Tumor Lysis Syndrome: EBM guidelines

Definition: Tumor lysis syndrome (TLS) is characterized by a group of metabolic derangements including hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia.caused by the massive and abrupt release of cellular components into the blood after the rapid lysis of malignant cells. It is observed most frequently in patients with malignancies with high proliferative rate, large tumor burden, or high sensitivity to cytotoxic therapy such as acute lymphoblastic leukemia (ALL) and Burkitt's lymphoma after the initiation of cytotoxic therapy.

Pathogenesis and Clinical Consequences

The release of intracellular metabolites, including nucleic acids, proteins, phosphorus, and potassium after the initiation of cytotoxic chemotherapy or cytolytic antibody therapy can overwhelm normal homeostatic mechanisms, potentially leading to hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, and uremia. The crystallization of uric acid or calcium phosphate in renal tubules can further result in impaired renal function. Further, the precipitation of calcium can lead to secondary hypocalcemia, which may be either symptomatic or asymptomatic In some cases, TLS can lead to acute renal failure and even death due to uric acid or calcium phosphate precipitation, xanthine crystallization, tumor infiltration in the kidney, tumor-associated obstructive uropathy, drug associated nephrotoxicity, and/or acute sepsis. The relative risk of developing TLS is significantly higher in patients with high uric acid levels (8 mg/dL) and high phosphorus levels.

Clinical manifestations: The clinical features of TLS may include nausea, vomiting, diarrhea, anorexia, lethargy, edema, fluid overload, hematuria, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope, and possible sudden death. Although symptoms may occur before the start of chemotherapy, they are observed more commonly within 12 to 72 hours after the initiation of cytoreductive therapy. Complications resulting from TLS can compromise the efficacy or further administration of chemotherapy.

Classification

There is currently no universally accepted system for classification and grading. The most recent and preferred is Cairo and Bishop classification system based on defining laboratory or clinical TLS (LTLS or CTLS). This system distinguishes between patients who do not require therapeutic intervention versus those experiencing life-threatening clinical abnormalities.
This classification and grading system is currently being used by Children's Oncology Group Under this system, LTLS is considered to be present if levels of two or more serum values of uric acid, potassium, phosphate, or calcium are more than or less than normal at presentation or if they change by 25% within 3 days before or 7 days after the initiation of treatment (Table 1). CTLS requires the presence of LTLS in addition to one or more of the following significant clinical complications: renal insufficiency, cardiac arrhythmias/ sudden death, and seizures (Table 2). LTLS is considered to be either present or absent (Table 1), whereas the grade of CTLS is defined by the maximal grade of the clinical manifestation (Table 2).

Incidence and Risk Factors

TLS occurs most frequently in patients with NHL and other hematologic malignancies, particularly Burkitt's lymphoma, ALL, and acute myeloid leukemia (AML). The overall incidence of LTLS and CTLS ranges from 14%-17% and 3%-5% in patients with AML, 21%-30% and 5%-8% in those with ALL, and 19%-40% and 6%-20% in patients with NHL, respectively.

The syndrome is observed less frequently in other hematologic malignancies, including chronic lymphocytic leukemia on fludarabine (0.5%), NHL treated with the anti-CD20 monoclonal antibody rituximab (0.04% to 0.05%) and promyelocytic leukemia (<0.05%).
Although occurrences are rare, a literature review revealed 45 case reports of TLS in patients with solid tumors, with a mortality rate of one in three in this patient set. Certain intrinsic tumor-related factors, therapy related factors and several conditions may predispose patients to developing TLS (Table 3-4)

Guidelines for prevention and management

The potential severity of complications resulting from the development of TLS necessitates measures for prevention in high-risk patients and prompts treatment in the event that symptoms arise. Recognition of risk factors, close monitoring of at-risk patients, and appropriate interventions are the key to preventing or managing TLS.

