Cancer Association of South Africa (CANSA)

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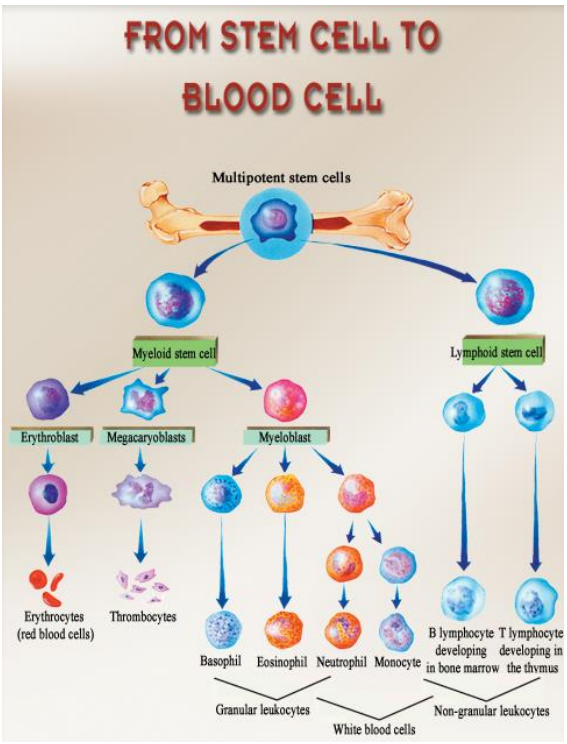
Fact Sheet on Childhood Acute Myeloid Leukaemia (AML)

Introduction

Leukaemia is a cancer of the white blood cells. All blood cells are produced in the bone marrow, the spongy substance at the core of some of the bones in the body.



Bone marrow contains:

- red blood cells, which will carry oxygen around the body
- platelets, which will help the blood to clot and control bleeding
- white blood cells, which will help to fight infection.

[Picture Credit: Blood Cell Formation]

There are two different types of white blood cells: lymphocytes and myeloid cells (including neutrophils). These white blood cells work together to fight infection. Normally white blood cells develop, repair and reproduce themselves in an orderly and controlled way. In leukaemia, however, the process gets out of control and the cells continue to divide in the bone marrow, but do not mature.

These immature dividing cells fill up the bone marrow and stop it from making healthy blood cells. As the leukaemia cells are immature, they cannot work properly. This leads to an increased risk of infection. Because the bone marrow cannot make enough healthy red blood cells and platelets, symptoms such as anaemia and bruising can occur.

There are four main types of leukaemia: acute lymphoblastic (ALL), acute myeloid (AML), chronic lymphocytic (CLL) and chronic myeloid (CML). Chronic leukaemias occur mostly in adults, and are

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extremely rare in children and young people. Each type of leukaemia has its own characteristics and treatment.

Jones, L., McCarthy, P. & Bond, J. 2020.
"Comprehensive cataloguing of the acute myeloid leukaemia (AML) genome has revealed a high frequency of mutations and deletions in epigenetic factors that are frequently linked to treatment resistance and poor patient outcome."

Auger, N., Goudie, C., Low, N., Healy-Profitós, J., Lo, E. & Luu, T.M. 2019.
BACKGROUND: Previous studies provide conflicting evidence of a link between maternal substance use and risk of childhood cancer.
METHODS: We analyzed a cohort of 785,438 newborns in Quebec (2006-2016). We identified infants whose mothers had problematic illicit drug, tobacco, or alcohol use before or during pregnancy. The primary outcomes were childhood hematopoietic cancer or solid tumors within 0-5 years of age. Using Cox proportional hazards models, we computed hazard ratios (HR) and 95% confidence intervals (CI) for the association between maternal substance use and childhood cancer, adjusted for potential confounders.
RESULTS: A total of 925 cases of cancer occurred during 3.5 million person-years of follow-up. Children exposed to any maternal substance use had marginally elevated cancer incidence rates compared with unexposed children (29.4 vs. 26.1 per 100,000 person-years). Maternal illicit drug use was associated with the risk of acute lymphoblastic leukemia (HR 1.63, 95% CI 0.79-3.36) and fibrosarcoma (HR 2.11, 95% CI 0.86-5.16). Maternal tobacco use was associated with acute myeloid leukemia (HR 2.01, 95% CI 0.72-5.60) and fibrosarcoma (HR 2.13, 95% CI 1.05-4.32), but a weak association with neuroblastoma (HR 1.21, 95% CI 0.61-2.40) and renal tumors (HR 1.14, 95% CI 0.42-3.13) also appeared to be present.
CONCLUSIONS: We found a potential association between maternal substance use and certain types of early childhood cancer. Although effects were modest, maternal substance use may contribute to some types of childhood cancer, especially leukemia and fibrosarcoma.

