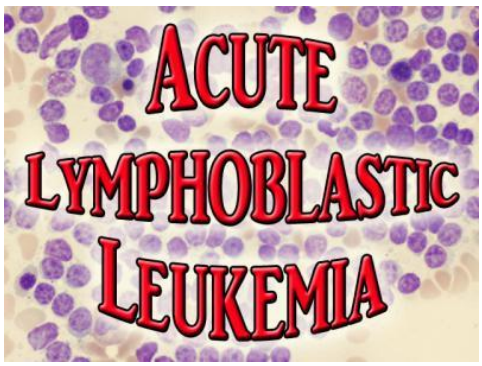
Cancer Association of South Africa (CANSA)

Research • Educate • Support

Fact Sheet
on
Adult Acute Lymphoblastic Leukaemia (ALL)

Introduction

The word *leukaemia* literally means 'white blood' and is used to describe a variety of cancers that begin in the blood-forming cells (lymphocytes) of the bone marrow.



[Picture Credit: ALL]

Leukaemias are divided into two major types:

- Acute Leukaemia which usually progresses quickly with many immature white cells
- Chronic Leukaemia which usually progresses more slowly and has more mature white cells

Adult Acute Lymphoblastic Leukaemia

Adult acute lymphoblastic leukaemia (ALL) is a type of cancer involving the bone marrow where blood cells are formed. In ALL too many lymphocytes are formed. Another name for acute lymphoblastic leukaemia is acute lymphocytic leukaemia. If not treated adequately and early enough, ALL can get worse quickly.

The risk for acute lymphoblastic leukaemia is greater in individuals who have previously had chemotherapy or have received radiotherapy in the past.

Malard, & Mohty, M. 2020.

"Acute lymphoblastic leukaemia develops in both children and adults, with a peak incidence between 1 year and 4 years. Most acute lymphoblastic leukaemia arises in healthy individuals, and predisposing factors such as inherited genetic susceptibility or environmental exposure have been identified in only a few patients. It is characterised by chromosomal abnormalities and genetic alterations involved in differentiation and proliferation of lymphoid precursor cells. Along with response to treatment, these abnormalities are important prognostic factors. Disease-risk stratification and the development of intensified chemotherapy protocols substantially improves the outcome of patients with acute lymphoblastic leukaemia, particularly in children (1-14 years), but also in adolescents and young adults (15-39 years). However, the outcome of older adults (≥40 years) and patients with relapsed or refractory acute lymphoblastic leukaemia remains poor. New

immunotherapeutic strategies, such as monoclonal antibodies and chimeric antigen receptor (CAR) T cells, are being developed and over the next few years could change the options for acute lymphoblastic leukaemia treatment."

Incidence of Adult Acute Lymphoblastic Leukaemia in South Africa

In providing the incidence figures of Leukaemia in South Africa, the outdated National Cancer Registry (2016) does not make provision for the reporting of the different types of Leukaemia – it also does not differentiate between acute and chronic Leukaemia - neither does it provide for different statistics for cases of adult and childhood Leukaemia - except in the 'Frequency of Histologically Diagnosed Cancer in South Africa' Section of the Registry .

According to the National Cancer Registry (2016) the following number of Leukaemia cases was histologically diagnosed in South Africa during 2016:

Group - Males 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	264	1:801	0,68%
Asian males	10	1:659	1,02%
Black males	135	1:1 233	1,03%
Coloured males	17	1:1 105	0,33%
White males	102	1:354	0,48%

Group - Females 2016	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	227	1:1 107	0,54%
Asian females	9	1:798	0,72%
Black females	117	1:1 846	0,59%
Coloured females	21	1:844	0,41%
White females	80	1:465	0,49%

The frequency of histologically diagnosed cases of Leukaemia in South Africa for 2016 was as follows (National Cancer Registry, 2016):

Group - Males 2016	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	156	15	28	20	46	34	53	12
Asian males	1	0	1	1	1	3	2	0
Black males	45	11	22	10	18	15	13	1
Coloured males	1	1	2	3	4	2	4	0
White males	8	3	3	6	23	14	34	11

Group - Females 2016	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	38	26	17	26	31	37	37	15
Asian females	2	0	0	1	2	3	1	0
Black females	31	22	11	12	16	13	10	2
Coloured females	1	3	1	3	2	3	8	0
White females	4	1	5	10	11	18	18	13

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.

