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APPHON/ROHPPA supportive care guidelines are developed by Atlantic Provinces health professional specialists using evidence-based or best practice references. Format and content of the guidelines will change as they are reviewed and revised on a periodic basis. Care has been taken to ensure accuracy of the information. However, any physician or health professional using these guidelines will be responsible for verifying doses and administering medications and care according to their own institutional formularies and policies and acceptable standards of care.

Clinical Practice Guidelines for the Management of Tumor Lysis Syndrome

The objective of this guideline:
1. To facilitate the care of patients at risk for tumor lysis syndrome.
2. To increase recognition of potential signs and symptoms of tumor lysis syndrome.
3. To provide information about interventions to decrease the risk of tumor lysis syndrome.
4. To provide information about interventions to treat tumor lysis syndrome and the metabolic effects of tumor lysis syndrome.

The clinical questions addressed in this guideline are:
1. Who are the patients at highest risk of developing tumor lysis syndrome.
2. What interventions can decrease the risk or consequences of tumor lysis syndrome.
3. What interventions can treat tumor lysis syndrome.

These guidelines apply to all newly diagnosed or relapsed pediatric oncology patients. For patients identified as at risk, the guideline provides relevant information.

Target users of these guidelines are all health professionals within the Atlantic Provinces caring for children and youth at risk for tumor lysis syndrome.

Information for this guideline was obtained from sources obtained through the Children's Oncology Group and from a Medline search of "tumor lysis," "tumor lysis syndrome," "rasburicase" [published in English language], as well as secondary references from the literature reviewed. Preference was given to information obtained from randomized controlled trials where available and where not, best practice information was used to determine the intervention recommendations contained in this guideline. Congruence with the Children's Oncology Group

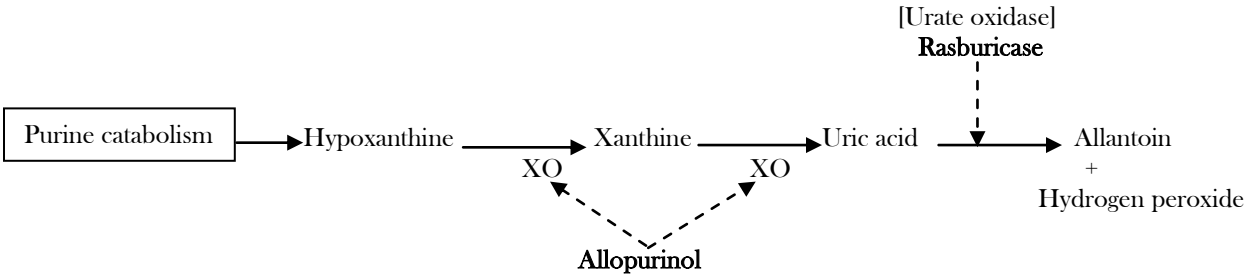
guidelines in Supportive Care of Children with Cancer, ed Altman, 2004 was maintained unless evidence to the contrary was available.

Background

Tumor lysis syndrome (TLS) is a significant complication associated with initial chemotherapy for various subtypes of lymphomas and leukemias and other tumors with a high growth fraction. The incidence of TLS was 6% in a trial of 788 patients with non-Hodgkin lymphoma (NHL) or acute lymphoblastic leukemia (ALL) and of these patients 37% died of TLS (Del Toro, 2005). TLS results from the release of intracellular metabolites including, potassium, uric acid and phosphate. This can lead to severe metabolic abnormalities that include hyperuricemia, hyperphosphatemia, hypocalcemia and hyperkalemia. The most likely cause of death from TLS is hyperkalemia. Arrhythmia may be aggravated by hypocalcemia. Acute renal failure can occur from precipitation of uric acid within renal tubules and/or due to renal involvement from the underlying malignancy. Cancers, particularly hematopoietic tumors, with a high growth fraction and high sensitivity to chemotherapy are more frequently associated with TLS, especially when patients present with a high tumor burden. Early identification of high-risk patients with pre-existing hyperuricemia and/ or hyperphosphatemia is critical for the implementation of prophylactic measures to prevent TLS.

Increased production of uric acid by tumor cell lysis results in precipitation of uric acid in the acidic environment of the renal tubules and collecting ducts. Uric acid can cause glomerular and tubular cell toxicity by endothelial dysfunction, oxidant stress, cell disruption, platelet activation and induction of inflammatory cytokines [Lamiere, 2005]. Lactic acidosis secondary to leukostasis may increase uric acid precipitation. Phosphate released during tumor lysis can lead to precipitation with calcium, and so to hypocalcemia. When the calcium-phosphate product exceeds 6 $mmol^2/L^2$, calcium-phosphate complexes precipitate in the microvasculature especially in an alkaline environment and can lead to renal failure. Potassium is also released with tumor lysis. Renal failure will potentiate hyperkalemia. The risk of renal failure is increased by dehydration, acidic urine and decreased urinary flow.

