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Primer

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Tumour lysis syndrome

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Abstract

Tumour lysis syndrome (TLS) represents a critical oncological emergency characterized by extensive tumour cell breakdown, leading to the swift release of intracellular contents into the systemic circulation, outpacing homeostatic mechanisms. This process results in hyperuricaemia (a by-product of intracellular DNA release), hyperkalaemia, hyperphosphataemia, hypocalcaemia and the accumulation of xanthine. These electrolyte and metabolic imbalances pose a significant risk of acute kidney injury, cardiac arrhythmias, seizures, multiorgan failure and, rarely, death. While TLS can occur spontaneously, it usually arises shortly after the initiation of effective treatment, particularly in patients with a large cancer cell mass (defined as ≥500 g or ≥300 g/m^2 of body surface area in children). To prevent TLS, close monitoring and hydration to improve renal perfusion and urine output and to minimize uric acid or calcium phosphate precipitation in renal tubules are essential. Intervention is based on the risk of a patient of having TLS and can include rasburicase and allopurinol. Xanthine, typically enzymatically converted to uric acid, can accumulate when xanthine oxidases, such as allopurinol, are administered during TLS management. Whether measurement of xanthine is clinically useful to optimize the use of allopurinol or rasburicase remains to be determined.

Sections

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Introduction

Tumour lysis syndrome (TLS) is a severe metabolic condition that typically occurs during the treatment of bulky malignancies with effective therapies, posing a potential life-threatening risk. It is characterized by the rapid release of intracellular contents into the bloodstream, either spontaneously as very rapidly growing cancers outgrow their supply of nutrients or in response to therapy[1–3] (Fig. 1). TLS is particularly evident in rapidly proliferating, bulky and chemosensitive tumours, leading to distinct clinical manifestations such as hyperuricaemia, hyperkalaemia, hyperphosphataemia and hypocalcaemia[1,2]. The ensuing metabolic imbalances and cytokine release can progress to toxic effects, including renal failure, cardiac arrhythmias, seizures, haemodynamic instability and multiorgan failure, ultimately resulting in mortality[4].

The definition of TLS depends on both laboratory abnormalities and clinical findings. It is advised that patients newly diagnosed with cancer undergo screening for TLS by measuring serum potassium, phosphorus, calcium, uric acid and creatinine levels to establish baseline levels. The Howard–Pui classification defines patients with laboratory TLS (LTLS) as having values of serum potassium, phosphorus, uric acid and creatine above the upper limits of the normal range (or below, in the case of calcium) or an increase of ≥25% from baseline (or decrease of serum calcium levels of 25% or more from from baseline[2,5] (Box 1). Clinical TLS (CTLS) is defined as LTLS coexisting with renal dysfunction, cardiac involvement, neurological involvement or death[2]. Importantly, these criteria exclude manifestations directly attributable to other causes, such as a patient with a known seizure disorder whose seizures are unlikely to have been caused by hypocalcaemia[2].

Patients with TLS may not consistently exhibit simultaneous occurrence of all metabolic abnormalities. The Howard–Pui guidelines[2], modified from the Cairo–Bishop classification[5], require two or more metabolic abnormalities within the same 24-h period, occurring between 3 days before and 7 days after anticancer therapy initiation, and include a 25% variation in metabolites as a laboratory abnormality even it does not fall outside the age-specific and sex-specific normal range for that metabolite. Symptomatic hypocalcaemia, regardless of serum levels, serves as a CTLS criterion[2,5]. Finally, renal dysfunction is interpreted according to the Acute Kidney Injury Network criteria, distinguishing pre-existing kidney impairment from TLS-induced acute kidney injury (AKI), defined as a serum creatinine increase of ≥0.3 mg/dl, or an increase to ≥1.5 times the upper limit of the normal range for age and sex (if no prior creatinine value is available), or an average urine output below 0.5 ml/kg/h for at least 6 h (ref. 6).

In this Primer, we examine the diagnosis, epidemiology, risk factors, pathophysiology, monitoring, prevention and treatment of TLS as well as its long-term impact on health and quality of life. We emphasize recent updates on physiological mechanisms, novel therapeutic interventions and renal consequences, including short-term, intermediate-term and long-term perspectives. We also describe the mechanism and consequences of rapid cancer cell breakdown, risk-adapted therapeutic interventions and current treatment modalities. The article also addresses complications of TLS-associated AKI, including electrolyte imbalances and fluid shifts, along with intermediate-term to long-term repercussions like chronic kidney disease (CKD). Strategies for preventing and managing TLS-related AKI are also discussed.

Epidemiology

Estimating the incidence of TLS remains challenging due to variations in cancer types, treatment approaches and TLS preventive measures. The absence of a universally accepted definition for TLS has historically contributed to the lack of clear incidence data. However, with the advent of new, highly effective targeted therapies, incidence rates are thought to be on the rise. The National Inpatient Sample (NIS) study involving 28,370 patients with a discharge diagnosis of TLS between 2010 and 2013 reported an increase in TLS incidence from 16% to 23% during the 3-year study period ($P < 0.01$)[7]. TLS has been increasingly reported in several malignancies that were historically associated with no or low risk of TLS, including chronic lymphocytic leukaemia (treated with venetoclax), mantle cell lymphoma (treated with alvocidib), multiple myeloma (treated with carfilzomib) and indolent B cell lymphoma (treated with alvocidib)[8–11].

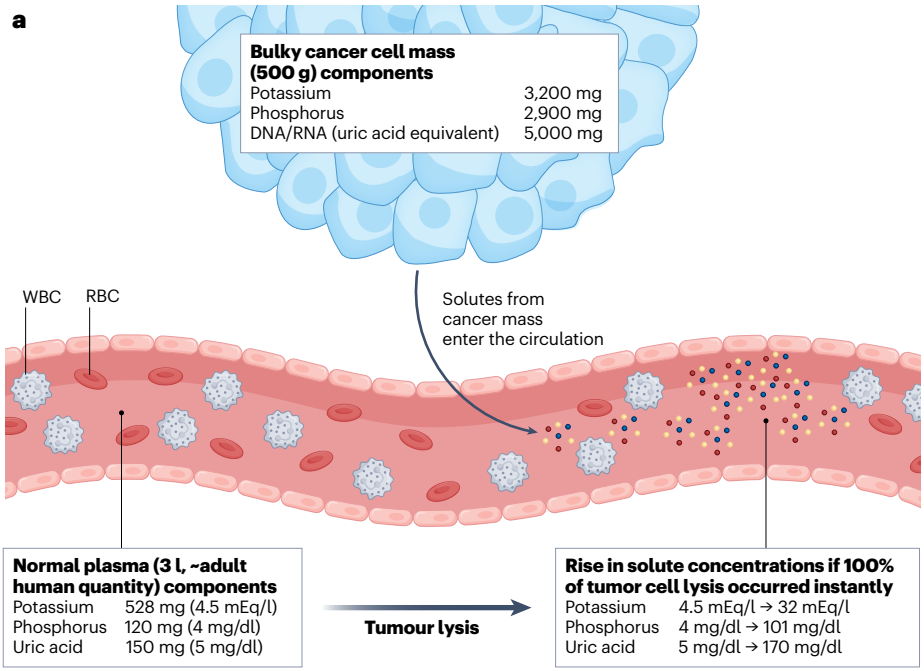
Associated cancers

In the NIS study, the most prevalent malignancies were reported to be non-Hodgkin lymphoma (NHL), solid tumours, acute myeloid leukaemia (AML) and acute lymphoblastic leukaemia (ALL)[7]. Multivariate analysis revealed that a diagnosis of AML or a solid tumour independently predicted higher mortality rates than those of patients with ALL[7]. Investigators concluded that a TLS diagnosis in patients with solid tumours signalled a high tumour burden (defined as ≥500 g of cancer) and an increased overall risk of death[7]. A systematic review of reports describing the occurrence of TLS amongst patients with solid tumours found hepatocellular carcinoma (17%), lung cancer (13%) and melanoma (10%) to be the most common types of cancer associated with TLS[12]. Metastatic disease emerged as the predominant risk factor, accounting for 75% of cases, which is not surprising since it is associated with a higher burden of disease[12].

