

## REVIEW ARTICLE

## Tumor Lysis Syndrome

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CME



**T**UMOR LYSIS SYNDROME IS A PATHOPHYSIOLOGICAL STATE THAT OCCURS when the ability of the body to maintain electrolyte–uric acid homeostasis is overwhelmed as a result of the destruction of malignant cells and the attendant massive release of cellular contents, including nucleic acids. This disorder was first described more than 100 years ago,<sup>1</sup> and its consequences, as well as prophylaxis, treatment, and prognosis, were first reported in the 1960s.<sup>2</sup> As recently as 1975, some physicians considered hyperphosphatemia–hypocalcemia to be a previously unrecognized complication of tumor lysis.<sup>3</sup> The continuous development of antineoplastic therapies has rendered tumor lysis syndrome a less predictable and increasingly important aspect of the care of patients with cancer. In this article, we review the epidemiology and pathophysiology of tumor lysis syndrome; risk factors, prophylaxis, and treatment; and the evolution of the syndrome that has coincided with a continually expanding list of new therapies.

## EPIDEMIOLOGY

Tumor lysis syndrome is observed most commonly in patients with bulky, chemosensitive hematologic cancers (e.g., highly proliferative lymphomas and acute leukemias) who are undergoing intensive induction therapy.<sup>4-8</sup> The reported incidence of the syndrome varies widely (5 to 70%), depending on the era of reporting, the underlying cancer, and the definition used.<sup>4-11</sup> Tumor lysis syndrome has also been observed in less predictable clinical settings. It has occurred as a spontaneous disorder,<sup>12-14</sup> as a manifestation of occult cancer,<sup>15</sup> in association with glucocorticoids,<sup>16</sup> in patients with traditionally nonchemosensitive cancers,<sup>17</sup> and after radiation therapy.<sup>18</sup> The syndrome may exist concurrently with hemophagocytic lymphohistiocytosis<sup>19</sup> or disseminated intravascular coagulation.<sup>20</sup> In complex clinical contexts, the presence of tumor lysis syndrome may confound diagnostic considerations, requires prompt recognition, and may warrant urgent treatment. Providers who care for patients with a potential or proven cancer must understand the current scope of this syndrome. Its occurrence can prolong the hospital stay, increase the costs of care, and contribute to clinically significant complications and excess mortality.<sup>7,9</sup> Early recognition could potentially improve clinical outcomes.

Although the occurrence and severity of tumor lysis syndrome can reasonably be anticipated on the basis of the tumor type and volume, the intensity of the induction regimen, and pretreatment laboratory values and renal function,<sup>6,9,10</sup> nuances influence the prediction of risk, particularly with new therapies. Risk assessment and monitoring should be considered in any patient with cancer who is ill enough to be receiving initial antineoplastic therapy in the hospital. The literature is replete with instances of tumor lysis syndrome occurring in patients for whom the risk would have been considered negligible.<sup>17,18</sup> In such cases, a cursory base-

## KEY POINTS

## TUMOR LYSIS SYNDROME

- The epidemiology of tumor lysis syndrome is evolving with the introduction of newer therapies.
- The occurrence of tumor lysis syndrome has become a less predictable but increasingly important aspect of the care of patients with cancer.
- With the availability of rasburicase, hyperphosphatemia has replaced hyperuricemia as the main cause of nephrotoxic effects in tumor lysis.
- Careful attention to fluid management and prevention of volume overload may diminish the risk of in-hospital death.
- In patients with acute leukemias or aggressive lymphomas, cytoreduction before the initiation of disease-specific induction therapy may reduce the incidence and severity of subsequent tumor lysis.

line assessment and follow-up might have identified patients in whom tumor lysis syndrome developed unexpectedly. The most common cancers and therapies associated with tumor lysis are listed in Table 1.

## PATHOPHYSIOLOGY

Electrolyte levels are maintained within very narrow ranges to allow for the safe execution of critical physiological processes, such as insulin regulation, hormone secretion, and the propagation of action potentials through muscle fibers and conductive tissues. Normal fluctuations are quickly corrected by compensatory homeostatic (principally renal) mechanisms. In patients receiving antineoplastic therapy, modest cell lysis may cause transient metabolic alterations that have no important physiological consequences. However, rapid and extensive tumor lysis can have acute, serious physiological consequences, which in extreme cases can be lethal (Fig. 1). The increased risk of death from tumor lysis syndrome is due principally to cardiac complications associated with severe acute hyperkalemia and hypocalcemia, particularly in patients with coexisting conditions.<sup>23</sup>

