Tumor lysis syndrome (TLS)

Treatment Guidelines

DEFINITION

Tumor lysis syndrome (TLS) is an oncologic emergency that is caused by massive tumor cell lysis with the release of large amounts of potassium, phosphate, and nucleic acids into the systemic circulation.

Cairo-Bishop definition:

Clinical TLS: laboratory TLS plus one or more of the following that was not directly or probably attributable to a therapeutic agent: increased serum creatinine concentration (≥1.5 times the ULN), cardiac arrhythmia/sudden death, or a seizure

RISK FACTORS

The risk is greatest in patients treated for hematologic malignancies; the tumors most frequently associated with TLS are clinically aggressive NHLs and acute lymphoblastic leukemia (ALL), particularly Burkitt lymphoma/leukemia

Intrinsic tumor-related factors:

1. High tumor cell proliferation rate
2. Chemosensitivity of the malignancy
3. Large tumor burden, as manifested by bulky disease >10 cm in diameter and/or a white blood cell count >50,000 per microL, a pretreatment serum lactate dehydrogenase (LDH) more than two times the upper limit of normal, organ infiltration, or bone marrow involvement

Clinical features that predispose to the development of TLS:

1. Pretreatment hyperuricemia (serum uric acid >7.5 mg/dL [446 micromol/L]) or hyperphosphatemia
2. A preexisting nephropathy or exposure to nephrotoxins
3. Oliguria and/or acidic urine
4. Dehydration, volume depletion, or inadequate hydration during treatment

CLINICAL MANIFESTATIONS (signs and symptoms)

The symptoms associated with tumor lysis syndrome (TLS) largely reflect the associated metabolic abnormalities (hyperkalemia, hyperphosphatemia, and hypocalcemia).

They include nausea, vomiting, diarrhea, anorexia, lethargy, hematuria, heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, flank pain if there is renal pelvic or ureteral stone formation, acute kidney injury and possible sudden death.

DIAGNOSIS

The combination of volume depletion, hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia strongly support the diagnosis of TLS over other causes.

In patients with TLS, a sample of blood obtained by a wide-bore needle or, preferably an indwelling cannula should be used to obtain a biochemical profile of the patient for monitoring, including of serum sodium, potassium, chloride, and bicarbonate.

✓ Urine pH and output.
✓ CT scanning of the abdomen and retroperitoneum immediately if renal failure or mass lesion in the abdomen are present.
✓ ECG monitoring.
✓ Histologic findings.
✓ Blood chemistry
RISK STRATIFICATION AND PREVENTION

A risk stratification system for TLS was proposed using the type of malignancy, the burden of disease, treatment, expected response to treatment, and renal function and the recommended therapy varied according to the risk category.

Management of tumor lysis syndrome requires the initiation of prevention measures in high-risk patients prior to cancer treatment, as well as the prompt initiation of supportive care for patients who develop acute TLS during treatment.

<table>
<thead>
<tr>
<th>Tumor lysis syndrome (TLS) prophylaxis recommendations based on TLS risk</th>
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<td><strong>Low risk disease (LRD)</strong></td>
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<td>Most solid tumors</td>
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<td>MM</td>
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<tr>
<td>CML</td>
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<tr>
<td>Indolent NHL</td>
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<tr>
<td>HL</td>
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<tr>
<td>CLL and WBC &lt; 50 x 10^9/L treated only with alkylating agents</td>
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<tr>
<td>AML and WBC &lt; 25 x 10^9/L and LDH &lt; 2x ULN</td>
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<tr>
<td>Adult intermediate grade NHL and LDH within normal limits</td>
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<tr>
<td>Adult ALCCL</td>
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<tr>
<td>Monitoring</td>
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<tr>
<td>Hydration</td>
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<td>±Allopurinol</td>
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* Contraindicated in patients with a history consistent with glucose-6-phosphate dehydrogenase. In these patients, rasburicase should be substituted with allopurinol.


The main prophylactic strategies for patients who do not have established TLS are intravenous (IV) hydration and the use of hypouricemic agents, such as allopurinol and rasburicase, and it is generally selected based on the estimated risk of TLS.
**Intravenous hydration (the cornerstone of preventing TLS)**

**Goal:** is to improve renal perfusion and glomerular filtration, and induce a high urine output to minimize the likelihood of uric acid or calcium phosphate precipitation in the tubules.

**Dose:** children and adults at risk for TLS initially receive 2 to 3 L/m per day of IV fluid (or 200 mL/kg per day in children weighing ≤10 kg).

