January/February 2023

JOURNAL OF CLINICAL PATHWAYS®
THE FOUNDATION OF VALUE-BASED CARE

SPECIAL REPORT

Tumor Lysis Syndrome: Early Diagnosis and Management

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EXECUTIVE SUMMARY

Though eradication of cancer cells is the objective of anticancer therapy, the resulting release of potassium, nucleic acids, phosphates, and cytokines from dying cancer cells into the bloodstream can cause cardiac arrhythmias, renal failure, seizures, and even death. This multi-system complication of anticancer therapy – tumor lysis syndrome (TLS) – has become more common with the introduction of new, highly effective cancer therapies, particularly in patients with tumors that are highly sensitive to chemotherapy, such as endometrial cancer, hepatocellular carcinomas, and chronic leukemias. While every patient who receives chemotherapy should be monitored for TLS, clinicians should know how to stratify patients according to TLS risk and employ appropriate prophylaxis based on risk category. Proper hydration and administration of the hypouricemic agents allopurinol or rasburicase are core preventive measures, regardless of risk level, with rasburicase the preferred option in high-risk patients. Management of established TLS centers on hydration to maintain high urine output and administration of rasburicase to lower hyperuricemia. If these measures prove insufficient, dialysis, renal replacement therapy, and/or infusions of appropriate medications to address cardiotoxicity may be required. Given its multisystem effects, TLS monitoring, prevention, and management require a collaborative effort on the part of hospitalists, oncologists, hematologists, intensive care unit physicians, and nephrologists.

Table of Contents

JOURNAL OF CLINICAL PATHWAYS
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Special Report

Tumor Lysis Syndrome: Early Diagnosis and Management

The National Cancer Institute estimated that roughly 1.9 million people would be diagnosed with cancer in the United States in 2022.[1] Cancer is a leading cause of morbidity and mortality in the United States and the second leading cause of death.[2] Given the high prevalence of cancer, clinicians must be aware of the significant complications of cancer and its management.[3] A serious complication of cancer is tumor lysis syndrome (TLS).[3]

TLS is a common, acute, life-threatening disease primarily in patients with hematologic cancers and solid tumors.[4] TLS occurs because of the initiation of chemotherapy or spontaneously. Rapid lysis of proliferating tumor cells causes metabolic imbalances such as hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, all of which can lead to cardiac arrhythmia, seizures, renal failure, and sudden death.[5]

As TLS can be lethal, it is imperative to establish the diagnosis early, which requires vigilant risk assessment, prevention, laboratory monitoring, and aggressive intervention. This review summarizes diagnosis, pathophysiology, and evidence-based guidelines for the prevention and management of TLS.[2]

EPIDEMIOLOGY

TLS in the US: Incidence and Prevalence

The incidence and prevalence of TLS vary depending on the patient population, treatment regimens, and prophylactic procedures undertaken. The past decade has seen a rapid growth of highly effective novel anticancer therapies, and the risk of TLS in certain cancers seemed even higher. Thus ensued the development of strict preventive measures, stepwise dosing, and therapeutic sequencing strategies that significantly reduce the incidence of TLS.[6]

A study including 788 adult and pediatric patients with acute leukemia or non-Hodgkin lymphoma demonstrated how the incidence of TLS varied according to laboratory or clinical TLS—18.9% versus 5%, respectively.[8] The most common malignancies associated with TLS include non-Hodgkin lymphoma (30%), solid tumors (20%), acute myeloid leukemia (AML) (19%), and acute lymphocytic leukemia (ALL) (13%).[2]

TLS in the US: Mortality

TLS is less common now, provided adequate prevention and monitoring. However, clinicians must keep in mind that the consequences may be fatal when they do occur. The condition is life-threatening, and when not recognized early on and aggressively treated, it is linked to a significantly increased risk for poor outcomes, with overall inpatient mortality of approximately 21%.[2]