Management of Hyperuricemia

Fluids and hydration. Aggressive hydration and diuresis are fundamental to the prevention and management of TLS. The combination of hydration and enhanced urine flow promotes the excretion of uric acid and phosphate by improving intravascular volume, renal blood flow, and glomerular filtration. Vigorous hydration is recommended for all patients in the intermediate to- high risk groups or for those with diagnosed LTLS or CTLS, with the exception of patients presenting with renal failure or oliguria. It is important to attempt to achieve equal fluid intake and urinary output if at all possible.
Pediatric patients should receive 2 to 3 L/m^2/d (or 200 mL/kg/d if<10 kg; volume adapted to patient age, cardiac function, and urine output) IV of a solution consisting of one quarter of normal saline/5% dextrose. Urine output should be monitored closely and be maintained within a range of 80 to 100 mL/m^2/h (4 to 6 mL/kg/h if < 10 kg). If there is no evidence of acute obstructive uropathy and/or hypovolemia, diuretics may be used to maintain output within this range if necessary. Potassium, calcium, and phosphate should be withheld initially from hydration fluids. Urine-specific gravity should be monitored and maintained at <1.010 **(level of evidence: V; grade of recommendation: D).** Guidelines for hydration in adult patients are the same as those for pediatric patients. Fluid intake should be maintained at approximately one to two times maintenance, with a urine output of 80 to 100 mL/m^2/h **(level of evidence: V; grade of recommendation: D**).

Alkalinization. Historically, alkalinization had been recommended for pediatric patients receiving treatment for hyperuricemia, particularly those treated with allopurinol, to promote excretion of uric acid in the urine. However, this practice is currently not recommended, because there is no unequivocal evidence of efficacy. Further, alkalinization may increase the risk of precipitation of calcium phosphate crystals. Because of these potential complications and lack of evidence of benefit, alkalinization is only indicated for patients with metabolic acidosis, in which case sodium bicarbonate may be considered based on the standards of the institution. Alkalinization for patients who will receive treatment with allopurinol is controversial. Alkalinization is additionally not required in patients receiving rasburicase **(level of evidence: V; grade of recommendation: D).**

Allopurinol Administration

Allopurinol is a xanthine analog which, when converted in vivo to oxypurinol, acts as a competitive inhibitor of xanthine oxidase, thereby blocking the conversion of the purine metabolites xanthine and hypoxanthine to uric acid. Use of allopurinol has been shown to decrease the formation of uric acid and to reduce the incidence of obstructive uropathy

caused by uric acid precipitation in patients at risk for developing TLS. The use of allopurinol can be considered as a prophylactic option for patients with a medium risk of developing TLS (Table 4). Allopurinol is contraindicated in patients with a pre-existing allergy to allopurinol or who develop a severe hypersensitivity reaction while receiving treatment with this agent.
In pediatric patients, allopurinol is administered at a dose of 50 to 100 mg/m2 every 8 hours orally (maximum dose, 300 mg/m2/d) or 10 mg/kg/d divided every 8 hours (maximum dose, 800 mg/d). For patients unable to take allopurinol orally, IV administration may be considered, at a dose of 200 to 400 mg/m2/d in one to three divided doses (maximum dose, 600 mg/d).
Treatment with allopurinol should be initiated in intermediate risk patients no more than 12 to 24 hours before the start of induction chemotherapy. Treatment may be continued until uric acid levels are normalized, and tumor burden, WBC count, and other laboratoryvalues have returned to low-TLS risk levels as defined in Table 4. It should be noted that allopurinol only prevents the formation of uric acid and does not reduce uric acid produced before the initiation of treatment. Therefore, for patients with pre-existing severe hyperuricemia (> 7.5 mg/dL), treatment with rasburicase is preferred **(level of evidence: II; grade of recommendation: B).**
Allopurinol can also cause an increase in serum levels and crystal deposition of the purine precursors xanthine and hypoxanthine, which can result in acute obstructive uropathy. In addition, because allopurinol also reduces the degradation of other purines, particularly 6-mercaptopurine, dose reductions of 50% to 70% of 6-mercaptopurine and/or azathioprine are recommended when this agent is administered concomitantly with allopurinol. Because allopurinol is excreted by the kidneys, a dose reduction of 50% is recommended in patients with renal insufficiency.
The guidelines for allopurinol dosages and administration for adult patients are the same as those for pediatric patients. Treatment may be started 1 to 2 days before the start of induction chemotherapy and may be continued for up to 3 to 7 days afterwards, based on the ongoing risk of TLS development **(level of evidence: II; grade of recommendation: B).**