A study of 1,791 paediatric patients with NHL, of whom half were thought to be at high risk of TLS and therefore received rasburicase prophylaxis, found an overall TLS incidence of 4.4%, with the highest rates observed in Burkitt leukaemia (26.4%) and advanced-stage Burkitt lymphoma (14.9%)[13]. In a study involving 772 adult patients with AML receiving allopurinol prophylaxis, 12% experienced LTLS and 5% experienced CTLS. The study found that a pretreatment creatinine level exceeding 1.4 mg/dl significantly ($P < 0.0001$) predicted TLS development. Furthermore, CTLS was associated with a higher risk of death during induction therapy compared with LTLS (79% versus 23%; $P < 0.001$), and CTLS was considered the cause of death in 19 (2%) of the 772 patients[14].

Risk factors

Factors influencing TLS development include disease-related factors, such as tumour burden, cellular proliferation rate and sensitivity to therapy, as well as patient-related factors such as pre-existing renal conditions, dehydration, acidosis and hyperuricaemia[2,8,15–20]. Additionally, treatment-related factors such as cytoreductive therapy intensity and therapeutic sequencing are also thought to be risk factors[21] (Box 2). The emergence of highly effective, new anticancer therapies has escalated the risk of TLS, underscoring the need for robust preventive measures, precise dosing and strategic therapeutic sequencing to mitigate the risk[8]. After disease bulk, defined as ≥500 g of cancer cell mass (or ≥300 g/m^2 of body surface area in children), the most important risk factor for TLS is the adequacy of prophylactic supportive care measures, including comprehensive hydration and the administration of hypouricaemic agents such as rasburicase[5,22,23]. The choice of prophylactic measures is informed by careful assessment of the anticipated TLS risk, taking into account factors such as the underlying disease, disease severity and planned therapeutic interventions. Note that, in patients with non-bulky disease, TLS risk is low regardless of any other



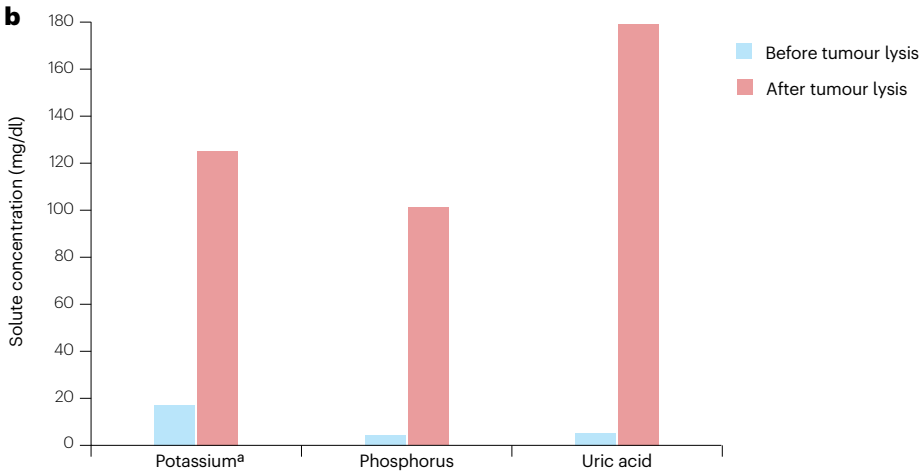


Fig. 1 | Cellular solute content based on the cancer cell mass. a, A 500 g mass of cancer contains ~3,200 mg of potassium, 2,900 mg of phosphorus and sufficient DNA to produce 5,000 mg of uric acid once it is metabolized. These quantities represent 6 times the potassium in the plasma, 24 times the phosphorus and 33 times the uric acid. If all solutes were released instantaneously from a 500 g cancer lesion, the plasma concentrations of potassium would increase to a fatal 32 mEq/l, phosphorus to 101 mg/dl and uric acid to 170 mg/dl. In reality, tumour lysis occurs over a period of hours or days and patients with normal renal function can excrete large amounts of potassium, phosphorus and uric acid. However, uric acid crystals adhere to the urothelium and initiate a cascade of inflammation, cell death and additional crystal formation that causes acute kidney injury[65–69]. Once acute kidney injury occurs, the ability of the kidneys to excrete phosphorus and potassium is impaired and the patient is at risk of clinical tumour lysis syndrome[2]. **b**, Graphical representation of solute changes if 100% of tumour lysis occurred instantly. RBC, red blood cell; WBC, white blood cell. In the boxes, potassium concentration units are in mEq/l, the standard unit for medical practice worldwide. In the bar chart, all concentration units are mg/dl so that all three solutes can be graphed in the same chart. The conversion between unit systems is 1 mEq/l = 3.91 mg/dl.

risk factor[2]. Conversely, patients with bulky disease (≥500 g cancer mass in adults or ≥300 g/m^2 of body surface area in children) are at high risk of TLS even when they lack other risk factors[2].

Age and sex. Though TLS can affect individuals across all age groups, elderly patients with compromised renal function are highly susceptible; patient age ≥60 years correlated with increased risk of both CTLS and LTLS[14]. Patients with AML and aged ≤50 years were found to have CTLS rates of 3% compared with 10% in those >70 years. Older age is an even more important risk factor when renal function is already compromised and, in this study, patients with creatinine concentrations >1.4 mg/dl had 23% CTLS versus 3% in patients with lower values[14]. However, age may not always serve as an independent prognostic factor due to potential variations in dosages of initial therapies (which may be reduced in older patients) and implementation of enhanced supportive care measures for patients at higher risk[14,24]. A multicentre study of paediatric ALL identified T cell phenotype (OR 4.7), age 1 year or younger (OR 8.6), and age ≥10 years (OR 2.2) as risk factors for TLS[25]. Some studies, though not all, have noted a higher TLS risk in men[14,24–27].

Prophylaxis and treatment. Considering the availability of highly effective treatment for TLS, such as rasburicase, an international consensus panel in 2008 developed a risk stratification system categorizing patients into low-risk (<1%), intermediate-risk (1–5%) and high-risk (>5%) groups based on CTLS probability[28] (Box 3).