Usually, children receive allopurinol, IV hydration and urine alkalinization to prevent or treat TLS. Allopurinol is metabolized in the liver to its active derivative oxypurinol and prevents the formation of uric acid by inhibiting the enzyme xanthine oxidase. However, allopurinol does not decrease previously formed uric acid and can increase the uric acid precursors xanthine and hypoxanthine. Increased xanthine and hypoxanthine can lead to nephropathy because of their reduced solubility in alkaline pH environments [Yim et al, 2003]. Whereas the half-life for allopurinol is about 1.5 hours, that of oxypurinol is 18-40 hours [Pea, 2005]. The dose of allopurinol should be adjusted in the presence of renal failure as oxypurinol is excreted through the kidney.



In contrast, urate oxidase catalyzes the enzymatic oxidation of uric acid and converts uric acid into allantoin. Allantoin is about 5-10 times more soluble than uric acid, thus readily excreted in the urine. However, the production of allantoin is accompanied by the production of hydrogen peroxide and thus the drug is contraindicated in patients with G6PD deficiency. Although other mammals naturally produce urate oxidase, humans do not. A non-recombinant aspergillus-derived urate oxidase was used effectively in Europe over the past 20 years in patients with TLS. However, this non-recombinant urate oxidase was associated with dose limiting allergic reactions and is not available in Canada. A recombinant form of urate oxidase (rasburicase) has been approved by the FDA and Health Canada for the initial management of plasma uric acid levels in pediatric patients greater than one month of age with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy. In a randomized controlled trial of rasburicase versus oral allopurinol, both allopurinol and rasburicase were effective in reducing uric acid levels in children with hematological malignancies at risk for TLS [Goldman, 2001]. At a dose of 0.15 mg/kg, the half-life is approximately 16-17.4 hours, at a dose of 0.2 mg/kg, the half-life is 21.1 hours [Yim, 2003]. An effect on the uric acid level is normally seen within 4 hours. Rasburicase alters creatinine or phosphate levels only indirectly [Pui, 2001a][Shin, 2005]. Alkalinization of the urine is not required with rasburicase, thus decreasing the risk of calcium-phosphate crystal precipitation in the renal tubules [Lameire, 2005]. Because rasburicase is degraded by hydrolysis, the clearance of rasburicase is not dependent on renal or hepatic function [Ueng, 2005].

Patients at Risk for Tumor Lysis Syndrome

- Patients with diseases that exhibit a high proliferation rate, a high tumor growth fraction and are highly sensitive to cytotoxic therapy, particularly
- Patients who present with uric acid levels > 480 μmol/L or > 25 % increase from baseline (prior to starting chemotherapy) (IWK reference values; girls: 103-315 μmol/L, boys < 10 yrs: 103-315 μmol/L, boys ≥ 10 yrs: 238-435 μmol/L);
- Patients with ALL, AML and NHL are at risk for TLS, especially: patients with T-Cell Leukemia, Burkitt's and other B-Cell Non Hodgkin Lymphomas, a significantly elevated WBC > 50 x 10^9 /L, elevated phosphate and/or LDH greater than 2x institutional upper limits, are at a higher risk for developing TLS;
- Patients who are dehydrated at presentation have an increased risk;
- Patients who have evidence of renal involvement on ultrasound or CT scan before treatment may be more likely to develop TLS after chemotherapy [Alavi, 2006];
- Children with other solid tumors are at much lower risk [Baeksgaard, Soreneson, 2003]. TLS has been rarely but occasionally described in metastatic rhabdomyosarcoma and neuroblastoma.

Signs and Symptoms associated with Tumor Lysis Syndrome [Davidson et al, 2004]

- The most dangerous feature of tumor lysis syndrome is **hyperkalemia**: [develops about 6-72 hours after starting chemotherapy]
- Neuromuscular - weakness, parasthesias, areflexia, ascending paralysis, muscle cramps, respiratory failure, confusion, apathy
- **Cardiac** - bradycardia, asystole, heart block; ECG-peaked/tented T waves, ST segment depression, first degree AV block, QRS widening, short QT interval, loss of p wave
- Nausea, abdominal cramping, diarrhea

Hyperphosphatemia: [develops about 24-48 hours after starting chemotherapy]

- Can induce hypocalcemia
- Muscle cramps
- Arrhythmias
- Seizures
- Ectopic calcifications

