Chapter 4: Tumor Lysis Syndrome

Amaka Edeani, MD,* and Anushree Shirali, MD†

*Kidney Diseases Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland; and †Section of Nephrology, Yale University School of Medicine, New Haven, Connecticut

INTRODUCTION

Tumor lysis syndrome (TLS) is a constellation of metabolic abnormalities resulting from either spontaneous or chemotherapy-induced tumor cell death. Tumor cytotoxicity releases intracellular contents, including nucleic acids, proteins, and electrolytes into the systemic circulation and may lead to development of hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia. Clinically, this results in multiorgan effects such as AKI, cardiac arrhythmias, and seizures (1,2). TLS is the most common oncologic emergency (3), and without prompt recognition and early therapeutic intervention, morbidity and mortality is high.

DEFINITION

Hande and Garrow (4) first initiated a definition of the clinical and pathologic characteristics of patients at risk for developing TLS. Based on a retrospective analysis of 102 patients with non-Hodgkin lymphoma (NHL), they classified TLS as laboratory TLS (LTLS) or clinical TLS (CTLS). Cairo and Bishop (1) modified these criteria to formulate a commonly used classification system for TLS. This system (Table 1) defines LTLS when two or more of the following abnormalities are met within 3 days before or 7 days after the initiation of chemotherapy: 1) 25% decrease from baseline in serum calcium, and/or 2) 25% increase from baseline in the serum values of uric acid, potassium, or phosphorous.

The Cairo and Bishop definition assumes adequate volume expansion and prophylaxis with a hypouricemic agent. LTLS is defined as CTLS (Table 1) when LTLS is accompanied by one or more clinical manifestations such as cardiac arrhythmia, death, seizure, or AKI with an elevated serum creatinine >1.5 times upper limit of normal. Additionally, this definition of CTLS assumes that the clinical manifestations are not caused directly by the therapeutic agent. Last, a third class specifies patients with normal laboratory and clinical parameters as having no LTLS or CTLS.

Cairo and Bishop also proposed a grading system combining the definitions of no TLS, LTLS, and CTLS, with the maximal clinical manifestations in each affected organ defining the grade of TLS (1). Although this grading system attempts to provide uniform definitions to TLS severity, it is not widely used in clinical practice.

The Cairo-Bishop classification is not immune to critique despite its common use. Specifically, patients with TLS may not always have two or more abnormalities present at once, but one metabolic derangement may precede another (2). Furthermore, a 25% change from baseline may not always be significant if it does not result in a value outside the normal range (2). From a renal standpoint, Wilson and Berns (5) have noted that defining AKI on the basis of a creatinine value >1.5 times the upper limit of normal does not clearly distinguish CKD from AKI. Thus, they propose using established definitions of AKI in CTLS such as an absolute 0.3 mg/dL increase or relative 50% increase in creatinine over baseline. Finally, they point out that the Cairo-Bishop classifications cannot be applied to spontaneous TLS, which is common with high-risk malignancies, as chemotherapy is a required criterion for LTLS and CTLS.

EPIDEMIOLOGY AND RISK FACTORS

TLS is most commonly described in NHL, particularly Burkitt-type lymphoma (BTL), as well as other hematologic malignancies, such as acute lymphocytic and lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) (6–8), and less commonly in chronic

Correspondence: Anushree Shirali, Section of Nephrology, Yale University School of Medicine, PO Box 208029, New Haven, Connecticut 06520-8029.

Table 1. Cairo-Bishop definition of laboratory tumor lysis syndrome and clinical tumor lysis syndrome

Laboratory Tumor Lysis Syndrome	
Metabolite or electrolyte	**Criterion for diagnosis**
Uric acid	≥8 mg/dL or 25% increase from baseline
Potassium	≥6 mEq/L or 25% increase from baseline
Phosphorus	≥6.5 mg/dL (children), ≥4.5 mg/dL (adults), or 25% increase from baseline
Calcium	≥25% decrease from baseline
Clinical Tumor Lysis Syndrome	
LTLS and one or more of the following: 1) creatinine × ≥1.5 ULN (age >12 years of age or age adjusted); 2) cardiac arrhythmia or sudden death; 3) seizure	

LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal.

leukemias (9–11) and multiple myeloma (12,13). More rarely, TLS has also been described with solid malignancies (14,15) with particular features, including large tumor burden, metastatic disease, specifically in the liver, short doubling time, increased chemosensitivity, and elevated uric acid and lactate dehydrogenase (LDH) (15). Among solid tumors, small-cell carcinoma of the lung, germ cell tumors, neuroblastoma, and breast carcinoma have all been linked to development of TLS (8). TLS is usually associated with cytotoxic chemotherapy but reports have also linked it to the use of imatinib (11), bortezomib (12), corticosteroids (16,17), rituximab (18), methotrexate (19), and thalidomide (13,20). There are also case reports of TLS following total body irradiation (21) and chemoembolization (22). Last, TLS may also be spontaneous, i.e., not requiring initiation of cytotoxic therapy. This has been most frequently described in BTL (23–25).

