Tumor lysis syndrome (TLS) is a pattern of metabolic and electrolyte disturbances that can occur following the initiation of cytotoxic therapy. It can result in life-threatening hemodynamic and renal complications if it is not managed correctly. Despite many advances in supportive care and monitoring, TLS still poses considerable danger to many patients with cancer. Most of the severe complications of TLS can be prevented through measures, such as hydration, alkalinization, and use of the uric acid-lowering agents allopurinol and rasburicase. Nursing assessment and management is essential in preventing and treating TLS. This article provides an overview of the pathology and potential complications of TLS, methods of identifying high-risk patients, how to prevent TLS, and how to manage complications, focusing on the nurse's role in management and monitoring. (Adv Stud Nurs. 2006;4(3):41-48)
Tumor lysis syndrome can result in life-threatening complications. Hyperkalemia can cause cardiac complications, such as ventricular arrhythmias that can lead to multiple organ failure and death, in addition to central nervous complications, such as seizures. Hyperphosphatemia and hyperuricemia can lead to precipitation of calcium phosphate salts in the kidney, which can cause obstructive nephropathy. The buildup of nucleic acids, xanthines, and uric acid can compromise renal function, potentially resulting in acute renal failure. Patients who develop acute renal failure and require dialysis face extended hospital stays and high costs (Figure 3). Early identification of high-risk patients is essential.

**INCIDENCE OF TUMOR LYSIS SYNDROME**

The precise incidence of TLS is unknown, but incidence varies according to treatment regimen, age, and disease. Some of the newer and more aggressive therapies, with high doses and more challenging types of therapy, can rapidly reduce tumors and prolong survival, but they seem to cause TLS more often. Complications tend to be more severe in older adults and in older children. Leukemia and lymphoma commonly proliferate and break down rapidly, leading to a higher rate of TLS than other types of cancer.

**IDENTIFYING PATIENTS AT RISK**

**DIAGNOSIS**

The nurse first assesses a patient's risk for TLS based on diagnosis. Patients who have diseases with a high tumor growth fraction or high proliferative rate and who are known to be highly sensitive to chemotherapy, radiation, or any other therapy are at the highest risk. Therefore, the diseases of most concern are acute lymphocytic and acute myelogenous leukemia (specifically, T-cell acute leukemia), particularly in patients with an extremely high white blood cell count (WBC) or tumor burden, and any of the high-grade B-cell non-Hodgkin's lymphomas, such as Burkitt's lymphoma and lymphoblastic lymphoma. Diseases with lesser but demonstrated risk include some of the intermediate- and low-grade B-cell non-Hodgkin's lymphomas, such as large-cell and chronic lymphocytic leukemia; multiple myeloma; some solid and germ cell tumors; small-cell lung carcinoma; breast carcinoma; medulloblastoma; and neuroblastoma.

**DISEASE BULK**

A demonstrated large tumor burden is a risk factor for TLS. Children or adults who present with a large abdominal mass, commonly seen in lymphoma, and patients with a mediastinal mass are at high risk.
Lymphadenopathy and hepatosplenomegaly can also be risk factors indicating malignant disease infiltration into the lymph tissues, liver, and spleen. The liver and spleen could be swollen because they are assisting in hematopoiesis, or because they are actually infiltrated with leukemia or lymphoma cells.

It is essential to monitor the lactate dehydrogenase (LDH) level. Laboratory values can vary, but an elevated level of LDH that is indicative of a high tumor burden, rapid malignant proliferation, or both clearly puts a patient at high risk.

Renal insufficiency also puts a patient at risk for TLS. Children do not often have renal insufficiency because they are usually without comorbidities, but adults could have a history of renal issues. In both children and adults, changes in renal function could simply be because of days of illness and dehydration.

Time Frame

Patients are at greatest risk for severe TLS in the first 2 to 3 days of hydration and therapy, and they remain at risk for up to 7 days.

Cairo-Bishop Risk Grading

Cairo and Bishop present a TLS risk grading system to determine the need for assertive prevention and care. The first part of the system is based on laboratory uric acid, potassium, phosphorus, and calcium levels. When 2 or more of these values are abnormal 3 days before or 7 days after initiation of chemotherapy, more caution and earlier intervention may be warranted (Table 1). The second part of the grading system is based on clinical status, clinical TLS being defined as laboratory TLS plus 1 or more of the following criteria: elevated creatinine (≥1.5 × the upper limit of normal, adjusted by age), cardiac arrhythmia/sudden death, and seizure, based on potassium and calcium and not attributable to a therapeutic agent. The risk grades of 0 to V incorporate laboratory and clinical TLS (Table 2).

