Sheffield Children's NHS
NHS Foundation Trust

Tumour Lysis Syndrome: Prevention and Management

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Intended Audience

This document contains information and clinical guidelines for the management of children under the care of, or being referred to, Sheffield Children's Hospital Oncology and Haematology department. It is to be used by staff within SCH(NHS)FT, shared care centres and referring district general hospitals, whenever they are caring for these children.

Purpose

The aim of this document is to allow staff to identify patients at risk of Tumour Lysis Syndrome, and to commence appropriate preventative therapy.

Identification and management of patients with established tumour lysis syndrome is also described.

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1 Introduction

Following the administration of chemotherapy, rapid neoplastic cell lysis may occur, particularly in acute leukaemia and lymphoma. This may result in metabolic complications including hyperuricaemia and hyperphosphataemia. Occasionally these problems may be present at diagnosis due to rapid cell turnover, and be exacerbated if there is any renal involvement by disease. More often they arise during induction chemotherapy.

Children most at risk are those with bulky lymphomas, particularly T or B cell NHL, and/or where there is renal involvement. Children with high white cell count (in excess of 100 x 10^9/L) leukaemia (usually T cell leukaemia) are also considered to be at increased risk.

Primary complications include hyperkalaemia and hyperphosphataemia; the latter may lead to secondary hypocalcaemia. Renal dysfunction occurs due to a combination of hyperuricaemia and hyperphosphataemia with intrarenal deposition of calcium. Renal insufficiency leads to a further rise in serum potassium, urea and creatinine, and there may also be problems of water overload.

Tumour Lysis Syndrome is an oncological emergency and any child with suspected TLS must be discussed with the On Call Oncology Consultant at Sheffield Children's Hospital immediately.

2. Definition of Tumour Lysis Syndrome

Patients may have metabolic abnormalities alone (laboratory TLS) or metabolic and clinical signs (clinical TLS). Laboratory TLS often progresses to clinical TLS, but this can be prevented with early recognition and appropriate management.

Laboratory TLS

- Two or more of the following within 3 days before and 7 days after starting treatment
    - Uric acid >476 umol/l or 25% increase from baseline
    - Potassium >6.0 mmol/l or 25% increase from baseline
    - Phosphate >2.1 mmol/l or 25% increase from baseline
    - Calcium <1.75 mmol/l or 25% decrease from baseline

Clinical TLS

- A patient with laboratory TLS and at least one of
    - Creatinine≥1.59 x ULN (age>12 years or age-adjusted)
    - Cardiac arrhythmia
    - Sudden death
    - Seizure

Calculation of rises from baseline are not routinely carried out, and there are various potential confounders, but it is vital to regular measure and monitor changes in the above biochemical parameters to ensure that early TLS is recognised and appropriate management commenced.

3. Baseline Investigations

Pre treatment investigations in children with bulky lymphomas or leukaemia with a high white cell count (> 100 x 10^9/L) **MUST** include:

1. Chest X ray +/- lateral (to assess tracheal patency) if mediastinum is enlarged
2. Baseline urate, urea, creatinine, electrolytes, Ca, Mg, PO4
3. Check G6PD status as need to know status prior to prescribing Rasburicase
4. Weight

- Renal ultrasound to assess parenchymal infiltration is required for patients with bulky leukaemia or high count ALL with impaired renal function or TLS. Occasionally in NHL there may also be an obstructive element due to nodal compression of ureters
- A central venous line may be needed for fluid administration and monitoring

4. Risk Assessment

Low Risk	Most solid tumours ALCL Stage 1 or 2
Intermediate Risk	Acute leukaemia (unless meet high risk criteria) ALCL Stage 3 or 4 Bulky neuroblastoma or Germ Cell Tumour
High Risk	ALL or AML with WCC > 100 Burkitt lymphoma/leukaemia or lymphoblastic lymphoma High grade lymphoma with bulky disease (LDH >2 x ULN or scan)

4.1 Risk Assessment Modification for Renal Dysfunction

Patients should be treated in a higher risk group if renal dysfunction or renal involvement (low → intermediate, intermediate → high)

5. Preventative Measures

The peak risk of lysis is within 24 hours from start of chemotherapy, so close observation and monitoring is essential. Risk from metabolic problems may persist for up to 5-7 days.

Avoid use of nephrotoxic drugs where possible

Discuss need for and safety of IV contrast agents with radiologist prior to CT/MR imaging

5.1 Low Risk Patients

- Observation and monitoring (fluid status, chemistry)
- Treat as intermediate risk if develop biochemical signs of lysis

5.2 Intermediate Risk Patients

- Start intravenous fluids at least 12 hours before chemotherapy. Use 0.45% sodium chloride with 5% glucose at rate of 3000mls/m^2/day (125mls/m^2/hr). In general **DO NOT ADD POTASSIUM to IV fluids** and do not use 0.9% sodium chloride solutions.