The incidence of TLS varies based on the underlying malignancy and the definition of TLS. Most incidence data are from older, retrospective studies that precede the Cairo-Bishop classification, so there is considerable heterogeneity in the data. In a review of 102 patients with high-grade NHL and using the Hande-Garrow classification, LTLS was seen in 42% of patients, with CTLS occurring only in 6% (4). In BTL, however, 56% and 11% of patients met criteria for LTLS and CTLS, respectively. Mato *et al.* (26) studied 194 patients receiving induction therapy for AML and found a TLS incidence of 9.8%. In a mixed adult and pediatric study of 788 European patients with acute leukemia or NHL (27), the overall incidence of LTLS and CTLS was 18.9% and 5%, respectively. When classified by tumor type, LTLS and CTLS incidence rates of 14.7% and 3.4% were seen in AML patients, respectively; 21.4% and 5.2% in ALL patients, respectively; and 19.6% and 6.1% in patients with NHL, respectively (27). Wössman *et al.* (28) reviewed the incidence and complications of 1,791 children with NHL and reported an overall incidence of 4.4%, of which 26% had B-cell ALL (B-ALL).

Risk stratification

Risk factors (2,29) for TLS include cancer and patient-specific factors. Increased tumor burden is the most cancer-specific risk factor and is demonstrated by elevated LDH (28), white blood cell count >50,000/mm^3, massive liver metastasis (14), bone marrow involvement (2), cancer stage, proliferation rate of cancer cells, and cell sensitivity to cytotoxic therapy. Patient-related factors include age, volume depletion, preexisting CKD, hyperuricemia, and hyponatremia. Recognition of these high-risk factors is an important step in the management of TLS. In 2008, an expert panel (7) developed a TLS risk classification system, based on published evidence and expert opinion, in which malignancies as were described as low (<1% chance), intermediate (1%–5% chance), or high risk (>5% chance) for developing TLS. Classification into these risk groups incorporates type of histology, extent of disease, renal involvement or dysfunction, and type of induction therapy (Table 2).

Other factors that have been shown to be predictive of TLS include male sex and presence of splenomegaly (26,28,30). Certain cytogenetic shifts may also portend greater risk for TLS. Specifically, MYCN gene mutation in neuroblastoma (31), t(8;14)(q24;q32) in L3 type of acute lymphoblastic leukemia (32), and inv(16)(p13;q22) in acute myelocytic leukemia (33) are all linked to more aggressive disease and greater risk for TLS.

PATHOPHYSIOLOGY AND CLINICAL MANIFESTATIONS

TLS is a direct consequence of cell lysis and release of intracellular products. When clearance of these products, by excretion (renal or hepatic excretion or phagocytosis by the reticuloendothelial system) (23), is impaired and their serum burden increases, the clinical sequelae of TLS may occur. Of these cellular products, nucleic acids (converted to uric acid), potassium, and phosphorus are particularly important in the pathophysiology of TLS.

Hyperuricemia

The nucleic acids adenine and guanine are metabolized to xanthine, which is further metabolized by xanthine oxidase to the water-insoluble uric acid (5) (Figure 1). Because humans lack a functional gene for urate oxidase (uricase), which further metabolizes uric acid to the freely soluble and excretable allantoin, patients with high-risk malignancy are susceptible to rapid increases in serum uric acid. Uric acid is freely filtered at the glomerulus, and handling in the renal proximal tubule

Table 2. Risk classification of TLS according to type of malignancy, extent of disease, and presence or absence of renal dysfunction

Type of malignancy	Risk
Solid tumor	Low
Myeloma	Low
Chronic leukemia	CML: low
	CLL w/alkylating agents: low
	CLL w/targeted or biological agents: intermediate
Lymphoma: Burkitt type	Early stage and LDH $<2 \times$ ULN: intermediate
	Early stage and LDH $>2 \times$ ULN: high
	Advanced stage: high
Lymphoma: non-Burkitt type	
Anaplastic large cell	Child with stage III/IV disease: intermediate
	All others: low
Lymphoblastic lymphoma	Early stage and LDH $<2 \times$ ULN: intermediate
	Early stage and LDH $>2 \times$ ULN: high
	Advanced stage: high
Hodgkin, small lymphocytic, follicular, marginal zone B cell, MALT, nonblastoid mantle cell, cutaneous T cell	Low
Adult T-cell lymphoma, diffuse large B cell, peripheral T cell, transformed, or blastoid mantle cell	Adult with normal LDH: low
	Child with stage I/II disease: low
	Adult with LDH > ULN and nonbulky disease: intermediate
	Adult with LDH > ULN and bulky disease: high
	Child with stage III/IV disease and LDH $<2 \times$ ULN: intermediate
	Child with stage III/IV disease and LDH $>2 \times$ ULN: high
Leukemia:-Burkitt type	High
Leukemia: non-Burkitt type; acute myeloid leukemia (AML); acute lymphoblastic Lleukemia (ALL)	AML with WBC $<25 \times 10^9$/L and LDH $<2 \times$ ULN: low
	AML with WBC $<25 \times 10^9$/L and LDH $>2 \times$ ULN: intermediate
	AML with WBC = 25–100 $\times 10^9$/L: intermediate
	ALL with WBC $<100 \times 10^9$/L and LDH $<2 \times$ ULN: intermediate
	ALL with WBC $<100 \times 10^9$/L and LDH $>2 \times$ ULN: high
	ALL with WBC $>100 \times 10^9$/L: high
Renal dysfunction	**Risk**
Absent	If low risk disease, no change
	If intermediate risk disease and normal UA, phosphorus, and potassium, no change
	If UA, phosphorus, or potassium > ULN, intermediate risk disease becomes high risk
Present	Low risk disease become intermediate risk
	Intermediate risk disease becomes high risk

