Tumor Lysis Syndrome

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Practice Gaps

Along with knowledge of how to evaluate a pediatric patient with a suspected malignancy, general pediatricians must maintain a high level of suspicion of tumor lysis syndrome for initial management and timely patient referral. This syndrome is largely preventable, and certainly manageable, with prompt diagnosis and appropriate intervention.

Objectives

After completing this article, readers should be able to:

1. Define and diagnose tumor lysis syndrome (TLS).
2. Recognize the risk factors for TLS.
3. Stratify pediatric patients with cancer according to risk of developing TLS.
4. Identify interventions to prevent TLS.
5. Discuss management strategies for patients with TLS.

INTRODUCTION

Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency that occurs when cancer cells break down, either spontaneously or after initiation of cytotoxic chemotherapy, and release their intracellular contents into the bloodstream. This massive release of uric acid, potassium, and phosphorous, which under normal physiologic conditions are excreted in the urine, can lead to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. These metabolic derangements increase the risk of severe complications, including acute kidney injury (AKI), cardiac arrhythmias, seizures, and even death. TLS is the most common oncologic emergency, and it occurs most frequently in children with acute leukemia and non-Hodgkin lymphoma. TLS is often preventable; clinicians must maintain a high index of suspicion and rely on effective prevention and treatment strategies. This review will serve to update the readership on TLS in pediatric oncology patients, including the definition, common risk factors, epidemiology, pathophysiology, and clinical consequences, as well as preventive and management measures for children with suspected or newly diagnosed cancers.

DEFINITION OF TLS

TLS consists of a constellation of laboratory findings, including hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia and the consequential

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ABBREVIATIONS

AKI	acute kidney injury
ALL	acute lymphoblastic leukemia
HRD	high-risk disease
IRD	intermediate-risk disease
LRD	low-risk disease
TLS	tumor lysis syndrome

clinical toxicities from these metabolic abnormalities. The widely accepted classification system for TLS in pediatrics, initially proposed by Hande and Garrow in 1993, (1) modified by Cairo and Bishop in 2004, (2) and remodified by Howard et al in 2011, (3) includes definitions for both laboratory and clinical TLS (Table 1). Laboratory TLS is defined as a level above or below the limits of normal for age for 2 or more of the following serum values: elevated uric acid, potassium, or phosphorus and decreased calcium. These abnormalities must also be present during the same 24-hour period and within 3 days before or up to 7 days after the initiation of chemotherapy. Clinical TLS requires the presence of laboratory TLS plus 1 of the following clinical sequelae: increased creatinine level, seizures, cardiac dysrhythmia, or death. The definition of clinical TLS presumes that the symptom of TLS exhibited is definitely or at least probably a direct consequence of at least 1 of the laboratory TLS metabolic abnormalities.

PATHOPHYSIOLOGY OF TLS

When malignant cells lyse spontaneously or as a consequence of cytotoxic chemotherapy, they release their intracellular contents, most problematic of which are potassium, phosphorus, and nucleic acids. Nucleic acids are metabolized into uric acid. Hyperkalemia can cause life-threatening arrhythmias and even sudden death. Hyperphosphatemia can result in intravascular calcium phosphate salt formation and can crystallize in various organs, including the kidney, leading to AKI. The net loss of serum calcium as a consequence of precipitation also can lead to symptomatic hypocalcemia, which can include an array of symptoms such as tetany, seizures, and dysrhythmia (particularly in the context of hyperkalemia, or as a consequence of calcium phosphate precipitation in the cardiac conduction system).

Hyperuricemia is the consequence of massive purine breakdown (Fig 1). Renal clearance of uric acid, a relatively insoluble metabolite, is highly dependent on glomerular filtration rate and urine pH (exacerbated by urine acidification). An elevated uric acid burden, beyond the body's normal coping mechanisms, can lead to uric acid crystallization in the renal collecting system, resulting in AKI. Xanthine can also precipitate in the renal collecting system, and thus crystal-induced AKI can be caused by calcium phosphate, uric acid, and xanthine precipitation and obstruction.

