

# Tumor Lysis Syndrome

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● **Tumor lysis syndrome (TLS) is an acute, life-threatening disease among adults and children that is associated with the initiation of cytoreductive therapy in the treatment of malignancy. A pattern of metabolic derangements occurs as a result of a massive release of intracellular contents into the systemic circulation. Characteristic findings include hyperuricemia, hyperphosphatemia, hyperkalemia, hypocalcemia, and uremia, all of which can lead to cardiac arrhythmia, seizures, renal failure, and sudden death. The incidence of TLS appears to be increasing because of a rapidly growing armamentarium of highly effective biologic and targeted therapies. Risk assessment and prevention are at the forefront of management and rely on clinician awareness, prophylactic measures, and vigilant laboratory monitoring. Established TLS requires early, aggressive intervention with intravenous hydration, electrolyte management, and the use of hypouricemic agents. This review highlights the central role of diagnostic laboratory criteria for TLS, and summarizes the clinical findings, pathophysiology, and evidence-based guidelines for the prevention and management of TLS.**

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The pattern of metabolic derangements known as tumor lysis syndrome (TLS) was first described decades ago with the introduction of chemotherapy into clinical practice.<sup>1</sup> Tumor lysis syndrome is caused by the brisk and massive destruction of tumor cells and is most frequently observed in patients with highly proliferative hematologic malignancies following the initiation of chemotherapy. The release of intracellular contents, including nucleic acids, electrolytes, and cytokines, into the systemic circulation leads to characteristic laboratory findings, including hyperuricemia, hyperphosphatemia, hyperkalemia, secondary hypocalcemia, and uremia. Tumor lysis syndrome is a medical emergency that, without prompt intervention, can result in significant morbidity related to cardiac arrhythmias, seizures, renal failure, and possibly death.<sup>2</sup> Renal failure in TLS is a poor prognostic indicator associated with increased

mortality and leads to greater resource use and longer, more costly hospital stays.<sup>3–5</sup> In addition, TLS-related complications can preclude further administration of antitumor therapies.

The incidence of TLS is not well defined because of a historical lack of standardized diagnostic criteria and the variability of patient populations and treatment regimens. In the current era of rapidly evolving, highly effective targeted therapies, tumors that were once rarely associated with this syndrome are increasingly described in the literature.<sup>6,7</sup> Monoclonal antibodies and tyrosine kinase inhibitors are 2 examples of widely used targeted therapies that have been shown to induce TLS as single-agent therapies or in combination with conventional chemotherapies. Morbidity and mortality may be higher with newer therapies because of a lack of recognition, inadequate prophylaxis, and delayed treatment.<sup>7</sup> Prevention is the most effective approach in the algorithm for managing TLS, and in recent years expert panels have published evidence-based guidelines for risk stratification, prevention, and treatment of TLS.<sup>8–10</sup> Clinician awareness, adequate prophylactic measures, vigilant laboratory analyte monitoring, and early treatment intervention are essential to minimize TLS-related complications.

## DEFINITION

Laboratory criteria are of primary importance in establishing a diagnosis of TLS. The most widely recognized diagnostic criteria for TLS were proposed in 1993 by Hande and Garrow<sup>11</sup> to distinguish patients with laboratory TLS (LTLS) from those with clinical TLS (CTLTS), which has a worse prognosis and greater risk of death.<sup>12</sup> The original criteria required a 25% change from baseline in the implicated laboratory analyte values occurring within 4 days after the initiation of cancer therapy. The criteria were revised by Cairo and Bishop<sup>1</sup> in 2004 to include patients who have metabolic abnormalities at baseline (spontaneous TLS) and to extend the time frame from the initiation of cytotoxic therapy at which the laboratory abnormalities are considered diagnostic.

## Laboratory TLS

Laboratory TLS is defined as having at least 2 isolated metabolic derangements, including hyperuricemia, hyperphosphatemia, hyperkalemia, or hypocalcemia, according to threshold analyte values listed in Table 1, that occur within 3 days prior to and up to 7 days after the initiation of cytotoxic therapy. The definition also includes a 25% change from baseline in any of the involved analytes to encompass values that may be within normal reference intervals; however, normal values are not likely to be clinically significant, and removal of this criterion has been proposed.<sup>2</sup> Hypocalcemia

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**Table 1. Cairo-Bishop Definition for Laboratory and Clinical Tumor Lysis Syndrome (TLS)<sup>a</sup>**

Laboratory TLS	Clinical TLS
Two or more of the following laboratory abnormalities within 3 days prior to and up to 7 days after initiation of cytotoxic therapy <sup>b</sup> : Uric acid $\geq 8$ mg/dL Potassium $\geq 6$ mEq/L Phosphate $\geq 6.5$ mg/dL for children $\geq 4.5$ mg/dL for adults Calcium $\leq 7$ mg/dL OR 25% change from baseline in any of the above analytes	Laboratory TLS plus 1 or more of the following:  Creatinine $\geq 1.5$ times the upper limit of normal <sup>c</sup> Cardiac arrhythmia Seizure Sudden death

<sup>a</sup> Reprinted and modified with permission. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol.* 2004;127(1):3–11.<sup>1</sup>

<sup>b</sup> This assessment assumes that the patient has or will receive adequate hydration and a hypouricemic agent(s).

