Chapter 2
Diagnosis and Treatment-Related Complications of Acute Leukemia

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Introduction

Acute leukemia remains the most common malignancy in children and accounts for one third of all pediatric cancer diagnoses, with 75% of those being acute lymphoblastic leukemia (ALL) [1]. In the United States, there are approximately 3,100 children and adolescents under 20 years of age who are diagnosed with ALL each year and 750 who are diagnosed with acute myeloid leukemia (AML) [2]. Significant progress has been made in the treatment of pediatric leukemias over the past 70 years with current long-term survival rates above 90% for ALL and 60–70% for AML, compared to virtually 0% survival in the 1950s [3, 4]. This improvement has been attributed to the introduction of prophylactic intrathecal therapy; intensification of multi-agent chemotherapy; refined treatment stratification based on somatic mutations and early treatment response measured by minimal residual disease; introduction of targeted chemotherapeutic agents; and overall advances in supportive care [3, 5]. Most of these developments have been accomplished through randomized clinical trials performed by major international cooperative study groups [3]. Recent research has been directed toward risk stratification and response-based prognostic factors to allow for intensification of treatment for high-risk patients and decreasing acute toxicities and long-term sequelae through targeted novel agents, leukemia signal pathway inhibitors, immunotherapy, and cellular therapy [6].

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Despite our advances in treatment and improvements in survival, 2–4% of patients with leukemia still experience treatment-related deaths [7]. These are most often attributable to infections; bleeding or thrombosis; tumor burden complications such as superior vena cava syndrome, hyperleukocytosis, leukostasis, and tumor lysis syndrome; and therapy-induced organ toxicities [7]. Here, we will review some of the most common toxicities and oncologic emergencies associated with the diagnosis and treatment of childhood acute leukemia that may require management in the pediatric intensive care unit (PICU).

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) is characterized by metabolic abnormalities resulting from the rapid release of intracellular contents from malignant cells into the bloodstream. This process can overwhelm the patient's normal physiologic mechanisms of maintaining homeostasis and result in life-threatening hyperkalemia, hyperuricemia, hyperphosphatemia, hypocalcemia, and/or uremia. Both uric acid and calcium phosphate, when serum levels become high enough, can precipitate in the renal tubules leading to acute renal failure, worsened electrolyte abnormalities, and even death [6, 8]. TLS may occur spontaneously related to high tumor burden and increased cell turnover but is most commonly observed 12–72 h after the initiation of chemotherapy secondary to leukemic cell death and cell lysis [6, 8, 9]. The incidence of TLS in AML is 3.4% compared to 5.2% for ALL [10]. Risk factors for developing TLS in ALL and AML include high presenting white blood cell count (hyperleukocytosis) and pre-existing kidney injury (dehydration, oliguria, anuria, renal insufficiency or failure) [8, 9, 11]. Patients have a higher risk for developing TLS (defined as >5%) when the white blood count (WBC) is >50,000 for AML compared to >100,000 for ALL. Likewise, intermediate risk for developing TLS (1–5%) is seen with a WBC between 10,000–50,000 for AML and 50,000–100,000 in ALL. Patients are at a lower risk for developing TLS (<1%) when WBC is <10,000 in AML and <50,000 in ALL [8, 11].

TLS Classification and Grading

A classification system was previously developed to differentiate clinical tumor lysis syndrome (CTLS) and laboratory tumor lysis syndrome (LTLS) to help identify which patients may require immediate therapeutic intervention [3]. LTLS is present if patients have either serum levels above the high end of normal or a 25% change from baseline in two or more of the following lab values: uric acid, potassium, phosphate, and calcium within 3 days before or 7 days after starting chemotherapy. CTLS is defined by the presence of LTLS plus one or more of the three most significant clinical complications associated with TLS: renal insufficiency,

cardiac arrhythmias/sudden death, and/or seizures. Clinical signs of TLS may include nausea, vomiting, lethargy, edema, fluid overload, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, altered mental status, and/or death secondary to electrolyte abnormalities [6, 8, 9]. At diagnosis and during induction or re-induction chemotherapy, while patients are at greatest risk of developing TLS, vigilant electrolyte monitoring of serum uric acid, phosphate, potassium, creatinine, calcium, and lactate dehydrogenase (LDH) should be performed in addition to strict fluid management and monitoring total fluid input and urine output. Laboratory evaluations for TLS should begin every 4–6 h or more frequently based on the clinical condition and/or laboratory results in patients at risk for this oncologic complication [8, 11].

TLS Management

Aggressive hydration and diuresis are the main treatments of TLS to improve a patient's intravascular volume, maintain renal perfusion, and increase urinary flow. This enhances glomerular filtration and urinary excretion of uric acid and phosphate with the goal to decrease crystal formation [6, 8, 9]. Patients should receive 2–4 times of their daily fluid maintenance (3 L/m^2/d or 200 mL/kg/d if <10 kg) without the addition of potassium, calcium, or phosphate. Urine output should be maintained at >100 mL/m^2/h (>3 mL/kg/h if <10 kg) with a urine-specific gravity <1.010 [6, 9]. Diuretics may be required to maintain adequate urine output but are contraindicated in patients with hypovolemia or obstructive uropathy [8]. Although urine alkalinization was historically part of TLS management, it is no longer recommended as it can lead to metabolic alkalosis and worsen obstructive uropathies during the treatment of hyperuricemia [8, 9]. Below we will discuss each of the electrolyte derangements and treatment strategies which are also summarized in Table 2.1.