Childhood Acute Myeloid Leukaemia (AML)
Leukaemia is a cancer of the white blood cells. White blood cells help to fight infection.

There are two different types of white blood cell – lymphoid cells (also known as lymphocytes) and myeloid cells. Normally these cells repair and reproduce themselves in an orderly and controlled way. In leukaemia, however, the process gets out of control and the cells continue to divide but do not mature.

Acute myeloid leukaemia is an overproduction of immature myeloid cells, called myeloblasts or blast cells.

Immature myeloid cells fill up the bone marrow and stop it making healthy blood cells. As these cells are immature, they cannot work properly. This puts the child at increased risk of infection. Symptoms such as bruising and anaemia are caused by the bone marrow's inability to make enough healthy red blood cells and platelets.

Classification of Paediatric Myeloid Malignancies

The major subtypes of AML include the following:

- **M0:** Acute myeloblastic leukaemia without differentiation.[6,7] M0 AML, also referred to as minimally differentiated AML, does not express myeloperoxidase (MPO) at the light microscopy level but may show characteristic granules by electron microscopy. M0 AML can be defined by expression of cluster determinant (CD) markers such as CD13, CD33, and CD117 (c-KIT) in the absence of lymphoid differentiation.
- **M1:** Acute myeloblastic leukaemia with minimal differentiation but with the expression of MPO that is detected by immunohistochemistry or flow cytometry.
- **M2:** Acute myeloblastic leukaemia with differentiation.
- **M3:** Acute promyelocytic leukaemia (APL) hypergranular type. (Refer to the Acute Promyelocytic Leukaemia [APL] section of this summary for more information.)
- **M3v:** APL, microgranular variant. Cytoplasm of promyelocytes demonstrates a fine granularity, and nuclei are often folded. M3v has the same clinical, cytogenetic, and therapeutic implications as FAB M3.
- **M4:** Acute myelomonocytic leukaemia (AMML).
- **M4Eo:** AMML with eosinophilia (abnormal eosinophils with dysplastic basophilic granules).
- **M5:** Acute monocytic leukaemia (AMoL).
  M5a: AMoL without differentiation (monoblastic).
  M5b: AMoL with differentiation.
- **M6:** Acute erythroid leukaemia (AEL).
  M6a: Erythroleukemia.
  M6b: Pure erythroid leukaemia (myeloblast component not apparent).
  M6c: Presence of myeloblasts and proerythroblasts.
- **M7:** Acute megakaryocytic leukaemia (AMKL).

Other extremely rare subtypes of AML include acute eosinophilic leukaemia and acute basophilic leukaemia.

Incidence of Childhood Acute Myeloid Leukaemia in South Africa

In providing the incidence figures of leukaemia in South Africa, The National Cancer Registry (2017) does not make provision for the reporting of the different types of leukaemia – it also does not differentiate between acute and chronic leukaemia.

According to the National Cancer Registry (2017) the following number of leukaemia cases was histologically diagnosed in South Africa during 2017. Histologically diagnosed means that a sample of tissue (blood, in this case) was forwarded to an approved laboratory where a specially trained pathologist confirmed the diagnosis of Leukaemia.

Group – Boys 0 to 19 Years 2017	Actual No of Cases
All boys	82
Asian boys	0
Black boys	66
Coloured boys	7
White boys	9

Group – Girls 0 to 19 Years 2017	Actual No of Cases
All girls	40
Asian girls	1
Black girls	32
Coloured girls	1
White girls	6

The frequency of histologically diagnosed cases of leukaemia in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Boys 2017	0 – 4 Years	5 – 9 Years	10 – 14 Years	15 – 19 Years
All boys	19	25	24	14
Asian boys	0	0	0	0
Black boys	16	20	21	9
Coloured boys	0	5	1	2
White boys	3	1	3	3

Group - Girls 2017	0 – 4 Years	5 – 9 Years	10 – 14 Years	15 – 19 Years
All girls	11	17	5	10
Asian girls	0	0	0	1
Black girls	7	15	4	6
Coloured girls	1	0	0	0
White girls	3	2	1	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 boys' and 'all girls', however, always reflect the correct totals.

Signs and Symptoms of Acute Childhood Myeloid Leukaemia (AML)

Unlike other cancers Acute Childhood Myeloid Leukaemia (AML) does not occur in stages. Instead, it tends to be found spread throughout the bloodstream at the time of diagnosis, and may have invaded an organ. As a result of its ability to affect the whole body at once, it must be treated aggressively as soon as possible. AML's early symptoms mimic common diseases like the flu, so it can often go undiagnosed.