The acute kidney injury associated with tumor lysis syndrome is complex, multifactorial, and incompletely understood. It is principally a consequence of the direct effects of hyperuricemia and hyperphosphatemia.<sup>24,25</sup> Baseline renal dysfunction or prerenal azotemia and the use of nephrotoxic medications augment the risk of acute kidney injury. Uric acid is poorly soluble in plasma, and the degree of hyperuricemia is a predictor of acute kidney injury and tumor lysis

syndrome in the context of cancer.<sup>6,26</sup> Historically, renal injury was considered to result from uric acid crystals precipitating in and obstructing renal tubules. However, in animal models, crystal-dependent mechanisms are insufficient to explain the occurrence of acute kidney injury.<sup>27</sup> Also, although uric acid levels in patients with cancer have a nearly linear association with creatinine levels, the rapid kinetic association between a reduction in uric acid levels and a reduction in creatinine levels suggests that uric acid deposition is not the major direct cause of acute kidney injury.<sup>25</sup>

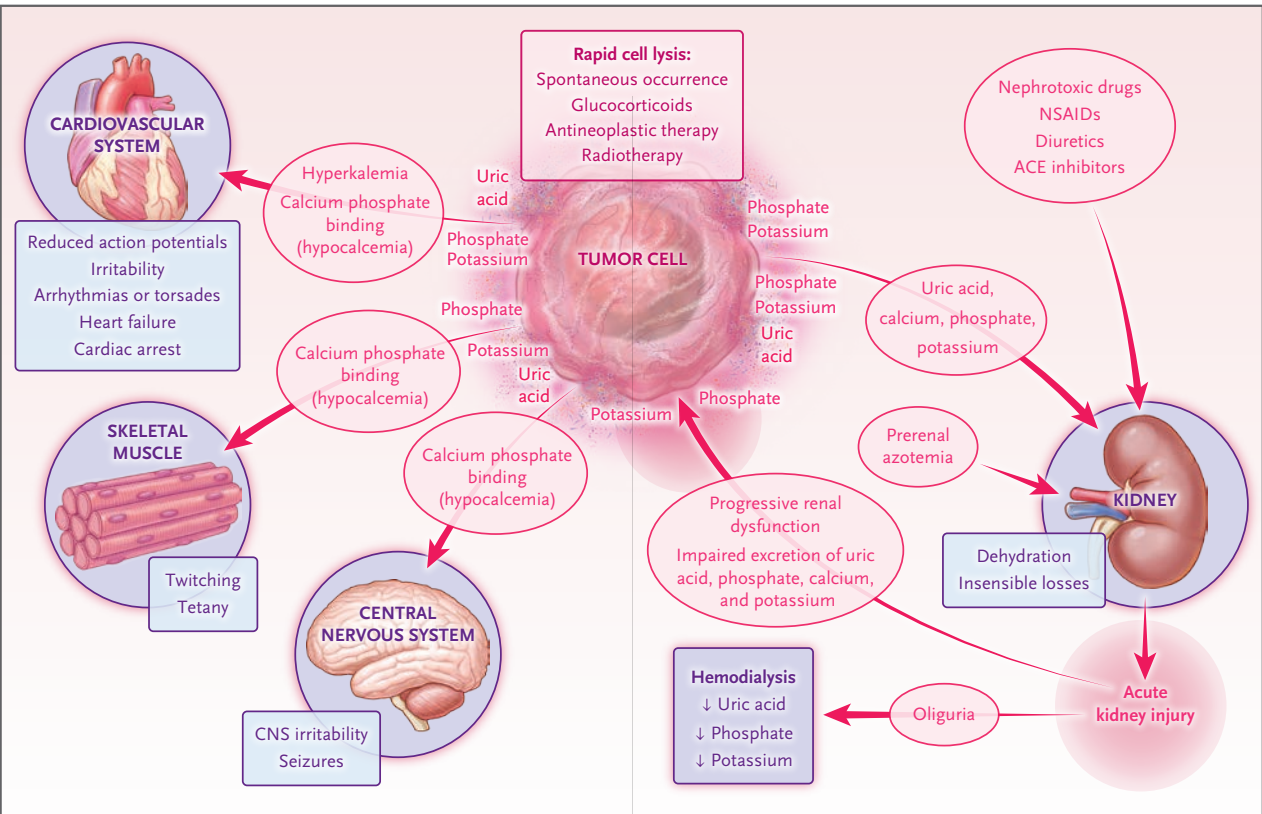
Additional complex and indirect crystal-independent mechanisms may be important. Extracellular histone levels are markedly increased during tumor lysis, and the increase is associated with the severity of the acute kidney injury.<sup>27</sup> Soluble uric acid can up-regulate proinflammatory cytokines (e.g., intracellular adhesion molecule 1), which leads to activation of innate immunity through toll-like receptor 4.<sup>28</sup> Xanthine is less soluble than uric acid, but potentially nephrotoxic xanthine crystals have been observed in the urine of patients with tumor lysis syndrome.<sup>29</sup>

