

# Tumour lysis syndrome: new therapeutic strategies and classification

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## Summary

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, hyperphosphatemia, 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 alkalization 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.

**Keywords:** tumour lysis syndrome, allopurinol, rasburicase.

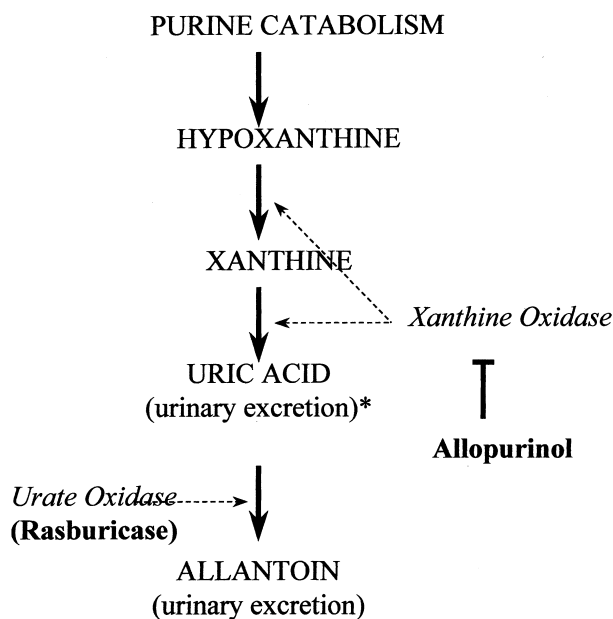
## Pathophysiology

Not long after the introduction of cytotoxic chemotherapy into the clinical practice of oncology and malignant haematology, severe metabolic derangements occurring shortly after the initiation of therapy were observed (Frei *et al*, 1963; Zusman *et al*, 1973; O'Regan *et al*, 1977; Cohen *et al*, 1980; Hande *et al*, 1981; Tsokos *et al*, 1981; Bishop & Coccia, 2000). The consistent observation of these metabolic abnormalities, primarily in the context of lymphoma and leukaemia treatment, led to the term, tumour lysis syndrome (TLS).

While TLS may occur spontaneously prior to administration of therapy, it is most commonly observed after the initiation of cytotoxic chemotherapy. In tumours with a high proliferative rate, a relatively large tumour burden, and a high sensitivity to cytotoxic agents, the initiation of therapy often results in the rapid release of intracellular anions, cations and the metabolic products of proteins and nucleic acids into the bloodstream (Tannock, 1978). Hyperuricaemia results from rapid release and catabolism of intracellular nucleic acids (Seegmiller *et al*, 1963; Van den Berghe, 2000). Purine nucleic acids are catabolized to hypoxanthine, then xanthine, and finally uric acid by xanthine oxidase (Fig 1). Uric acid clearance occurs in the kidney, and in normal circumstances approximately 500 mg of uric acid is excreted through the kidneys each day (Klinenberg *et al*, 1965). Uric acid has a pKa of 5.4–5.7 and is poorly soluble in water. At normal concentrations and at physiological blood pH, over 99% of uric acid is in the ionized form (Klinenberg *et al*, 1965).

Hyperphosphataemia results from the rapid release of intracellular phosphorous from malignant cells, which may contain as much as four times the amount of organic and inorganic phosphorous as compared to normal cells (Frei *et al*, 1963). Initially, the kidneys are able to respond to the increased concentration of phosphorous from tumour lysis by increased urinary excretion and decreased tubular re-absorption of phosphorous. Eventually, however, the tubular transport mechanism becomes saturated and serum phosphorous levels rise. The development of hyperphosphataemia may be further exacerbated by acute renal insufficiency associated with uric acid precipitation or other complications of tumour therapy (Vachvanichsanong *et al*, 1995). Hyperphosphataemia can lead

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\* A normal endpoint of purine metabolism in humans

Fig 1. Mechanism of action: rasburicase and allopurinol. Depicted is the pathway of purine catabolism. Rasburicase is a recombinant form of urate oxidase, an enzyme that converts uric acid to allantoin. In comparison, allopurinol acts by inhibiting the endogenous enzyme xanthine oxidase, thereby inhibiting formation of uric acid. (From Goldman *et al*, 2001. Copyright American Society of Hematology, used with permission.)

to the development of acute renal failure after the precipitation of calcium phosphate in renal tubules during TLS (Wechsler *et al*, 1994).

Hyperkalaemia may also be a life-threatening consequence of TLS and is partly a result of the kidneys' inability to clear the massive quantities of potassium released by lysed tumour cells (Cohen *et al*, 1980). Hyperkalaemia results from initial lysis of tumour cells and then becomes exacerbated by the development of uraemia (renal failure) and is occasionally secondary to excess iatrogenic administration of potassium during induction therapy. The rapid rise in serum potassium may result in severe arrhythmias and sudden death (Cohen *et al*, 1980).

