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COMMENTARY

# Pediatric Acute Lymphocytic Leukemia

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## Introduction

Leukemia is a type of cancer that most commonly affects the bone marrow and other blood forming organs to produce an increased number of blastic leukocytes. Additionally, leukemia isn't just a cancer that affects the white blood cells, it also affects the erythrocytes. The effect that leukemia has on the erythrocytes could also cause various types of anemia. Moreover, leukemia is responsible for 1 out of 3 cancers found in the pediatric group [1]. But in the years 2013-2017, leukemia and lymphoma accounted for nearly 40% of all cancers found in people less than 20 years old [2].

### *Types of Leukemia*

Furthermore, there are different types of leukemia and are categorized as chronic (slow) or acute (fast). Digging deeper into the types of leukemias, there are 2 major types of variants, lymphocytic and myelogenous [3]. Myelogenous leukemia is a type of leukemia that starts in the bone marrow while lymphocytic leukemia starts in the white blood cells (leucocytes). These 2 types also come in a chronic and acute form. There are also more rare types of leukemias like hairy cell leukemia, myelodysplastic syndromes, and myeloproliferative disorders [4].

### *Acute Lymphocytic Leukemia*

The most common of these leukemias in children is acute lymphocytic leukemia (ALL). Approximately, 75% of all leukemia cases around the world are diagnosed in children residing in the United States [3].

## Symptoms

Acute lymphocytic leukemia being an extremely rare and fast paced disease. Many times, children diagnosed with acute lymphocytic leukemia experience little to no symptoms within the months, weeks, and even days before being diagnosed due to the white blood cells in the blood expanding at a rapid rate [5].
The most common or first symptom is extreme fatigue. Many patients cannot move for the reason that when their blood count is checked, their red blood cell count

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is drastically low, and they are not getting enough oxygen. Developing pneumonia is also really common. Antibiotics do not work after developing pneumonia because the immune system is really low [5].

Symptoms of Acute Lymphocytic Leukemia are the following:

- Anemia occurs when red blood cells are not produced due to the center of the bones overflowing with Leukemic cells.
- Bleeding and/or bruising happens when the bone marrow does not manufacture sufficient platelets also known as megakaryocytes.
- Bone and joint pain can occur due to the bone marrow being overfilled with leukemic blasts.
- Recurrent fevers/infections may demonstrate elevated quantities of white blood cells that are immature and do not fight infection.
- Abdominal pain happens when leukemic cells gather in the kidneys, liver, and spleen occasioning the expansion of the organs.
- Swollen lymph nodes can occur when leukemia cells gather in the lymph nodes causing them to swell.
- Difficulty breathing happens when cells build up together in the thymus and underneath the breastbone surrounding the throat [6].

## Diagnosis

The identification of a disease is known as a diagnosis. There are two tests that can accurately diagnose acute lymphocytic leukemia in children and determine the severity of the disease: blood testing and bone marrow tests [7]. A blood sample must be taken before a blood test may start. Since pediatric oncologists work with children, a lancet, a device that pricks a finger to draw blood from the capillary vein found there, must be used to take a sample of their blood [7]. Once pediatric oncologists collect their blood samples and send them to a lab, a complete blood count and blood smear will be performed to determine if the kids have leukemia and make a diagnosis. A complete blood count is a numerical result of how many blood cells are in a patient's blood [7]. An abnormal blood cell count in children is a critical indicator for any pediatric oncologist to begin to suspect leukemia. A blood smear is a droplet of blood that is put on a glass slide and examined under a microscope [7]. A closer examination of a pediatric patient's blood may further bring a pediatric oncologist to make a diagnosis because a change in the appearance of these cells may lead them to suspect ALL. A pediatric oncologist's concerns may be raised by an unusual blood cell count and a change in the appearance of a child's blood cells, but ALL cannot be definitively identified without analyzing a sample of the child's bone marrow cells. Bone marrow is a semi-solid tissue found within the spongy, also known as cancellous, portions of bones. The spongy tissue can be found within a person's hip and thigh bones. There are two bone marrow sample collection methods that can be utilized: bone marrow aspiration and biopsy. Both of these procedures are typically carried out simultaneously, but both are necessary for testing ALL. A little amount of liquid bone marrow is aspirated using a syringe after a thin, hollow needle is introduced into the bone to perform a bone marrow aspiration [7]. The aspiration is then typically followed by a bone marrow biopsy. A slightly larger needle that is inserted down into the bone to remove a little bit of bone and marrow [7]. Pressure will be provided to the area once the biopsy is completed to aid in stopping any bleeding.

## Stages of Progression

Usually, the progression or stages of cancers are categorized by Stage I, II, III, or IV. This is determined by how far away the cancer cells moved from where it originally began. For example, in breast cancer, if the tumor is located only in the breast, this would mean the cancer is in Stage I. If the cancer cells travel into the brain or the liver, it would be identified as stage IV [8].