RISK ASSESSMENT OF TLS

TLS most commonly occurs in patients with tumors that have both a high proliferation rate and a great tumor mass. In children, these tumors are predominantly hematologic malignancies, such as acute lymphoblastic leukemia (ALL), Burkitt leukemia/lymphoma, and diffuse large B-cell lymphoma. (4)(5) The lack of a historically unified definition of TLS has made estimating the incidence in children challenging. However, 2 multicenter studies in Europe reported a TLS incidence of 4.4% in non-Hodgkin's lymphoma and 8.4% in Burkitt leukemia and ALL. (6) Generally, the incidence of TLS depends on the type of tumor and tumor

TABLE 1. Definitions of Laboratory and Clinical TLS

Laboratory TLS (≥2)
Uric acid > the ULN range for age
Potassium ≥6.0 mEq/L (≥6.0 mmol/L)
Phosphorus ≥6.5 mg/dL (≥2.1 mmol/L)
Calcium (corrected) ≤7.0 mg/dL (≤1.75 mmol/L)
Clinical TLS (≥1)
Serum creatinine ≥1.5× the ULN for age
Cardiac arrhythmia or sudden death
Seizure
Neuromuscular instability

TLS=tumor lysis syndrome, ULN=upper limit of normal.

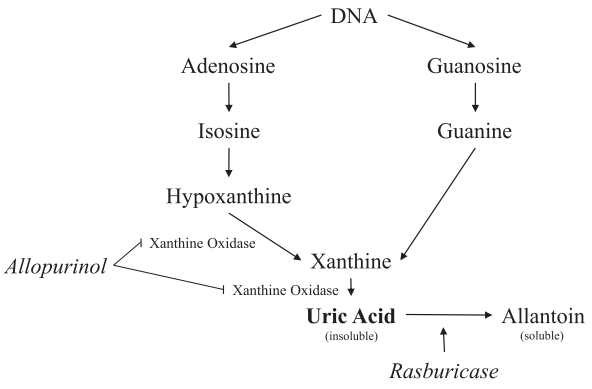

Figure 1. Nucleic acid breakdown and mechanisms of action of allopurinol and rasburicase. On cell lysis, DNA is released from the nucleus and enzymatically degraded eventually into xanthine and uric acid, which is insoluble. Xanthine oxidase converts hypoxanthine to xanthine, and xanthine to uric acid. Allopurinol is a purine analogue and an inhibitor of xanthine oxidase. This medication prevents new uric acid from being formed; excesses of hypoxanthine and guanine do not contribute to renal calculi. Rasburicase enzymatically converts insoluble uric acid into an inactive and water-soluble metabolite, allantoin, which is readily excreted in the urine. This medication reduces serum uric acid levels.

cellular burden and on other risk factors, such as premorbid patient characteristics such as renal insufficiency and hydration status. Burkitt lymphoma/leukemia typically has such a high tumor proliferation rate that it can outgrow its own metabolic needs, resulting in spontaneous and severe tumor lysis at presentation. On the other hand, TLS can occur in children with slow-growing tumors if the tumor is causing urinary tract obstruction. Finally, the risk of TLS should be considered in parallel with the effectiveness of therapies to cause cell lysis. Historically untreatable cancers are being targeted more effectively, which could lead to TLS in cancer types previously deemed lower risk.

In 2008, an international panel of experts in pediatric and adult oncology, as well as experts in TLS pathophysiology, prophylaxis, and treatment, met in an effort to develop a comprehensive TLS risk stratification system. This panel developed a final model of low-, intermediate-, and high-risk TLS classification (Figs 2 and 3). (7) Burkitt leukemia/lymphoma and ALL are the highest-risk cancers, and Burkitt leukemia is always a high-risk disease (HRD) for TLS. Burkitt lymphoma risk and ALL risk depend on the tumor stage and presenting white blood cell count, respectively. Solid tumors, on the other hand, are almost always considered low-risk diseases (LRD); however, in the new era of more effective targeted therapies, and for certain chemosensitive tumors such as neuroblastoma, the TLS risk may be considered intermediate. As for lymphomas, aside from Hodgkin lymphoma, which is always considered an LRD, the risk for TLS tends to depend on the tumor stage and the lactate dehydrogenase level, which is a marker of cell proliferation and turnover.