Hypocalcaemia may be asymptomatic or symptomatic. Hypocalcaemia results from hyperphosphataemia (see above) and the precipitation of calcium phosphate crystals in the renal tubules (Wechsler *et al*, 1994). When the calcium phosphorus multiple exceeds 70, there is a significant risk of calcium phosphate deposition in the kidney and other tissues that secondarily leads to systemic hypocalcaemia (Frei *et al*, 1963; Zusman *et al*, 1973; O'Regan *et al*, 1977). Occasionally, a low albumin may suggest hypocalcaemia and, in cases of hypoalbuminaemia, an ionized calcium is required to determine if there is true hypocalcaemia (Wechsler *et al*, 1994; Vachnichsanong *et al*, 1995).

Uraemia is another common manifestation of TLS (Frei *et al*, 1963; Tsokos *et al*, 1981; Bishop & Coccia, 2000). Uraemia may be secondary to multiple mechanisms during TLS. The most common cause of uraemia during TLS is uric acid crystal formation in the renal tubules secondary to hyperuricaemia. Other mechanisms of uraemia during TLS include calcium phosphate deposition, tumour infiltration in the kidney, tumour-associated obstructive uropathy, drug associated-nephrotoxicity and/or acute sepsis (Frei *et al*, 1963; Tsokos *et al*, 1981; Bishop & Coccia, 2000). As uraemia may be secondary to multiple causes during TLS, investigations into causes other than hyperuricaemia should be pursued when patients develop uraemia during cytoreductive therapy for haematological malignancies.

### Incidence

In a retrospective study of 102 patients with high-grade non-Hodgkin's lymphoma (NHL), the incidence of TLS was reported to be 42% (Hande & Garrow, 1993), although the incidence of clinically significant TLS was only 6%. TLS has been reported most commonly in acute lymphoblastic leukaemia and high-grade NHL, in particular Burkitt's lymphoma (Hande & Garrow, 1993). Other haematological malignancies that have been less commonly associated with TLS include chronic lymphocytic leukaemia, acute myeloid leukaemia and plasma cell disorders including multiple myeloma, and isolated plasmacytomas. In addition, there have been anecdotal reports of TLS in a variety of other haematological malignancies including low-grade and intermediate-grade NHL, Hodgkin's disease, chronic myeloid leukaemia (CML) in blast crisis and myeloproliferative disorders. TLS has also been reported to occur in solid tumours with high proliferative rates and a high response rate to cytotoxic therapy, such as testicular cancer, breast cancer and small cell lung cancer.

The identification of patients at risk for the development of TLS is the most important aspect of management so that prophylactic measures may be initiated prior to the initiation of therapy (Hande & Garrow, 1993; Bishop & Coccia, 2000). Patients with decreased urinary flow, pre-existing hyperuricaemia, renal failure, dehydration or acidic urine are at increased risk for TLS (Frei *et al*, 1963; Tsokos *et al*, 1981). There are also tumour-related risk factors for TLS, which include high tumour cell proliferation rate, size and chemosensitivity.

### Definition and classification

Although there is a general consensus for a broad definition of TLS as a set of metabolic complications that can arise from treatment of a rapidly proliferating neoplasm, there have been very few attempts to apply a specific definition to this syndrome (Hande & Garrow, 1993; Razis *et al*, 1994; Kedar *et al*, 1995). Hande and Garrow (1993) attempted to qualify the clinical and pathological characteristics of patients at risk

for the development of TLS through a retrospective analysis of 102 patients with 'intermediate' to 'high-grade' NHL. As part of their analysis, they classified TLS as either laboratory TLS (LTLS) or clinical TLS (CTLS). The designations were made to distinguish patients who had laboratory evidence of TLS but did not require a specific therapeutic intervention from those patients who experienced life-threatening clinical abnormalities that required a specific intervention (e.g. haemodialysis).

As previously described, there have been many general definitions of TLS but a uniform, generally accepted definition is still lacking. A uniform diagnosis would aid in determining the exact incidence of TLS. With the development of new therapies for the prevention of TLS, the necessity of a uniform definition becomes more relevant if these therapies or future therapies are to be compared. Recent studies have relied on the measurement of hyperuricaemia, which is of questionable clinical relevance with regard to outcome, and criteria that are more clinically relevant would be useful (Goldman *et al*, 2001; Pui *et al*, 2001). There have been prior attempts to develop clinically relevant classification and grading systems, but they all have limitations and inadequacies. The National Cancer Institute (NCI) Common Toxicity Criteria (CTC) 2.0 grading system and the newly proposed Common Terminology Criteria for Adverse Events (CTCAE) 3.0 grading system only grade TLS as grade 3 'present' or grade 4 'death' (CTCAE 3.0 only) and still lack a concise definition. The most complete and referenced classification system for TLS is by Hande and Garrow (1993). This classification is attractive in that it makes the distinction between laboratory and clinical aspects of TLS. As described above, only a minority of patients with LTLS develop CTLS (i.e. require a clinical intervention beyond preemptive measures). However, the Hande-Garrow classification system has several shortcomings. First, the definition of LTLS requires a 25% increase in the baseline laboratory value and does not take into account those patients who present with already abnormal values. Secondly, it requires that these changes occur within 4 d of the initiation of therapy. This may potentially exclude patients who have clinical evidence of TLS at presentation, who develop it while being prepared for treatment, or who develop TLS beyond 4 d of therapy.