Hyperphosphatemia contributes to renal injury directly, as well as indirectly by binding ionized calcium, which causes acute hypocalcemia and calcium phosphate deposition in renal tubules. Hypocalcemia can confer a predisposition to tetany, seizures, and arrhythmias (probably through prolongation of QT intervals, which leads to torsades de pointes).<sup>30,31</sup> Hospitalized patients with tumor lysis syndrome and coexisting conditions are at increased risk for arrhythmias and in-hospital death.<sup>23</sup> Acute kidney injury

**Table 1. Cancers and Therapies Most Commonly Associated with Tumor Lysis Syndrome.**

Cancer	Therapy	Evidence
Acute myeloid leukemia	Intensive induction chemotherapy (e.g., cytarabine- or anthracycline-based regimens)	Razis et al., <sup>5</sup> Mato et al. <sup>6</sup>
Acute lymphoblastic leukemia or lymphoma	Anthracycline-based induction chemotherapy	Rios-Olais et al. <sup>7</sup>
Burkitt's lymphoma	Intensive induction therapy (e.g., CODOX-M or IVAC)*	Wössmann et al., <sup>4</sup> Barnes et al. <sup>8</sup>
Advanced-stage, aggressive lymphomas (e.g., diffuse large B-cell lymphoma)	Intensive induction therapy	Calvache et al. <sup>11</sup>
Chronic lymphocytic leukemia with nodal masses of ≥10 cm or nodal masses of ≥5 cm and peripheral lymphocytosis (lymphocyte count of ≥25,000/ $\mu$ l)	Venetoclax	Roberts et al., <sup>21</sup> AbbVie <sup>22</sup>

\* CODOX-M denotes cyclophosphamide, doxorubicin, vincristine, and methotrexate, and IVAC ifosfamide, etoposide, and cytarabine.



**Figure 1. Pathophysiology of Tumor Lysis Syndrome.**

Rapid lysis of cells leads to the release of intracellular substances (principally uric acid, potassium, and phosphorus) into the serum, with effects on the cardiovascular system, skeletal muscles, central nervous system, and kidneys. The effects on the kidney may be exacerbated by the presence of prerenal azotemia plus concurrent treatment with nephrotoxic medications. Acute kidney injury may lead to oliguria, which impairs the ability to manage fluid and electrolyte balance. Progressive renal injury or the inability to rapidly clear potassium, phosphorus, and uric acid may lead to an indication for renal replacement therapy. ACE denotes angiotensin-converting enzyme, CNS central nervous system, and NSAIDs nonsteroidal antiinflammatory drugs.

**Table 2. Diagnostic Criteria for Tumor Lysis Syndrome.\***

Laboratory Criteria	Clinical Criteria
Uric acid level of $\geq 8.0$ mg/dl (476 $\mu\text{mol/liter}$ ) in adults or above the ULN in children or a 25% increase from baseline	Acute kidney injury defined by a creatinine level $\geq 1.5$ times the ULN, an increase in the creatinine level of $\geq 0.3$ mg/dl (26.5 $\mu\text{mol/liter}$ ), or urine output of $<0.5$ ml/kg/hr for 6 hr or more
Inorganic phosphorus level of $\geq 4.5$ mg/dl (1.5 mmol/liter) in adults or $\geq 6.5$ mg/dl (2.1 mmol/liter) in children or a 25% increase from baseline	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperphosphatemia
Potassium level of $\geq 6.0$ mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Corrected calcium level of $<7.0$ mg/dl (1.75 mmol/liter) or ionized calcium level of $<4.5$ mg/dl (1.12 mmol/liter) <sup>†</sup>	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability, hypotension, or heart failure probably or definitely caused by hypocalcemia

\* The diagnostic criteria assume maintenance of adequate hydration and administration of one or more hypouricemic agents. At least two laboratory criteria and one clinical criterion must be met during a 24-hour period within 3 days before or 7 days after treatment. ULN denotes upper limit of the normal range.

<sup>†</sup> The formula for corrected calcium is as follows: serum calcium +  $[0.8 \times (\text{normal albumin level} - \text{patient albumin level})]$ .

in critically ill patients is associated with an increased risk of complications, mortality, and complexity of care.<sup>32,33</sup> Preventing or minimizing the effects of acute kidney injury in this patient population could reduce the costs of care and improve both in-hospital and long-term outcomes.

Clinical and laboratory diagnostic criteria for tumor lysis syndrome were proposed by Cairo and Bishop in 2004,<sup>34</sup> with subsequent modifications proposed by Howard et al. (Table 2).<sup>35</sup> The Cairo–Bishop criteria (Table 3)<sup>34</sup> or the National Cancer Institute Common Toxicity Criteria for Adverse Events<sup>36</sup> can be used to grade the severity of tumor lysis, as well as individual clinical and laboratory results.

#### PROPHYLAXIS AND TREATMENT

The goals of prophylaxis and treatment for tumor lysis syndrome are to prevent or minimize serious or life-threatening electrolyte disturbances and acute kidney injury while maintaining extracellular volume. We consider several essential related steps toward meeting these goals.