Morbidity and mortality

TLS is associated with serious morbidity and a high risk of mortality. In the NIS study, which carefully analysed morbidity and mortality rates in TLS in the post-rasburicase era in the USA, the in-hospital mortality

Box 1 | Howard–Pui definitions of laboratory and clinical tumour lysis syndrome

Laboratory tumour lysis syndrome

- Uric acid ≥8.0 mg/dl (475.8 µmol/l) (adults) or above the upper limit of the normal range for age (children) or a 25% increase from the baseline value
- Potassium ≥6 mmol/l or a 25% increase from the baseline value
- Phosphate ≥4.5 mg/dl (adults) or ≥6.5 mg/dl (children) or a 25% increase from the baseline value
- Calcium <7.0 mg/dl (1.75 mmol/l) or ionized calcium <4.5 mg/dl (1.12 mmol/l) or a 25% decrease from the baseline value

Clinical tumour lysis syndrome

Meets criteria for laboratory tumour lysis syndrome, plus any of the following:

- Renal dysfunction (creatinine >1.5 times normal values or a rise in creatinine of 0.3 mg/dl above the baseline value)
- Cardiac arrhythmia or sudden death, which indicates symptomatic hyperkalaemia or hypocalcaemia
- Neurological involvement (seizures, tetany), which indicates symptomatic hypocalcaemia

This Box draws on concepts and data developed in refs. 2 and 5.

rate was 21%, with a median hospital stay of 10 days[7]. Predictors of mortality included age, Elixhauser comorbidity score (a composite score that includes multiple comorbidities like congestive heart failure, diabetes and 28 other comorbidities) and cancer type[7]. Multiple studies have shown that in-hospital mortality rates in patients with CTLS and solid tumours are higher compared with haematological malignancies, ranging from 28% to 59%, reaching 100% in pancreatic cancer and cholangiocarcinoma, 67% in gastrointestinal stromal tumours, 58% in hepatocellular carcinoma, 54% in colorectal cancer, and 50% in gastric cancer[7,12,17,29]. Meanwhile, in haematological malignancies, the mortality rate was lower, reporting the following results according to major cancer types: AML (28%), NHL (19%) and ALL (9%)[7]. Note that these mortality rates reflect death directly from CTLS plus death from any other cause, which may be associated with TLS sequelae like renal failure or other causes in patients with newly diagnosed cancer.

Survival rates in adults with ALL who developed TLS were considerably lower than in adults with ALL who did not develop TLS (3-year overall survival rate 19.4% versus 41%; $P = 0.016$)[24]. Similarly, adults with refractory or relapsed multiple myeloma, treated with B cell maturation antigen-targeted chimaeric antigen receptor T cell therapy had lower survival if they developed TLS (median overall survival, 5.0 months versus 39.8 months; $P < 0.001$)[30]. In critically ill patients requiring urgent chemotherapy, non-survivors were reported to have higher rates of TLS at presentation compared with survivors, and patients treated with rasburicase had a higher 1-year survival rate than those without rasburicase treatment[31]. However, this study represents the most severely affected patients for whom all clinicians would use rasburicase at standard doses and therefore the findings are not surprising. Although rasburicase effectively reduces uric acid, the need for dialysis and duration of hospital stay, systematic reviews and meta-analyses that have compared mortality rates before and after its introduction did not find strong evidence of its effect on mortality rates[32,33]. This may in part be because not all patients received timely rasburicase and the possibility of confusion between LTLS, which can be successfully managed in almost all cases, and CTLS, which can lead to severe complications, need for dialysis and intensive care, and death. In the NIS study, the development of LTLS did not influence mortality during induction therapy and CTLS was associated with a significantly increased mortality rate (79% versus 23%; $P < 0.001$)[14].

Health systems context

In low-income and middle-income countries (LMICs), TLS management often diverges from guidelines established in high-income countries due to financial constraints and limited access to rasburicase[12,15,34–42]. Even in high-income countries, some clinicians use rasburicase doses lower than those recommended by the FDA[43,44]. Some studies have demonstrated that reduced doses of rasburicase can effectively manage TLS; however, the standard FDA-approved dosing remains the best practice for ensuring consistent and reliable results, thereby reducing the risks associated with underdosing and potential complications[45–47]. Several studies conducted in LMICs, focusing on children with acute leukaemias and lymphomas, have shown an increased risk of TLS development, in part attributed to delayed diagnosis with a higher probability of bulky disease and pre-existing renal damage at diagnosis[34]. These studies emphasize the need for proper TLS prophylaxis, especially in resource-limited settings. Financial and infrastructure constraints in LMICs can affect the ability to deliver optimal supportive care, especially when intensive care unit support or rasburicase are needed[36–42].

Mechanisms/pathophysiology

Rapid tumour lysis overcomes homeostatic mechanisms

Homeostatic mechanisms meticulously regulate electrolytes and metabolites in the bloodstream. In TLS, the widespread disruption of tumour cells leads to uncontrolled permeability and the efflux of intracellular contents, thereby overwhelming the body's homeostatic mechanisms, particularly if AKI develops[48]. The intracellular solutes released include nucleic acids, notably purine nucleotides that are converted to uric acid, as well as intracellular ions such as potassium and phosphorus[2]. TLS can manifest spontaneously, particularly in patients with haematological malignancies with rapid cellular turnover rates[7]. The likelihood of TLS depends on total cancer cell mass and its chemosensitivity to initial therapy[2,15,49]. TLS can be caused by chemotherapy, immunotherapy, radiotherapy, chemoembolization, chimaeric antigen receptor T cells and general anaesthesia[50–52]. The development of new, highly effective anticancer agents, like venetoclax, inadvertently raises TLS incidence[53–57].

In cases of TLS associated with solid tumours, necrosis within the tumour mass itself is frequently observed[51,58]. Autopsy findings indicate that necrosis within the tumour is the main pathological feature in cases presenting with TLS[51]. Microemboli and necrosis of non-tumour cells are additional features that seem to directly contribute to widespread tissue damage[51]. Furthermore, the deposition of calcium phosphate and uric acid in various tissues is thouhgt to be a pathological feature of TLS[49]. These deposits are secondary to the metabolic disturbances occurring in TLS, particularly hyperphosphataemia and hyperuricaemia.

In addition to high cancer cell mass, risk factors for TLS include pre-existing conditions like volume depletion, hyperuricaemia, CKD and electrolyte disturbances. Volume depletion decreases the

glomerular filtration rate, leading to decreased clearance of solutes, including uric acid, phosphorus and potassium[48].

Hyperuricaemia initiates cascade of homeostatic disruption

The first event that occurs during TLS is the release of intracellular contents, including uric acid and phosphorus. Release of uric acid results in an acute elevation of serum and urine concentrations, which in turn leads to super-saturation in the urinary filtrate and crystal formation[2,59]. Crystals adhere to the urothelium and cause additional crystal growth, inflammation, direct urothelial damage, and tubular obstruction with death of associated nephrons[2,60]. Individuals with pre-existing elevated uric acid levels are more likely to experience TLS-induced hyperuricaemia, uric acid crystallization and accumulation in tissues[1,2].

The uric acid-induced loss of renal function reduces the ability of the kidneys to secrete the large potassium and phosphorus load that increases during TLS. Hyperphosphataemia results from rapid release of intracellular phosphate from tumour cells as well as decreased urinary clearance. Phosphate binds with serum calcium, forming calcium phosphate crystals, which deposit in tissues and precipitate in the kidneys, worsening AKI that has been initiated by uric acid crystal precipitation in renal tubules and associated inflammation. Calcium phosphate can also precipitate in the cardiac conducting system, leading to an increased risk of heart block and cardiac dysrhythmias[61–63]. Calcium phosphate precipitation also depletes serum calcium and causes secondary hypocalcaemia, with the attendant risks of dysrhythmias and seizures[2,64]. It is tempting to treat hypocalcaemia in asymptomatic patients but this can increase calcium phosphate precipitation. Although electrolyte imbalances are primarily implicated in the development of cardiac arrhythmias, the role of crystal deposition in the cardiac conducting system is less clear but remains undesirable[7]. Therefore, hypocalcaemia should only be treated when dysrhythmia, neurological or musculoskeletal symptoms are present[2]. Any patient with TLS who experiences cardiac arrest should be assumed to have hyperkalaemia and hypocalcaemia as potential contributing causes, as standard resuscitation methods will be ineffective if abnormal potassium and calcium concentrations are not corrected.