Hyperuricemia

After the release of intracellular nucleic acids into the bloodstream, adenine and guanine are metabolized to xanthine, which is then broken down to uric acid by the enzyme xanthine oxidase which results in hyperuricemia [12]. Hyperuricemia is defined as serum uric acid >476 μmol/L or 8 mg/dL [8, 9]. In the presence of an acidic urine, uric acid can crystallize in the renal tubules causing obstruction, which can lead to acute obstructive neuropathy and renal dysfunction [9].

There are multiple medications available for treatment of hyperuricemia in addition to aggressive IV hydration to help improve renal excretion. The most commonly used medication, allopurinol, inhibits xanthine oxidase and prevents formation of new uric acid; however it does not reduce elevated levels of pre-existing

Table 2.1 Electrolyte derangements associated with TLS and their management

Fluid management		Aggressive IV hydration (without K^+, phosphate or Ca^{+2}) at 2−4x maintenance rate (3 L/m^2/d or 200 mL/kg/d if ≤10 kg)
		Maintain urine output at ≥100 mL/m^2/h. (≥3 mL/kg/h if ≤10 kg) with a urine specific gravity ≤1.010
		Diuretics can be used to maintain urine output (furosemide 0.5–1.0 mg/kg) but are contraindicated in patients with hypovolemia or obstructive uropathy
Electrolyte abnormalities		Monitor serum uric acid, phosphate, potassium, creatinine, calcium, and LDH every 4–6 h
Hyperuricemia	≥476 μmol/L or 8 mg/dL or 25% increase from baseline	Allopurinol: 50–100 mg/m^2/dose PO every 8 h – maximum 300 mg/m^2/d or 10 mg/kg/d divided every 8 h – maximum dose 800 mg/d. Can be given IV 200–400 mg/m^2/day IV in 1–3 divided doses – maximum 600 mg/d
		Urate oxidase (rasburicase): 0.2 mg/kg IV daily to BID
Hyperkalemia	>6.0 mmol/L or > 6.0 mg/L or 25% increase from baseline	Asymptomatic: sodium polystyrene sulfonate (1 g/kg with 50% sorbitol)
		Symptomatic: insulin (0.1 units/kg IV) and glucose infusion (25% dextrose 2 mL/kg) or sodium bicarbonate (1 to 2 mEq/kg IV push)
		Arrhythmias: calcium gluconate (100 to 200 mg/kg/dose) by slow IV infusion (not through the same line as sodium bicarbonate due to the risk of precipitation)
		Dialysis if severe
Hyperphosphatemia	>2.1 mmol/L or 25% increase from baseline	Phosphate binders such as aluminum hydroxide (50–150 mg/kg/day PO or NG q6hr)
		Dialysis if severe
Hypocalcemia	≤1.75 mmol/L or 25% decrease from baseline	Symptomatic: calcium gluconate 50–100 mg/kg IV
Dialysis		Renal dysfunction
		Volume overload
		Persistent electrolyte derangements which do not respond to medical management
		Acidosis
		Uremia

uric acid [8, 9, 13]. Dosing for allopurinol ranges 50–100 mg/m^2/dose PO every 8 h (maximum 300 mg/m^2/d) or 10 mg/kg/d divided every 8 h (maximum dose 800 mg/d). In addition, allopurinol can be given 200–400 mg/m^2/day IV in one to three divided doses (maximum 600 mg/d) [8, 9]. When used prophylactically in pediatric patients with a variety of cancers including acute leukemia at high risk for

developing TLS, it prevented hyperuricemia in 92% of patients [14]. Allopurinol can be started prophylactically 12–24 h prior to the start of chemotherapy and continued for 3–7 days or until uric acid levels and other TLS labs have normalized and risk for ongoing TLS has decreased [8]. Limitations to the use of allopurinol include its inability to break down preformed uric acid; the associated increase in levels of xanthine and hypoxanthine, both of which have lower solubility in urine and can precipitate in the renal tubules; its interference with renal clearance of other purine chemotherapies (i.e., 6-mercaptopurine); and its renal excretion which requires a dose reduction in patients with renal failure [8, 9, 15, 16].

In patients with acute leukemia found to have hyperuricemia at diagnosis, treatment with recombinant urate oxidase (rasburicase) is indicated and allows for rapid breakdown of the pre-existing uric acid to allantoin which is renally excreted without precipitation [9, 15, 17]. Rasburicase (0.2 mg/kg) is administered IV once daily in 50 mL normal saline over 30 min and can be repeated daily or twice daily as needed. Clinical judgment should be used for duration of therapy based on response and subsequent uric acid levels [6, 8, 16]. Once rasburicase is given, blood samples to measure uric acid levels should be immediately placed on ice and run within 4 h of collection [8].

Rasburicase is more potent and faster-acting than allopurinol [16, 17]. Goldman et al. [16] performed a randomized study in children with acute leukemia and lymphoma comparing oral allopurinol to IV rasburicase which found that 4 h after the first dose, patients randomized to rasburicase had an 86% decrease in uric acid levels compared to a 12% decrease in the allopurinol group ($p < 0.0001$). In a retrospective review by Cairo et al. [13] comparing pediatric and adult patients with TLS treated with either allopurinol or rasburicase, the rasburicase group had more effective treatment of their hyperuricemia which was associated with significantly shorter ICU stays, overall hospital stays, and lower total inpatient costs. Rasburicase is contraindicated in patients with G6PD deficiency which can result in a hemolytic crisis when given.

