

## REVIEW ARTICLE

## CURRENT CONCEPTS

## The Tumor Lysis Syndrome

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THE TUMOR LYSIS SYNDROME IS THE MOST COMMON DISEASE-RELATED emergency encountered by physicians caring for children or adults with hematologic cancers.<sup>1-4</sup> Although it develops most often in patients with non-Hodgkin's lymphoma or acute leukemia, its frequency is increasing among patients who have tumors that used to be only rarely associated with this complication.<sup>5-8</sup> The tumor lysis syndrome occurs when tumor cells release their contents into the bloodstream, either spontaneously or in response to therapy, leading to the characteristic findings of hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia.<sup>1-3</sup> These electrolyte and metabolic disturbances can progress to clinical toxic effects, including renal insufficiency, cardiac arrhythmias, seizures, and death due to multiorgan failure.

Although optimal methods of risk classification and treatment have been difficult to define, uniform standards for management of the tumor lysis syndrome are beginning to evolve. Indeed, several groups have advocated guidelines for risk stratification and made recommendations for evaluating risk and for prophylactic therapy for the tumor lysis syndrome.<sup>2,9</sup> This review of the tumor lysis syndrome summarizes current strategies for risk assessment, prophylaxis, and therapy. The following case illustrates the clinical challenges.

## CASE REPORT

An 8-year-old boy was referred to an otolaryngologist for tonsillectomy after several months of increased snoring, fatigue, sore throat, enlarged tonsils, and gradually increasing painless and nontender cervical lymphadenopathy. Two days before the scheduled procedure, his parents took him to the local emergency department after he had been unable to sleep because of congestion, sore throat, and difficulty breathing. The physician in the emergency department documented nasal congestion, enlarged tonsils that touched in the midline, and significant anterior and posterior cervical adenopathy. Dexamethasone (4 mg) was administered intramuscularly, and loratadine was prescribed. During the next 36 hours, the patient's congestion and breathing improved somewhat, but malaise developed and he vomited repeatedly. He returned to the emergency department, where he appeared ill and was found to be moderately dehydrated. Evaluation showed a white-cell count of 84,600 per cubic millimeter, with circulating lymphoblasts; a sodium level of 133 mmol per liter; potassium, 5.9 mmol per liter; bicarbonate, 16 mmol per liter; creatinine, 1.0 mg per deciliter (88.4  $\mu$ mol per liter); phosphorus, 8.5 mg per deciliter (2.7 mmol per liter); calcium, 6.7 mg per deciliter (1.7 mmol per liter); uric acid, 12.3 mg per deciliter (732  $\mu$ mol per liter); and lactate dehydrogenase, 4233 IU per liter. Chest radiography revealed a small mediastinal mass, and an electrocardiogram was normal. The pa-

tient was given two boluses of normal saline (20 ml per kilogram of body weight), rasburicase (0.15 mg per kilogram), and 800 mg of aluminum hydroxide; intravenous fluids (2500 ml per square meter of body-surface area per day) were administered, and he was transferred by ambulance to a tertiary care center, where he was admitted to the intensive care unit and T-cell acute lymphoblastic leukemia was diagnosed. His course was complicated by oliguria, hyperphosphatemia (a peak of 11.2 mg per deciliter [3.6 mmol per liter] of phosphorus, on day 3), an increased creatinine level (a peak of 3.8 mg per deciliter [318.2  $\mu$ mol per liter], on day 5), and hypertension that resolved after 2 months. He did not require dialysis, and more than 5 years after diagnosis, he remains in remission.

#### DEFINITION OF THE TUMOR LYSIS SYNDROME

In the current classification system of Cairo and Bishop,<sup>10</sup> the tumor lysis syndrome can be classified as laboratory or clinical (Table 1). Laboratory tumor lysis syndrome requires that two or more of the following metabolic abnormalities occur within 3 days before or up to 7 days after the initiation of therapy: hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia. Clinical tumor lysis syndrome is present when laboratory tumor lysis syndrome is accompanied by an increased creatinine level, seizures, cardiac dysrhythmia, or death. A few refinements could improve this classification. First, it should be stipulated that two or more metabolic abnormalities be present simultaneously, because some patients may present with one abnormality, but later another one may develop that is unrelated to the tumor lysis syndrome (e.g., hypocalcemia associated with sepsis). Second, in contrast to Cairo and Bishop's definition, a 25% change from baseline should not be considered a criterion, since such increases are rarely clinically important unless the value is already outside the normal range. Third, any symptomatic hypocalcemia should constitute clinical tumor lysis syndrome. Our patient met the criteria for laboratory tumor lysis syndrome when he returned to the emergency department, and he met the criteria for clinical tumor lysis syndrome the next day, when his creatinine level increased from 1.0 mg per deciliter to 2.1 mg per deciliter (185.6  $\mu$ mol per liter).