CML, chronic myeloid leukemia; CLL, chronic lymphocytic leukemia; MALT, mucosa-associated lymphoid tissue; LDH, lactate dehydrogenase; AML, acute myeloid leukemia; WBC, white blood cell count; ALL, acute lymphocytic and lymphoblastic leukemia; UA, urinalysis; ULN, upper limit of normal.

is a combination of reabsorption and secretion via the luminal urate/anion exchanger urate transporter 1 (URAT-1) and the basolateral organic anion transporter (OAT) (34). URAT-1 is an apical membrane transporter and exchanges anions for urate absorption from the tubular lumen. It is critical in regulating urate levels and is targeted by uricosuric and antiuricosuric agents (34). When the capacity to transport luminal uric acid is overwhelmed, there is potential for uric acid to crystallize within the tubular lumen. An acidic urine pH favors this process.

Uric acid crystals can cause direct tubular injury by obstruction, but other pathways for injury include induction of chemokine-mediated inflammation from monocyte chemoattractant protein-1 (MCP-1) (35) and macrophage migration inhibition factor (MIF) (36). There are also crystal-independent mechanisms which target hemodynamics. These include increased peritubular capillary pressures, increased vasoconstriction, and decreased blood flow (5,37–39). Uric acid may also prevent recovery from AKI in TLS, as it has been shown to inhibit proximal tubule cell proliferation (38). These diverse mechanisms are united in their propensity to cause AKI. Clinically, hyperuricemia is unlikely to cause symptoms because urinary crystallization of uric acid does not result in the renal colic, which is typical of uric acid nephrolithiasis.

Hyperkalemia

Massive tumor cell lysis releases potassium into the extracellular environment, leading to severe hyperkalemia when uptake capacity by muscle and liver is exceeded, especially in

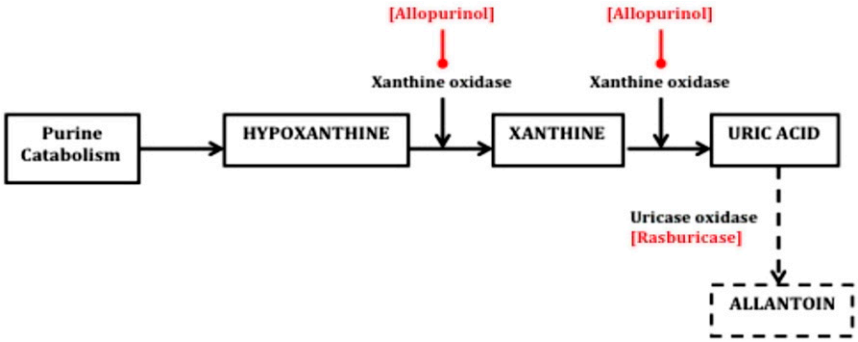

Figure 1. Schematic of purine metabolism. Allopurinol acts an inhibitor of xanthine oxidase via its active metabolite, oxypurinol. Dashed arrow and box indicate arm of metabolism not constitutively present in humans; this conversion of uric acid to water-soluble allantoin is stimulated clinically by the administration of rasburicase (recombinant urate oxidase). Black arrows denote enzyme stimulation; red lines denote inhibition.

the setting of CKD or AKI. Muscle weakness may be the initial symptom, but cardiac arrhythmia, manifested initially by peaked T waves, widened QRS complexes, and sine waves, is the feared complication.

Hyperphosphatemia and hypocalcemia

Because phosphate is an intracellular electrolyte, cell lysis releases significant amounts of it. However, malignant hematologic cells may contain four times more intracellular phosphate in comparison to normal mature lymphoid cells (3), making hyperphosphatemia a particular issue with tumor cell lysis. Because phosphorus excretion is tied to kidney function, hyperphosphatemia occurs when the kidney's excretory capacity is overwhelmed. Thus, preexisting CKD or AKI enhances risk for hyperphosphatemia with TLS. Spontaneous tumor lysis, however, is less commonly associated with hyperphosphatemia and may be due to rapid uptake of extracellular phosphate by residual highly metabolically active tumor cells (5). Hyperphosphatemia may cause nausea, vomiting, diarrhea, or lethargy, but it exerts its predominant toxicity by binding to calcium cations. This results in secondary hypocalcemia and its downstream neuromuscular and cardiovascular effects such as cramps, hypotension, tetany, and arrhythmias. Additionally, calcium–phosphate precipitates may deposit in tissues, as seen in nephrocalcinosis, including the renal interstitium.

AKI

AKI in TLS may be either due to the aforementioned effects of acute urate nephropathy or hyperphosphatemic nephrocalcinosis affecting the renal tubulointerstitium or a combination of the two. Some studies have suggested that a urine uric acid to creatinine ratio of >1 may be specific to uric acid nephropathy (40), but another study has noted high uric acid to creatinine ratios in AKI from other etiologies (41).