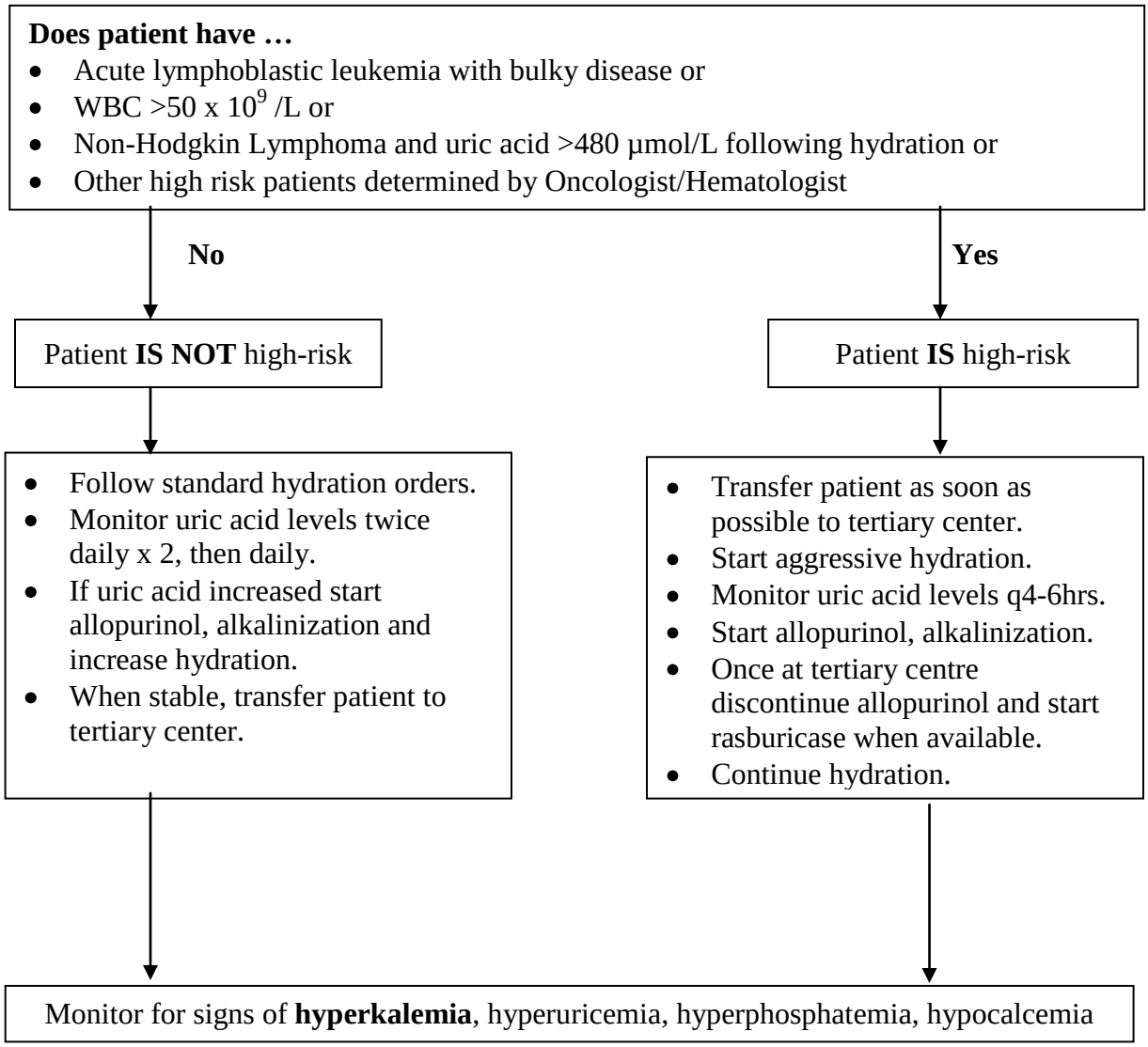
Hypocalcemia: [develops about 24-48 hours after starting chemotherapy]

- Slowed ventricular repolarization, prolonged QT interval, decreased or inverted T wave
- Ventricular arrhythmias, 2:1 heart block, cardiac arrest; hypotension
- Can potentiate the arrhythmias caused by hyperkalemia
- Tetany, numbness, tingling, muscle cramps, grimacing, convulsions, delirium, confusion
- Abdominal spasms and cramps
- Hyperactive reflexes, carpopedal spasm
- Laryngospasm
- + Chvostek (tap with reflex hammer anterior to earlobe, just below the zygomatic arch gives pursing of lips), + Trousseau (carpal spasm with blood pressure cuff at pressure > systolic pressure)

Hyperuricemia: [develops about 48-72 hours after starting chemotherapy]