#### RISK STRATIFICATION

Developing a risk-based strategy for prophylaxis and monitoring can help facilitate early detec-

tion of tumor lysis. Table 1 lists cancers and therapies associated with the highest risk, but the prediction of risk can be subtle and at times misleading. For example, individual cases of tumor lysis syndrome or small series of cases have been reported with the use of cytotoxic therapy and several classes of targeted therapies in patients with tumors considered to be inherently low risk (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).<sup>17,18,37-43</sup> Surrogates of a high tumor burden (hyperuricemia, leukocytosis, and elevated lactate dehydrogenase levels) and advanced age have been independent predictors of risk.<sup>6</sup> However, traditionally high-risk tumors treated with current regimens (e.g., Burkitt's lymphoma treated with a dose-adjusted infusional regimen and acute myeloid leukemia treated with a hypomethylating agent and venetoclax) appear to carry a lower risk of tumor lysis than do those treated with historically more intensive regimens.<sup>44,45</sup> The frequent introduction of targeted therapies has also changed the risk landscape. Hospitalized patients with a clinically significant tumor burden and coexisting disorders require some vigilance (with appropriate laboratory evaluations at baseline and after treatment), even in the case of inherently low-risk cancers. The occurrence of mild prerenal azotemia and associated hyperkalemia may be a sign of preexisting, unrecognized

**Table 3. Cairo-Bishop Grading Classification of Tumor Lysis Syndrome.\***

Clinical or Laboratory Finding	Grade 0	Grade I	Grade II	Grade III	Grade IV	Grade V
Laboratory criteria for tumor lysis syndrome	Absent	Present	Present	Present	Present	Present
Creatinine	<1.5 times the ULN	1.5 times the ULN	>1.5–3.0 times the ULN	>3.0 to 6.0 times the ULN	>6.0 times the ULN	NA†
Cardiac arrhythmia	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled or controlled with a device (e.g., defibrillator)	Life-threatening (e.g., arrhythmia associated with heart failure, hypotension, syncope, or shock)	NA†
Seizure	None	None	One brief generalized seizure; one or more seizures well controlled by anticonvulsants, or infrequent focal motor seizures not interfering with activities of daily living	Seizure with altered consciousness or seizure disorder with breakthrough generalized seizures despite medical intervention	Seizures of any kind that are prolonged, repetitive, or difficult to control (e.g., status epilepticus or intractable epilepsy)	NA†

\* Elements of tumor lysis syndrome can also be graded with appropriate clinical Common Terminology Criteria for Adverse Events terms for clinical trials or institutional data collection.

† Grade V is fatal; NA denotes not applicable.

spontaneous or glucocorticoid-induced tumor lysis in a patient with an occult or clinically apparent but untreated cancer.

#### PROPHYLAXIS

##### *Baseline Evaluation and Preparation*

Preparation for induction therapy requires baseline measurement of uric acid, potassium, and phosphorus levels and renal function (plus lactate dehydrogenase levels in patients with hematologic cancers or germ-cell tumors). Current and anticipated future medications with the potential to cause or exacerbate acute renal injury should be reviewed (e.g., nonsteroidal antiinflammatory agents, angiotensin-converting–enzyme inhibitors and angiotensin-receptor blockers, certain antibiotic agents, and potentially, radiographic contrast materials). When possible, consideration should be given to whether these agents can be withheld or alternative agents can be substituted throughout the period of anticipated risk, particularly in patients with renal dysfunction at baseline. Potential drug–drug interactions (e.g., the effect of azole antifungal agents on the half-life of venetoclax) need to be recognized, with appropriate dose adjustments or monitoring for toxic effects.<sup>46</sup>

##### *Uric Acid Prophylaxis*

Cellular destruction releases purine nucleic acids, which are metabolized to hypoxanthine and xanthine and subsequently to uric acid (Fig. 2). Allopurinol and febuxostat are xanthine oxidase inhibitors that reduce plasma uric acid levels by inhibiting production. Two randomized trials comparing allopurinol and febuxostat did not show superiority of either agent.<sup>47,48</sup> On the basis of cost and familiarity, allopurinol is the preferred initial oral agent, with febuxostat generally reserved for patients with hypersensitivity to allopurinol. Dose reductions are recommended for both agents in patients with reduced creatinine clearance. The use of xanthine oxidase inhibitors has rarely been associated with xanthine crystal nephropathy.<sup>49</sup> For outpatients with low-risk hematologic cancers, laboratory tests for tumor lysis are performed at baseline and allopurinol is administered for 7 to 10 days. Tumor lysis tests are often repeated 24 to 48 hours after initiation of the first cycle of therapy, and patients are monitored for any mild metabolic abnormalities; monitoring is



continued until any such abnormalities are resolved.