The association between AKI and TLS has been demonstrated across various populations and tumor subtypes (5). Annemans *et al.* (27) found that in patients with leukemia and NHL who had TLS, 45% had AKI. A smaller pediatric cohort of B-cell NHL or ALL noted renal insufficiency in 20% percent of the study population (42). Although the data were not broken down into cause of AKI, the incidence of TLS was similar at 17%, suggesting that AKI and TLS were also linked in this population. AKI due to TLS may be asymptomatic or include symptoms of uremia, including nausea, vomiting, and lethargy.

MANAGEMENT

Prophylaxis and monitoring

Prevention of TLS begins with recognition of risk factors and close laboratory and clinical monitoring. Patients at highest risk of developing TLS (Table 2) require intensified monitoring with more frequent electrolyte checks. Patients with high-risk disease may be prone to lactic acidosis from massive tumor cell necrosis. Because acidosis inhibits uric acid excretion (43), prompt recognition and correct of acidosis may prevent or ameliorate uric acid nephropathy. Additionally, nonsteroidal anti-inflammatory drugs, iodinated radiocontrast dye, and other potentially nephrotoxic therapeutic agents should be avoided to abrogate the risk of AKI from TLS.

Volume expansion

Delivery of crystalloid intravenous fluids (IVFs) is recommended for all patients and is essential for those with higher TLS risk. Volume expansion supports adequate intravascular volume and renal blood flow, which maintain glomerular filtration. This is the cornerstone of uric acid, potassium, and phosphate excretion and may delay and prevent the need for renal replacement measures (2,6,44). High-dose IVFs up to 3 L have been recommended (2), for a target urine output of ≥ 2 mL/kg/h. Diuretics may be necessary if patients develop volume overload, but routine use is not recommended to avoid volume depletion.

Urinary alkalinization

Alkalinization makes physiologic sense, as increasing urine pH from 5 to 7 can increase the solubility of uric acid >10-fold (28). However, urinary alkalinization decreases calcium–phosphate solubility (2), thereby exacerbating its precipitation

and deposition. Furthermore, if urinary alkalinization results in rising serum pH, free calcium may bind albumin more avidly and further exacerbate hypocalcemia (45). Thus, urinary alkalinization is not recommended in the management of TLS (2,6,45).

Allopurinol

Allopurinol is converted in vivo to oxypurinol and as a xanthine analog acts as a competitive inhibitor of xanthine oxidase and blocks the conversion of purines to uric acid (6,46) (Figure 1). This prevents hyperuricemia but does not treat preexisting hyperuricemia (6). Furthermore, because oxypurinol also inhibits the conversion of xanthine to uric acid, serum and urine xanthine levels may rise and precipitate xanthine crystal deposition in the renal tubules and xanthine-induced obstructive nephropathy (47). Administration of allopurinol is recommended for prophylaxis in patients with low and intermediate risk of developing TLS (2,6). Smalley *et al.* (48) studied 1,172 patients to evaluate the efficacy and safety of intravenous allopurinol in patients with hyperuricemia. They noted reduced uric acid levels in 57% of adults and 88% of children. When used as prophylactic therapy, allopurinol prevented an increase in uric acid levels in 93% of adults and 92% of children.

Because oxypurinol excretion is by the kidney, dose adjustments are necessary for patients with CKD and AKI. Allopurinol has been associated with a hypersensitivity syndrome with rash, acute hepatitis, and eosinophilia (45,49). Allopurinol reduces the clearance of purine-based chemotherapeutic agents such as 6-mercaptopurine and azathioprine (6). It may also interact with azathioprine and cyclophosphamide in potentiating severe bone marrow suppression (6,45).

Febuxostat

Febuxostat is a novel xanthine oxidase inhibitor lacking the hypersensitivity profile of allopurinol. Because it is metabolized to inactive metabolites by the liver, adjustment for reduced GFR is not necessary. It has been proposed as a viable alternative to allopurinol in TLS prophylaxis for patients with allopurinol hypersensitivity or renal dysfunction (45). A recently completed phase III study of febuxostat versus allopurinol in TLS prevention found significantly lower serum uric acid in the febuxostat but found no significant difference in serum creatinine change compared with allopurinol (50). Febuxostat use has been limited by its significant cost compared with generically available allopurinol (45).

Rasburicase

Rasburicase (Elitek) is an *Aspergillus*-derived recombinant urate oxidase approved by the US Food and Drug Administration (FDA) in 2002 for the initial management of hyperuricemia in pediatric patients with leukemia, lymphoma, and solid tumor malignancies receiving anticancer therapy (51). It was subsequently approved for use in adults in 2009 (51). Rasburicase catalyzes the conversion of uric acid to allantoin, carbon dioxide, and hydrogen peroxide (Figure 1). Allantoin is 5- to 10-fold more soluble than uric acid (52) and is readily excreted. Prior to FDA approval, 1,069 adult and pediatric patients received rasburicase on a compassionate use basis (53). Decreased serum uric acid levels were observed in 99% of children and 100% of adults. Hemodialysis was performed in only 2.8% of patients. In a study of 131 patients with newly diagnosed leukemia or lymphoma, Pui *et al.* (54) reported a decrease in plasma uric acid concentrations from 9.7 to 1 mg/dL ($P = 0.0001$) in 65 patients who presented with hyperuricemia and a decrease from 4.3 to 0.5 mg/dL ($P = 0.0001$) in the remaining patients. There was negligible toxicity, and no patients required dialysis.

