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Hyperleukocytosis and Exchange Transfusion in Pediatric Acute Leukemia: Literature Review

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ABSTRACT

Hyperleukocytosis is a life-threatening oncologic emergency frequently encountered in patients with acute leukemia. It is defined as a peripheral leukocyte count exceeding 100,000/µL and is most commonly observed in acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). This condition is associated with severe complications, including leukostasis, tumor lysis syndrome (TLS), and disseminated intravascular coagulation (DIC), which significantly contribute to early mortality. The management of hyperleukocytosis remains challenging due to its rapid progression and high risk of fatal complications. Current strategies focus on aggressive supportive care, prevention of metabolic disturbances, and rapid cytoreduction using leukapheresis, exchange transfusion, or early initiation of chemotherapy. This review summarizes current evidence regarding the clinical and laboratory manifestations, prognosis, complications, and management of hyperleukocytosis, emphasizing the importance of early recognition and individualized treatment to improve patient outcomes.

Keywords: acute leukemia; hyperleukocytosis; leukostasis; tumor lysis syndrome; exchange transfusion; cytoreduction

INTRODUCTION

Hyperleukocytosis is one of the leading causes of mortality in patients with acute leukemia. It is defined as a peripheral blood leukocyte count exceeding 100,000/µL and is commonly observed in patients with acute leukemia, particularly acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML)[16]. Hyperleukocytosis can lead to several severe complications, including leukostasis, tumor lysis syndrome (TLS), and disseminated intravascular coagulation (DIC), resulting in a poor prognosis [27].

Hyperleukocytosis complicated by leukostasis, characterized by increased blood viscosity and leukocyte aggregation, constitutes a hematologic emergency, with early mortality rates reaching up to 50% during induction therapy or within 30 days thereafter [3]. The management of acute hyperleukocytosis remains a significant clinical challenge. This is due to the need for rapid and precise intervention in the setting of high early mortality rates and the complexity of managing hyperleukocytosis-related emergencies. Standard management includes tumor lysis prevention, urine alkalinization, aggressive hydration, administration of allopurinol, cytoreduction, and appropriate supportive care [21].

Leukemia is the most common childhood cancer in Indonesia, accounting for 34.8% of all pediatric cancer cases in 2020, with fewer than 30% of cases achieving a cure. According to World Health Organization (WHO) data from 2019, leukemia-related mortality in Indonesia reached 11,314 cases, ranking leukemia as the fifth leading cause of cancer-related death, with hyperleukocytosis identified as one of the major contributing factors. At Dr. Soetomo General Hospital, Surabaya, leukemia, particularly acute lymphoblastic leukemia, accounted for 82.8% of pediatric cancer cases, with an average of 126 new cases annually, making it the most prevalent pediatric malignancy between 2016 and 2020 [2]. This is closely related to hyperleukocytosis, which is observed in approximately 10.2–19.2% of ALL cases and 12.6–21.7% of AML cases, and is

associated with early mortality rates of up to 50% during induction therapy or within the first 30 days [16]. Globally, ALL accounted for 23.1% of total leukemia cases in 2017, while AML represented approximately 80% of leukemia cases in adults [6,23]. These data underscore the importance of improving the quality of hyperleukocytosis management to reduce leukemia-related mortality.

ACUTE LEUKEMIA

Acute leukemia is a malignancy of the blood and bone marrow characterized by the uncontrolled proliferation of immature white blood cells and a rapid disease onset [17]. It is one of the most common malignancies in children, accounting for more than 31% of all cancers diagnosed in children under 15 years of age. In general, leukemia arises from dysfunction in normal leukocyte production within the bone marrow, which may ultimately lead to bone marrow failure and impaired hematopoiesis [19].

Based on the lineage of the precursor cells, acute leukemia is classified into two main types: acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). ALL is the most frequently encountered type, representing approximately 80% of all acute leukemia cases worldwide, whereas AML is less common but is generally associated with a poorer prognosis [13].

Epidemiology

Acute leukemia is the most common childhood malignancy, contributing to more than 31% of all cancers diagnosed in children younger than 15 years [19]. The average incidence of acute leukemia is approximately 4–4.5 cases per 100,000 children per year. Among acute leukemia cases, ALL accounts for approximately 83%, while AML represents about 17% [22]. ALL is the most prevalent subtype, with an incidence of approximately 25 cases per 100,000 children in high-income countries, and a peak incidence between 2 and 6 years of age as reported in 2021 [9]. In contrast, AML is less common in the pediatric population, with an incidence of approximately 1.5 cases per 100,000 children [24].