Table 1. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uric acid</td>
<td>X ≥8 mg/dL (476 µmol/L) or 25% increase from baseline</td>
</tr>
<tr>
<td>Potassium</td>
<td>X ≥6.0 mEq/L (6.0 mmol/L) or 25% increase from baseline</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>X ≥6.5 mg/dL (2.1 mmol/L; children), X ≥6.5 mg/dL (2.1 mmol/L; adults?), or 25% increase from baseline</td>
</tr>
<tr>
<td>Calcium</td>
<td>X ≤7.0 mg/dL (1.75 mmol/L) or 25% decrease from baseline</td>
</tr>
</tbody>
</table>

Assessment assumes hydration (± alkalinization) and uric acid-lowering agent will be started.

*8 is the high normal, but it can be a little higher without cause for alarm in adults; in children, this number is used strictly.

PATIENT ASSESSMENT

OBTAINING AND ASSESSING LABORATORY VALUES

After assessing the patient’s risk factors, the nurse obtains laboratory values. Most important are the renal values, LDH, and WBC. Serum calcium-phosphorus solubility product factor (serum calcium × serum phosphorus) is also important. Calcium will bind with excess phosphorus, resulting in hypocalcemia, and if the calcium-phosphorus level reaches 60 or higher, calcium phosphate salts precipitate, which can lead to obstructive nephropathy.2,6

RADIOLOGY

Radiologic procedures to assess TLS risk typically include a chest X ray and renal ultrasound. Use of intravenous (IV) contrast material should be avoided in these procedures because of the additional stress it places on the kidneys to excrete the “heavy” contrast substance. Chest and abdominal computed tomography scans are also frequently used to assess tumor size and location, in addition to assessing risk for TLS.

Special attention should be paid to the abdomen in radiologic scans. Sometimes renal dysfunction is caused not by hyperuricemia but by the lymphoma pressing on the renal blood flow or the kidneys, which may require intervention before the patient begins therapy. Looking for mediastinal masses is also important.6

OBTAINING THE PATIENT HISTORY

Obtaining the patient history is another area where the nurse plays an essential role in being alert for signs of TLS. Signs of obstructive nephropathy include flank pain, hematuria, and decreased urine output. Lethargy, nausea and vomiting, edema, and oliguria can indicate hyperuricemia. Hypocalcemia signs include muscle cramps, twitching, numbness, tingling, carpopedal spasms, and seizures.7 The most potentially life-threatening abnormality is hyperkalemia, and some of its symptoms, such as nausea, diarrhea, cramping, and weakness, can be a result of the patient’s disease or short-term illness rather than TLS. The nurse must determine whether the patient is having more specific symptoms, such as irregular heartbeat, ventricular arrhythmias, QRS widening, heart block, or especially elevated T waves.8

Obtaining a history can be difficult in children, but the child and family may be able to provide much of the necessary information, such as how often the child is going to the bathroom. Edema is one of the symptoms more obvious to children—little boys notice their testes may be swollen, and older children may notice other signs of swelling. A decline in the use of true fine motor skills can indicate spasms in children.

The nurse then completes the physical assessment: checking vital signs, respiratory function, blood pressure, and cardiac function, and examining the patient for lymphadenopathy, abdominal masses, ascites, edema, and weight changes.

PREVENTION OF TUMOR LYSIS SYNDROME

The foundation of managing TLS is prevention,
before and during cytotoxic therapy. Metabolic stability should be established before initiating treatment, if the nature of the disease allows for a delay.3

**HYDRATION**

Hydration is the first and most important line of prevention. IV fluid should be 3000 mL/m²/24 hours or more (amount may vary depending on age and comorbidities) and continued for several days to maintain a urine output of more than 100 cc/m²/hour and a urine specific gravity of less than 1.010.2,6 It is especially important to work with physicians and residents to ensure that the patient receives no additional potassium during hydration, even if the patient’s potassium level is normal,2,3 because the patient will be exposed to an elevated level of potassium when lysis begins.

