GUIDELINE FOR MANAGEMENT AND PREVENTION OF ACUTE TUMOUR LYSIS SYNDROME IN HAEMATOLOGICAL MALIGNANCIES

This guidance does not override the individual responsibility of health professionals to make appropriate decision according to the circumstances of the individual patient in consultation with the patient and /or carer. Health care professionals must be prepared to justify any deviation from this guidance.

The purpose of this guideline is to predict and prevent adult patients with haematological malignancies from developing serious tumour lysis syndrome and to ensure that early recognition and management in a timely and efficient manner, to improve the outcome for these patients.

Patients with haematological malignancies who require treatment with chemotherapy are covered by this guideline.

This guideline is for use by the following staff groups :

Staff involved in the treatment of patients with haematological malignancies.

Lead Clinician(s)

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This is the most current document and should be used until a revised version is in place

Key amendments to this guideline

Date	Amendment	Approved by:
Oct 19	New document approved for 3 years at MSC	Medicines Safety Committee

Abbreviations:
TLS: Tumor Lysis Syndrome

ULN: Upper Limit of Normal
SCLC: Small cell Lung Cancer
CML: Chronic Myeloid Leukaemia
CLL: Chronic Lymphocytic Leukaemia
LN: Lymph node
ALC: Absolute lymphocyte count
SmPC: Summary of product characteristics
AML: Acute Myeloid Leukaemia
ALL: Acute Lymphoblastic Leukaemia
BC: Blast Crisis
SLL: Small Lymphocytic Lymphoma
MALT lymphoma: Lymphoma involving mucosa associated tissue
CTCL: Cutaneous T cell Lymphoma
ALCL: Anaplastic large Cell Lymphoma
ATLL: Adult T Cell leukaemia/Lymphoma
DLBCL: Diffuse Large B Cell Lymphoma
PTCL: Peripheral T Cell Lymphoma
LRD: Low Risk Disease
IRD: Intermediate Risk Disease
HRD: High Risk Disease
G6PD: Glucose 6 Phosphate Dehydrogenase deficiency
IV: Intravenous
BNF: British National Formulary
BCSH: British Committee for Standards in Haematology
HDU: High Dependency Unit
ITU: Intensive Care Unit
USS Ultrasound
CVP: Central venous pressure

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Introduction

Tumour Lysis Syndrome (TLS) is a life-threatening complication when rapid lysis of tumour cells leads to release of cellular contents into circulation, resulting in a metabolic disturbance characterised by hyperuricaemia, hyperphosphataemia, hyperkalaemia and hypocalcaemia, which may lead to uraemia and/ or acute oliguric renal failure, seizures, cardiac arrhythmias and sudden death. It occurs as a direct result of the action of chemotherapy for malignant disease, most commonly in the treatment of haematological malignancies. Therefore it is important to prevent it, and recognise and treat early to improve patient outcome.
Clinical TLS is rare, affecting 3-6% of all patients with high-grade malignancies. However, it can result in significant adverse outcomes. Therefore it is important to risk-stratify and identify those patients at high-risk of developing TLS and treat prophylactically. Furthermore, there should be prompt investigations to rule out TLS if the patient is deemed high-risk and treatment should be initiated as soon as possible to reduce the risk of a poor outcome.

Details of Guideline

1. Definition of Tumour Lysis Syndrome

1.1. Laboratory TLS

The presence of 2 or more of the following abnormalities in a patient with cancer or undergoing treatment for cancer within 3 days prior to and up to 7 days after initiation of treatment

Electrolytes	Levels
Uric acid*	>360µmol/l or 25% increase from baseline
Potassium	≥6.0mmol/l or 25% increase from baseline
Phosphate	≥1.5mmol/l or 25% increase from baseline
Albumin corrected calcium	≤1.75mmol/l or 25% decrease from baseline

*Not included if rasburicase has been administered within previous 24 hours

1.2. Clinical TLS

Laboratory TLS plus at least one of:

- Creatinine ≥1.5 x ULN
- Cardiac arrhythmia
- Seizure
- Sudden death

2. Prevention of TLS

2.1. Risk Assessment of TLS

TLS can develop rapidly and is difficult to treat once established. The key to management is to recognise those patients at risk and use prophylactic measures to prevent its occurrence.