Recombinant Urate Oxidase Administration and Treatment Duration

*U*rate oxidase converts uric acid into allantoin, which is five to 10 times more soluble in urine than uric acid. A recombinant form of urate oxidase with a high specific activity is available. Rasbricase is much more effective in reducing the level of uric acid, creatinine and achieving the control of other meatbolites involved in tumor lysis syndrome. The use of recombinant urate oxidase (rasburicase) is recommended for the treatment of pediatric patients with hyperuricemia associated with LTLS or CTLS, or in the initial management of patients considered to be at high risk of developing TLS (Table 4).
In addition, for patients in the intermediate-risk group, rasburicase is recommended if hyperuricemia develops despite prophylactic treatment with allopurinol **(level of evidence: II; grade of recommendation: B).** Rasburicase is contraindicated in patients with a known G6PD deficiency and in pregnant or lactating females.Screening for G6PD deficiency should include a thorough history of prior drug-induced hemolytic anemia, ethnic background, and available semiquantitative laboratory tests. Definitive testing, including measurement of RBC NADPH formation is recommended.
The US Food and Drug Administration–approved dosing guidelines recommend 0.15 to 0.2 mg/kg once daily in 50 mL of normal saline as an IV infusion over 30 minutes for 5 days. However, rasburicase has demonstrated activity even at lower doses and for shorter duration. Therefore, a dose of 0.10 to 0.2 mg/kg daily, dependent on whether the intention is prevention or treatment may be used (Table 5). Duration of treatment can range from 1 to 7 days. It is important that uric acid levels be monitored regularly and used as a guide to modulate dosing with rasburicase. In certain cases, such as in patients experiencing massive

tumor lysis, it may be necessary to increase the administration schedule to twice daily. Treatment is not necessary when uric acid is extremely low or no longer detectable.
Potential serious adverse reactions are rare and include anaphylaxis, rash, hemolysis, methemoglobulinemia, fever, neutropenia (with or without fever), respiratory distress, sepsis, and mucositis.
At room temperature, rasburicase will cause the degradation of uric acid within blood samples, thereby interfering with accurate measurement. Therefore, samples should immediately be placed on ice until the completion of assay, which is preferably done within 4 hours of collection. Guidelines for rasburicase usage in adults are identical to those provided above for pediatric patients. **(level of evidence: II; grade of recommendation: B).**

Management of Hyperphosphatemia

It is of particular importance to treat hyperphosphatemia in pediatric patients (Table 6). For asymptomatic hyperphosphatemia, initial treatment consists of eliminating phosphate from intravenous solutions, maintaining adequate hydration, and the administration of phosphate binders. For severe hyperphosphatemia, hemodialysis, peritoneal dialysis, or continuous venovenous hemofiltration has been used **(level of evidence: V; grade of recommendation: D).**
Aluminum hydroxide 50 to 150 mg/kg/d is administered in divided doses orally or nasogastrically every 6 hours. Its use should be limited to 1 to 2 days to avoid cumulative aluminum toxicity. Because pediatric patients might find the taste of aluminum hydroxide objectionable, other phosphate binders, such as calcium carbonate (eg, low calcium levels), sevelamer hydroxide, and lanthanum carbonate may alternatively be used. Calcium carbonate should not be used in patients with elevated calcium levels. Phosphate clearance was found to be better with hemodialysis as compared with continuous venovenous hemofiltration or peritoneal dialysis. The above recommendations are valid for adult patients **(level of evidence: V; grade of recommendation: D).**

Management of Hyperkalemia

In pediatric patients, oral and IV sources of potassium should be eliminated as long as the risk of TLS exists (Table 6). Immediate intervention is indicated if serum potassium is greater than 7.0 to 7.5 mEq/L or the ECG shows widening of QRS complex. For asymptomatic patients, the standard treatment is sodium polystyrene sulfonate 1 g/kg administered orally or rectally (avoid this route in neutropenic patients). For symptomatic patients, more intense intervention is recommended, such as rapid-acting insulin (0.1 U/kg administered IV) and glucose infusion (25% dextrose 2 mL/kg).Sodium bicarbonate (1 to 2 mEq/kg administered via IV push) can be given to induce influx of potassium into cells. Calcium gluconate (100 to 200 mg/kg/dose) via slow infusion with ECG monitoring for bradycardia can be given for treatment of life-threatening arrhythmias. However, sodium bicarbonate and calcium should not be administered through the same line **(level of evidence: V; grade of recommendation: D).** Elevated potassium levels should be verified immediately with a second sample to rule out fictitious hyperkalemia from hemolysis during phlebotomy. Patient ECG and cardiac rhythm should be closely followed, along with evaluation of electrolyte levels. The above recommendations are valid for adult patients **(level of evidence: V; grade of recommendation: D).**

Management of Hypocalcemia

For asymptomatic pediatric patients, no intervention is recommended (Table 6). Symptomatic patients may be treated with calcium gluconate 50 to 100 mg/kg IV, administered slowly with EKG monitoring **(Level of evidence: V; grade of recommendation: D).** Care must be taken

because increased calcium might increase the risk of calcium phosphate precipitation in the tissues and consequential obstructive uropathy. The above recommendations are valid for adult patients **(level of evidence: V; grade of recommendation: D**).