**ALKALINIZATION**

Alkalinization is a common but more controversial preventative measure. When used, urine pH should not exceed 7.0.4 Decreasing the acidity of the renal environment makes it less conducive to hosting xan-thines and uric acid. Sodium bicarbonate can be administered orally, in the patient’s IV maintenance, or as intermittent boluses, according to physician or institution preference. Serum bicarbonate should be less than 30 mEq/L and discontinued when uric acid is normal or serum phosphorus is elevated, and urine pH should be maintained between 7.0 and 7.5. If the urine becomes too alkaline, calcium and phosphate can precipitate in the kidney.2,6

**ALLOPURINOL**

Allopurinol has long been used to help prevent TLS. It blocks uric acid production by inhibiting xanthine oxidase, and it is effective in preventing further development or buildup of uric acid (Figure 4).3,4

Allopurinol is predominantly administered orally. It is also available in an IV formulation. For young children, the tablets must be crushed up and administered 3 times a day, but it is easily given.

Because allopurinol does not typically produce an immediate response, it may not provide enough renal protection for high-risk patients.6 It also does not affect the uric acid that has already formed, which is a concern in patients with an elevated level of uric acid.5 Allopurinol administration can also result in hypoxanthine and xanthine accumulation.1,3

**RASBURICASE**

Rasburicase is a newer uric acid-lowering agent, and it is currently the only pharmacologic alternative to allopurinol. It is a recombinant urate-oxidase enzyme derived from the *Aspergillus flavus* gene, and it works by oxidizing uric acid into the water-soluble substance allantoin, which the kidney excretes easily (Figure 5).4

---

![Figure 4. Allopurinol Mechanism of Action](image1)

Allopurinol: Blocks Uric Acid Production

![Figure 5. Rasburicase Mechanism of Action](image2)

Rasburicase: Converts Uric Acid to Allantoin and Promotes Excretion
Rasburicase has been used for a few decades in Europe and was approved by the US Food and Drug Administration in 2002 for pediatric use. It is available only as an IV drug, and it is administered once a day as a 15- to 30-minute infusion. It is approved for use for 5 days but, in practice, does not often require more than 1 to 3 doses, an advantage clinically and financially. It has been shown to be effective in decreasing uric acid level, and it also prevents xanthine buildup because it works at the end of the uric acid metabolic pathway. Because it induces a rapid response, patients do not need to be alkalinized, and it can help prevent the delay of chemotherapy.

In its current recombinant form, rasburicase does not commonly cause significant allergic reactions, sensitivities, or the development of neutralizing antibodies, as does the more "pure" form used in Europe. However, some studies have reported that antibodies to rasburicase developed in small numbers of patients, thus caution is recommended when retreatment is considered. Incidence of antibodies may be detected 1 to 6 weeks after infusion.

Nurses administering rasburicase should be aware that its rapid action can degrade uric acid in blood samples at room temperature, resulting in an artificially low level of uric acid. Therefore, when obtaining tumor lysis laboratory values, blood samples should be collected in prechilled heparin tubes, immediately placed in ice, and should be analyzed within 4 hours of collection.

RASBURICASE VERSUS ALLOPURINOL

Comparative clinical data

Goldman et al performed a randomized, multicenter trial comparing allopurinol and rasburicase in 52 patients aged 4 months to 17 years with leukemia or lymphoma who were at high risk for TLS. Patients received allopurinol 10 mg/kg orally every 8 hours or rasburicase 0.2 mg/kg IV daily for 5 to 7 days. The primary endpoint was control of uric acid level during the first 96 hours of therapy, as determined by area under the curve. Baseline uric acid levels were 6.8 ± 3.4 mg/dL and 7.7 ± 3.5 mg/dL in patients receiving allopurinol and rasburicase, respectively.

The investigators found that patients receiving rasburicase experienced a rapid and dramatic response—4 hours after the first dose, patients achieved an 86% reduction in uric acid versus a 12% reduction with allopurinol (P < .0001). The median time to achieve a uric acid level of less than 8 mg/dL following first dose in patients receiving rasburicase and allopurinol was 4 hours and 23 hours, respectively. One patient receiving allopurinol developed renal failure requiring assisted renal support versus none of the patients receiving rasburicase. No patients developed antibodies to rasburicase.