2.1.1. Risk factors

- High tumour burden
- High grade tumour with rapid cell turnover
- Pre-existing renal impairment or renal involvement by tumour
- Increased age
- Treatment with highly active, cell-cycle specific agents
- Concomitant use of drugs that increase uric acid level – including alcohol, ascorbic acid, aspirin, caffeine, cisplatin, diazoxide, thiazide, diuretics, adrenaline(epinephrine), ethambutol, pyrazinamide, levodopa, methyldopa, nicotinic acid, phenothiazines and theophylline.

2.1.2. Risk Stratification (Table.1)

Disease subtype	Baseline Risk score	Upgrade if	Following are present
		Renal dysfunction or involvement	Raised urate, Potassium or Phosphate
Solid Tumour • Majority of cases • Bulky germ cell, neuroblastoma or SCLC	Low risk Intermediate	- **High**	- **High**
Myeloma	Low	-	-
CML Chronic Phase	Low	Intermediate*	Low
CLL • Alkylator alone • Targeted/Biological Rx • (treatment with venetoclax in CLL patients with LN size ≥5 cm, ALC≥25) (see venetoclax SmPC)	Low Intermediate **High**	Intermediate* **High** **High**	Low **High** **High**
AML/CML Myeloid BC • WBC <25 LDH<2 ULN • WBC <25 LDH≥2 ULN	Low Intermediate Intermediate	Intermediate* **High** **High**	Low **High** **High**

• WBC 25-100 • WBC ≥100	**High**	**High**	**High**
ALL or CML Lymphoid BC • WBC <100 LDH <2 ULN • WBC <100 LDH ≥2 ULN • WBC ≥100	Intermediate **High** **High**	**High** **High** **High**	**High** **High** **High**
Burkitt Lymphoma or Lymphoblastic lymphoma	**High**	**High**	**High**
Hodgkin, SLL, Follicular, marginal, MALT, Mantle(non-blastoid), CTCL	Low	Intermediate*	Low
ALCL (adult)	Low	Intermediate*	Low
ATLL, DLBCL, PTCL, Transformed disease, Mantle cell (Blastoid) • LDH ≤ ULN • LDH >ULN <2ULN Non-bulky • Bulky(>10cm) or LDH > 2 ULN	 Low Intermediate **High**	 Intermediate* **High** **High**	 Low **High** **High**

*Low risk disease (LRD) is upgraded to intermediate risk disease (IRD) if there is renal dysfunction or renal involvement, but not upgraded if uric acid/ potassium/phosphate are raised.

Intermediate disease (IRD) is upgraded to High Risk Disease (HRD) if there is either renal dysfunction or renal involvement, or any of following are raised: uric acid, potassium, phosphate.

2.2. Pre-treatment biochemical assessment and TLS screen

- Urea
- Creatinine
- Uric acid
- Phosphate
- Potassium
- Albumin
- Corrected Calcium
- LDH

- Consider baseline G6PD screen in an “at risk” patient.

2.3. Prevention – Management according to Risk

2.3.1. Prophylaxis recommendations (BCSH Guideline) (Table.2)

Low risk Disease	Intermediate Risk Disease	High Risk Disease
Monitoring	Monitoring	Monitoring
Hydration	Hydration	Hydration
±Allopurinol	Allopurinol	Rasburicase*

*Contraindicated in patients with a history consistent with G6PD deficiency. In these patients, rasburicase should be substituted with allopurinol.