Cortes *et al.* (55) compared response rates in dosing rasburicase alone versus rasburicase followed by allopurinol versus allopurinol alone. They reported a plasma uric acid response rate of 87% in the rasburicase group, 78% in the rasburicase followed by allopurinol group, and 66% in the allopurinol group, with a significantly greater response for rasburicase compared with allopurinol in the overall study population ($P = 0.001$), in patients at high risk for TLS (89% versus 68%; $P = 0.012$), and in those with baseline hyperuricemia (90% versus 53%; $P = 0.015$). Of note, there are no prospective studies to date that have examined the impact of rasburicase on relevant clinical end points such as morbidity from AKI. Nonetheless, rasburicase should be used for prophylaxis in patients with high risk of developing TLS (7). The FDA-approved dosing guidelines recommend 0.2 mg/kg in 50 mL normal saline as a 30-minute intravenous infusion once daily for up to 5 days (51). Length of treatment is related to control of plasma uric acid levels, but use of rasburicase for >5 days is rarely needed (6,51). In comparison with generically available allopurinol, rasburicase is significantly more expensive (up to $3,600 per 7.5-mg vial) (45), and in most published studies, one-time dosing was sufficient to suppress hyperuricemia.

Rasburicase does not require dosing adjustment for GFR and is not known to have any known clinically relevant drug–drug interactions (51,56). Adverse reactions are rare but may include rash, increased liver enzyme levels, headaches, fever, vomiting, and nausea (56).

Rasburicase is active ex vivo, so blood samples for serum uric acid levels must be stored on ice to avoid erroneously low results (45). Patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency can develop significant methemoglobinemia and hemolysis due to oxidative stress triggered by hydrogen peroxide (57,58). Accordingly, patients should have G6PD status tested prior to starting rasburicase.

RRT

The need for renal replacement has significantly reduced since the advent of rasburicase, but about 1.5% of children and 5% of adults require dialysis during induction therapies (53). Indications for RRT are similar to those for AKI from other causes, but due to the rapid onset of the clinical manifestations of TLS, the threshold for initiating dialytic therapies is lower than in other situations. Although intermittent hemodialysis (IHD) may be sufficient for most patients, continuous RRT (CRRT) at high dialysate or replacement fluid flow rates (>3-4 L/h) may be necessary in those patients with severe TLS who

experience rebound in serum potassium and phosphorous levels with IHD (45,59,60).

PROGNOSIS

There are many confounding factors that impact clinical outcomes in patients with malignancies, particularly in those who have TLS, but AKI appears to be a significant predictor of short- and long-term mortality from TLS. A study comparing hematologic cancer patients without AKI to patients with AKI (61) showed significantly lower hospital mortality (7% and 21%, respectively) and 6-month mortality (51% and 66%, respectively) in patients without AKI. TLS is most common during initial presentation of disease because relapsed malignancies are significantly more chemoresistant (5). There are fewer case reports of TLS in recurrent disease (62).

CONCLUSIONS

TLS is a common oncologic emergency that requires immediate diagnosis and prompt treatment to avoid morbidity and mortality. Understanding the diagnostic criteria for TLS, knowing the tumor types at high risk for TLS, and instituting prophylactic and treatment measures are essential for the nephrologist who treats patients with malignant diseases.

TAKE HOME POINTS

- TLS is the most common oncologic emergency.
- The risk of TLS depends on tumor type but is also influenced by other factors.
- There is a high burden of AKI in patients with TLS.
- Prophylaxis with volume expansion is the mainstay of preventing TLS in any patient-risk category.
- Patients at high risk for TLS should receive rasburicase for initial treatment of hyperuricemia.

ACKNOWLEDGMENTS

Dr. Edeani's work is supported by the intramural Research Program of the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health.