In an attempt to provide a unified definition with clinical relevance, we developed a modified version of the Hande-Garrow classification system (Tables I and II). Our goals in the development of this modified version were for it to be practical and reproducible, address the shortcomings of the Hande-Garrow classification system, and be clinically relevant. We propose that patients are classified into three groups. The first group has no evidence of either laboratory and/or clinical TLS (No TLS) at the time of presentation. This group could further be broken down to low risk [non-haematological malignancies, low tumour burden, low chemosensitivity, low white blood cell (WBC) count and/or low lactate dehydrogenase (LDH) levels, etc.] *versus* high risk (haematological malignancies, i.e. Burkitt's, lymphoblastic lymphoma, high tumour burden, high WBC count, high LDH level and/or high chemosensitiv-

Table I. Cairo-Bishop definition of laboratory tumour lysis syndrome.

Uric acid	$x \geq 476 \mu\text{mol/l}$ or 25% increase from baseline
Potassium	$x \geq 6.0 \text{ mmol/l}$ or 25% increase from baseline
Phosphorous	$x \geq 2.1 \text{ mmol/l}$ (children), $x \geq 1.45 \text{ mmol/l}$ (adults) or 25% increase from baseline
Calcium	$x \leq 1.75 \text{ mmol/l}$ or 25% decrease from baseline

Modified from Hande and Garrow (1993).

Laboratory tumour lysis syndrome (LTLS) 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 d before or 7 d after the initiation of chemotherapy. This assessment assumes that a patient has or will receive adequate hydration ( $\pm$  alkalinization) and a hypouricaemic agent(s).

Table II. Cairo-Bishop definition of clinical tumour lysis syndrome.

- (1) Creatinine\*:  $x \geq 1.5 \text{ ULN}^\dagger$  (age >12 years or age adjusted)
- (2) Cardiac arrhythmia/sudden death\*
- (3) Seizure\*

Modified from Hande and Garrow (1993).

Clinical tumour lysis syndrome (CTLS) assumes the laboratory evidence of metabolic changes and significant clinical toxicity that requires clinical intervention. CTLS is defined as the presence of LTLS and any one or more of the above-mentioned criteria.

\*Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration).

$^\dagger$ Creatinine levels: patients will be considered to have elevated creatinine if their serum creatinine is 1.5 times greater than the institutional upper limit of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: > 1 <12 years, both male and female, 61.6  $\mu\text{mol/l}$ ;  $\geq 12$  < 16 years, both male and female, 88  $\mu\text{mol/l}$ ;  $\geq 16$  years, female, 105.6  $\mu\text{mol/l}$ ;  $\geq 16$  years, male, 114.4  $\mu\text{mol/l}$ .

ity). The basic definition of LTLS of the Hande-Garrow classification system is relatively practical and easily reproducible. However, to address the issue of patients who present with abnormal values, our definition uses serum levels above the high end of normal in addition to 25% increases above baseline (Table I). In addition, abnormal values that occur within 3 d before and 7 d after the start of therapy are used in the definition of LTLS. The definition of CTLS was developed to address the issue of clinical relevance. Similar to the Hande-Garrow classification system, we required the presence of LTLS. In addition we required the presence of one or more of the three most significant clinical complications associated with TLS: renal insufficiency, cardiac arrhythmias/sudden death and seizures (Table II). There is no currently accepted grading system for LTLS and/or CTLS, including the recent version of the NCI grading system (3.0), and therefore we propose a uniform grading system that incorporates our definitions of no TLS, LTLS and CTLS (Table III). The maximal clinical manifestation (renal, neuro, cardiac) defines the grade of TLS. This grading system is currently being evaluated in the new Children's Oncology Group newly

**Table III.** Cairo–Bishop grading classification of tumour lysis syndrome.

	Grade 0*	Grade I	Grade II	Grade III	Grade IV	Grade V
LTLS	–	+	+	+	+	+
Creatinine†/‡	≤1.5 × ULN	1.5 × ULN	>1.5–3.0 × ULN	>3.0–6.0 × ULN	>6.0 ULN	Death§
Cardiac arrhythmia‡	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator)	Life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)	Death§
Seizure‡	None	–	One brief generalised seizure; seizure(s) well controlled by anti-convulsants 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 (e.g. status epilepticus, intractable epilepsy)	Death§

Clinical tumour lysis syndrome (CTLS) requires one or more clinical manifestations along with criteria for laboratory tumour lysis syndrome (LTLS). Maximal CTLS manifestation (renal, cardiac, neuro) defines the grade.