- Nausea, vomiting, diarrhea, anorexia
- Flank pain, anuria, oliguria, cloudy urine, sediment in urine
- Acute joint pain

Prevention and Treatment of Tumor Lysis Syndrome for Community/Regional and Tertiary Centres



Prevention of Tumor Lysis Syndrome

- Evaluate for symptoms of renal failure, hyperkalemia, hypocalcemia;
- Serum creatinine, BUN, sodium, potassium, calcium, phosphate, uric acid, blood gas; every 4-6 hours during risk period;
- Urine specific gravity, pH per void; consider urinary catheterization;
- Twice daily weight during initial induction treatment;
- Vital signs every 4 hours;
- Baseline LDH;
- Cardiac monitor if clinically indicated (K+ >5.5 mmol/L);
- Aggressive hydration with 3000 mL/m^2/day (125 mL/m^2/hr) (or 200 mL/kg/day if <10 kg) of D5W+ 0.45%NaCl (no potassium) to attain and maintain a urine output of $\geq$100 mL/m^2/hr and maintain urine specific gravity of <1.010 prior to the start of chemotherapy. Caution: excess hydration without correction of severe anemia may result in severe dilutional anemia;
- Correct metabolic acidosis if present. For example if bicarbonate low (critical value <10 mmol/L) give bicarbonate;
- If plasma oncotic pressure low due to decreased protein, give albumin;
- Maintain urine output of $\geq$100 mL/m^2/hr once chemotherapy initiated;
- Abdominal ultrasound warranted in any patient with renal failure and in patients with B-NHL/B-ALL to assess renal parenchymal infiltration;
- Chest x-ray including PA and lateral to assess for mediastinal mass;
- Consider urinary alkalinization if utilizing allopurinol and maintain urine pH 6.5-7.5 prior to start of chemotherapy. If increased phosphate or serum bicarbonate >30 mEq/L or uric acid level controlled consider discontinuation of alkalizination;
- Strict attention to fluid balance, maintain even Input and Output, recheck balance at least every 6 hours during treatment induction;
- Administer furosemide (0.5-1 mg/kg/dose, maximum 40 mg) or mannitol (0.5 gm/kg/dose, maximum 20 gm) to increase urine output if needed. Mannitol is contraindicated if oliguria present (urine output <0.5 mL/kg/hr); do renal ultrasound to ensure no renal obstruction;
- A minimum of a daily physical exam for signs of dyspnea, rales, wheezing, cardiac arrhythmias, edema, ascites, neuromuscular changes and gastrointestinal complaints;
- Aim to establish metabolic stability prior to the start of cytotoxic therapy;
- Minimize exogenous potassium or phosphorous intake;
- Avoid IV contrast and nephrotoxic medications when possible;
- For elevated WBC (>200,000/mm^3; or >200 x 10^9/L) and multiple metabolic abnormalities, leukopheresis or exchange transfusion may be considered;
- For persistent oliguria and diffusely enlarged kidneys low dose renal radiation may be considered;
- Consider placing dialysis compatible catheter as initial central line and/or ICU admission for those at very high risk for TLS - those already in partial renal failure and/or Burkitt's or T-cell ALL with high tumor burden;
- For worsening TLS and development of acute renal failure despite maximal medical and nursing intervention, hemofiltration or dialysis may be warranted;
- Provide patient and family with the necessary information and support.

Treatment

Hyperuricemia: begin 24-48 hours prior to start of cytoreductive therapy;

- Vigorous hydration - 3000 mL/m^2/day (125 mL/m^2/hr)(or 200 mL/kg/day if <10 kg) of D5W+0.45%NaCl - Caution: excess hydration without correction of severe anemia may result in severe dilutional anemia;
- Forced diuresis with furosemide if necessary;
- Alkalinization (avoid over alkalinization as may lead to hypocalcemia by shifting ionized calcium to non-ionized form and to calcium-phosphate crystalluria and precipitation of hypoxanthine). Aim to maintain urine pH between 6.5-7.5 with $NaHCO_3$ 120 mEq/m^2/ day IV to increase solubility of uric acid (0.2% NaCl + 40 mEq $NaHCO_3$ /L). Discontinue alkalinization as soon as uric acid controlled or in the presence of an increased phosphate. Decrease or discontinue if serum bicarb > 30 mEq/L. Alkalinization is not necessary if the child is receiving rasburicase;
- Start allopurinol or rasburicase.