REFERENCES

1. Cairo MS, Bishop M. Tumor lysis syndrome: New therapeutic strategies and classification. *Br J Haematol* 127: 3–11, 2004
2. Howard SC, Jones DP, Pui C. The tumor lysis syndrome. *N Engl J Med* 364: 1844–1854, 2011
3. Flombaum CD. Metabolic emergencies in the cancer patient. *Semin Oncol* 27: 322–334, 2000
4. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. *Am J Med* 94: 133–139, 1993
5. Perry Wilson F, Berns JS. Onco-nephrology: Tumor lysis syndrome. *Clin J Am Soc Nephrol* 7: 1730–1739, 2012
6. Coiffier B, Altman A, Pui C, Younes A, Cairo MS. Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An evidence-based review. *J Clin Oncol* 26: 2767–2778, 2008
7. Cairo MS, Coiffier B, Reiter A, Younes A, Baruchel A, Bosly A, Goldman SC, Leverger G, Ohyashiki K, Panagiotidis P, Pession A, Pui CH, Ribera JM, Rosti G, Rule S, Tsukimoto I, Zinzani PL. 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* 149: 578–586, 2010
8. Baeksgaard L, Sørenson JB. Acute tumor lysis syndrome in solid tumors: A case report and review of the literature. *Cancer Chemother Pharmacol* 51: 187–192, 2003
9. Jensen M, Winkler U, Manzke O, Diehl V, Engert A. Rapid tumor lysis in a patient with B-cell chronic lymphocytic leukemia and lymphocytosis treated with an anti-CD20 monoclonal antibody (IDEC-C2B8, rituximab). *Ann Hematol* 77: 89–91, 1998
10. Cech P, Block JB, Cone LA, Stone A. Tumor lysis syndrome after tamoxifen flare. *N Engl J Med* 315: 263–264, 1986
11. Al-Kali A, Farooq S, Tfayli A. Tumor lysis syndrome after starting treatment with Gleevec in a patient with chronic myelogenous leukemia. *J Clin Pharm Ther* 34: 607–610, 2009
12. Sezer O, Vesole DH, Singhal S, Richardson P, Stadtmauer E, Jakob C, Boral AL, Esseltine DL, Mehta J. Bortezomib-induced tumor lysis syndrome in multiple myeloma. *Clin Lymphoma Myeloma* 7: 233–235, 2006
13. Fuente N, Mane JM, Barcelo R, Muñoz A, Perez-Hoyos T, Lopez-Vivanco G. Tumor lysis syndrome in a multiple myeloma patient treated with thalidomide. *Ann Oncol* 15: 537, 2004
14. Mirrakhimov AE, Ali AM, Khan MK, Barbaryan A. Tumor lysis syndrome in solid tumors: An up to date review of the literature. *Rare Tumors* 6: 68–76, 2014
15. Gemici C. Tumour lysis syndrome in solid tumors. *Clin Oncol* 18: 773–780, 2006
16. Lerza R, Botta M, Barsotti B, Schenone E, Mencoboni M, Bogliolo G, Pannacciulli I, Arboscello E. Dexamethasone-induced acute tumor lysis syndrome in a T-cell malignant lymphoma. *Leuk Lymphoma* 43: 1129–1132, 2002
17. Tiley C, Grimwade D, Findlay M, Treleaven J, Height S, Catalano J, Powles R. Tumour lysis following hydrocortisone prior to a blood product transfusion in T-cell acute lymphoblastic leukemia. *Leuk Lymphoma* 8: 143–146, 1992
18. Jabr F. Acute tumor lysis syndrome induced by rituximab in diffuse large B-cell lymphoma. *Int J Hematol* 82: 312–314, 2005
19. Simmons ED, Somberg KA. Acute tumor lysis syndrome after intrathecal methotrexate administration. *Cancer* 67: 2062–2065, 1991
20. Lee CC, Wu YH, Chung SH, et al. Acute tumor lysis syndrome after thalidomide therapy in advanced hepatocellular carcinoma. *Oncologist* 11: 87–88, 2006
21. Linck D, Basara N, Tran V, Chen WJ. Peracute onset of severe tumor lysis syndrome immediately after 4 Gy fractionated TBI as part of reduced intensity preparative regimen in a patient with T-ALL with high tumor burden. *Bone Marrow Transplant.* 31: 935–937, 2003
22. Hsieh PM, Hung KC, Chen YS. Tumor lysis syndrome after transarterial chemoembolization of hepatocellular carcinoma: Case reports and literature review. *World J Gastroenterol* 15: 4726–4728, 2009
23. Cohen LF, Balow JE, Magrath IT, Poplack DG, Zeigler JL. Acute tumor lysis syndrome: A review of 37 patients with Burkitt's Lymphoma. *Am J Med* 68: 486–491, 1980
24. Iversen U, Iversen OH, Bluming AZ, Zeigler JL, Kyalwasi S. Cell kinetics of African cases of Burkitt lymphoma. A preliminary report. *Eur J Cancer* 8: 305–308, 1972
25. Jasek AM, Day HJ. Acute spontaneous tumor lysis syndrome. *Am J Hematol* 47: 129–131, 1994
26. Mato AR, Riccio BE, Qin L, Heitjan DF, Carroll M, Loren A, Porter DL, Perl A, Stadtmauer E, Tsai D, Gewirtz A, Luger SM. A predictive model