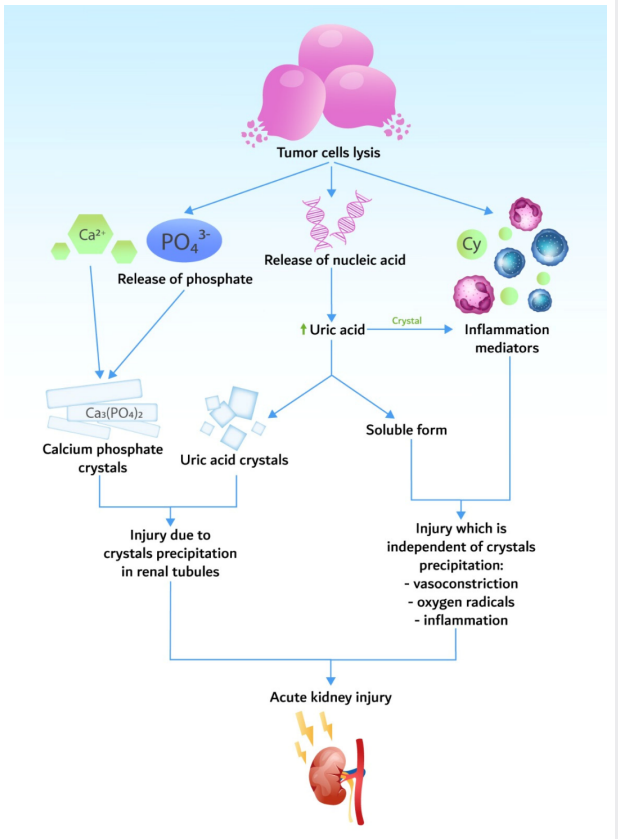

Figure 1. Pathogenesis of tumor lysis syndrome, resulting in acute kidney injury[8]

Patients with TLS have several predictors of short- and long-term mortality, but acute kidney injury (AKI) is the most important one.[6] A single-center study in France reported that in-hospital and 6-month mortality rates were significantly higher in patients with TLS-related AKI (51% and 66%, respectively) than in patients with TLS but without AKI (7% and 21%, respectively).[6] After adjustment for acute disease severity, the presence of AKI was associated with higher hospital mortality (OR: 10.41;

TABLE 1. Cairo-Bishop definition of tumor lysis syndrome[8]

Laboratory TLS = modification of at least 2 parameters within 24 h	– Uric acid ≥ 8 mg/dL – Potassium ≥ 6 mg/dL – Phosphate ≥ 4.5 mg/dL	Or 25% increase	within 3 to 7 days after chemotherapy initiation
	– Calcium ≤ 7 mg/dL	Or 25% decrease	
Clinical TLS = laboratory TLS + 1 organ dysfunction or death	– Renal dysfunction (creatinine > 1.5 x normal values) – Cardiac involvement (arrhythmias) – Neurological involvement (seizures, tetany) – Death		

TLS - tumor lysis syndrome

95% CI: 2.01–19.170; p = 0.005) and 6-month mortality (OR: 5.61; 95% CI: 1.64–54.66; p = 0.006), compared to patients without renal injury.[6,7]

PATHOGENESIS

TLS occurs when massive lysis of tumor cells releases potassium, phosphates, nucleic acid, and cytokines into the bloodstream. These metabolic imbalances can result in several issues, such as cardiac arrhythmia, renal failure, seizures, and sudden death.[6]

Renal failure can occur due to hyperuricemia and hyperphosphatemia. Metabolism of the nucleic acids causes hyperuricemia, leading to renal dysfunction as uric acid precipitates into the renal tubules.[8] Hyperphosphatemia consequently leads to hypocalcemia as the phosphate binds to calcium, forming a complex that deposits in body tissues.[8] Hypocalcemia can lead to cardiac arrhythmias, tetany, seizures, and death.[9] Additionally, cardiac arrhythmias and sudden death can result from hyperkalemia.[9] The massive release of potassium in the bloodstream and decreased clearance of potassium due to AKI can cause muscle fatigue, paralysis, arrhythmia, and death.[8,9] Furthermore, cytokines released from tumor cells can trigger a systemic inflammatory response.[8]

TLS CLASSIFICATION

According to the classification system of Cairo and Bishop, TLS can be classified as laboratory or clinical.[3,10] It can be defined as laboratory TLS when it is undetected clinically. It requires that 2 or more of the following metabolic abnormalities occur within 3 days before or up to 7 days after the initiation of chemotherapy: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.[3,10] Clinical tumor lysis syndrome is defined as the presence of the criteria of laboratory tumor lysis syndrome accompanied by an increased creatinine level, seizures, cardiac dysrhythmia, or death.[3,10] In the Cairo and Bishop definition, a 25% change from baseline should not be considered a criterion, because such increases are rarely clinically important unless the value is already outside the normal range.[7,10] Also, any symptomatic hypocalcemia should represent clinical tumor lysis syndrome. [10]