Between 1990 and 2021, global incidence and mortality rates of childhood leukemia declined, particularly in high-income countries, largely due to advances in diagnostic methods and therapeutic strategies. However, low- and middle-income countries continue to experience higher mortality rates, reflecting disparities in healthcare access and quality. In terms of sex distribution, acute leukemia demonstrates higher incidence and mortality rates in males, with a male-to-female ratio of approximately 1.7:1 [17].

In Indonesia, leukemia is the most common childhood cancer, accounting for 34.8% of all pediatric cancer cases in 2020, with fewer than 30% of affected children achieving a cure. According to World Health Organization (WHO) data from 2019, leukemia-related deaths in Indonesia reached 11,314, ranking leukemia as the fifth leading cause of cancer-related mortality, with hyperleukocytosis being a major contributing factor. At Dr. Soetomo General Hospital, Surabaya, leukemia, particularly acute lymphoblastic leukemia, accounted for 82.8% of pediatric malignancies, with an average of 126 new cases annually between 2016 and 2020 [2]. Globally, ALL accounted for 23.1% of total leukemia cases in 2017, whereas AML represents approximately 80% of leukemia cases in adults [6,23].

Pathophysiology of Acute Leukemia

The exact pathophysiology and etiology of acute leukemia remain incompletely understood. However, genetic, epigenetic, and environmental factors have been shown to contribute to the development of acute leukemia in children [19]. The pathophysiological mechanisms also vary depending on the lineage of the leukemic precursor cells.

In general, acute leukemia is initiated by chromosomal translocations or genetic mutations occurring during fetal development. These primary genetic alterations may be exacerbated by secondary genetic events triggered by postnatal exposure to teratogens. Environmental factors such as pesticide exposure, high-dose radiation, and infections after birth further increase the risk of leukemia development in children [19].

The accumulation of these genetic and environmental insults leads to oncogene activation and tumor suppressor gene inactivation, resulting in impaired apoptosis and excessive proliferation of lymphoid or myeloid cells. This process ultimately disrupts normal hematopoiesis within the bone marrow [22].

Clinical and Laboratory Manifestation of Acute Leukemia

Clinical manifestations of acute leukemia vary depending on the leukemia subtype. Early presentations are often nonspecific and may resolve transiently, including anorexia, malaise, and fever. Overall, the clinical features of acute leukemia reflect bone marrow failure, extramedullary infiltration by leukemic cells, and systemic effects of malignant proliferation.

Common manifestations observed in both ALL and AML include pallor, fatigue, exercise intolerance, mucosal bleeding or epistaxis, and fever [19]. Lymphadenopathy, hepatosplenomegaly, and testicular enlargement are frequently observed due to extramedullary hematopoiesis or leukemic infiltration of organs [26]. Certain clinical features, such as subcutaneous nodules (“blueberry muffin” lesions) and gingival infiltration, occur more frequently in AML and may help differentiate it from ALL.

Laboratory findings typically reveal pancytopenia on complete blood count, characterized by decreased hemoglobin, leukocyte, and platelet levels [22]. Pancytopenia results from the replacement of normal hematopoietic stem and progenitor cells by

immature leukemic blasts within the bone marrow, leading to impaired production of red blood cells, neutrophils, and platelets [7].

In high-risk acute leukemia, hyperleukocytosis and leukostasis may occur due to interactions between leukemic progenitor cells and endothelial cells, resulting in massive release of blasts into the peripheral circulation [3]. Peripheral blood smear examination typically demonstrates a predominance of blast cells [22].

Diagnosis of Acute Leukemia

The diagnosis of acute leukemia is initially suspected based on clinical manifestations and complete blood count findings. Definitive diagnosis requires bone marrow aspiration with morphological assessment, immunophenotyping, and genetic analysis [22].

Bone marrow examination is diagnostic of acute leukemia when hypercellularity and a blast percentage of ≥20% are identified [14]. Differentiation between AML and ALL relies on blast morphology: larger blasts with the presence of Auer rods are suggestive of AML, whereas smaller to medium-sized blasts with scant cytoplasm are more characteristic of ALL [10].