Recommended guidelines for the use of allopurinol:

- Start alkalinization as described above;
- a) Allopurinol PO (10 mg/kg/day or 200-300 mg/m^2/day divided BID-QID; maximum 300 mg/dose or 800 mg/day);

  or
- b) If patient unable to tolerate allopurinol PO may give allopurinol IV over 30-60 minutes (200 mg/m^2/day in 1-3 divided doses; maximum dose of 600 mg/day). Available through the Health Canada Special Access Program.
- It is recommended that chemotherapy not be started in patients with hyperuricemia for at least 1-2 days after allopurinol therapy is initiated to allow uric acid to be excreted (Cheson, 2005). Allopurinol should be cautiously used in patients with impaired renal function because it may lead to increased uric acid load in the kidney without it being excreted and it may lead to poorly soluble xanthine in the kidney, which is less soluble than uric acid. Occasional cases of xanthine nephropathy and calculi have been reported (Lameire, 2005).
- 6-mercaptopurine's oral bioavailability is increased by allopurinol (6-mercaptopurine dose should be reduced by 75%);
- Azathiopurine is converted to mercaptopurine and the dose of azathiopurine should be reduced by 66%;
- Cyclosporin levels may be increased by allopurinol and so therapeutic drug monitoring of cyclosporin is advised;
- Aluminum hydroxide may interfere with the absorption of allopurinol, so that allopurinol administration should be spaced by at least 1 hour before or 2 hours after aluminum containing antacids;
- Theophylline concentrations may be increased by allopurinol;
- Warfarin metabolism may be decreased by allopurinol resulting in as increased anti-coagulation. Prothrombin time should be monitored;
- It has been hypothesized that bone marrow suppression might be aggravated by using allopurinol in combination even with other immunosuppressive agents which may interfere with purine biosynthesis, namely mycophenolate mophetil, so their coadministration should be avoided [Pea, 2005]. Of concern, the incidence of renal

failure with allopurinol prophylaxis and treatment in high-risk patients with stage IV Burkitt's lymphoma/B-cell leukemia has historically approached 25% [Bowman, 1996].

Allopurinol IV infusion:

- Allopurinol IV over 30-60 minutes (200 mg/m^2/day in 1-3 divided doses; maximum dose of 600 mg/day). Dilute with D5W or 0.9% NaCl to a final concentration not to exceed 6 mg/mL;
- Infuse allopurinol in a separate line from the chemotherapy administration line. If not possible, flush line prior to the administration of allopurinol with a minimum of 15 mL 0.9% NaCl. Flush line with 0.9% NaCl following administration;
- Vital signs as clinically indicated;
- Discontinue with the first sign of an allergic reaction.

Recommended guidelines for the use of Rasburicase:

- Level of Evidence: 1+ (Evidence from well conducted meta analyses, systematic reviews of RCTs, or RCTs with a low risk of bias)
- Grade of Recommendation: A (Requires at least one meta analysis, systematic review or RCT rated as 1++, and directly applicable to the target population; or a systematic review of RCTs, or a body of evidence consisting principally of studies related as 1+, directly applicable to the target population and demonstrating overall consistency of results)[Based on SIGN,2000]
- Indications for use:
  a) Age > 1 month [Fasturtec®, Sanofi-Synthelabo Inc. product monograph]
  b) Patients with acute lymphoblastic leukemia with bulky disease or WBC > 50 x 10^9 /L or NHL **and** c) Uric acid > 480 µmol/L following hydration d) Other high risk patients determined by the Oncologist/Hematologist;
- Stop allopurinol, if this has been initiated;
- Begin 24 hours prior to the start of cytoreduction therapy. (The overall elimination half-life is 18 hours);
- May give chemotherapy as soon as 4 hours after first dose of rasburicase;
- Contraindicated for patients with known G6PD deficiency, known history of anaphylaxis or hypersensitivity reactions, hemolytic reactions or methemoglobinemia reactions to rasburicase or any of the diluents;
- Depending on patient's acuity and urgency to begin therapy, G6PD screening may be considered for patients of African or Mediterranean ancestry prior to the start of therapy;
- Contraindicated in pregnancy;
- Vigorous hydration - 3000 mL/m^2/day (125 mL/m^2/hr)(or 200 mL/kg/day if <10 kg) of D5W+0.45%NaCl;
- Alkalinization is not required;
- Rasburicase 0.15 mg/kg/dose IV over 30 minutes;
- There are discrepancies in the recommendations for the length of treatment with rasburicase. The product monograph recommends treatment for as long as 5 days (Fasturec,® Sanofi-Synthelabo, 2003). We are recommending the use of 1 dose and re-evaluate the need for more doses based on persistent elevation of uric acid and ongoing tumor lysis risk factors (burden of disease, renal compromise);

- **After rasburicase therapy is begun, blood specimens for uric acid determinations should be placed in pre-chilled tubes containing heparin anticoagulant and placed on ice immediately and kept on ice until analyzed by the laboratory within 4 hours. A refrigerated centrifuge is recommended to obtain most reliable uric acid levels. This process for measuring uric acid levels should be continued for 4 days following the last dose of rasburicase [Ueng, 2005];**
- No drug interactions are known (Pea, 2005).