<sup>c</sup> Not directly or probably related to a therapeutic agent.

as a diagnostic criterion is debated because in TLS it is a secondary phenomenon to hyperphosphatemia.<sup>13</sup> However, the calcium level may be an important indicator of calcium phosphate binding and precipitation in tissues. An elevated serum lactate dehydrogenase (LDH) level is a surrogate biomarker for rapid cell turnover and is important for TLS risk assessment, but it is not a diagnostic criterion.

### Clinical TLS

Clinical TLS includes renal, cardiac, or neurologic consequences resulting from the underlying metabolic derangements. Clinical TLS must meet the diagnostic criteria for LTLS and, in addition, include at least 1 of the following: renal insufficiency with a creatinine level of at

least 1.5 times the upper limit of normal (ULN), cardiac arrhythmias, seizures, or sudden death. Howard et al<sup>2</sup> further proposed that symptomatic hypocalcemia be considered an inclusion criterion for CTLS. A grading system for measuring the severity of clinical TLS was also proposed by Cairo and Bishop<sup>1</sup> (Table 2), and is based on the degree of creatinine elevation, and the degree of medical intervention required for, or the refractoriness to medical intervention of, cardiac arrhythmias or seizures. This system is graded from 0 to 5 and expands on the National Cancer Institute Common Terminology Criteria for Adverse Events, in which grading consists of the presence of TLS (grade 3), life-threatening consequences or urgent intervention indicated (grade 4), and death (grade 5).<sup>14</sup>

**Table 2. Cairo-Bishop Grading of Clinical Tumor Lysis Syndrome (TLS)<sup>a</sup>**

Complication	Grade					
	0	1	2	3	4	5
LTLS	Absent	Present	Present	Present	Present	Present
Creatinine <sup>b,c</sup>	<1.5 times the ULN	1.5 times the ULN	>1.5 to 3.0 times the ULN	>3.0 to 6.0 times the ULN	>6.0 times the ULN	Death <sup>d</sup>
Cardiac arrhythmia <sup>b</sup>	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically; controlled with device (eg, defibrillator)	Life-threatening (eg, associated with CHF, hypotension, syncope, shock)	Death <sup>d</sup>
Seizure <sup>b</sup>	None	Not applicable	One brief, generalized seizure; seizure(s) well controlled by anticonvulsants; infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Any prolonged, repetitive, or difficult-to-control seizure (eg, status epilepticus, intractable epilepsy)	Death <sup>d</sup>

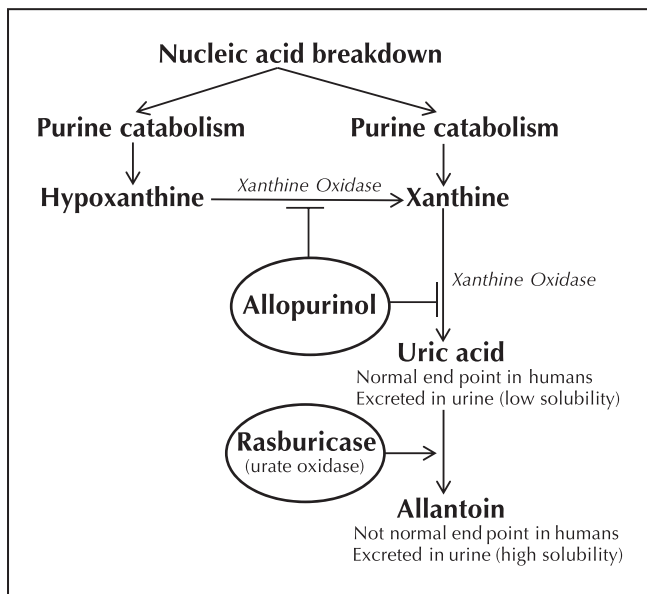
Abbreviations: ADL, activities of daily living; CHF, congestive heart failure; LTLS, laboratory tumor lysis syndrome; ULN, upper limit of normal.

<sup>a</sup> Maximal clinical TLS manifestation (renal, cardiac, or neurologic) defines the grade. Reprinted with permission. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol.* 2004;127(1):3–11.<sup>1</sup>

<sup>b</sup> Not directly or probably attributable to a therapeutic agent.

<sup>c</sup> If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: older than 1 year to younger than 12 years of age, both male and female, 0.7 mg/dL; 12 years to younger than 16 years, both male and female, 1.0 mg/dL; and 16 years and older, female 1.2 mg/dL, male 1.3 mg/dL.