#### PATHOPHYSIOLOGY

When cancer cells lyse, they release potassium, phosphorus, and nucleic acids, which are metabolized into hypoxanthine, then xanthine, and finally uric acid, an end product in humans (Fig. 1).<sup>12</sup> Hyperkalemia can cause serious — and occasionally fatal — dysrhythmias. Hyperphosphatemia can cause secondary hypocalcemia, leading to neuromuscular irritability (tetany), dysrhythmia, and seizure, and can also precipitate as calcium phosphate crystals in various organs (e.g., the kidneys, where these crystals can cause acute kidney injury).<sup>13</sup> Uric acid can induce acute kidney injury not only by intrarenal crystallization but also by crystal-independent mechanisms, such as renal vasoconstriction, impaired autoregulation, decreased renal blood flow, oxidation, and inflammation.<sup>14-16</sup> Tumor lysis also releases cytokines that cause a systemic inflammatory response syndrome and often multiorgan failure.<sup>17-19</sup>

The tumor lysis syndrome occurs when more potassium, phosphorus, nucleic acids, and cytokines are released during cell lysis than the body's homeostatic mechanisms can deal with. Renal excretion is the primary means of clearing urate, xanthine, and phosphate, which can precipitate in any part of the renal collecting system. The ability of kidneys to excrete these solutes makes clinical tumor lysis syndrome unlikely without the previous development of nephropathy and a consequent inability to excrete solutes quickly enough to cope with the metabolic load.

Crystal-induced tissue injury occurs in the tumor lysis syndrome when calcium phosphate, uric acid, and xanthine precipitate in renal tubules and cause inflammation and obstruction (Fig. 2).<sup>20,23</sup> A high level of solutes, low solubility, slow urine flow, and high levels of cocrystallizing substances favor crystal formation and increase the severity of the tumor lysis syndrome.<sup>24-26</sup> High levels of both uric acid and phosphate render patients with the tumor lysis syndrome at particularly high risk for crystal-associated acute kidney injury, because uric acid precipitates readily in the presence of calcium phosphate, and calcium phosphate precipitates readily in the presence of uric acid. Also, higher urine pH increases the solubility of uric acid but decreases that of calcium phosphate. In patients treated with allopurinol, the accumulation of xanthine, which is a precursor of uric

**Table 1. Definitions of Laboratory and Clinical Tumor Lysis Syndrome.\***

Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dl (475.8 $\mu$ mol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dl (1.5 mmol/liter) in adults or >6.5 mg/dl (2.1 mmol/liter) in children	
Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dl (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter)†	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury‡	Not applicable	Increase in the serum creatinine level of 0.3 mg/dl (26.5 $\mu$ mol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hr for 6 hr

\* In laboratory tumor lysis syndrome, two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward. Clinical tumor lysis syndrome requires the presence of laboratory tumor lysis syndrome plus an increased creatinine level, seizures, cardiac dysrhythmia, or death.

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 – albumin in grams per deciliter).

‡ Acute kidney injury is defined as an increase in the creatinine level of at least 0.3 mg per deciliter (26.5  $\mu$ mol per liter) or a period of oliguria lasting 6 hours or more. By definition, if acute kidney injury is present, the patient has clinical tumor lysis syndrome. Data about acute kidney injury are from Levin et al.<sup>11</sup>

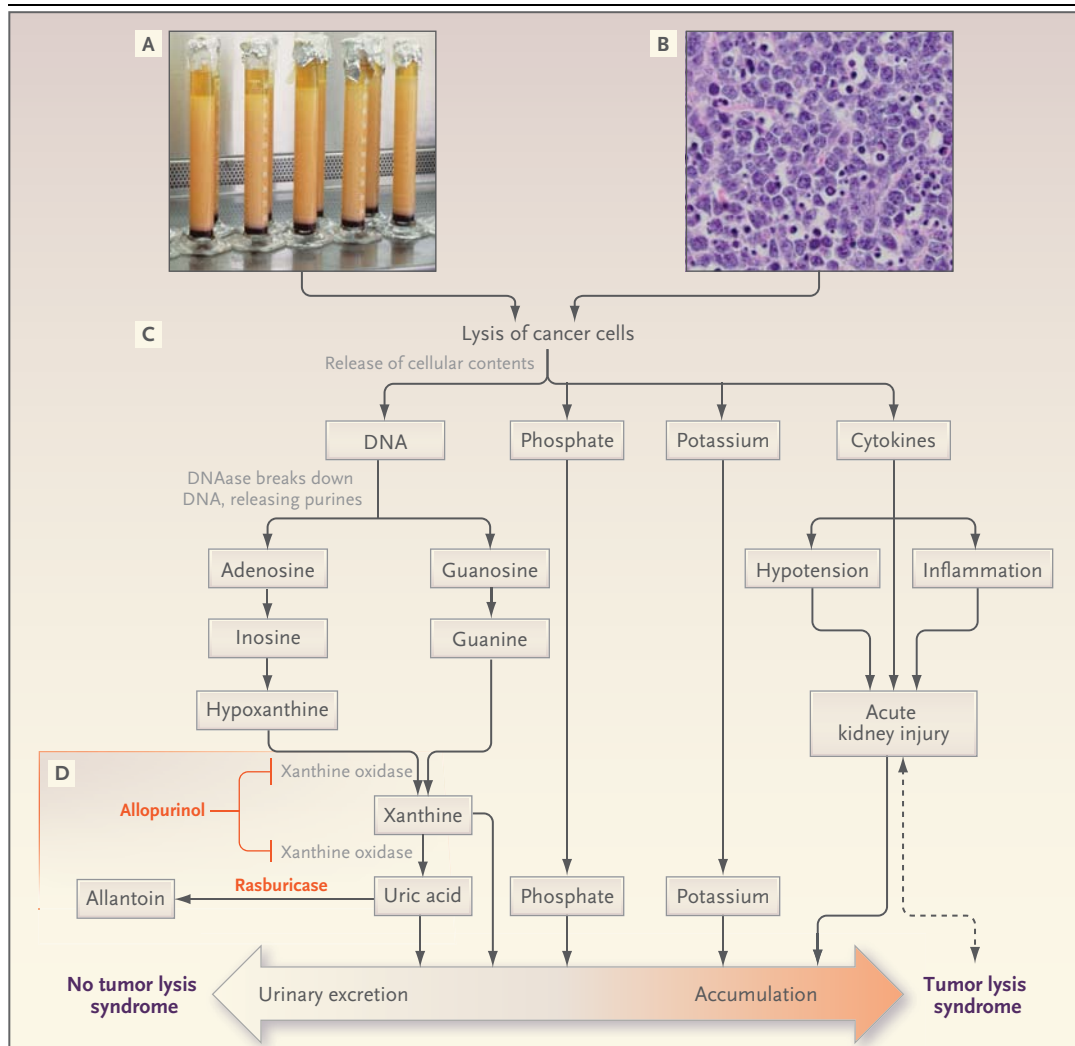
acid and has low solubility regardless of urine pH, can lead to xanthine nephropathy or urolithiasis (Fig. 1).<sup>20,27</sup>