Uric acid oxidase enzymatically converts uric acid to a more soluble metabolite (allantoin) but is functionally inactive in humans. Rasburicase is a recombinant urate oxidase that decreases uric acid levels more rapidly than xanthine oxidase inhibitors do,<sup>50</sup> but without a clear reduction in the risk of renal complications in the context of tumor lysis prophylaxis or treatment. Rasburicase is associated with hypersensitivity or anaphylactic reactions in approximately 1% percent of patients, and neutralizing antibodies have been measured in up to 18% of persons who were previously exposed to rasburicase.<sup>51</sup> Although the dose recommendation on the label for rasburicase is weight based (0.2 mg per kilogram of body weight, administered daily for up to 5 days), ample prospective data have shown that a single dose of 1.5 to 7.5 mg abrogates hyperuricemia within 24 to 36 hours in most persons.<sup>52-56</sup> Additional doses can be considered as needed.<sup>54</sup> Rasburicase remains active *ex vivo*, and uric acid samples should be collected in pre-cooled heparinized tubes, transported in ice water,

and analyzed within 4 hours to avoid falsely low values.<sup>51</sup>

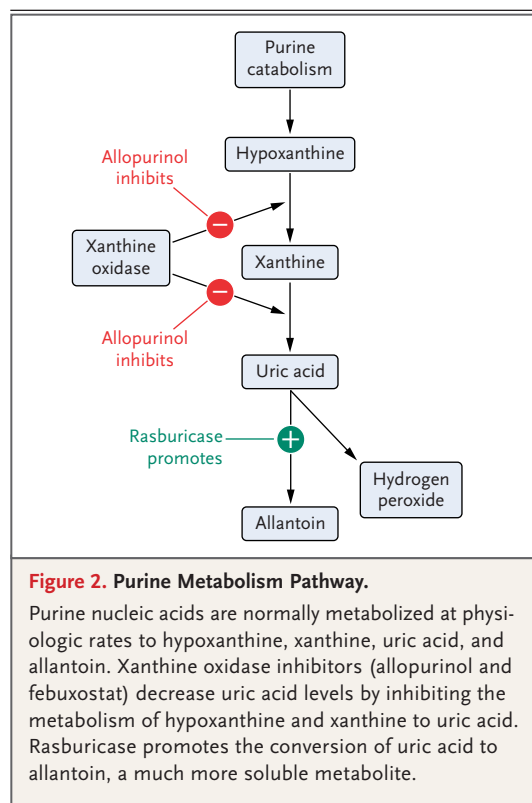
Rasburicase prophylaxis is considered for patients with highly proliferative tumors (e.g., acute myeloid leukemia with a white-cell count of >50,000 per microliter, acute lymphoblastic leukemia with a white-cell count of >100,000 per microliter, Burkitt's lymphoma, and high-grade B- or T-cell lymphomas) plus a baseline uric acid level that exceeds 8 mg per deciliter (476  $\mu\text{mol}$  per liter) and a creatinine level higher than 1.5 times the baseline level or the upper limit of the normal range. Rasburicase prophylaxis is also a consideration for patients in whom the administration of higher fluid volumes may be challenging (e.g., those with preexisting heart failure or chronic kidney disease).

Rasburicase produces hydrogen peroxide as a by-product of its activity (Fig. 2), which creates a source of oxidative stress. This by-product could potentially cause hemolytic anemia, methemoglobinemia, or both in persons with glucose-6-phosphate dehydrogenase (G6PD) deficiency. Rasburicase is therefore contraindicated in patients with known G6PD deficiency. The associated methemoglobinemia or hemolytic anemia is usually mild but has been severe after a single dose.<sup>57</sup> Methylene blue may be administered for methemoglobinemia, since it catalyzes the reaction that reduces methemoglobin to hemoglobin. However, administration of methylene blue in patients with G6PD deficiency could theoretically exacerbate the process or lead to hemolysis by increasing oxidative stress on red cells.<sup>58</sup> Alternative therapies include dextrose and ascorbic acid.<sup>59</sup> The use of exchange transfusions has been reported in this context.<sup>60</sup> Persons at high risk for G6PD deficiency (e.g., persons of Mediterranean or African ancestry) should be screened before administration. Measuring G6PD levels during an acute episode of hemolysis or methemoglobinemia may lead to falsely low results.

A single dose of 3 mg of rasburicase for high-risk patients is often sufficient as prophylaxis against tumor lysis, with additional doses as clinically indicated.<sup>61</sup> Electrolyte management is discussed below.