Adverse reactions/contraindications

Neither allopurinol nor rasburicase commonly causes problems in children or adults. The most common adverse reaction to allopurinol is a rash, and patients who have had any type of allergic response to it in the past, such as severe rash or liver toxicity, should not repeat the drug. The most common adverse reactions to rasburicase are fever, nausea, vomiting, and headache. Allergic reactions to rasburicase can include anaphylaxis, rash, hemolysis, and methemoglobinemia. Patients should be monitored for allergy and hypersensitivity because the immunogenicity of rasburicase varies by patient. Patients with glucose 6-phosphate dehydrogenase deficiency should not receive rasburicase. Nurses should screen patients of African-American or Mediterranean ancestry for this deficiency and ask about family history.

Cost

Oral allopurinol is less expensive than rasburicase but, at a cost of $485.95 for a 500-mg vial, the IV preparation of allopurinol is more expensive than allopurinol tablets ($0.05–$0.11 per 100-mg tablet). Rasburicase is $386.78 per 1.5-mg vial and, as mentioned, treatment may require 1 to 5 doses. Clinical considerations should outweigh cost if a patient can be prevented from going to the intensive care unit (ICU), undergoing dialysis, or undergoing hemofiltration.

CAIRO-BISHOP RECOMMENDATIONS

Cairo and Bishop present recommendations for the use of allopurinol and rasburicase (Table 3). The investigators suggest that rasburicase be used for patients at higher risk for TLS, who would probably benefit more from the faster-acting drug. A WBC of approximately 50 000 is one of the guidelines they use to determine who is at greatest risk. Other factors include disease type, renal status, and the aggressiveness of the planned treatment.

Some centers use a WBC of closer to 100 000 as a guideline. Some pharmacies may not have rasburicase on formulary. There will need to be more education and implementation processes instituted over the next few years.
PROCEEDINGS

Ongoing thorough monitoring and assessment are essential, including ensuring hydration and checking vital signs at least every 4 hours. Tumor lysis laboratory values should be obtained every 6 to 12 hours minimum, especially during the first few days of treatment. The nurse also should continuously monitor cardiac, respiratory, neuromuscular, and gastrointestinal function, in addition to checking for edema and weight changes.

Cardiac monitoring can be challenging because not all centers have the ability to monitor hematology/oncology patients outside of the ICU. Sometimes patients will need to be moved to the ICU to ensure proper monitoring. In the ICU, more intensive nursing is provided until the patient is deemed metabolically and hemodynamically stable. Patients who show signs of hyperkalemia must be monitored; intervention will be required if the patient has an abnormal heart rate or rhythm or a potassium level of 6.5 mEq/L or more or calcium level of 7.0 mg/dL or less.

MANAGEMENT OF TUMOR LYsis

Syndrome Complications

Patients with hyperkalemia should receive IV furosemide or another appropriate diuretic. Oral sodium polystyrene sulfonate is an option, but it is not indicated if potassium is rising quickly. A glucose and insulin infusion can be helpful, in addition to IV sodium bicarbonate, pushing the extra potassium and phosphorus back into the cell. IV calcium gluconate is effective and also helps prevent hypocalcemia, but it is not a first choice because of the potential of developing calcium salts in the kidneys. Dialysis may be necessary in severe cases.

For patients with hyperuricemia, treatment begins with vigorous hydration. Alkalinization with allopurinol is appropriate for most patients, and rasburicase is recommended for higher-risk patients. If the patient develops acute renal failure that does not respond to more conservative management, hemofiltration or dialysis may be necessary.

To treat hyperphosphatemia, an oral phosphate binder, such as aluminum hydroxide, is recommended; phosphates in diet and medication should also be restricted. Additionally, a glucose and insulin infusion can be effective.

Table 3. Recommendations for Uric Acid-Lowering Therapy

<table>
<thead>
<tr>
<th>Uric acid level</th>
<th>Allopurinol</th>
<th>Rasburicase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Elevated</td>
<td></td>
</tr>
<tr>
<td>Elevated</td>
<td>Normal</td>
<td></td>
</tr>
</tbody>
</table>

Tumor type

| Nonhematologic; Burkitt's lymphoma, Hodgkin's lymphoma, lymphoblastic, CML lymphoma, ALL, AML |

Tumor burden

| WBC count ≤50 × 10⁹/L >50 × 10⁹/L |
|----------------------------------|----------------------------------|
| LDH ≤2 × normal >2 × normal      |

Cytoreductive intensity

<table>
<thead>
<tr>
<th>Mild</th>
<th>Aggressive</th>
</tr>
</thead>
</table>

Kidney tumor infiltration

| Absent | Present |

ALL = acute lymphocytic leukemia; AML = acute myelogenous leukemia; CML = chronic myeloid leukemia; LDH = lactate dehydrogenase; WBC = white blood cell.