Monitoring during treatment:

Check laboratory and clinical TLS parameters 4 to 6 hours after the initial administration of chemotherapy. The TLS parameter consists of levels of uric acid, phosphate, potassium, creatinine, calcium, and LDH, as well as fluid input and urine output. For all patients, uric acid levels should be re-evaluated 4 hours after administration of rasburicase and every 6 to 8 hours thereafter until resolution of TLS, for example, until normalization of LDH levels **(level of evidence: V; grade of recommendation: D).**

For adult intermediate-risk patients, patients should be monitored for at least 24 hours after the completion of chemotherapy. For multiagent chemotherapeutic regimens in which the different drugs are administered over several days, monitoring should continue for 24 hours after the administration of the final agent of the first cycle. If rasburicase is not used in the initial management of the patient, electrolyte levels should be determined 8 hours after chemotherapy. If TLS has not occurred after 2 days, the likelihood is essentially zero that the patient will experience TLS **(level of evidence: V; grade of recommendation: D).**

For pediatric and adult patients at high risk of TLS, cytotoxic chemotherapy should only be administered once patients are located in a facility with ready access to dialysis. Although dialysis usage has been reduced since the introduction of rasburicase, as many as 3% of patients (1.5% of pediatric patients and 5% of adult patients) still require this procedure. A nephrology specialist should therefore be notified in advance regarding high-risk patients. A renal consultation be obtained immediately if urine output is progressively decreasing (oliguria or anuria), if there is persistent or elevated urea (> 150mg/dl), phosphate(>10mg/dl) or potassium levels(>7mmol/L), or in the case of life threatening hypocalcemia inspite of optimal conservative measures.

Summary of guidelines for management of tumor lysis syndrome:

High-Risk Patients

In the case of pediatric patients, although those at high risk are clear candidates for aggressive intervention and those at low risk might be observed only, the classification and treatment approach for intermediate-risk patients is still not clearly defined (Fig 2). The best management of TLS is prevention. Adequate hydration and urine output are of high importance in preventing TLS.

Along with hydration, rasburicase should be used in the initial management of pediatric patients considered to be at high risk. Additionally, these patients should be admitted to an intensive care unit or similarly monitored nursing area of the hospital. If the nurse-topatient ratio is favorable, the patient may be placed on a standard hospital floor with close monitoring, but the patient should have ready access to intensive care unit facilities if his or her clinical condition deteriorates.A renal expert should be notified regarding the patient in case dialysis is required. Delaying tumor therapy until these measures can be taken will help prevent TLS and its complications, but the aggressive nature of many malignancies will require a case-by-case decision based on the patient's condition **(level of evidence: II; grade of recommendation: A).**

Intermediate-risk patients: For intermediate-risk pediatric patients, in addition to hydration, allopurinol may be used as an initial antihyperuricemic treatment as described in allopurinol Administration. Initial management with a single dose of rasburicase might also be considered in pediatric patients **(level of evidence: V; grade of recommendation: D).**

Low-risk: For pediatric patients unlikely to develop TLS, it is the opinion of the panel that a watch-and-wait approach with close monitoring is entirely appropriate **(level of evidence: V; grade of recommendation: D).** The above recommendations are valid for adult patients **(level of evidence: V; grade of recommendation: B).**

Table 1. Cairo-Bishop Definition of Laboratory Tumor Lysis Syndrome

Element	Value	Change From Baseline	
Uric acid	≥476 µmol/L or 8 mg/dL	25% increase	
Potassium	≥6.0 mmol/L or 6 mg/L	25% increase	
Phosphorus	≥2.1 mmol/L for children or ≥1.45 mmol/L for adults	25% increase	
Calcium	≤1.75 mmol/L	25% decrease	

NOTE. Two or more laboratory changes within 3 days before or 7 days after cytotoxic therapy.

Table 2. Cairo-Bishop Clinical Tumor Lysis Syndrome Definition and Grading

	Grade					
Complication	0	1	2	3	4	5
Creatinine*†	≤1.5 x 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 indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with CHF, hypotension, syncope, shock)	Death
Seizure*	None	—	One brief generalized seizure; seizure(s) well controlled by anticonvulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

NOTE. Laboratory tumor lysis syndrome and at least one clinical complication.