#### Fluid Management

Patients with newly diagnosed or relapsed cancer may have a predisposition to prerenal azotemia



because of poor oral intake, increased insensible or gastrointestinal fluid losses, and stress-induced reduction of cardiac output or ineffective circulating volume due to sepsis. Azotemia in conjunction with nephrotoxic medications may lead to acute kidney injury in susceptible patients. Calculating the fractional excretion of sodium can assist in the estimation of the extent of prerenal azotemia in patients with relatively normal renal function who are not receiving diuretics.<sup>62</sup>

Judicious fluid and blood-pressure management includes replacement of insensible and gastrointestinal fluid losses and maintenance of appropriate diuresis to minimize the nephrotoxic effects of the products of tumor lysis. Administration of intravenous fluids begins 24 to 48 hours before the initiation of therapy in order to correct any volume depletion and to establish the patient's ability to receive intravenous fluids and maintain adequate urine output, with or without diuretics. Although high-quality prospective data are lacking, a common recommendation is to administer 1 to 3 liters of fluids (generally 0.9% saline) per square meter of body-surface area per day in order to maintain a urine output of 2 ml per kilogram per hour, particularly during the first 24 to 72 hours after the initiation of systemic therapy, when the risk of tumor lysis is greatest. One of the first clinical manifestations of acute kidney injury may be oliguria, and therefore accurate monitoring of urine output is important to prevent volume overload and to signal the need for more intensive renal or fluid management.

The occurrence of fluid overload in patients with tumor lysis syndrome has been associated with an increased probability of hypoxemia, pulmonary edema, admission to an intensive care unit, and indications for renal replacement therapy in children,<sup>63</sup> as well as with an increased risk of death among adults with newly diagnosed acute myeloid leukemia.<sup>64</sup> In lower-risk scenarios and outpatient settings, 1 to 2 liters of intravenous fluids are provided at the time of initial therapy, and patients are instructed to maintain a daily oral fluid intake of 2 to 3 liters for the subsequent 5 to 7 days.

Alkalinization was historically thought to improve uric acid solubility and reduce renal crystal

deposition, but with effective management of hyperuricemia, alkalinization is no longer recommended. It inhibits phosphorus excretion and may exacerbate hyperphosphatemia, which increases the risk of renal calcium phosphate precipitation or enhanced hypocalcemia with an attendant risk of tetany, seizures, or arrhythmias. Urine crystals (uric acid or calcium phosphate) appear to be very uncommon in patients treated according to current algorithms for management of tumor lysis.<sup>27</sup>

#### *Additional Preemptive Considerations before Disease-Specific Therapy*

Patients with newly diagnosed acute leukemias often present with hyperleukocytosis and clinical (symptomatic) leukostasis, which has been associated with an increased risk of tumor lysis and poor short-term outcomes in patients with acute myeloid leukemia.<sup>65,66</sup> Leukapheresis, hydroxyurea, and low-intensity chemotherapy are often cited as strategies for cytoreduction of the disease burden before induction therapy, particularly for patients with leukostasis. However, the effect of these initial or ancillary measures in mitigating tumor lysis and improving postdischarge outcomes has not been clearly established.<sup>65-70</sup> The American Society for Apheresis recommends consideration of leukapheresis in patients with leukostasis, and prophylactic cytoreduction is recommended in those with acute myeloid and lymphoid leukemias.<sup>71</sup> The placement of apheresis catheters carries an attendant risk of bleeding in patients who have baseline thrombocytopenia or coagulopathies. The guiding principle for managing newly diagnosed or relapsed acute leukemia with hyperleukocytosis is to reduce the white-cell count urgently and safely and initiate disease-specific remission-induction therapy as quickly as possible.

Glucocorticoids can lead to rapid tumor lysis in patients with lymphomas.<sup>16</sup> Theoretically, the use of "prephase" glucocorticoids could gently mitigate the severity of subsequent tumor lysis, given that this prephase treatment is low-intensity therapy and is associated with a decline in the serum lactate dehydrogenase level, which is a surrogate for tumor burden and a predictor of tumor lysis.<sup>6,72</sup> Despite a lack of direct data to support a reduction in the risk or severity of

subsequent tumor lysis syndrome, for patients with a high tumor volume or poor functional status, prephase glucocorticoids are often administered while staging is completed and an initial treatment plan is finalized. Prephase glucocorticoids can ameliorate hyperbilirubinemia in patients with hepatic involvement with lymphoma, which allows for the subsequent administration of full-dose induction therapy. This approach has been associated with improvements in functional status and a decreased incidence of severe neutropenia and first-cycle febrile neutropenia.<sup>72</sup> In a retrospective study of pediatric acute lymphoblastic leukemia, prephase glucocorticoids were associated with an 88% reduction in the risk of tumor lysis syndrome.<sup>73</sup>

Delaying the administration of rituximab has not been shown to affect outcomes in at least one randomized trial involving patients with diffuse large B-cell lymphoma.<sup>74</sup> Deferring the administration of rituximab for a few days to a week after initiating chemotherapy may reduce the risk of tumor lysis and infusion-related reactions.