Signs and symptoms of Childhood Acute Myeloid Leukaemia (AML) can be divided into the following: (1) those caused by a deficiency of normally functioning cells, (2) those due to the proliferation and infiltration of the abnormal leukemic cell population, and (3) constitutional symptoms.

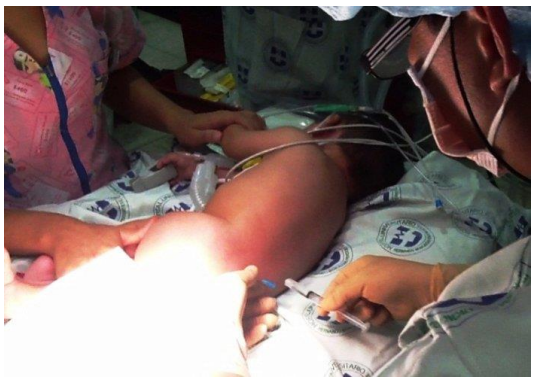
Symptoms due to a deficiency of normally functioning cells include the following:

- Cytopaenia (a reduction in the number of blood cells) - can result from a deficiency of normally functioning cells
- Anaemia - characterised by pallor, fatigue, tachycardia, and headache

- Haemorrhage - most commonly, easy bruising, petechiae, epistaxis (nose bleeds), gingival (gum) bleeding
- Frequent persistent infections
- Breathlessness
- Flu-like symptoms
- Fever - should initially always be attributed to infection
- Chills
- Malaise (not feeling well)
- Joint pains

Diagnosis of Childhood Acute Myeloid Leukaemia (AML)

A number of tests are performed to evaluate a child suspected of having leukaemia. The initial test will be a blood test called a complete blood count (CBC). The treating paediatrician or family doctor may order blood tests before referring the child to a specialist. Those tests are often repeated by the oncologist.



[Picture Credit: Lumbar Puncture]

Although leukaemia cells may be found in the blood, most commonly the diagnosis and classification of leukaemia is confirmed by looking at a sample of bone marrow under the microscope.

A spinal tap (lumbar puncture) is usually performed to look for leukaemia in the central nervous system.

Following these tests, the doctor may request the laboratory to perform cytogenetics tests (tests that check the leukaemia's chromosomes for mistakes, also called mutations).

Treatment of Childhood Acute Myeloid Leukaemia (AML)

The treatment for AML is often shorter and more intensive than for Acute Lymphoblastic Leukaemia (ALL). The total duration of treatment for AML is around six months and children will usually be admitted to hospital for the full duration of their treatment. This is because the intensive treatment can make children very unwell and they need a high level of supportive care.
The main treatment is chemotherapy. There are two phases of treatment – remission induction and post-remission treatment.

Remission induction - the initial aim of treatment for AML is to achieve a state called remission where almost all leukaemic cells have been killed, allowing production of normal blood cells to resume.

Remission induction usually includes one or two blocks of a combination of chemotherapy drugs in high doses given over a few days at intervals of one or two weeks.

Post-remission treatment - post-remission treatment (also known as consolidation or post-induction treatment) aims to destroy any remaining leukaemic cells and to prevent the disease from returning. This phase usually involves two or three more blocks of the same drugs used in remission induction.

Elgarten, C.W. & Aplenc, R. 2020.
Purpose of review: Despite advances in therapy over the past decades, overall survival for children with acute myeloid leukemia (AML) has not exceeded 70%. In this review, we highlight recent insights into risk stratification for patients with pediatric AML and discuss data driving current and developing therapeutic approaches.
Recent findings: Advances in cytogenetics and molecular profiling, as well as improvements in detection of minimal residual disease after induction therapy, have informed risk stratification, which now relies heavily on these elements. The treatment of childhood AML continues to be based primarily on intensive, conventional chemotherapy. However, recent trials focus on limiting treatment-related toxicity through the identification of low-risk subsets who can safely receive fewer cycles of chemotherapy, allocation of hematopoietic stem-cell transplant to only high-risk patients and optimization of infectious and cardioprotective supportive care.
Summary: Further incorporation of genomic and molecular data in pediatric AML will allow for additional refinements in risk stratification to enable the tailoring of treatment intensity. These data will also dictate the incorporation of molecularly targeted therapeutics into frontline treatment in the hope of improving survival while decreasing treatment-related toxicity.

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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Blood Cell Formation
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