Abbreviations: ULN, upper limit of normal; CHF, congestive heart failure; ADL, activities of daily living.

* Not directly or probably attributable to therapeutic agent.

†If no institutional ULN is specified, age/sex ULN creatinine may be defined as follows: > 1 to < 12 years of age, both male and female, 61.6 µmol/L; ≥12 to < 16 years, both male and female, 88 µmol/L; ≥16 years, female 105.6 µmol/L, male 114.4 µmol/L.

Table 3. Risk Factors for Tumor Lysis Syndrome

Characteristic	Risk Factor
Tumor type	Burkitt's lymphoma Lymphoblastic lymphoma Diffuse large-cell lymphoma ALL Solid tumors with high proliferative rates and rapid response to therapy
Tumor burden/extent of disease	Bulky disease (>10 cm) Elevated LDH (> 2x ULN) Elevated WBC (>25,000/μL)
Renal function	Preexisting renal failure Oliguria
Baseline uric acid	Baseline serum/plasma uric acid > 450 μmol/L (7.5 mg/dL)
Effective and rapid cytoreductive therapy	Disease-specific therapy, varies according to tumor type

Abbreviations: ALL, acute lymphoblastic leukemia; LDH, lactate dehydrogenase

Table 4. Patient Stratification by Risk

	Risk		
Type of Cancer	High	Intermediate	Low
NHL	Burkitt's, lymphoblastic, B-ALL	DLBCL	Indolent NHL
ALL	WBC ≥100,000	WBC 50,000-100,000	WBC ≤50,000
AML	WBC ≥50,000, monoblastic	WBC 10,000-50,000	WBC ≤10,000
CLL		WBC 10,000-100,000 Tx w/fludarabine	WBC ≤10,000
Other hematologic malignancies (including CML and multiple myeloma) and solid tumors		Rapid proliferation with expected rapid response to therapy	Remainder of patients

Abbreviations: NHL, non-Hodgkin's lymphoma; B-ALL, Burkitt's acute lymphoblastic leukemia; DLBCL, diffuse large B-cell lymphoma; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia, CLL, chronic lymphocytic leukemia; Tx, treatment; CML, chronic myeloid leukemia.

Table 5. Recommended Rasburicase Dosing

Tumor Lysis Syndrome Profile	Baseline Uric Acid		Dose (mg/kg)	Duration*
	mg/dL	mmol/L		
High risk	> 7.5	450	0.20	Based on plasma uric acid levels
Intermediate risk	< 7.5	450	0.15	Based on plasma uric acid levels
Low risk	< 7.5	450	0.10†	Clinical judgment

* The average duration of therapy is 2 days, but can vary from 1 day to 7 days. †Dosages as low as 0.05 mg/kg have been used successfully in groups of patients in at least one clinical trial.

Table 6. Management of Electrolyte Abnormalities

Abnormality	Management Recommendation
Hyperphosphatemia	
Moderate, ≥2.1 mmol/L	Avoid IV phosphate administration Administration of phosphate binder
Severe	Dialysis, CAVH, CVVH, CAVHD, or CVVHD
Hypocalcemia, ≤1.75 mmol/L	
Asymptomatic	No therapy
Symptomatic	Calcium gluconate 50-100 mg/kg IV administered slowly with ECG monitoring
Hyperkalemia	
Moderate and asymptomatic, ≥6.0 mmol/L	Avoid IV and oral potassium ECG and cardiac rhythm monitoring Sodium polystyrene sulphonate
Severe (> 7.0 mmol/L) and/or symptomatic	Same as above, plus: Calcium gluconate 100-200 mg/kg by slow IV infusion for life-threatening arrhythmias Regular insulin (0.1 U/kg IV) + D25 (2 mL/kg) IV Sodium bicarbonate (1-2 mEq/kg IV push). However, sodium bicarbonate and calcium should not be administered through the same line. Dialysis
Renal dysfunction (uremia)	Fluid and electrolyte management Uric acid and phosphate management Adjust renally excreted drug doses Dialysis (hemo- or peritoneal) Hemofiltration (CAVH, CVVH, CAVHD, or CVVHD)

Abbreviations: IV, intravenous; CAVH/CAVHD, continuous arterial-venous hemodialysis; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis.