Risk Factors for Adult Acute Lymphoblastic Leukaemia

There are only a few known risk factors for acute lymphocytic leukaemia (ALL). The following are risk factors acute lymphoblastic leukaemia:

Radiation exposure - being exposed to high levels of radiation is a risk factor for both acute lymphoblastic leukaemia (ALL) according to Finch (2007).

Exposure to paint – according to Baily, *et al*., 2011, exposure to paint

Exposure to Certain Chemicals - the risk of ALL may be increased by exposure to certain chemotherapy drugs and certain chemicals, including benzene and other solvents. Benzene is a solvent used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, and gasoline-related industries, and is also present in cigarette smoke, as well as some glues, cleaning products, detergents, art supplies, and paint strippers. Chemical exposure is more strongly linked to an increased risk of AML than to ALL. (Khalade, *et al*., 2010; Yanfeng, *et al*., 2014).
The International Agency for Research on Cancer (IARC) recently classified formaldehyde as a human carcinogen (cancer causing agent) that causes nasopharyngeal cancer and also concluded that there is ''strong but not sufficient evidence for a causal association between leukaemia and occupational exposure to formaldehyde'' (Zhang, *et al.),*

Exposure to benzene - exposure to the chemical called benzene at work increases the risk of developing ALL. Exposure to benzene may occur in petrol, chemical, pharmaceutical and rubber industries. Benzene is also used in shoe production and the printing industry. The higher the level of exposure over many years, the greater the risk. There is benzene in traffic pollution but the levels are likely to be too low to increase leukaemia risk. Benzene is also in cigarette smoke. (Khalade, *et al*., 2010; Yanfeng, *et al*., 2014).

Smoking and coffee - a review of studies (meta analysis) in 2009 has shown that smoking in the home by parents may increase the risk of ALL in their children. This includes smoking by the father in the time before conception. Data from the French ESCALE study in 2013 suggests that drinking more than 2 cups of coffee a day may slightly increase the risk of childhood ALL. More research is, however, needed on this. (Thomopoulos, *et a*l., 2015)

Certain Viral Infections - infection with the human T-cell lymphoma/leukaemia virus-1 (HTLV-1) can cause a rare type of T-cell acute lymphocytic leukaemia. Most cases occur in Japan and the Caribbean area.

In Africa, the Epstein-Barr virus (EBV) has been linked to Burkitt's lymphoma, as well as to a form of acute lymphocytic leukaemia. Research has identified viruses, such as the Human T-cell Lymphotropic Virus type 1 (HTLV1), and Human Immunodeficiency Virus (HIV), as potential causes in some cases.

Human T-cell Lymphotropic virus or Human T-lymphotropic virus Type 1 (HTLV1), also called the Adult T-cell lymphoma virus type 1 is a retrovirus that has been implicated in several kinds of diseases including very aggressive adult T-cell lymphoma (ATL), HTLV-1-associated myelopathy uveitis, strongyloides stercoralis hyper-infection and some other diseases. However, only about 1–5% of infected persons are thought to develop cancer as a result of the infection with HTLV-I over their lifetime. (Moschovi, *et al*., 2016).

Inherited syndromes - acute lymphocytic leukaemia does not appear to be an inherited disease. It does not seem to run in families, so a person's risk is not increased if a family member has, or has had, the disease. But there are some inherited syndromes with genetic changes that seem to raise the risk of ALL.
These include:

- Down syndrome
- Klinefelter syndrome
- Fanconi anaemia
- Bloom syndrome
- Ataxia-telangiectasia
- Neurofibromatosis

(Stieglitz & Loh, 2013; Takafumi & Kanakura, 2016).

Race/ethnicity - acute lymphocytic leukaemia is more common in whites than in African Americans, but the reasons for this are not clear. According to statistics in the 2013 South African National Cancer Registry it would appear that this also applies to White men in South Africa. (Bhatia, *et al*., 2002; Lim, *et al*., 2014).
Sex - acute lymphocytic leukaemia is slightly more common in males than in females. The reason for this is unknown. According to statistics in the 2013 South African National Cancer Registry it would appear that this also applies in South Africa. (Pui, *et al.,* 1999).