<sup>d</sup> Mortality probably or definitively attributable to clinical TLS.



Catabolism of purines and mechanism of action of hypouricemic agents. Reprinted from Abu-Alfa AK, Younes A. Tumor lysis syndrome and acute kidney injury: evaluation, prevention, and management. *Am J Kidney Dis.* 2010;55(5)(suppl 3):S1-S13, with permission from Elsevier.<sup>13</sup>

## CLINICAL FEATURES

Tumor lysis syndrome generally occurs within 12 to 72 hours following the initiation of cytotoxic therapy, although manifestations arise infrequently prior to receiving therapy—called spontaneous TLS—or may extend beyond 72 hours after treatment initiation. Symptoms reflect the underlying metabolic abnormalities and may include nausea, vomiting, diarrhea, anorexia, weakness, lethargy, hematuria, cardiac dysrhythmias, seizures, muscle cramps, tetany, and syncope. The cascade of pathophysiologic events that is initiated by extensive tumor lysis can lead to multiorgan failure, with renal and cardiac failure being most common, or to sudden death.

## PATHOGENESIS

### Hyperuricemia

Hyperuricemia is a hallmark of TLS that, along with hyperphosphatemia, can lead to acute kidney injury. Purine-containing nucleic acids (adenosine and guanine) released into the serum are catabolized to uric acid and, when present in excess, surpass the renal tubular capacity for uric acid excretion. In the catabolic pathway, nucleic acids are first metabolized to hypoxanthine and xanthine, which are subsequently converted to uric acid through the enzymatic action of xanthine oxidase (Figure). Uric acid is poorly soluble in water, and the solubility is markedly reduced in the physiologically acidic environment of the distal tubules and collecting system. Thus, uric acid crystals readily precipitate when concentrated in the renal circulation, leading to renal tubule obstruction and obstructive uropathy, with compromised glomerular filtration and reduced urine output.<sup>15,16</sup>

Xanthine nephropathy and xanthine lithiasis can also occur in patients with tumor lysis who are receiving allopurinol, a widely used hypouricemic agent. Allopurinol

blocks uric acid synthesis through its active metabolite, oxypurinol, which is a xanthine analog and competitive inhibitor of xanthine oxidase. Blockage of this pathway leads to accumulation of the uric acid precursors xanthine and hypoxanthine, of which hypoxanthine is more soluble and more easily excreted than uric acid. However, xanthine is a less soluble metabolite than uric acid, and its accumulation can lead to xanthine precipitation.<sup>15,17,18</sup> Xanthine levels are not routinely measured, and the incidence of xanthine nephropathy and its contribution to acute renal injury in TLS are unknown.

Urate oxidase, or uricase, is an enzyme present in most mammals that oxidizes uric acid to the water-soluble and readily excreted metabolite allantoin. Allantoin is 5- to 10-fold more soluble than uric acid. Urate oxidase is absent in humans because of a missense mutation, but pharmacologic urate oxidase is available and used in the prevention and treatment of hyperuricemia.<sup>16,17</sup> Urate oxidase was originally purified from the fungus *Aspergillus flavus* and caused frequent allergic reactions. Rasburicase is a recombinant preparation biosynthesized from a strain of genetically modified *Saccharomyces cerevisiae* containing cDNA from *A. flavus* that encodes for urate oxidase.<sup>17</sup> Rasburicase is highly effective at rapidly reducing uric acid levels without increasing the levels of uric acid precursors, and therefore does not risk xanthine nephropathy.

### Hyperphosphatemia and Hypocalcemia

Tumor cells often contain higher concentrations of phosphate than their normal counterparts, and the amount of phosphate released varies by tumor type.<sup>9</sup> In massive tumor lysis, mechanisms of renal tubular excretion of phosphate become saturated. The excess serum phosphate binds to calcium and results in secondary hypocalcemia and calcium phosphate deposition throughout the body. Hypocalcemia can range from asymptomatic to life-threatening cardiac conduction abnormalities or seizures, and calcium phosphate deposition in the heart can cause fatal dysrhythmias. Nephrocalcinosis is the precipitation of calcium phosphate crystals in the renal tubules that can result in nephrolithiasis and cause or further provoke an obstructive uropathy.<sup>16</sup> The risk of calcium phosphate precipitation in tissues increases when the calcium phosphate product (phosphate concentration multiplied by the calcium concentration) exceeds 60 mg<sup>2</sup>/dL<sup>2</sup>, and a product of 70 mg<sup>2</sup>/dL<sup>2</sup> or greater may be an indication for renal replacement therapy.<sup>9</sup>