Hyperkalemia

Hyperkalemia is defined as a serum potassium >6.0 mmol/L and results from massive cellular degradation and release of intracellular potassium [9]. Supplemental oral and IV potassium should be eliminated in patients at risk for TLS, and continuous cardiac monitoring should be used for patients who develop hyperkalemia. Immediate intervention may be required if levels are greater than 7.0–7.5 mmol/L or there is ECG evidence of widening QRS complexes or peaked T waves. Asymptomatic patients can be treated with sodium polystyrene sulfonate (1 g/kg with 50% sorbitol). Symptomatic patients can be treated with rapid-acting insulin (0.1 units/kg IV) and glucose infusion (25% dextrose 2 mL/kg) or sodium bicarbonate (1–2 mEq/kg IV push) to induce the influx of potassium into the cells. In patients with arrhythmias, calcium gluconate (100–200 mg/kg/dose) by slow IV infusion can be given, but not through the same line as sodium bicarbonate due to the risk of precipitation [6, 8, 11].

Hyperphosphatemia

Hyperphosphatemia secondary to release of intracellular phosphate can result in tissue precipitation after binding to calcium (calcium phosphate) which can lead to hypocalcemia, acute obstructive uropathy, and renal failure. Phosphorus levels >2.1 mmol/L should be treated with aggressive hydration and phosphate binders such as aluminum hydroxide 50–150 mg/kg/day enterally given every 6 h. If hyperphosphatemia is severe, patients should receive hemodialysis or continuous venovenous hemofiltration (CVVH) [6, 8, 11].

Hypocalcemia

Hypocalcemia occurs due to precipitation of calcium with phosphate in the setting of hyperphosphatemia and is defined as serum calcium <1.75 mmol/L [8, 9]. In general, treatment of asymptomatic hypocalcemia is not recommended due to the risk of increased precipitation with phosphate and worsening acute kidney injury. Typically, the hypocalcemia resolves without treatment as TLS improves. For patients who have symptomatic hypocalcemia causing muscular, cardiovascular, or neurologic complications, calcium gluconate (50–100 mg/kg IV) can be used for treatment; however, this will increase the risk of calcium phosphate precipitation and acute kidney injury such that the risks/benefits should be weighed for each patient [8, 9].

Indications for Dialysis

Although rasburicase has dramatically decreased the need for dialysis in patients with moderate/severe TLS, about 1.5% of pediatric patients still require this for renal insufficiency, volume overload, acidosis, persistent electrolyte derangements, and/or uremia which are not responsive to medical management [6, 9, 15]. Hemodialysis is the preferred modality for rapid clearance of potassium and uric acid in the setting of life-threatening hyperkalemia or hyperuricemia [9, 12, 18]. Otherwise, continuous renal replacement (CRRT) (such as continuous venovenous hemodialysis (CVVHD), CVVH, continuous arteriovenous hemofiltration (CAVHD), or continuous arteriovenous hemodialysis (CAVHD)) is preferred at high dialysate flow rates (3–4 L/h) to decrease the rate of rebound hyperkalemia and hyperphosphatemia [12, 18, 19]. CRRT is the preferred modality for hyperphosphatemia because clearance is time dependent [12, 19]. Peritoneal dialysis is generally not recommended in children with TLS due to its poor uric acid clearance [9, 12].

Hyperleukocytosis and Leukostasis

Hyperleukocytosis is defined as a WBC count greater than 100,000/mm^3 [20]. Symptoms and complications from hyperleukocytosis are secondary to leukostasis which is the accumulation of peripheral leukemic blasts in the vasculature resulting in increased blood viscosity, microvascular obstruction, and/or tissue hypoxia [20–22]. Interactions between blasts and endothelial cells which result in the secretion of cytokines and adhesion receptors are also thought to play a role in further blast recruitment and endothelial damage leading to leukostasis [20, 22, 23]. Although hyperleukocytosis is more common in ALL than AML, hyperviscosity and leukostasis occur at lower WBC counts in patients with AML (100,000/μL compared to >400,000/μL in ALL) resulting in higher rates of clinical symptoms and early death (9–16% for AML compared to 2–6% in ALL) [20–25]. This difference is likely secondary to the larger mean cell volume of myeloblasts (particularly FAB subtypes M4 and M5) which are twice as large as lymphoblasts and therefore cause a higher fractional volume of leukocytes and increased viscosity at a lower total WBC count [20, 22, 23]. For patients with AML, the following features have been associated with hyperleukocytosis: infants less than 1 year of age; FAB subtypes M1, M4, or M5; chromosomal rearrangements in 11q23; inversion chromosome 16; or having FLT3-ITD [20, 25]. For ALL, patients are at greater risk of developing hyperleukocytosis if they have infant ALL, T-cell ALL with a mediastinal mass, or if their leukemias have chromosomal rearrangements involving 11q23 or translocations of t(4:11), t(1:19), and t(9:22) or loss of p16 [20, 22].

The higher rates of early morbidity and mortality seen in patients with hyperleukocytosis are attributed to intraparenchymal brain hemorrhage, pulmonary leukostasis syndrome (defined as infiltrates on chest x-ray, tachypnea, and hypoxia), severe TLS, and/or disseminated intravascular coagulopathy (DIC) [20–22]. Due to this risk of early mortality, children presenting with WBC counts over 100,000/μL should be evaluated for symptoms of hyperleukocytosis and leukostasis including respiratory distress, hypoxemia, diffuse interstitial or alveolar infiltrates, altered mental status, headache, dizziness, visual field changes, seizures, signs of right ventricular overload, myocardial ischemia, priapism, acute limb ischemia, bowel infarctions, and renal vein thrombosis [20, 22].