Calcium phosphate can precipitate throughout the body (Fig. 2). The risk of ectopic calcification is particularly high among patients who receive intravenous calcium.<sup>13</sup> When calcium phosphate precipitates in the cardiac conducting system, serious, possibly fatal, dysrhythmias can occur. Acute kidney injury developed in our patient as a result of the precipitation of uric acid crystals and calcium phosphate crystals and was exacerbated by dehydration and acidosis that developed because the tumor lysis syndrome had not been suspected and no supportive care was provided.

#### EPIDEMIOLOGY

The incidence and severity of the tumor lysis syndrome depend on the cancer mass, the potential for lysis of tumor cells, the characteristics of the patient, and supportive care (Table 2). The vari-

ability of patient cohorts and lack of standard criteria have contributed to a wide range of reported incidences (see Table 1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).<sup>28</sup> The greater the cancer mass, the greater the quantity of cellular contents released after the administration of effective anticancer therapy. Cancers with a high potential for cell lysis include high-grade lymphomas, acute leukemias, and other rapidly proliferating tumors. However, the potential for cell lysis must be considered along with the effectiveness of therapy, as highlighted by a case of tumor lysis syndrome in an adult who died after treatment with cetuximab for metastatic colon carcinoma, a cancer in which the tumor lysis syndrome had not been previously reported.<sup>5</sup> Indeed, the tumor lysis syndrome increasingly has been reported in patients with cancers that previously had been rarely associated with this complication, such as endometrial cancer, hepatocellular carcinoma, chronic lymphocytic leukemia, and chronic myelogenous leuke-



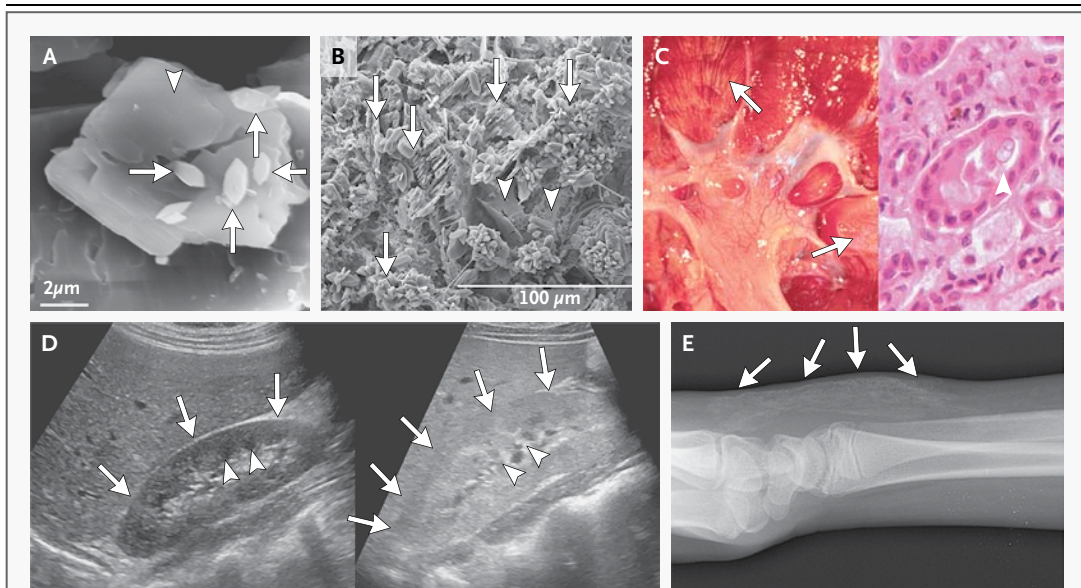
**Figure 1. Lysis of Tumor Cells and the Release of DNA, Phosphate, Potassium, and Cytokines.**