### Hyperkalemia

Potassium is a primarily intracellular electrolyte that is regulated through renal excretion. Hyperkalemia is another consequence of massive tumor lysis that can precipitate cardiac dysrhythmias and sudden death. Calcium helps to stabilize the cardiac membrane by directly blocking the effects of potassium on the resting membrane potential of cardiomyocytes. Thus, hypocalcemia exacerbates hyperkalemia-induced cardiotoxicity and cardiac dysrhythmias. A potassium level greater than 7.0 mEq/L is generally considered a hyperkalemic emergency and can be potentiated by ongoing tumor lysis, hypocalcemia, and/or renal impairment.<sup>9,10</sup>

### Acute Renal Injury

Acute renal injury is an independent predictor of short-term and long-term mortality in TLS.<sup>5</sup> It occurs through

crystal-dependent and crystal-independent mechanisms. Crystal-dependent mechanisms include obstructive uropathy as a result of uric acid or calcium phosphate precipitation, as described above. Decreased urinary output can result in volume overload and cardiac failure, and low-flow states can, in turn, exacerbate crystal precipitation. Urine alkalinization to a pH above 6.5 was once a common practice for the prevention and treatment of hyperuricemia in TLS. An alkaline environment keeps uric acid in its more soluble ionized form and prevents crystallization in the renal tubules. However, urine alkalinization lacks proven efficacy for the prevention of obstructive uropathy in hyperuricemia, and conversely may worsen renal function by inciting precipitation of calcium phosphate, which is less soluble in an alkaline environment.<sup>13,15</sup> With the widespread use of hypouricemic agents to prevent hyperuricemia, this controversial practice is no longer recommended, particularly in the absence of metabolic acidosis.<sup>2,9,10</sup> Crystal-independent mechanisms include loss of autoregulation, renal vasoconstriction, and local inflammation.<sup>13</sup> Tumor lysis–induced hypercytokinemia can result in hypotension, systemic inflammation, and multiorgan failure.<sup>2</sup>

### INCIDENCE

The incidence of TLS is not well defined because of the heterogeneity of patient populations and treatment regimens, as well as differences in TLS prophylaxis and the historical lack of a universal definition for TLS. Tumor lysis syndrome is observed most frequently in patients with highly proliferative hematologic malignancies, including high-grade non-Hodgkin lymphomas (NHLs), acute lymphoblastic leukemia (ALL), and acute myeloid leukemia (AML). In 2 multicenter trials evaluating 1791 children with NHL, the overall incidence of TLS was 4.4%, with the highest incidence in subgroups with B-cell ALL (26.4%) and advanced-stage Burkitt lymphoma (14.9%). A multi-institutional study of adults (n = 433) and children (n = 322) with acute leukemia or NHL reported an overall incidence for LTLS and CTLS of 18.9% and 5.0%, respectively. Subgroup analysis showed respective rates of 21.4% and 5.2% for ALL, 19.6% and 6.1% for NHL, and 14.7% and 3.4% for AML.<sup>3</sup> In a study of 772 adult patients with AML who received allopurinol prophylaxis, the incidences of LTLS and CTLS were 12% and 5%, respectively. A pretreatment creatinine level greater than 1.4 mg/dL strongly predicted the development of TLS, and CTLS was associated with a higher risk of death during induction therapy (79% versus 23%,  $P < .001$ ), whereas LTLS was not associated with higher mortality (24% versus 22%,  $P = .72$ ).<sup>12</sup> Tumor lysis syndrome has also been described in less aggressive and indolent hematologic malignancies and in rare cases of solid tumors, including (but not limited to) small cell carcinoma, breast carcinoma, germ cell tumors, neuroblastoma, and melanoma.<sup>19</sup>

The development of TLS has been long recognized with the use of conventional chemotherapy, corticosteroids, and radiation therapy. However, a recent systematic review showed that the incidence of TLS, or lack thereof, has not been a focus of reporting in the most recent literature of novel and targeted therapies for hematologic malignancies.<sup>6</sup> Hence, the incidence and optimal prevention and management strategies among these new therapies are unknown. Newer cytoreductive therapies implicated in the development of TLS include monoclonal antibodies, immunother-

apies, biologic agents, and other targeted therapies, such as tyrosine kinase inhibitors.<sup>20</sup> Tumor lysis syndrome–related fatalities have been reported with the introduction of novel therapies into clinical practice, which have resulted in modifications, such as stepped dosing and halting of clinical trials.<sup>21,22</sup> Table 3 provides a nonexhaustive list of novel agents with published literature in which TLS has been observed.<sup>6</sup>

