

Guidelines for the Management of Tumour Lysis Syndrome in Adults

Tumour Lysis Syndrome (TLS) is a life-threatening complication that arises when the rapid lysis of tumour cells leads to the release of excessive quantities of cellular contents into the systemic circulation resulting in a metabolic disturbance characterised by:

- Hyperkalaemia
- Hyperphosphataemia
- Hyperuricaemia
- Hypocalcaemia

This metabolic derangement may lead to acute oliguric renal failure and cardiac arrhythmias.

TLS can occur spontaneously in tumours with a very high proliferative rate, as well as following initiation of treatment. It can be classified as laboratory TLS (with no clinical manifestations) or clinical TLS (patients with life-threatening clinical abnormalities).

Diagnosis of Tumour Lysis Syndrome

TLS may be classified according to clinical or laboratory features.

Laboratory Screen for TLS

This needs to include: Urea, Creatinine, Uric acid / Urate*, Phosphate, Potassium, Albumin corrected Calcium

*Samples for urate from patients who have received rasburicase within the last 24 hours require special handling - collect into pre-chilled lithium heparin tubes, deliver to lab on ice, lab must separate at 4°C and analyse within four hours. Failure to adhere to this protocol will lead to underestimation of urate due to ex vivo conversion to allantoin.

Cairo-Bishop definition of laboratory TLS

Laboratory TLS is considered present if levels of 2 or more serum values of the following are abnormal at presentation (as specified below), or if they change by 25% within 3 days before, until 7 days after, cytotoxic therapy:

Urate / Uric acid*	≥ ULN or 25% increase from baseline
Potassium	≥ 6.0 mmol/l or 25% increase from baseline
Phosphate	≥ 1.45 mmol/l or 25% increase from baseline
Albumin corrected Calcium	≤ 1.75 mmol/l or 25% decrease from baseline

* If rasburicase has been administered within previous 24 hours, result is not valid unless the sample was sent on ice and analysed within 4 hours.

Cairo-Bishop definition of clinical TLS

Laboratory evidence of TLS plus 1 or more of:

Cr > 1.5 x ULN

Cardiac arrhythmia / sudden death

Seizure

Reason for Update: review of rasburicase dose for TLS prevention; rasburicase in 50ml; plus general update	Approved by Chair of Alliance TSSG: Dr J De Vos
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Prevention of Tumour Lysis Syndrome

Since TLS can develop rapidly and is difficult to treat once established, prevention is of prime importance. The identification of patients at risk for the development of TLS is the most important aspect of management, so that prophylactic measures may be initiated prior to initiation of therapy.

This table provides a summary of management - see below for more details.

Risk Group ^a	Disease Type	Preventative Strategies
High risk	Burkitt Lymphoma Burkitt-type ALL Other ALL with WBC $\geq 100 \times 10^9/L$ AML with WBC $\geq 50 \times 10^9/L$ N.B. TLS can precede chemotherapy	Intravenous fluids (approximately 3L/m ² /day, aiming to maintain urine output above 100ml/m ² /hour) Rasburicase TLS screen Consider delaying chemotherapy for 24-48 hours if possible.
Moderate risk ^b	AML with WBC 10 - 50 x 10 ⁹ /L Other ALL High grade NHL with bulky disease CML accelerated phase / blast crisis, or where rapid response to therapy expected	Intravenous fluids (approximately 3L/m ² /day, aiming to maintain urine output above 100ml/m ² /hour) Allopurinol (up to 600mg/day, adjusted for renal function) TLS screen
Low risk ^b	AML with WBC < 10 x 10 ⁹ /L Myeloma CLL Hodgkin's Lymphoma Other NHL Other CML and myeloproliferative disorders	Allopurinol (usual dose 300mg od, adjusted for renal function)

^a Modified from Cairo et al and Coiffier et al.

^b Patients with these disorders can be placed in a higher risk group if there is tumour involving the kidney, pre-existing renal failure or LDH > 2 x ULN.

High risk patients

As soon as a "high risk" diagnosis is suspected, a TLS screen should be undertaken.

Unless there is oliguria or acute renal dysfunction, initially hydrate at 3L/m²/day with intravenous fluids. Diuretics (furosemide, mannitol) may be required to maintain urine output > 100ml/ m²/hour.

