Oncologic Complications Resulting in Metabolic Disturbances: Tumor Lysis Syndrome

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Definition:

Tumor lysis syndrome (A – 1) (TLS) is a metabolic disorder that results from the rapid release of intracellular contents (potassium, phosphorus and nucleic acids) into the circulation upon the rapid death of cells. The amounts of these intracellular products may exceed the body's compensatory measures and cause four metabolic abnormalities:

Hyperuricemia (A – 2)
Hyperkalemia (A – 3)
Hyperphosphatemia (A – 4)
Hypocalcemia.

Each of these electrolyte imbalances can occur individually or in combination, and severe increases in electrolyte concentrations can alter organ function.

Risk Factors:

Patients with large, rapidly growing tumors or pre-existing renal dysfunction are at greatest risk of TLS. Large tumor burdens may be clinically evident as hyperleukocytosis (increased white cell count [WBC] greater than 100,000/mm^3), an increased concentration of lactose dehydrogenase (LDH), an increased concentration of uric acid, and massive enlargement of organs. Types of organ enlargement that might be seen are lymphadenopathy, a mediastinal mass and hepatosplenomegaly or other large abdominal tumors. Patients with chemosensitive tumors are also at risk of TLS. Therefore, this syndrome is most commonly associated with chemosensitive diseases that have a large tumor burden such as any leukemia with a high WBC count, Burkitt's lymphoma and lymphocytic lymphoma.

The metabolic abnormalities of TLS can be exacerbated if the patient is dehydrated, has renal insufficiency and/or is septic at the time of treatment.

Clinical Presentation:

Tumor lysis syndrome is an early complication of therapy, usually occurring 24 to 48 hours after the initiation of therapy and lasting no more than 1 week. The organ systems most commonly affected by TLS are the cardiac, neurologic, renal, and gastrointestinal (GI) systems (A – 5). Early symptoms may include generalized weakness, fatigue, tachycardia, diarrhea, vomiting, abdominal pain and cramping. Diagnosis is commonly based on the findings of laboratory serum studies (A – 6): increased concentrations of serum uric acid, potassium and phosphorus and a decreased concentration of serum calcium may result in arrhythmia, tetany-like symptoms, and tingling and numbness.

As the metabolic impairments progress, the renal tubules may be obstructed, and the patient may complain of back or flank pain. Renal obstruction may lead to acute renal failure.

Medical Management:

Patients who are at risk of TLS should receive preventive measures such as administration of allopurinol (Zyloprim) or rasburicase (Elitek) and sodium bicarbonate. Further, simultaneous vigorous hydration and diuresis before and after chemotherapy or radiation treatment are usually implemented. Therefore, each patient's electrolyte concentrations should be evaluated every 6 to 8 hours during the first 72 hours of chemotherapy or radiation treatment.

Most patients with newly diagnosed TLS are dehydrated; therefore, their intravascular volume must be expanded by the administration of fluids. Vigorous hydration with hypotonic fluids such as D5 ¼ N. Saline (2 to 4 times the maintenance amount) help to dilute solutes, increase renal blood flow and glomerular filtration and flush renal tubules. Close monitoring to detect any fluid overload is achieved by the following procedures:

evaluating fluid intake and output
measuring daily weights
checking for edema.

Diuretics such as furosemide (Lasix) or mannitol (a parenteral osmotic diuretic) may be administered to maintain urine output and to prevent circulatory overload.

For the treatment of hyperuricemia, allopurinol, an inhibitor of xanthine oxidase, is given. Use of this drug leads to a decrease in the production of uric acid but an increase in the concentration of the xanthines, which are more soluble than uric acid. Patients who have lysis of a significant number of tumor cells and are taking allopurinol may be at risk of xanthine nephropathy, which can cause the formation of kidney stones.

Sodium bicarbonate (20-40 mEq/l) is often added to the IV fluid to assist with excretion of uric acid and xanthine. However, urine alkalinization could lead to the precipitation of calcium phosphate in the renal tubules, which could further complicate the renal failure that is common in this patient population. Therefore, each patient's concentration of serum electrolytes and renal function should be carefully monitored.

The new drug currently used to treat TLS is Elitek (rasburicase). Rasburicase is a superior alternative for the treatment of hyperuricemia. Rasburicase converts uric acid to allantoin, which is 5 to 10 times more soluble than uric acid and does not require urine alkalinization; thus, this drug enhances the excretion of phosphate. If a patient is given rasburicase, the administration of sodium bicarbonate is not necessary.

Hyperkalemia is most effectively treated with hydration. If the potassium concentration is 6 mEq/l, kayexalate may be given orally or as an enema. Kayexalate is a resin that absorbs the potassium within the GI tract, and the potassium-bound resin is removed from the body by defecation.

