only through clinical trials. Patients interested in participating in a clinical trial should view the *Understanding Clinical Trials* fact sheet on the Foundation's website (visit lymphoma.org/publications), and the *Clinical Trials Search Request Form* at lymphoma.org, talk to their physician, or contact the Foundation's Helpline for an individualized clinical trial search by calling (800) 500-9976 or emailing helpline@lymphoma.org.

Follow-up

Disease relapse and infections are common with this cancer. It is important to seek medical attention for fever or other symptoms related to improper functioning of the immune system.

Patients with AITL should have regular visits with their physician. During these visits, medical tests (such as blood tests and CT scans or at times PET scans) may be required to evaluate the need for additional treatment.

Some treatments can cause long-term side effects (occur during treatment and continue for months or years) or late side effects (appear only months, years or decades after treatment has ended). These side effects can vary based on the following factors:

- Duration of treatment (how long was the treatment given).
- Frequency of treatment (how often was the treatment administered).
- Type of treatment given.
- Age and gender of the patient.
- Patient overall health at the time of treatment.

A physician will check for these side effects during follow-up care. Visits may become less frequent the longer the disease remains in remission.

Table 1: Selected Agents Under Investigation for AITL in Phase 2 or 3 Clinical Trials.

Agent (drug)	Class (type of treatment)
Azacitidine (Vidaza)	Chemotherapy
AUTO4	Immunotherapy; CAR T-cell therapy, anti-TRBC1
Daratumumab (Darzelex)	Immunotherapy; monoclonal antibody, anti-CD38
Duvelisib (Copiktra)	Targeted therapy; PI3K inhibitor
Pembrolizumab (Keytruda)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1
Sintilimab (Tyvyt)	Immunotherapy; immune checkpoint inhibitor, anti-PD-1

AITL, angioimmunoblastic T-cell lymphoma; CAR T, chimeric antigen receptor; PD-1, programmed cell death protein 1; PI3K, phosphoinositide-3-kinase; TRBC1, T-cell receptor beta constant 1.

Patients and their care partners are encouraged to keep copies of all medical records. These include test results as well as information on the types, amounts, and duration of all treatments received. Medical records are important for keeping track of any side effects resulting from treatment or potential disease recurrences. The Foundation's award-winning *Focus On Lymphoma* mobile app (lymphoma.org/mobileapp) or the *Lymphoma Care Plan* (lymphoma.org/publications) can help patients manage this documentation.

Lymphoma Care Plan

Keeping your information in one location can help you feel more organized and in control. This also makes it easier to find information pertaining to your care and saves valuable time. The Foundation's Lymphoma Care Plan document organizes information on your health care team, treatment regimen, and follow-up care. You can also keep track of health screenings and any symptoms you experience to discuss with your health care provider during future appointments. The Lymphoma Care Plan document can be accessed by visiting lymphoma.org/publications.

Patient Education Programs

The Foundation also offers a variety of educational activities, including live meetings and webinars for individuals looking to learn directly from lymphoma experts. These programs provide the lymphoma community with important information about the diagnosis and treatment of lymphoma, as well as information about clinical trials, research advances and how to manage/cope with the disease. These programs are designed to meet the needs of a lymphoma patient from the point of diagnosis through long-term survivorship. To view our schedule of upcoming programs, please visit lymphoma.org/programs.

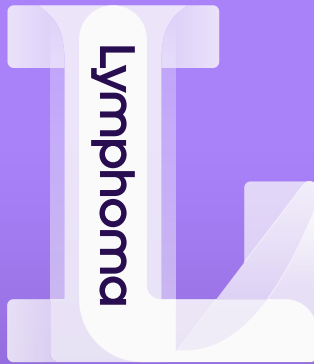
Helpline

The Foundation's Helpline staff are available to answer your general questions about lymphoma and treatment information, as well as provide individual support and referrals to you and your loved ones. Callers may request the services of a language interpreter. The Foundation also offers a one-to-one peer support program called the Lymphoma Support Network and clinical trials information through our Clinical Trials Information Service. For more information about any of these resources, visit our website at lymphoma.org, or contact the Helpline at (800) 500-9976 or helpline@lymphoma.org.

Para información en Español, por favor visite lymphoma.org/es. (For Information in Spanish please visit lymphoma.org/es).

Focus on Lymphoma Mobile App

Focus on Lymphoma is the first app to provide patients and their care partners with tailored content based on lymphoma subtype, and actionable tools to better manage diagnosis and treatment. Comprehensive lymphoma management, conveniently in one secure and easy-to-navigate app, no matter where you are on the care continuum. Get the right information, first, with resources from the entire Lymphoma Research Foundation content library, use unique tracking and reminder tools, and connect with a community of specialists and patients. To learn more about this resource, visit our website at lymphoma.org/mobileapp, or contact the Foundation's Helpline at (800) 500-9976 or helpline@lymphoma.org.



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