Cancer Association of South Africa (CANSA)

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Fact Sheet
On
Burkitt Lymphoma

Introduction

Lymphoma is a type of cancer involving cells of the immune system, called lymphocytes. Lymphoma also represents many different cancers of lymphocytes - about 35 different subtypes.

The Lymphatic System

The lymphatic system is network of vessels that helps keep bodily fluid levels in balance and defends the body against infections. It is responsible to drain lymphatic fluid from the tissues back into the bloodstream. It is made up of a network of lymphatic vessels that transports the lymph - a clear, watery fluid containing protein, salts, glucose, urea, and other substances - throughout the body.

The spleen, located in the upper left part of the abdomen under the ribcage, works as part of the lymphatic system to protect the body, clearing worn out red blood cells and other foreign bodies from the bloodstream to help fight off infection.

[Picture Credit: Lymphatic System]

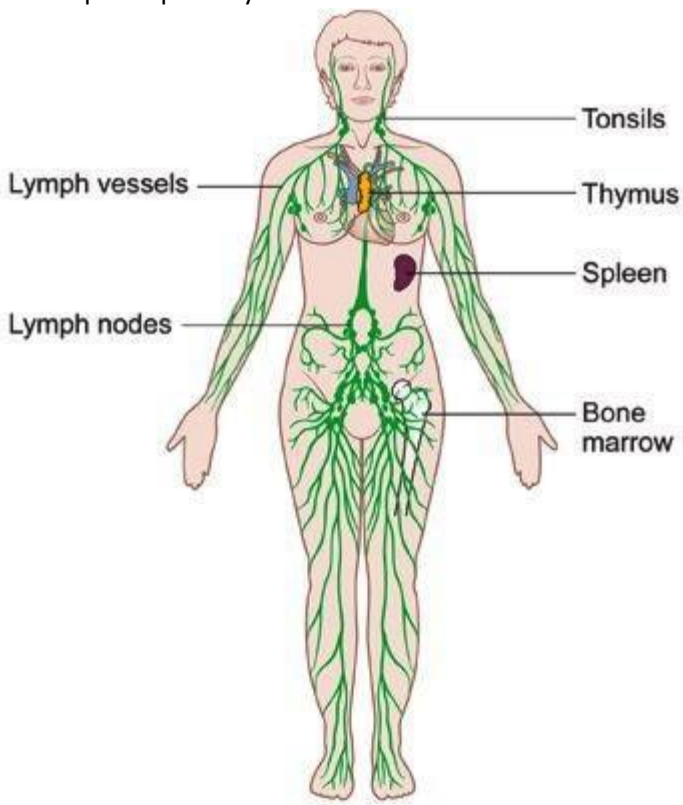

Diagram of the lymphatic system
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One of the lymphatic system's major jobs is to collect extra lymph fluid from body tissues and return it back to the bloodstream.

The lymphatic system also helps defend the body against germs like viruses, bacteria, and fungi that can cause illnesses. Those organisms are filtered out in the lymph nodes, which are small masses of tissue located along the network of lymph vessels. The nodes house

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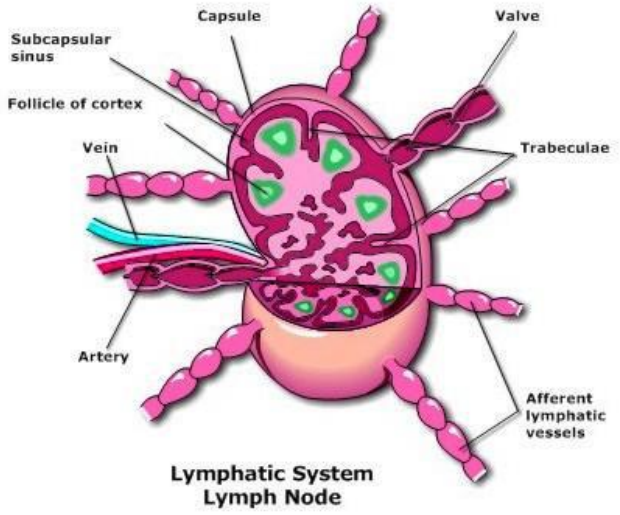
lymphocytes, a type of white blood cell. Some of those lymphocytes make antibodies which are special proteins that fight off germs and stop infections from spreading by trapping disease-causing germs and destroying them.