Having an identical twin with ALL - someone who has an identical twin who develops ALL in the first year of life has an increased risk of getting ALL. (Hecht, *et al*., 1988).

[Picture Credit: Identical Twins]

Being overweight - some studies show that people who are very overweight (obese) have a slightly higher risk for leukaemia than people with a normal bodyweight. (Orgel, *et al*., 2014).

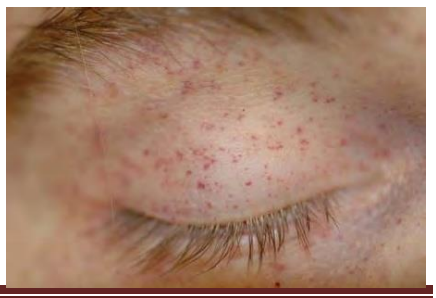
Uncertain, unproven or controversial risk factors - other factors that have been studied for a possible link to ALL include:

- Exposure to electromagnetic fields (such as living near power lines or using cell phones)
- Workplace exposure to diesel, gasoline, pesticides, and certain other chemicals
- Smoking
- Exposure to hair dyes

So far, none of these (uncertain, unproven or controversial) factors have been linked conclusively to ALL. Research in these areas continues.

Signs and Symptoms of Adult Acute Lymphoblastic Leukaemia

[Picture Credit: Petechiae]



Signs and symptoms of acute lymphocytic leukaemia may include:

- Bleeding from the gums
- Easy bruising or bleeding

- Petechiae (flat, pinpoint spots under the skin caused by bleeding)
- Bone pain
- Pain or feeling of fullness below the ribs
- Pain in the bones or joints
- Fever or night Sweats
- Frequent infections
- Frequent or severe nosebleeds
- Lumps caused by swollen lymph nodes in and around the neck, underarm, abdomen or groin which are usually painless
- Pale skin
- Shortness of breath
- Weakness, fatigue or a general decrease in energy
- Weight loss and loss of appetite

Diagnosis of Adult Acute Lymphoblastic Leukaemia
Blood specimens are usually taken and sent to the laboratory for diagnosis.

Different leukaemias are diagnosed according to the type of white blood cell affected and the speed with which the cancer progresses.

Adult acute lymphoblastic leukaemia is an acute leukaemia meaning that it is more aggressive and progresses quickly. It affects a type of white blood cell called lymphoid cells.

The following tests and procedures may be used:

- Physical examination and history: An examination of the body to check general signs of health, including checking for signs of disease, such as infection or anything else that seems unusual. A history of the patient's health habits and past illnesses and treatments will also be taken.

- Complete Blood Count (CBC): A procedure in which a sample of blood is drawn and checked for the following:
  - The number of red blood cells and platelets.
  - The number and type of white blood cells.
  - The amount of haemoglobin (the protein that carries oxygen) in the red blood cells.
  - The portion of the blood sample made up of red blood cells.

- Blood chemistry studies: A procedure in which a blood sample is checked to measure the amounts of certain substances released into the blood by organs and tissues in the body. An unusual (higher or lower than normal) amount of a substance can be a sign of disease in the organ or tissue that makes it.
- Peripheral blood smear
- Bone marrow aspiration and biopsy

Treatment of Adult Acute Lymphoblastic Leukaemia
The treatment for acute lymphoblastic leukaemia varies depending on:

- The type of ALL
- The general health of the patient
- The age and level of fitness of the patient

Different types of ALL may be treated differently. Researchers and doctors continue to look for better combinations of treatments, as well as new treatments. They test these in clinical trials. The doctor may suggest that a patient joins a trial.

Immunotherapy – administering medicines that stimulate the body's immune system to fight the cancer.

Several different types of immunotherapy are currently being explored for the treatment of leukaemia. They fall into several broad categories, including adoptive cell therapy, monoclonal antibodies, checkpoint inhibitors, therapeutic vaccines, adjuvant immunotherapies, and cytokines.

The phases of treatment for ALL - doctors usually divide treatment for adult acute lymphoblastic leukaemia into different phases:

- remission induction
- consolidation
- maintenance

This treatment usually takes 2 years. The maintenance treatment takes up most of this time. It is a long time to have treatment. The good news is that most people do very well with treatment.

