

## Emergencies in Pediatric Oncology

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Every year 165 children and adolescents per million under the age of 19 are diagnosed with cancer. Childhood cancer long-term survival rate has dramatically changed within the past five decades, from less than 20% before 1970's to more than 80% nowadays. These excellent outcomes are due to well-designed international cooperative trials, new therapies and aggressive multimodal treatment strategies as well as enhanced supportive care. The early recognition and the appropriate management of emergent cancer- and anticancer therapy-related complications are critical in maintaining and further improving outcomes for children with malignancies. Oncologic emergencies in pediatric patients can occur at any point in the course of the disease. Some emergencies are the initial presentation, some arise in the patient with an established diagnosis as complications of therapy, and some develop at the time of disease progression or recurrence.

The emergencies can be classified to mechanical, metabolic and hematologic. Mechanical oncologic emergencies are usually divided by system to cardiothoracic (superior vena cava syndrome and superior mediastinal syndrome, cardiac tamponade, pleural and pericardial effusions, pneumothorax and pneumomediastinum), gastrointestinal (gastrointestinal hemorrhage, bowel obstruction and perforation, neutropenic enterocolitis or typhlitis, cholecystitis and biliary obstruction, pancreatitis, hepatic sinusoidal obstruction syndrome or veno-occlusive disease), genitourinary (obstruction of the urinary tract, acute renal failure, renal vein thrombosis), and neurologic (increased intracranial pressure, spinal cord compression, acute alterations in consciousness, cerebral arterial or venous thrombosis, intracerebral hemorrhage, seizures). Metabolic emergencies comprise tumor lysis syndrome, hypercalcemia and syndrome of inappropriate secretion of antidiuretic hormone/hyponatremia). Hematologic emergencies include hyperleukocytosis (associated with metabolic derangements accompanying tumor lysis syndrome and possible pulmonary leukostasis and intracranial hemorrhage or thrombosis), emergencies associated with cytopenias (thrombocytopenia with hemorrhage, neutropenia with severe infectious complications) and abnormalities of hemostasis (disseminated intravascular coagulation, thrombosis) [1,2].

This article briefly describes the most common emergencies in pediatric oncology. The awareness and the working knowledge of all care providers are critical in achieving good outcomes for children with malignancies.

*Superior vena cava syndrome (SVCS) and superior mediastinal syndrome (SMS).* SVCS refers to the signs and symptoms resulting from compression or obstruction of the superior vena cava. Primary SVCS is most commonly caused by an anterior/superior mediastinal mass, with venous thrombosis from central venous lines being the second cause. SMS refers to the coexistence of tracheal compression and airway compromise. The most frequent symptoms of SVCS and SMS in children are dyspnea, cough, shortness of breath, orthopnea, dysphagia, hoarseness and headache. Symptoms are typically aggravated when the child is in the supine position, and often progress rapidly over days. Characteristic physical findings are facial, neck and upper arm swelling, facial plethora and cyanosis, conjunctival suffusion, jugular and thoracic venous distension, and wheezing or stridor. Diagnosis is usually confirmed by a posterior-anterior and lateral chest radiograph. A computed tomography (CT) scan more accurately assesses the mass and the extent of tracheal compression, and evaluates anesthetic risk. The differential diagnosis of a mediastinal mass in pediatric patients depends on the age of the child, the mediastinal compartment involved, and the progression of symptoms.

Management of children with mediastinal malignancies may be challenging. It is imperative to obtain the diagnosis by the most expeditious and the least invasive procedure possible, as respiratory distress and cardiovascular collapse may occur with sedation or general anesthesia. In life-threatening situations, establishing a tissue diagnosis may be impossible, and it is necessary to start empiric therapy (systemic steroids, chemotherapy, in rare occasions radiation therapy) [3].

*Tumor lysis syndrome (TLS).* TLS consists of metabolic abnormalities resulting from the death of malignant cells and massive release of intracellular contents into the circulation. The classic triad of TLS includes hyperuricemia, hyperkalemia, and hyperphosphatemia which in turn leads to secondary hypocalcemia. Precipitation of uric acid crystals and calcium phosphate within the renal tubules leads to acute kidney injury. Hyperkalemia can cause cardiac dysrhythmia and arrest.

TLS can occur prior to any cytotoxic therapy in children with tumors that have rapid cell turnover and large volume, and up to one week from the initiation of therapy. Conditions at higher risk for TLS include acute leukemias with hyperleukocytosis and

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massive extramedullary disease (organomegaly, bulky mediastinal or abdominal masses), Burkitt's lymphoma, and lymphoblastic lymphoma. Signs and symptoms of TLS are nonspecific: decreased urine output, fatigue, nausea, vomiting, muscle cramps, edema, and neurologic changes. On physical examination, special attention is given to blood pressure, cardiac rate and rhythm, and signs of cerebral hypoxia. Interventions should be initiated to prevent TLS in children at risk for TLS, and aggressive measures should be started if there is evidence for TLS. These include hyperhydration with intravenous fluids without potassium and the appropriate use of acid uric-lowering drugs. Allopurinol (with urine alkalization) should be given to children at low or intermediate risk for TLS, and rasburicase to those at high risk. Rasburicase is a potent and fast-acting uricolytic agent that metabolizes uric acid to allantoin, which is 5 to 10-fold more soluble than uric acid, rendering it readily excretable by kidneys. Ongoing assessment for fluid input and output, body weight, edema, cardiac, respiratory and/or neurologic changes are mandatory. Close laboratory monitoring (initially every 3 to 6 hours, then spread out as the lysis improves) includes complete blood count, serum uric acid, creatinine, urea nitrogen, potassium, calcium, phosphate, magnesium, and lactate dehydrogenase. The principles of prevention of TLS form the basis for the treatment of already established TLS. The therapy should be intensified or extended if critical to life-threatening complications develop. Dialysis may be necessary in case of severe hyperkalemia, hyperphosphatemia, renal failure, and oliguria or anuria [4,5].

