

# The history of treating established tIs nursing essay

[Health & Medicine](#), [Nursing](#)



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## **Introduction**

Tumour lysis syndrome (TLS) is a constellation of metabolic abnormalities which results in an oncologic emergency <1, 2, 3>. It is caused due to the rapid destruction of large number of neoplastic cells resulting in an immense release of potassium, phosphate & nucleic acids. The nucleic acids are then converted into uric acid causing hyperuricemia, possibly uric acid precipitating in the renal tubules and possible acute renal failure <4 5>. TLS incidence is not clear, but it most often occurs after instigation of cytotoxic therapies in patients with both clinically and highly aggressive lymphomas (especially the Burkitt subtype) and acute lymphoblastic leukemia (AML). It can also occur unexpectedly in malignancies with high proliferation rates, large tumour burden or extreme sensitivity to cytotoxic treatments <6, 7>. In frequency studies for non-Hodgkin lymphoma, laboratory TLS occurred at 42% and clinical TLS at about 6% (described later). In pediatric patients,

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laboratory TLS has been seen as high as 70% but clinically significant TLS only occurred in about 3% of the cases <8>. In addition, there are certain clinical features which predispose patients to TLS such as 1. dehydration, volume depletion or inadequate hydration during treatment; 2. pre-existing nephropathy or prior exposure to nephrotoxins; 3. pre-treatment of hyperuricemia and/or oliguria <6, 7, 9>. There have been few attempts to specifically define TLS <10, 11>. Cairo-Bishop classification (2004) defines TLS as: Laboratory TLS: Any two or more abnormal serum values seen within either three days before or seven days after beginning chemotherapy ensuring that the patient is adequately hydrated and a hypouricemic agent has been used <9, 10>. Values are presented Table 1. Clinical TLS: Includes laboratory TLS along with one or more of the following occurrences (that cannot be attributed to the use of the therapeutic agent) <9, 10> Increased serum creatinine concentration ( $\geq 1.5$  times the upper limit of normal) <9, 10> cardiac arrhythmia or sudden death <9, 10> seizure <9, 10> Table 1: Laboratory TLS definition (Cairo-Bishop classification) <5, 7> NOTE: Two or more laboratory changes within three days before or seven days after cytotoxic therapy. A grading system to help outline the degree of severity of TLS has also been developed <9, 10>.

## Prevention

The clinical impact of TLS due to its potentially severe complications warrants preventive measures in patients <7>. In a retrospective study of 772 consecutive patients given induction therapy for AML, the risk of death from clinical TLS was significantly higher due to hemorrhage and renal failure

- 79% vs. 23% in patients without TLS <12>. In addition to the increased risk of mortality, patients with TLS have higher rates of treatment related complications such as acute renal failure requiring dialysis resulting in a much longer hospital stay and additional financial costs <13>. IV Hydration: The cornerstone of prevention is aggressive intravenous hydration. Excessive hydration should induce higher urine output to prevent precipitation of uric acid in nephrons. However, caution should be exercised in patients who are already renally insufficient or have cardiac dysfunction <7>. The recommended doses for both children and adults is 2 - 3 L/m<sup>2</sup> of IV fluid per day. Urine output should be closely monitored. The duration of hydration depends on tumour burden and type of chemotherapy used <7>. Urinary Alkalinization: The use of either sodium bicarbonate and/or acetazolamide is both unclear and controversial <5>. In the past alkanization of urine to pH 6.5 - 7.0 or higher was recommended to prevent the formation of uric acid <14>. However, there is no data showing improved efficacy. Moreover, alkalinization can potentially cause hyperphosphatemia due to calcium phosphate deposits in kidneys, heart and other organs once the neoplastic cells burst <5>. Hypouricemic agents: The two most commonly used agents are allopurinol and rasburicase <5>.

### **Allopurinol:**

Allopurinol is used due to its mechanism of action; it blocks the formation of new uric acid by preventing hypoxanthine and xanthine metabolism, as seen in Figure 1 <15>. The dose recommended for oral administration is 100 mg/m<sup>2</sup> every 8 hours to a maximum of 800 mg/day. For renal failure

patients, a 50% dose reduction is recommended <12>. In IV administration, the daily maximum is 600 mg, with a recommended dose of 200 to 400 mg/m<sup>2</sup> in one to three divided doses. Treatment is initiated 2 - 4 days prior to chemotherapy and continued for 3 - 7 days afterwards until normalization of biochemical parameters especially serum uric acid is seen <16, 17>. Of note, is that allopurinol only blocks the production of new uric acid (Refer to Figure 1). Hence, it doesn't reduce the serum uric acid levels seen prior to treatment. Since the metabolism of hypoxanthine and xanthine is blocked, their accumulation can result in acute renal failure due to blockage of tubules <15>. Moreover, allopurinol has potential interactions with cyclophosphamide, methotrexate, ampicillin and thiazide diuretics. Therefore, rasburicase is the preferred hypouricemic agent <5> (referred to later). (Soluble) Figure 1: Endogenous production of uric acid. Allopurinol acts on both xanthine and hypoxanthine and prevents their metabolism. However, Rasburicase, acts on uric acid and makes it into the soluble metabolite allantoin <5>.