### RISK FACTORS

The risk for developing TLS varies considerably based on tumor type and well-recognized disease-, patient-, and treatment-specific factors (Table 4).<sup>1,2,6,8,9</sup> Among patients with either hematologic or solid tumors, bulky disease and tumors that are highly sensitive to cytoreductive therapy pose the greatest risk of TLS. The LDH level serves as a surrogate for rapid cell turnover (tumor lysis), and higher levels equate to greater risk. The white blood cell (WBC) count represents tumor bulk in some hematologic malignancies, whereas in lymphomas and solid tumors, size 10 cm or greater, or widely metastatic disease generally constitutes increased tumor bulk. Preexisting renal disease; renal obstruction; low-flow urinary states, such as inadequate hydration or hypotension; and concurrent use of nephrotoxic agents compromise the kidney's adaptive capacity to deal with the metabolic effects of tumor lysis, which increase the risk for developing TLS and can exacerbate TLS-related complications.<sup>13</sup>

### RISK ASSESSMENT

Current evidence-based guidelines for the prevention of TLS in adults and children depend on risk assessment for stratifying patients as being at low (<1%), intermediate (1%–5%), or high (>5%) risk for developing TLS.<sup>8</sup> An international expert panel proposed the first risk stratification model in 2008, based principally on tumor type and WBC count,<sup>9</sup> and it was updated in 2010 to incorporate all malignancies and known risk factors, including histologic diagnosis, disease burden, age at diagnosis for particular tumors, use of particular cytotoxic agents or biologic therapies, and a final adjustment based on renal function.<sup>8</sup> Risk stratification is summarized in Table 5. Patients with aggressive hematologic malignancies considered to be at high risk include Burkitt lymphoma, ALL, and AML. Risk is further stratified based on stage and LDH level for the high-grade NHLs, and based on WBC count and LDH level for ALL and AML. A WBC count of  $100 \times 10^3/\mu\text{L}$  or higher and an LDH level 2 times the ULN or higher generally place patients in higher-risk groups. The NHLs that are categorized as high, intermediate, or low risk by age, stage, and LDH level include adult T-cell lymphoma, diffuse large B-cell lymphoma, transformed lymphoma, and blastoid variants of mantle cell lymphoma. Low-risk patients include those with Hodgkin lymphoma, low-grade NHL, myeloma, chronic lymphocytic leukemia treated with alkylating agents, and most solid tumors. Chronic lymphocytic leukemia treated with targeted or biologic therapies and bulky, chemosensitive solid tumors increases the patient's risk to intermediate. Lastly, risk is adjusted to the next higher risk group in patients with low- and intermediate-risk leukemia and lymphoma with either renal dysfunction, renal involvement by tumor, or—for intermediate-risk patients only—elevated uric acid (except in the setting of preexisting gout-related hyperuricemia), phosphate, or



**Table 3. Novel Agents Associated With Tumor Lysis Syndrome (TLS)<sup>a</sup>**

Agent	Class	Treated Malignancies	Observed TLS Incidence Single-Agent/Combination Therapy
<b>Monoclonal antibodies</b>			
Brentuximab	Anti-CD30 and antimicrotubular agent (monomethyl auristatin E)	ALCL	1.7%
Cituximab	EGFR inhibitor	Metastatic colon carcinoma	Case reports
Obinutuzumab	Anti-CD20	CLL, NHL, relapsed/refractory DLBCL	3%–5%
Ofatumumab	Anti-CD20	Relapsed/refractory DLBCL, relapsed CLL	0%/0% grades 3–4 TLS (with lenalidomide)
Rituximab	Anti-CD20	Indolent and aggressive NHLs, PTLD	Low incidence in case reports and case series
<b>Kinase inhibitors</b>			
Alvociclib (flavopiridol)	CDK inhibitor	AML	4.2%/42.2%
Dasatinib	Bcr-Abl and Src TKI	Chronic/accelerated/blast phase CML, Ph <sup>+</sup> ALL	3.4%/4.2%
Dinaciclib	CDK inhibitor	ALL, AML, relapsed/refractory CLL	15%
Ibrutinib	Bruton TKI	CLL/SLL	0%/6.7%
Idelalisib	Small-molecule inhibitor of PI3K	Refractory/relapsed MCL and CLL, previously treated indolent NHL	0%
Imatinib	Bcr-Abl TKI	Chronic/blast phase CML, Ph <sup>+</sup> ALL, metastatic GIST	Case reports
Nilotinib	Bcr-Abl TKI	Accelerated phase CML	Case reports
Sorafenib	VEGFR TKIs	HCC, RCC	Case reports
Sunitinib	VEGFR TKIs	GIST, RCC	Case reports
<b>Chimeric immunoreceptors</b>			
CAR-T	CD19 targeted	Persistent B-cell malignancies after allogeneic HCT	10%
<b>Proteasome inhibitors</b>			
Bortezomib	Reversible proteasome inhibitor	MM	1.4%–5% (±dexamethasone)
Carfilzomib	Irreversible proteasome inhibitor	Relapsed/refractory MM	0.4%–4.3%
Oprozomib	Structural analog of carfilzomib	MM, Waldenström macroglobulinemia	2.4%
<b>Immunomodulatory agents</b>			
Lenalidomide	Analog of thalidomide	CLL (initial therapy), relapsed/refractory CLL or NHL	0%–4%/1.7% with rituximab
Thalidomide	Unknown mechanism of action	MM, HCC	Case reports
<b>Bcl-2 inhibitors</b>			
Venetoclax	Small-molecule Bcl-2 inhibitor	Relapsed/refractory CLL	3.2%–8.9% (2 fatalities)/2.7% (fatality) with rituximab

