Management of Tumour Lysis Syndrome in Adult Patients

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Contents

1. Outline of procedure

To provide information to Haematology and Oncology staff for the prevention and management of tumour lysis syndrome (TLS).

2. Area of application

This guideline applies to all adult SACT services across the North region, except for the administrative areas of Argyll and Bute in NHS Highland, which are linked to the WoSCAN governance framework.

The guidelines may not be appropriate to every patient and in all cases an individual patient's circumstances may dictate an alternative approach.

3. Objective

This guideline covers the prevention and treatment of TLS in adults.

Please refer to the appropriate guidelines for metabolic derangement or renal failure related to other causes. Contact the relevant Specialist Childrens' Cancer Treatment Centre if TLS is suspected in a child.

TLS is an emergency caused by massive lysis of malignant cells and release of intracellular components. The subsequent significant electrolyte and metabolic abnormalities include hyperuricaemia, hyperphosphataemia, hypocalcaemia and hyperkalaemia.

The cornerstones of management are recognition of the high risk patient and appropriate pre-emptive treatment.

4. Stages of the process

Diagnosis

In the context of imminent or recent initiation of cytoreductive therapy for malignant disease, presence of *laboratory TLS* is defined (Cairo and Bishop, 2004) as two or more of

- Raised uric acid: ≥ 476 µmol/L or 25% increase from baseline
- Raised phosphate: ≥ 1.45 mmol/L or 25% increase from baseline
- Raised potassium: ≥ 6.0 mmol/L or 25% increase from baseline
- Low calcium: ≤ 1.75 mmol/L or 25% decrease from baseline

A *clinical diagnosis of TLS* can be made if acute renal failure (creatinine ≥ 1.5 x ULN), cardiac arrhythmia or seizures occur in conjunction with the Cairo-Bishop laboratory features above.

Symptoms/signs of TLS include nausea, vomiting, diarrhoea, anorexia, lethargy, oedema, fluid overload, haematuria, congestive heart failure, muscle cramps, tetany, syncope.

Management of established *clinical TLS* involves: IV fluids, rasburicase, cardiac monitoring, Intensive Care Unit admission, frequent laboratory tests and renal replacement therapy if necessary. See Section 5 “Management of Established TLS”

Risk assessment and stratification

Prior to starting chemotherapy (including steroid monotherapy), the patient’s potential to develop TLS must be considered. The assessment takes into account disease type (see Table 1), white cell count and additional risk factors, including existing renal dysfunction and signs of TLS.

Individuals with evidence of *laboratory TLS* at presentation should be treated as for high risk disease.

An individual’s risk of tumour lysis should be upgraded (low to intermediate risk, or intermediate to high risk) if any one of the following is present (with the exception of individuals with solid tumours or myeloma):

- Pre-existing nephropathy/renal impairment
- Acidosis
- Hypotension
- Prior exposure to a nephrotoxic agent
- Renal involvement by underlying disease process
- Dehydration

Table 1: Prophylaxis based on risk stratification (High risk)

Risk Category	Diagnosis	Contributing Risk Factor	Prophylaxis
High	Laboratory TLS at presentation		Hydration*: 2-3 L/m^2/day Rasburicase 3mg daily until markers of TLS have returned to normal
	Burkitt lymphoma stage III/IV	LDH > 2 x ULN	Hydration*: 2-3 L/m^2/day Rasburicase 3mg if no established clinical or laboratory TLS. Febuxostat 120mg/day for 7-9 days if rasburicase contraindicated. Electrolyte monitoring: every 6-8 hours
	Burkitt leukaemia		
	Lymphoblastic lymphoma stage III/IV	LDH > 2 x ULN	
	ALL	WCC > 100 x 10^9/L or LDH > 2 x ULN	
	AML	WCC > 100 x 10^9/L	
	Adult T-cell leukaemia/lymphoma, DLBCL, transformed high grade lymphoma, mantle cell lymphoma	Bulky disease or LDH > 2 x ULN	
	Metastatic germ cell tumour	Bulky	
	CLL	If treated with venetoclax (BCL2 inhibitor)	Follow advice in SmPC re. electrolyte monitoring, hydration and antihyperuricaemic agents

* Hydration should be administered to maintain urine output > 100 ml/m^2/h. Suitable IV fluids are hypotonic or isotonic: 0.45% sodium chloride in 5% dextrose, or 0.9% sodium chloride.