If possible, consideration should be given to delaying initiation of chemotherapy for 24 – 48 hours whilst supportive measures are initiated.

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Rasburicase for prevention of TLS should be administered before initiating administration of Day 1 of chemotherapy.

Rasburicase is a recombinant form of urate oxidase, an enzyme present in most living organisms but not humans. This catalyzes the oxidation of uric acid to allantoin. Allantoin is at least 5 times more soluble than uric acid and is readily excreted by the kidneys. Allopurinol blocks the conversion of xanthines to uric acid, so this will reduce the effect of rasburicase. Therefore do **not** give allopurinol and rasburicase together.

Rasburicase administration for TLS prevention:

Rasburicase 3mg (fixed dose) once daily for a minimum of 2 doses*, starting 24 hours before chemotherapy

* BCSH 2015 guidance recommends a single 3mg dose of rasburicase, followed by careful monitoring of clinical and biochemical parameters, with repeat dosing if required.

However, as approximately 20% of patients have been shown to require a second dose, local agreement is to prescribe 3mg daily for a minimum of 2 days as standard, to minimise the risks of under-management.

Administer as an IV infusion in 50 ml sodium chloride 0.9% over 30 minutes

No dose adjustment required for renal or hepatic impairment.

The most common side effect is allergic reactions, mainly rash and urticaria.

Contra-indicated in patients with G6PD deficiency. (These patients should be treated with fluids and allopurinol, and monitored carefully)

Allopurinol may be used if required, **only after** completing rasburicase therapy.

Once chemotherapy has commenced, a TLS screen should be undertaken at + 4 hours and **at least** once daily thereafter for 3 – 5 days.

Moderate risk patients

Allopurinol should ideally be commenced at least 24 hours prior to chemotherapy.

N.B. Rasburicase may be considered for patients with severe hypersensitivity to allopurinol.

Once chemotherapy has commenced, a TLS screen should be undertaken at + 4 hours and repeated the following day as a minimum.

Hydrate intravenously at 3L/m²/day. Diuretics (furosemide, mannitol) may be required to maintain urine output > 100ml/m²/hour.

Continue high fluid intake for at least 48 hours after starting chemotherapy.

Low risk patients

Commence allopurinol prior to chemotherapy.

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Treatment of Established TLS

Any patient with evidence of laboratory TLS, with or without clinical TLS, as defined on page 1, should be discussed immediately with their haematology / oncology Consultant.

General measures for treatment of laboratory TLS with or without clinical TLS include:

- Ensure vigorous hydration to maintain urine output > 100ml/ m²/hour
- Ensure correction of high potassium (according to local guidelines)
- In the absence of contraindications, initiate rasburicase at a dose of **0.2 mg/kg/day (dose for treatment of TLS)**. The duration of treatment should be determined by the clinical response.
 - Administer rasburicase as an IV infusion in 50 ml sodium chloride 0.9% over 30 minutes.
 - Give once daily for 3 to 7 days, until there is normalisation of uric acid, renal function and electrolytes.
- Allopurinol should be stopped when rasburicase is commenced.
- Seek ICU / renal specialist advice as haemofiltration / dialysis may be required: intractable fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia are indications for renal dialysis.
- Correction of low calcium should be avoided when there is concurrent high phosphate because of the risk of precipitation of insoluble calcium phosphate. Only symptomatic hypocalcaemia should be corrected.
- Moderate / asymptomatic hyperphosphataemia may be initially treated by maintaining adequate hydration and use of an oral phosphate binder eg Alu-Caps. Insulin/glucose for management of hyperkalaemia will also assist in lowering a raised phosphate. However, a renal specialist should be notified regarding the patient, in case dialysis is required.
- Alkalinisation of urine is not recommended when using rasburicase – although uric acid is 15 times more soluble at pH 7 than at pH 5, uric acid levels will be rapidly reduced when rasburicase is used. In contrast, phosphate is more soluble in acid medium and so there is an increased risk of calcium phosphate precipitation in the kidney if urine is alkalinised.

However, alkalinisation may be considered if rasburicase is not available and the patient is severely acidotic.

References: Jones, G et al; Br J Haem 2015; 169 (5): 661 – 671 (BCSH guidelines)
Coiffier, B et al; JCO 2008; 26 (16): 2767 - 2777
Cairo et al; Br J Haem 2004; 127: 3 – 11

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