MANAGEMENT OF TLS

TLS management centers on maintaining a high index of suspicion, identifying patients at higher risk for TLS, and using an aggressive prophylactic strategy to prevent the laboratory and clinical manifestations of TLS. This effort requires aggressive volume repletion and/or expansion and prevention of and treatment of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Any pediatric patient that presents with concerns for a new malignancy should undergo up-front measurement of serum uric acid, potassium, phosphorus, and calcium levels, as well as serum creatinine levels, along with consideration of empirical intravenous fluid administration. A quick risk stratification should be considered then, which includes a differential diagnosis of the malignancy at hand, as well as specific disease features, such as disease stage and initial white blood cell count. In addition, serum lactic dehydrogenase levels can provide insight into the rate of cell turnover and risk of TLS.

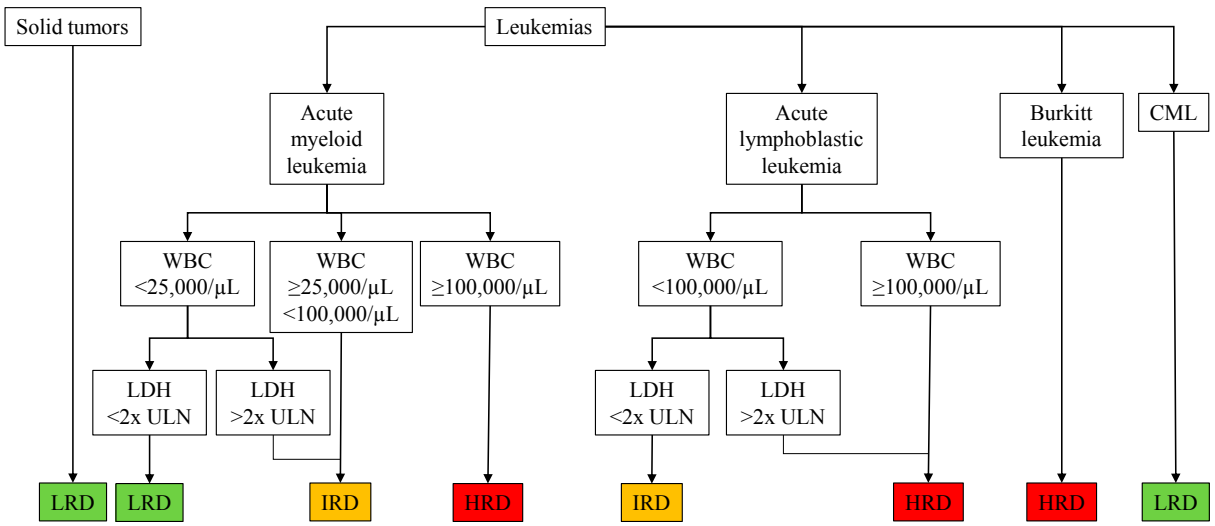

Figure 2. Tumor lysis syndrome risk assessment for pediatric solid tumors and acute leukemias. Solid tumors are generally low-risk disease (LRD), unless the tumor is bulky and sensitive to chemotherapy, such as neuroblastoma or germ cell tumors, and are then considered intermediate-risk disease (IRD). Classification of acute myeloid leukemia and acute lymphoblastic leukemia depends on white blood cell (WBC) counts and lactate dehydrogenase (LDH) levels. Burkitt leukemia is always classified as a high-risk disease (HRD). All WBC counts are reported in conventional measurement units. Conversion to SI units: 25,000/μL (25×10^9/L); 100,000/μL (100×10^9/L). CML=chronic myelogenous leukemia, ULN=upper limit of normal. (Adapted with permission from Cairo MS, Coiffier B, Reiter A, Younes A; TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome [TLS] in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol.* 2010;149(4):578–586.)

