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# Lymphoproliferative Diseases - Etiology, Epidemiology, Pathophysiology, Diagnosis and Therapy

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**ABSTRACT**

Lymphoproliferative disorders (LPDs) are a heterogeneous group of conditions characterized by uncontrolled lymphocyte proliferation, resulting in monoclonal lymphocytosis, lymphadenopathy, and bone marrow infiltration.

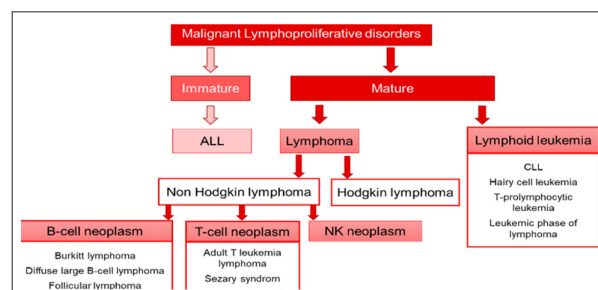
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**Introduction**

Lymphoproliferative disorders (LPD) comprise a heterogeneous group of diseases characterized by uncontrolled production of lymphocytes that cause monoclonal lymphocytosis, lymphadenopathy and bone marrow infiltration [1,2]. These diseases often occur in immunocompromised individuals. There are two subsets of lymphocytes: T and B cells that regenerate uncontrollably to produce immunoproliferative disorders, which are prone to immunodeficiency, a dysfunctional immune system, and lymphocyte dysregulation. Several gene mutations have been described as causes of LPD that can be iatrogenic or acquired [1].

Chronic lymphoproliferative disorders are immunomorphologically and clinically heterogeneous. Common features of these processes include various immunophenotypes (T, B, and NK cells) and terminal deoxynucleotidyl transferase negativity [2].

Lymphoproliferative disorders encompass a wide range of subtypes, each with distinct characteristics and clinical manifestations (Figure 1)



**Etiology Disease**

Infections with Human immunodeficiency virus (HIV), human T-cell lymphotropic virus type 1 (HTLV-1), human herpes virus-8 (HHV8) and Epstein-Barr virus are all associated with an increased risk of certain types of lymphoproliferative disease, most probably by causing immunosuppression. Infection with HTLV-1, especially in early childhood, is strongly related to the development of adult T-cell leukaemia/lymphoma with an estimated cumulative lifetime risk of approximately 5% [3].

Higher risk of developing chronic lymphoproliferative disorders have patients with receiving long-term immunosuppressive drug therapy such as transplant recipients and patients with autoimmune diseases [4]. An increased risk is also seen in patients suffering from a variety of autoimmune conditions, for example, rheumatoid arthritis, Sjögren’s syndrome and coeliac

disease, independent of immunosuppressive treatments. Also, occupations related to agriculture have been associated with an excess risk of lymphoproliferative disease leading to suggestions that contact with herbicides, pesticides and solvents could be important determinants of risk.

Pathophysiology.

Lymphoproliferative disorders originate when physiological mechanisms of control of proliferation of both T and B cells break down, resulting in the uncontrolled and autonomous increase of immune cells leading to lymphocytosis and lymphadenopathy, and often involvement of extranodal sites, e.g., bone marrow. In immunocompromised patients, EBV can cause a mild disease. However, in immune-suppressed transplant patients, immunosurveillance may be compromised by the lack of T cells, leading to a proliferation of EBV-infected B-lymphocytes and post-transplant lymphoproliferative disorder (PTLD). Polyclonal PTLD can form tumor masses and presents with symptoms of a mass effect. Monoclonal forms of PTLD can manifest as a disseminated malignant lymphoma [5,6].

### Diagnosis

The diagnostic criteria for LPD established by the World Health Organization (WHO), iwCLL, the National Comprehensive Cancer Network (NCCN), and the European Society for Medical Oncology (ESMO). In the group of lymphoproliferative diseases, morphology still remains one of the bases of classification, but the immunophenotype and genetic characteristics of the tumor contribute to the objectivity of the diagnosis, increase the reproducibility of the classification and sometimes provide significant prognostic information. Flow cytometry (FCM) has become a method of choice for immunologic characterization of chronic lymphoproliferative disease. The diagnosis of the different lymphoma entities is based on a combination of morphology, immunophenotype, EBER in situ hybridization, FISH analysis, and B-cell clonality analysis. Advances in the understanding of diffuse large B cell lymphoma herald a transition to a molecular genetic classification. This genetic classification is based on mutational profile, somatic copy number alterations, and structural variants [6,7].

### Treatment

In the last decade there has been a considerable change in the treatment of LPD and an increase in overall survival. Biological therapies or targeted therapies have been added to conventional chemotherapy which, selectively, try to stop or, in some cases, prevent the progression of tumour cells. These therapies include a series of monoclonal antibodies, checkpoint inhibitors, bispecific antibodies, and chimeric antigen receptor T (CAR-T) cell therapies, receptor analogues and small molecules designed to bind to different molecular targets (8). Cellular therapies,

particularly CAR-T, emerge as a potential revolution for the R/R of several types of NHL, considered incurable until a few years ago. Nonetheless, these advancements call for further investigations, especially in optimizing combination strategies, managing resistance mechanisms, and refining administration timing

These drugs have advantages over chemotherapy in terms of potency and specificity and, theoretically, produce less adverse effects. However, if these drugs are correlated with a greater number of infections it is a difficult fact to establish, since there is a large number of factors that lead to confusion [8,9].

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