ACUTE TUMOUR LYSIS SYNDROME (TLS)
GUIDELINES FOR THE PREVENTION AND MANAGEMENT

1. **INTRODUCTION**

Acute tumour lysis syndrome (TLS) is characterized by a group of metabolic derangements caused by the massive and abrupt release of cellular components into the blood after the rapid lysis of malignant cells. The release of intracellular metabolites, including nucleic acids, proteins, phosphorus, and potassium, can overwhelm normal homeostatic mechanisms, potentially leading to hyperuricaemia, hyperkalaemia, hypophosphatemia, hypocalcaemia, and uraemia. The crystallization of uric acid or calcium phosphate in renal tubules can further result in impaired renal function. Clinical manifestations of TLS include nausea, vomiting, diarrhoea, anorexia, paraesthesia, muscle cramps, tetany, fluid overload, cardiac arrhythmias, seizures, haematuria, renal impairment, and death.

TLS is observed most frequently after the initiation of cytotoxic therapy, although it may also occur spontaneously, in malignancies with a high proliferative rate, large tumour burden, or high sensitivity to cytotoxic therapy.

**Summary of Evidence**

There is a paucity of high-level and high-grade published studies on the subject of tumour lysis syndrome. The recommendations outlined below are primarily based on consensus statements and expert opinion.

**Principles of Management of Acute Tumour Lysis Syndrome**

- Identify patients at risk, initiate preventative measures prior to chemotherapy, and monitor for clinical and laboratory features of TLS.
- Detect features of TLS promptly and initiate supportive therapy early.

**THE BEST MANAGEMENT OF TLS IS PREVENTION.**
2. **EVALUATION OF PATIENT RISK FACTORS**

<table>
<thead>
<tr>
<th>Very High Risk</th>
<th>High Risk</th>
<th>Low Risk</th>
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<tbody>
<tr>
<td>• ALL, WBC ≥50</td>
<td>• ALL, WBC &lt;50</td>
<td>• Remainder of patients e.g. low bulk solid tumours</td>
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<td>• AML, WBC ≥50</td>
<td>• AML, WBC &lt;50</td>
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<tr>
<td>• Non-Hodgkin’s lymphoma</td>
<td>Other patient/tumour risk factors:</td>
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<td>Other patient/tumour risk factors:</td>
<td>• Nephrotoxic drugs</td>
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<td>• Abdominal organ involvement</td>
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<td>• Tumour infiltration of kidneys</td>
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<td>• Pre-existing renal failure</td>
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<tr>
<td>• Acute sepsis</td>
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<tr>
<td>• Nephrotoxic drugs</td>
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<td></td>
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<tr>
<td>• Hypovolemia and oliguria</td>
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<tr>
<td>• Bulky tumour</td>
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<td>• Rapid proliferation</td>
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<tr>
<td>• Elevated LDH</td>
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<tr>
<td>• High sensitivity to therapy</td>
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3. **PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME**

**All High risk**

Aggressive hydration and diuresis:

- IV hydration with 0.45% Sodium Chloride/5% Dextrose (NO ADDED POTASSIUM) at 3 L/m²/day (125 mL/m²/hr), usually capped at 188 mL/hr (4500 mL/day) for patients >1.5m².
  - Volume can be increased up to 6 L/m²/day, adapted to patient age, cardiac function and urine output.
  - Hydration should start **at least 24 hours** before tumour-specific therapy where possible.

- Maintain urine output ≥1 mL/kg/hr (≥2 mL/kg/hr in children <10 kg).
  - If oliguria, the measurement of urine specific gravity or osmolality may be useful in defining the hydration status.
  - Diuretics may be needed to maintain adequate urine output; give Furosemide 0.5-1 mg/kg (max. 40 mg). (DIURETICS CONTRAINDICATED IN HYPOVOALAEMIA OR OBSTRUCTIVE UROPATHY)

- HDU level of monitoring.

- Administration of Antihyperuricaemic Agent at least 24 hours prior to cytotoxic chemotherapy where possible:
  
  **Very High Risk**
  - Initial management with Rasburicase.

  **High Risk**
  - Initial management with Allopurinol.
  - Rasburicase may be considered in the initial management; this is the Oncology/Haematology Consultant’s decision.
    - If hyperuricaemia develops or serum phosphate increases above upper limit of normal initiate Rasburicase therapy.
    - If a dose of Rasburicase has been given, Allopurinol need not be given that same day.

  **Low Risk**
  
  Adequate hydration, clinical Judgment and close monitoring
4. **MONITORING**

**All High Risk**

Monitor laboratory and clinical TLS parameters for at least 72 hours after initiation of cytotoxic chemotherapy:

- Strict monitoring of fluid input and output
- Twice daily weights
- Check blood pressure 1-4 hourly
- Check oncology profile and serum uric acid levels, 4-6 hours after initial administration of chemotherapy and every 6-8 hours thereafter or more frequently if abnormal. Result trends are also important; if there is a 20% rise in phosphate, potassium or uric acid levels, even if within the normal value ranges, more frequent checks should be made. Biochemical monitoring should continue until resolution of TLS risk, for example, after serum potassium peak, normalization of high white cell count.

- Biochemical features of acute tumour lysis syndrome:
  - Hyperuricaemia
  - Hyperphosphatemia
  - Hyperkalaemia
  - Hypocalcaemia
  - Rising urea and creatinine

**If Rasburicase has been given all subsequent blood samples for uric acid measurement should be placed on ice immediately on collection, and sent to the lab speedily.** (Rasburicase causes further degradation of uric acid within blood samples at room temperature, thereby giving falsely lower uric acid levels).