Treatment of hyperleukocytosis focuses on aggressive hyperhydration (2–4 times maintenance fluids), treatment of any underlying TLS, and prompt cytoreduction of the leukemia which can be achieved with leukapheresis, hydroxyurea, and/or induction chemotherapy [6, 20, 22, 23, 25]. One particular problem in hyperleukocytosis is that if the WBC count is not reduced prior to the start of induction chemotherapy, leukostasis, TLS, and DIC can be further worsened with treatment [22]. In this setting, hydroxyurea can be very efficient in reducing the WBC count, often by 50–80% within 24–48 hours, and can be given orally at doses of 50–100 mg/kg/day [20]. Leukapheresis can be a life-saving procedure in which WBCs are rapidly removed from the peripheral circulation and plasma, while the

RBCs and platelets are returned to the patient through a closed-circuit cell apheresis [22, 23]. The main indication for this is evidence of leukostasis-related complications [22]. The use of leukapheresis in asymptomatic hyperleukocytosis is controversial, and there has been no general consensus regarding its prophylactic use for the prevention of leukostasis in pediatric leukemia. Additionally, leukapheresis is not recommended for treatment of patients with acute promyelocytic leukemia (APL) due to its association with worsening of the coagulopathy and increased risk of death [6, 23].

To date, there have been no randomized trials evaluating the benefits of leukapheresis, and there are currently no guidelines for when or how long to use it once it has been initiated in pediatrics [20, 23]. One study that examined the early complications in hyperleukocytosis and leukapheresis in patients with pediatric leukemia demonstrated that leukapheresis resulted in an average WBC count reduction of 53%, and there was no significant difference in responses to induction treatment in patients who underwent leukapheresis compared to those who did not [23]. Another recent Children's Oncology Group (COG) study of patients with AML demonstrated that leukapheresis did not reduce induction mortality [25]. Potential disadvantages of leukapheresis include requiring placement of a large bore central venous catheter which may require anesthesia and can predispose patients to bleeding or thrombosis at the catheter site; limited availability for apheresis at the pediatric center; patient blood loss; fragmentation of the WBCs leading to possible DIC and early death; requiring citrate as the anticoagulant in the apheresis circuit which can lead to hypocalcemia; and/or the potential delay of induction chemotherapy while awaiting apheresis [20, 23]. Additionally, packed red blood cell (PRBC) transfusions and high hemoglobin concentrations in patients with hyperleukocytosis can result in increased blood viscosity and have been associated with worsening leukostasis and increased morbidity and mortality [6, 20–23, 25]. Therefore, PRBCs should be transfused cautiously, and only after treatment for hyperleukocytosis is initiated as long as the patient is hemodynamically stable. Because severe thrombocytopenia is a known risk factor for central nervous system (CNS) hemorrhage in patients with hyperleukocytosis [26] and platelets do not significantly add to blood viscosity [6], platelets should be transfused liberally for the treatment of thrombocytopenia [25] to maintain a platelet goal of >50,000 in the setting of hyperleukocytosis.

Mediastinal Masses and Superior Vena Cava Syndrome

Anterior mediastinal masses are characteristic of T-cell ALL and estimated to occur in 53–64% of newly diagnosed pediatric patients [27]. These masses, caused by thymic enlargement, can result in compression of the trachea and/or mediastinal vessels and heart, leading to superior vena cava syndrome (SVCS) and cardiorespiratory compromise [27, 28]. The superior vena cava carries blood from the head, arms, and upper torso to the heart, supplying one third of the body's venous return [29]. Compression of this vessel can cause increased venous pressure in the upper

body resulting in edema of the head, neck, and arms, often with cyanosis, plethora, and distended superficial vessels leading to thrombosis, cerebral edema, and/or hemodynamic instability secondary to decreased venous return [29]. As the trachea and the right mainstem bronchus are more compressible in children, especially in infants and toddlers compared to adults, respiratory symptoms can be more pronounced [29]. Common clinical signs of a mediastinal mass include shortness of breath, cough, stridor, respiratory distress, orthopnea, dyspnea, chest pain, syncope, hoarseness, and dysphagia, all of which may be worsened by the supine position [30–33].

As part of the work-up for newly diagnosed patients with acute leukemia, posterior-anterior and lateral chest x-rays should be performed to evaluate for the presence of a mediastinal mass. In patients who are found to have mediastinal widening or cardiorespiratory symptoms, chest computed tomography (CT) with contrast and echocardiogram can be performed (as long as the patient is clinically stable) in order to assess the severity of cardiopulmonary compression (Fig. 2.1) [28, 30]. The CT can be performed in the prone position if the supine position exacerbates symptoms [6]. Anterior mediastinal masses can be due to other malignancies as well including Hodgkin and non-Hodgkin lymphoma and less frequently neuroblastoma, germ cell tumors, or other sarcomas [2].

Children with anterior mediastinal masses may be at significant risk of life-threatening complications from general anesthesia, including death from airway obstruction and cardiovascular collapse which is estimated to occur in 15% of cases [30, 34, 35]. This is primarily due to direct airway compression, decreased lung volumes and compliance, loss of normal bronchial smooth muscle tone, and loss of normal negative pressure on the trachea with inspiration. In addition, there is the