[Picture Credit – Lymph Node]

Types of Lymphoma

Lymphomas fall into one of two major categories, namely:

- Hodgkin's lymphoma (HL, previously called Hodgkin's disease)
- Non-Hodgkin's Lymphoma (NHL, all other lymphomas)

These two types of lymphoma often occur in the same places, may be associated with the same symptoms, and often have similar appearance upon physical examination. However, they are readily distinguishable via microscopic examination.

Hodgkin's lymphoma (HL) develops from a specific abnormal B lymphocyte lineage. Non-Hodgkin's Lymphoma (NHL) may derive from either abnormal B or T cells and are distinguished by unique genetic markers. Burkitt's Lymphoma forms part of the Non-Hodgkin's Lymphomas.

Many of the NHL subtypes look similar, but they are functionally quite different and respond to different therapies with different probabilities of cure. HL subtypes are microscopically distinct, and typing is based upon the microscopic differences as well as extent of disease.

Burkitt's Lymphoma

Burkitt's lymphoma is a very fast growing form of non-Hodgkin's lymphoma and for this reason Alternative names include: B-cell lymphoma; High-grade B-cell lymphoma. Burkitt's lymphoma is rare outside of Africa.

Graham, B.S. & Lynch, D.T. 2020.

"Burkitt lymphoma (BL) is an aggressive non-Hodgkin B-cell lymphoma. The disease is associated with Epstein Barr virus (EBV), human immunodeficiency virus (HIV), and chromosomal translocations that cause the overexpression of oncogene C-MYC. The World Health Organization (WHO) classifies BL into three clinical groups: endemic, sporadic and immunodeficiency-related. The endemic form is linked to malaria and EBV. The immunodeficiency-related variant is associated with HIV and to a lesser extent, organ transplantation. With intense chemotherapy treatment disease prognosis is excellent in children but poor in adults."

Noy, A. 2020.
"Burkitt's lymphoma (BL) is a rare and highly aggressive Non-Hodgkin lymphoma (NHL) with a germinal center phenotype, a nearly universal myc oncogene translocation to an enhancer element and a proliferation index greater than 95%.[1] Bcl-2 is not expressed as opposed to double-hit or triple-hit lymphoma. Genetic mutations and aberrancy involving the phosphatidylcholine 3-kinase and cyclin-dependent kinase pathways are also involved.[2-5] Rarely patients present with stage I disease and others are considered as high risk if greater than stage I or with elevated LDH or masses greater than 10 cm."

Causes, Incidence, and Risk Factors of Burkitt's Lymphoma
Burkitt's Lymphoma (BL) was first discovered in children in certain parts of Africa, but it now also occurs in other parts of the world. Burkitt's Lymphoma is named after the doctor who first described this kind of tumour in children in Africa. This type of Burkitt's Lymphoma is known as endemic or African-type Burkitt's Lymphoma. Butkitt's Lymphoma can also affect people who have poor immunity.

The different types are:

Endemic Burkitt's Lymphoma - this is found in central Africa, usually in children, and is strongly linked to reduced resistance to a common virus called the Epstein-Barr virus (EBV). The jaw bone is often affected, which is rare in other types of BL.

Sporadic Burkitt's Lymphoma – which is linked with the Epstein-Barr virus. It causes glandular fever, but less clearly than with endemic Burkitt's Lymphoma.

Immunodeficiency-associated Burkitt's Lymphoma - this usually occurs in people with HIV or Aids, or in people who are taking medicines (immunosuppressive drugs) after an organ transplant.

Non-Burkitt's Lymphoma – a type of small, non-cleaved lymphoma that has a somewhat different appearance under the microscope, which usually occurs in adults.