**Hyperleukocytosis.** Hyperleukocytosis is arbitrarily defined as a white blood cell (WBC) count of greater than 100,000 per  $\mu\text{L}$ . It is present at the time of diagnosis in approximately 10% pediatric cases of acute lymphoblastic leukemia (ALL) with two age peaks in infants less than 1 year of age and teenagers, 5% to 20% cases of acute myeloid leukemia (AML), and in virtually all children with chronic myelogenous leukemia. Hyperleukocytosis results in hyperviscosity and leukostasis. Which may cause devastating multisystem organ dysfunction. Neurologic manifestations include headache, seizures, mental status changes, blurred vision, papilledema, and retinal vascular distension. Pulmonary leukostasis and secondary pulmonary hemorrhage causes dyspnea, tachypnea, and pulmonary infiltrates on chest radiograph. Other organ systems may be involved. In addition, patients with hyperleukocytosis are at risk for TLS, metabolic derangements, coagulopathy, and acute renal failure. Severe metabolic abnormalities are more frequent in ALL, while disseminated intravascular coagulation is most common in AML patients.

Patients should be monitored very closely for vital signs and laboratory parameters. Aggressive supportive care is directed at prevention or correction of TLS. Platelets should be transfused at counts below  $20,000/\text{mm}^3$  to prevent cerebral hemorrhage, or in the presence of active mucosal or visceral bleeds. Platelet transfusions do not add substantially to blood viscosity. In contrast, red blood cell transfusions are withheld whenever possible as they further increase viscosity. Leukapheresis and/or exchange transfusion may contribute to rapid leukocyte reduction with acceptable risk. Specific cytotoxic therapy must be initiated as soon as life-threatening complications have been corrected [2,5].

**Febrile neutropenia** Febrile neutropenia (FN) is the most common complication of anticancer therapy that can lead to delays in the treatment and dose reductions of chemotherapy, which compromise treatment efficacy. FN is defined as a single oral temperature of >

38.3°C (101°F) or a temperature of 38°C (100.4°F) sustained over at least one hour or reported from two consecutive readings in a two-hour period, and absolute neutrophil count (ANC) of less than  $0.5 \times 10^9$  ( $<500/\mu\text{L}$ ), or a count of  $1.0 \times 10^9$  ( $<1000/\mu\text{L}$ ) with a predicted decrease below  $0.5 \times 10^9$  in next 48 hours in cancer patients and hematopoietic stem-cell transplantation recipients. FN is a medical emergency, as these patients are at high risk for life-threatening infections. A careful history and physical examination are essential in the initial assessment of patients with FN. Areas at special risk include central venous line sites, sites of recent invasive procedures, oropharynx/periodontium, respiratory tract, skin and perineum/perirectal area. It should be noted that the absence of fever in a neutropenic cancer patient with localizing signs and symptoms does not exclude infection, particularly in children receiving steroids as a part of their treatment. Besides, clinical signs of infection may be subtle owing to the lack of inflammatory cells. Blood cultures should be obtained at the onset of FN from all lumens of central venous lines. Peripheral blood cultures, although increase the identification of true bacteremia compared with central cultures alone, are not necessary, given the additional time, pain, and isolation of contaminants. Urine culture is obtained routinely. Other cultures (stool, wound, cerebrospinal fluid) are obtained based on clinical suspicion. A chest radiograph should be done in all patients with respiratory signs or symptoms. The pathologic finding prompts consideration for CT imaging. Broad-spectrum antibiotics should be started within 60 minutes in all febrile neutropenic patients (30 minutes in case of systemic compromise/sepsis). Any delay in awaiting the results of cultures may permit the progression of infection, and increases morbidity and mortality. Patients may be classified as low- or high-risk according several risk factors: duration and severity of neutropenia, cancer type and cancer status, bone marrow involvement, type of treatment, and significant medical comorbidities. Monotherapy with an antipseudomonal beta-lactam, a fourth-generation cephalosporin, or a carbapenem is recommended as initial empirical therapy in pediatric high-risk FN. The addition of a second gram-negative agent or a glycopeptide is reserved for patients who are clinically unstable, when a resistant infection is suspected, or for centers with a high rate of resistant pathogens. No definitive consensus exists regarding optimal duration of empirical antibiotics. In general, therapy is discontinued in patients who have negative blood cultures at 48 hours, who have been afebrile for at least 24 hours, and who have evidence of bone marrow recovery. Empirical antifungal or antiviral therapy is not routinely recommended unless there is a high risk for or suspicion of a fungal or viral infection. Patients at high-risk for invasive fungal disease are those with AML, high-risk ALL or relapsed acute leukemia, children undergoing allogeneic hematopoietic stem cell transplantation, those with prolonged neutropenia and those receiving high-dose corticosteroids [6,7].

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