If an abnormality is seen on an electrocardiogram (EKG) or if the potassium concentration is >6.5 mEq/l, the patient may receive 10% glucose (0.5 g/kg) with 0.3 units of regular insulin per gram of glucose, infused over 1 hour. Insulin and dextrose raise the plasma insulin levels; this increase causes a shift of potassium into the intracellular compartment.

Another treatment for hyperkalemia (serum potassium concentration >7 mEq/dl and abnormalities seen on EKGs) is intravenously administered calcium gluconate with cardiac monitoring. In some cases sodium bicarbonate is given as an IV bolus to alkalinize the plasma and shift the potassium from the extracellular to the intracellular compartment.

Hyperphosphatemia is treated with phosphate-binding antacids such as aluminum hydroxide (Amphogel; Basalgel) or calcium carbonate. Further, dietary intake of phosphate-containing foods such as soft drinks, milk, cheese, eggs, nuts and legumes should be restricted.

Hypocalcemia can be treated with IV infusions or orally administered calcium supplements such as calcium tablets. Oral calcium intake can also be increased through use of foods high in calcium content such as dairy products (milk, cheese, ice cream, etc).

Invasive procedures to relieve acute renal failure include hemodialysis, hemofiltration and peritoneal dialysis. Other treatments for acute renal failure are leukopheresis, exchange transfusions and low-dose steroid therapy.

Nursing Interventions:

Because of the critical nature of TLS, the patient is often treated in the intensive care unit. Psychosocially, this setting may be alarming to the patient and family. The nurse should provide proper preparation, explanation and support to the patient and family regarding the nature of TLS and the need for close monitoring.

Nursing interventions should be geared toward preventing TLS and/or minimizing its occurrence. This goal can be accomplished by identifying patients at risk and carefully monitoring responses to treatments. These responses can be monitored by laboratory tests and nursing assessments such as determining whether uric acid crystals are present in urine.

Nursing activities should also focus on accurate measurement of fluid intake and output, weight, urine specific gravity, urine pH (which should be greater than 7) and hematologic status. At the time of vigorous hydration, nursing management should include astute observation to detect any

signs of fluid overload (A – 7), which, if present, should be promptly managed. Urine output should also be maintained at a rate of least 1 ml/kg per hour.

Because the kidneys are the primary organs that eliminate potassium, uric acid and phosphorus, the patient's renal function should be carefully assessed. This assessment should include evaluation of renal panel measurements (blood urea nitrogen [BUN], creatinine and electrolytes) and adequacy of urine output. It is imperative for the nurse to carefully maintain an accurate record of intake and output with calculation of urine output (cc/kg per hour). Renal failure in patients with TLS can be fatal.

Further clinical assessment should include checking for Chvostek's and Trousseau's signs (A – 8), arrhythmias and neuromuscular irritability suggesting hypocalcemia. If a patient is experiencing hypocalcemia, seizure precautions should be implemented.

Patient and Family Education:

Patient and family education should include the provision of information regarding TLS, its manifestations and self-care (A – 9) to prevent relapse.

Helpful Web Links:

RxList.com, Atlanta, GA
Product Information (Lasix; furosemide)
http://www.rxlist.com/cgi/generic/furos.htm

Great Ormond Hospital for Children – Institute for Child Health, London
Allopurinol 2nd Ed. Information for Children and Families
http://www.ich.ucl.ac.uk/factsheets/families/F040240/

RxList.com, Atlanta, GA
Product Information (Elitek; rasburicase)
http://www.rxlist.com/cgi/generic3/elitek.htm

Orangebook.com, St. Louis, MO Product Information: (Kayexalate; sodium polystyrene sulfonate suspension)
http://www.edsorangebook.com/Drugs%20R%20to%20U/kayexelate.htm

Medscape WebMD (via Google.com) - Prevention and Treatment of Hyperuricemia in Hematologic Malignancies
Michael S. Cairo, MD

eMedicine.com, Omaha, NE
Tumor Lysis Syndrome
Amit P. Sarnaik, MD
http://www.emedicine.com/ped/topic2328.htm

CancerConsultants Oncology Resource Center, Ketchum, ID
TLS: Managing Side Effects, Treatment and Prevention
http://patient.cancerconsultants.com/supportive_treatment.aspx?id=997

Wikipedia.com – Tumor Lysis Syndrome
http://en.wikipedia.org/wiki/Tumor_lysis_syndrome

Nursing Center – American Journal of Nursing
Tumor Lysis Syndrome (also available for Continuing Education Credit)
http://www.nursingcenter.com/prodev/cearticleprint.asp?CE_ID=498304

Related Cure4Kids Seminars:

Seminar #80: Tumor Lysis Syndrome
Stanley Chaleff, MD, Eric Lowe, MD and Dennis Jay, PhD
http://www.cure4kids.org/seminar/80