Abbreviations: ALCL, anaplastic large cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; Bcl-2, B-cell lymphoma-2 gene product; Bcr-Abl, fusion oncogene product of Abelson tyrosine kinase and breakpoint cluster genes; CAR-T, chimeric antigen receptor T cells; CDK, cyclin-dependent kinase; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; HCC, hepatocellular carcinoma; HCT, hematopoietic cell transplantation; MCL, mantle cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; Ph<sup>+</sup>, Philadelphia chromosome positive; PI3K, phosphatidylinositol 3-kinase; PTLD, posttransplantation lymphoproliferative disorder; RCC, renal cell carcinoma; SLL, small lymphocytic lymphoma; Src, gene product of src family kinases; TKI, tyrosine kinase inhibitor; VEGFR, vascular endothelial growth factor receptor.

<sup>a</sup> Data are derived from Howard et al<sup>6</sup> and Bose and Qubaiah.<sup>7</sup>

potassium levels. Although widely used, this stratification has not been validated in prospective trials and best clinical judgment must be applied to individual patient scenarios.

### PREVENTION

There is a great deal of overlap in the prevention and management of TLS, and both involve the monitoring of fluid status and laboratory analytes, and the use of hypouricemic agents. Prevention of TLS and related complications is focused on the preservation of renal function and close monitoring for the development of TLS. Expert panels have published guidelines with the

following general risk-based prevention strategies for pediatric and adult patients (Table 5)<sup>9,10</sup>:

- Low risk: a “watch and wait” strategy may be appropriate and includes vigilant monitoring of laboratory parameters and fluid status, with a low threshold for intravenous fluids and consideration of allopurinol prophylaxis.
- Intermediate risk: aggressive intravenous hydration and administration of prophylactic allopurinol, with vigilant monitoring of laboratory parameters and fluid status. Rasburicase can be considered for the initial hypouricemic agent and should be initiated in place of allopurinol if hyperuricemia develops.

**Table 4. Risk Factors for Tumor Lysis Syndrome**

Disease-related factors	
Rapid cellular proliferation rate	Elevated serum LDH (>2 times the ULN)
High tumor burden	
Bulky tumors (>10 cm)	Widely metastatic disease
	Elevated WBC count (>25 × 10 <sup>3</sup> /μL)
Sensitivity to cytoreductive therapy	
Renal infiltration or outflow tract obstruction by tumor	
Patient-related factors	
Preexisting renal disease/uremia	
Nephropathy	Renal failure or oliguria
	Urinary tract obstruction
Pretreatment hyperuricemia or hyperphosphatemia	
Hypovolemia or hypotension	
Acidic urine	
Treatment-related factors	
Intensity of cytoreductive therapy	
Single-agent versus combination therapy	Disease-specific, varies according to tumor type
Inadequate hydration during cytoreductive therapy	
Concurrent use of nephrotoxic agents	

Abbreviations: LDH, lactate dehydrogenase; ULN, upper limit of normal; WBC, white blood cell.

Data derived from Coiffier et al.<sup>9</sup>

- High risk: aggressive intravenous hydration and administration of prophylactic rasburicase, with vigilant monitoring of laboratory parameters and fluid status. Allopurinol should be substituted for rasburicase for patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

The classification and approach to patients at intermediate risk is not as clearly defined as that for low- and high-risk groups, and for all groups, therapeutic decision-making is ultimately based on judicial clinical judgment. Prophylaxis should be started prior to the initiation of antitumor therapy whenever possible.

## MANAGEMENT

### Analyte Monitoring

It is important to obtain baseline analyte values prior to the initiation of cytoreductive therapy or administration of hypouricemic agents. The frequency of analyte testing is based on the TLS risk assessment. Analyte monitoring to include uric acid, electrolytes, LDH, and creatinine, at intervals of every 4 to 6 hours, is generally appropriate for high-risk patients or for those with overt TLS, every 6 to 8 hours for intermediate-risk patients, and daily for low-risk patients, but it ultimately depends on the clinical condition of the patient and underlying comorbidities.<sup>2,9</sup> It is probably most clinically relevant to maintain an index of suspicion based on analyte trends rather than absolute analyte cutoffs.<sup>10</sup> It is important to consider that uric acid levels may remain normal in patients with an emerging TLS who are administered a prophylactic hypouricemic agent. For patients who receive rasburicase, laboratories must develop

protocols to collect uric acid samples in prechilled tubes that are placed immediately on ice and kept on ice throughout rapid transport to the laboratory for immediate run on the instrument to prevent rapid *in vitro* uric acid breakdown, and a spuriously low assay result.<sup>10,16</sup>