Rafei, H., Kajian, H.M. & Jabour, E.J. 2020.
"The past decade has witnessed tremendous progress in the treatment of acute lymphoblastic leukaemia (ALL), primarily due to the development of targeted therapies, including tyrosine kinase inhibitors targeting BCR-ABL1 tyrosine kinase, monoclonal antibodies targeting cell surface antigens (CD19, CD20 and CD22), bispecific antibodies and chimeric antigen receptor T- cell therapy. A number of new therapies have been approved by the US Food and Drug Administration in the past 5 years, including blinatumomab in 2014, inotuzumab ozagamicin in 2017 and tisagenlecleucel in 2017 for relapsed/refractory ALL. This has led to tremendous improvement in long-term survival, of more than 50% in patients with precursor B-ALL [50-70% in patients with Philadelphia chromosome (Ph)-positive ALL)], 50-60% in T-ALL and 80% in mature B-ALL. Research is ongoing to optimize the benefit of targeted therapeutics with the goal of decreasing the use of cytotoxic therapies."

Foà, R., Bassan, R., Vitale, A., Elia, L., Piciocchi, A., Puzzolo, M.C., Canichella, M., Viero, P., Ferrara, F., Lunghi, M., Fabbiano, F., Bonifacio, M., Fracchiolla, N., Di Bartolomeo, P., Mancino, A., De Propris, M.S., Vignetti, M., Guarini, A., Rambaldi, A., Chiaretti, S. & GIMEMA Investigators. 2020.
Background: Outcomes in patients with Philadelphia chromosome (Ph)-positive acute lymphoblastic leukemia (ALL) have improved with the use of tyrosine kinase inhibitors. Molecular remission is a primary goal of treatment.
Methods: We conducted a phase 2 single-group trial of first-line therapy in adults with newly diagnosed Ph-positive ALL (with no upper age limit). Dasatinib plus glucocorticoids were administered, followed by two cycles of blinatumomab. The primary end point was a sustained molecular response in the bone marrow after this treatment.

Results: Of the 63 patients (median age, 54 years; range, 24 to 82) who were enrolled, a complete remission was observed in 98%. At the end of dasatinib induction therapy (day 85), 29% of the patients had a molecular response, and this percentage increased to 60% after two cycles of blinatumomab; the percentage of patients with a molecular response increased further after additional blinatumomab cycles. At a median follow-up of 18 months, overall survival was 95% and disease-free survival was 88%; disease-free survival was lower among patients who had an *IKZF1* deletion plus additional genetic aberrations (*CDKN2A* or *CDKN2B*, *PAX5*, or both [i.e., *IKZF1* ^{plus}]). *ABL1* mutations were detected in 6 patients who had increased minimal residual disease during induction therapy, and all these mutations were cleared by blinatumomab. Six relapses occurred. Overall, 21 adverse events of grade 3 or higher were recorded. A total of 24 patients received a stem-cell allograft, and 1 death was related to transplantation (4%).
Conclusions: A chemotherapy-free induction and consolidation first-line treatment with dasatinib and blinatumomab that was based on a targeted and immunotherapeutic strategy was associated with high incidences of molecular response and survival and few toxic effects of grade 3 or higher in adults with Ph-positive ALL. (Funded by Associazione Italiana per la Ricerca sul Cancro and others; GIMEMA LAL2116 D-ALBA EudraCT number, 2016-001083-11; ClinicalTrials.gov number, NCT02744768.).

Kim, Y.A., Ju, H.Y., Park, H.J., Lee, N.Y., Lee, H.J., Lee, H. & Ghang, H. 2020.
"This study used Korean national data to investigate the relationship between treatment patterns and outcomes in Korean adolescent and young-adult (AYA) acute lymphoblastic leukaemia (ALL) patients. Chemotherapy incorporating L-asparaginase was considered paediatric-inspired (PI), as opposed to adult protocols. In total, 65·3% of patients received PI therapy. Five-year overall survival (OS) of PI-treated patients outperformed adult protocols (63·1% vs. 40·4%; P < 0·0001); this trend was maintained within various age subgroups. Younger age, L-asparaginase therapy, and radiotherapy corresponded with superior OS by multivariable analysis. OS tends to improve with PI protocols that include L-asparaginase in AYA ALL, suggesting that therapy protocol is critical in the treatment performance of this group."