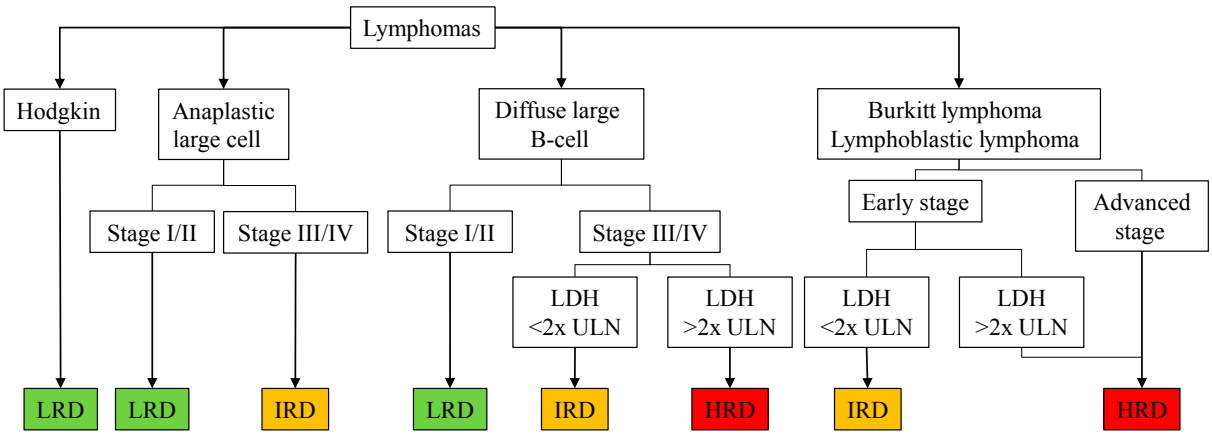

Figure 3. Tumor lysis syndrome risk assessment for pediatric lymphomas. Hodgkin lymphoma is always characterized as low-risk disease (LRD), whereas classification of Burkitt lymphoma, lymphoblastic lymphoma, diffuse large B-cell lymphoma, and anaplastic large cell lymphoma depends on disease stage and lactate dehydrogenase (LDH) levels. HRD=high-risk disease, IRD=intermediate-risk disease, ULN=upper limit of normal. (Adapted with permission from Cairo MS, Coiffier B, Reiter A, Younes A; TLS Expert Panel. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome [TLS] in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol.* 2010;149(4):578–586.)

All pediatric patients at intermediate or high risk for TLS should continue to receive intravenous hydration to optimize kidney function and minimize acidosis. This is often achieved with hyperhydration using 1.5 to 2 times maintenance intravenous fluids (without potassium), or 2,500 to 3,000 mL/m² per day to maintain urine output of 3 to 5 mL/kg per hour. Close laboratory monitoring for fluid overload and third spacing is important. Although hydration is the preferred method of optimizing urine output, loop diuretics may also be used. If oliguria occurs or persists despite aggressive hydration and diuretics, evaluation by a pediatric nephrologist is highly recommended. Close monitoring of laboratory TLS is also a key strategy through serial measurements of serum uric acid, potassium, phosphorus, calcium, and creatinine levels. Patients with HRD should have these tests measured every 4 to 8 hours; patients with intermediate-risk disease (IRD) should undergo laboratory testing every 8 to 12 hours; and patients with LRD may need testing only once or twice daily. TLS burden for IRD and HRD tends to peak around day 3 of cytoreductive chemotherapy, but TLS can occur as far as 7 days after treatment initiation. (8)