1: Rampello E. et al The management of tumor lysis syndrome. Nat Clin Pract Oncol. 2006 Aug;3(8):438-47.

The manifestation of tumor lysis syndrome (TLS) occurs when the destruction of tumor cells releases breakdown products that overwhelm the excretory mechanisms of the body. A cardinal sign is hyperuricemia, leading to uric acid nephropathy. Other signs are hyperkalemia, hyperphosphatemia and secondary hypocalcemia. Conventional management of TLS consists of aggressive intravenous hydration,diuretic therapy, urinary alkalization, and inhibition of urate production by high-dose allopurinol. Urate oxidase has been used in the management of patients at risk for TLS and recently the recombinant urate oxidase rasburicase was developed. Several data indicate that rasburicase is effective and well tolerated in the prevention and treatment of chemotherapy-induced hyperuricemia. Treatment options of hyperkalemia include sodium polystyrene sulfonate, hypertonic glucose and insulin, loop diuretics, and bicarbonate. Treatment of hyperphosphatemia reduces dietary phosphate intake and includes phosphate binders such as aluminum hydroxide and aluminum carbonate. When recurrent hypocalcemia is present, a continuous intravenous infusion of calcium gluconate can be initiated. Hemodialysis should be considered for every patient with excessively elevated uric acid, phosphate and/or potassium and in those patients with acute renal failure to control urinary volume and manage uremia.

2: Coiffier B et al Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008 Jun 1;26(16):2767-78.

PURPOSE: Tumor lysis syndrome (TLS) has recently been subclassified into either laboratory TLS or clinical TLS, and a grading system has been established. Standardized guidelines, however, are needed to aid in the stratification of patients according to risk and to establish prophylaxis and treatment recommendations for patients at risk or with established TLS. METHODS: A panel of experts in pediatric and adult hematologic malignancies and TLS was assembled to develop recommendations and guidelines for TLS based on clinical evidence and standards of care. A review of relevant literature was also used. RESULTS: New guidelines are presented regarding the prevention and management of patients at risk of developing TLS. The best management of TLS is prevention. Prevention strategies include hydration and prophylactic rasburicase in high-risk patients, hydration plus allopurinol or rasburicase for intermediate-risk patients, and close monitoring for low-risk patients. Primary management of established TLS involves similar recommendations, with the addition of aggressive hydration and diuresis, plus allopurinol or rasburicase for hyperuricemia. Alkalinization is not recommended. Although guidelines for rasburicase use in adults are provided, this agent is currently only approved for use in pediatric patients in the United States. CONCLUSION: The potential severity of complications resulting from TLS requires measures for prevention in high-risk patients and prompts treatment in the event that symptoms arise. Recognition of risk factors, monitoring of at-risk patients, and appropriate interventions are the key to preventing or managing TLS. These guidelines should assist in the prevention of TLS and improve the management of patients with established TLS.

3: Cairo MS,et al Tumour lysis syndrome: new therapeutic strategies and classification. Br J Haematol. 2004 Oct;127(1):3-11.

Tumour lysis syndrome (TLS) describes the metabolic derangements that occur with tumour breakdown following the initiation of cytotoxic therapy. TLS

results from the rapid destruction of malignant cells and the abrupt release of intracellular ions, nucleic acids, proteins and their metabolites into the extracellular space. These metabolites can overwhelm the body's normal homeostatic mechanisms and cause hyperuricaemia, hyperkalaemia, hyperphosphaetemia, hypocalcaemia and uraemia. TLS can lead to acute renal failure and can be life-threatening. Early recognition of patients at risk and initiation of therapy for TLS is essential.
There is a high incidence of TLS in tumours with high proliferative rates and tumour burden such as acute lymphoblastic leukaemia and Burkitt's lymphoma. The mainstays of TLS prophylaxis and treatment include aggressive hydration and diuresis, control of hyperuricaemia with allopurinol prophylaxis and rasburicase treatment, and vigilant monitoring of electrolyte abnormalities. Urine alkalinization remains controversial. Unfortunately, there have been few comprehensive reviews on this important subject. In this review, we describe the incidence, pathophysiological mechanisms of TLS and risk factors for its development. We summarise recent advances in the management of TLS and provide a new classification system and recommendations for prophylaxis and/or treatment based on this classification scheme.

4: Goldman SC,et al A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood. 2001 May 15;97(10):2998-3003.