### **Rasburicase:**

Rasburicase rapidly lowers uric acid by metabolizing it into the more soluble allantoin (Refer to Figure 1). It is the preferred hypouricemic agent and is a recombinant version of urate oxidase which is absent in humans <18>. Rasburicase is much more efficacious than allopurinol in both pediatric and adult patients <18>. In the only Phase III trial comparing allopurinol to rasburicase in hematological cancers, it was found that uric acid levels were lowered within four hours after the first dose of rasburicase. The groups that

received either rasburicase alone or in combination with allopurinol had superior outcomes in terms of time to lower serum uric acid levels as well as incidence of TLS <19>. The dosing recommended for rasburicase varies depending on risk stratification for TLS as well as serum uric acid levels <7>. High risk patients or baseline serum uric acid level  $\geq 446 \mu\text{mol/L}$ : rasburicase dose is 0. 20 mg/kg given once <7>. Intermediate risk patients or baseline uric acid  $\leq 446 \mu\text{mol/L}$ : rasburicase dose is 0. 15 mg/kg given once <7>. Dose can be given twice daily if massive tumour lysis <7>. Duration of therapy can vary from 1 - 7 days depending on the patient's needs <7>. It should be noted that rasburicase is contraindicated in pregnant/ lactating women and individuals with a glucose -6-phosphate dehydrogenase deficiency as it can cause severe haemolysis and methemoglobinemia <5>.

## **Monitoring Guidelines**

Monitoring is done by checking urine output and serum electrolyte levels especially serum uric acid. For high risk patients, serum uric acid levels should be evaluated every six to twelve hours especially after the first dose of rasburicase. Their serum electrolyte levels for phosphate, potassium, creatinine, calcium and lactate dehydrogenase should be tested every four to six hours after initiation of chemotherapy <7>.

## **Treating Established TLS**

Despite prophylaxis approximately 3-5% of patients will develop either laboratory TLS or clinical TLS. As noted earlier, TLS can also occur spontaneously especially in hematological cancers <5>. Individuals presenting with TLS require urgent intensive supportive care with constant

cardiac monitoring and electrolyte measurements every four to six hours. Effective management necessitates the initiation of rasburicase at 0.20 mg/kg with repeating doses if needed to remove uric acid build-up in the kidneys. A loop diuretic may be started as well <7>. For electrolyte abnormalities, different strategies are used. But as mentioned before electrolytes namely potassium, uric acid, phosphate, creatinine and calcium are monitored every four to six hours <7>. Hyperkalemia : Often considered the most fatal component of TLS due to its ability to induce cardiac arrhythmias and possibly result in sudden death. Hence potassium and phosphate intake should be limited. Frequent measurements are done. Continuous cardiac monitoring and administration of sodium polystyrene sulfonate is recommended. Glucose plus insulin or beta agonists and even calcium gluconate can be used to reduce cardiac irregularities. If needed, haemodialysis can be performed for removal of excess potassium <5, 7>. Symptomatic hypocalcaemia: Treat with calcium at its lowest doses only to relieve symptoms due to the fear of hyperphosphatemia. Therefore, if asymptomatic, don't treat until the underlying hyperphosphatemia has been corrected. If patients experience tetany or cardiac arrhythmia give calcium corrective therapy regardless of their phosphate levels <5, 7>. In spite of using aggressive uric acid lowering therapies if hyperphosphatemia does occur excessive hydration and a phosphate binder use are recommended <5, 7>. Use of renal replacement therapy: Some patients will develop acute kidney injury requiring renal replacement. Rasburicase has greatly reduced the incidence of acute kidney injury and in turn the use of renal replacement therapy <7, 20>. The parameters for using renal replacement in TLS are a

little lower due to the fear of rapid potassium release and accumulation of uric acid. The indications for renal replacement in TLS are: " 1. hyperphosphatemia induced symptomatic hypocalcaemia; 2. persistent hyperkalemia; 3. severe oliguria or anuria " <5>. Prognosis for return to normal kidney function is excellent if therapy is initiated early and rapidly reduces elevated serum uric acid and phosphate levels <5>.

## **Summary**

TLS is an oncologic emergency and requires immediate supportive care. It is most frequently seen in patients with hematological malignancies and those with large tumour burden or high sensitivity to cytotoxic treatments.

Prophylaxis with IV hydration is the best treatment for TLS