Renal pathophysiology

Tumour lysis occurs over a period of hours or days and patients with normal renal function can excrete large amounts of potassium, phosphorus and uric acid. However, the large amounts of uric acid produced by tumour lysis leads to hyperuricaemia followed by high concentrations of uric acid in the urinary filtrate, leading to the formation of crystals that adhere to the urothelium and initiate a cascade of inflammation, cell death, and additional crystal formation that causes AKI[2,65–69]. Uric acid, with poor solubility in acidic environments like urine, accumulates in the kidneys, forming crystals in the renal tubules and potentially causing AKI[70] (Figs. 2 and 3). Once AKI occurs, the ability of the kidneys to excrete phosphorus and potassium is impaired and the patient is at risk of CTLS[2]. Uric acid can also induce AKI not only through intrarenal crystallization but also via crystal-independent mechanisms, including renal vasoconstriction, impaired autoregulation, decreased renal blood flow, oxidation and inflammation[71].

Patients with CKD have decreased nephron mass, typically with higher serum uric acid levels, making them more susceptible to the effects of hyperuricaemia due to reduced urinary clearance[72,73]. The additional insult further propagates renal injury and results in further loss of nephrons[72]. This, in turn, causes the faster development of electrolyte derangements such as hyperkalaemia and hyperphosphataemia.

The presence of hyperphosphataemia, which is common in CKD, exacerbates this process by causing calcium levels to decline by the precipitation of calcium phosphate crystals that can contribute to renal tubular obstruction[74]. Parenchymal and tubular deposition of calcium phosphate salts contributes to renal damage.

TLS results in a marked increase in circulating extracellular histones, which can potentiate endothelial damage and lead to AKI[75]. The histones activate endothelial cells through Toll-like receptor 4 (TLR4), leading to inflammation and disruption of the endothelial barrier[76,77]. This disruption enhances vascular permeability, exacerbating tissue oedema and further compromising kidney function and damaging other tissues, including the lungs[78]. Moreover, histones contribute to a pro-coagulant state, increasing thrombosis risk within the renal microvasculature and impairing renal blood flow and oxygenation. Lastly, some patients may experience lasting effects, including the development of CKD[79].

Cardiac dysrhythmias

Hyperkalaemia and hypocalcaemia can disrupt cardiac function. Hyperkalaemia affects cardiac myocytes by altering the normal electrical activity and contractility of these cells[80]. Normally, the resting membrane potential is maintained at −80 to −90 mV by selective permeability of the cell membrane and the sodium-potassium ATPase pump. Elevated potassium levels outside the cell during hyperkalaemia bring the membrane potential closer to the threshold for action

Box 2 | Factors associated with tumour lysis syndrome

Disease-related factors

- Bulky cancer (≥500 g in adults or 300 mg/m^2 body surface area in children), as indicated by any of the following:
  - Masses (tumours or lymph nodes) >10 cm in diameter
  - Advanced-stage or metastatic disease with multiple lesions
  - Bone marrow infiltration ≥40%
- Sensitivity to cytoreductive therapy
- Renal infiltration or obstruction of the outflow tract by a tumour

Patient-related factors

- Existing kidney disease or uraemia
- Obstruction of the urinary tract
- Hyperuricaemia or hyperphosphataemia prior to treatment
- Hypovolaemia or hypotension
- Presence of acidic urine or low urine output

Treatment-related factors

- Initial therapy (chemosensitivity)
- Intensity of the initial cytoreductive regimen
- Single-agent therapy versus combination therapy
- Disease-specific treatment depending on tumour type
- Inadequate hydration prior to and during cytoreduction
- Concomitant use of nephrotoxic drugs

This Box draws on concepts and data developed in ref. 21.

potential generation (which triggers myocardial contraction), and this excitability can result in cardiac dysrhythmias. The less negative resting membrane potential also affects excitability, reduces action potential duration, impairs repolarization, and increases the likelihood of premature contractions and arrhythmias. The sudden release of intracellular potassium can lead to severe, life-threatening hyperkalaemia because potassium concentration gradients between the serum and cytoplasm of cardiac myocytes lead to depolarization and contraction unrelated to signals from the sinus node (that is, dysrhythmia)[80,81]. This is often observed when serum potassium concentration rises rapidly and there is no time for equilibration by increasing the concentration within cardiac myocytes[82]. Patients with CKD or pre-existing chronic hyperkalaemia may be perfectly stable with chronically high potassium concentrations in both serum and cardiac myocytes but, when serum potassium rises rapidly, they are at high risk of complications[83].

Hypocalcaemia can result in hypocalcaemic cardiomyopathy, which is marked by decreased left ventricular contractility. It also causes QT prolongation, which is visible on an electrocardiogram (ECG). QT prolongation is a measure of delayed ventricular repolarization calculated as the time between the start of the Q wave of the ECG and the end of the T wave[84,85]. This prolongation indicates a delay in the heart's electrical system to reset (repolarize) after each beat. Delayed ventricular repolarization leaves the myocardium vulnerable to the next depolarization signal, which can trigger a ventricular arrhythmia or torsades de pointes, a specific type of ventricular tachycardia associated with hypotension, poor perfusion and high risk of devolving into ventricular fibrillation, which is lethal if left untreated[48,86,87]. The risk of cardiac dysrhythmia is especially high when hyperkalaemia and hypocalcaemia occur at the same time. Thus, TLS puts patients at risk of cardiac dysrhythmia by two mechanisms, and hyperphosphataemia sets the stage for both.

Neurological and musculoskeletal complications

Neurological complications, particularly seizures, are primarily associated with hypocalcaemia[21]. Seizures occur in ~1% of hospitalized patients with TLS as reported in the NIS study in the USA, which includes TLS cases from 2010 to 2013 (ref. 7). Calcium is involved in membrane stability and neurotransmitter release and excitability. When calcium levels are low, there is a decrease in the threshold potential required to generate an action potential, leading to increased neuronal excitability[88]. This increased excitability can manifest as muscle twitching, spasms (tetany) and paraesthesias[88–91]. Furthermore, in the setting of hypocalcaemia, the reduced availability of calcium can impair neurotransmitter release and result in central nervous system (CNS) manifestations, including altered mentation, cognitive deficits and seizures. Serum hypocalcaemia leads to low calcium levels in cerebrospinal fluid, which leads to increased neuronal excitability in the CNS[88]. Indeed, raising the calcium concentration in cerebrospinal fluid in experimental models decreases synaptic excitability and reduces susceptibility to seizures[92,93]. Hypocalcaemia not only affects neuronal excitability in the CNS but also in skeletal muscles, manifesting as muscle weakness, muscle spasms or tetany, and muscle damage marked by elevated creatine kinase levels[89,94–97].