Prophylaxis for and treatment of hyperuricemia is aimed at maintaining normal serum levels of uric acid. For patients with IRD or HRD with normal or mildly elevated serum uric acid levels, allopurinol should be administered to prevent uric acid formation. Allopurinol, a xanthine oxidase inhibitor, is effective at inhibiting new uric acid formation and is an appropriate first-line therapy for patients without significantly elevated serum uric acid levels (Fig 1). Allopurinol is administered, usually by the oral route, at 100 mg/m² per dose every 8 hours, or 10 mg/kg per day divided every 8 hours, with a maximum dose of 800 mg/d. In patients who present with high serum levels of uric acid, allopurinol is an ineffective treatment because it does not directly reduce the uric acid that has already accumulated in the serum. Patients with hyperuricemia should receive rasburicase, a recombinant urate oxidase that converts uric acid to water-soluble allantoin. Indications for rasburicase vary but generally include a serum uric acid level greater than 8 mg/dL (>475.88 μmol/L), a rapid increased in uric acid level (a 25% increase from baseline), or a suboptimal response to hyperhydration and allopurinol therapy. Rasburicase is administered intravenously at a dose of 0.1 to 0.2 mg/kg as a single dose. Rasburicase has been shown to be more effective than allopurinol in the prevention of TLS; however, its benefits should be weighed against its high costs. (9) It is important to remember that serum uric acid level interpretation after rasburicase administration can be misleading because ex vivo enzymatic lysis of uric acid (in the sample test tube) may continue if the sample is not immediately placed in an ice bath to halt the enzymatic reaction. In addition, rasburicase can provoke methemoglobinemia in patients with glucose-6-phosphate dehydrogenase deficiency.

Hyperkalemia is managed largely by prevention. Parenteral or oral supplementation of potassium should not be administered to patients at risk for TLS until the risk has resolved. It is important to review the patient's medication list because several commonly used medications, such as nonsteroidal anti-inflammatory drugs, angiotensin-converting enzymes, angiotensin-receptor blockers,

and others, can impair potassium tubular secretion (Table 2). Patients with any clinical signs or symptoms of hyperkalemia, which include severe muscle weakness, electrocardiogram findings that demonstrate peaked T waves and/or QRS widening, or serum potassium levels approaching or surpassing 6 mEq/L (6 mmol/L) should be monitored for arrhythmias in an intensive care environment. If life-threatening hyperkalemia is identified, a variety of emergency interventions are indicated. Prompt administration of parenteral calcium gluconate is critical to reduce cardiac muscle excitability and the risk of dysrhythmias. Next, potassium-lowering strategies include promotion of potassium influx into cells with medications such as insulin and β-adrenergic agnostics (albuterol) and with optimization of potassium excretion in the urine (with loop diuretics) or gut (with sodium polystyrene sulfonate). In rare cases when a potassium-sparing approach leads to symptomatic hypokalemia, supplementation should be performed carefully with close monitoring to ensure that kidney function and urine output are optimized. Parenteral or oral supplementation of potassium should not be administered to patients at risk for TLS until the risk has resolved, which is typically after 3 days of chemotherapy.

TABLE 2. List of Drugs That Can Contribute to Hyperkalemia

Drugs that induce extracellular potassium movement
—Digoxin
—β blockers
—Mannitol
—Verapamil
Drugs that reduce aldosterone activity
—ACE inhibitors
—Angiotensin II receptor blockers
—Direct renin inhibitors
—NSAIDs
—Calcineurin inhibitors
—Aldosterone antagonists
—Potassium-sparing diuretics
—Trimethoprim, pentamidine
Potassium-containing interventions
—Penicillin G
—Stored blood products

Hyperphosphatemia is both prevented and managed with hyperhydration and dietary restriction of phosphorous with administration of phosphate binders such as calcium acetate or sevelamer. If hyperphosphatemia cannot be managed with these conservative strategies, the use of furosemide (to promote hyperfiltration) or dialysis is indicated. Parenteral calcium administration should be avoided unless symptomatic hypocalcemia or concerns for hyperkalemia-induced arrhythmias are noted. Exposure to intravenous calcium in a patient with hyperphosphatemia can promote calcium phosphate precipitation that can contribute to AKI. Serum calcium levels often normalize when the serum phosphate and uric acid levels normalize.