Atallah-Yunes, S.A., Murphy, D.J. & Noy, A. 2020.
"Burkitt lymphoma is a rare and aggressive non-Hodgkin lymphoma with three classifications: endemic, sporadic, and immunodeficiency-related. High-intensity chemotherapeutic regimens have considerably improved overall survival for patients with Burkitt lymphoma. In this Review of HIV-associated Burkitt lymphoma, we summarise expert opinion and provide general recommendations for the treatment of Burkitt lymphoma in patients with HIV on the basis of retrospective and prospective studies, taking into consideration immune status, CD4 cell counts, the presence of systemic disease, and the risk of CNS involvement or relapse. We also discuss the role of rituximab and antiretroviral therapy. We highlight the reasons behind the possible different mechanisms of lymphomagenesis in HIV-associated Burkitt lymphoma and endemic Burkitt lymphoma, which indicate that HIV might have either a direct or indirect oncogenic role in Burkitt lymphoma. We discuss the possible mechanisms by which HIV and HIV proteins could directly contribute to lymphomagenesis. Identifying these mechanisms might lead to the development of therapies that have fewer toxic effects than high-intensity chemotherapeutic regimens."

Incidence of Burkitt's Lymphoma in South Africa

According to the outdated National Cancer Registry (2017), known for under reporting, the following number of Burkitt's Lymphoma cases were histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	66	1:4 090	0,17%
Asian males	1	1:7 435	0,10%
Black males	51	1:4 000	0,39%
Coloured males	5	1:5 682	0,11%
White males	9	1:3 691	0,04%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	59	1:6 897	0,14%
Asian females	0	-	-
Black females	50	1:6 689	0,26%
Coloured females	3	1:8 065	0,07%
White females	6	1:5 077	0,04%

The frequency of histologically diagnosed cases of Burkitt's Lymphoma in South Africa for 2017 were as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	6	4	12	26	11	5	1	1
Asian males	0	0	0	0	1	0	0	0
Black males	4	4	11	22	7	2	1	0
Coloured males	2	0	0	2	0	1	0	0
White males	0	0	1	2	3	2	0	1

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	9	10	22	14	3	1	0	0
Asian females	0	0	0	0	0	0	0	0
Black females	8	9	19	11	2	1	0	0
Coloured females	0	1	1	1	0	0	0	0
White females	1	0	2	2	1	0	0	0

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

Symptoms of Burkitt's Lymphoma

Burkitt's lymphoma is often first be noticed as a swelling of the lymph nodes (glands) in the neck, groin, or under the arm. These swollen lymph nodes are usually painless, but can grow very rapidly. The disease can also start in the ovaries, testes, brain, and spinal fluid.

Symptoms include:

- Fever
- Night sweats
- Unexplained swollen lymph nodes
- Unexplained weight loss

[Picture Credit: Burkitt's Lymphoma]

Tests for Burkitt's Lymphoma

Tests used in the diagnosis of Burkitt's Lymphoma include:

- Bone marrow biopsy
- Chest x-ray
- CT scan of the chest, abdomen, and pelvis
- Complete blood count (CBC)
- Examination of the spinal fluid
- Lymph node biopsy
- PET scan

Risk Factors of Burkitt's Lymphoma

Risk Factors for Burkitt's Lymphoma include:

Graham, B.S. & Lynch, D.T. 2020.

"Burkitt lymphoma (BL) is an aggressive non-Hodgkin B-cell lymphoma. The disease is associated with Epstein Barr virus (EBV), human immunodeficiency virus (HIV), and chromosomal translocations that cause the overexpression of oncogene C-MYC. The World Health Organization (WHO) classifies BL into three clinical groups: endemic, sporadic and immunodeficiency-related. The endemic form is linked to malaria and EBV. The immunodeficiency-related variant is associated with HIV and to a lesser extent, organ transplantation. With intense chemotherapy treatment disease prognosis is excellent in children but poor in adults."

Diagnosis of Burkitt's Lymphoma

The following must be fulfilled as minimal diagnostic criteria for the diagnosis of Vurkitt's Lymphoma:

- Presence of B cell markers in tumour (CD20 and/or CD79)
- 95% or higher MKI67 expression
- Cytogenetic or FISH evidence of t(8;14)(q24;32), or t(14;18)(q32;q21) and 3q27 affecting the c-myc gene

Diagnostic Tests Required Before Commencing Treatment include:

- HIV test
- Determination of Hepatitis B & C status

- Electrocardiogram (ECG)
- Echocardiogram or MUGA scan
- Blood urea and electrolyte determination
- Liver function test
- Bone scan
- Creatinine Clearance test
- Lactate dehydrogenase test
- Urate determination
- CT scan
- MRI scan of brain and spinal cord