The graduated cylinders shown in Panel A contain leukemic cells removed by leukapheresis from a patient with T-cell acute lymphoblastic leukemia and hyperleukocytosis (white-cell count, 365,000 per cubic millimeter). Each cylinder contains straw-colored clear plasma at the top, a thick layer of white leukemic cells in the middle, and a thin layer of red cells at the bottom. The highly cellular nature of Burkitt's lymphoma is evident in Panel B (Burkitt's lymphoma of the appendix, hematoxylin and eosin). Lysis of cancer cells (Panel C) releases DNA, phosphate, potassium, and cytokines. DNA released from the lysed cells is metabolized into adenosine and guanosine, both of which are converted into xanthine. Xanthine is then oxidized by xanthine oxidase, leading to the production of uric acid, which is excreted by the kidneys. When the accumulation of phosphate, potassium, xanthine, or uric acid is more rapid than excretion, the tumor lysis syndrome develops. Cytokines cause hypotension, inflammation, and acute kidney injury, which increase the risk for the tumor lysis syndrome. The bidirectional dashed line between acute kidney injury and tumor lysis syndrome indicates that acute kidney injury increases the risk of the tumor lysis syndrome by reducing the ability of the kidneys to excrete uric acid, xanthine, phosphate, and potassium. By the same token, development of the tumor lysis syndrome can cause acute kidney injury by renal precipitation of uric acid, xanthine, and calcium phosphate crystals and by crystal-independent mechanisms. Allopurinol inhibits xanthine oxidase (Panel D) and prevents the conversion of hypoxanthine and xanthine into uric acid but does not remove existing uric acid. In contrast, rasburicase removes uric acid by enzymatically degrading it into allantoin, a highly soluble product that has no known adverse effects on health.

5-8,29-32 Characteristics of patients that confer high risk include preexisting chronic renal insufficiency, oliguria, dehydration, hypotension, and acidic urine.

The adequacy of fluid management affects both the development and the severity of the tumor lysis syndrome. Thus, disastrous cases of the tumor lysis syndrome occurred in patients with





**Figure 2. Crystals of Uric Acid, Calcium Phosphate, and Calcium Oxalate.**

Crystallization of uric acid and calcium phosphate are the primary means of renal damage in the tumor lysis syndrome. The presence of crystals of one solute can promote crystallization of the other solutes. A scanning electron micrograph (Panel A) shows large uric acid crystals (arrowhead), which served as seeds for the formation of calcium oxalate crystals (arrows). Reprinted from Bouropoulos et al.<sup>21</sup> with the permission of the publisher. In Panel B, a scanning electron micrograph shows numerous small calcium oxalate crystals (arrows) formed on larger uric acid crystals (arrowheads). Reprinted from Grases et al.<sup>22</sup> with the permission of the publisher. The kidney shown in Panel C was examined at the autopsy of a 4-year-old boy who had high-grade non-Hodgkin's lymphoma and died of acute tumor lysis syndrome. Linear yellow streaks of precipitated uric acid in the renal medulla are shown in the left panel (arrows); a single tubule containing a uric acid crystal (arrowhead) is shown in the right panel. Reprinted from Howard et al.<sup>13</sup> with the permission of the publisher. In Panel D, in the normal kidney on the left, the medullary pyramids are visible deep in the kidney (arrowheads) and are surrounded by the renal cortex (arrows), which is darker than the collecting system and adjacent liver. The ultrasonographic image on the right shows a kidney from a patient with the tumor lysis syndrome, in which there is loss of the normal corticomedullary differentiation (arrowheads) and poor visualization of the renal pyramids. The brightness is similar to that of the adjacent liver (arrows), and the kidney is abnormally enlarged. Soft-tissue calcification of the dorsum of the distal forearm (Panel E) occurred in a 15-year-old boy with acute lymphoblastic leukemia and an initial white-cell count of 283,000 per cubic millimeter in whom tumor lysis syndrome, hyperphosphatemia, and symptomatic hypocalcemia developed. Several weeks after the treatment of hypocalcemia with multiple doses of intravenous calcium carbonate administered by means of a peripheral intravenous catheter in the dorsum of the hand, ectopic calcification was confirmed radiographically (arrows). Reprinted from Howard et al.<sup>13</sup> with the permission of the publisher.

nonhematologic cancer who received effective anticancer treatment but no intravenous fluids or monitoring because the tumor lysis syndrome was not anticipated.<sup>5,32</sup> In contrast, in many countries, patients with a bulky Burkitt's lymphoma who have a high potential for lysis have a low risk of clinical tumor lysis syndrome because they routinely receive aggressive treatment with hydration and rasburicase, a recombinant urate oxidase enzyme that is a highly effective uricolytic agent (Table 1 in the Supplementary Appendix). Children with Burkitt's lymphoma who received rasburicase were a fifth as likely to undergo dialysis as those who received allopurinol, illustrating the

dramatic difference that supportive care can make, even when other risk factors for the tumor lysis syndrome are the same.<sup>33</sup> This was seen in the 8-year-old boy in the vignette.