\*No laboratory tumour lysis syndrome (LTLS).

†Creatinine levels: patients will be considered to have elevated creatinine if their serum creatinine is 1.5 times greater than the institutional upper limit of normal (ULN) below age/gender defined ULN. If not specified by an institution, age/sex ULN creatinine may be defined as: > 1 < 12 years, both male and female, 61.6 µmol/l; ≥ 12 < 16 years, both male and female, 88 µmol/l; ≥ 16 years, female, 105.6 µmol/l; ≥ 16 years, male 114.4 µmol/l.

‡Not directly or probably attributable to a therapeutic agent (e.g. rise in creatinine after amphotericin administration).

§Attributive probably or definitely to CTLS.

diagnosed advanced B-NHL study of chemoimmunotherapy and rasburicase (COG ANHL01P1) (unpublished observations).

## Clinical manifestations and management of TLS

### General clinical manifestations and treatment

Clinical manifestations may include nausea, vomiting, lethargy, oedema, fluid overload, congestive heart failure, cardiac dysrhythmias, seizures, muscle cramps, tetany, syncope and possibly sudden death. The clinical manifestations may have their onset prior to initiation of cytotoxic therapy but more commonly present within 12–72 h after administration of cytotoxic therapy.

The principle feature in the successful management of acute TLS is maintaining a high index of suspicion, immediately identifying patients at high risk of developing TLS (see above) and aggressively instituting a proactive prophylactic strategy to prevent and/or reduce the severity of the clinical manifestations of acute TLS. Tumour therapy should be delayed, if possible, in patients at high risk for the development of TLS until prophylactic measures can be initiated. Unfortunately, a delay in therapy is not possible for many patients because of the aggressive nature of their underlying malignancy. In this clinical situation, a decision must be made regarding the relative risks in the delay of tumour therapy *versus* the risk of developing or exacerbating TLS and its associated complications including acute renal failure. Regardless of time con-

straints, the patient should have reliable venous access and be treated in an intensive care or haematology/oncology unit with personnel who are trained and familiar with the complications associated with TLS.

### Fluids and alkalinisation

Unless a patient presents with signs of acute renal dysfunction and oliguria, vigorous hydration (3 l/m<sup>2</sup>/d) (2× maintenance) and aggressive diuresis (avoid in hypovolaemia) is a mainstay of therapy. Increased hydration and accompanying increase in urine flow improves intravascular volume, enhances renal blood flow and glomerular filtration, and promotes urinary excretion of uric acid and phosphate (Andreoli *et al*, 1986; Silverman & Distelhorst, 1989; Jones *et al*, 1995). Patients should receive anywhere between two and four times daily fluid maintenance (approximately 3 l/m<sup>2</sup>/d or 200 ml/kg/d if ≤10 kg) and maintain a urine output of ≥100 ml/m<sup>2</sup>/h (3 ml/kg/h if ≤10 kg). Despite adequate hydration (3 l/m<sup>2</sup>/d), diuretics may be required if there is no evidence of acute obstructive uropathy and/or hypovolaemia to maintain a urine output of ≥100 ml/m<sup>2</sup>/h (≥3 ml/kg/h if ≤10 kg). Such diuretics may include mannitol (0.5 mg/kg) or furosemide (0.5–1.0 mg/kg). In the event of severe oliguria or anuria, a single dose of furosemide (2–4 mg/kg) may be considered to improve or initiate urinary output. The urine specific gravity should be maintained at ≤1.010. Potassium, calcium and phosphate should not be initially added to hydration fluids so as to avoid hyperkalaemia, hyperphosphataemia and/or

calcium phosphate precipitation (Andreoli *et al*, 1986; Silverman & Distelhorst, 1989; Jones *et al*, 1995).

Urine alkalinization (urine pH  $\geq 7.0$ ) has historically been a general recommendation for the prevention and/or treatment of TLS (Ten Harkel *et al*, 1998). An alkaline urine ( $\geq$  urine pH 6.5) promotes the urinary excretion of urate (Jones *et al*, 1995; Ten Harkel *et al*, 1998). However, the current use of sodium bicarbonate to alkalinize the urine is controversial. The maximal solubility of urate occurs at a pH of 7.5 and at alkaline urine pH ( $\geq 6.5$ ) the solubility of xanthine and hypoxanthine significantly decreases, leading to the development of urinary xanthine crystals during and after allopurinol therapy (see below) (Tsokos *et al*, 1981; Andreoli *et al*, 1986; Jones *et al*, 1995; Ten Harkel *et al*, 1998). Overzealous systemic and urinary alkalinization may lead to metabolic alkalosis and/or xanthine obstructive uropathies.

