Critical Care of the Pediatric Immunocompromised Hematology/Oncology Patient

An Evidence-Based Guide

Christine N. Duncan
Julie-An M. Talano
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To families of children with cancer and hematological disorders that we have cared for in our ICUs

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Part II Critical Care Management

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Part I
Predisposing Diseases and Specific Considerations in Critical Illness

Chapter 1
The Changing Landscape of the Critical Care of Pediatric Immunocompromised Hematology and Oncology Patients

Christine N. Duncan

Immunocompromised children and adolescent patients who have hematologic or oncologic diseases represent a small percentage of patients treated in pediatric intensive care units (PICUs) but have a disproportionately high mortality rate. A single-center study of 1278 patients admitted to a pediatric hematology-oncology service over an 11-year period found an admission rate of 4.2% with an overall PICU mortality rate of 38.9% [1]. Risk factors for PICU admission included older age, diagnosis of nonmalignant disease, and treatment with HCT. A more recent retrospective multicenter cohort analysis of almost 250,000 consecutive PICU admissions using the Virtual PICU Systems database identified 10,365 patients diagnosed with a malignancy who were admitted to PICUs for reasons other than perioperative admissions during the study period [2]. Children with cancer accounted for 11.4% of all PICU deaths and had mortality of 6.8% (43% in those who were mechanically ventilated) compared to 2.4% in patients without malignancy.

Outcome data regarding patients admitted to PICUs who have nonmalignant hematologic or immunologic diseases is limited, with the exception of those treated with hematopoietic cell transplantation (HCT). Far more is known about patients with oncologic diagnoses, and the literature is most robust regarding those treated with HCT. The survival of children with hematologic and oncologic diseases has improved in recent years despite remaining higher than those of other patients treated in the PICU (Table 1.1). A meta-analysis of mortality trends of children treated in the PICU after HCT over time showed a significant decrease in mortality associated with the year of inclusion as did a large single-center study comparing outcomes over time [3, 4]. However, interpreting comparisons of mortality across multiple

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Table 1.1 Published mortality of hematology, oncology, and HCT patients over time

Reference	Study period	Population	Number of PICU patients	PICU mortality (%)
Hayes et al. [5]	1987–1997	HCT	39	73
Hallahan et al. [6]	1987–1996	Oncology and HCT	150	27
Diaz De Heredia et al. [7]	1991–1995	HCT	31	45
Lamas et al. [8]	1991–2000	HCT	44	70
Kache et al. [9]	1992–2004	HCT	81	82 (1992–1999) 41 (2000–2004)
Cheuk et al. [10]	1992–2002	HCT	19	84
Diaz et al. [11]	1993–2001	HCT	42	69
Jacobe et al. [12]	1994–1998	HCT	40	44
Heying et al. [13]	1995–1999	Oncology (no HCT)	48	25
Tamburro et al. [4]	1996–2004	Oncology and HCT	329	41
Tomaske et al. [14]	1998–2001	HCT	26	58
Gonzalez-Vincent et al. [15]	1998–2002	HCT	36	53
Hassan et al. [16]	1998–2008	HCT	19	17
Faraci et al. [1]	1999–2010	Hematology/ oncology	54	39
Asperberro et al. [17]	2000–2006	HCT	53	51
Bartram et al. [18]	2000–2008	Sickle cell disease	46	7
Chima et al. [19]	2004–2010	HCT	155	37
Duncan et al. [20]	2005–2006	HCT	129	38
Zinter et al. [21]	2009–2012	HCT	1102	16.2
Zinter et al. [2]	2009–2012	Oncology	10,365	6.8
Rowan et al. [22]	2009–2014	HCT	222	60

HCT hematopoietic cell transplantation

studies must be done with caution. The published literature is comprised almost exclusively of retrospective studies, and the inclusion criteria are not consistent across studies. Some studies include only those felt to be at highest risk for worst outcome, specifically HCT patients supported with mechanical ventilation, whereas others include patients with all oncology diagnoses and admitted to the PICU for all indications. There are multiple reasons for the improved outcomes including scientific advances in critical care, hematology, oncology, and HCT. Equally important have been advances in supportive care and infectious disease management.

The severity of illness of immunocompromised hematology and oncology patients admitted to PICUs is broad including planned postoperative admissions, semi-urgent admissions of patients with worsening illness, and the emergent transfer of rapidly decompensating children. Equally broad are the reasons for critical

illness in this diverse population including infection, organ compromise, and complications of the primary disease. The management of critically ill immunocompromised children and adolescents must be guided by the primary disease and patient's treatment. General principles of the initial management and stabilization of critically ill hematology and oncology patients, in most cases, can follow practices applied to other children. Thereafter, the management is strongly influenced not only by the reason for the need for critical care, but by the unique features of the underlying disease as well. For example, the early care of a child with sickle cell anemia experiencing acute respiratory dysfunction may mirror that of a patient with acute lymphoblastic leukemia or one with severe combined immune deficiency. After the primary stabilization of the patient, an understanding of the underlying disease is key to the next steps of diagnosis and management. In the example, one may consider acute chest syndrome as the cause of the respiratory distress in the patient with sickle cell anemia. Clearly this would not be on the list of potential etiologies in a child with leukemia in whom infection may be a chief concern. The therapy that the child receives to treat the primary disease is important as the critical illness may be a direct result or influenced heavily by the treatment. A clear example is that of children undergoing HCT who may have organ compromise, bleeding, infection, graft-versus-host disease, and other toxicities related to the recent and past therapy in addition to underlying comorbidities.

A goal of this textbook is to provide an understanding of the specific aspects of different diagnoses and therapies that impact the critical care of immunocompromised hematology and oncology patients. It is unrealistic to expect PICU providers to have a comprehensive understanding of all the diseases and therapies used in this population and for hematologists-oncologists to fully understand advances in ICU care. This is particularly true given the rapidly changing landscape of pediatric hematologic and oncologic care. Recent years have seen the development and expanded use of molecularly targeted medications, chimeric antigen receptor T-cell (CAR-T) therapy, and gene therapy. Each of these and other emerging therapies carry unique risks. Because of the complexity of diagnoses and treatment, a collaborative relationship between the PICU and the disease-specific teams is important to the care of these patients. Different models for cooperative care are addressed later in this text.

Multiple research consortia including the Pediatric Acute Lung Injury and Sepsis Investigators and Pediatric Blood and Marrow Transplant Consortium have focused on the care of immunocompromised hematology and oncology patients. The work of these and other groups is important as the community works to improve the survival of these vulnerable patients.

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Chapter 2
Diagnosis and Treatment-Related Complications of Acute Leukemia

Lauren Pommert, Steven Margossian, and Michael Burke

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