#### RISK ASSESSMENT

Acute kidney injury is associated with high morbidity and mortality,<sup>34</sup> and its prevention requires an awareness of the patient's a priori risk of the tumor lysis syndrome and careful monitoring for early signs of it. Models that predict the risk of the tumor lysis syndrome have been developed for adults with acute myeloid leukemia<sup>35,36</sup> and chil-

**Table 2. Risk Factors for the Tumor Lysis Syndrome.**

Category of Risk Factor	Risk Factor	Comments
Cancer mass	Bulky tumor or extensive metastasis	The larger the cancer mass or the higher the number of cells that will lyse with treatment, the higher the risk of clinical tumor lysis syndrome.
	Organ infiltration by cancer cells	Hepatomegaly, splenomegaly, and nephromegaly generally represent tumor infiltration into these organs, and therefore a larger tumor burden than that of patients without these findings.
	Bone marrow involvement	Healthy adults have 1.4 kg of bone marrow. A marrow that has been replaced by leukemic cells contains a cancer mass greater than 1 kg and therefore represents bulky disease.
	Renal infiltration or outflow-tract obstruction	Cancers that infiltrate the kidney or obstruct urine flow predispose to nephropathy from other causes, such as the tumor lysis syndrome.
Cell lysis potential	High rate of proliferation of cancer cells	Lactate dehydrogenase level is a surrogate for tumor proliferation. The higher the level, the greater the risk of the tumor lysis syndrome.
	Cancer-cell sensitivity to anticancer therapy	Cancers that are inherently more sensitive to therapy have a higher rate of cell lysis and a greater risk of the tumor lysis syndrome than the other cancers.
Features on patient presentation	Intensity of initial anticancer therapy	The higher the intensity of initial therapy, the greater the rate of cancer-cell lysis and the risk of the tumor lysis syndrome. For example, some protocols for acute lymphoblastic leukemia begin with a week of prednisone monotherapy, and others begin with a combination of a glucocorticoid, vincristine, asparaginase, and daunorubicin. A patient treated on the latter protocol would have a higher risk of the tumor lysis syndrome.
	Nephropathy before diagnosis of cancer	A patient with preexisting nephropathy from hypertension, diabetes, gout, or other causes has a greater risk for acute kidney injury and the tumor lysis syndrome.
Supportive care	Dehydration or volume depletion	Dehydration decreases the rate of urine flow through renal tubules and increases the level of solutes (e.g., phosphorus, uric acid) that can crystallize and cause nephropathy.
	Acidic urine	Uric acid has a lower solubility in acidic urine and therefore crystallizes more rapidly. A patient who presents with acidic urine and hyperuricemia usually already has uric acid crystals or microcrystals in the renal tubules.
	Hypotension	Hypotension decreases urine flow and increases the level of solutes that can crystallize. Hypotension can also independently cause acute kidney injury.
	Exposure to nephrotoxins	Vancomycin, aminoglycosides, contrast agents for diagnostic imaging, and other potential nephrotoxins increase the risk of acute kidney injury from lysis of cancer cells.
Exogenous potassium	Inadequate hydration	Initial boluses of normal saline until the patient is euvolemic followed by infusion of suitable intravenous fluids at two times the maintenance rate (about 180 ml/hr in an adult who can tolerate hyperhydration) increases the rate of urine flow through renal tubules, decreases the level of solutes that can crystallize and cause acute kidney injury, and decreases the time that those solutes remain in the tubules so that even if microcrystals form they may not have time to aggregate into clinically important crystals before removal by the high flow of urine.
	Exogenous potassium	Unless the patient has severe hypokalemia or a dysrhythmia from hypokalemia, potassium should not be included in the intravenous fluids, and potassium (from food or medications) should be minimized until the risk period for the tumor lysis syndrome has passed.
	Exogenous phosphate	Restricting dietary phosphate and adding a phosphate binder reduce the exogenous load of phosphate so that the kidneys need only excrete the endogenous load of phosphate released by cancer-cell lysis.
	Delayed uric acid removal	Allopurinol prevents formation of new uric acid by inhibiting xanthine oxidase and preventing conversion of xanthine to uric acid. It does not remove existing uric acid and does increase urinary excretion of xanthine, which can crystallize and cause nephropathy. Rasburicase is an enzyme that rapidly removes uric acid by converting it to allantoin, which is highly soluble and readily excreted in the urine. The longer the uric acid level remains high, the greater the risk of crystal formation and acute kidney injury.

dren with acute lymphoblastic leukemia<sup>37</sup> treated with hydration and allopurinol (but not rasburicase). These models lack a standard definition of the tumor lysis syndrome, use different primary end points (i.e., either clinical tumor lysis syndrome or any type of the tumor lysis syndrome), lack standardized supportive care guidelines, and have complex scoring systems. Experts have issued management guidelines for the tumor lysis syndrome,<sup>2,9,38</sup> but further guidance awaits simple risk-prediction models that have a standardized definition of the tumor lysis syndrome and uniform supportive care guidelines for each cancer type.<sup>28</sup> We present a practical approach for clinicians (Fig. 3, and Table 2 in the Supplementary Appendix).