Standard therapy in the United States for malignancy-associated hyperuricemia consists of hydration, alkalinization, and allopurinol. Urate oxidase catalyzes the enzymatic oxidation of uric acid to a 5 times increased urine soluble product, allantoin. Rasburicase is a new recombinant form of urate oxidase available for clinical evaluation. This multicenter randomized trial compared allopurinol to rasburicase in pediatric patients with leukemia or lymphoma at high risk for tumor lysis. Patients received the assigned uric acid-lowering agent for 5 to 7 days during induction chemotherapy. The primary efficacy end point was to compare the area under the serial plasma uric acid concentration
curves during the first 96 hours of therapy (AUC(0-96)). Fifty-two patients were randomized at 6 sites. In an intent-to-treat analysis, the mean uric acid AUC(0-96) was 128 +/- 70 mg/dL.hour for the rasburicase group and 329 +/- 129 mg/dL.hour for the allopurinol group (P <.0001). The rasburicase versus allopurinol group experienced a 2.6-fold (95% CI: 2.0-3.4) less exposure to uric acid. Four hours after the first dose, patients randomized to rasburicase compared to allopurinol achieved an 86% versus 12% reduction (P <.0001) of initial plasma uric acid levels. No antirasburicase antibodies were detected at day 14. This randomized study demonstrated more rapid control and lower levels of plasma uric acid in patients at high risk for tumor lysis who received rasburicase compared to allopurinol. For pediatric patients with advanced stage lymphoma or high tumor burden leukemia, rasburicase is a safe and effective alternative to allopurinol during initial chemotherapy.

5: Jeha S,et al Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. Leukemia. 2005 Jan;19(1):34-8.

The recombinant urate oxidase, rasburicase (Elitek, Sanofi-Synthelabo, Inc.), has recently received regulatory approval for the prevention and treatment of hyperuricemia in children with leukemia, lymphoma, and solid tumors. Prior to approval, 682 children and 387 adults in the US and Canada received rasburicase on compassionate-use basis. Uric acid concentration

declined rapidly in both adult and pediatric patients after rasburicase treatment. Similar responses were observed in patients treated with subsequent courses. Possible drug-related adverse events, including allergic reactions, were uncommon. These data confirm that rasburicase is effective and safe for the treatment and prophylaxis of children and adults with malignancy-associated hyperuricemia.

6: Coiffier B, et al Efficacy and safety of rasburicase (recombinant urate oxidase) for the prevention and treatment of hyperuricemia during induction chemotherapy of aggressive non-Hodgkin's lymphoma: results of the GRAAL1 (Groupe d'Etude des Lymphomes de l'Adulte Trial on Rasburicase Activity in Adult Lymphoma) study. J Clin Oncol. 2003 Dec 1;21(23):4402-6.

PURPOSE: Hyperuricemia and tumor lysis syndrome are well-known complications during induction treatment of aggressive non-Hodgkin's lymphomas (NHLs). Usual prophylaxis and treatment of hyperuricemia consist of hydration, alkalinization, and administration of allopurinol. This study was designed to evaluate the efficacy and the safety of rasburicase (recombinant urate oxidase) in adult patients with aggressive NHL during their first cycle of chemotherapy. PATIENTS AND METHODS: A total of 100 patients from Groupe d'Etude des Lymphomes de l'Adulte centers, with diffuse large B-cell lymphoma (n = 79); anaplastic large-cell lymphoma (n = 6); peripheral T-cell lymphoma (n = 8); transformation of indolent lymphoma (n = 5); Burkitt's lymphoma (n = 1); and lymphoblastic lymphoma (n = 1) were enrolled from May 2001 to June 2002. Before chemotherapy,66% of patients had elevated lactate dehydrogenase (LDH), including 28% with LDH above 1,000 U/mL. Eleven percent of patients were hyperuricemic (uric acid [UA] > 450 mmol/L or > 7.56 mg/dL). Rasburicase 0.20 mg/kg/d intravenously for 3 to 7 days was started the day before or at day 1 of chemotherapy. UA levels were measured 4 hours after rasburicase injection, then daily during treatment. RESULTS: All patients responded to rasburicase, as defined by normalization of UA levels maintained during chemotherapy. The control of UA was obtained within 4 hours after the first injection of the drug. Creatinine levels and other metabolites were also controlled with the administration of rasburicase. No patient exhibited increased creatinine levels or required dialysis during chemotherapy. CONCLUSION: Rasburicase is the treatment of choice to control UA and prevent tumor lysis syndrome in adult patients with aggressive NHL.