Management of Acute Leukemia

Management of acute leukemia consists of curative and supportive therapies. Supportive care aims to address leukemia-related complications and includes blood transfusions, antibiotic therapy, nutritional support, and psychosocial interventions [22]. Adequate supportive care is essential, as it reduces treatment-related mortality and improves overall survival outcomes [20].

Curative treatment primarily involves chemotherapy and is delivered through several phases, including induction, consolidation, intensification, and maintenance therapy [22]. The induction phase typically spans the first four weeks of chemotherapy initiation and plays a critical role in determining relapse risk, as induction failure or minimal residual disease (MRD) positivity is associated with a higher likelihood of disease recurrence [5].

Chemotherapeutic regimens vary according to leukemia subtype. Patients with ALL are commonly treated with vinca alkaloids, corticosteroids, and asparaginase, whereas patients with AML often receive all-trans-retinoic acid (tretinoin) in combination with anthracyclines and cytarabine [19].

HYPERLEUKOCYTOSIS

Hyperleukocytosis is defined as a condition characterized by an abnormally high concentration of leukocytes in the circulation, with a leukocyte count exceeding 100,000/µL [18]. Hyperleukocytosis is considered an oncologic emergency and is most commonly observed in patients with acute leukemia, particularly acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). This condition is closely associated with increased morbidity and mortality among affected patients [16].

Hyperleukocytosis frequently occurs in patients with acute leukemia, especially ALL and AML. According to World Health Organization (WHO) data from 2019, leukemia-related mortality in Indonesia reached 11,314 cases, ranking leukemia as the fifth leading cause of cancer-related death, with hyperleukocytosis identified as one of the major contributing factors. At Dr. Soetomo General Hospital, Surabaya, leukemia, particularly acute lymphoblastic leukemia, accounted for 82.8% of pediatric cancer cases, with an average of 126 new cases per year, making it the most prevalent pediatric malignancy between 2016 and 2020 [2]. This high prevalence is closely linked to hyperleukocytosis, which is observed in approximately 10.2–19.2% of ALL cases and 12.6–21.7% of AML cases [16]. A retrospective study conducted in Thailand that reviewed medical records of pediatric patients diagnosed with acute leukemia between 1998 and 2017 reported an incidence of hyperleukocytosis of 16.6% in ALL patients and 20.3% in AML patients. The study also demonstrated that hyperleukocytosis was more commonly observed in older pediatric patients [16].

Clinical and Laboratory Manifestation of Hyperleukocytosis

Clinical manifestations in patients with hyperleukocytosis are often diverse and nonspecific. Symptoms elicited during history taking frequently reflect features of both leukostasis and the underlying leukemia. Common presenting complaints include fever, joint pain, dizziness, nausea and vomiting, dyspnea, hemoptysis, blurred vision, headache, ataxia, oliguria, and anuria. On physical examination, patients commonly appear pale and may exhibit signs of bleeding as well as organomegaly, including splenomegaly, hepatomegaly, and lymphadenopathy [15]. The clinical presentation varies depending on the type of leukemia and patient-related risk factors such as age and sex. In patients with acute lymphoblastic leukemia (ALL), manifestations frequently include a mediastinal mass, hepatomegaly, and splenomegaly. In contrast, patients with acute myeloid leukemia (AML) more commonly present with fever, splenomegaly, and lymphadenopathy [16]. Overall, the clinical manifestations of hyperleukocytosis are primarily driven by leukocyte aggregation and microvascular obstruction, which may result in tissue hypoxia and subsequent organ dysfunction. The respiratory and central nervous systems are the most frequently affected, reflecting the predilection of leukostasis for the pulmonary and cerebral microcirculation.

Laboratory manifestations in patients with hyperleukocytosis tend to be more characteristic and consistent than the clinical manifestations. The hallmark laboratory finding is a markedly elevated leukocyte count, typically exceeding 50,000/µL, with differential counts showing lymphocytosis or the presence of circulating blast cells.

Peripheral blood smear examination often reveals a high proportion of immature leukocytes, particularly blasts [15]. Metabolic abnormalities are commonly observed as a result of increased cell turnover and tumor lysis. These abnormalities include hyperuricemia, hyperphosphatemia, hypocalcemia, metabolic acidosis, and hypoxemia. Such laboratory findings reflect the underlying pathophysiological processes associated with hyperleukocytosis and are closely related to the development of tumor lysis syndrome (TLS) and other life-threatening complications [15]. Additional laboratory abnormalities may include evidence of coagulopathy, such as prolonged coagulation times and elevated markers of disseminated intravascular coagulation, particularly in patients with severe disease. Collectively, these laboratory findings highlight the importance of prompt laboratory assessment and close monitoring to guide early intervention and prevent secondary complications.