In the case of leukemia, the blood cells themselves are the malignant cells. The production of blood cells goes out of control causing the cancer to spread throughout your body. These new cells that are produced are abnormal and won't efficiently function as they were meant to do. Healthy cells will be caught by the crossfire causing buildup and crowds will start to form [9]. At the time of a diagnosis, leukemia cells are present in the blood and in the bone marrow. Using this information, it is either an active disease or it's in remission [8].

## DNA Mutations and Genetics

Acute Lymphocytic Leukemia (ALL) is the most common cancer found in pediatrics. While there is no found direct cause of this disease it has been linked mainly to both genetic alterations and a phenomenon of DNA mutations. ALL arises from the malignant transformation of progenitor B- and T-cells in the bone marrow into leukemic cells. Genes that help keep cell division under control or cause cells to die at the right time are called tumor suppressor genes. A translocation seen in mostly all cases of childhood

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ALL is the swap between chromosomes 9 and 22 also known as the Philadelphia Chromosome [3]. The swap between the chromosomes causes the oncogenes to help the leukemic cells grow within the body. Intensive treatment due to a poor prognosis illustrates that there is a complex intrachromosomal amplification of chromosome 21 that is most common to pediatric ALL patients. Secondary deletions or mutations may cause alterations in lymphoid transcription factors, cell cycle regulations, and tumor suppression [10]. Studies have indicated that many ALL mutations are present at low variant allele frequency and therefore become subclonal [11]. In Acute Lymphocytic Leukemia, Hyperdiploidy is defined as the non-random gain of chromosomes, increasing the modal chromosome number of leukemic blasts from 46 to between 51 and 65 or 67. Leukemic cells experiencing near or low hypodiploid tend to undergo a process that causes the hyperdiploid clone to double causing the drastic increase in number of chromosomes found in ALL patients predominantly in children [12]. The increase of hyperdiploid clones leads to what is called masked hyperdiploidy which is found in 60-65% of ALL patients, 25-30% being children [13]. Masked hyperdiploidy is clinically challenging for patients battling with ALL and serves as one of many DNA abnormalities contained in this disease. In addition, genetics has led to some of the world's most underlying diseases and disorders. Inherited genes play a key role in the growth and or demise of leukemic cells in pediatric ALL patients. Several genetic conditions have taken a severe part in the development of Acute Lymphocytic Leukemia, these conditions include but not limited to Down syndrome, Neurofibromatosis type 1, Bloom syndrome, Fanconi anemia, Ataxia-telangiectasia, and Li-Fraumeni syndrome [14]. Although these conditions can contribute to ALL, Down syndrome has played the predominant contribution to this disease. Down syndrome is defined as a genetic disorder caused by the presence of all or part of a third copy of chromosome 21. Down syndrome affects 1 in every 700 infants which allows for an increased risk of developing leukemia. Since children with Down syndrome have an extra copy of chromosome 21 they are more likely to have faulty genes; these children are 33 times more likely to develop ALL [15]. Children with down syndrome not only have an increased risk of developing ALL, but they have an increased 2.1% cumulative risk of developing the disease before the age of 5 [14].

## Treatment Options

### *Chemotherapy*

Chemotherapy is one of the main treatments for cancerous patients. This treatment is used to reduce the number of cancer cells in the body. Although very helpful, chemotherapy can decrease health through the removal of healthy cells. Depending on the patient, they are capable of feeling fatigue, hair loss, and having several infections [16]. Chemotherapy can differ depending on a patient's health status and the type of cancer they are experiencing.

### *Radiation Therapy*

Radiation Therapy is a form of treatment that focuses on the removal of cancerous cells. This therapy can be a very laborious process, so it requires a lot of patience. Radiation therapy can be very similar to chemotherapy in the fact that it requires an immense number of time. External radiation therapy is a form of treatment associated with radiation therapy. This treatment heals places where acute leukemia has expanded in a child's system [14].

### *Chemotherapy With Stem Cell Transplant*

Chemotherapy with stem cell transplant is similar to chemotherapy, but it is not the primary treatment for children. Children aren't able to take large doses of chemotherapy because of their development [17]. With stem cell transplant, children are able to have a greater outcome. This means that children are able to have a higher intake of chemotherapy.

### *Targeted Therapy*

Targeted therapies are forms of treatments that specifically target a certain type of cancer cells, while avoiding healthy tissues [14]. This is a preferred treatment route due to the fact that standard treatments like chemotherapy and radiation therapy destroy normal, non-cancer cells. This is partially counterintuitive because in killing healthy cells, the body loses important stationary cells that continue growth.

Tyrosine Kinase Inhibitor (TKIs) Therapy
This form of treatment is specific to blocking the enzyme, tyrosine kinase, that causes an overproduction of white blood cells within the body. Three of the most common TKI medications are: imatinib mesylate, dasatinib, and ruxolitinib. These three drugs

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are used in several other cancers and conditions; they can help stop the growth of cancerous cells and may even help in killing malignant cells [14].