### Hyperphosphataemia

Hyperphosphataemia is usually defined by a phosphorus  $\geq 2.1$  mmol/l in children or  $\geq 1.45$  mmol/l in adults and appears secondary to the acute release of cellular phosphate into the peripheral blood during acute degradation of malignant cells. Severe hyperphosphataemia may be associated with nausea, vomiting, diarrhoea, lethargy and seizures. More importantly, hyperphosphataemia may result in tissue precipitation of calcium phosphate, resulting in hypocalcaemia (see below), metastatic calcification, intrarenal calcification, nephrocalcinosis, nephrolithiasis and additional acute obstructive uropathy (Andreoli *et al*, 1986; Jones *et al*, 1995).

Phosphorus levels  $\geq 2.1$  mmol/l suggest the need for medical intervention. Initial treatment of hyperphosphataemia includes deleting phosphate from intravenous solutions and the administration of oral forms of phosphate binders such as aluminium hydroxide by oral or nasogastric administration at a dose of 15 ml (50–150 mg/kg/24 h) q6 h. Patients with hyperphosphataemia should not receive calcium infusions. Occasionally, hyperphosphataemia is quite severe despite oral aluminium hydroxide therapy and requires more aggressive therapy. Continuous peritoneal dialysis, haemodialysis or continuous venovenous haemofiltration (CVVH) have been successfully employed in patients with acute TLS and severe hyperphosphataemia (Heney *et al*, 1990; Sakarcin & Quigley, 1994; Jones *et al*, 1995). The clearance of phosphorus is significantly better following haemodialysis *versus* CVVH *versus* continuous peritoneal dialysis (9.8 vs. 1.0 vs. 0.3 mg/min) (Table IV; Heney *et al*, 1990; Sakarcin & Quigley, 1994; Jones *et al*, 1995).

### Hypocalcaemia

Hypocalcaemia is a metabolic disturbance that commonly occurs in association with hyperphosphataemia and tissue precipitation of calcium phosphate during acute TLS. Hypocalcaemia is defined as a serum calcium of  $\leq 1.75$  mmol/l or an

Table IV. Management of electrolyte abnormalities associated with TLS.

Treatment of electrolyte abnormality
<b>Hyperphosphataemia</b>
Moderate ( $\geq 2.1$ mmol/l)
Avoid i.v. phosphate administration
Aluminium hydroxide p.o. 15 ml (50–150 mg/kg/24 h) q6
Severe
Dialysis, CAVH, CVVH, CAVHD or CVVHD
<b>Hypocalcaemia</b> ( $\leq 1.75$ mmol/l)
Asymptomatic
No therapy
Symptomatic
Calcium gluconate 50–100 mg/kg i.v.
<b>Hyperkalaemia</b>
Moderate and asymptomatic ( $\geq 6.0$ mmol/l)
Avoid i.v. and oral potassium
ECG and cardiac rhythm monitoring
Sodium polystyrene sulphonate (Kayexalate <sup>®</sup> , Bayer Corporation, Myerstown, PA, USA)
Severe ( $>7.0$ mmol/l) and/or symptomatic
Same as above, plus
Calcium gluconate (100–200 mg/kg) i.v. and/or
Regular insulin (0.1 unit/kg i.v.) + D25 (2 ml/kg) i.v.
Dialysis
<b>Renal dysfunction (uraemia)</b>
Fluid and electrolyte management
Uric acid and phosphate management
Adjust renally excreted drug doses
Dialysis (haemo- or peritoneal)
Haemofiltration (CAVH, CVVH, CAVHD or CVVHD)

CAVH, continuous arteriovenous haemofiltration; CVVH, continuous venovenous haemofiltration; CAVHD, continuous arteriovenous haemodiafiltration; CVVHD, continuous venovenous haemodiafiltration.

ionized calcium of  $\leq$  ionised institutional limits. Severe hypocalcaemia is one of the most critical clinical manifestations of TLS and may be associated with muscular, cardiovascular and/or neurological complications. Muscular manifestations include muscle cramps and spasms, paresthesias, tetany; cardiac abnormalities include ventricular arrhythmias, heart block, hypotension; and neurological complications may include confusion, delirium, hallucinations and seizures. Severe neurological and/or cardiac complications as mentioned above may lead to more devastating clinical manifestations including bradycardia, cardiac failure, coma and rarely death (Andreoli *et al*, 1986; Jones *et al*, 1995; Jeha, 2001).

Treatment of asymptomatic hypocalcaemia is generally not recommended. The risk of precipitating metastatic calcification is high, especially in the setting of hyperphosphataemia, and therefore if patients are asymptomatic the hypocalcaemia will generally resolve without treatment as tumour lysis improves (Jones *et al*, 1995; Jeha, 2001). In patients with symptomatic hypocalcaemia, intravenous calcium gluconate (50–100 mg/kg/i.v./dose) may be administered to correct the

clinical symptoms; however this may increase the calcium phosphate solubility factor product and increase the risk of calcium phosphate deposition and an increase in acute obstructive uropathy (Table IV). (Jones *et al*, 1995).