- ECG monitoring should be instigated in the event of hyperkalaemia, hypocalcaemia, or other symptoms and signs of TLS e.g. paraesthesia, muscle cramps, tetany, seizures. ECG features of hyperkalaemia include peaked T waves, flattened P waves, prolonged PR interval, widened QRS complexes, deep S wave. In hypocalcaemia, QT interval lengthening, and arrhythmias may occur.

**Low Risk**

Clinical monitoring: fluid input, urine output, clinical judgement on further monitoring.
### MANAGEMENT OF BIOCHEMICAL ABNORMALITIES

<table>
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<th>Abnormality</th>
<th>Management Recommendation</th>
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<tr>
<td>Hyperuricaemia</td>
<td>- Aggressive hydration 3-6 L/m²/day&lt;br&gt;- Give Rasburicase&lt;br&gt;- Notify nephrologist if rising uric acid levels despite above measures</td>
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<td>Hyperkalaemia*</td>
<td>- If suspected check plasma potassium immediately: Take sample in heparinised capillary tube and analyse on blood gas machine on PICU, this should give a more accurate potassium level (See monitoring above).&lt;br&gt;- Avoid IV and oral potassium&lt;br&gt;- ECG and cardiac rhythm monitoring&lt;br&gt;- Salbutamol 2.5-5 mg nebulised or 4 micrograms/kg IV over 5 minutes; repeat if necessary&lt;br&gt;- 5-10 mL/kg/hr of 10% Dextrose with soluble insulin 0.05-0.2 unit/kg/hr IV&lt;br&gt;- Polystyrene Sulfonate Resins 125-250 mg/kg (max. 15 g) 3-4 times daily orally (except neonates) or rectally. &lt;br&gt;- Repeat potassium level in 1-2 hours&lt;br&gt;- Correct acid/base balance&lt;br&gt;- Notify nephrologist</td>
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<td>Moderate, Potassium 6.0-7.0 mmol/l</td>
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<td>Severe, Potassium &gt;7.0 mmol/l and/or symptomatic (ECG changes)</td>
<td>Same as above, plus:&lt;br&gt;- Calcium gluconate 10% 0.5 mL/kg IV (initial max. 20 mls) over 5-10 mins, repeated as necessary.&lt;br&gt;- Dialysis</td>
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<td>Hyperphosphatemia, Moderate, ≥ 2.1 mmol/l</td>
<td>- Avoid IV phosphate administration&lt;br&gt;- Administer phosphate binder e.g. calcium carbonate, see BNF for age-related doses under “phosphate binding in renal failure and hypophosphatemia” &lt;br&gt;- Notify nephrologist</td>
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<td>Severe, &gt; 3.33 mmol/l</td>
<td>- Dialysis</td>
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<td>Hypocalcaemia, ≤ 1.75 mmol/l</td>
<td>- No therapy</td>
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<tr>
<td>Asymptomatic</td>
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<td>Hypocalcaemia, ≤ 1.75 mmol/l Symptomatic e.g. paraesthesia, muscle cramps, tetany, long QT on ECG</td>
<td>- Calcium gluconate 10% 0.5 mL/kg IV (initial max. 20 ml) over 5-10 mins, administered slowly with ECG monitoring, repeated as necessary.</td>
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6. **NEPHROLOGIST REFERRAL**

For patients at high risk of TLS, cytotoxic chemotherapy should only be administered once patients are located in a facility with ready access to dialysis.

Urgent nephrologist consultation when:

- Low urine output despite adequate hydration and trial of diuretic.
- Severe, unmanageable hypertension
- Volume overload
- Rising creatinine despite other measures
- Rising urea despite other measures
- Hyperkalaemia >7 mmol/L or >6 mmol/L and increasing, in spite of increased hydration and diuretics
- Symptomatic hypocalcaemia
- Persistent elevated phosphate levels >3.3 mmol/L or rapidly rising phosphate levels
- Rising uric acid levels despite Rasburicase
## Administration of Antihyperuricaemic Agents

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<th>Agent</th>
<th>Recommended dose</th>
<th>Duration</th>
<th>Notes</th>
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<tr>
<td>Allopurinol</td>
<td>100 mg/m²/dose every 8 hours PO (maximum, 300 mg/day)</td>
<td>Start 1-2 days before start of induction chemotherapy; continue up to 3-7 days afterwards, until laboratory parameters, tumour burden, WBC count have returned to low-TLS risk levels.</td>
<td>Reduce dose in renal failure, according to degree of impairment: seek pharmacist’s advice. Reduction 6-mercaptopurine doses by 65%-75% with concomitant allopurinol.</td>
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<td>Rasburicase</td>
<td>0.2 mg/kg once daily 30 minute IV infusion in 50 ml 0.9% sodium chloride</td>
<td>Consultant’s decision on duration of use.</td>
<td>Contraindicated in glucose-6-phosphate Dehydrogenase-deficient patients, patients with a known history of anaphylaxis or hypersensitivity reactions, haemolytic reactions, or methemoglobinemia reactions to rasburicase or any of the excipients. No dose reduction is required in renal failure.</td>
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References


4. Oxford Handbook of Clinical Haematology. 2010


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<th>Version:</th>
<th>3</th>
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<tr>
<td>Ratified by:</td>
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<td>Date ratified:</td>
<td>11&lt;sup&gt;th&lt;/sup&gt; May 2016 (v3)</td>
</tr>
<tr>
<td>Name of originator/author:</td>
<td>Karen Selwood (Advanced Nurse Practitioner - Oncology)</td>
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<td>Name of responsible committee:</td>
<td>Chemotherapy Committee</td>
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