A clinician should perform a differential diagnosis to distinguish TLS from other causes of acute kidney injury such as sepsis, obstructive renal disease, chemotherapeutic agents, contrast dyes, rhabdomyolysis, vasculitis, and primary glomerulopathies.[3] Additionally, a thorough clinical history is of utmost importance. Testing should include urinalysis and urine microscopy, comprehensive metabolic panel, uric acid, lactate dehydrogenase (LDH), complete blood count, and renal ultrasound.[3] The Cairo-Bishop criteria for the diagnosis of laboratory and clinical TLS are presented in **Table 1**.[8]

Clinical Features

The clinical presentation is directly linked to the biochemical imbalances observed in this disorder, which include hypocalcemia, hyperkalemia, hyperphosphatemia, and hyperuricemia.[3] Each biochemical disorder is typically represented by a collection of clinical symptoms. For instance, patients with hypocalcemia may present with symptoms of nausea, vomiting, spasms, tetany, seizures, and cardiac dysrhythmias.[3] Hyperphosphatemia may be a key cause of renal impairment and cardiac arrhythmias.[3] Patients with hyperkalemia present with fatigue, ECG abnormalities, cardiac arrhythmias, and cardiac arrest.[3] Hyperuricemia is not likely to cause symptoms but should be monitored as it can lead to acute renal injury.[11] Therefore, it is crucial to be aware of these symptoms if they arise in patients with cancer, especially those with tumors in a high-risk group.[3]

PREVENTION OF TLS

Risk Factors

There are several risk factors associated with TLS that include patient characteristics and tumor risk factors.

The risk factors associated with tumors are the type of tu-

Table 2. TLS prophylaxis recommendation based on TLS risk[15]

Low Risk Disease (LRD)	Intermediate Risk Disease (IRD)	High Risk Disease (HRD)
ST*	N/A	N/A
MM	N/A	N/A
CML	N/A	N/A
Indolent NHL	N/A	N/A
HL	N/A	N/A
CLL†	N/A	N/A
AML and WBC <25 x 10^9/l and LDH <2 x ULN	AML with WBC 25-100 x 10^9/l AML and WBC <25 x 10^9/l and LDH ≥2 x ULN	AML and WBC ≥100 x 10^9/l
Adult Intermediate grade NHL and LDH <2 x ULN	Adult Intermediate grade NHL and LDH ≥2 x ULN	N/A
Adult ALCL	Childhood ALCL stage III/IV	N/A
N/A	Childhood intermediate grade NHL stage III/IV with LDH <2 x ULN	N/A
N/A	ALL and WBC <100 x 10^9/l and LDH <2 x ULN	ALL and WBC ≥100 x 10^9/l and/or LDH ≥2 x ULN
N/A	BL and LDH <2 x ULN	BL stage III/IV and/or LDH ≥2 x ULN
N/A	LL stage I/II and LDH <2 x ULN	LL stage III/IV and/or LDH ≥2 x ULN
N/A	N/A	IRD with renal dysfunction and/or renal involvement IRD with uric acid, potassium and/or phosphate >ULN
Prophylaxis recommendations		
Monitoring Hydration ±Allopurinol	Monitoring Hydration Allopurinol	Monitoring Hydration Rasburicase‡

ST, solid tumours; MM, multiple myeloma; CML, chronic myeloid leukaemia; NHL, non-Hodgkin lymphoma; HL, Hodgkin lymphoma; CLL, chronic lymphoid leukaemia; AML, acute myeloid leukaemia; WBC, white blood cell count; LDH, lactate dehydrogenase; ULN, upper limit of normal; ALCL, anaplastic large cell lymphoma; N/A, not applicable; ALL, acute lymphoblastic leukaemia; BL, Burkitt lymphoma/leukaemia; LL, lymphoblastic lymphoma.

* Rare solid tumours, such as neuroblastoma, germ cell tumours and small cell lung cancer or others with bulky or advanced stage disease, may be classified as IRD.

†CII treated with fludarabine, rituximab and/or those with high WBC [≥50 x 10^9/l], should be classified as IRD.