### Hyperkalaemia

Hyperkalaemia, usually defined by a potassium of  $\geq 6.0$  mmol/l, results from massive cellular degradation and efflux of potassium during acute TLS and may be life threatening. General clinical manifestations may include: nausea, anorexia, vomiting and diarrhoea. More specific complications include neuromuscular and cardiac abnormalities. Neuromuscular signs and symptoms may include muscle weakness, cramps, paresthesias and possible paralysis. Cardiac manifestations may include peaked T-waves on an electrocardiogram (ECG), asystole, ventricular tachycardia or fibrillation, syncope and possible sudden death (Andreoli *et al*, 1986; Jones *et al*, 1995; Jeha, 2001).

In patients who are asymptomatic, the treatment of choice is sodium polystyrene sulphonate (1 g/kg with 50% sorbitol) orally or per rectum. In patients that are symptomatic, more acute therapeutic measures are required, including rapid acting insulin (0.1 unit/kg i.v.) and glucose infusion (25% dextrose 2 ml/kg) (Jones *et al*, 1995; Kelly & Lange, 1997). Close and continuous monitoring of the ECG and cardiac rhythm and frequent electrolyte evaluation are required during periods of hyperkalaemia. Supplemental oral and i.v. potassium should be avoided during acute TLS, especially in patients with elevated serum potassium (Table IV).

### Hyperuricaemia

Hyperuricaemia is usually defined as a uric acid  $\geq 476$   $\mu\text{mol/l}$  and as mentioned earlier, is the result of a breakdown of large quantities of nucleic acids (purine catabolism) (Fig 1) from necrotic malignant cells (Bishop & Coccia, 2000). When the excretory capacity of the renal tubule is exceeded, hyperuricaemia develops and, in the presence of an acid pH, uric acid crystals form in the renal tubule, leading to intraluminal renal tubular obstruction and the development of acute renal obstructive uropathy and renal dysfunction (Andreoli *et al*, 1986; Jones *et al*, 1995). If the hyperuricaemia results in acute obstructive uropathy, other clinical manifestations may include haematuria, flank pain, hypertension, azotemia acidosis, oedema, oliguria, anuria, lethargy and somnolence (see below) (Jones *et al*, 1995; Jeha, 2001).

Allopurinol is a xanthine analogue that, when converted *in vivo* to oxypurinol, is a competitive inhibitor of xanthine oxidase (see above), which inhibits the metabolism of xanthine and hypoxanthine to uric acid (Krakoff & Meyer, 1965; Spector, 1977). Allopurinol has been demonstrated to effectively decrease the formation of new uric acid and reduce the incidence of uric acid obstructive uropathy in patients with malignant disease at risk of TLS (Krakoff & Meyer, 1965;

Table V. Hypouricaemic agents.

#### Allopurinol

100 mg/m<sup>2</sup>/dose q8 h (10 mg/kg/d divided q8 h) p.o. (maximum 800 mg/d) or 200–400 mg/m<sup>2</sup>/d in 1–3 divided doses i.v. (maximum 600 mg/d)  
Reduce dose by 50% or more in renal failure  
Reduce 6-mercaptopurine and/or azathioprine doses by 65–75% with concomitant allopurinol  
Adjust doses of drugs metabolized by P<sub>450</sub> hepatic microsomal enzymes with concomitant allopurinol

#### Rasburicase

Avoid in glucose-6-phosphate dehydrogenase deficient patients  
0.05–0.20 mg/kg i.v. over 30 min  
To measure uric acid levels place blood sample immediately on ice to avoid continual pharmacological *ex vivo* enzymatic degradation  
10% incidence of antibody formation

Goldman *et al*, 2001). Allopurinol is administered at a dose of 100 mg/m<sup>2</sup>/dose q8 h (10 mg/kg/d divided q8 h) p.o. (maximum 800 mg/d) or 200–400 mg/m<sup>2</sup>/d in 1–3 divided doses i.v. (maximum 600 mg/d) (Table V). However, allopurinol has several limitations that require consideration. As allopurinol only prevents new uric acid formation, it does not reduce uric acid produced prior to allopurinol initiation. A second limitation of treatment with allopurinol is that serum levels of the purine precursors, xanthine and hypoxanthine, are increased (DeConti & Calabresi, 1966; Spector, 1977). As xanthine is less soluble in urine in comparison with uric acid, xanthine nephropathy resulting in acute obstructive uropathy may develop (Band *et al*, 1970; Landgrebe *et al*, 1975). The third limitation is that allopurinol reduces the degradation of other purines, including 6-mercaptopurine (6-MP) and azathioprine. A dose reduction of 50–70% of each of these purines, especially 6-MP, is recommended during concomitant use with allopurinol. Recently, an intravenous preparation of allopurinol has become available (Smalley *et al*, 2000). As allopurinol is excreted in the kidney, the dose of allopurinol should be adjusted during clinical conditions of renal failure.