Evens, A.M., Danilov, A.V., Jagadeesh, D., Sperling, A.L., Kim, S.H., Vaca, R.A., Wei, C., Rector, D., Sundaram, S., Reddy, N., Lin, Y., Farooq, U., D'Angelo, C., Bond, D., Berg, S., Churnetski, M.C., Godara, A., Khan, N., Choi, Y.K., Sarraf Yazdy, M., Rabinovich, E., Varma, G., Karmali, R., Mian, A., Savani, M., Burkart, M., Martin, P., Ren, A., Chauhan, A., Diefenbach, C.S., Straker-Edwards, A., Klein, A., Blum, K., Boughan, K., Smith, S.E., Haverkos, B.M., Orellana-Noia, V.M., Kenkre, V., Zayac, A.S., Ramdial, J., Maliske, S., Epperla, N., Venugopal, P., Feldman, T., Smith, S.D., Stadnik, A., David, K.A., Naik, S., Lossos, I.S., Lunning, M., Caimi, P.F., Kamdar, M., Palmisiano, N., Bachanova, V., Portell, C.A., Phillips, T., Olszewski, A.J. & Alderuccio, J.P. 2020.
"We examined adults with untreated Burkitt lymphoma (BL) from 2009-2018 across 30 US cancer centers. Factors associated with progression-free survival (PFS) and overall survival (OS) were evaluated in univariate and multivariate Cox models. Among 641 BL patients, baseline features included: median age 47 years; HIV+ 22%; ECOG performance status (PS) 2-4 in 23%; >1 extranodal site 43%; advanced-stage 78%; and central nervous system (CNS) involvement 19%. Treatment-related mortality (TRM) was 10% with most common causes being sepsis, gastrointestinal bleed/perforation, and respiratory failure. With 45-month median follow-up, 3-year PFS and OS rates were 64% and 70%, respectively, without differences by HIV status. Survival was better for patients who received rituximab vs. not (3-year PFS 67% vs. 38%; OS 72% vs. 44%; P<0.001) without difference based on setting of administration (inpatient/outpatient). Collectively, outcomes for adult BL in this real-world analysis appeared more modest compared with results of clinical trials and smaller series. In addition, prognostic factors at diagnosis identified patients with divergent survival rates."

Turro, J., Singh, P., Sarao, M.S. Tadepalli, S. & Cheriyath, P. 2019.
Background: Burkitt lymphoma is a rare, aggressive and rapidly fatal, B-cell non-Hodgkin's lymphoma. It has an incidence of 0.4/100,000 age-adjusted to the USA standard population. Here we describe the case of a 77-year-old patient who presented with Burkitt lymphoma.
Case: A 77-year-old male presented to his primary care physician with fatigue and listlessness and was referred to the hospital with a white blood cell count (WBC)-23.7 K/uL (neutrophils 37%, lymphocyte 11%, blasts 9%) and platelets-19 K/uL. During his stay in the hospital, repeat investigations revealed WBC-29.9 K/uL (neutrophils 22%, lymphocyte 27%, atypical lymphocytes 5%, blasts 20%) and platelets-10 K/uL with no evidence of mucosal bleeds, neck or abdominal masses or generalized lymphadenopathy. Bone marrow aspirate revealed the presence of MYC rearrangements (8q24) on flow cytometry and fluorescent in-situ hybridization (FISH), indicative but not typical of BL. He was transfused with platelets due to a rapidly deteriorating platelet count and episodes of epistaxis. He was discharged after four days with a plan of outpatient chemotherapy over a period of 4 months. An Ommaya reservoir was placed in the right ventricle for intrathecal

chemotherapy. After four months of chemotherapy, computerized tomography of the chest, abdomen, and pelvis confirmed remission. A magnetic resonance imaging of the brain a month after completion of chemotherapy revealed metastatic lymphoma in the temporal, parietal and occipital lobes. He was discharged to hospice for palliative care.
Conclusion: Unconventional presentations, as seen in our case of a leukemia-like picture in the absence of a bulky disease, are the quagmire that might delay aggressive management and result in poorer outcomes.