Box 3 | International consensus classification of tumour lysis syndrome risk groups

Low-risk cancers

- Most solid tumours
- Multiple myeloma
- Adult intermediate-grade non-Hodgkin lymphomas with lactate dehydrogenase (LDH) within 2× the upper limit of the normal range (ULN)
- Indolent lymphomas
- Adult anaplastic large cell lymphoma
- Chronic lymphocytic leukaemia (CLL) with a white blood cell count (WBC) <50×10^9/l treated only with alkylating agents
- Chronic myeloid leukaemia
- acute myeloid leukaemia (AML) with WBC <25×10^9/l and LDH of <2× ULN

Intermediate-risk cancers

- Rare, highly chemotherapy-sensitive solid tumours (for example, neuroblastoma, germ cell tumour, small-cell lung cancer) with bulky or advanced-stage disease
- Plasma cell leukaemia
- CLL treated with fludarabine, rituximab, lenalidomide or venetoclax and lymph node ≥5 cm or absolute lymphocyte count ≥25×10^9/l, or those with high WBC ≥50×10^9/l
- AML with WBC of 25–100×10^9/l or WBC <25×10^9/l and LDH ≥2× ULN
- Adult T cell leukaemia/lymphoma, diffuse large B cell, transformed and mantle cell lymphomas with LDH above ULN, non-bulky
- Childhood anaplastic large cell lymphoma, stage III–IV
- Childhood intermediate-grade non-Hodgkin lymphoma stage III–IV with LDH ≥2× ULN
- Acute lymphoblastic leukaemia and WBC <100×10^9/l and LDH <2× ULN
- Burkitt lymphoma and LDH <2× ULN

High-risk cancers

- Burkitt leukaemia or lymphoma stage III–IV and/or LDH ≥2× ULN
- Lymphoblastic lymphoma stage III–IV and/or LDH ≥2× ULN
- Stage III–IV childhood diffuse large B cell lymphoma with LDH ≥2× ULN
- Adult T cell leukaemia/lymphoma, diffuse large B cell, transformed and mantle cell lymphomas with bulky disease and LDH ≥2× ULN
- Acute lymphoblastic leukaemia and WBC ≥100×10^9/l and/or LDH ≥2× ULN
- AML and WBC ≥100×10^9/l
- CLL treated with venetoclax and lymph node ≥10 cm, or lymph node ≥5 cm and absolute lymphocyte count ≥25×10^9/l
- Intermediate-risk disease with renal dysfunction or renal involvement by cancer
- Intermediate-risk disease with uric acid, potassium or phosphate above ULN
- Hyperuricaemia at presentation

This Box draws on concepts and data developed in ref. 28.

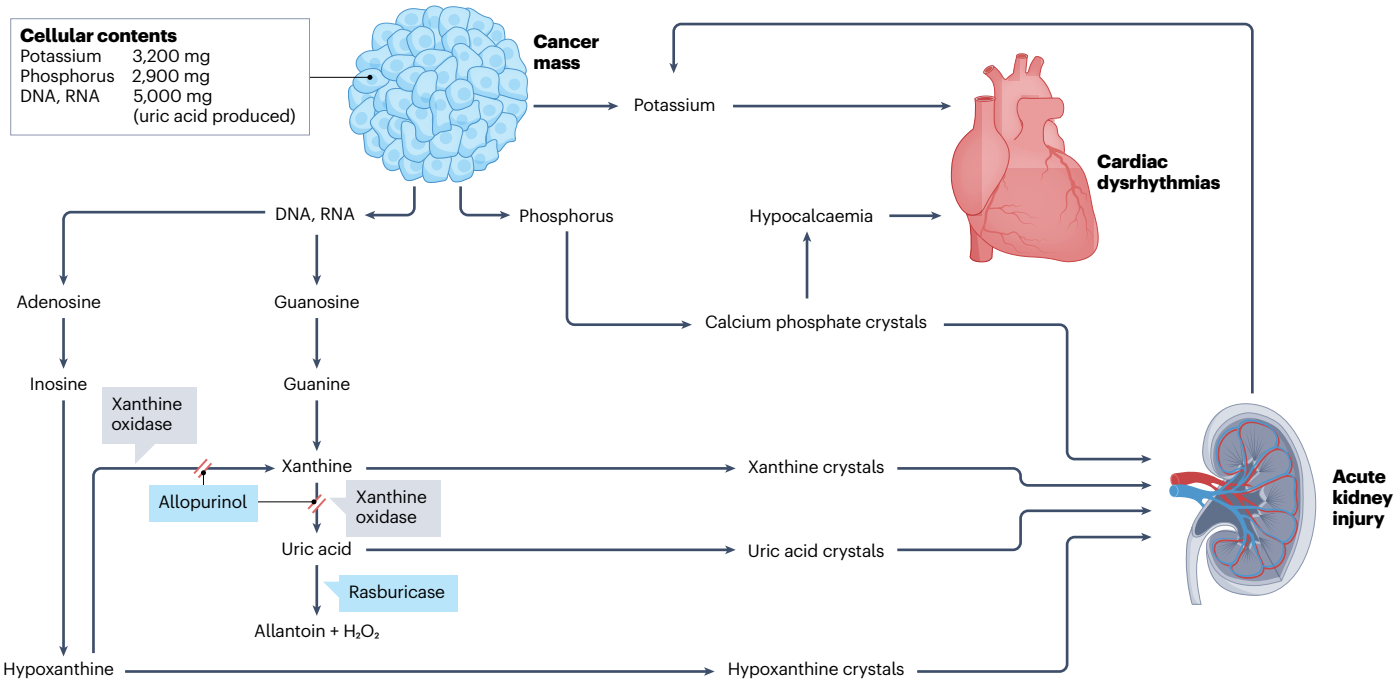


Fig. 2 | Crystal-induced renal injury and cardiac dysrhythmias during tumour lysis syndrome. Tumour lysis is the expected, and desired, result of anticancer therapy. Tumours release phosphorus, potassium and DNA, which is quicky metabolized to hypoxanthine, xanthine, and uric acid. Uric acid crystals can adhere to the urothelium and initiate a cascade of events that lead to acute kidney injury and the inability to handle the large phosphate and potassium loads from tumour lysis[66,69]. This leads to accumulation of these solutes and tumour lysis syndrome. Unfortunately, the increase in phosphorus that accompanies tumour lysis leads to calcium phosphate crystal formation that can further damage the kidneys and precipitate in the cardiac conducting system and soft tissues. Urine alkalinization that is sometimes used to increase the solubility of uric acid decreases the solubility of calcium phosphate and should not be used in patients with hyperphosphataemia. Finally, hyperphosphataemia causes secondary hypocalcaemia that can lead to seizures, tetany and cardiac dysrhythmias[2].

Haemodynamic consequences

The effect of TLS on haemodynamics extends beyond cardiomyopathy or arrhythmias potentiated by hypocalcaemia or hyperkalaemia. Tumour lysis also results in the release of massive amounts of cytokines, precipitating a systemic inflammatory response and distributive shock[50,98–101]. This cascade can lead to multiple organ failure and, in severe cases, can result in cardiac arrest[99]. Cytokines potentially implicated in haemodynamic instability include tumour necrosis factor (TNF), IL-6 and IL-10 (refs. 50,98,99,102,103). The intricate interplay between electrolyte derangements, cardiac function and conductivity, and cytokine release underscores the complex and potentially severe cardiovascular implications associated with TLS[100,101].