- Patients due to receive chemotherapy for any haematological malignancy should have a risk assessment for TLS (Grade1B) and it should be documented in the notes.
- **Individual TLS prophylaxis plan should be documented in the notes.**

2.3.2. Low Risk patients

- Low risk patients can be managed with careful attention to the monitoring and measurement of fluid status and laboratory results with a low threshold for recourse to intravenous fluids and consideration of allopurinol if needed (Grade 2C).
- Patients considered to be at low risk of TLS should be started on allopurinol 300mg daily (reduce dose if impaired renal function- please see SmPC) prior to the start of treatment and can commence chemotherapy as an outpatient. They should be advised to drink plenty of fluids daily (3 litre per day) but no special monitoring is necessary.

2.3.3. Intermediate Risk patients

- Intermediate risk patients should be offered allopurinol prophylaxis along with increased hydration post-initiation of treatment or until risk of TLS has resolved. (Grade 2C)
- Patients considered to be at intermediate risk category should receive allopurinol 300mg daily (provided normal renal function/renal dose) with start of chemotherapy, along with hydration and monitoring.

2.3.4. High Risk patients

- High risk patients should be offered prophylaxis with rasburicase along with increased hydration (e.g. IV 0.9% sodium chloride 3 Litre/m^2/day to maintain urine output of 100ml/m^2/hr. Furosemide can be considered if urine output is inadequate), and monitoring of fluid balance and TLS blood tests (6 hr and 18 hr after 1st dose chemo, then 24 hourly if no evidence of TLS.
- Rasburicase should be avoided in patients with G6PD deficiency. Such patients should be treated with allopurinol and monitored carefully. (Grade 2C)

- Daily blood tests for TLS monitoring up to 3 to 5 days to monitor signs of clinical and biochemical TLS. Follow guideline for treatment of TLS if established TLS develop.
- Urate assay, taken whilst patients are on rasburicase, must be sent to the laboratory on ice to prevent falsely low assay results. (Grade 1B)
- In high risk adults, in the absence of established clinical or laboratory TLS, TLS can be prevented in the majority of patients using a single fixed dose of 3 mg rasburicase but this must be followed by carefully monitoring of clinical and biochemical parameters with repeat dosing (up to 3 to 7 days) if required. Alternatively rasburicase up to 0.2mg/Kg /day (BNF and SmPC indicated dosage for both prophylaxis and treatment of TLS) can be considered in individual setting in prevention of TLS in high risk patients.
- 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. (Grade 2C)
- Urinary alkalinisation is not recommended in TLS prophylaxis. (Grade 1C)

2.3.5. Rasburicase

Rasburicase is a recombinant form of Urate oxidase, an enzyme present in most living organisms but not humans. This catalyses the oxidation of uric acid to allantoin, which is at least 5 times more soluble than uric acid and is more easily excreted in the urine.

Allopurinol blocks the conversion of xanthines to uric acid, so this will reduce the effect of rasburicase; therefore **DO NOT** give allopurinol and rasburicase together.

It is used in prevention or treatment of TLS (see risk assessment). It is also considered in patients with high urate and unable to tolerate aggressive hydration.

2.3.5.1. Protocol for use:

- Ensure patient is G6PD negative prior to the use (if positive, use aggressive hydration with allopurinol).
- It is contraindicated in G6PD deficiency patients.
- Dose: 0.2mg/Kg/day in 50ml 0.9% sodium chloride over 30 minutes for prevention and treatment of TLS (BNF and SmPC). However 3mg single dose and review and repeat if necessary for first 3-7 days of chemotherapy is recommended by BCSH guideline.

3. Treatment of TLS ± Clinical TLS

- Multidisciplinary approach with involvement with Haematologist, nephrologist and intensive care physicians. Intensive care/high dependency facility or haematology centre offering higher level of care as defined by BCSH should be considered. (Grade 1C)
- All patients should receive aggressive intravenous hydration 0.9% sodium chloride (or alternate with 5% glucose) 3 litre/m^2/day.