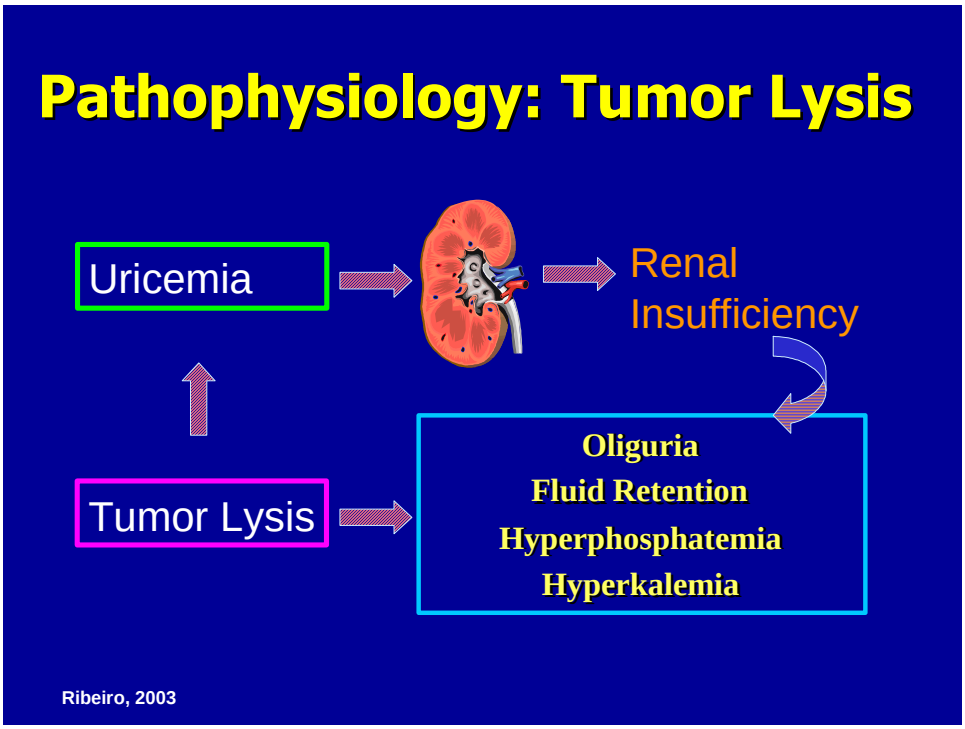
Seminar #199: Early Complications of Children with Leukemia/Lymphoma: Tumor Lysis Syndrome
Raul C. Ribeiro, MD
http://www.cure4kids.org/seminar/199

Seminar #593: ALL Presenting with Severe Anemia, Acidosis, Hypernatremia and Tumor Lysis Syndrome
Virginia Harrod, MD, PhD, Terrence Geiger, MD, PhD
http://www.cure4kids.org/seminar/593

Seminar #830: Acute Complications of Childhood Leukemia
Scott Howard, MD, MS
http://www.cure4kids.org/seminar/830

APPENDIX

A – 1 Pathophysiology of TLS



Courtesy of Raul Ribeiro, MD
St. Jude Children's Research Hospital

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A – 2 Hyperuricemia

The most common clinical electrolyte abnormality associated with TLS is hyperuricemia (an elevated level of serum uric acid). Uric acid is the end product of purine breakdown. On average the kidneys excrete 500 mg of uric acid daily; however, in patients with TLS, the increased quantity of uric acid exceeds the excretory capacity of the renal tubules; the result is hyperuricemia. Signs of hyperuricemia include nausea, vomiting, lethargy, agitation, hypertension, renal dysfunction and the formation of renal stones. If renal dysfunction occurs, the BUN and creatinine levels will be increased.

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A – 3 Hyperkalemia

Hyperkalemia is the most dangerous immediate consequence of TLS. Potassium is an intracellular ion that is released as tumor cells break down. Elevation of the serum potassium concentration is most often noted 12 hours after the initiation of chemotherapy. Hyperkalemia usually occurs before hyperphosphatemia and can be aggravated by acidosis (a condition in which the extracellular concentration of potassium increases as the intracellular concentration decreases), hyponatremia and hypocalcemia.

Hyperkalemia can result in cardiac, neuromuscular and GI irritability. Hyperkalemia causes a delay in cardiac conduction and repolarization leading to atrioventricular block, ventricular tachyarrythmia and asystole. Muscle weakness and irritability, cramping, twitching and paresthesias are neuromuscular manifestations of hyperkalemia. Increased peristaltic movement secondary to hyperkalemia may cause nausea, vomiting, intestinal colic and diarrhea.