  Additives such as calcium may be required as clinically indicated, see below.

- Allopurinol 100mg/m^2 PO TDS should be started before chemotherapy (with IV fluids, see below) and continue for 5 days.

  NB. Maximum recommended dose in children <15 years old is 400mg/day.

- Potential use of oral phosphate binding agents are recommended in some international guidelines, but are not available in the UK.

5.3 High Risk Patients

- Start intravenous fluids at least 12 hours before chemotherapy. Use 0.45% sodium chloride with 5% glucose at rate of 3000mls/m^2/day (125mls/m^2/hr). In general **DO NOT ADD POTASSIUM to IV fluids** and do not use 0.9% sodium chloride solutions.

  Additives such as calcium may be required as clinically indicated, see below.

- Prescribe rasburicase 200microgram/kg/day infused over 30 minutes in 0.9% sodium chloride. (See Appendix 1). This must always be discussed with a consultant.
- Allopurinol should not be prescribed alongside rasburicase.
- Rasburicase must not be prescribed to patients with G6PD deficiency or if known to be allergic to the drug. Use allopurinol instead.
- Potential use of oral phosphate binding agents are recommended in some international guidelines, but are not available in the UK.

5.4 Urinary Alkalinisation

- Urinary alkalinisation is not routinely recommended in TLS prophylaxis.

6. Monitoring during initial chemotherapy

It is essential that an accurate fluid balance is recorded.

Blood pressure should be checked hourly.

The child should be weighed at least daily, and preferably twice daily.

Measure electrolytes, urate, calcium and phosphate 8 – 12 hourly for patients in high risk group. NB. If the patient is receiving rasburicase, there is no need to recheck urate. (See appendix 1)

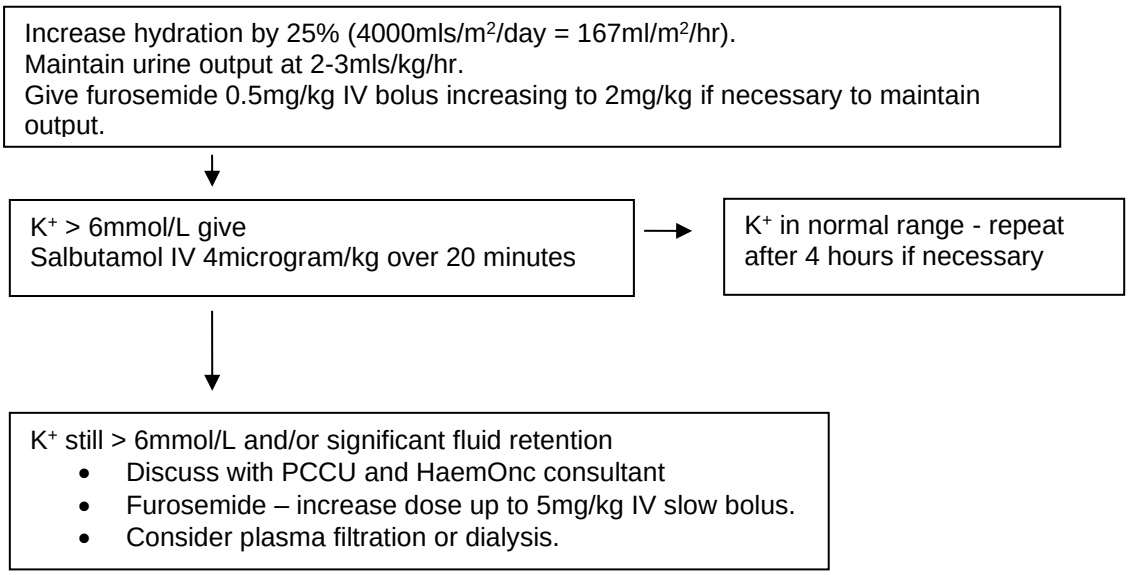
If WCC is very high and laboratory potassium result is grossly elevated without ECG signs of hyperkalaemia, immediately check a free flowing capillary sample on the blood gas analyser, as the apparently elevated potassium result from the lab may be an *in vitro* effect.

If there is ECG or other evidence to support the laboratory result, manage this as indicated below whilst confirmation of the result is obtained.

A cardiac monitor can be used to detect early signs of hyperkalaemia; these include elevation of T waves, and widening of QT. A portable monitor is available for loan from PICU with example print-outs of expected abnormalities.