for the detection of tumor lysis syndrome during AML induction therapy. *Leuk Lymphoma* 47: 877–883, 2006
27. Annemans L, Moeremans K, Lamotte M, Garcia Conde J, van den Berg H, Myint H, Pieters R, Uyttebroeck A. Incidence, medical resource utilization and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukemia and non-Hogkin's lymphoma in four European countries. *Leuk Lymphoma* 44: 77–83, 2003
28. Wössman W, Schrappe M, Meyer U, Zimmermann M, Reiter A. Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. *Ann Hematol* 82: 160–165, 2003
29. Tosi P, Barosi G, Lazzaro C, Lis V, Marchetti M, Morra E, Pession A, Rosti G, Santoro A, Zinzani PL, Tura S. Consensus conference on the management of tumor lysis syndrome. *Haematologica* 93: 1877–1885, 2008
30. Montesinos P, Lorenzo I, Martín G, Sanz J, Pérez-Sirvent ML, Martínez D, Ortí G, Algarra L, Martínez J, Moscardó F, de la Rubia J, Jarque I, Sanz G, Sanz MA. Tumor lysis syndrome in patients with acute myeloid leukemia: Identification of risk factors and development of a predictive model. *Haematologica* 93: 67–74, 2008
31. Kushner BH, LaQuaglia MP, Modak S, Cheung NK. Tumor lysis syndrome, neuroblastoma, and correlation between lactate dehydrogenase levels and MYCN-amplification. *Med Pediatr Oncol* 41: 80–82, 2003
32. Fenaux P, Lai JL, Miaux O, Zandecki M, Jouet JP, Bauters F. Burkitt cell acute leukemia (L3 ALL) in adults: A report of 18 cases. *Br J Haematol* 71: 371–376, 1989
33. Seftel MD, Bruyere H, Copland M, Hogge DE, Horsman DE, Nantel SH, Shepherd JD, Lavoie JC, Le A, Sutherland HJ, Toze CL, Nevill TJ. Fulminant tumour lysis syndrome in acute myelogenous leukemia with inv(16)(p13;q22). *Eur J Haematol* 69: 193–199, 2002
34. Enomoto A, Kimura H, Chairoungdua A, Shigeta Y, Jutabha P, Cha SH, Takeda M, Sekine T, Igarashi T, Matsuo H, Kikuchi Y, Oda T, Ichida K, Hosoya T, Shimokata K, Niwa T, Kanai Y, Endou H. Molecular identification of a renal urate-anion exchanger that regulates blood urate levels. *Nature* 417: 447–452, 2002
35. Umekawa T, Chegini N, Khan SR. Increased expression of monocyte chemoattractant protein-1 (MCP-1) by renal epithelial cells in culture on exposure to calcium oxalate, phosphate and uric acid crystals. *Nephrol Dial Transplant* 18: 664–669, 2003
36. Kim YG, Huang XR, Suga S, Mazzali M, Tang D, Metz C, Bucala R, Kivlighn S, Johnson RJ, Lan HY. Involvement of macrophage migration inhibitory factor (MIF) in experimental uric acid nephropathy. *Mol Med* 6: 837–848, 2000
37. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: Implication on cell proliferation and nitric acid production of human vascular cells. *J Am Soc Nephrol* 16: 3553–3562, 2005
38. Han HJ, Lim MJ, Lee YJ, Lee JH, Yang IS, Taub M. Uric acid inhibits renal proximal tubule cell proliferation via at least two signaling pathways involving PKC, MAPK, cPLA2 and NF-kappaB. *Am J Physiol Renal Physiol* 292: F373–F381, 2007
39. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med* 359: 1811–1821, 2008
40. Davidson MB, Thakkar S, Hix JK, Bhandarkar ND, Wong A, Schreiber MJ. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med* 116: 546–554, 2004
41. Tungsanga K, Boonwichit D, Lekhakula A, Setprija V. Urine uric acid and urine creatinine ratio in acute renal failure. *Arch Intern Med* 144: 934–937, 1984
42. Cairo MS, Gerrard M, Sposto R, Auperin A, Pinkerton CR, Michon J, Weston C, Perkins SL, Raphael M, McCarthy K, Patte C; FAB LMB96 International Study Committee. Results of a randomized international study of high-risk central nervous system B non-Hodgkin lymphoma and B acute lymphoblastic leukemia in children and adolescents. *Blood* 109: 2736–2743, 2007
43. Lieber C, Jones D, Losowsky M, Davidson CS. Interrelation of uric acid and ethanol metabolism in man. *J Clin Invest* 41: 1863–1870, 1962
44. Jones DP, Mahmoud H, Chesney W. Tumor lysis syndrome: Pathogenesis and management. *Pediatr Nephrol* 9: 206–212, 1995
45. Perry Wilson F, Berns JS. Tumor lysis syndrome: New challenges and recent advances. *Adv Chronic Kidney Dis* 21: 18–26, 2014
46. Krakoff IH, Meyer RL. Prevention of hyperuricemia in leukemia and lymphoma: Use of allopurinol, a xanthine oxidase inhibitor. *JAMA* 193: 1–6, 1965
47. LaRosa C, McMullen L, Bakdash S, Ellis D, Krishnamurti L, Wu HY, Moritz ML. Acute renal failure from xanthine nephropathy during management of acute leukemia. *Pediatr Nephrol* 22: 132–135, 2007
48. Smalley RV, Guaspari A, Haase-Statz S, Anderson SA, Cederberg D, Hohneker JA. Allopurinol: Intravenous use for prevention and treatment of hyperuricemia. *J Clin Oncol* 18: 1758–1763, 2000
49. Arellano F, Sacristan JA. Allopurinol hypersensitivity syndrome: A review. *Ann Pharmacother* 27: 337–343, 1993
50. Spina M, Nagy Z, Ribera JM, Spina M, Nagy Z, Ribera FM, Federico M, Aurer I, Jordan K, Borsaru G, Pristupa AS, Bosi A, Grosicki S, Glushko NL, Ristic D, Jakucs J, Montesinos P, Mayer J, Rego EM, Baldini S, Scartoni S, Capriati A, Maggi CA, Simonelli C. A randomized double-blind phase III pivotal study of febuxostat versus allopurinol in the prevention of tumor lysis syndrome: Florence study. *J Clin Oncol* 32: 5s, 2014
51. Elitek (Rasburicase) Package Label. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/103946s5083lbl.pdf. Accessed April 30, 2015
52. Brogard JM, Coumaros D, Franckhauser J, Stahl A, Stahl J. Enzymatic uricolysis: A study of the effect of a fungal urate-oxydase. *Rev Eur Etudes Clin Biol* 17: 890–895, 1972
53. Jeha S, Kantarjian H, Irwin D, Shen V, Shenoy S, Blaney S, Camitta B, Pui CH. Efficacy and safety of rasburicase (Elitek™), in the management of a malignancy-associated hyperuricemia in pediatric and adult patients: Final results of a multicenter compassionate use trial. *Leukemia* 19: 34–38, 2005
54. Pui C, Mahmoud HH, Wiley JM, Woods GM, Leverger G, Camitta B, Hastings C, Blaney SM, Relling MV, Reaman GH. Recombinant urate oxidase for the prophylaxis or treatment of hyperuricemia in patients with leukemia or lymphoma. *J Clin Oncol* 19: 697–704, 2001
55. Cortes J, Moore JO, Maziarz RT, Wetzler M, Craig M, Matous J, Luger S, Dey BR, Schiller GJ, Pham D, Abboud CN, Krishnamurthy M, Brown A Jr, Laadem A, Seiter K. Control of plasma uric acid in adults at risk for tumor lysis syndrome: Efficacy and safety of rasburicase alone and rasburicase followed by allopurinol compared with allopurinol alone—Results of a multicenter phase III study. *J Clin Oncol* 28: 4207–4213, 2010
56. Sood AR, Burry LD, Cheng DKF. Clarifying the role of rasburicase in tumor lysis syndrome. *Pharmacotherapy* 27: 111–121, 2007
57. Sonbol MS, Yadav H, Vaidya R, Rana V, Witzig TE. Methemoglobinemia and hemolysis in a patient with G6PD deficiency treated with rasburicase. *Am J Hematol* 88: 152–154, 2013
58. Bontant T, Le Garrac S, Avran D, Dauger S. Methaemoglobinaemia in a G6PD-deficient child treated with rasburicase. *BMJ Case Rep* 2014
59. Agha-Razii M, Amyot SL, Pichette V, Cardinal J, Ouimet D, Leblanc M. Continuous veno-venous hemodiafiltration for the treatment of spontaneous tumor lysis syndrome complicated by acute renal failure and severe hyperuricemia. *Clin Nephrol* 54: 59–63, 2000
60. Sakarcan A, Quigley R. Hyperphosphatemia in tumor lysis syndrome: The role of hemodialysis and continuous veno-venous hemofiltration. *Pediatr Nephrol* 3: 351–353, 1994
61. Darmon M, Guichard I, Vincent F, Schlemmer B, Azoulay E. Prognostic significance of acute renal injury in acute tumor lysis syndrome. *Leuk Lymphoma* 51: 221–227, 2010
62. Hummel M, Buchheidt D, Reiter S, Bergmann J, Adam K, Hehlmann R. Recurrent chemotherapy-induced tumor lysis lysis syndrome (TLS) with renal failure in a patient with chronic lymphocytic leukemia: Successful treatment and prevention of TLS with low-dose rasburicase. *Eur J Haematol* 75: 518–521, 2005