**Monitoring:** urine output should be monitored closely and maintained within a range of 80 to 100 mL/m² per hour (2 mL/kg per hour for both children and adults, 4 to 6 mL/kg per hour if ≤10 kg).

**Choice of hydration fluid:**

- Depends on the clinical circumstances
- Initial use of 5 percent dextrose one-quarter normal (isotonic) saline, because acute lymphoblastic leukemia (ALL) patients receive steroid during remission induction, which can cause sodium retention and hypertension
- In patients with hyponatremia or volume depletion, isotonic saline should be the initial hydration fluid
- Potassium and calcium should be withheld from the hydration fluid, at least initially due to the risk of hyperkalemia and hyperphosphatemia with calcium phosphate precipitation once tumor breakdown begins.

**Duration of hydration:**

- Should depend on the tumor burden, the type of chemotherapy used (some regimens induce TLS several days later), the drug sensitivity of the tumor, the patient’s ability to drink, and renal function.
- IV hydration should be continued at least until tumor burden (as indicated by blast cell count as well as liver and spleen size in patients with leukemia, and serum lactate dehydrogenase [LDH] level or tumor size in those with solid tumors) is largely resolved, there is no evidence of significant tumor lysis (as indicated by serum uric acid and phosphorus level), and patient can drink adequately with good urine output.

**Use of diuretics:**

- Can be used to maintain the urine output if needed
- Contraindicated in patients with hypovolemia or obstructive uropathy
- Loop diuretics such as furosemide are preferable because they increase potassium secretion

IV hydration can lead to potentially dangerous fluid overload in patients with underlying acute kidney injury or cardiac dysfunction. In this setting, close monitoring of vital signs and urine output is mandatory, transfusion (if needed) should be given slowly and in low volume, and diuretics can be given to maintain urine output. Monitoring in an intensive care unit.
(ICU) may be required. Prior to initiation of IV hydration, reversible forms of acute kidney injury (eg, urinary tract obstruction) should be corrected.

**Urinary alkalinization**
- Drugs: acetazolamide and/or sodium bicarbonate
- The role of urinary alkalinization is unclear and controversial
- Only indicated in patients with metabolic acidosis
- If used, it should be initiated when the serum uric acid level is high and discontinued when hyperphosphatemia develops
- Not used in patients who receiving rasburicase

**Hypouricemic agents**

**Allopurinol**
- A hypoxanthine analog that competitively inhibits xanthine oxidase, blocking the metabolism of hypoxanthine and xanthine to uric acid
- It effectively decreases the formation of new uric acid and reduces the incidence of obstructive uropathy in patients with malignant disease at risk for TLS
- Indicated for the initial management of adult and pediatric patients at intermediate risk for TLS as long as pretreatment uric acid levels are not elevated
- The usual allopurinol dose: in adults is 100 mg/m² every eight hours (maximum 800 mg per day), in children, the dose is 50 to 100 mg/m² every eight hours (maximum 300 mg/m² per day) or 10 mg/kg per day in divided doses every eight hours
- Dose must be reduced by 50 percent in the setting of acute kidney injury due to potential for accumulation of allopurinol and metabolites.
- Dose should be reduced to 200 mg daily for creatinine clearance 10 to 20 mL/minute, ≤100 mg daily for creatinine clearance 3 to 10 mL/minute, and ≤100 mg/dose at extended intervals for creatinine clearance < 3 mL/min in adults
- For patients who are unable to take oral medications, IV allopurinol can be administered at a dose of 200 to 400 mg/m² per day, in one to three divided doses (maximum dose 600 mg per day)
- Treatment is generally initiated 24 to 48 hours before the start of induction chemotherapy. It is continued for up to three to seven days afterward until there is normalization of serum uric acid and other laboratory evidence of tumor lysis (eg, elevated serum LDH levels)
- Screening for HLA-B*58:01 allele is advised for high-risk patients (certain Asian populations), with avoidance of the drug in those with the inherited high-risk allele

**Rasburicase**
- Urate oxidase (uricase), which catalyzes oxidation of uric acid to the much more water-soluble compound allantoin
- Is well tolerated, rapidly breaks down serum uric acid, and is effective in preventing and treating hyperuricemia and TLS
- Indicated for the initial management of most pediatric and adult patients at high risk for TLS, especially those with impaired renal or cardiac function
The EMA and FDA dosing guidelines both recommend a rasburicase dose of 0.2 mg/kg once daily for up to five (FDA) or seven (EMA) days.