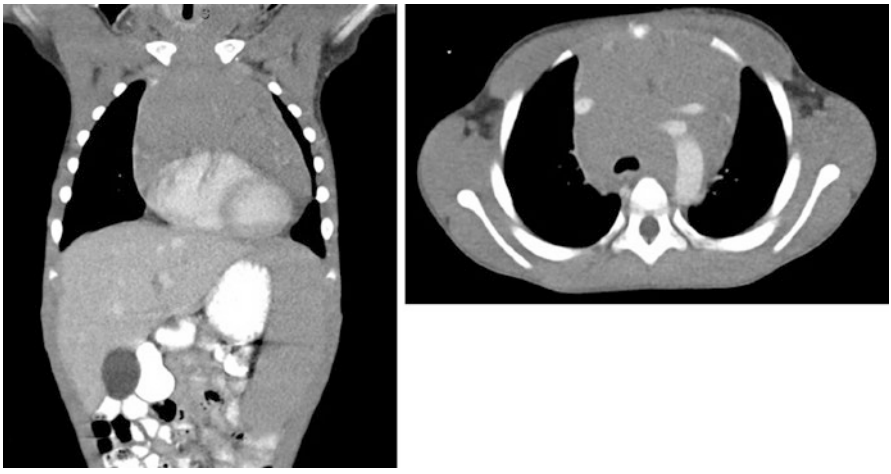

Fig. 2.1 CT images of patient with T-cell ALL demonstrate a large anterior mediastinal mass measuring approximately 8.8 cm × 3.3 cm and causing narrowing and mass effect on the SVC, brachiocephalic veins, and trachea

potential for cardiac compression, decreased venous return, and decreased cardiac output [28, 34, 36]. Conscious sedation and anti-anxiolytics may also be contraindicated as they can decrease respiratory drive and dilate peripheral vessels which can lead to decreased venous return [6]. Children are at greater risk of anesthetic complications if their mediastinal mass is >45% of the chest diameter; they have orthopnea or acute respiratory distress, have compression of the mainstem bronchus, and/or have a tracheal cross-sectional area <50% predicted or evidence of SVCS [28, 31, 33, 34]. Management of airway collapse in these patients can be extremely difficult as masses at or below the level of the carina may cause an inability to ventilate or oxygenate despite endotracheal intubation [28]. Recommendations for children with mediastinal masses who are undergoing general anesthesia include maintenance of spontaneous ventilation, avoidance of muscle relaxants, immediate availability of airway manipulation tools (reinforced tracheal tubes, mainstem bronchus intubation, rigid bronchoscopy), and the availability of heliox and cardiopulmonary bypass [31]. Arterial extracorporeal membrane oxygenation (ECMO) has been successfully used to support a patient through diagnosis and treatment of their mediastinal mass [37].

Management of SVCS and airway compression caused by a leukemic mediastinal mass involves treatment of the underlying malignancy with chemotherapy which results in the mass rapidly shrinking over a period of days to weeks [29, 33, 34]. Intravenous corticosteroids (methylprednisolone or dexamethasone 1 mg/kg every 6 hours) should be given empirically to patients who have respiratory or cardiovascular compromise [32, 33, 36]. In addition, tumor lysis syndrome precautions should be initiated when steroid treatment is started [6]. Supportive care management includes elevation of the head of the bed to decrease hydrostatic pressure, supplemental oxygen, and anticoagulation for any thrombosis-related SVC obstruction [32].

CNS Emergencies

Patients with acute leukemia may be at increased risk for CNS complications either from the leukemia itself or the therapy required to treat it. These can range from arterial/venous thrombosis, intracranial hemorrhage (ICH), CNS leukemia (often in the setting of hyperleukocytosis), chemotherapy-related toxicities effecting the CNS, cranial irradiation, and leukemia-associated coagulopathies or infection [6].

In regard to ICH, patients at greatest risk include those with acute promyelocytic leukemia (APL) as a result of the significant coagulopathy associated with this form of AML and patients with hyperleukocytosis (WBC >400,000 × 10^9/L in ALL [21]; WBC >100,000 × 10^9/L in AML [20]), secondary to hyperviscosity and subsequent leukostasis [6, 38]. Patients with ICH typically present with altered mental status, acute motor and/or speech impairments, headache, vomiting, and/or seizures [6]. Treatment in both of these cases is primarily supportive with platelets and plasma to correct the coagulopathy and minimize further bleeding with the potential for leu-

kapheresis to decrease blood viscosity in cases of hyperleukocytosis [6]. In cases where the CNS event escalates to increased intracranial pressure and the risk of herniation exists, emergent neurosurgical intervention may be necessary.

Systemic and intrathecal chemotherapy as well as CNS irradiation can result in arterial ischemic strokes and/or venous thromboembolism [6]. Venous thromboembolism can be relatively common in patients with acute leukemia and is discussed in further detail in the thrombosis section of this chapter. In patients who experience an arterial ischemic stroke, treatment is often supportive and aimed at maximizing cerebral perfusion. Typically, patients are maintained in the supine position for 48 hours and kept normothermic, normoglycemic, and normotensive or minimally hypertensive with adequate circulating blood volumes to minimize morbidities and potential mortality [6]. Data supporting the safety and efficacy of thrombolytic therapy in pediatric patients with arterial thrombosis is lacking and therefore has not been routinely recommended.

Methotrexate, an antimetabolite which inhibits folate synthesis, is associated with a 3–15% incidence of neurotoxicity in patients with leukemia which includes subacute leukoencephalopathy [38]. The mechanism is thought to be disruption of CNS folate homeostasis and/or direct neuronal damage from the cytotoxic agents [39]. Patients can present with transient stroke-like hemiparesis and/or weakness, encephalopathy, seizures, aphasia, and emotional liability that can wax and wane and typically develops 2–14 days after receiving methotrexate either intravenously or intrathecally [38, 39]. If MRI of the brain is performed, it typically demonstrates characteristic white matter hyperintensities on T2-weighted and fluid-attenuated inversion recovery consistent with cytotoxic edema in the white matter tracts [38, 39]. The CSF is typically normal, and electroencephalogram (EEG), when performed, shows nonspecific diffuse or focal slowing [38]. Most neurologic symptoms will resolve within 7 days including MRI findings returning to normal. Additionally, patients typically will tolerate subsequent methotrexate treatment without recurrence of similar CNS symptoms [38, 39].