Table 2: Prophylaxis based on risk stratification (Intermediate risk)

Risk Category	Diagnosis	Contributing Risk Factor	Prophylaxis
Intermediate	Burkitt lymphoma early stage	LDH < 2 x ULN	Hydration*: 2-3 L/m^2/day. Rasburicase if uric acid ≥476 µmol/L. Allopurinol 300mg/day for 7 days (or until risk of TLS has been resolved) if uric acid < 476 µmol/L. Febuxostat 120mg/day for 7-9 days if allopurinol contraindicated. Electrolyte monitoring is recommended every 8-12 hours. However, for outpatients, the frequency of monitoring should be determined on an individual patient basis as clinically indicated.
	Adult T-cell leukaemia/lymphoma, DLBCL, transformed high grade lymphoma, mantle cell lymphoma	ULN < LDH < 2 x ULN, non bulky	
	Lymphoblastic lymphoma stage I/II	LDH < 2 x ULN	
	ALL	WCC < 100 x 10^9/L and LDH < 2 x ULN	
	AML	WCC 25-100 x 10^9/L or LDH > 2 x ULN	
	CLL	If treated with CD20 antibody (e.g. Rituximab, Obinutuzumab) or fludarabine AND WCC > 50 x 10^9/L or bulky nodal disease.	
	CML	If experiencing an accelerated blast crisis	
	Rarely highly chemotherapy-sensitive tumours	e.g. germ cell tumour, small cell lung cancer with bulky/advanced stage disease, neuroblastoma	
	Plasma cell leukaemia		

* Hydration should be administered to maintain urine output > 100 ml/m^2/h. Suitable IV fluids are hypotonic or isotonic: 0.45% sodium chloride in 5% dextrose, or 0.9% sodium chloride. Oral hydration may be considered adequate.

Table 3: Prophylaxis based on risk stratification (Low risk)

Risk Category	Diagnosis	Contributing Risk Factor	Prophylaxis
Low	Indolent NHL		Oral hydration and close monitoring of fluid status. Electrolyte monitoring: every 12-24 hours. Low threshold for recourse to IV fluids and consideration of allopurinol.
	Adult anaplastic large cell lymphoma (ALCL)		
	Adult intermediate-grade NHL	LDH < 1 x ULN	
	Lymphoblastic lymphoma stage I/II	LDH < 2 x ULN	
	Hodgkin lymphoma (most patients)		
	AML	WCC < 25 x 10^9/L and LDH < 2 x ULN	
	CLL (most patients)	WCC < 50 x 10^9/L; treated only with alkylating agents	
	CML (most patients)		
	Multiple myeloma (in the absence of other risk factors)		
	Most solid tumours		

Abbreviations: ALL – acute lymphocytic leukaemia; AML – acute myeloid leukaemia; CLL – chronic lymphocytic leukaemia; CML – chronic myeloid leukaemia; DLBCL – diffuse large B-cell lymphoma; NHL – non Hodgkin's lymphoma; ULN – upper limit of normal.

5. Management of established TLS

The management of established TLS requires a multidisciplinary approach with involvement of haematologists, nephrologists and intensive care physicians.

Treatment of TLS addresses its primary metabolic disturbances: hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia. Treatment of laboratory abnormalities should be prioritised by treating life-threatening or potentially life-threatening issues first, followed by symptomatic electrolyte disorders. In general, asymptomatic electrolyte abnormalities should be monitored but not actively treated. See table 2, below.

Important:

- Do not add potassium to hydration fluids
- Intractable fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia are indications for renal dialysis
- Dialysis should be continued until adequate recovery of renal function, resolution of electrolyte imbalance and recovery of appropriate urine output
- Peritoneal dialysis is not recommended for TLS
- Do not alkalinise urine

Table 4: Treatment of electrolyte abnormalities

Electrolyte abnormality	Signs/Symptoms	Action
Hyperuricaemia Urate ≥ 476 µmol/L or 25% increase from baseline	Nausea, vomiting, lethargy, anorexia, haematuria, olig-/anuria	Give rasburicase unless contraindicated - EITHER 0.2mg/kg/day (3-7 days) - OR 6mg/day repeated as necessary *Dose as per local preference*. Use allopurinol only if rasburicase is contraindicated. Use febuxostat if both rasburicase and allopurinol contraindicated. Aggressive hydration: 3 L/m^2 every 24 hours. If hyperuricaemia persists or rasburicase contraindicated contact renal team urgently to discuss need for dialysis.
Hyperphosphataemia Phosphate ≥ 1.45 mmol/L or 25% increase from baseline	[indirect, due to hypocalcaemia]	Control with hydration and maintenance of high urine output. Uncontrolled hyperphosphataemia is an indication for dialysis. High phosphate levels are difficult to control other than by dialysis: Oral phosphate binders (e.g. aluminium hydroxide) are slow to act and poorly tolerated by ill patients. They should be seldom used except if patient is considered unfit for dialysis or as a temporary measure where immediate access to renal dialysis is not available.
Hypocalcaemia Adjusted Calcium ≤ 1.75 mmol/L or 25% decrease from baseline	Lengthening of QT interval on ECG (ventricular arrhythmias), muscle cramps, tetany, seizures	Continuous cardiac monitoring. No treatment unless symptomatic. If symptomatic give calcium gluconate 1g (10ml of 10% solution) by slow IV injection over 10 minutes under continuous ECG monitoring.*
Hyperkalaemia **Moderate:** Potassium 6.0-6.9 mmol/L or 25% increase from baseline	Cardiac arrhythmias	Continuous cardiac monitoring. Management as per local guidelines: Emergency Management of Hyperkalaemia in Adults.[5,6]
Severe: Potassium ≥ 7.0 mmol/L	Cardiac arrhythmias	Haemodialysis
Oliguria and fluid retention		Furosemide (IV) 0.5mg/kg or mannitol.