CASE STUDY

AN OLDER CAUCASIAN BOY WITH A HIGH LEUKOCYTE COUNT, SUBSTANTIAL LYMPHADENOPATHY, AND SPLENOMEGALY

When Alex, a 10-year-old Caucasian boy, initially appeared for evaluation, he had a high leukocyte count (79 K/µL), substantial lymphadenopathy, an enlarged spleen, and a large mediastinal mass, which are all risk factors for tumor lysis syndrome (TLS). In addition, his age bordered the age at which risk of TLS becomes elevated in children.

Results of laboratory analysis revealed a potassium level of 4.1 mEq/L, and a phosphorus level of 4 mg/dL. The uric acid level was 16.1 mg/dL, which is extremely and atypically high for pediatric patients. The calcium level was 9.6 mg/dL, the blood urea nitrogen level (BUN) was 12 mg/dL, and the creatinine level was 1 mg/dL, which was not ideal but not that severely elevated. The lactate dehydrogenase (LDH) level was 6323 U/L, which prompted tremendous concern because an LDH level of 300 to 500 U/L is within normal limits.

(continued on page 48)
In response, the second-year resident who evaluated Alex ordered hydration. She also ordered supplemental potassium chloride (20 mEq/L), administered in 3000 mL of intravenous fluid per square meter every 24 hours, which was inappropriate but was corrected. A bone-marrow specimen obtained by aspirated biopsy tested positive for T-cell leukemia, which is another risk factor for TLS. Initiation of chemotherapy was ordered as soon as metabolic stability could be achieved.

After alkalinization, hydration, and allopurinol were administered, Alex’s urine was found to have a pH of 8 and a specific gravity of 1.017. Additional hydration was required. After additional hydration, a typical 4-drug induction chemotherapy regimen consisting of daunorubicin, vincristine, prednisone, and L-asparaginase was initiated. Eight hours later, urinary output decreased such that Alex was only producing 120 mL of urine in 4 hours, and the leukocyte count was 31.8 K/µL, which indicated that Alex had experienced massive tumor lysis in the past 8 hours. Laboratory results included a potassium level of 5.4 mEq/L, which had crept up since the previous test, and a phosphorus level of 14.5 mg/dL, which had more than tripled since the previous test. Other findings included a uric acid level of 11 mg/dL, which was still elevated; a low calcium level of 5.1 mg/dL, which had decreased; a creatinine level of 1.7 mg/dL, which had increased; and a BUN level of 38 mg/dL, which had more than tripled since the previous test.

Because the most recent uric acid and potassium levels prompted extreme concern in the nursing staff, Alex received glucose therapy, insulin therapy, and intensive monitoring in the intensive care unit (ICU) for the first few days after initiation of chemotherapy. However, although he remained in the ICU for a few days, Alex never required hemofiltration or dialysis. Within 4 days of ICU admission, results of laboratory testing became normal, and leukocyte count had decreased to 1.2 K/µL, which prompted his transfer to the hematology/oncology unit. Although Alex eventually had a good outcome, he would have been deemed a high-risk patient for TLS and would have benefited from initiation of rasburicase therapy before initiation of chemotherapy.

Hypocalcemia should be managed by first treating hyperphosphatemia. If the hypocalcemia does not resolve and the patient is experiencing seizures or cardiac symptoms, seizure precautions and IV calcium gluconate are warranted.\(^2\)\(^3\)

**Conclusions**

Nurses play a pivotal role in the prevention and early recognition of TLS by identifying high-risk patients; using measures, such as hydration, alkalinization, and uric acid-lowering therapy; and vigilant monitoring. With advances in risk assessment, monitoring, and supportive care, in addition to the new option of rasburicase, fewer patients may now develop TLS.

**References**

4. Landier W. Tumor lysis syndrome. Presented at: Southern California Association of Pediatric Oncology Nurses Annual Meeting; May 3, 2002; San Diego, Calif.