Cytarabine, a pyrimidine nucleoside analogue, commonly given in high systemic doses or intrathecally for patients with AML, can also cause an acute encephalopathy characterized by cerebellar dysfunction with dysarthria, nystagmus, gait ataxia, confusion, and/or somnolence 2–5 days after treatment. MRI of the brain may demonstrate white matter changes in the cerebellum, and CSF studies are typically normal [38]. Symptoms tend to improve over the course of weeks; however, complete resolution of symptoms is seen in only 30% of patients, and further cytarabine treatment is often excluded [38]. Intrathecal chemotherapy, in general, can cause an aseptic meningitis or chemical arachnoiditis which affects up to 10% of patients with leukemia. Patients typically present with headache, meningismus, nausea, vomiting, fever, and/or altered mental status where the CSF analysis shows a pleocytosis with negative cultures. Clinical care is again predominantly supportive, and patients can typically go on to receive further intrathecal chemotherapy without additional complications [38].

Nelarabine, a purine analogue used in the treatment of T-cell ALL, has been associated with acute neurotoxicity characterized by Guillain-Barre-like demyelin-

ating ascending neuropathy which occurred in 1.3% of pediatric patients during the early phase trials [40–42]. When this occurs, care is supportive, and symptoms generally seem to be reversible after discontinuation of this medication; however, reports of death do exist [40].

Posterior reversible encephalopathy (PRES) can also be seen in patients undergoing leukemia treatment. This reversible neurologic complication is characterized by headache, altered mental status, seizure, vision changes, and brain MRI white matter changes in the bilateral parieto-occipital lobes [38, 43, 44]. The underlying mechanism is not fully understood but is proposed to be related to sudden elevations in blood pressure and medication-induced vascular endothelial damage resulting in capillary leakage and vasogenic edema [38, 43]. Patients are at greater risk of PRES if they have hypertension and renal impairment or are on specific immunosuppressive medications such as calcineurin inhibitors in patients treated with hematopoietic cell transplantation [38, 43]. This complication occurs most commonly during induction therapy where high-dose steroids are given but has been associated with other chemotherapeutic medications including vincristine, intrathecal methotrexate, cytarabine, and asparaginase [38, 43]. This condition is reversible when recognized promptly and is highly treatable with antihypertensive and antiepileptic medications [38, 43]. In most cases, PRES resolves in about 48 hours with the brain MRI findings resolving over 3–6 months [44].

Other causes for seizures in patient with leukemia which have not already been discussed include electrolyte disturbances (e.g., hyponatremia secondary to vincristine-induced SIADH), CNS leukemia, and primary CNS infections. The evaluation of patients presenting with seizures should include at a minimum, a CBC, electrolyte, creatinine, BUN, hepatic function panel, and coagulation profile in addition to CNS imaging and an EEG once the patient has been stabilized. Electrolyte derangements should be corrected, anticonvulsant therapy should be used, and antibiotics and antifungal medications are indicated in patients with fevers and meningeal signs and those in whom infection is a concern [6].

Spinal cord compression secondary to epidural involvement of leukemia (most often with chloromas) is a very rare presentation of acute leukemia or relapsed disease and is more commonly seen in patients with AML; however, case reports in ALL exist [45–47]. Spinal hematomas resulting in cord compression can be a complication of lumbar punctures, particularly in patients who have profound thrombocytopenia and/or coagulopathy [48]. Symptoms of spinal cord compression can include back pain, extremity weakness, sensory abnormalities, paralysis, and urinary or fecal incontinence/retention [6]. Early symptom recognition is critical and essential to achieve better outcomes of spinal cord compression-related symptoms [46]. MRI of the spine remains the gold standard for diagnosis [6]. Initial treatment includes dexamethasone to decrease vasogenic cord edema (pediatric dosing of 1–2 mg/kg followed by 0.25–0.5 mg/kg every 6 hours has been suggested) followed by chemotherapy, radiation, and/or surgery to reduce or remove the mass [6, 45, 46].

Thrombosis

Venous thrombosis (VT) can be a relatively common complication of treatment in children with acute leukemia. A meta-analysis of 1,752 pediatric patients with acute leukemia from 17 prospective trials demonstrated an incidence of 5.2% for symptomatic thrombosis [49]. Risk factors for thrombosis include the underlying leukemia burden, presence of central venous catheters (CVL), chemotherapy-induced coagulation defects, and/or pro-thrombotic hereditary risk factors [49, 50]. The most common sites of thrombosis include central venous catheters (usually in the upper extremities) and the cerebral venous sinuses [49, 51]. Line-associated thromboses typically present with upper extremity pain or swelling and CVL dysfunction, whereas sinus venous thromboses present with headache, seizure, and/or acute neurologic changes [50]. The risk for thrombosis development is greatest during induction therapy for ALL when patients have their highest leukemia burden while undergoing cytolysis from the chemotherapy which includes asparaginase and glucocorticoids, both known to raise the risk VT [49, 51]. Glucocorticoids increase pro-clotting factor VIII and von Willebrand factor and decrease plasminogen and alpha-2 plasmin, both of which have fibrinolytic effects [52]. Asparaginase depletes several hemostatic proteins including plasminogen, antithrombin, and fibrinogen which increase the risk of thrombosis [53]. Reexposure to asparaginase is feasible and safe in patients who have previously developed an asparaginase-associated VT and is typically given in conjunction with anticoagulation once the previous thrombosis has resolved [50, 51].