Jordaens, S., Cooksey, L., Freire Boullosa, L., Van Tendeloo, V., Smits, E., Mills, K.I., Orchard, K.H. & Guinn, B.A. 2020.
"Acute lymphoblastic leukaemia (ALL) in adults is a rare and difficult-to-treat cancer that is characterised by excess lymphoblasts in the bone marrow. Although many patients achieve remission with chemotherapy, relapse rates are high and the associated impact on survival devastating. Most patients receive chemotherapy and for those whose overall fitness supports it, the most effective treatment to date is allogeneic stem cell transplant that can improve overall survival rates in part due to a 'graft-versus-leukaemia' effect. However, due to the rarity of this disease, and the availability of mature B-cell antigens on the cell surface, few new cancer antigens have been identified in adult B-ALL that could act as targets to remove residual disease in first remission or provide alternative targets for escape variants if and when current immunotherapy strategies fail. We have used RT-PCR analysis, literature searches, antibody-specific profiling and gene expression microarray analysis to identify and prioritise antigens as novel targets for the treatment of adult B-ALL."

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/

Medical Disclaimer

This Fact Sheet is intended to provide general information only and, as such, should not be considered as a substitute for advice, medically or otherwise, covering any specific situation. Users should seek appropriate advice before taking or refraining from taking any action in reliance on any information contained in this Fact Sheet. So far as permissible by law, the Cancer Association of South Africa (CANSA) does not accept any liability to any person (or his/her dependants/ estate/heirs) relating to the use of any information contained in this Fact Sheet.

Whilst CANSA has taken every precaution in compiling this Fact Sheet, neither it, nor any contributor(s) to this Fact Sheet can be held responsible for any action (or the lack thereof) taken by any person or organisation wherever they shall be based, as a result, direct or otherwise, of information contained in, or accessed through, this Fact Sheet.

Sources and References Consulted or Utilised

American Cancer Society
http://www.cancer.org/cancer/leukemia-acutelymphocyticallinadults/detailedguide/leukemia-acute-lymphocytic-risk-factors

Bassan, R., Brüggemann, M., Radcliffe, H.S., Hartfield, E., Kreuzbauer, G. & Wetten, S. 2019. A systematic literature review and meta-analysis of minimal residual disease as a prognostic indicator in adult B-cell acute lymphoblastic leukemia. *Haematologica*. 2019 Mar 19. pii: haematol.2018.201053. doi: 10.3324/haematol.2018.201053. [Epub ahead of print]. PMID: 30890593.

Bassan, R., Hoelzer, D., Thomas, X., Montesinos, P., Pavlu, J., McKendrick, J., Kudlac, A., Barlev, A., Barber, B. & Cong, Z. 2019. Clinician Concepts of Cure in Adult Relapsed and Refractory Philadelphia-Negative B Cell Precursor Acute Lymphoblastic Leukemia: A Delphi Study. A*dv Ther*. 2019 Apr;36(4):870-879. doi: 10.1007/s12325-019-00910-z. Epub 2019 Mar 7. PMID: 30847777.

Bhatia, S., Sather, H.N., Heerema, N.A., Trigg, M.E., Gaynon, P.S. & robinson, L.L. 2002. Racial and ethnic differences in survival of children with acute lymphoblastic leukemia. *Blood*. 2002 Sep 15;100(6):1957-64.

Center for Environmental Health Studies
http://www.clarku.edu/mtafund/prodlib/jsi/Leukemia_and_Exposure_to_Ionizing_Radiation.pdf

Cleveland Clinic
http://my.clevelandclinic.org/disorders/acute_lymphocytic_leukemia/hic_adult_acute_lymphoblastic_leukemia.aspx

Cox, E., Wade, R., Peron, M., Dietz, K.C., Eastwood, A., Palmer, S. & Griffin, S. 2019. The Clinical and Cost Effectiveness of Inotuzumab Ozogamicin for the Treatment of AdultRelapsed or Refractory B-Cell Acute Lymphoblastic Leukaemia: An Evidence Review Group Evaluation of a NICE Single Technology Appraisal. Pharmacoeconomics. 2019 Mar 19. doi: 10.1007/s40273-019-00779-4. [Epub ahead of print] Review. PMID: 30887470.