Historically, urine alkalization to achieve urine pH levels of 6.5 to 7.5 was commonly recommended to minimize the formation of calcium urate crystals. Urine alkalization is no longer universally recommended and is even discouraged. Calcium phosphate, as well as xanthine and hypoxanthine (intermediate metabolites of purine degradation increased when allopurinol is administered), are poorly soluble in alkalinized urine and may more readily crystallize in a basic environment. (10)

CONCLUSION

TLS is the most common life-threatening emergency in children with malignancies. When the intracellular components of malignant cells are released into the blood, either spontaneously or after the onset of chemotherapy, they can overwhelm the body's normal excretory renal capacity and lead to renal, cardiac, and muscle toxicities directly related to the excess electrolyte concentrations. As such, TLS requires a high index of suspicion and early and prompt intervention to prevent and/or treat any laboratory or clinical symptoms that are present. TLS should be considered and screened for in all children with newly diagnosed malignancies; however, certain cancers, due to their large tumor burden and high proliferation rate (such as ALL and Burkitt leukemia/lymphoma), put children at highest risk. Management of TLS consists of early prevention with hydration, frequent monitoring, prevention of hyperuricemia with allopurinol, and prompt interventions for elevated serum uric acid, potassium, or phosphate levels or low calcium levels. The current era of pediatric oncology offers novel and targeted agents to patients with previously difficult-to-treat cancers; however, this may further complicate the ability to predict accurately which patients are at highest risk for TLS. Therefore, it continues to be critical for clinicians to maintain a high index of suspicion and a watchful eye for TLS in all children with malignancies.

Summary

- On the basis of strong clinical evidence, tumor lysis syndrome (TLS) is the most common life-threatening emergency in childhood malignancies that occurs when cancer cells break down, either spontaneously or after initiation of cytotoxic chemotherapy, and release their intracellular contents into the bloodstream. (2)(3)(4)(5)(7)
- The intracellular release of uric acid, potassium, and phosphorous, which, under normal physiologic conditions are excreted in the urine, can lead to hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Based on strong clinic evidence, these metabolic derangements increase the risk of severe complications, including acute kidney injury, cardiac arrhythmias, seizures, and even death. (2)(3)(4)(5)(7)
- TLS most commonly occurs in rapidly dividing hematologic malignancies that have both a high tumor proliferation rate and a large tumor burden at presentation. This most commonly occurs with acute lymphoblastic leukemia, Burkitt leukemia/lymphoma, and diffuse large B-cell lymphoma. (4)(5). Burkitt lymphoma/leukemia is well-known to have a very high tumor proliferation rate and can outgrow its own metabolic capacity, resulting in spontaneous and severe tumor lysis at presentation.
- On the basis of strong evidence, TLS management centers on maintaining a high index of suspicion, identifying patients at higher risk for TLS, and employing an aggressive prophylactic strategy to prevent the laboratory and clinical manifestations of TLS. (2)(7)
- Based on expert opinion, any pediatric patient who presents with concerns for a new malignancy should undergo up-front measurement of serum uric acid, lactate dehydrogenase, potassium, phosphorus, and calcium levels, as well as serum creatinine levels, along with consideration of aggressive volume repletion and/or expansion to optimized renal function. (2)(3)(4)(5)
- Based on strong evidence, all pediatric patients at intermediate or high risk for TLS should continue to receive intravenous hydration to optimize kidney function and minimize acidosis. (7) This is often achieved with hyperhydration (without potassium) to maintain a urine output of 3 to 5 mL/kg per hour. Close monitoring for fluid overload and third spacing is important. Close monitoring of laboratory TLS is also a key strategy through serial measurements of serum uric acid, potassium, phosphorus, calcium, and creatinine levels. Prophylaxis (with allopurinol) and treatment of hyperuricemia are aimed at maintaining normal serum levels of uric acid.
- Based on strong evidence, patients who develop signs or symptoms of TLS require prompt interventions relying on a multidisciplinary approach with the support of pediatric nephrologists and intensive care physicians to rapidly treat any TLS-induced metabolic derangements and maximize outcomes. (2)(3)(4)(5)(7)

