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

- Every new patient and/or those commencing a new line of therapy should have a risk assessment for TLS. This should be personalised and include consideration of disease, patient and therapy factors.
- 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 Paediatric Oncology/Haematology consultant on call has responsibility for recommending instigation of the below assessment and management relating to this guideline.

Definitions:

- **Laboratory TLS**: two or more of the following abnormalities within 3 days prior and up to 7 days after initiating anti-cancer therapy
  - Uric Acid ≥476 micromol/L or 25% increase from baseline
  - Potassium ≥6 mmol/L or 25% increase from baseline
  - Phosphate ≥2.1 mmol/L or 25% increase from baseline
  - Calcium ≤1.75 micromol/L or 25% decrease from baseline

- **Clinical TLS:** A patient with laboratory TLS and at least one of the following:
  - Creatinine ≥1.5x ULN (age >12 or age adjusted)
  - Cardiac arrhythmia
  - Sudden death
  - Seizure

THE BEST MANAGEMENT OF TLS IS PREVENTION.

2. RISK STRATIFICATION

TLS Risk Stratification Considerations:

- Disease histology (see section 3 below)
- Assessment of disease burden/rapid proliferation (see section 3 below)
- Patient related factors: renal dysfunction/renal involvement/abdominal organ involvement, nephrotoxic drugs, frailty, ability to manage prophylactic strategies - such as fluid intake compliance, concomitant issues such as hypovolaemia, oliguria, sepsis other organ dysfunction
- Assessment of pre-existing spontaneous laboratory or clinical TLS
- Treatment specific therapeutic agents in certain disease have a higher associated risk of TLS so consideration needs to be given as to whether any of these 'upgrade' a patient's risk. Refer to individual SACT protocol containing novel agents for further information (including but not limited to 'Venetoclax based regimens for the treatment of Relapsed/Refractory Acute Myeloid Leukaemia (r/r AML) and initial treatment of AML in those unfit for standard induction chemotherapy')

3. EVALUATION OF DISEASE RISK FACTORS

High Risk	Intermediate Risk	Low Risk
• ALL, WBC ≥100 x 10^9/L and/or bulky disease • AML, WBC ≥100 x 10^9/L • Burkitt Lymphoma advanced stage or LDH ≥2x ULN and/or bulky disease • Lymphoblastic Lymphoma with LDH ≥2x ULN and/or bulky disease	• ALL, WBC <100 x 10^9/L • AML, WBC <100 x 10^9/L • Burkitt Lymphoma early stage or LDH <2x ULN • Lymphoblastic Lymphoma with LDH <2x ULN and no bulky disease	• Hodgkin lymphoma • Early stage high-grade lymphomas with normal LDH and no-bulky disease • Remainder of patients e.g. low bulk solid tumours
ALL: Acute Lymphoblastic Leukaemia AML: Acute Myeloid Leukaemia		

4. PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME

High and Intermediate Risk

All high and intermediate 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 4L/m^2/day, adapted for renal function, cardiac function and fluid status.
    - Hydration should start **at least 24 hours** before tumour-specific therapy where possible.
    - Caution should be exercised in patients with high count leukaemia and low haemoglobin as hyperhydration may cause further haemodilution and exacerbate anaemia.
- 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 (possible on 3B).
- Administration of anti-hyperuricaemic agent at least 24 hours prior to cytotoxic chemotherapy where possible:

High Risk

- Initial management with rasburicase.
    - Patients should ideally be tested for G6PD deficiency before administration (rapid point of care testing is available in most laboratories out of hours). Rasburicase can cause severe haemolytic anaemia or methemoglobinemia in patients who are G6PD deficient.
    - Consideration should be made to give rasburicase without waiting for a G6PD result in urgent situations. This decision should be made by the Oncology/Haematology consultant on call after considering the risks and benefits for an individual patient.
    - Lack of G6PD testing availability or a delay in results SHOULD NOT DELAY URGENT TREATMENT with rasburicase.
    - Patients at higher risk of G6PD deficiency are boys, as well as those of African, Mediterranean or Asian descent (G6PD deficiency is an X-linked condition but in high prevalence areas homozygous mutations in girls are not uncommon).

Intermediate

- Initial management with allopurinol.
- Rasburicase may be considered for initial management if patient cannot take allopurinol or at the discretion of the Oncology/Haematology Consultant.
- 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

- If prophylaxis required, consider initial management with hydration and allopurinol.

5. MONITORING

For high and intermediate risk patients

Monitor laboratory and clinical TLS parameters for at least 72 hours after initiation of cytotoxic chemotherapy with frequency tailored to predicted risk and results to date, reviewed at least daily:

- 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.

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.

Ensure clear communication to out of hours/on call teams regarding patients who are at risk of TLS or are being treated for TLS. This is particularly important when patients are located in clinical areas less familiar with the management of haematological malignancies and TLS.

6. 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	• 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
Hyperphosphatemia, Severe, > 3.33mmol/	• 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.

7. 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
- Severe metabolic acidosis that is refractory to medical management

8. 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. Allopurinol should be stopped when rasburicase is commenced and can be recommenced 24 hours after the last dose of rasburicase.
Rasburicase	0.2mg/kg every 24 hours 30 minute IV infusion in 50ml 0.9% sodium chloride NB: No 'single fixed dose' is recommended in children, all prescriptions should be at the above dose	3-5 days typically required, consultant discretion up to 7 days.	Note rasburicase is a critical medicine and should be administered within 1 hour of prescribing Contraindicated in G6PD 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. Use 'Q24H' frequency on Meditech (not 'OD') Rasburicase 1.5mg injection and 7.5mg in injection are available on ward 3B (Omnicell) and in the Night Room for access out of hours. Refer to BNFC/SPC for further information

9. **ABBREVIATIONS**

ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
ECG	electrocardiogram
G6PD	glucose-6- phosphate-dehydrogenase
LDH	lactate dehydrogenase
TLS	tumour lysis syndrome
ULN	upper limit of normal
WBC	white blood cell count

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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
Whole document	Whole document	Version 6: Revisions made throughout entire document to bring in line with BSH guideline.	To reflect current recommendations