An alternative to inhibiting uric acid formation by inhibiting xanthine oxidase with allopurinol is to promote the catabolism of uric acid to allantoin by urate oxidase. In comparison with uric acid, allantoin is five to ten times more soluble in urine (Brogard *et al*, 1972). Urate oxidase is an endogenous enzyme commonly found in many mammalian species but not in humans, secondary to a nonsense mutation in the coding region during hominoid evolution (Yeldandi *et al*, 1991). A non-recombinant urate oxidase, extracted from *Aspergillus flavus* species, has been demonstrated to reduce uric acid levels in patients at risk of TLS and has been available in France since 1975 and in Italy since 1984 (Masera *et al*, 1982; Pui *et al*, 1997; Patte *et al*, 2002).

Recently, the gene coding for the urate oxidase was isolated as a cDNA clone from the *A. flavus* species and expressed in the yeast *Saccharomyces cervaciae* strain to yield large quantities of

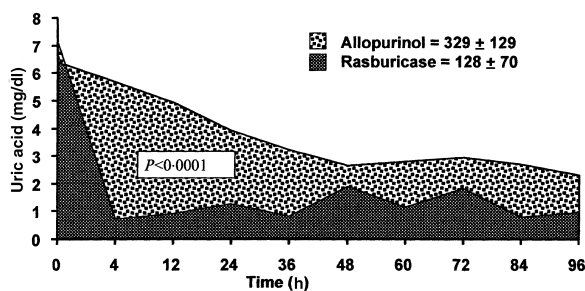


Fig 2. Uric acid area under the curve 0–96 h. Uric acid area under the curve (AUC) 0–96 h in patients with haematological malignancies at risk for TLS treated with either allopurinol ( $n = 27$ ) or rasburicase ( $n = 25$ ) during initial cytoreduction chemotherapy ( $P = 0.0007$ ). (From Goldman *et al*, 2001. Copyright American Society of Hematology, used with permission.)

the pure recombinant form of urate oxidase (rasburicase) (Legoux *et al*, 1992). Pui *et al* (2001) initially reported the prophylactic use of rasburicase (0.15–0.20 mg/kg i.v. q.i.d. for 5–7 d) in 66 children with haematological malignancies at risk of TLS who presented with normouricaemic levels (uric acid <476  $\mu\text{mol/l}$ ). Pui *et al* (2001) demonstrated a significant reduction of the median uric acid level of 256–30  $\mu\text{mol/l}$  ( $P = 0.0001$ ) within 4 h. Despite subsequent administration of cytoreductive therapy, the median uric acid level remained at or below 30  $\mu\text{mol/l}$ . Pui *et al* (2001) demonstrated that rasburicase within 4 h of therapy significantly decreased the median uric acid level from 577 to 60  $\mu\text{mol/l}$  ( $P = 0.0001$ ) in 65 patients with hyperuricaemia. Lastly, in the only randomized trial to date between allopurinol and rasburicase in patients at risk of acute TLS, we demonstrated that rasburicase significantly reduced the exposure to uric acid and area under the curve for mean uric acid ( $\text{AUC}_{0-96}$ ) in patients with hyperuricaemia compared with allopurinol ( $9639 \pm 5176$  vs.  $26180 \pm 7200$   $\mu\text{mol/l/h}$ ) ( $P < 0.0007$ ) (Fig 2; Table V) (Goldman *et al*, 2001). The use of rasburicase for the prevention and treatment of hyperuricaemia has recently been reported (Pui, 2002; Cairo, 2003; Ribeiro & Pui, 2003). Rasburicase should be avoided in patients with G-6PD deficiency. A small minority of patients can develop bronchospasm after the initial administration of rasburicase, and appropriate medications (e.g. diphenhydramine, epinephrine) should be available at the bedside.

#### Recommended guidelines to prevent and/or treat hyperuricaemia

Patients considered to have no LTLS or CTLs and with a low risk of developing TLS would be candidates for allopurinol prophylaxis. Low-risk factors for TLS include non-haematological malignancies, haematological malignancies with low proliferative rates (i.e. CML, Hodgkin's disease), patients with low tumour burdens (i.e. low WBC count,  $\leq 50 \times 10^9/\text{l}$ , and normal LDH levels), patients receiving low intensity

Table VI. Recommendations for hyperuricaemia agents.

	Allopurinol	Rasburicase
Uric acid level	Normal	Elevated
Tumour type	Non-haematological Hodgkin's lymphoma, CML	Burkitt's lymphoma, lymphoblastic lymphoma, ALL, AML
Tumour burden		
WBC count	$\leq 50 \times 10^9/\text{l}$	$> 50 \times 10^9/\text{l}$
LDH	$\leq 2 \times$ normal	$> 2 \times$ normal
Cytoreductive intensity	Mild	Aggressive
Kidney tumour infiltration	Absent	Present

CML, chronic myeloid leukaemia; ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; WBC, white blood cell; LDH, lactate dehydrogenase.

cytoreductive therapy, patients with pre-existing normal uric acid, patients with adequate hydration and without tumour infiltration in the kidney (Table VI).