Diagnosis, screening and prevention

Diagnosis

The diagnosis of TLS relies on laboratory abnormalities[1,2,4]. It is recommended that patients newly diagnosed with cancer undergo screening for TLS by measuring serum potassium, phosphorus, calcium, uric acid and creatinine. Given the potential seriousness of complications associated with TLS, maintaining vigilance for this adverse event is crucial. This vigilance should commence before the initiation of therapy, regardless of the perceived risk, especially in the current era of precision medicine utilizing highly effective, targeted, immune-based and cellular anticancer therapies. It is crucial to monitor early indicators of rising phosphate or potassium levels (even if they remain within safe limits) shortly after treatment initiation. Early intervention can prevent these levels from reaching dangerous levels. Recent expert consensus guidelines, developed through a modified Delphi method, highlight key parameters for monitoring TLS[104]. Urine output, creatinine, blood urea nitrogen, phosphate and uric acid are considered important for monitoring renal function, whilst urine pH, sodium, chloride, carbon dioxide and carbonate are not[104]. Whilst testing for potassium levels is essential, the need for an ECG or continuous cardiac monitoring would depend on the severity of ongoing TLS, affected by the tumour bulk, specific anticancer drug used, and the presence of hyperkalaemia or hypocalcaemia[104].

Screening and monitoring

The monitoring frequency depends on age, cancer type, tumour burden, specific anticancer treatment, renal function and comorbidity. Decisions regarding inpatient or outpatient care should be based on the degree of TLS risk, the severity of ongoing TLS as determined by the levels of uric acid, phosphorus and potassium, comorbidity, and the presence of large mediastinal mass, which can cause airway obstruction, cardiovascular compression and pulmonary embolism[105,106]. Additional considerations for decision-making include distance between the patient's home and treatment centre, treatment adherence, and financial status.

Outpatient monitoring. Full-service medical centres generally monitor patients in the outpatient setting every 12 h. In the outpatient setting, on the first day of treatment for newly diagnosed or relapsed cancer,

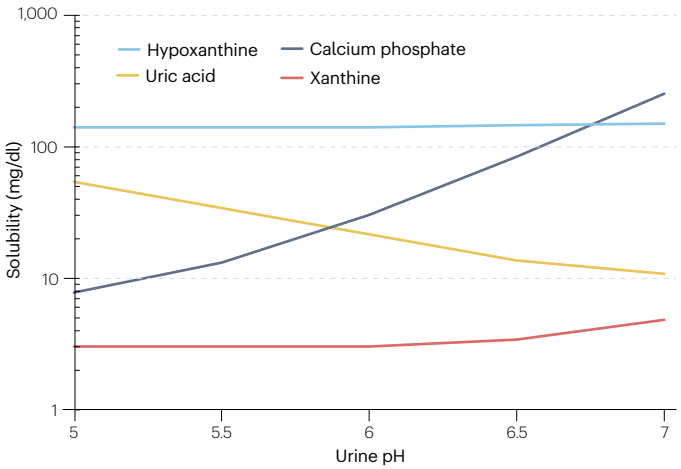


Fig. 3 | pH-dependent solubility of calcium phosphate, uric acid, xanthine and hypoxanthine guides urine alkalinization in patients at risk of tumour lysis syndrome. Uric acid solubility increases dramatically as urine pH increases, with a solubility of 254 mg/dl at a pH of 7 compared with only 7.8 mg/dl at a pH of 5, so the rate of uric acid crystal formation is much lower in alkaline urine. For this reason, urine alkalinization was commonly practised for patients at risk of tumour lysis syndrome prior to the availability of rasburicase. Unfortunately, calcium phosphate is much less soluble at alkaline pH and thus more likely to crystalize. In places with access to rasburicase, uric acid can be removed enzymatically and urine alkalinization is contraindicated. When rasburicase is not available, the decision to alkalinize depends on whether uric acid is elevated (favours alkalinization) or phosphate is elevated (favours avoiding alkalinization). Most importantly, xanthine has low solubility regardless of urine pH and xanthine nephropathy can occur when patients with a high cancer cell burden are treated with allopurinol, which leads to xanthine accumulation. Adapted with permission from ref. 212, Cambridge University Press.

consensus guidelines[2,104] suggest monitoring patients at low risk of TLS once daily. However, there is no consensus on the monitoring frequency for patients at intermediate risk. Generally, these patients are monitored at most twice daily or every 12 h until they are no longer at risk, and there is no laboratory evidence for TLS.

Inpatient monitoring. Patients with LTLS or CTLS or those at high risk should receive treatment in the inpatient setting. There is no uniform agreement on the optimal monitoring frequency for inpatients at intermediate risk. Amongst a modified Delphi panel of experts, two-thirds of the panellists favoured a monitoring interval of twice daily or every 12 h (ref. 104). The challenge with patients at intermediate risk stems from the inherent complexity of TLS; the patient population is heterogeneous and some are treated as outpatients. For adult inpatients at high risk, the consensus recommends monitoring every 6 h, with those exhibiting CTLS or LTLS undergoing monitoring every 4 h (ref. 104). Some panellists emphasized the challenges associated with implementing monitoring intervals of <8 h in their centres because of constraints related to insufficient time for receiving laboratory results and adjusting treatment[104]. In contrast, paediatric patients are routinely monitored every 4–6 h (ref. 104). Panellists underscore that patients with hyperkalaemia or hyperphosphataemia should receive more frequent monitoring, and consultation with a nephrologist is warranted when the patient has a potential need for dialysis[104].

Prevention

Prophylactic measures are essential for patients at high or intermediate risk of TLS. The primary aim of prophylaxis is to safeguard renal function by maintaining adequate urine output, lowering blood levels of uric acid, phosphate and potassium, and rectifying other metabolic imbalances[104]. Additionally, management should encompass the prevention of dysrhythmias and neuromuscular complications, with special attention given to older adults[61,107].

Prophylactic strategies primarily revolve around expanding fluid volume and reducing uric acid levels, achieved through the administration of hypouricaemic agents[104]. For patients at low risk without extensive disease involvement, allopurinol is often recommended, whilst paediatric patients at high risk or with substantial disease burden may benefit more from rasburicase, which rapidly and effectively reduces and prevents hyperuricaemia[45,108–110]. Consensus-based recommendations for TLS prophylaxis, with some adjustments, are outlined in Table 1 (ref. 104).

Optimal hydration aims to expand extracellular fluid volume and improve renal perfusion and glomerular filtration. The objective is to stimulate ample urine production to dilute the harmful solutes released during tumour lysis, thereby reducing the risk of uric acid or calcium phosphate precipitation in the tubules. For patients at low risk, oral fluid intake of 2–3 l/m^2 is recommended before initiating any anticancer therapy with TLS potential[104]. For patients at intermediate or high risk, continuous isotonic saline infusion at a large volume based on hydration status and cardiac function is recommended. Close monitoring of hydration status and urine output is essential, with assessments scheduled every 6–8 h. Adults should maintain urine output above 100 ml/m^2/h (ref. 104) whilst young children should aim for over 2–4 ml/kg/h (refs. 3,4). Before initiating aggressive intravenous hydration, correctable forms of AKI, such as urinary tract obstruction, should be addressed.

However, intravenous hydration carries the risk of fluid overload in patients with underlying AKI or cardiac dysfunction or in older patients, especially if there are signs of volume overload such as interstitial oedema[104]. These patients require a personalized approach based on a comprehensive assessment of fluid status, ongoing clinical monitoring and regular adjustments based on individual response. In such instances, close monitoring of vital signs, urine output and symptoms of volume overload (such as peripheral oedema, increasing body weight or, changing respiratory status) is crucial. Transfusion, if necessary, should be administered cautiously and in small volumes to mitigate this risk. Diuretics are not routinely recommended because they may cause volume contraction, compromising renal haemodynamics and accentuating the risks of TLS and AKI[111]. Diuretic use is contraindicated in patients with hypovolaemia (low blood volume) or obstructive nephropathy[112]. The choice of diuretic for patients with TLS remains uncertain; however, loop diuretics like furosemide may be preferred as they promote diuresis and potentially enhance potassium secretion[111]. Thiazides should be avoided as they elevate uric acid levels and nephrotoxic drugs should be excluded from the treatment regimen[2,111].