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1. A 5-year-old boy presents with a 10-cm jaw mass that has doubled in size in the past month. Laboratory and imaging studies are ordered. Which of the following laboratory findings is most consistent with laboratory tumor lysis syndrome (TLS)?
   A. Hypocalcemia.
   B. Hypokalemia.
   C. Hyponatremia.
   D. Hypophosphatemia.
   E. Hypouricemia.
2. A 9-year-old girl presents with a large mediastinal mass, a white blood cell (WBC) count of 135,000/μL (135$\times 10^9$/L) with 80% blasts, and a uric acid level of 10 mg/dL (594.9 μmol/L). She is being prepared for induction chemotherapy. Which of the following findings is most consistent with clinical TLS in this patient?
   A. Ejection fraction less than 50%.
   B. Liver transaminase levels greater than 2 times the upper limit of normal for age.
   C. Serum C-reactive protein level 5 times the upper limit of normal for age.
   D. Serum creatinine level greater than 1.5 times the upper limit of normal for age.
   E. Serum lactate dehydrogenase level greater than the upper limit of normal for age.
3. Which of the following patients would most likely be at highest risk for TLS?
   A. A 22-month-old boy diagnosed as having Wilms tumor.
   B. A 2-year-old girl with periorbital ecchymosis and an 8-cm right adrenal mass.
   C. A 6-year-old boy with a WBC count of 122,000/μL (122$\times 10^9$/L) with 55% blasts, a hemoglobin level of 7.5 g/dL (75 g/L), and a platelet count of 29$\times 10^3$/μL (29$\times 10^9$/L).
   D. An 11-year-old girl with a WBC count of 2,000/μL (2$\times 10^9$/L) with 90% blasts, a hemoglobin level of 4.5 g/dL (45 g/L), and a platelet count of 5$\times 10^3$/μL (5$\times 10^9$/L).
   E. A 17-year-old boy with a 5-cm left supraclavicular lymph node, weight loss, and night sweats.
4. A 4-year-old boy is brought to the clinic for evaluation of a 2-month history of bone pain and recurrent fever. He is found to have hepatosplenomegaly and pancytopenia. Serum uric acid and potassium levels are within the reference range but there is hypocalcemia and hyperphosphatemia. Which of the following is the most appropriate initial management for this patient?
   A. Hyperhydration with alkalization to maintain urine pH 6.5 to 7.5.
   B. Hyperhydration and allopurinol therapy.
   C. Maintenance hydration and allopurinol therapy.
   D. Maintenance hydration and calcium carbonate supplementation.
   E. Maintenance hydration and parenteral calcium therapy.
5. A 10-year-old girl presents with cervical lymphadenopathy and dyspnea. She is found to have a large mediastinal mass and pancytopenia. On day 3 of chemotherapy she has a serum potassium level of 6.2 mEq/L (6.2 mmol/L), a serum calcium level of 6.0 mg/dL (1.5 mmol/L), a serum phosphorus level of 7 mg/dL (2.3 mmol/L), and a serum uric acid level of 10 mg/dL (594.9 μmol/L). Which of the following is the most appropriate management plan for this patient?
   A. Cardiac telemetry and administration of rasburicase.
   B. Maintenance fluid hydration and repeat laboratory studies in 24 hours.
   C. Measurement of cardiac ejection fraction and administration of allopurinol.
   D. Monitoring of urine output and administration of allopurinol.
   E. Monitoring of urine pH and administration of rasburicase.

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