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A – 4 Hyperphosphatemia and Hypocalcemia

Organic and inorganic phosphorus is abundant in leukemic cells and is released as these cells break down. Additionally, metabolic acidosis may shift intracellular phosphate to the extracellular space. Hyperphosphatemia occurs 12 to 24 hours after the initiation of chemotherapy. Hyperphosphatemia may then lead to the precipitation of calcium phosphate, leading to renal insufficiency and hypocalcemia. These metabolic abnormalities may result in cardiac arrhythmias, renal insufficiency, muscle cramping/twitching and changes in mental status. Hyperkalemia and hypocalcemia will produce hyperactive deep tendon reflexes. Two signs that are indicative of hypocalcemia and, if present, can be observed during physical assessment are Chvostek's and Trousseau's signs (A – 8).

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A – 5 Clinical Manifestations of TLS

Renal Problems (mostly due to hyperuricemia)
- Decreased urine output
- Increased concentration of BUN and serum creatinine
- Increased concentration of serum uric acid
- Crystallization of uric acid in renal tubules
- Acute renal failure

Cardiac Arrythmias (mostly due to hyperkalemia and partly due to hypocalcemia)
- Atrioventricular blocks
- Ventricular tachycardia
- Ventricular fibrillation
- Cardiac arrest/asystole

Neuromuscular Irritability (mostly due to hypocalcemia)
- Tetany
- Carpopedal spasms
- Muscle cramps
- Hyperactive deep tendon reflex (DTR)
- Confusion, delirium, hallucination
- Seizures
- Digital and perioral paresthesias

Gastrointestinal Effects (mostly due to hyperphosphatemia)
- Nausea and vomiting
- Intestinal colic
- Diarrhea

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A – 6 Pertinent Laboratory Values Associated with TLS

Uric Acid	> 8.0 mg/L
Potassium	> 5.5 mEq/L
Phosphorus	> 7.0 mg/dl
Calcium	< 7.0 mg/dl
BUN	> 50 mg/dl
Creatinine	> 1.6 mg/dl
LDH	> 1500 IU/L
Arterial Blood Gas	low in patients with metabolic acidosis

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A – 7 Manifestations of Fluid Overload

Shortness of breath
Cough
Rales detected by auscultation
Distention of neck veins
Weight gain and swelling, especially of distal areas
Decreased urinary output
Feeling of fullness
Increased blood pressure
Increased heart rate

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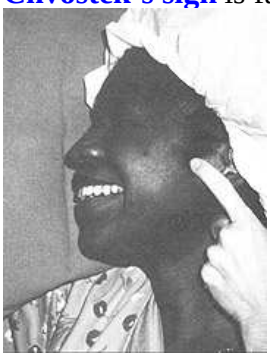
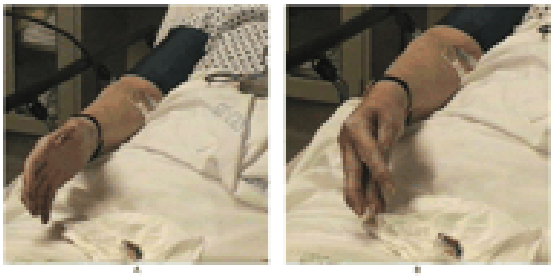
A – 8 Chvostek's and Trousseau's signs

Chvostek's sign is facial twitching that occurs when a site near the tragus nerve is tapped.



Society of Otorhinolaryngology and Head-Neck Nurses, Inc, New Smyrna Beach, Fl
www.sohnnurse.com/ thyroidectomy.html

Trousseau's sign is a carpopedal spasm that occurs after blood flow in the arm is occluded. A spasm in the hand and wrist is caused by compression of the forearm of a patient who has undue neuromuscular excitability as a result of hypocalcaemia. The thumb is adducted, the fingers bunched and the wrist flexed.



The New England Journal of Medicine, Waltham, MA
http://content.nejm.org/cgi/reprint/343/25/1855.pdf

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A – 9 Manifestations of TLS and Self Care

Tell the patient and family to notify the primary care provider if any of the following signs appear.

Nausea, vomiting, lack of appetite
Watery stools, frequent stools – increased diaper changes
Muscle cramps, spasms, twitching or weakness
Increased fatigue - any change in the patient's activity or play pattern
Numbness or tingling – dropping objects, clumsy behavior
Decreased frequency of urination – decreased diaper changes
Pain in the side – holding or favoring a side, crying, inconsolability
Cloudy or bloody urine
Weight gain or swelling – sudden increase in shoe size
Shortness of breath
Pain and swelling in the joints
Change in mental status – irritability, listlessness, restlessness
Seizure activity

Self Care:

Continuation of high-volume fluid intake
Dietary restrictions on foods that contain potassium or phosphorus (examples are cheese, milk, nuts, legumes, poultry, fish, meats and carbonated drinks)
Monitoring of weight to detect any sudden gain
Monitoring of fluid intake and urine output

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