The choice of hydration fluid depends on the specific clinical context. According to expert recommendations, for patients undergoing remission induction for ALL who are receiving steroids, initial hydration with 5% dextrose and one-quarter normal saline is advised[112]. This fluid helps mitigate sodium retention and hypertension, which are common adverse effects of steroid use during this phase of treatment[112]. For patients presenting with hyponatraemia (low sodium) or volume

depletion, isotonic saline is preferred. Caution is warranted during tumour breakdown as the risk of hyperkalaemia and hyperphosphataemia increases. Consequently, potassium and phosphate should be withheld from hydration fluid to prevent hyperkalaemia and calcium phosphate precipitation[112].

The optimal duration of hydration lacks standardized guidelines and is contingent upon various factors such as tumour bulk, chemotherapy regimen (some treatments induce TLS several days later), drug sensitivity, the patient's oral intake capability and renal function. Intravenous hydration should be continued until the tumour burden has decreased substantially, tumour lysis subsides and the patient demonstrates adequate oral intake with satisfactory urine output.

Historically, urinary alkalinization using acetazolamide or sodium bicarbonate was employed to enhance uric acid solubility[113–115]. However, this practice is now discouraged due to the availability of rasburicase, which effectively breaks down uric acid and can rapidly resolve hyperuricaemia without the need for urinary alkalinization. Furthermore, alkalinization poses risks such as calcium phosphate deposition in vital organs, including kidneys and heart, particularly in the presence of marked hyperphosphataemia[116,117]. Alkalosis (excessive blood alkalinity) also increases the likelihood of calcium binding to albumin, raising the risk of tetany and cardiac arrhythmias[111,118,119]. Thus, sodium bicarbonate administration is reserved for patients with severe metabolic acidosis[112]. In regions where rasburicase is unavailable, urine alkalinization may be considered for patients with high uric acid levels and normal serum phosphorus. However, vigilance is paramount, and alkalinization should be swiftly reversed upon the onset of hyperphosphataemia.

Management

Management of hyperuricaemia

Allopurinol. For the initial management of both adult and paediatric patients at low or intermediate risk of TLS, many clinicians use allopurinol instead of rasburicase, partly because the latter is more costly and less available, provided that pretreatment uric acid levels are within normal limits[17,37,38]. Allopurinol, a hypoxanthine analogue, competitively inhibits xanthine oxidase, thus impeding the conversion of hypoxanthine and xanthine to uric acid (Fig. 2). This mechanism

Table 1 | Prophylaxis and management of laboratory and clinical tumour lysis syndrome

Parameter	Recommendations
Monitoring	Inpatient monitoring of creatinine, phosphate, calcium and uric acid every 4–6 h for patients at high risk of TLS
	ECG or continuous cardiac monitoring for patients at risk of cardiac arrhythmia
Hydration	Administer a saline bolus followed by continuous intravenous infusion at a rate of 2–3 l/m^2 per day. For patients receiving glucocorticoids, avoid dextrose-containing fluids
	Avoid fluids containing potassium, calcium or phosphate such as lactated Ringer solution
	Assess hydration status every 6–8 h to ensure optimal fluid balance and prevent dehydration or symptomatic fluid overload (not including peripheral oedema)
	Aim for a urine output of ≥100 ml/m^2/h for adults and >2 ml/kg/h in children
	Avoid use of diuretics, which can worsen renal function. Diuretics should only be used for patients with symptomatic fluid overload at risk of requiring dialysis to remove excess fluid. Furosemide slows uric acid elimination, so mannitol is preferred if a diuretic is required for symptomatic fluid overload.
Hyperuricaemia	Regular laboratory assessments and hyper-hydration as outlined above
	Rasburicase for patients at high risk of TLS or with hyperuricaemia (uric acid above the upper limits of the normal range) at presentation
	Refrain from urine alkalinization if rasburicase is available as it can worsen calcium phosphate crystallization and cause AKI
	Some clinicians consider allopurinol for patients at lower risk, though it has not been shown to improve TLS or prevent AKI and has been associated with xanthine nephropathy in the setting of bulky cancer
Hyperphosphataemia	Incorporate a dietary regimen that restricts phosphate intake
	Optimize hydration through increased intravenous fluid administration
	Ensure intravenous solutions are devoid of phosphate content
	Administer phosphate binders such as calcium carbonate, sevelamer or lanthanum carbonate
	Dialysis or haemofiltration is only necessary if severe hyperphosphataemia is accompanied by other issues that warrant such intervention (life-threatening hyperkalaemia, symptomatic fluid overload)
Hypocalcaemia	Monitor in the intensive care unit and consult a nephrologist and intensive care unit physician
	Continous cardiac monitoring
	Asymptomatic hypocalcaemia does not require treatment
	For symptomatic hypocalcaemia, administer calcium gluconate intravenously at the lowest effective dose
Hyperkalaemia	Monitor in the intensive care unit and consult a nephrologist and intensive care unit physician
	Continuous cardiac monitoring in patients with potassium levels ≥6 mmol/l or those with AKI
	Arrhythmia and acute cardiotoxicity require urgent administration of calcium gluconate
	If ECG changes are observed, administer intravenous calcium gluconate over 30 min even in the absence of arrhythmia
	Manage hyperkalaemia with sodium polystyrene sulfonate, sodium zirconium cyclosilicate or patiromer
	In cases of refractory or severe hyperkalaemia, or if arrhythmia occurs, administer rapid-acting insulin, glucose or dextrose infusion, and sodium bicarbonate
	Consider administering albuterol via inhalation as needed

AKI, acute kidney injury; ECG, electrocardiogram; TLS, tumour lysis syndrome.

effectively curtails new uric acid formation, consequently reducing the likelihood of obstructive uropathy in patients with malignant disease at risk of TLS[120,121]. Oral allopurinol is a cost-effective medication; in scenarios where oral administration is not feasible, intravenous allopurinol is a viable alternative but is much more costly than oral allopurinol[122]. It should also be noted that, whilst allopurinol decreases uric acid formation, it does not directly reduce pre-existing serum uric acid. Some experts recommend initiating allopurinol 2–3 days before anticancer treatment, continuing until TLS risk decreases and serum uric acid normalizes[104].

Febuxostat. Febuxostat, an alternative xanthine oxidase inhibitor, is an orally administered drug used for the management of chronic hyperuricaemia in gout[123]. Unlike allopurinol, it does not need dose adjustment for mild to moderate renal impairment and has fewer drug–drug interactions. Despite having efficacy comparable to that of allopurinol and being approved for TLS use in the European Union, the USA and Japan, febuxostat is less commonly used than allopurinol, primarily due to its higher cost[124]. Two long-term studies in patients with gout and cardiovascular disease yielded conflicting results regarding a potential association with higher all-cause and cardiovascular mortality with febuxostat when compared with allopurinol[125,126]. Febuxostat can be considered in patients with allopurinol hypersensitivity[127–129]. Most importantly, patients with bulky disease should avoid receiving allopurinol or febuxostat since they decrease synthesis of uric acid at the expense of accumulation of xanthine, which has even lower solubility (and higher rates of crystallization) than uric acid, potentially exacerbating TLS and AKI when a substantial load of purines is released into the circulation during tumour lysis[130–132] (Figs. 2 and 3).