The pediatric CHEST guidelines suggest that anticoagulation for thrombosis should be with either (1) low-molecular-weight heparin (LMWH) or (2) unfractionated heparin (UFH) followed by LMWH for a minimum of 3 months until the precipitating factor has resolved (e.g., use of asparaginase) [54]. But therapy must be tailored to the individual patient. Therapeutic LMWH heparin is typically started at 1 mg/kg/dose every 12 h and should be monitored to target anti-Xa activity (range, 0.5–1.0 units/mL) in a serum sample taken 4–6 hours after subcutaneous injection (>3rd dose) [54]. As the mechanism of heparin anticoagulation involves antithrombin III (AT), some centers periodically monitor AT levels during anticoagulation and replete when levels fall below 50–75% [2]. Thrombolysis therapy should be used only for life- or limb-threatening thrombosis [54]. Because a CVL generally remains in place in these patients, prophylactic LMWH anticoagulation is often continued until the line is removed; however, the risk-benefit ratio for treatment of VT should be evaluated on an individual basis in this complex patient population [54]. The risk of bleeding complications in pediatric patients with leukemia on anticoagulation is relatively low at 2%, and thus often the benefit of preventing further thrombosis may outweigh the potential risk of bleeding [49].

Typhlitis

Typhlitis, also known as neutropenic enterocolitis, is an important gastrointestinal complication observed in patients with acute leukemia characterized by abdominal pain, fever, and neutropenia [6, 55, 56]. Abdominal distension, diarrhea, nausea, vomiting, and GI bleeding can also occur, and symptoms typically improve rapidly upon neutrophil recovery [6, 55, 57, 58]. The incidence is estimated to be ~10% in pediatric patients with leukemia and is seen more frequently in patients with AML compared to those with ALL. It is important to note that typhlitis is associated with a 5–20% mortality rate, most often from sepsis [55–57, 59].

The pathogenesis of typhlitis is thought to be multifactorial. The most common associations include chemotherapy, underlying immunosuppression, mucositis, impaired vascular blood flow to the intestines, and/or bacterial overgrowth and translocation leading to bowel wall edema, mucosal ulceration, and necrosis. This pathology most often affects the cecum and transverse colon, although other areas of the colon and the rectum can be involved [6, 55–57]. Symptoms can be diagnosed clinically or by imaging with abdominal CT or ultrasound which can demonstrate bowel wall edema and, in advanced stages, pneumatosis and/or abdominal free air [6, 56]. Bacteremia and sepsis are common complications of typhlitis with the most likely causative organisms being *Pseudomonas* species, *Escherichia coli*, *Clostridium* species, *Staphylococcus* species, *Streptococcus* species, and *Enterococcus* species [6]. Fungal pathogens as the causative organism in typhlitis, including *Candida* and *Aspergillus* species, are less common but have been reported [6].

Overall outcomes for typhlitis tend to be good with conservative medical management alone which includes bowel rest, parenteral nutrition, abdominal decompression, and broad-spectrum antibiotics to cover gram-negative organisms, anaerobes, and fungi, with the occasional use of granulocyte colony-stimulating factor (G-CSF) to improve neutrophil recovery [6, 55–58]. Surgical intervention is required in 4–8% of cases due to clinical deterioration despite conservative management, the presence of bowel necrosis, complete bowel obstruction, intestinal perforation, and/or abdominal abscess requiring drainage [6, 56, 58, 60].

A retrospective chart review of a large pediatric center in the United Kingdom identified 40 oncology patients who developed typhlitis during a 5-year period, 67% of whom had a diagnosis of acute leukemia [56]. One hundred percent of these patients presented with abdominal pain, and 78% presented with the typical triad of fever, abdominal pain, and neutropenia. Thirty-seven patients (92.5%) were treated with conservative medical management, and three patients required surgery (bowel necrosis ($n = 1$) and bowel perforation ($n = 2$)). One child died within 24 h of the diagnosis of typhlitis in the conservatively treated group due to *Pseudomonas aeruginosa* septicemia. A second retrospective chart review of children with acute leukemia over a 3-year period at a single pediatric institution identified a 4.5% incidence of typhlitis (10 patients) in patients who were admitted with neutropenic fever, 7.4% of patients with ALL, and 28.5% of patients with AML [57]. Again, 100% of

patients presented with abdominal pain and 90% had fever and nausea. The median duration of symptoms was 6 days (range, 2–11 days), and median period of neutropenia was 14 days (range, 3–25 days). All patients in this cohort were treated conservatively with medical management. Three patients developed bacteremia with *Candida* species (1), *E. coli* (1), and *viridans* group strep (1), and two died of sepsis with multi-organ failure. Overall, typhlitis in a child with acute leukemia can be successfully treated with conservative management; however, early diagnosis and treatment remain critical to mitigate potential mortality.

Pancreatitis

Between 2 and 18% of patients treated with asparaginase, an essential chemotherapeutic agent in the treatment of ALL, develop acute pancreatitis, which is a cause of substantial morbidity [6, 61–64]. Asparaginase, available in three commercial formulations (native *E. coli* L-asparaginase, pegylated-asparaginase, and *Erwinia* L-asparaginase), works by reducing plasma concentrations of asparagine by metabolizing it into aspartic acid and ammonia. This asparagine depletion results in the deprivation of this amino acid in the leukemic blasts resulting in cell death [61, 63]. The use of asparaginase in multi-agent chemotherapy regimens has improved survival in ALL, and early discontinuation of this therapy, most commonly the result of hypersensitivity or pancreatitis, has been associated with inferior outcomes [63, 65, 66].