- Alternative dose recommendations based on risk stratification: 1-High-risk patients or a baseline uric acid level ≥8 mg/dL (473 micromol/L) – rasburicase 0.2 mg/kg, 2- Intermediate-risk patients with baseline uric acid rasburicase 0.15 mg/kg

- Rasburicase is supplied in vials containing 1.5 or 7.5 mg, the dose is generally rounded to the closest number of full vials, in adults, a flat dose of 3 mg is commonly used

- Doses are generally administered once daily, although if tumor lysis is massive, an increase to twice daily dosing may be needed.

- Length of treatment has generally been based on clinical judgment, depending on tumor burden, type of cancer and anticancer treatment, and blood uric acid levels following the first dose (average duration is two days, but can vary from one to seven days)

- It is recommended that all patients receive allopurinol after rasburicase treatment

- The rasburicase label carries a Boxed Warning about the risks of hemolysis, hemoglobinuria, methemoglobinemia, interference with serum uric acid measurements, and anaphylaxis

- Rasburicase should not be given to patients with G6PD deficiency because hydrogen peroxide, a byproduct of uric acid breakdown, can cause severe hemolysis in this setting
  - If administration of rasburicase is needed in an emergency situation and the results of G6PD testing are not available, rasburicase should be given at a single low dose (eg, 0.02 to 0.05 mg/kg and no more than 3 mg), and hemodialysis should be readily available in the event of significant hemolysis.
  - A second dose should only be given if there was no evidence of hemolysis or methemoglobinemia.
  - If hemolysis occurs, rasburicase should be immediately and permanently discontinued. An alternative hypouricemic agent, such as allopurinol or febuxostat together with saline hydration, should be used.

**Febuxostat**

- A new hypouricemic drug that may be used in patients with hyperuricemia who cannot tolerate allopurinol in a setting in which rasburicase is either not available or contraindicated.
- An orally administered, potent, selective inhibitor of xanthine oxidase

**TREATMENT OF ESTABLISHED TUMOR LYSIS SYNDROME:**

- Despite appropriate preventive measures, approximately 3% to 5% of patients develop laboratory (and/or) clinical evidence of TLS, and despite the prophylactic use of rasburicase, also it’s can occur in patients who didn’t start chemotherapy yet, primarily in patients with non-Hodgkin lymphoma (NHL) or acute leukemia.
Patients who present with, or develop TLS during therapy should receive intensive supportive care with continuous cardiac monitoring and measurement of electrolytes, creatinine, and uric acid every 4 to 6 hours.

Appropriate management in this case:

- Combination of treating specific electrolyte abnormalities, the use of rasburicase at 0.2 mg/kg (if it was not given initially), with repeated doses as necessary.
- Wash out the obstructing uric acid crystals with fluids with/without a loop diuretic
- Appropriate use of renal replacement therapy
- Early consultation with an expert in renal medicine is advisable

**Electrolyte abnormalities:**

General guidelines for management of electrolyte abnormalities associated with TLS were provided by the 2008 International Expert Panel. These guidelines are valid for children, but some modification is needed in adults (e.g., adults with hyperkalemia who have electrocardiogram (ECG) changes related to hypocalcemia are generally given 1000 mg of calcium gluconate, rather than 100 to 200 mg/kg. (typical dosing regimen for children).

<table>
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<tr>
<th>Electrolytes</th>
<th>Treatment</th>
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| Hyperkalemia | ✓ The most dangerous component of TLS because it can cause sudden death due to cardiac dysrhythmias.  
 ✓ Patients should limit potassium intake during the risk period for TLS.  
 ✓ Frequent measurement of serum potassium (every 4 to 6 hours), continuous cardiac monitoring  
 ✓ Administration of oral potassium lowering agents (patiromer or sodium polystyrene sulfonate), are recommended in patients with TLS and acute kidney injury.  
 ✓ Glucose plus insulin or beta-agonists can be used as temporizing measures, and calcium gluconate may be used to reduce the risk of cardiac dysrhythmia.  
 ✓ If needed, hemodialysis and hemofiltration effectively removes potassium. |
| Hypocalcemia | ✓ Asymptomatic patients with hypocalcemia do not require treatment.  
 ✓ Symptomatic hypocalcemia should be treated with calcium at the lowest doses required to relieve symptoms.  
 ✓ To avoid calcium-phosphate precipitation, most symptomatic acutely hypocalcemic patients with hyperphosphatemia due to TLS (particularly if the calcium phosphate product is >60 mg²/dL²) should not be treated with calcium until hyperphosphatemia is corrected.  
 ✓ In most situations, clinicians use other oral phosphate binders, even though there are no good studies demonstrating efficacy.  
 ✓ Patients with severe symptoms of hypocalcemia (tetany or cardiac arrhythmia), should be considered for calcium replacement regardless of the phosphate level |
- Hyperphosphetemia.