- Potassium must NOT be added to the hydration fluid. (Grade 1A)
- Urinary alkalinisation is NOT recommended in the treatment of TLS. (Grade 1C)
- A urinary catheter should be passed with careful monitoring of fluid balance and urine output to maintain 100ml/m^2/hr.
- Allopurinol is NOT the drug of choice in established TLS except in the presence of G6PD deficiency or allergic to rasburicase.
- In absence of contraindication, rasburicase at a dose of 0.2 mg/Kg/day as a 30 min infusion in 50ml 0.9% sodium chloride, should be given if patient has not already received it, or repeated again if a repeat sample (must be sent on ice) shows a measurable uric acid level above 12mmol/l. The duration of treatment should be determined by the clinical response. (Grade 1B)
- An ECG should be performed.
- Blood monitoring of U&Es, corrected calcium, phosphate, and urate should be every 2 – 6 hrs depending on the severity.
- Asymptomatic hypocalcaemia should not be treated. (Grade 2C)
- Symptomatic hypocalcaemia should be treated with a short infusion of calcium gluconate at a dose applicable to the age/weight of the patient and close monitoring of calcium levels, phosphate levels, and renal function. (Grade 1C)
- Patients with potassium level ≥6mmol/l or having experienced a 25% increase in potassium level from the baseline should have cardiac monitoring. (Grade 2C)
- Intractable fluid overload, hyperkalaemia, hyperuricaemia, hyperphosphataemia or hypocalcaemia are indications for renal dialysis. (Grade 1A)
- Peritoneal dialysis is not recommended for the treatment of TLS. (Grade 1C)
- Dialysis should continue there is adequate recovery of renal function, resolution of severe electrolyte imbalance and recovery of urine output. (Grade 1A)

3.1. Hyperphosphataemia

- A level of >1.5mmol/l in adult is abnormal.
- May lead to nausea, vomiting, diarrhoea, lethargy, fits and precipitation of calcium phosphate
- IV and oral calcium supplements should be avoided.
- Levels>2.1mmol/l may be treated with oral chelation using a phosphate binder. This is slow to act and poorly tolerated and so should not be routinely used. (eg. Aluminium hydroxide oral 50-150 mg/kg/day in 4 divided doses)
- Levels >4mmol/l will usually require more aggressive therapy usually with haemodialysis or haemofiltration and must be discussed urgently with the renal team.

3.2. Hypocalcaemia

- If asymptomatic then this should not be treated but it will correct as other abnormalities improve.

- If <1.75mmol/l and symptomatic with severe tetany, seizures or prolonged QT interval on ECG then 10mL of 10% calcium *gluconate IV* (2.2mmol) by slow IV injection ***over 5 minutes*** can be given peripherally. (Risk of nephrocalcinosis)

3.3. Hyperkalaemia

- If >6mmol/l but <7mmol/l in an asymptomatic patient, initiate ECG monitoring.
- Exclude IV potassium from IV fluid.
- Follow Trust Guideline "Emergency Management Of Hyperkalaemia Quick Reference Guide for management of the patient"
- Patient should be monitored on HDU/ITU.
- Haemodialysis should be discussed with renal team/ITU.

3.4. Poor urine output

- IV Furosemide 2-4 mg/kg should be given and discuss with the renal team.
- CVP monitoring may be required.
- If the patient has intra-abdominal nodal disease then USS should be performed to exclude hydronephrosis.
- Haemodialysis or hemofiltration should be considered for volume overload, uncontrolled acidosis or other metabolic disturbances. It should be discussed with ITU and renal team.

Monitoring Tool

Page/ Section of Key Document	Key control:	Checks to be carried out to confirm compliance with the policy:	How often the check will be carried out:	Responsible for carrying out the check:	Results of check reported to: *(Responsible for also ensuring actions are developed to address any areas of non-compliance)*	Frequency of reporting:
	WHAT?	**HOW?**	**WHEN?**	**WHO?**	**WHERE?**	**WHEN?**
	Patients with haematological malignancy treated with chemotherapy that received rasburicase should have had a risk assessment for TLS completed.	Audit, spot-checks, analysis of incident trends, monitoring of attendance at training.)	2021	Staff involved in the treatment of patients with haematological malignancies.	Audit present in Haematology Journal Club	2021
	High risk adults should be offered prophylaxis with a single 3-mg dose of rasburicase along with increased hydration (exception- full dose as per BNF for certain individual high risk patients)	Audit				
	No patients should undergo urinary alkalinisation for TLS prophylaxis	Audit				
	For patients receiving rasburicase: Any urate assays taken whilst the patient was receiving it should be sent to the laboratory on ICE.	Audit				
	No patient with established TLS	Audit				