7: Trifilio S, et al Reduced-dose rasburicase (recombinant xanthine oxidase) in adult cancer patients with hyperuricemia. Bone Marrow Transplant. 2006 Jun;37(11):997-1001.

Recombinant urate oxidase (rasburicase) lowers uric acid levels rapidly to very low levels at the labeled dose of 0.15-0.2 mg/kg daily for 5 days. Our past experience showed that a lower dose (3 mg) lowered uric acid levels sufficiently in most patients. A retrospective review was conducted to determine the effect of a fixed 3 mg dose of rasburicase in 43 adult patients with cancer undergoing hematopoietic stem cell transplantation or receiving chemotherapy who had elevated or rising uric acid levels (6.4-16.8 mg/dl; median 9.6). Six patients received a second dose of rasburicase (3 mg in four patients and 1.5 mg in two patients) 24 h later. Patients received allopurinol, adequate hydration, as well as other supportive therapy as required. Uric acid levels declined by 6-95% (median 43%) within the first 24 h after rasburicase administration, and levels at 48 h were 9-91% (median 65%) lower than the baseline levels. Serum creatinine changed by < or =10% in 21 patients, increased by >10% in four patients and decreased by >10% in 18 patients. No significant renal dysfunction developed in any of the patients. We conclude that rasburicase is effective

in lowering uric acid levels at a fixed dose of 3 mg, which is much lower than the recommended dose.

8: Annemans L, et al Pan-European multicentre economic evaluation of recombinant urate oxidase (rasburicase) in prevention and treatment of hyperuricaemia and tumour lysis syndrome in haematological cancer patients. Support Care Cancer. 2003 Apr;11(4):249-57.

GOALS: Hyperuricaemia (HU) and tumour lysis syndrome (TLS) are complications of acute myeloid/lymphoid leukaemia (AML/ALL) and non-Hodgkin lymphoma (NHL) leading to increased morbidity and mortality. The objective was to assess incremental cost-effectiveness ratios (ICER) of preventing /treating HU and TLS with recombinant urate oxidase, rasburicase (Fasturtec/Elitek). PATIENTS AND METHODS: Incidence and costs of HU and TLS were based on a multi-country chart review. Life expectancy at the time of diagnosis was based on published survival rates and age at diagnosis. Reductions of HU/TLS following treatment with rasburicase were based on clinical trial data. RESULTS: Prevention with rasburicase appears highly cost-effective in children (ICER between Eur 425 and Eur 3054 per life-year saved, LYS). In adults, prevention is more cost-effective in NHL and ALL (maximum ICER of Eur 41383 and Eur 32126 per LYS). Treatment of established HU/TLS with rasburicase is cost-saving in children and highly cost-effective in adults. The results are robust in children. In adults, the prevention strategy appears sensitive to the risk of HU/TLS. CONCLUSIONS: In conclusion, rasburicase,in addition to the demonstrated clinical benefit, is an economically attractive new option in the treatment of HU, both in adults and children. In prevention the drug has an attractive economic profile in children, and is cost-effective in adults with ALL and NHL.

10: Annemans L,et al Incidence, medical resource utilisation and costs of hyperuricemia and tumour lysis syndrome in patients with acute leukaemia and non-Hodgkin's lymphoma in four European countries. Leuk Lymphoma. 2003 Jan;44(1):77-83.

Hyperuricemia (HU) and tumour lysis syndrome (TLS) are complications of acute leukaemia and non-Hodgkin lymphoma (NHL) leading to increased morbidity and mortality. The objective of this study was to define incidence and calculate health care cost associated with HU and TLS. 788 acute leukaemia and NHL patients from Belgium, The Netherlands, Spain and UK were screened retrospectively for HU and TLS. Resource use related to HU and TLS was recorded and costs were calculated applying local unit costs. Results showed that HU occurred in 18.9% of patients, and 27.8% of them fulfilled TLS criteria. The cost of HU without TLS was 672 euros (SE 181), the cost of TLS 7,342 euros (SE 1,412). TLS requiring dialysis incurred an average cost of 17,706 euros. In conclusion, it is noted that the observed incidence rates were lower than earlier reports. In addition, some risk factors for HU and TLS (e.g. paediatric patients versus adults) were not associated with increased rates of HU or TLS as a consequence of higher rates of prevention. TLS cases incurred 11 times higher costs than HU cases in which TLS was absent. The main cost drivers in TLS are interventions requiring intensive care.