### Hydration

Maintaining a high urine output with adequate hydration is the most important aspect of TLS prevention and management, because this improves renal perfusion and glomerular filtration, and minimizes acidosis, all of which serve to prevent the precipitation of uric acid and calcium phosphate crystals in the renal tubules.<sup>13</sup> In patients at intermediate-to-high risk for TLS and those with established TLS, hyperhydration with hypotonic or isotonic solution is recommended, with a goal to maintain equal fluid balance and a high urine output.<sup>8,10</sup> Given the risk for electrolyte derangement, potassium, phosphate, and calcium should not be added to the hydration solution. Urine alkalization to promote uric acid excretion is no longer recommended because of a lack of clear efficacy and the potential for precipitating xanthine and calcium phosphate in the renal tubules.<sup>2,9,10</sup> Volume status must be very carefully monitored to prevent volume overload, particularly in patients with renal failure or cardiac dysfunction, and diuretics may be necessary to maintain urine output. Loop diuretics are often favored because they promote potassium excretion. However, diuretics must be avoided in hypovolemia or obstructive uropathy.

### Hypouricemic Agents

Allopurinol is a xanthine oxidase inhibitor that blocks *de novo* synthesis of uric acid and is the preferred prophylactic agent in low-to-intermediate risk patients. Allopurinol has several limitations. First, because it does not break down preexisting uric acid, urate nephropathy can develop in the 2 to 3 days it takes to have a therapeutic effect and is not the preferred agent in the presence of hyperuricemia. Furthermore, xanthine nephropathy must be considered in patients who develop TLS while receiving appropriate prophylactic therapy with allopurinol.<sup>18</sup> Second, allopurinol is excreted by the kidneys and must be dose reduced or discontinued in patients with renal insufficiency. Third, hypersensitivity reactions have occurred. Asian populations have a higher frequency of the HLA-B\*58:01 allele, which is associated with severe adverse cutaneous reactions with allopurinol use.<sup>23</sup> Lastly, because allopurinol reduces purine degradation, chemotherapeutic agents, such as 6-mercaptopurine and azathioprine, must be dose reduced by 50% to 70% when concurrently administered. Any patient who develops TLS while receiving allopurinol prophylaxis should be switched to rasburicase.<sup>10</sup>

Rasburicase is a recombinant urate oxidase that converts uric acid to the highly soluble form allantoin. It is highly effective at preventing and treating hyperuricemia and, in the absence of contraindications, is the preferred prophylactic agent for patients at high risk for TLS and the treatment of choice for established TLS.<sup>10</sup> Unlike allopurinol, rasburicase rapidly reduces uric acid levels without a therapeutic delay and breaks down deposits of uric acid.<sup>17,24,25</sup> Elevated serum phosphate and serum creatinine levels have also been shown to decrease with the use of rasburicase.<sup>17</sup> Rasburicase is generally well tolerated and does not require renal dosing; however, there is a risk for severe hypersensitivity reactions, such as anaphylaxis,

**Table 5. Tumor Lysis Syndrome (TLS) Risk Assessment and Recommended Prophylaxis for Lymphomas, Acute and Chronic Leukemias, Myeloma, and Solid Tumors<sup>a</sup>**

Cancer Type	High Risk (TLS Risk >5%)	Intermediate Risk (TLS Risk 1%–5%) <sup>b</sup>	Low Risk (TLS Risk <1%) <sup>c</sup>
Lymphomas and acute leukemias			
Lymphomas	Burkitt or lymphoblastic lymphoma Advanced stage or Early stage and LDH $\geq 2$ times the ULN	Burkitt or lymphoblastic lymphoma Early stage and LDH <2 times the ULN	Cutaneous T-cell lymphoma Follicular lymphoma Hodgkin lymphoma MALT lymphoma Mantle cell lymphoma (nonblastoid variant) Marginal zone lymphoma Small lymphocytic lymphoma
ALL	WBC $\geq 100 \times 10^3/\mu\text{L}$ or LDH $\geq 2$ times the ULN	WBC <100 $\times 10^3/\mu\text{L}$ and LDH <2 times the ULN	
AML	WBC $\geq 100 \times 10^3/\mu\text{L}$	WBC 25 to <100 $\times 10^3/\mu\text{L}$ or LDH $\geq 2$ times the ULN	WBC <25 $\times 10^3/\mu\text{L}$ and LDH <2 times the ULN
Other lymphomas (categorized by age and disease stage)			
Anaplastic large cell lymphoma		Children with advanced stage	Children with early stage Adults
ATL, DLBCL, mantle cell lymphoma (blastoid variant), peripheral T-cell lymphoma, and transformed lymphoma	Children with stage III or IV and LDH $\geq 2$ times the ULN Adults with bulky disease and LDH >ULN	Children with stage III or IV and LDH <2 times the ULN Adults with nonbulky disease and LDH >ULN	Children with stage I or II Adults with normal LDH
Chronic leukemias, myeloma, and solid tumors			
CML			Chronic phase
CLL		Treatment using targeted and/or biologic therapies	
Myeloma			Myeloma
Solid tumors		Chemosensitive bulky solid tumors (eg, germ cell tumors, neuroblastoma, SCLC)	Solid tumors not meeting criteria for intermediate risk
Prophylaxis recommendations	Monitoring Hydration Rasburicase <sup>d</sup>	Monitoring Hydration Allopurinol or rasburicase <sup>d,e</sup>	Monitoring Hydration Consider allopurinol <sup>f</sup>