‡Contraindicated in patients with a history consistent with glucose-6 phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol.

mor, tumor volume (tumors > 10 cm), metastatic disease, tumor growth rate (LDH > 2 times normal value), level of leukocytosis (> 25,000/mm^3), and sensitivity to chemotherapy (germ cell tumors, small cell lung cancer, etc.).[8] Additionally, there are certain tumors that are highly sensitive to chemotherapy and therefore can have a higher incidence of TLS, such as endometrial cancer, hepatocellular carcinomas, and chronic leukemia.[8]

Patient characteristics that can lead to TLS are the male gender, age > 65 years, pretreatment serum creatinine > 1.4 mg/dL, renal obstruction, pretreatment serum uric acid > 7.5 mg/dL, and associated conditions (hypotension, hypovolemia, nephrotoxic drugs, chronic kidney disease).[8]

Furthermore, the medication list of the patient should be thoroughly reviewed. Chemotherapy and other substances and drugs are associated with TLS. Chemotherapy associated with TLS include intrathecal chemotherapy, interferon, steroids, radiation therapy, and bortezomib–cyclophosphamide–dexamethasone combination as well as fludarabine and rituximab.[8] Other substances and drugs include alcohol, caffeine, thiazide diuretics, acetylsalicylic acid, cisplatin, methyldopa, theophylline, pyrazinamide, diazoxide, and ethambutol.[8]

Risk Stratification

Proper risk stratification of patients is of high importance for a more efficient therapeutic approach and to decrease morbidity and mortality. Every patient that is receiving chemotherapy should be assessed for TLS.

According to Cairo-Bishop, patients are broadly classified into three risk categories: high risk (> 5% of patients develop TLS), intermediate risk (1% to 5% of patients develop TLS), and low risk (< 1% of patients develop TLS).[5] Patients with aggressive hematologic malignancies considered to be at high risk include Burkitt lymphoma, ALL and AML.[5] Low-risk patients include those with Hodgkin lymphoma, low-grade NHL, myeloma, chronic lymphocytic leukemia, and most solid tumors.[5] The risk is adjusted to the next higher risk group in

Table 3. Recommendations for prevention and treatment of tumor lysis syndrome[12]

	Low Risk Disease (LRD)	Intermediate Risk Disease (IRD)	High Risk Disease (HRD)
Diagnostic measures	• No specific measures	• Daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy	• At least twice daily monitoring of laboratory abnormalities before and during the first 7 days of anticancer therapy
Preventive measures	• Moderate hydration is recommended	• Vigorous hydration • Keep urinary output > 100 mL/h • Treatment with allopurinol or febuxostat should be started at least 24 hours before initiation of anticancer therapy and should be continued till normalization of uric acid levels and signs of large tumor burden are absent	• Vigorous hydration • Keep urinary output >100 mL/h • Single dose 6 mg of rasburicase. Repeat doses as necessary. In case of contraindication treatment with febuxostat
Treatment of established tumor lysis syndrome	• Admission to intensive care unit with continuous cardiac monitoring and monitoring of laboratory abnormalities every 4-6 hours • Early nephrology consultation to estimate the indications for renal replacement therapy • Correction of electrolyte abnormalities • Vigourous hydration keep urinary output >100 ml/h • Single dose 6 mg of rasburicase. Repeat doses as necssary. In case of contraindication, treatment with febuxostat		

patients with renal dysfunction, renal involvement by tumor, or elevated levels of uric acid, phosphate, and potassium. [5]

Prevention

Prevention of TLS begins with a thorough risk stratification and close monitoring of symptoms and lab work at least twice-daily before and during the first 7 days of anticancer therapy, especially in patients at high-risk. Recommendations for prevention and treatment of TLS are listed in **Table 3**.[12] A comprehensive medication history should be performed to evaluate the medications that could be contributing to TLS and should be effectively discontinued.[11]

Immediate recognition of TLS symptoms and diagnosis are of paramount importance to prevent the occurrence of clinical TLS. Hydration with hypouricemic agents (allopurinol and rasburicase) are the foundation of TLS management.[13] Rasburicase, a recombinant urate oxidase, metabolizes urate in allantoin, a compound 10 times more soluble than uric acid.[13] In general, patients with a low risk of developing TLS should be monitored for development of TLS; normal hydration and no prophylaxis for hyperuricemia should be given except in cases of signs of metabolic changes.[15] Patients with an intermediate risk of developing TLS should be monitored, hydration increased, and administered allopurinol for up to 7 days.[14] The standard recommended dosing schedule for allopurinol in prevention of TLS is 200 to 400 mg/m^2/day in 1 to 3 divided doses for adults, up to a maximum of 800 mg daily. In children, the recommended dose is 300 to 450 mg/m^2/day in three divided doses up to 400 mg daily.[14] In patients with high risk of developing TLS, perform frequent monitoring, increase hydration, and administer rasburicase. Rasburicase has a recommended dose of 0.1 to 0.2 mg/kg on the first day, repeated daily up to 7 days.[14] Also, management of hyperkalemia and hyperphosphatemia should be based on TLS treatment guidelines. The TLS prophylaxis recommendation based on TLS risk is summarized in **Table 2**.[15]