	should have hydration fluid with added potassium.					
	Patients with established TLS should be given rasburicase at a dose of 0.2 mg/kg/day, unless it is contraindicated.	Audit				
	Rasburicase treatment should be continued until the TLS has resolved.	Audit				
	All patients with established TLS and intractable fluid overload, hyperkalaemia, hyperphosphataemia or hypocalcaemia should have renal dialysis considered.	Audit				
	No patients with TLS should be treated with peritoneal dialysis.	Audit				

References

1. Jones, G.L., Will, A., Jackson, G.H., Webb, N.J.A. & Rule, S. (2015) Guideline 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, 169, 661-671.
2. Cairo, M.S., Coiffier, B.,Reiter, A. & Younes, A. (2010) 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. British Journal of haematology, 149, 578-586.
3. Cairo, M.S. & Bishop, M. (2004) Tumour lysis syndrome: new therapeutic strategies and classification. British Journal of Haematology, 127, 3-11.
4. British National Formulary September 2017- March 2018.
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7. Venetoclax SmPC - https://www.medicines.org.uk/emc/product/2267#POSOLOGY 14/01/2019
8. Guideline for Management of Tumour Lysis Syndrome: London Cancer North and East 2015.
9. Allopurinol SmPC - https://www.medicines.org.uk/emc/product/7487/smpc 14/01/2019
10. Worcestershire acute nhs trust hyperkalaemia guideline http://www.treatmentpathways.worcsacute.nhs.uk/medicine/renal/emergeny-management-of-hyperkalaemia/

Contribution List

This key document has been circulated to the following individuals for consultation;

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This key document has been circulated to the chair(s) of the following committee's / groups for comments;

Committee
Haematology Governance Meeting
Medicines Safety Committee

Supporting Document 1 - Equality Impact Assessment Tool

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

		Yes/No	Comments
1.	**Does the policy/guidance affect one group less or more favourably than another on the basis of:**	No	
	• Race	No	
	• Ethnic origins (including gypsies and travellers)	No	
	• Nationality	No	
	• Gender	No	
	• Culture	No	
	• Religion or belief	No	
	• Sexual orientation including lesbian, gay and bisexual people	No	
	• Age	No	
2.	**Is there any evidence that some groups are affected differently?**	No	
3.	**If you have identified potential discrimination, are any exceptions valid, legal and/or justifiable?**	No	
4.	**Is the impact of the policy/guidance likely to be negative?**	No	
5.	**If so can the impact be avoided?**	No	
6.	**What alternatives are there to achieving the policy/guidance without the impact?**	No	
7.	**Can we reduce the impact by taking different action?**	No	

If you have identified a potential discriminatory impact of this key document, please refer it to Human Resources, together with any suggestions as to the action required to avoid/reduce this impact.

For advice in respect of answering the above questions, please contact Human Resources.

Supporting Document 2 – Financial Impact Assessment

To be completed by the key document author and attached to key document when submitted to the appropriate committee for consideration and approval.

	Title of document:	Yes/No
1.	Does the implementation of this document require any additional Capital resources	No
2.	Does the implementation of this document require additional revenue	No
3.	Does the implementation of this document require additional manpower	No
4.	Does the implementation of this document release any manpower costs through a change in practice	No
5.	Are there additional staff training costs associated with implementing this document which cannot be delivered through current training programmes or allocated training times for staff	No
	Other comments:	No

If the response to any of the above is yes, please complete a business case and which is signed by your Finance Manager and Directorate Manager for consideration by the Accountable Director before progressing to the relevant committee for approval.