Rasburicase infusion:
- Rasburicase dose 0.15 mg/kg/dose in 50 mL 0.9% NaCl (final volume) IV over 30 minutes (no filter) once daily;
- Infuse in a separate line from the chemotherapy administration line. If not possible, flush line prior to the administration of rasburicase with a minimum of 15 mL 0.9% NaCl. Flush line with 0.9% NaCl following administration;
- Vital signs as clinically indicated;
- Pre-medication is not necessary but diphenhydramine and epinephrine should be available for emergency management of allergic/anaphylactic reaction;
- Discontinue rasburicase if signs or symptoms of anaphylaxis, methemoglobinemia or unexpected toxicity.

Hyperkalemia: the most likely electrolyte disturbance to be fatal.
- Consult Nephrology and ICU;
- Stop all potassium intake;
- If extremely urgent K+ >7 mmol/L - give calcium chloride 10 mg/kg slow IV infusion. Do not administer in same line as sodium bicarbonate; onset within minutes, duration only 30 minutes. Give if severe cardiac arrhythmias;
- If urgent give - Insulin and glucose - glucose 0.5 gm/kg/hr with regular insulin 0.1 unit/kg/hr. Monitor glucose closely and adjust infusion rates; onset in 30 minutes, duration several hours;
- If less urgent give - Oral Sodium polystyrene sulfonate (kayexalate) - removes 1 mEq K+ per every gram of resin; Dose: 1 gm/kg (maximum 30 gm) PO/PR q6h. For oral or rectal administration: mix 1 gm of powder in 3-4 mL of 20% sorbitol or water; onset of **effect** @ 2-4hrs; if absolutely necessary, kayexalate may be given rectally;
- IV furosemide (1-2 mg/kg, maximum 40 mg).

Hyperphosphatemia:
- Low phosphate diet;
- Discontinue phosphate containing medications;
- Aluminum hydroxide 150 mg/kg/day divided q4-6h. Limited to 1-2 days to avoid aluminum toxicity;
- Calcium carbonate may be added in place of aluminum hydroxide if hypocalcemia is present; 125 mg elemental calcium/dose po TID and 250 mg elemental calcium/dose po TID with each meal. Monitor and titrate dose based on serum phosphate and calcium levels;
- Maintain urine output >3 mL/kg/hr and use furosemide or mannitol if necessary;

- IV glucose/insulin used rarely; glucose 0.5 gm/kg/hr with regular insulin 0.1 unit/kg/hr. Monitor glucose closely and adjust infusion rates; onset in 30 minutes, duration several hours [Devita 2005].

Hypocalcemia: (ionized calcium < 0.75 mmol/L)

- Consult Nephrology and ICU;
- Control hyperphosphatemia as above;
- Oral calcium carbonate if asymptomatic;
- If symptomatic, give 10 mg/kg of calcium chloride IV over 5-10 minutes; may repeat q4-6h if needed; discontinue as soon as symptoms resolve;
- Consider hemodialysis;
- Seizure precautions.

Considerations for hemodialysis - consult nephrology:

- Severe hyperkalemia >6.5 mmol/L, non responsive to above measures;
- Volume overload secondary to oliguria/anuria, causing respiratory or cardiovascular compromise;
- Severe hyperphosphatemia causing symptomatic hypocalcemia, non responsive to above measures;
- Severe hypocalcemia - symptomatic;
- Severe hyperuricemia >400 µmol/L uncontrolled by above measures;
- Severe uremia - urea > 40 mmol/L;
- Severe metabolic acidosis with pH <7.2 or HCO_3 <10;
- Neurologic symptoms secondary to uremia or electrolyte imbalance;
- Coagulopathy secondary to uremic platelet dysfunction

Appendix 1

Cairo-Bishop Classification of Tumor Lysis Syndrome [Cairo MS, Bishop M. 2004.]

Laboratory tumor lysis syndrome	
uric acid	>476 µmol/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
Laboratory tumor lysis is defined as either a >25% change or level above or below normal, as defined above, for any two or more serum values of uric acid, potassium, phosphate and calcium within 3 days before or 7 days after initiation of chemotherapy.	
Clinical tumor lysis syndrome	
creatinine >1.5 x upper limit of normal or progressive oliguria/anuria	
cardiac arrhythmia/ sudden death	
seizure	

Cairo-Bishop Grading Classification of Tumor Lysis Syndrome [Cairo MS, Bishop M. 2004.]

