1.0 Introduction

For the purposes of this guideline, tumour lysis syndrome (TLS) is defined as metabolic derangement resulting from abrupt and massive breakdown of malignant cells and the release of intracellular contents into the circulation which overwhelms the patient’s excretory ability. Both laboratory and clinical TLS have been described. Laboratory TLS results in high serum urate, potassium, phosphate and/or low calcium concentrations and rarely leads to clinical TLS (renal insufficiency and/or increased serum creatinine concentration, cardiac arrhythmia or seizure).

Identification of patients at risk of developing TLS and prompt initiation of preventative interventions are critical to avoiding clinical TLS. This guideline outlines the recommended standard of care for the prevention of TLS at The Hospital for Sick Children.

2.0 Abbreviations

Tumour lysis syndrome: TLS
White blood cell: WBC
Lactate dehydrogenase: LDH
Acute Myelogenous Leukemia: AML
Acute Lymphoblastic Leukemia: ALL
Anaplastic large-cell lymphoma: ALCL
Glucose-6-Phosphate Dehydrogenase: G6PD

3.0 Clinical Practice Recommendation

3.1 Patients at risk of tumour lysis syndrome

- Patients at **high risk** of developing TLS include:
  - newly diagnosed/relapsed with Burkitt’s lymphoma
  - newly diagnosed with lymphoblastic lymphoma with advanced or bulky disease
  - newly diagnosed patients with leukemia
    - a WBC count greater than or equal to $100 \times 10^9/L$ and/or LDH greater than 2 x ULN
    - serum urate concentrations greater than 475 µmol/L OR
    - pre-existing renal impairment

- Patients at **intermediate risk** of developing TLS include:
  - ALL patients with WBC less than $100 \times 10^9/L$ and LDH less than 2 x ULN
  - AML patients with WBC 25 to $100 \times 10^9/L$
  - AML patients with WBC less than $25 \times 10^9/L$ and LDH greater than 2 x ULN
  - Highly chemotherapy sensitive solid tumours (e.g. neuroblastoma, germ cell tumour) with advanced or bulky disease
  - ALCL

- Patients at **low risk** of developing TLS include:
### Guidelines for the Prevention of Tumour Lysis Syndrome

- diagnosed with:
  - most solid tumours
  - haematological malignancies with a low proliferative rate (e.g. CML in chronic phase, Hodgkin lymphoma) who present with:
    - a normal serum urate concentration (less than or equal to 360 µmol/L)
    - WBC less than $25 \times 10^9/L$
    - no clinical evidence of significant tumour burden (e.g. no mediastinal mass, no hepatosplenomegaly)
    - no pre-existing renal impairment

Other factors which may be associated with an increased risk of developing TLS include:

- dehydration

### 3.2 Laboratory Investigations

Serum creatinine, urea, urate, potassium, sodium, phosphate, calcium, albumin, LDH concentrations and a WBC count with differential should be determined whenever a diagnosis of a malignancy is suspected. If albumin is low, consider the need to determine serum ionized calcium concentrations.

With the exception of LDH, it is recommended that these tests be repeated q8 to 12h or less frequently if clinically stable (patients at low or intermediate risk of TLS) or q4 to 6h (patients at higher risk of TLS) until antineoplastic therapy is initiated and for at least 3 days thereafter. Bloodwork frequency may be reduced over this time as clinically permissible. LDH need only be determined once at presentation.

### 3.3 Strategies aimed at preventing TLS

Preventive strategies are aimed at minimizing laboratory TLS and preventing clinical TLS. These strategies should be continued until antineoplastic therapy has reduced the patient’s tumour burden and serum creatinine and urate are stable. A period of three to five days following administration of initial antineoplastic therapy is usually required.

#### Hydration

All patients newly diagnosed or relapsed with a malignancy that entails a risk of TLS other than those who present in acute renal failure or with oliguria should:

- receive IV hydration with 0.9% sodium chloride at 3 L/m$^2$/day (or 200 mL/kg/day if child is less than or equal to 10kg). Monitoring of serum sodium concentration (along with tumor lysis laboratory monitoring) is recommended to avoid hyper/hyponatremia, especially in the setting of impaired urine output
- receive furosemide or mannitol to maintain a urine output of at least 80% of total fluid intake every four hours (i.e. at least 2.4 L/m$^2$/day or 160 mL/kg/day if child is less than or equal to 10kg); diuretics should not be given if contraindicated (e.g. in the presence of hypovolemia)
- not receive potassium, calcium or phosphate in hydration fluids, at least initially
- have their weight assessed daily

Hydration should begin as soon as a risk of TLS is suspected, ideally, 24 to 48 hours prior to administration of antineoplastic therapy.