Pancreatitis typically occurs within 2 weeks of asparaginase exposure where patients present with a constellation of symptoms that can include abdominal pain, nausea, vomiting, fever, back pain, hypotension, elevated serum amylase and lipase (at least three times the upper limit of normal), and/or characteristic findings of pancreatitis on abdominal imaging [62, 64]. In severe cases, acute pancreatitis can lead to a systemic inflammatory response (SIRS) resulting in pancreatic hemorrhage, necrosis, intestinal perforation, and/or sepsis and carries a 2% overall mortality rate [62]. Late complications of asparaginase-associated pancreatitis include the development of pancreatic pseudocysts, insulin-dependent diabetes, and chronic/relapsing pancreatitis or abdominal pain [62, 64]. Treatment of acute pancreatitis is predominantly supportive management with fluid resuscitation, broad-spectrum antibiotics to cover gram-negative and anaerobic organisms (at least until an infection can be ruled out), complete bowel rest, parenteral nutrition, IV narcotics for pain control, and close clinical monitoring for further complications [6, 64]. Fortunately, most cases of asparaginase-associated pancreatitis are self-limited and can be treated medically; however, surgical drainage of pancreatic abscesses, pseudocyst, or necrotizing pancreatitis may be required based on the patient's clinical course, presence of obstruction, and/or severe abdominal pain [6]. Further treatment with asparaginase should be discontinued in cases of severe grade 3–4 pancreatitis, as there is an almost 50% risk of subsequent pancreatitis with asparaginase reexposure [62, 64].

Acute Promyelocytic Leukemia and Differentiation Syndrome

Acute promyelocytic leukemia (APL) is a subtype of AML occurring in 5–10% of children with de novo AML, characterized by a block in differentiation at the promyelocytic stage of hematopoiesis caused by a reciprocal translocation between the promyelocytic (PML) gene on chromosome 15 and the retinoic receptor α (RAR-α) gene on chromosome 17 [67, 68]. APL is considered a medical emergency and, in pediatrics, can be associated with a 7.4% risk of death during induction therapy due to profound disseminated intravascular coagulopathy (DIC) and differentiation syndrome [67, 69–71]. Treatment for the coagulopathy is early initiation of chemotherapy and aggressive replacement of coagulation factors with fresh frozen plasma, fibrinogen, and/or cryoprecipitate in addition to platelet transfusions to maintain fibrinogen concentration above 100–150 mg/dL, platelets above $>50 \times 10^9$/L, and PT/PTT near-normal range [68–70]. Leukapheresis must be avoided in this patient population due to increased risk of fatal hemorrhage secondary to the overwhelming release of anticoagulant factors from leukemic cells during the pheresis procedure [69].

All-trans retinoic acid (ATRA) and arsenic (ATO) therapy have become the standard of care in standard-risk APL patients to differentiate the leukemic promyelocytes into mature granulocytes [68, 70]. In high-risk patients, ATRA in combination with anthracycline-based chemotherapy has led to significantly improved outcomes for this disease with 10-year overall survival of 89% and event-free survival of 76% [72]. ATRA should be started at the first suspicion of APL at a pediatric dose of 25 mg/m^2 divided twice a day [68, 72].

Differentiation syndrome (DS), formerly known as retinoic acid syndrome, is a relatively common and serious complication occurring in 10–20% of pediatric patients with APL who are receiving induction therapy with ATRA and/or ATO and is associated with a 4% risk of death [70]. It is clinically characterized by unexplained fever, weight gain, peripheral edema, dyspnea with interstitial pulmonary infiltrates, pleuro-pericardial effusions, hypotension, and/or renal failure [6, 69, 70, 73]. These symptoms can occur at any time within days to weeks of starting ATRA or ATO, with most frequent occurrences in the first and third weeks of treatment [73]. Patients with a WBC >10,000/μL (considered high risk) are at increased risk of this complication [68, 73]. The pathogenesis of DS is not fully understood but is thought that ATRA/ATO therapy may lead to a systemic inflammatory response syndrome (SIRS), endothelial damage with capillary leak and occlusion of the microcirculation, and tissue infiltration, resulting in the DS phenotype [73]. At the earliest clinical suspicion of DS, dexamethasone 0.5–1 mg/kg (max 10 mg per dose) IV every 12 h should be started to help mitigate the syndrome [69]. ATRA, ATO, and other chemotherapy should only be stopped if symptoms are life-threatening and should be resumed when symptoms resolve [69, 73]. Prophylactic use of steroids in patients with APL and an elevated WBC count has been associated with decreased morbidity from DS in adults with APL, but due to a lack of data in pediatrics, this practice remains controversial in children [6, 70].

Conclusion

Due to large collaborative and international randomized clinical trials conducted by the COG and other pediatric consortia over the past 50 years, survival rates of children with acute leukemia have significantly improved. However, these patients continue to suffer from disease-related and treatment-related complications associated with a 2–4% death rate, often requiring ICU management. To further decrease these toxicities and risk of death, research has been aimed at identifying potential genetic risk factors and certain phenotypic patient subsets that might predispose one to develop certain acute organ toxicities and/or disease-related complications. If discoveries could be made, such as identifying a genetic polymorphism to a specific chemotherapeutic agent predicting increased toxicity, guidelines could be developed for treatment adaptation to decrease treatment-related toxicities and long-term organ effects which would improve the overall quality of life for these patients. Leukemia treatment in the next decade will incorporate cellular-based therapies including chimeric antigen receptor therapies. This treatment modality has a unique set of toxicities which will be reviewed elsewhere in this textbook.

In summary, a myriad of possible serious disease and/or treatment-related complications exist for children and young adults with acute leukemia, many of which may necessitate ICU management. This chapter outlined the diagnosis and management of these oncologic emergencies, most of which can be successfully treated through a team-based approach incorporating both oncology and ICU care.

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