	Grade 0	**Grade I**	**Grade II**	**Grade III**	**Grade IV**	**Grade V**
Lab TLS	No	Yes	Yes	Yes	Yes	Yes
creatinine	< 1.5 x upper limit normal [ULN]	1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 x ULN	death
cardiac arrhythmia	none	intervention not indicated	non-urgent medical intervention	symptomatic and incompletely controlled medically or controlled with device	life-threatening	death
seizure	none	none	one brief generalized seizure, well controlled or infrequent focal motor seizures not interfering with ADL	seizure with altered consciousness, poorly controlled, breakthrough seizures	prolonged seizures, repetitive difficult to control	death
Clinical tumor lysis syndrome requires one or more clinical manifestation along with criteria for laboratory tumor lysis syndrome						
Maximal clinical tumor lysis syndrome manifestation[s][renal, cardiac, neurologic] defines grade						

Appendix II

Clinical Trials for Rasburicase

study	N	Criteria for Use	Dose	Results	
Pui et al, 2001a	131	B-cell ALL ALL with WBC > 50 x 10^9/L ALL with bulky disease NHL with large tumor burden uric acid > 480µmol/L + serum creatinine or LDH > twice ULN	0.15 mg/kg/dose (first 12 patients) 0.2 mg/kg/dose once daily (11 patients q12h)	11/12 achieved normal uric acid by 48 hours median uric acid 342 µmol/L to 30 µmol/L at 4 hours (156-2028 to 4.8 to 924 µmol/L) 1 n/v; 1 anaphylaxis 14% developed antibodies	
Pui et al, 2001b	245	Compassionate use Cancer patients with or at high risk for hyperuricemia	0.2 mg/kg/dose	117 pediatric treatment	56 pediatric prophylaxis
				Uric acid: Pre: 372-2016 Post: 0-486	Uric acid: Pre: 72-414 Post: 0-210
				4 children and 6 adults required dialysis	

Key: ALL = Acute lymphoblastic leukemia; NHL = non-Hodgkin=s lymphoma; UA = uric acid; Scr = serum creatinine; LDH = lactic dehydrogenase; ULN = upper limit of normal

.

Comparative Trial

Study	Agent	Criteria for Use	Results
Goldman et al, 2001	Rasburicase = 27 PO allopurinol = 25	Stage III/IV NHL ALL (WBC > 25 x 10^9/L) ALL or NHL with uric acid > 480 µmol/L	1 rasburicase patient with hemolysis withdrawn; uric acid > 480 µmol/L @ baseline normalized in 4 hrs for rasburicase patients and 24 hrs for allopurinol; patients receiving rasburicase had a significantly shorter time exposed to an increased uric acid level [AUC][p<.0001] Dialysis in one allopurinol patient with PO_4 = 6.5 mmol/L

Appendix III

Adverse Reactions for Allopurinol and Rasburicase

Allopurinol	Rasburicase
Rash 1.5% (Incidence may be higher in patients receiving concomitant amoxicillin or ampicillin)	Fever (5-46%), nausea (27%), vomiting (50%) , headache (26%)
	Constipation (20%), diarrhea (≤1-20%), mucositis (2-15%), abdominal pain (20%)
	Rash 13%
	Neutropenia (2%)
	Hemolysis < 1% [with G6PD deficiency]
	Methemoglobinemia < 1% [with G6PD def]
With IV: hypo or hyper tension, flushing, bradycardia, apnea < 1%	Allergic reactions/anaphylaxis < 1%
Renal failure/insufficiency 1.2%	Cardiac failure < 1%
Nausea 1.3%	
Vomiting 1.2%	
Cardiac failure < 1%	
Warnings: Discontinue with the first sign of the appearance signs that may indicate an allergic reaction.	**Warnings:** Discontinue with the first sign of a serious hypersensitivity reaction, hemolysis, or methemoglobinemia.

Uric oxidase produces excess hydrogen peroxide as it breaks down uric acid. In patients with G6PD deficiency, the hydrogen peroxide can lead to hemolysis and methemoglobinemia [Browning, Kruse, 2005].

Comparison costing

Drug	Dosage	Costs per/day- adult
Allopurinol oral	800 mg/day	$0.12
Allopurinol IV	600 mg/day	$600
Rasburicase	0.15 mg/kg/day (based on 70 kg patient)	$874

Appendix IV

Physician Pre-Printed Orders for Tumor Lysis Syndrome

Patient: _____

Height _____cm Weight _____kg BSA _____m^2 Date _____
(dd/mm/yyy)

Allergies: _____

The following orders will be carried out by a nurse **ONLY ON THE AUTHORITY OF A PHYSICIAN.**

For more information, refer to APPHON Guidelines for Management of Tumor Lysis Syndrome.