MANAGEMENT

It is essential to have a high level of suspicion for TLS; therefore, management of this condition involves a multidisciplinary approach including nephrologists, hematologists, intensive care unit physicians, hospitalists, and oncologists. The clinical condition can change rapidly requiring frequent monitoring, the availability of specialized teams and facilities, and aggressive treatment.

Fluid Hydration

The first step in the management of TLS is maintaining a high urine output through hydration to prevent uric acid and calcium phosphate complexes from precipitating in the kidney.[14] The aim is to maintain a urine output of 100 mL/m^2/h for older patients using isotonic solutions, with no added potassium to avoid increasing hyperkalemia, and monitoring hourly.[14] The process of monitoring fluid balance can be performed by daily weigh-ins of the patient.[14]

Hyperuricemia

Although allopurinol is useful in lowering hyperuricemia as prophylaxis of TLS, it is not the drug of choice in the treatment of established TLS. In contrast, rasburicase can break down uric acid more significantly than allopurinol, and patients should be switched to this if they develop TLS. The standard recommended dose is 0.2 mg/kg/day given as a 30-min infusion for 3 to 7 days. [14]

Hypophosphatemia and Hypocalcemia

If hydration and timely administration of rasburicase do not prevent significant hyperphosphatemia, the next step is dialysis.[14] Intractable fluid overload, hyperkalemia, hyperuricemia, hyperphosphatemia, or hypocalcemia are indications for renal dialysis.[13] Additionally, asymptomatic hypocalcemia should not be treated as it can precipitate further calcium phosphate deposition in the kidneys.[14] However, symptomatic hypocalcemia should be treated with calcium gluconate. [14]

Hyperkalemia

Finally, it is recommended that cardiac monitoring should be performed on patients with potassium levels greater than or equal to 6 mmol/l.[13] Acute cardiotoxicity should be treated with a short infusion of calcium gluconate; also, intravenous salbutamol, insulin, and glucose can be effective. [14]

Renal Replacement Therapy

Due to the use of urate oxidase therapy, the need for renal dialysis has decreased in patients at risk of TLS. A study in Germany evaluated pediatric patients with Burkitt lymphoma/leukemia using urate oxidase and monitored care outcomes over 11 years. Over the course of the study, the incidence of TLS was 20·5% vs. 9·4% in periods one and three, respectively. However, when this measure described fails to prevent renal deterioration and significant fluid overload or hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia developed, renal dialysis is indicated.[14,16] In patients with a high risk of TLS, chemotherapy should be administered, with access to renal replacement therapy (RRT). Renal dialysis is indicated when there is significant fluid overload and metabolic imbalances. [6]

The choice of the RRT technique depends on the laboratory data, malignant cell turnover, clinical condition of the patient, and volume status. Intermittent hemodialysis is preferred in patients with severe hyperkalemia and severe hyperuricemia. In critically ill patients, continuous hemofiltration hemodialysis is the reasonable choice. For patients with severe hyperphosphatemia, continuous veno-venous hemodiafiltration has been proven as the most effective method of phosphate control.[6] Peritoneal dialysis is not recommended for the treatment of TLS.[14]

CONCLUSION

TLS is an onco-metabolic emergency resulting from rapid cell death that can occur because of chemotherapy or spontaneously. The ever-expanding advances in chemotherapy pose a risk of TLS development even in patients with malignancies that were previously classified as having a low risk for this complication.

Clinicians should stratify every hospitalized cancer patient for the risk of TLS, and an aggressive prophylactic approach is mandatory to limit the occurrence of TLS. The care of patients with TLS requires a multi-disciplinary approach with close collaboration between hospitalists, hematologists, intensive care physicians, oncologists, and nephrologists. ◆

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