  - Despite treatment with a hypouricemic agent, hyperphosphatemia remains a major problem in TLS and can cause acute kidney injury.
  - Strategies aimed at lowering serum phosphate levels (aggressive hydration and phosphate binder therapy) should be used in conjunction with control of uric acid in patients who have established TLS or who are at high risk of developing TLS.
Management of electrolyte abnormalities in tumor lysis syndrome

<table>
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<tr>
<th>Abnormality</th>
<th>Management recommendation</th>
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<td><strong>Hyperphosphatemia</strong></td>
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<tr>
<td>Severe</td>
<td>Dialysis, CVVH, CVVHD, or CVVHD</td>
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**Hypocalcemia**, total serum calcium $<0.75$ mmol/L (7 mg/dL) or ionized calcium $<0.8$ mmol/L (3.2 mg/dL)

- Asymptomatic: No therapy.
- Symptomatic: Calcium gluconate administered slowly with ECG monitoring; patients with acute hypocalcemia and hyperphosphatemia should not be treated with calcium until the hyperphosphatemia is corrected (unless they have tetany or a cardiac arrhythmia from hypocalcemia).

- Calcium gluconate: Adult: 1 g (10 mL of 10 percent solution); Pediatric: 50 to 100 mg/kg, slow IV infusion (maximum 50 to 100 mg per minute) in large vein. May be repeated after 5 to 10 minutes if symptoms or ECG changes persist.

**Hyperkalemia**

- Moderate and asymptomatic, $0.6-6.0$ mmol/L: Avoid IV and oral potassium. ECG and cardiac rhythm monitoring.
- Sodium polystyrene sulfonate: Adult: 15 to 30 grams orally; Pediatric: 1 gram/kg orally, Oralit 1 to 2 hours, repeat every 4 to 6 hours up to four times daily or as needed based on repeat serum K+ level.
- Severe ($>7.0$ mmol/L) and/or symptomatic: Same as above, plus:
  - To stabilize cardiac membranes:
    - For patients with ECG changes (loss of the QRST complex or loss of P-waves but not peaked T-waves alone), give calcium gluconate by slow IV infusion to prevent life-threatening arrhythmias.
    - Calcium gluconate: Adult: 1 g (10 mL of 10 percent solution); Pediatric: 50 to 100 mg/kg, slow IV infusion (maximum 50 to 100 mg per minute) in large vein. May be repeated after 5 to 10 minutes if ECG changes persist.
  - To temporarily shift potassium into cells:
    - IV calcium gluconate: Adult: regular insulin (30 units) IV plus 100 mL of a 50 percent dextrose solution (D50) IV; Pediatric: regular insulin (0.1 unit/kg) IV plus 25 percent dextrose solution (D25S) 6.5 grams/kg (2 mL/kg of D25S) IV over thirty minutes. May be repeated after thirty to sixty minutes. Monitor fergrenstick glucose closely.
    - Sodium bicarbonate can be given to induce infusion of potassium into cells; if patient is acidic. Sodium bicarbonate and calcium solutions should not be administered through the same line due to incompatibility.
    - Sodium bicarbonate: Adult: 40 to 60 mL; Pediatric: 1 to 2 mL/kg, slow IV infusion over five to ten minutes.
    - Ringer's acetate infusions: Albutalor per nephrology or metaraminol dose inulin.
    - Albutalor: Adult: 10 to 20 mg in 4 mL saline or metaraminol over 20 minutes or 10 to 20 puffs per metered dose inhaler over 10 to 20 minutes; Pediatric: 0.5 to 3.5 mg/kg per nebulization.
    - Dialysis

**Uremia (renal dysfunction)**

- Fluid and electrolyte management
- Urine acid and phosphate management
- Adjust renally excreted drug doses
- Dialysis (hemo- or peritoneal)
- Hemofiltration (CAH, CVVH, or CVVH-D2)

Pediatric dose should not exceed usual adult dose.

IV, intravenous; CAH: continuous arterio-venous hemofiltration; CVVH: continuous veno-venous hemofiltration; CVVHD: continuous veno-venous hemodialysis; ECG: electrocardiogram.