## MANAGEMENT

Optimal management of the tumor lysis syndrome should involve preservation of renal function. Management should also include prevention of dysrhythmias and neuromuscular irritability (Fig. 3).

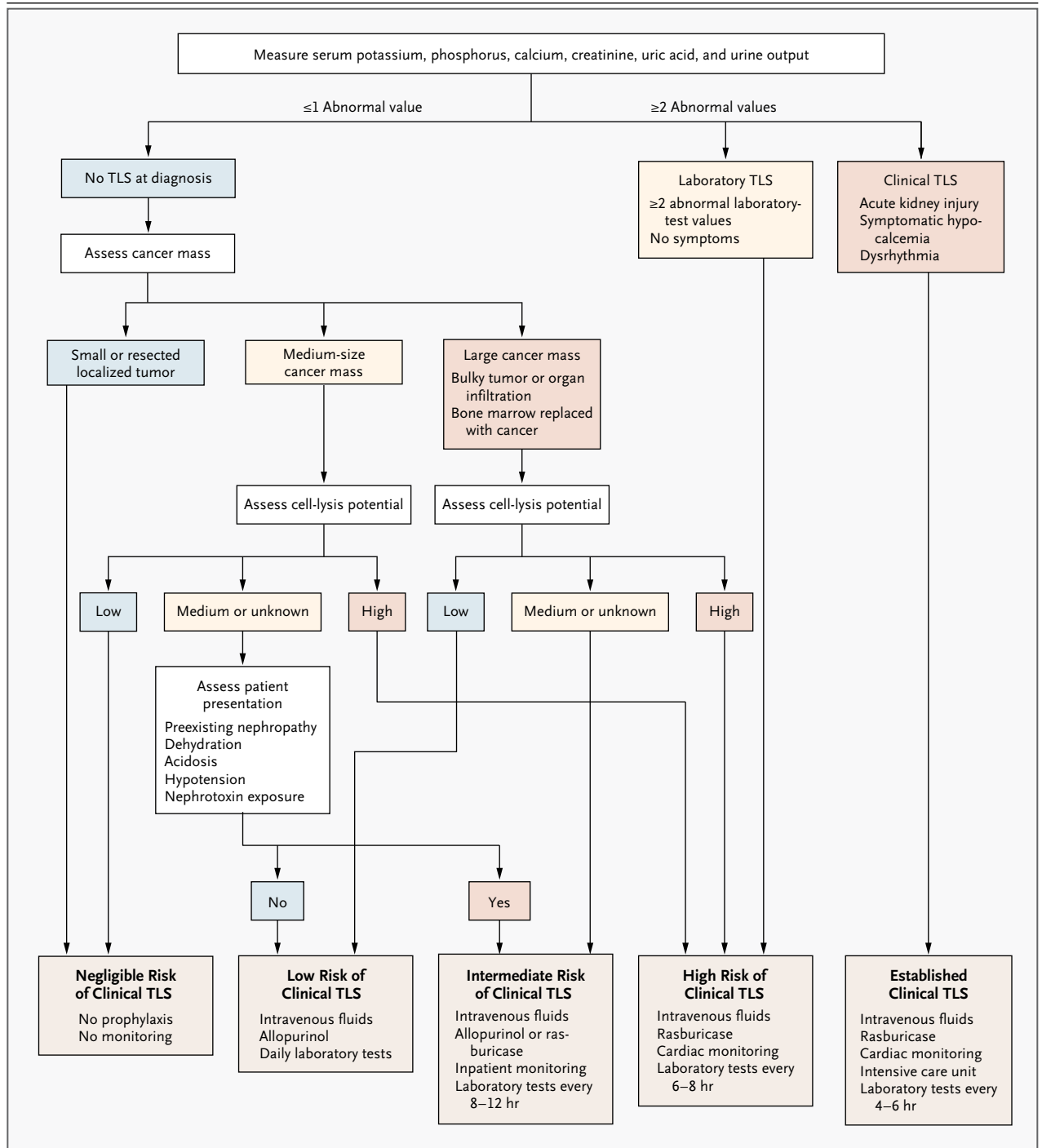
### PREVENTION OF ACUTE KIDNEY INJURY

All patients who are at risk for the tumor lysis syndrome should receive intravenous hydration to rapidly improve renal perfusion and glomerular filtration and to minimize acidosis (which lowers urine pH and promotes the precipitation of uric acid crystals) and oliguria (an ominous sign). This is usually accomplished with hyperhydration by means of intravenous fluids (2500 to 3000 ml per square meter per day in the patients at highest risk). Hydration is the preferred method of increasing urine output, but diuretics may also be necessary. In a study involving a rat model of urate nephropathy with elevated serum uric acid levels induced by continuous intravenous infusion of high doses of uric acid, high urine output due to treatment with high-dose furosemide or congenital diabetes insipidus (in the group of mice with this genetic modification) protected the kidneys equally well, whereas acetazolamide (mild diuresis) and bicarbonate provided only moderate renal protection (no more than a low dose of furosemide without bicarbonate).<sup>39</sup> Hence, in patients whose urine output remains low after achieving an optimal state of hydration, we recommend the use of a loop diuretic agent (e.g., furosemide) to promote diuresis, with a target urine output of at least 2 ml per kilogram per hour.