Management of Hyperleukocytosis

The management of hyperleukocytosis is primarily focused on preventing and reducing secondary complications, particularly those related to leukostasis, through intensive supportive care and rapid cytoreduction. Cytoreductive therapy aims to achieve a rapid decrease in circulating leukocyte counts and can be accomplished through leukapheresis or exchange transfusion. In addition to cytoreduction, comprehensive management includes aggressive hydration, urine alkalinization, administration of allopurinol, and initiation of induction chemotherapy when clinically feasible [25].

Hydration therapy in patients with hyperleukocytosis is intended to promote adequate diuresis and renal perfusion. This can be achieved by administering parenteral fluids, such as 5% dextrose in 0.225% normal saline, at two to three times the maintenance fluid requirement or approximately 2–3 L/m^2/day. Urine alkalinization and allopurinol administration are aimed at increasing urine pH to approximately 7.5, thereby preventing uric acid crystal formation and reducing plasma uric acid concentrations [16].

Leukapheresis remains one of the most commonly employed cytoreductive modalities in the management of hyperleukocytosis, particularly in patients with symptomatic leukostasis. However, emerging evidence suggests that alternative strategies, including exchange transfusion and early initiation of chemotherapy without invasive cytoreduction, may be effective and safe in selected patient populations. These evolving approaches highlight the need for individualized treatment strategies based on disease severity, leukemia subtype, and available resources.

Prognosis of Hyperleukocytosis

Hyperleukocytosis is generally associated with a poor prognosis due to the high risk of severe and potentially fatal complications, including leukostasis and disseminated intravascular coagulation (DIC). These complications significantly contribute to early mortality, particularly in patients with acute myeloid leukemia (AML).

Studies have reported early mortality rates of up to 50% among patients with AML and hyperleukocytosis, occurring during induction chemotherapy or within the first 30 days after diagnosis [3]. The presence of hyperleukocytosis at diagnosis is therefore considered a strong adverse prognostic factor, as it is associated with increased morbidity, treatment-related complications, and reduced overall survival. Early recognition and prompt, aggressive management of hyperleukocytosis are critical to improving patient outcomes. Advances in supportive care, cytoreductive strategies, and early initiation of definitive leukemia treatment play a key role in reducing early mortality and improving prognosis in affected patients.

Complication of Hyperleukocytosis

- *Leukostasis*

Leukostasis is a clinical syndrome commonly observed in patients with hyperleukocytosis and is characterized by the accumulation of blast cells within the pulmonary and cerebral microvasculature. This condition results from obstruction of small arteries and capillaries by aggregates or thrombi composed of leukemic blast cells. Leukostasis occurs more frequently in patients with acute myeloid leukemia (AML) than in those with acute lymphoblastic leukemia (ALL) [22].

The accumulation of blast cells leads to microvascular obstruction and subsequent tissue hypoxia. Clinically, leukostasis may manifest as respiratory distress, neurological abnormalities, and various forms of organ dysfunction associated with impaired perfusion [4].

The most common clinical manifestations of leukostasis involve the respiratory and central nervous systems. Respiratory symptoms include dyspnea and tachypnea, while neurological manifestations may include dizziness, headache, confusion, and tinnitus [16].

Management of leukostasis follows the same fundamental principles as the management of hyperleukocytosis, with rapid cytoreduction as the primary goal. Cytoreductive strategies include leukapheresis and systemic chemotherapy to reduce circulating leukocyte burden and alleviate microvascular obstruction [11].

- *Tumor Lysis Syndrome (TLS)*

Tumor lysis syndrome (TLS) is a constellation of metabolic abnormalities, including hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia, and lactic acidosis. TLS is a life-threatening oncologic emergency that frequently culminates in acute organ failure, particularly acute kidney injury. This syndrome most commonly occurs in patients with leukemia, especially following aggressive chemotherapy [1].

TLS is more likely to occur in patients with malignancies associated with high leukocyte counts. Tumors are stratified into three risk categories for TLS development: high-risk, intermediate-risk, and low-risk tumors. High-risk tumors account for more than 64.5% of TLS cases and include acute lymphoblastic leukemia (5.2–23%), acute myeloid leukemia with leukocyte counts exceeding 75,000/μL (18%), Burkitt lymphoma (14.9%), and B-cell acute lymphoblastic leukemia (26.4%) [1].