Patients with cancer often have coexisting disease- or age-related cardiorenal conditions, which may make complications such as arrhythmias more likely in the presence of tumor lysis syndrome.<sup>23</sup> In patients with very-high-risk tumor lysis, a nephrologist is consulted to establish a care plan before induction therapy is begun. In rare cases involving advanced-stage chronic kidney disease and a high risk of tumor lysis, a dialysis catheter may be placed preemptively before the initiation of disease-specific therapy.

#### TREATMENT OF ESTABLISHED TUMOR LYSIS

Monitoring trends in laboratory values during initial hydration may help predict the development and severity of subsequent tumor lysis. Depending on baseline values and the risk of tumor lysis, laboratory tests may be monitored every 6 to 12 hours during the period of greatest risk (the first 24 to 72 hours after the initiation of therapy). The frequency of these measurements is subsequently adjusted on the basis of the degree of metabolic or electrolyte disruption, and laboratory monitoring is eliminated as metabolic abnormalities resolve. With the availability

of rasburicase, acute kidney injury in patients with tumor lysis syndrome is more often caused by hyperphosphatemia than by hyperuricemia. Patients in whom acute metabolic abnormalities develop from established tumor lysis should be monitored with continuous telemetry and periodic electrocardiograms until the abnormalities resolve.

Hyperkalemia and hyperphosphatemia are managed by the redistribution or removal of potassium and phosphate. Hyperkalemia may require urgent management to prevent cardiac arrhythmias or death. Rapid correction is of greatest urgency in patients with potassium levels exceeding 6.5 mmol per liter and in those with symptoms (e.g., muscle weakness) or cardiac signs (e.g., electrocardiographic changes or arrhythmias). Electrocardiographic changes are relatively specific in predicting adverse events in patients with hyperkalemia, particularly the occurrence of prolonged PR or QRS intervals, bradycardia, and junctional rhythms.<sup>75</sup> The occurrence of tall, peaked T waves in a patient with hyperkalemia warrants immediate intervention but may be an early finding that is less likely to be associated with an adverse cardiac event.<sup>75</sup>

Management of acute hyperkalemia includes the administration of intravenous calcium (to antagonize the effects of potassium on cellular membranes) and therapies to preferentially redistribute potassium to cells (e.g., insulin with glucose or beta-agonists such as albuterol). Loop diuretics can increase renal potassium excretion in patients with normal or mildly impaired renal function. Cation exchangers (e.g., sodium zirconium cyclosilicate) bind potassium in the gastrointestinal tract, which facilitates removal. Continuous renal replacement therapy for hyperkalemia may be insufficient in extreme situations. In these instances, the addition or substitution of intermittent hemodialysis may restore electrolyte balances more quickly than continuous renal replacement therapy because of faster flow rates and larger dialyzers.<sup>76,77</sup>

Hyperphosphatemia may be the best predictor of acute kidney injury in patients with established tumor lysis. In one study, the occurrence of acute kidney injury was predicted with 84% specificity with a phosphorus cutoff value of 6.6 mg per deciliter (2.1 mmol per liter).<sup>24</sup> Hyper-



phosphatemia may lead to acute calcium phosphate nephropathy. Aggressive administration of intravenous saline with diuresis can increase phosphorus excretion. A retrospective pediatric study showed that oral phosphate binders (which reduce gastrointestinal absorption) decreased phosphorus levels, increased calcium levels, and decreased the calcium–phosphorus product.<sup>78</sup> Dialysis is most often considered in patients with clinically significant hyperphosphatemia, symptomatic hypocalcemia, and acute kidney injury. Continuous methods of dialysis are preferred in such patients because the efficacy of phosphorus removal is time dependent. Continuous dialysis also helps prevent rebound hyperphosphatemia, which can occur after intermittent hemodialysis.

Progressive or recurrent hyperuricemia is uncommon in patients who receive rasburicase prophylaxis. In patients at low risk who receive allopurinol as prophylaxis and subsequently have hyperuricemia from established tumor lysis, uric acid levels generally normalize rapidly after a single dose of rasburicase.

#### SPECIAL MANAGEMENT CONSIDERATIONS

##### *Venetoclax*

Venetoclax, currently the only B-cell lymphoma 2 inhibitor approved by the Food and Drug Administration (FDA), deserves special emphasis in the management of tumor lysis syndrome. In an early-phase trial, administration of high doses of venetoclax in patients with chronic lymphocytic leukemia (CLL) led to tumor lysis syndrome in 18% of participants (one of whom died) during dose escalation.<sup>21</sup> This finding led to the development of a step-up dosing schedule for patients with CLL, with specific guidance for assessment of the risk of tumor lysis, as well as for management and monitoring, on the basis of the tumor burden, peripheral-blood lymphocyte count, and baseline renal function.<sup>22</sup> Hospitalization is recommended for the administration of the first dose at each of the first two dose levels for patients at highest risk and those at intermediate risk who have an estimated creatinine clearance of less than 80 ml per minute. With the use of the step-up schedule, risk stratification, and appropriate prophylactic measures, laboratory evidence of tumor lysis has been re-

ported in 3% of outpatient dose escalations and 15% of inpatient escalations, with no clinical signs of tumor lysis.<sup>79</sup>