* Patients receiving sodium polystyrene sulfonate should be monitored for the development of hypocalcemia and hypermagnesemia.


Graphic 76281 Version 4.0
Renal replacement therapy in TLS:

- Even with optimal care for those patients, severe (AKI), develops in some patients and requiring renal replacement therapy.
- The need for dialysis during induction therapy for high-risk hematologic malignancies has substantially declined since the introduction of rasburicase.
- In countries where rasburicase is available, hyperuricemia is seldom an indication for dialysis after induction therapy for a hematologic malignancy. However, despite the use of rasburicase, approximately 1.5 percent of children and 5 percent of adults require dialysis during induction therapy.
- Indications for renal replacement therapy are similar to those in patients with other causes of acute kidney injury, although somewhat lower thresholds are used for patients with TLS because of potentially rapid potassium release and accumulation, particularly if urine output is low.

Indications for renal replacement therapy in patients with TLS:

1. Severe oliguria or anuria.
2. Intractable fluid overload.
3. Persistent hyperkalemia.
4. Hyperphosphatemia-induced symptomatic hypocalcemia.
5. A calcium-phosphate product $\geq 70$ mg$^2$/dL$^2$.

IMPORTANT NOTES:

- The prognosis for complete recovery of renal function is excellent if dialysis is initiated early to rapidly reduce serum uric acid and phosphate concentrations.
- Oliguria due to acute uric acid nephropathy responds quickly to hemodialysis with initiation of a diuresis usually occurring as the serum uric acid concentration falls below 10 mg/dL (595 micromol/L).
- Hemodialysis is efficient in removing uric acid, the clearance is approximately (70 to 100 mL/min), and serum uric acid levels fall by approximately 50% with each 6-hour treatment.
- Peritoneal dialysis is much less efficient with uric acid clearances below 10 mL/min.
- Depending on the dialyzer and blood flow, phosphate clearance usually ranges from 60 to 100 mL/min with hemodialysis.
- The phosphate burden in these patients can vary from 2 to 7 grams per day, as a result, it is frequently necessary to perform hemodialysis at 12 to 24-hour intervals.
- Phosphorus clearance with continuous arteriovenous hemodialysis (CAVHD), can reach 40 mL/min at a dialysate flow rate of four liters/hour, which can lead to the removal of up to 10 grams of phosphorus per day without the rebound hyperphosphatemia often seen after intermittent hemodialysis.
MONITORING GUIDELINES:

Laboratory turnover time must be rapid so that metabolic derangements can be addressed before life-threatening problems arise.

It is not necessary for all patients to undergo induction therapy in an ICU setting, except patients who’s at high risk (those with advanced Burkitt leukemia/lymphoma), they should be in ICU before chemotherapy is started.

The following monitoring considers the most important:

- ✔ Urine output (Urine output and fluid balance should be recorded frequently), electrolytes, and serum uric acid are the key factors to monitor in patients who are at risk for TLS.
- ✔ For children and adult who are at high risk for developing TLS should be tested for (serum concentrations of uric acid, phosphate, potassium, creatinine, calcium, and LDH, as well as fluid input and urine output), 4-6 hours after the initiation of chemotherapy and every 4-8 hours thereafter.
- ✔ Patients who are receiving rasburicase, (they consider at high risk for TLS), serum uric acid should be reevaluated after 4 hours of administration for the first dose and every 6 to 12 hours (depending on the risk and degree of tumor lysis), thereafter until normalization of serum LDH and uric acid levels.
  - ○ **NOTE:** blood samples for uric acid in patients treated with rasburicase should be collected in a pre-chilled tube and should be immediately placed on ice, and the test should be completed within four hours, if possible.
- ✔ Patients who are consider intermediate risk should be monitored for at least 24 hours after completion of chemotherapy.
- ✔ For multiagent regimens, monitoring should be maintained for 24 hours after administration of the final agent of the first cycle of therapy.
- ✔ When rasburicase did not use initially, (serum electrolytes) should be measured 8 hours after chemotherapy, and the patient might require a one-night hospital stay.
- ✔ Patients who are did not develop TLS within 72 hours of multiagent chemotherapy, they are considered very low risk of TLA.
- ✔ Specifc guidelines are available in the (US prescribing information) for hydration and blood chemistry monitoring for patients receiving venetoclax for chronic lymphocytic leukemia according to the risk for TLS.
REFERENCES:


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