TLS results from the massive release of intracellular ions and metabolites, such as potassium and phosphate, into the systemic circulation following rapid tumor cell breakdown. The kidneys play a critical role in maintaining electrolyte homeostasis by excreting these substances; however, the overwhelming load can lead to nephropathy and renal failure [1].

EXCHANGE TRANSFUSION

Exchange transfusion, also referred to as plasmapheresis, is a therapeutic procedure used to remove pathological components from the bloodstream, including antibodies, immune complexes, infectious agents, and toxins. The procedure involves separating, removing, and replacing the patient's blood or plasma with colloid solutions or donor blood products [12].

Indication

Exchange transfusion is commonly employed in the treatment of pediatric hematologic disorders. According to the eighth edition of the American Society for Apheresis (ASFA) guidelines, exchange transfusion is indicated for several conditions, including sickle cell anemia, neonatal polycythemia, babesiosis, Guillain–Barré syndrome, myasthenia gravis, heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, and Goodpasture syndrome [12]. Among these, hemolytic disease due to Rh incompatibility remains the most frequent indication for exchange transfusion [8].

In addition to hemolytic disorders, exchange transfusion is also used to manage physiological conditions, particularly neonatal hyperbilirubinemia. Most newborns, especially those with low birth weight and preterm infants, develop neonatal jaundice during the early weeks of life. While neonatal jaundice is often a normal physiological process, it may become pathological when bilirubin levels exceed safe thresholds, leading to bilirubin encephalopathy. In this context, exchange transfusion plays a crucial role in the Pediatric Intensive Care Unit (PICU) [12].

Procedure

The procedure for exchange transfusion is performed as follows:

(1) Initially, 10–20 mL of the child's blood is withdrawn, depending on body weight, without exceeding 10% of the estimated total blood volume.
(2) The withdrawn blood is discarded through a drainage line by adjusting the valve on a three-way stopcock. If additional laboratory tests are required, this blood may be used, as it has not yet mixed with donor blood.
(3) An equal volume of donor blood is slowly infused. The rate of withdrawal and infusion is approximately 2 mL/kg body weight per minute.
(4) After the donor blood is infused, a waiting period of approximately 20 seconds is observed to allow adequate circulation.
(5) The withdrawal and infusion cycle is repeated in the same manner until the targeted exchange volume is achieved.
(6) Each volume of blood removed and infused is carefully documented on the exchange transfusion observation sheet.
(7) When using blood preserved with acid–citrate–dextrose (ACD) or phosphate–citrate–dextrose (PCD), 1 mL of 10% calcium gluconate is administered intravenously for every 100 mL of transfused blood, particularly if the pre-transfusion serum calcium level is below 7.5 mg/dL. If calcium levels are within the normal range, calcium supplementation may not be necessary. Calcium gluconate should be administered slowly to avoid adverse effects such as bradycardia or cardiac arrest. Some studies recommend withholding calcium administration unless physical examination or electrocardiographic findings suggest hypocalcemia.
(8) Vital signs are closely monitored throughout the procedure. After completion, blood samples are obtained for post-exchange laboratory evaluation.
(9) If repeat exchange transfusion is not required, a silk purse-string suture or circular ligature is placed around the vein. When the catheter is removed, the suture encircling the umbilical vein is tightened [2].

Adverse Effect

Exchange transfusion may be associated with several adverse effects and complications, including pruritus, hypertension, and hypotension [12]. Additionally, metabolic disturbances such as hyperglycemia and serious complications such as sepsis have also been reported following exchange transfusion [8].

CONCLUSIONS

Hyperleukocytosis is a critical oncologic emergency associated with high early mortality in patients with acute leukemia. Severe complications such as leukostasis, disseminated intravascular coagulation, and tumor lysis syndrome significantly worsen prognosis if not promptly managed. Early recognition, rapid cytoreduction, and intensive supportive care remain the cornerstone of treatment. Although leukapheresis is widely used, alternative strategies, including exchange transfusion and early chemotherapy initiation, have shown promising results in selected patients. Individualized management based on clinical presentation, leukemia subtype, and available resources is essential. Further

studies are needed to establish standardized treatment algorithms and improve survival outcomes in patients with hyperleukocytosis.

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CONFLICT OF INTEREST
The authors declare no conflicts of interest related to this manuscript.

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