Monoclonal Antibodies
Moving on, monoclonal antibodies are laboratory-developed proteins that help fight specific diseases, such as cancer. This type of treatment is usually thought of as an option for patients with acute lymphocytic leukemia that doesn't respond to other common treatments. One monoclonal antibiotic infusion being studied and used in pediatrics is blinatumomab. Blinatumomab is more specifically used to treat B-cell ALL that is in remission, has recently come back, or when an ALL patient doesn't respond to other treatment options [14].

### *Immunotherapy*

Immunotherapy is an innovative type of treatment that focuses on assisting the body in its own natural defense mechanisms. This form of therapy effectively utilizes the substances created by the body or those made in a laboratory to direct more attention to a given disease, in this case, acute lymphocytic leukemia [14].

CAR T-cell Therapy
This form of treatment is a procedure in which some T cells are removed from the patient and given a special receptor. The new cells are known as chimeric antigen receptor (CAR) T cells. The CAR T cells are given via infusion and multiply in the patient's blood - attacking the cancerous cells. This treatment is also being studied in other cancers, as well as recurring childhood acute lymphocytic leukemia [14].

## Relapses

Relapsed Acute Lymphocytic Leukemia refers to when lymphoblastic stem cells become immature white blood cells or blasts. Instead of becoming healthy white blood cells they build up in the bone marrow, resulting in less room for healthy white blood cells, red blood cells, and platelets. Furthermore, resulting in these abnormal cells the inability to fight off infection [18]. After children's first treatment for acute lymphocytic leukemia about 85%-90% are cured; however, 10% to 15% of patients with pediatric acute leukemia experience relapse or have a slight chance of getting the disease again [19]. Acute lymphocytic leukemia is the most common fatal disease in children, which consists of 25% of all childhood cancers [20].

Studies show that most relapsed events occurred during the maintenance phase and after the finalization of chemotherapy [20]. Stem cell transplant is rarely used as initial treatment for children and adolescents with ALL, however It is used more often as part of treatment for ALL that relapses. Occasionally treatment for relapsed ALL is more intensive and critical than newly diagnosed ALL. Reinduction therapy is received at the time of the first relapse. If the second complete remission is a success, treatment options include: chemotherapy with or without radiation therapy and stem cell (bone marrow) transplantation.

## Prognosis

A prognosis is the likely course of an illness after a diagnosis. When it comes to the prognosis of children with acute lymphocytic leukemia, there are numerous crucial determinants. The white blood cell count of a child and their age are prime examples of the many important influential factors. White blood cells, also known as leukocytes, are located in the circulatory system to fight off infections. Children with ALL who have very high white blood cell counts (greater than 50,000 cells per cubic millimeter) when they are diagnosed are at higher risk and need more intensive treatment [21]. An overproduction in white blood cells is a main indicator for certain blood cancers or bone marrow diseases, such as ALL. In continuation, a pediatric patient's age is essential to determining their prognosis because of their B-cell count. B-cells, also known as B-lymphocytes, are located in the immune system to produce tumor-specific antigens that stop the development of cancer, such as ALL. B-cell counts are found by blood tests. Children between the ages of 1 and 9 with B-cell ALL tend to have better cure rates [21]. Physicians can plan their pediatric patients' future treatments once they have pediatric patients who have been diagnosed with B-cell ALL, a rare subtype of ALL, and know their B-cell count. When pediatric patients' white blood cell counts and/or their age are reported to clinicians, they are often divided into risk categories classified as low risk to extremely high risk, with higher risk kids receiving more intensive treatment.

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## Mortality Rate

What is a mortality rate? A mortality rate is the measure of the frequency of occurrence of death in a defined population during a specified interval. Acute lymphocytic leukemia has been found to be the most common form of childhood cancer. It is usually found in children from ages 3 to 5 and it affects boys slightly more than girls [22]. Approximately 6,000 cases of Acute Lymphocytic Leukemia (ALL) cases are diagnosed in the US each year. More than 50% of these cases are in pediatric patients. The five-year mortality rate for pediatric patients diagnosed with ALL is 10%. Even though childhood cancer rates have been increasing, death rates have been drastically decreasing [16].

## Survival Rate

A survival rate refers to the percentage of people in a study or treatment group who are still alive for a certain period of time after they were diagnosed with or started treatment for a disease. Each year roughly about 6,000 ALL cases are diagnosed. More than half of these cases are diagnosed in children. 90% of pediatric cases found can be cured [16]. St. Jude patients diagnosed with ALL have a 94% survival rate, which is the best worldwide outcome for ALL patients.

## Conclusion

In closing, acute lymphocytic leukemia (ALL) is a type of cancer that affects the blood and bone marrow of the body [9]. ALL is the most common pediatric leukemia, with approximately over 3,000 cases diagnosed in children. Even with being the most prevalent leukemia diagnosed in the pediatric group, only about 10% of patients succumb to ALL [16]. Unfortunately, a cure has not been found for this disease. Doctors, patients, and all corresponding parties await for more research to stop the progression and cure acute lymphocytic leukemia in all children.

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