Where choice occurs, check as appropriate.

ASSESSMENT AND MONITORING:

Monitor for signs of **hyperkalemia**; hyperphosphatemia; hypocalcemia; renal failure; vital signs q4hours; cardiac monitor if K+ is greater than 5.5 mmol/L or calcium less than 1.7 mmol/L (ionized less than 0.8 mmol/L).

INVESTIGATIONS:

- CBC, diff; at least daily plus every _____ hours for the first 3 days then reassess;
- NA, K, CREAT, BUN, blood gas, phosphate, calcium, uric acid (if receiving rasburicase order uric acid- rasb); every _____ hours. Reassess after the first 3 days;
- □ Urine specific gravity, each void; □ Urine pH, each void;
- Twice daily weights.
- Consult Nephrology, PICU.

TREATMENT: Date started: _____ (use m^2 from office chart = _____ m^2).

X **Total Hydration:** IV/PO at a total of 125 mL/m^2/hour = _____ mL/hour

□ Minimum IV rate 50 mL/m^2/hour use **Medline** of D5W + 0.45% NaCl. **DO NOT ADD POTASSIUM**. Aim for a urine output of > 100 mL/m5/hour = _____ mL/hour & specific gravity of < 1.010 prior to chemotherapy.

□ If alkalinization required: Stop above hydration and start D5W + 0.2% NaCl + 4 mEq % sodium bicarbonate at a total of 125 mL/ m^2/hour = _____ mL/hour. Aim to maintain urine pH between 6.5-7.5. Call MD if outside this range. **Do not alkalinize if using rasburicase.**

□ Allopurinol _____ mg PO _____
(10 mg/kg/day divided 2 to 4 times daily, maximum 300 mg/dose; 800 mg/day)

OR (if patient cannot tolerate PO)

□ Allopurinol _____ mg IV _____ over 30-60 minutes
(200 mg/ m^2/day divided 1 to 3 times daily, maximum 600 mg/day).
Available through Health Canada Special Access Program (Complete SAP form).

OR

□ **Rasburicase** _____ mg IV once daily over 30 minutes (0.15 mg/kg/day) in a final volume of 50 mL 0.9% NaCl. Do not filter. Reassess daily. Round to nearest 1.5 mg vial.

- **DO NOT GIVE** if known G6PD deficiency and/or known history of anaphylaxis or hypersensitivity reactions, hemolytic reactions, or methemoglobinemia reactions to rasburicase, or if pregnant.
- Place uric acid tubes IMMEDIATELY on ice and send to lab STAT. Continue to place tubes on ice for uric acid measurements, while patient is on rasburicase and for 4 days after last dose of rasburicase.
- Ensure Hypersensitivity Reaction Orders completed (Form #8511).

_____	_____	_____	_____
DATE (dd/mm/yyyy)	TIME (24hr/hhmm)	Physician Signature	Printed Surname/Registration #
_____	_____	_____	_____
DATE (dd/mm/yyyy)	TIME (24hr/hhmm)	Verified by (Nurse Signature)	Printed Surname

Appendix V

Guideline Development

Potential organizational barriers/cost implications to applying the recommendations found in this guideline include:

- inability to obtain IV allopurinol [delay due to need for Health Canada Special Access]
- cost of rasburicase [therefore to be used only for indications above; for these patients, costs of the drug will likely be recovered through prevention of complications]

Patient/ family preferences:

- not considered applicable
- appropriate information and support will be provided

Key review criteria for monitoring/ audit include:

- rasburicase used only for appropriate indications
- number of children requiring hemodialysis
- number of children requiring admission to PICU

The Guideline development group included:

- Tamara MacDonald, PharmD, pharmacist
- Dorothy Barnard, pediatric hematologist/oncologist

The individuals involved in the development of this guideline had no conflicts of interest with respect to the development of the guideline. The guideline was developed independently from any funding body.

The guideline was piloted at the IWK Health Centre in Halifax, Nova Scotia.

The guideline was externally reviewed by nephrology, pediatricians, hematologists, oncologists, nurses and a psychologist.

The guideline will be updated in July 2010 by the APPHON Guidelines Committee, and resubmitted to the APPHON Board and Cancer Care Nova Scotia Clinical Practice Guidelines Committee for ratification. If significant changes to the prevention and treatment of tumor lysis syndrome, changes based on new evidence or best practice, develop prior to July 2010, the guideline will be updated to reflect those changes. As per the standard practice for APPHON guidelines, individuals will be assigned to regularly review applicable literature to monitor for significant changes. If literature documenting evidence-based or best practice based indications for changes to this guideline, the guideline will be updated with the applicable information as soon as feasible.

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