* Calcium gluconate will reverse the clinical effects of hypocalcaemia in the short term, but will further increase calcium phosphate deposition in the renal tubules, potentially worsening acute kidney injury

6. Important notes about medication

Refer to individual product Summary of Product Characteristics (SmPC) available from www.medicines.org.uk for detailed information.

Rasburicase must be avoided in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Allopurinol: oral xanthine oxidase inhibitor

- Dose adjustment in renal impairment:

GFR	Allopurinol dose
≥ 50 ml/min	300mg daily
20-50 ml/min	200-300 mg/day
10-20 ml/min	100-200 mg/day
< 10 ml/min	100mg daily or on alternate days
Dialysed	See Renal Handbook

- ADRs: Hypersensitivity reactions uncommon.
- Drug interactions: mercaptopurine, azathioprine, ciclosporin, thiazide diuretics

Febuxostat: oral (non-purine) xanthine oxidase inhibitor

- 120mg once daily to be started two days before chemotherapy
- Dose adjustment in renal impairment: efficacy and safety not fully evaluated in patients with severe renal impairment (CrCl < 30 ml/min). No dose adjustment in mild/moderate renal impairment.
- ADRs: rare serious allergic/hypersensitivity reactions
- Drug interactions: azathioprine, mercaptopurine

Rasburicase: exogenous recombinant urate oxidase

Rasburicase can cause severe oxidative haemolysis in patients with G6PD deficiency (including female carriers) and is contraindicated in this group. Testing for G6PD deficiency is recommended unless northern European caucasian origin as very low incidence in this ethnic group.

Such patients should be treated with fluids and allopurinol/febuxostat and monitored carefully.

- ADRs: Allergic reactions, commonly rashes and urticaria. Rare: Hypotension, bronchospasm, rhinitis, severe hypersensitivity including anaphylaxis.
- Where rasburicase is being used in the treatment or prophylaxis of TLS, the addition of allopurinol is unnecessary and has the potential to reduce the effectiveness of rasburicase.
- Urate assays taken whilst patients are receiving rasburicase must be sent to the laboratory on ice to prevent falsely low assay results.

Venetoclax: B-cell lymphoma (BCL)-2 inhibitor

Specific guidance for prevention of tumour lysis syndrome:

- Changes in electrolytes consistent with TLS that require prompt management can occur as early as 6-8 hours following the first dose and at each dose increase
- Risk is based on multiple factors. Risk is increased by high tumour burden (e.g. any lymph node with diameter ≥ 5cm or lymphocytes ≥ 25 x 10^9/L) and further increased by reduced renal function (CrCl < 80ml/min). Employ more intensive measures as overall risk increases
- Prophylaxis consists of hydration and anti-hyperuricaemic agents starting 2 days before treatment
- Pre- and post-dose blood chemistry assessment
- Correction of any pre-existing blood chemistry abnormalities before treatment
- Hospitalisation may be considered

7. References

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Revision Date	Previous Revision Date	Summary of Changes	Changes Marked
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		Additional sentence - Specialist centre for TLS in child.	**Page 3 – section 3**
		Additional paragraphs - Description of TLS and cornerstones of management	**Page 3 – section 3**
		Rewording	**Page 4 – section 4**
		Table changed to bullet points – Subsection Diagnosis.	**Page 4 – section 4**
		Additional paragraph - Management of established TLS. Subsection Diagnosis	**Page 4 – section 4**
		Rewording - Subsection Risk assessment and stratification	**Page 4 – section 4**
		PI3K inhibitors removed from table 1. Table reconfigured and relabelled – Subsection Risk assessment and stratification	**Page 5 – section 4**
		Pre-emptive treatment incorporated into Tables 1,2&3 (previously Table 2). Febuxostat added – Subsection Risk assessment and stratification	**Pages 5-6 – section 4**
		Changed to Management of established TLS.	**Page 6 – section 5**
		Original Section 5 Responsibilities deleted.	**Page 6**
		Table 3 renumbered, Signs/Symptoms column added, and reconfigured and placed in new Section 5	**Page 7 – section 5 (new)**
		Important notes about medication reworded - adaptation of original Section 6 Other useful information. Febuxostat added. Allopurinol dose simplified.	**Page 8 – section 6 (new)**
		Reference to oral phosphate binders moved to new Table 4	**Page 7**
		References updated	**Page 9 – section 7**

* Changes marked should detail the section(s) of the document that have been amended i.e. page number and section heading (If there is no previous document, insert N/A into the boxes in the top row of the table below)