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

1. INTRODUCTION

Acute tumour lysis syndrome (TLS) is characterised 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, hyperphosphatemia, hypocalcaemia, and uraemia. The crystallisation 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.

Note: caution with administration of corticosteroids in patients with suspected malignancy as this could inadvertently cause tumour lysis. Avoid dexamethasone as an anti-emetic. Where possible check with a haematology/oncology consultant before prescribing any corticosteroid if malignancy suspected.

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

Very High Risk	High Risk	Low Risk
• ALL, WBC ≥50 • AML, WBC ≥50 • Non-Hodgkin's lymphoma Other patient/tumour risk factors: ○ Abdominal organ involvement ○ Tumour infiltration of kidneys ○ Chronic kidney disease ○ Acute kidney injury ○ Acute sepsis ○ Nephrotoxic drugs ○ Hypovolemia and oliguria ○ Bulky tumour ○ Rapid proliferation ○ Elevated LDH ○ High sensitivity to therapy	• ALL, WBC <50 • AML, WBC <50 Other patient/tumour risk factors: ○ Nephrotoxic drugs	• Remainder of patients e.g. low bulk solid tumours Other patient/tumour risk factors: ○ Nephrotoxic drugs

3. PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME

High and Very High Risk

All high and very high risk patients require aggressive hydration and diuresis:

- IV hydration with 0.45% Sodium Chloride/5% glucose (NO ADDED POTASSIUM) at 3L/m^2/day (125mL/m^2/hr), usually capped at 188ml/hr (4500ml/day) for patients >1.5m^2
    - Volume can be increased up to 6L/m^2/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 ≥1mL/kg/hr (≥2mL/kg/hr in children <10kg).
    - 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 0.5-1mg/kg (max. 40 mg). (DIURETICS CONTRAINDICATED IN HYPOVOLAEMIA 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 should not be given on that day.

Low Risk

Adequate hydration, clinical judgement and close monitoring.

4. MONITORING

High and Very 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.

5. MANAGEMENT OF BIOCHEMICAL ABNORMALITIES

Abnormality	Management Recommendation
Hyperuricaemia	• Aggressive hydration 3-6L/m^2/day • Give rasburicase • Notify nephrologist if rising uric acid levels despite above measures
Hyperkalaemia* *Pseudo-hyperkalaemia can occur in high WBC states as a result of cell lysis ex vivo; there will be no ECG changes and serum phosphate and calcium will be normal. Send blood gas for urgent potassium level.	Refer to 'Treatment of Hyperkalaemia Guideline' available on the Trust Intranet.
Hyperphosphatemia, Moderate, ≥ 2.1mmol/l Severe, > 3.33mmol/l	• Avoid IV phosphate administration • Administer phosphate binder e.g. calcium carbonate, see BNF for age-related doses under "phosphate binding in renal failure and hypophosphatemia" • Notify nephrologist • Dialysis
Hypocalcaemia, ≤ 1.75mmol/l Asymptomatic	• No therapy
Hypocalcaemia, ≤ 1.75mmol/l Symptomatic e.g. paraesthesia, muscle cramps, tetany, long QT on ECG	Calcium gluconate 10% 0.5mL/kg IV (initial max. 20ml) over 5-10 mins, administered slowly with ECG monitoring; repeated as necessary.

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 > 6mmol/L
- Symptomatic hypocalcaemia
- Persistent elevated phosphate levels > 3.3mmol/L or rapidly rising phosphate levels
- Rising uric acid levels despite rasburicase

7. ADMINISTRATION OF ANTIHYPERURICAEMIC AGENTS

Agent	Recommended dose	Duration	Notes
Allopurinol	100mg/m^2 (maximum 100mg) 8 hourly oral	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.	Avoid in renal impairment Rasburicase indicated due to risk stratification. Reduce 6-mercaptopurine doses by 65%-75% with concomitant allopurinol.
Rasburicase	0.2mg/kg once daily 30 minute IV infusion in 50ml 0.9% sodium chloride	Consultant's decision on duration of use.	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.

8. **ABBREVIATIONS**

ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
ECG	electrocardiogram
LDH	lactate dehydrogenase
TLS	tumour lysis syndrome
WBC	white blood cell count

References

1) Coiffier B, Altman A, Pui Ching-Hon, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: An evidence-based review. J Clin Oncol, 2008; 26: 2767-2778.

2) Feusner JH, Ritchey AK, Cohn SL, Billett AL. Management of Tumor Lysis Syndrome: Need for Evidence-Based Guidelines. J Clin Oncol. 2008 Dec 1; 26(34):5657-8.

3) Tosi P, Barosi G, Lazzaro C, Liso V, Marchetti M, Morra E, Pession A, Rosti G, Santoro A, Zinzani PL, Tura S. Consensus conference on the management of tumor lysis syndrome. Haematologica. 2008 Dec; 93(12):1877-85.

4) Oxford Handbook of Clinical Haematology. 2010

5) Ahee P, Crowe AV. The management of hyperkalaemia in the emergency department. J Accid Emerg Med 2000; 17: 188–191.

6) Cairos, Coiffier B, Reiter A, Younes, A. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant disease: an expert TLS panel consensus. British Journal of Haematology 2010; 149, 578-586.

7) Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. New England Journal of Medicine 2011; 364, 1844-1854.

8) Kelly KM, Lange B. Oncologic emergencies. Pediatr Clin North Am. 1997; 44(4):809-30.

9) BNF for children 2019-2020.

10) Will A, Tholouli E. The clinical management of tumour lysis syndrome on haematological malignancies. British Journal of Haematology 2011; 154, 3-13

11) Jones GL, Will A, Jackson GH, Webb N, Rule S. Guidelines for the management of Tumour Lysis Syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. British Journal of Haematology 2015; 169, 661-671.

12) Sanofi. Fasturtec 1.5mg/ml powder and solvent for concentrate for solution for infusion Summary of Product Characteristics (2021). Available at https://www.medicines.org.uk/emc/product/1316 [accessed 16/12/22]

13) Accord Healthcare Limited. Allopurinol 100mg Tablets Summary of Product Characteristics (2022). Available at https://www.medicines.org.uk/emc/product/6007 [accessed 16/12/22]

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Section Number	Page Number	Revision(s) made	Reason for revision(s)
1		Caution added re administration of corticosteroids in patients with suspected malignancy	For clarity and to minimise risk
2		Pre-existing renal failure changed to chronic kidney disease and acute kidney injury	Change to acceptable terminology
5		Biochemistry to reduce spin on oncology profile sampling removed	Not current practice
6		Threshold for nephrology referral changed to potassium > 6mmol/L	Earlier intervention preferrable
7		Allopurinol maximum dose added	For clarity
7		Allopurinol dose reduction in renal impairment removed	Allopurinol not indicated as per risk stratification
8		Abbreviations added	For clarity