Treatment of Burkitt's Lymphoma
Chemotherapy is usually used to treat this type of cancer.

Intensive systemic chemotherapy is the treatment of choice for this aggressive disease in all its stages. All clinical variants of Burkitt's lymphoma are generally treated the same.

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"Children with refractory or relapsed Burkitt lymphoma (BL) or Burkitt leukemia (B-AL) have a poor chance to survive. We describe characteristics, outcome, reinduction, and transplantation approaches and evaluate risk factors among children with progression of a BL/B-AL included in Non-Hodgkin's Lymphoma-Berlin-Frankfurt-Münster studies between 1986 and 2016. Treatment recommendation was reinduction including rituximab from the early 2000s followed by blood stem cell transplantation. The 3-year survival of the 157 children was 18.5 ± 3%. Survival significantly improved from 11 ± 3% before to 27 ± 5% after 2000 (P < .001), allowing for risk factor analyses among the latter 75 patients. Survival of 14 patients with relapse after initial therapy for low-risk disease (R1/R2) was 50 ± 13% compared with 21 ± 5% for 61 patients progressing after R3/R4 therapy (P < .02). A total of 25 of 28 patients with progression during first-line therapy, 31 of 32 with progression during reinduction, 15 of 16 not reaching a complete remission (CR) before transplantation, 9 of 10 treated with rituximab front-line, and all 13 patients not receiving rituximab during reinduction died. Forty-six patients received stem cell transplantation (20 autologous, 26 allogeneic). Survival after a regimen combining rituximab with continuous-infusion chemotherapy followed by allogeneic transplantation was 67 ± 12% compared with 18 ± 5% for all other regimen and transplantations (P = .003). Patients with relapsed BL/B-AL have a poor chance to survive after current effective front-line therapies. Progression during initial or reinduction chemotherapy and initial high-risk disease are risk factors in relapse. Time-condensed continuous-infusion reinduction followed by stem cell transplantation forms the basis for testing new drugs."

Crombie, J.L. & LaCasce, A.S. 2020.
"Burkitt lymphoma (BL) is a highly aggressive, B-cell, non-Hodgkin lymphoma (NHL) categorized into endemic, sporadic and immunodeficiency-associated subtypes. BL has distinct pathologic and clinical features, characterized by rapidly progressive tumors with high rates of extranodal involvement. Next generation sequencing (NGS) analyses have further characterized the genomic landscape of BL and our understanding of disease pathogenesis, though these findings have yet to influence treatment. Although the majority of patients are cured with intensive combination chemotherapy, given the paucity of randomized trials, optimal therapy has not been defined. Furthermore, treatment for elderly patients, patients with central nervous system (CNS) involvement, or those with relapsed disease, remains an unmet need. In this review, we highlight the clinical, pathologic,

and genomic features, as well as standard and emerging treatment options for adult patients with BL."

Zayac, A.S. & Olszewski, A.J. 2020.
"Genomic studies have revealed molecular mechanisms involved in the pathogenesis of Burkitt's lymphoma, including the ID3/TCF3-dependent centroblast gene expression program, tonic PI3K-AKT-mTOR signaling, and deregulation of cell cycle and apoptosis through mutations in cyclin D3, *CDKN2A*, or *TP53*. Unfortunately, these advances have not been translated into treatment, which relies on dose-intense cytotoxic chemotherapy. While most patients achieve long-term survival, options for relapsed/refractory disease are lacking, as Burkitt lymphoma is often excluded from clinical trials of novel approaches. The lower-intensity, dose-adjusted EPOCH plus rituximab (DA-EPOCH-R) regimen constitutes a major advance allowing for treatment of older and HIV-positive patients but needs augmentation to better address the central nervous system involvement. Furthermore, DA-EPOCH-R provides a platform for the study of targeted or immunotherapeutic approaches while de-escalating cytotoxic agents and their associated adverse effects. In this review we discuss the epidemiology and molecular genetics of BL, first-line treatment considerations, and potential novel treatment strategies."

About Clinical Trials
Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The South African National Clinical Trials Register provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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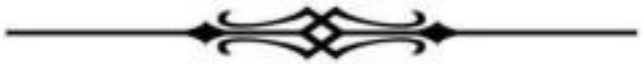

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Lymph Node
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