#### Alkalization is not recommended nor required.

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Allopurinol Prevents the metabolism of xanthine and hypoxanthine to uric acid by competitively inhibiting xanthine oxidase. Though allopurinol effectively prevents serum urate concentrations from increasing and decreases the incidence of uric acid nephropathy, it does not reduce the uric acid that is already present prior to administration of the drug. In addition, allopurinol results in increased concentrations of xanthine and hypoxanthine which in turn increases the risk of the precipitation of these 2 compounds, especially at higher pH.

Administration of allopurinol in doses provided in the SickKids' Drug Handbook and Formulary should be considered in patients at low risk of TLS if there are signs of metabolic changes and it is recommended for children at intermediate risk of developing TLS. Allopurinol should be continued for at least 72 hours after the initiation of antineoplastic therapy and discontinued only when serum urate concentrations are within normal limits and stable.

Rasburicase Rasburicase is a recombinant form of urate oxidase and catalyzes the conversion of uric acid into allantoin, a very soluble substance that is readily excreted in the urine. Unlike allopurinol, rasburicase will reduce pre-existing uric acid. Serum urate concentrations have been shown to decrease more rapidly after rasburicase than after allopurinol administration. Due to its high cost, rasburicase is a restricted drug at Sick Kids.

Administration of rasburicase is recommended for children who meet one or more of the following criteria below:

- who are at high risk of developing TLS
- exhibiting signs of clinical or progressive laboratory tumour lysis syndrome
- newly diagnosed/relapsed with leukemia or lymphoma who cannot take oral medications for physiological reasons e.g. intractable vomiting, impaired gastrointestinal absorption
- newly diagnosed/relapsed with leukemia or lymphoma who present with significant renal impairment (serum creatinine equal to or greater than 1.5 times the upper limit of normal for age); and
- who have developed allergic reactions to allopurinol.

Rasburicase is contraindicated in patients with G6PD deficiency. If the G6PD status of the patient is unknown, send blood for G6PD assay before giving the first dose. Notify the laboratory (ext 204202) of the need for a rapid result. Note: at present, assay is run during the day on Tuesdays through Fridays.

One dose of rasburicase may be administered prior to receipt of the G6PD assay result. However, the patient/family must be informed of the relative risks and the patient must be monitored for signs of hemolysis and continued therapy must be reevaluated once the patient's G6PD status is known.

Rasburicase must be prescribed only after consultation with a staff haematologist/oncologist. Although the manufacturer’s recommended dosing of rasburicase in paediatrics is 0.2 mg/kg/dose for 5 days, a single dose of rasburicase is often sufficient. Therefore, rasburicase should not be given for longer than 3 days.
There is literature to suggest that doses lower than the weight-based guideline are sufficient to treat patients at high risk of TLS. As a result, in addition to cost considerations, centres have instituted dose capitation for this drug. Therefore, rasburicase should be ordered as an individual dose at 0.2 mg/kg of ideal body weight to a maximum dose of 6 mg. The need for subsequent doses should be evaluated every 24 hours. Enhancement of either the rapidity or the extent of decline in serum urate concentration by giving rasburicase more frequently than q24h has not been demonstrated. Second or subsequent rasburicase doses should not be given if the serum urate concentration is within normal limits.

Once antineoplastic therapy has been initiated and the patient's serum urate concentration has reached normal levels and has remained stable for at least 24 hours, rasburicase should be discontinued. It is safe to resume allopurinol administration in patients who are able to take oral medications and who may benefit from ongoing TLS prophylaxis.

For at least 96 hours following administration of rasburicase, blood samples for determination of urate concentration must be sent to the lab on ice. The urate concentration of samples sent at room temperature will be reported as lower than actual.

Note that antibodies to rasburicase are known to develop. All patients receiving this agent should be monitored for signs and symptoms of an allergic response. Patients who are re-treated with rasburicase following a relapse may be at increased risk of developing hypersensitivity reactions.

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<tr>
<td>Rasburicase</td>
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*note that patients initially managed with rasburicase may subsequently be given allopurinol for ongoing TLS prevention

### 4.0 Implementation

**Facilitators to implementation**

These guidelines have been incorporated into the Kidcare TLS prevention and leukemia induction order sets.

**Key review criteria/indicators for monitoring and audit purposes:**

Incident reports and cases brought to Morbidity & Mortality rounds will serve as cues to conduct a thorough retrospective or prospective audit of the performance of this guideline.
5.0 Related Documents

See Clinical Practice Guideline "Management of children with children with acute leukemia and an elevated white cell count at diagnosis (hyperleucocytosis)".

6.0 References

Guidelines for the Prevention of Tumour Lysis Syndrome


7.0 Guideline Group and Reviewers


Revised by: L. Dupuis, T. Truong, O. Abla, A.M. Maloney, J. Hitzler, R. Grant (January 2010); J. Drynan-Arsenault, O.Abla, A. Koo (May 2016)

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Attachments:

Revision History.docx