Patients with either the presence of LTLS and/or CTLs would be better candidates for rasburicase therapy for prophylaxis and/or therapy of hyperuricaemia. High-risk factors for TLS would include haematological malignancies with high proliferative rates (i.e. Burkitt's lymphoma and T-cell lymphoblastic lymphoma), patients with high tumour burdens (i.e. high WBC count,  $\geq 50 \times 10^9/\text{l}$  and/or high LDH levels), patients with elevated uric acid levels, patients receiving intensive cytoreductive therapy, patients with poor hydration and/or patients with leukaemia/lymphoma infiltration of the kidney. While the original studies utilized a dose of 0.20 mg/kg/d, i.v. for 5–7 d, recent studies have demonstrated that lower doses (0.05–0.20 mg/kg) and/or a short treatment duration of 1–3 d may be as effective as the original dose and schedule and may be more cost-effective, reducing costs and exposure to rasburicase (Table V).

#### Uraemia and acute renal dysfunction

Acute renal dysfunction, azotaemia and a rising creatinine level are most commonly secondary to either acute uric acid crystal nephropathy, calcium phosphate deposition and nephrocalcinosis or a combination of the two, leading to an acute obstructive uropathy syndrome. Acute clinical manifestations may include uraemia resulting in nausea, vomiting and lethargy, oliguria/anuria leading to fluid retention, oedema, hypertension, congestive heart failure, metabolic disturbances and exacerbations of hyperphosphataemia and/or hyperkalaemia (see above), flank or back pain, haematuria and severe acidosis. Furthermore, acute obstructive uropathy may precipitate acute renal failure, confusion, somnolence, seizures and/or coma (Andreoli *et al*, 1986; Jones *et al*, 1995; Jeha, 2001).

Renal dysfunction may be multifactorial during acute TLS including, uric acid crystal obstructive uropathy, calcium

phosphate nephrocalcinosis, renal tumour infiltration, xanthinuria, ureteral obstruction, nephrotoxic drugs and/or intravascular volume depletion (Jones *et al*, 1995). There have been no prospective randomised studies comparing the incidence of renal failure and/or dialysis in patients with haematological malignancies at risk for TLS receiving allopurinol *versus* non-recombinant urate oxidase or rasburicase.

Careful monitoring of fluid intake and output, electrolyte management and management of hypertension are the cornerstone of the management of renal dysfunction associated with acute TLS. Secondary management of hyperuricaemia, hyperphosphataemia and avoidance of uric acid renal crystallization, xanthine renal crystallization and calcium phosphorus renal deposition, as mentioned earlier, are also critically important in the treatment and prevention of further renal dysfunction. Thirdly, dose modification of medications that are primarily renally cleared should be initiated during renal dysfunction and acute TLS. However, despite the best therapeutic approaches, some patients with increasing renal dysfunction and acute TLS require more aggressive measures, including either dialysis (haemodialysis and/or peritoneal dialysis) or haemofiltration (CVVH), continuous arteriovenous haemofiltration (CAVH), continuous arteriovenous haemodiafiltration (CAVHD), or continuous venovenous haemodiafiltration (CVVHD) (Jones *et al*, 1995). Indications for these assisted renal replacement therapies include any one or more of the following uncontrolled by medical management: (i) hyperphosphataemia, (ii) hyperkalaemia, (iii) hyperuricaemia, (iv) hypocalcaemia, (v) volume overload, (vi) uncontrolled hypertension, (vii) severe acidosis, and/or severe uraemia with central nervous system toxicity. For uric acid clearance, haemodialysis is superior to peritoneal dialysis, which is superior to CVVH (70–145 vs. 15 vs. 6.2 ml/min) (Table IV) (Jones *et al*, 1995).

## Conclusion

Tumour lysis syndrome is a constellation of metabolic derangements secondary to excessive purine catabolism that overrides normal physiological pathways, resulting in a precise clinical syndrome. Humans are especially vulnerable to developing TLS during states of increased purine catabolism because of the lack of the presence of urate oxidase to convert uric acid to allantoin. The recent availability of rasburicase will probably reduce the incidence and severity of this complication during cytolytic therapy in patients with haematological malignancies at high risk of developing TLS. Future prospective studies, however, are required to determine the following: (i) which subgroups of patients are at the highest risk of developing TLS, (ii) which dose and schedule of rasburicase is most effective for both prophylaxis and treatment, (iii) which patients only require allopurinol for prophylaxis and/or treatment, (iv) can rasburicase and allopurinol be used sequentially for prophylaxis and/or treatment, and (v) does rasburicase not only reduce uric acid levels but also reduce

morbidity and mortality from TLS? The proposed definition of LTLS and CTLS and grading classification should assist in the future prospective randomized studies that will be required to answer these remaining questions.

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