7. Treatment of established Tumour Lysis Syndrome

- Commence rasburicase unless contra-indicated
- Continue to hyperhydrate and monitor fluid balance
- Aim for urine output >4ml/kg/hr in infants, 100ml/m^2/hr in older children
- Furosemide should be used to drive urine output if required
- Hyperkalaemia should be managed as per flow chart below



- **Hypocalcaemia**

  Treat **ONLY** if symptomatic: there are risks of causing hyperphosphataemia.

  Symptomatic hypocalcaemia should be treated with calcium gluconate as continuous infusion of 1mmol/kg/day in hydration fluid (max dose 8.8mmol/24 hr, max rate 0.042mmol/kg/hr).

  If seizures occur in association with hypocalcaemia give 0.11mmol/kg up to max 4.5mmol (0.5ml/kg of 10% Calcium Gluconate solution) as bolus over 10 minutes. (See The Haematology & Oncology Unit Guidelines, section 5, Chemotherapy – Toxicity, Complications & Management, 1498 Electrolyte disturbances - Correction of - for Haematology & Oncology patients H&O/05/1498 - CG1498)

  Calcium, phosphate and renal function should be monitored carefully. Calcium infusion should be discontinued as soon as symptoms are controlled.

  Do not use calcium chloride solution as it may produce local vein toxicity and late ulceration.

- **CVVH/Dialysis**

  Early renal failure with fluid retention as demonstrated by weight gain and poor urine output may respond to increasing the furosemide (see above). If fluid overload is the major problem plasma filtration is usually preferable to dialysis. Discuss the patient with the ICU medical staff.

Dialysis may be required for the following situations. Peritoneal dialysis is not recommended.

- Uncontrollable hyperkalaemia, hyperuricaemia and hypocalcaemia
- Hyperphosphataemia > 4mmol/l
- Severe oliguria/anuria despite frusemide

8. References

8.1 Tumour Lysis Syndrome. BMJ Best Practice [accessed online 03/02/23] https://bestpractice.bmj.com/topics/en-gb/936/pdf/936/Tumour%20lysis%20syndrome.pdf

8.2 Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Cairo MS, Coiffier B, Reiter A, Younes A; TLS Expert Panel. Br J Haematol. 2010 May;149(4):578-86 [remains most recent version – checked online 03/02/23]

8.3 Guidelines for the management of tumour lysis syndrome inadults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Gail L Jones, Andrew Will, Graham H Jackson, Nicholas J A Webb and Simon Rule on Behalf of the British Committee for Standards in Haematology. British Journal of Haematology, 2015,169,661–671 [remains most recent version – checked online 03/02/23]

8.4 SPC Fasturtec. Online: https://www.medicines.org.uk/emc/product/1316/smpc [accessed online 03/02/2023]

8.5 BNFc. https://bnfc.nice.org.uk/ [accessed online 03/02/2023]

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Appendix 1- Rasburicase administration

RASBURICASE	
Presentation	Vials containing 1.5mg rasburicase (recombinant urate-oxidase enzyme) powder or 7.5mg rasburicase powder with solvent
Indications & Dosage	Treatment and prophylaxis of acute hyperuricaemia in patients with haematological malignancy with a high tumour burden and at risk of a rapid tumour lysis or shrinkage at initiation of chemotherapy. Dose :200microgram/kg once a day usually for 5-7 days
Side-effects	Fever, nausea, vomiting and occasionally diarrhoea, headache, hypersensitivity reactions, haemolytic anaemia, methaemoglobinaemia.
Reconstitution & Dilution	Reconstitute with diluent provided (Poloxamer 188 and WFI). Mix gently, DO NOT SHAKE ! Resulting concentrate contains 1.5mg in 1ml. For children > 0.5m2 dilute to 50mls with 0.9% sodium chloride. For infants < 0.5m2 dilute to 20mls.
IV bolus	Do not give as a bolus
Intermittent Infusion	Infuse over 30 minutes. Do not filter. Do not mix or infuse with any other drugs, nor with glucose containing solutions.
Cautions related to Administration	Do not give with Allopurinol Rasburicase can cause anaphylaxis, use with caution in patients with a known history of asthma or atopic eczema Rasburicase is contra-indicated in patients with G6PD deficiency
Comments	Store in a refrigerator To monitor a patient's uric acid level, a strict sample-handling procedure must be followed to minimise ex vivo degradation of the analyte: Blood must be collected into pre-chilled tubes containing heparin anticoagulant. Samples must be immersed in an ice/water bath. Plasma samples should immediately be prepared by centrifugation in a pre-cooled centrifuge (4°C). Finally, plasma must be maintained in an ice/water bath and analysed for uric acid within 4 hours.
References	SPC Fasturtec. Online: https://www.medicines.org.uk/emc/product/1316/smpc [accessed online 03/02/2023] BNFc. https://bnfc.nice.org.uk/ [accessed online 03/02/2023]

Checked by Karen Whitehouse January 2023

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