Finch, S.C. 2007. Radiation-induced leukaemia: lessons from history. *Best Pract Res*. 2007: 20(1):109-18.

Foà, R., Bassan, R., Vitale, A., Elia, L., Piciocchi, A., Puzzolo, M.C., Canichella, M., Viero, P., Ferrara, F., Lunghi, M., Fabbiano, F., Bonifacio, M., Fracchiolla, N., Di Bartolomeo, P., Mancino, A., De Propris, M.S., Vignetti, M., Guarini, A., Rambaldi, A., Chiaretti, S. & GIMEMA Investigators. 2020. Dasatinib-Blinatumomab for Ph-Positive Acute Lymphoblastic Leukemia in Adults. *N Engl J Med*. 2020 Oct 22;383(17):1613-1623.

Harvard Health Publications
http://www.drugs.com/health-guide/acute-lymphocytic-leukemia-all-in-adults.html

Hecht, T., Henke, M., Schempp, W., Bross, K.J. & Löhr, G.W. 1988. Acute lymphoblastic leukemia in adult identical twins. *Blut*. 1988 Jun;56(6):261-4.
cal Twins
https://www.google.co.za/search?q=identical+twins&source=lnms&tbm=isch&sa=X&ei=SQY0U9HcMsqM7AaIlIGIBw&sqi=2&ved=0CAYQ_AUoAQ&biw=1517&bih=666&dpr=0.9#facrc=_&imgdii=_&imgrc=MDjCsClgjuxUBM%253A%3BQmD0MHWSz4oNSM%3Bhttp%253A%252F%252Fwww.paulrichstudio.com%252Fblog%252Fwp-content%252Fuploads%252F2012%252F10%252Fidentical-twins-portland-portrait-photography-paulrichstudio021.jpg%3Bhttp%253A%252F%252Fwww.paulrichstudio.com%252Fblog%252Felizabeth-isabella-identical-twins%252F%3B900%3B600

Jordaens, S., Cooksey, L., Freire Boullosa, L., Van Tendeloo, V., Smits, E., Mills, K.I., Orchard, K.H. & Guinn, B.A. 2020. New targets for therapy: antigen identification in adults with B-cell acute lymphoblastic leukaemia. *Cancer Immunol Immunother*. 2020 May;69(5):867-877.

Khalade, A., Jaakkola, M.S., Pukkala, E. & Jaakkola, J.J. 2010. Exposure to benzene at work and the risk of leukemia: a systematic review and meta-analysis. *Environ Health*. 2010 Jun 28;9:31. doi: 10.1186/1476-069X-9-31.

Kim, Y.A., Ju, H.Y., Park, H.J., Lee, N.Y., Lee, H.J., Lee, H. & Ghang, H. 2020. Outcomes of acute lymphoblastic leukaemia in adolescent and young adult Korean patients. *Br J Haematol.* 2020 Mar;188(5):740-744.

Leukaemia and Lymphoma Research
https://leukaemialymphomaresearch.org.uk/information/leukaemia/acute-lymphoblastic-leukaemia-all

Lim, J.Y.A., Bhatia, S., Robison, & Yang, J.J. 2014. Genomics of Racial and Ethnic Disparities in Childhood Acute Lymphoblastic Leukemia. Cancer. Author manuscript; available in PMC 2015 Apr 1. Published in final edited form as: *Cancer*. 2014 Apr 1; 120(7): 955–962. Published online 2013 Dec 30. doi: 10.1002/cncr.28531. PMCID: PMC4015138 NIHMSID: NIHMS548623.

Malard, & Mohty, M. 2020. Acute lymphoblastic leukaemia. *Lancet*. 2020 Apr 4;395(10230):1146-1162.