REVIEW QUESTIONS

1. Which of the following cancers are considered high risk for tumor lysis syndrome?

   a. Lung cancer
   b. Lung cancer and patient has AKI
   c. Burkitt-type lymphoma, advanced stage
   d. Adult T-cell lymphoma and normal LDH
   e. ALL with WBC $<100 \times 10^9$/L and LDH $<2 \times$ ULN

Answer: c is correct. As shown in Table 2, the risk of TLS depends on type of malignancy, stage or extent of disease, and presence/absence of renal disease. Burkitt-type lymphoma that is in an advanced stage confers a high risk of TLS. Solid tumors such as lung cancer are considered low risk, and the presence of renal failure raises that to intermediate risk. Thus, answers a and b are incorrect. Adult T-cell lymphoma is considered low risk if LDH is normal and acute lymphoblastic leukemia with WBC $<100 \times 10^9$/L is considered intermediate risk if LDH $<2 \times$ ULN.

2. Which of the following electrolyte abnormalities define laboratory TLS?

   a. Hypokalemia
   b. Hypercalcemia
   c. Hypophosphatemia
   d. Hypernatremia
   e. Hypocalcemia

Answer: e is correct. As show in Table 2, laboratory TLS is defined by two or more abnormalities in serum electrolytes. These include a 25% increase from baseline in phosphorous, potassium, or uric acid or a 25% decrease from baseline in calcium. Thus, answers a, b, and c are incorrect. Serum sodium concentration is not directly affected in TLS; therefore, answer d is incorrect.

3. Rasburicase is part of the treatment regimen for tumor lysis syndrome because

   a. It increases urinary alkalinization
   b. It improves the ability of proximal tubular cells to recover from AKI
   c. It stimulates the URAT1 transporter to increase uptake of uric acid from the tubular lumen
   d. It catalyzes the conversion of uric acid into allantoin
   e. It prevents xanthine crystal deposition in tubular lumens

Answer: d is correct. Rasburicase, as shown in Figure 3, is recombinant urate oxidase that enzymatically transforms uric acid into allantoin. It has no known effect on urine pH, renal tubular cells, URAT1 transporters, or xanthine crystals. Thus, answers a–c and e are incorrect.