For patients with preexisting renal dysfunction, venetoclax has been administered safely after initial debulking with chemotherapy or immunotherapy.<sup>80</sup> Incorporation of an initial debulking strategy with low-risk agents (e.g., Bruton's tyrosine kinase inhibitors) in many combination regimens used in the current treatment of CLL has led to a reduction in the importance of hospitalization at the time of venetoclax initiation.<sup>81</sup>

Tumor lysis syndrome has also been observed with the combined administration of venetoclax and hypomethylating agents or low-dose cytarabine during induction therapy for acute myelogenous leukemia<sup>45</sup> and for mantle-cell lymphoma, which has led to recommended revisions in the dosing ramp-up.<sup>82</sup>

##### *Pseudohyperkalemia Confounding Assessment*

In patients with lymphoid cancers and extreme leukocytosis (e.g., >100,000 leukocytes per microliter), the laboratory artifact of pseudohyperkalemia may be observed. Pseudohyperkalemia, which is seen most commonly in patients with CLL, probably results from ex vivo lysis of fragile or senescent tumor cells due to the mechanical stress of collection into a vacuum tube, agitation of the tube during transport, or analysis of serum or plasma after cellular stress associated with centrifugation of the sample. Being able to distinguish pseudohyperkalemia from the hyperkalemia that may result from tumor lysis syndrome is important, because treating pseudohyperkalemia could theoretically lead to iatrogenic hypokalemia. Isolated hyperkalemia in the absence of hyperphosphatemia, hyperuricemia, or both after the initiation of therapy should provide reasonable reassurance that tumor lysis is not occurring, but an electrocardiogram may be required to clarify the clinical picture. Pseudohyperkalemia can be prevented with the use of specific phlebotomy techniques (e.g., drawing blood without repeated fist clenching or prolonged use of a tourniquet and gently aspirating blood with a syringe rather than with a vacuum tube), specific specimen-collection techniques (e.g., using heparinized tubes), a shortened time to analysis (e.g., analyzing the specimen urgently

or drawing a point-of-care sample), avoidance of centrifugation (e.g., analyzing a whole-blood sample with a blood-gas analyzer), and avoidance of postcollection trauma to the sample (e.g., avoiding the use of automated tube transporters).

#### *Additional New or Targeted Therapies*

Management of tumor lysis syndrome may be a challenge in patients with multiple myeloma because of clinically significant renal dysfunction at baseline. Bortezomib, daratumumab, bispecific antibodies, and chimeric antigen receptor T-cell therapies have all been associated with tumor lysis syndrome in retrospective and pharmacovigilance studies,<sup>83-85</sup> particularly in combination regimens. Immune checkpoint inhibitors are uncommonly associated with tumor lysis syndrome; however, more than 150 cases associated with immune checkpoint inhibitors have been reported to the FDA Adverse Event Reporting System, and the syndrome has led to hospitalization (in 29% of cases), life-threatening complications (in 5%), or death (in 44%).<sup>43</sup> Agents used in the reported cases included inhibitors of programmed cell death protein 1, programmed death ligand 1, and cytotoxic T-lymphocyte antigen 4; odds ratios suggest a higher risk with the use of two types of agents in combination, most often in patients with lung or thymic cancers.

## CONCLUSIONS

The scope of tumor lysis syndrome has changed considerably over the past two decades. Historically high-risk cancers are often treated with lower-intensity induction regimens today, which may mitigate the incidence and severity of tumor lysis. Aggressive cytoreductive management of

hyperleukocytosis in patients with acute myelogenous leukemia may also be reducing the risk, as compared with that in previous decades. However, the introduction of targeted therapies, particularly venetoclax in patients with CLL, has made tumor lysis relatively more common among patients with traditionally low-risk tumors. Electronic health records, which provide virtually instantaneous laboratory and supportive information, can be used to discern trends over time and manage tumor lysis in a more nuanced and timely way, particularly during the period of highest risk. Given that the complexity of medicine and the availability of modern therapeutics can be expected to increase, health care professionals need to practice with an enhanced degree of vigilance for situations in which tumor lysis may occur and must recognize the subtle early metabolic disturbances that may herald its onset.

Achieving the best outcomes for patients requires selecting treatment regimens with the best combined efficacy and safety outcomes in conjunction with expert pre- and post-treatment supportive care. Although rasburicase is highly effective in the management of hyperuricemia, high-quality prospective analyses of its cost-effectiveness are lacking. Current risk-based algorithms for rasburicase prophylaxis and treatment, including the use of rasburicase as a rapid salvage for xanthine oxidase inhibitor failures, are likely to strike the most appropriate balance between cost and effectiveness.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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