### Figure 3 (facing page). Assessment and Initial Management of the Tumor Lysis Syndrome.

This algorithm presents a guide to care at the time of patient presentation. Subsequent care depends on how the patient progresses. The tumor lysis syndrome unexpectedly develops in some patients who are at low risk, and they require more aggressive treatment, and some high-risk patients have no evidence of the tumor lysis syndrome after a few days of treatment and need less intensive care after the initial period. Assessment of risk factors for the tumor lysis syndrome requires clinical judgment. It may not always be clear whether mild or transient dehydration should count, whether a cancer mass is medium or large, or whether the potential for cell lysis of a particular cancer with a particular treatment is medium or high. In equivocal cases, other criteria can be useful to clarify the degree of risk: an elevated lactate dehydrogenase level (>2 times the upper limit of the normal range) and an elevated uric acid level at presentation are associated with an increased risk of the tumor lysis syndrome and can be used to help classify borderline cases into a suitable risk group. If it is difficult to distinguish between two categories, treat the patient as if he or she is in the higher-risk category. Because the algorithm presented is designed for use by both oncologists and non-oncologists, a conservative approach is presented to maximize safety. "Bulky tumor" includes the tumor mass from metastatic lesions. TLS denotes tumor lysis syndrome.

Reducing the level of uric acid, with the use of allopurinol and particularly with the use of rasburicase, can preserve or improve renal function and reduce serum phosphorus levels as a secondary beneficial effect.<sup>40</sup> Although allopurinol prevents the formation of uric acid, existing uric acid must still be excreted. The level of uric acid may take 2 days or more to decrease, a delay that allows urate nephropathy to develop (Fig. 1b in the Supplementary Appendix). Moreover, despite treatment with allopurinol, xanthine may accumulate, resulting in xanthine nephropathy.<sup>13,20,27</sup> Since the serum xanthine level is not routinely measured, its effect on the development of acute kidney injury is uncertain. By preventing xanthine accumulation and by directly breaking down uric acid, rasburicase is more effective than allopurinol for the prevention and treatment of the tumor lysis syndrome. In a randomized study of the use of allopurinol versus rasburicase for patients at risk for the tumor lysis syndrome, the mean serum phosphorus level peaked at 7.1 mg per deciliter (2.3 mmol per liter) in the rasburicase group (and mean uric acid levels decreased by 86%, to 1 mg per deciliter [59.5  $\mu$ mol per liter] at 4 hours) as compared with 10.3 mg per decili-



ter (3.3 mmol per liter) in the allopurinol group (and mean uric acid levels decreased by 12%, to 5.7 mg per deciliter [339.0  $\mu$ mol per liter] at 48 hours).<sup>41,42</sup> The serum creatinine level improved (decreased) by 31% in the rasburicase group but worsened (increased) by 12% in the allopurinol group. Pui and colleagues<sup>40</sup> documented no in-

creases in phosphorus levels and decreases in creatinine levels among 131 patients who were at high risk for the tumor lysis syndrome and were treated with rasburicase. Finally, in a multicenter study involving pediatric patients with advanced-stage Burkitt's lymphoma, in which all patients received identical treatment with chemotherapy



and aggressive hydration, the tumor lysis syndrome occurred in 9% of 98 patients in France (who received rasburicase) as compared with 26% of 101 patients in the United States (who received allopurinol) ( $P=0.002$ ).<sup>33</sup> Dialysis was required in only 3% of the French patients but 15% of the patients in the United States ( $P=0.004$ ). At the time of the study, rasburicase was not available in the United States.

Urinary alkalization increases uric acid solubility but decreases calcium phosphate solubility (Fig. 1a in the Supplementary Appendix). Because it is more difficult to correct hyperphosphatemia than hyperuricemia, urinary alkalization should be avoided in patients with the tumor lysis syndrome, especially when rasburicase is available.<sup>13</sup> Whether urine alkalization prevents or reduces the risk of acute kidney injury in patients without access to rasburicase is unknown, but the animal model of urate nephropathy suggested no benefit.<sup>39</sup> If alkalization is used, it should be discontinued when hyperphosphatemia develops. In patients treated with rasburicase, blood samples for the measurement of the uric acid level must be placed on ice to prevent *ex vivo* breakdown of uric acid by rasburicase and thus a spuriously low level. Patients with glucose-6-phosphate dehydrogenase deficiency should avoid rasburicase because hydrogen peroxide, a breakdown product of uric acid, can cause methemoglobinemia and, in severe cases, hemolytic anemia.<sup>43,44</sup> Rasburicase is recommended as first-line treatment for patients who are at high risk for clinical tumor lysis syndrome.<sup>9</sup> Because of cost considerations and pending pharmaco-economic studies, no consensus has been reached on rasburicase use in patients who are at intermediate risk for the tumor lysis syndrome; some have advocated use of a small dose of rasburicase in such patients.<sup>45,46</sup> Patients who are at low risk can usually be treated with intravenous fluids with or without allopurinol, but they should be monitored daily for signs of the tumor lysis syndrome.