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myelogenous leukemia; ATL, adult T-cell lymphoma; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; MALT, mucosa-associated lymphoid tumor; SCLC, small cell lung cancer; TLS, tumor lysis syndrome; ULN, upper limit of normal; WBC, white blood cell count.

<sup>a</sup> Data derived from Cairo et al.<sup>8</sup>

<sup>b</sup> Patients with leukemia or lymphoma and intermediate-risk disease are high risk when renal dysfunction and/or renal involvement are present, or uric acid, phosphate, or potassium levels are elevated.

<sup>c</sup> Patients with leukemia or lymphoma and low-risk disease are intermediate risk for TLS when renal dysfunction and/or renal involvement are present.

<sup>d</sup> Rasburicase is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency and should be substituted with allopurinol in these patients.

<sup>e</sup> Rasburicase can be considered in the initial management for intermediate-risk patients and is the preferred agent if hyperuricemia develops.

<sup>f</sup> Allopurinol prophylaxis in low-risk patients is based on clinical judgment.

particularly with repeat dosing.<sup>26</sup> Rasburicase is contraindicated in pregnant or lactating women and in patients with G6PD deficiency because of the risk of severe hemolytic anemia and methemoglobinemia.<sup>9,27</sup> Patients should be screened for risk factors of G6PD deficiency, including a history of drug-induced hemolytic reactions or an ethnic background of African American, Mediterranean, or Southeast Asian descent. Semiquantitative point-of-care screening tests are available, and a confirmatory test that quantitates enzyme activity is recommended.<sup>9</sup>

### Electrolyte Management

Patients with hyperkalemia or hypocalcemia should be placed on cardiac monitoring and have repeat analyte

testing every 4 to 6 hours because of the risk of fatal arrhythmias. A serum potassium level greater than 7.0 to 7.5 mEq/L or widening of the QRS complex requires immediate intervention.<sup>9,10</sup> Standard therapies to lower the potassium level include loop diuretics, insulin and glucose, inhaled  $\beta$ -agonists, polystyrene sulfate, and calcium gluconate for symptomatic hyperkalemia or electrocardiographic changes. These measures are often a temporizing bridge to hemodialysis.<sup>10</sup> Hyperphosphatemia is treated with phosphate binders. The presence of secondary hypocalcemia can be life-threatening and generally necessitates the use of hemodialysis. Asymptomatic hypocalcemia should not be treated with calcium administration because of the risk of increasing calcium phosphate deposition in the renal

tubules. Symptomatic hypocalcemia should be treated at the lowest dose to the point of symptom relief but not to normalization of the laboratory values.<sup>10</sup>

### Hemodialysis

Indications for hemodialysis include refractory volume overload, oliguria or anuria, persistent hyperkalemia or hyperuricemia despite the above measures, hyperphosphatemia-induced symptomatic hypocalcemia, and a calcium phosphate product of greater than 70 mg<sup>2</sup>/dL.<sup>2,9,10</sup> The need for hemodialysis appears to have been reduced since the addition of rasburicase to induction therapy.<sup>28</sup> Prophylactic hemodialysis in patients at risk for TLS may be appropriate in the setting of preexisting renal disease or acute renal injury at presentation, and further studies are needed.<sup>13</sup>

### CONCLUSIONS

We are in an exciting era of precision medicine, with a rapidly expanding armamentarium of highly effective biologic and targeted therapies for the treatment of malignancy. With increasingly effective cytoreductive therapy for hematologic and solid tumors comes the increased risk of TLS and related complications. In order to combat the high morbidity and potentially fatal outcomes in TLS, and to reduce associated health care costs, experts are moving toward a unified definition and standard of care that focus on clinician awareness, risk-based prevention, and early aggressive multidisciplinary intervention. Identifying TLS has traditionally been the responsibility of the clinician, but there may be an opportunity for clinical laboratories to develop predictive algorithms based on a combination of analyte levels or a temporal change in these levels that would aid in heightened awareness.

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