Mayo Clinic
http://www.mayoclinic.org/diseases-conditions/acute-lymphocytic-leukemia/basics/symptoms/con-20042915

MedicineNet.com
http://www.medicinenet.com/script/main/art.asp?articlekey=206196&ecd=mnl_day_081817

Medscape
http://emedicine.medscape.com/article/2004705-overview

Moschovi, M., Adamaki, M. & Vlahopoulos, S.O. 2016. Progress in Treatment of Viral Infections in Children with Acute Lymphoblastic Leukemia. *Oncol Rev*. 2016 Apr 15; 10(1): 300. Published online 2016 Jun 30. doi: 10.4081/oncol.2016.300. PMCID: PMC4943096.

National Cancer Institute
http://www.cancer.gov/cancertopics/pdq/treatment/adultALL/Patient/page1
http://www.meb.uni-bonn.de/Cancernet/CDR0000062864.html
http://www.cancer.gov/about-cancer/treatment/clinical-trials/what-are-trials

Orgel, E., Tucci, J., Alhushki, W., Malvar, W., Sposto, R., Fu, C.H., Freyer, D.R., Abdel-Azim, H. & Mittelman, S.D. 2014. Obesity is associated with residual leukemia following induction therapy for childhood B-precursor acute lymphoblastic leukemia. *Blood*. 2014 Dec 18;124(26):3932-8. doi: 10.1182/blood-2014-08-595389. Epub 2014 Oct 27.

Pui, C.H., Boyett, J.M., Relling, M.V., Harrison, P.L., Rivera, G.K., Behm, F.G., Sandlund, J.T., Ribeiro, R.C., Rubniz, J.E., Gajjar, A. & Evans, W.E. 1999. Sex differences in prognosis for children with acute lymphoblastic leukemia. *J Clin Oncol*. 1999 Mar;17(3):818-24.

Stieglitz, E. & Loh, M.L. 2013. Genetic predispositions to childhood leukemia. *Ther Adv hematol*. 2013 Aug; 4(4): 270–290. doi: 10.1177/2040620713498161. PMCID: PMC3734905.

Rafei, H., Kajian, H.M. & Jabour, E.J. 2020. Targeted therapy paves the cure of acute lymphoblastic leukaemia. Br J Haematol. 2020 Jan;188(2):207-223.

Richad-Carpenter, G., Kantarjian, H. & Jabbour, E. 2019. Recent advances in adult acut Lymphoblastic Leukemia. Curr Hematol Malig Rep. 2019 Mar 16. doi: 10.1007/s11899-019-00503-1. [Epub ahead of print]

Schroeder, M.P., Bastian, L., Eckert, C., Gökbuget, N., James, A.R., Tanchez, J.O., Schlee, C., Isaakidis, K., Häupl, B., Baum, K., Migueles Lozano, O.A., Kouidri, K., Pan, K.T., Urlaub, H., Schwartz, S., Burmeister, T., von Stackelberg, A., Hoelzer, D., Pfeiffer, H., Rieger, M.A,, Göllner, S., Oellerich, T., Horstman, M., Schrappe, M., Wolf, J., Kirschner-Schwabe, R., Brüggemann, M., Müller-Tidow, C., Serve, H., Neumann, M. & Baldus, C.D. 2019. Integrated analysis of relapsed B-cell precursor Acute Lymphoblastic Leukemia identifies subtype-specific cytokine and metabolic signatures. *Sci Rep*. 2019 Mar 12;9(1):4188. doi: 10.1038/s41598-019-40786-1. PMID: 30862934.

Takafumi, Y. & Kanakura, Y. 2016. Genetic abnormalities associated with acute lymphoblastic leukemia. *Cancer Sci*. 2016 Jun; 107(6): 721–725. Published online 2016 Apr 27. doi: 10.1111/cas.12927. PMCID: PMC4968601.

Thomopoulos, T.P., Ntouvelis, E., Diamantaras, A.A., Tzanoudaki, M., Baka, M., Hatzipanatelis, E., Kourti, M., Polychronopoulou, S., Sidi, V., Stiakakai, E., Moschovi, M., Kantzanou, M. & Petridou, E.T. 2015. Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis. *Cancer Epidemiol*. 2015 Dec;39(6):1047-59. doi: 10.1016/j.canep.2015.08.009. Epub 2015 Aug 29.

Zhang, L., Steinmaus,C., Eastmond, D.A. Xin, X.K. & Smith, M.T. 2008. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. *Rev. Mutat. Res*, doi:10.1016/j.mrrev.2008.07.002.