#### PREVENTION OF CARDIAC DYSRHYTHMIAS AND NEUROMUSCULAR IRRITABILITY

Hyperkalemia remains the most dangerous component of the tumor lysis syndrome because it can cause sudden death due to cardiac dysrhythmia. Patients should limit potassium and phosphorus intake during the risk period for the tumor lysis syndrome.<sup>47</sup> Frequent measurement of potassium

levels (every 4 to 6 hours), continuous cardiac monitoring, and the administration of oral sodium polystyrene sulfonate are recommended in patients with the tumor lysis syndrome and acute kidney injury. Hemodialysis and hemofiltration effectively remove potassium. Glucose plus insulin or beta-agonists can be used as temporizing measures, and calcium gluconate may be used to reduce the risk of dysrhythmia while awaiting hemodialysis.

Hypocalcemia can also lead to life-threatening dysrhythmias and neuromuscular irritability; controlling the serum phosphorus level may prevent hypocalcemia. Symptomatic hypocalcemia should be treated with calcium at the lowest dose required to relieve symptoms, since the administration of excessive calcium increases the calcium-phosphate product and the rate of calcium phosphate crystallization, particularly if the product is greater than 60 mg<sup>2</sup> per square deciliter (Fig. 2D and 2E). Hypocalcemia not accompanied by signs or symptoms does not require treatment. Despite the lack of studies that show the efficacy of phosphate binders in patients with the tumor lysis syndrome, this treatment is typically given. The role of renal phosphate leak in renal lithiasis and the use of phosphate binders have recently been reviewed in the *Journal*.<sup>48,49</sup>

#### MANAGEMENT OF SEVERE ACUTE KIDNEY INJURY

Despite optimal care, severe acute kidney injury develops in some patients and requires renal replacement therapy (Table 3 in the Supplementary Appendix). Although the indications for renal replacement therapy in patients with the tumor lysis syndrome are similar to those in patients with other causes of acute kidney injury, somewhat lower thresholds are used for patients with the tumor lysis syndrome because of potentially rapid potassium release and accumulation, particularly in patients with oliguria. In patients with the tumor lysis syndrome, hyperphosphatemia-induced symptomatic hypocalcemia may also warrant dialysis. Phosphate removal increases as treatment time increases, which has led some to advocate the use of continuous renal-replacement therapies in patients with the tumor lysis syndrome, including continuous venovenous hemofiltration, continuous venovenous hemodialysis, or continuous venovenous hemodiafiltration.<sup>50</sup> These methods of dialysis use filters with a larger pore size, which allows more rapid clearance of molecules that are

not efficiently removed by conventional hemodialysis (Table 3 in the Supplementary Appendix). One study that compared phosphate levels among adults who had acute kidney injury that was treated with either conventional hemodialysis or continuous venovenous hemodiafiltration showed that continuous venovenous hemodiafiltration more effectively reduced phosphate.<sup>51</sup> Much less is known about the dialytic clearance of uric acid, but in countries where rasburicase is available, hyperuricemia is seldom an indication for dialysis.<sup>40,44,52</sup> In our patient, once the tumor lysis syndrome was identified, treatment with intravenous fluids, phosphate binders, and rasburicase prevented the need for dialysis. Despite a potassium level of 5.9 mmol per liter, he had no dysrhythmia or changes on electrocardiography, but had he presented 1 day later, the tumor lysis syndrome may have proved fatal.

#### MONITORING

Urine output is the key factor to monitor in patients who are at risk for the tumor lysis syndrome and in those in whom the syndrome has developed. In patients whose risk of clinical tumor lysis syndrome is non-negligible, urine output and fluid balance should be recorded and assessed frequently. Patients at high risk should also receive intensive nursing care with continuous cardiac monitoring and the measurement of electrolytes, creatinine, and uric acid every 4 to 6 hours after the start of therapy. Those at intermediate risk should undergo laboratory monitoring every 8 to 12 hours,

and those at low risk should undergo such monitoring daily. Monitoring should continue over the entire period during which the patient is at risk for the tumor lysis syndrome, which depends on the therapeutic regimen. In a protocol for acute lymphoblastic leukemia, which featured up-front, single-agent methotrexate treatment,<sup>53</sup> new-onset tumor lysis syndrome developed in some patients at day 6 or day 7 of remission-induction therapy (after the initiation of combination chemotherapy with prednisone, vincristine, and daunorubicin on day 5 and asparaginase on day 6).

#### DECREASING THE RATE OF TUMOR LYSIS WITH A TREATMENT PREPHASE

Patients at high risk for the tumor lysis syndrome may also receive low-intensity initial therapy. Slower lysis of the cancer cells allows renal homeostatic mechanisms to clear metabolites before they accumulate and cause organ damage. This strategy, in cases of advanced B-cell non-Hodgkin's lymphoma or Burkitt's leukemia, has involved treatment with low-dose cyclophosphamide, vincristine, and prednisone for a week before the start of intensive chemotherapy. Similarly, many groups subscribe to a week of prednisone monotherapy for childhood acute lymphoblastic leukemia.

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