Rasburicase. In cases of rapidly progressive disease or chemotherapy-sensitive cancer, experts advise against delaying anticancer treatment while awaiting the effects of allopurinol to reduce uric acid production, instead favouring the use of rasburicase[17,37,38]. This recommendation is particularly emphasized in children undergoing treatment for conditions such as Burkitt leukaemia or lymphoma with a substantial tumour burden, T cell ALL or monoblastic leukaemia[104]. In cases of very bulky, highly treatment-sensitive tumours such as Burkitt leukaemia or lymphoma, some treatment guidelines recommend using a ‘prephase’ (preparatory phase of lower dose of chemotherapy to reduce tumour burden) before full-dose chemotherapy to mitigate the severity of TLS[104,133]. If hyperuricaemia or LTLS develops in patients during treatment, rasburicase should be initiated once the uric acid level surpasses 7.5 mg/dl (446 µmol/l)[104,111]. Rasburicase, a recombinant urate oxidase catalysing the oxidation of uric acid into the more soluble allantoin, lowers serum uric acid to 1 mg/dl (59 µmol/l) within 4 h at the standard dose approved by the FDA[108]. This rapid reduction surpasses allopurinol and has been shown to improve renal function in randomized trials in the paediatric setting[110,134]. This rapid reduction of uric acid, demonstrated in multiple large paediatric and adult studies, supports the efficacy and safety of rasburicase in patients at high risk of and those presenting with TLS[45,109,135–138]. Importantly, the rapid reduction of uric acid by rasburicase could potentially prevent crystallization of uric acid and co-precipitation with calcium phosphate while enhancing phosphate excretion[104,108].

Adult patients typically receive allopurinol and, when rasburicase is deemed necessary, both agents are often administered concurrently. However, simultaneous use raises concerns about the potential accumulation of xanthine, a less soluble by-product of allopurinol treatment, that causes xanthine nephropathy[139,140] (Figs. 2 and 3). Whilst most laboratories do not measure urine xanthine, urine microscopy can reveal yellowish and pinkish crystals[130]. The goal of therapy is to prevent urine crystal formation; therefore, the observation of crystals by urine microscopy suggests inadequate TLS prophylaxis. The amount of xanthine produced by lysis of cancer cells in patients treated with allopurinol is predictable based on its mass. A 500-g cancer mass contains sufficient DNA and RNA to produce ~4,500 mg of xanthine, which is converted into 5,000 mg of uric acid by xanthine oxidase. Allopurinol blocks the conversion of xanthine to uric acid, and xanthine is excreted in the urine rather than uric acid (Fig. 2). In a phase III trial comparing rasburicase alone, rasburicase followed by allopurinol, and allopurinol alone, rasburicase alone achieved a higher rate of serum uric acid normalization and a faster time to plasma uric acid control than allopurinol alone[137]. The response rate was also higher for rasburicase plus allopurinol compared with allopurinol alone, although the difference was not statistically significant; xanthine was not measured. Whilst further studies are required in adults, the paediatric approach generally involves initiating rasburicase alone in patients who have high risk of TLS and elevated uric acid levels and replacing it with allopurinol when the patient is no longer at high risk of TLS[17,83,104,110,134]. Although a pegylated form (chemically attached to polyethylene glycol to increase stability and half-life) of rasburicase is available (pegloticase, which has a long-lasting effect), this drug is mainly used in patients with chronic refractory gout and is rarely used in patients with cancer[141].

Rasburicase usage requirements. The FDA approval for rasburicase indicates once daily administration for a maximum of 5 days. As a costly drug, it is frequently given as a single dose or at lower doses than those approved in order to save cost[35,104,142–146]. However, such strategies would ideally be employed only in the context of a clinical trial with strict safety monitoring. This is because using lower doses or a single dose has been associated with the need for repeated rasburicase dosing after failure to control uric acid and, in some cases, the need for haemodialyses and death from TLS[35,143–147]. When employing a single dose or reduced dose of rasburicase, vigilant monitoring of uric acid is imperative to assess the necessity for additional dosing. Rasburicase should be infused over 30 min (ref. 104).

Several studies have compared hospitalization costs, length of stay and duration of critical care in patients treated for TLS with either rasburicase or allopurinol. In one paediatric study, treatment with rasburicase was associated with a significant reduction in critical care days (1.4 days versus 2.5 days; $P = 0.0001$) but not with a significant difference in length of stay (13.8 days versus 14.9 days; $P = 0.69$) or total cost (US$ 30,470 versus US$ 35,165; $P = 0.43$)[148]. In another analysis of paediatric patients with TLS treated in a real-world setting, rasburicase was associated with significantly shorter intensive care unit stay (2.5 days less; $P < 0.001$) and overall hospital stay (5 days less; $P = 0.02$) and lower total inpatient costs (US$ 20,038 less; $P < 0.02$) as compared with allopurinol[149]. In a pan-European multicentre economic study, treatment with rasburicase was found to be cost-effective for both children and adults in addition to demonstrating clinical benefits[150].

Because rasburicase remains active ex vivo and can lead to enzymatic degradation of uric acid, it is crucial that blood samples intended for determining uric acid levels be promptly placed on ice to deactivate the drug[142]. These samples should then be delivered immediately to the laboratory to prevent artificially low uric acid measurements, thereby avoiding the possibility of overlooking an ongoing TLS diagnosis[151].

For patients with a history of drug-induced haemolytic anaemia and/or belonging to a racial or ethnic background associated with glucose-6-phosphate dehydrogenase deficiency (including Mediterranean, African or Southeast Asian descent), an enzyme test should be conducted prior to rasburicase administration. This precaution is necessary because hydrogen peroxide, a by-product of enzymatic oxidation of uric acid by rasburicase, has the potential to induce haemolytic anaemia or methaemoglobinaemia[152,153].

Management of hyperphosphataemia

Hyperphosphataemia treatment options encompass a range of strategies, including dietary phosphate restriction, increased fluid intake, the exclusion of phosphate from intravenous solutions, and the administration of phosphate binders such as sevelamer, lanthanum, calcium-based binders and iron-based binders[2,104]. However, their effectiveness in promptly lowering serum phosphorus levels is limited due to the intracellular origin of phosphorus rather than dietary intake[2]. Despite this limitation, phosphate binders may hold value in patients experiencing ongoing TLS who are consuming unrestricted diets. When selecting a binder, careful consideration should be given to their specific characteristics. Lanthanum, for instance, can interfere with abdominal X-rays and manifest as radiopaque material[154]. Calcium carbonate and calcium acetate pose the risk of elevating calcium levels and predisposing the patient to calcium phosphate precipitation and tissue deposition[104]. In cases of severe hyperphosphataemia, haemodialyses or haemofiltration is an effective method for phosphorus removal. However, these interventions are typically reserved for instances accompanied by other clinical or laboratory indications necessitating dialysis such as life-threatening hyperkalaemia or symptomatic fluid overload[104].

Management of hypocalcaemia

Prophylactic measures for hypocalcaemia are not universally recommended across all risk levels of TLS. Moreover, the treatment of asymptomatic hypocalcaemia should be avoided to prevent the precipitation of calcium phosphate in various organs and tissues, which can lead to AKI or cardiac dysrhythmia[104]. Consensus guidelines recommend measuring both ionized and total calcium in patients with TLS[104]. Given that albumin levels are often low in these patients, measurement of ionized calcium levels is recommended, and only if the assay is not available, corrected calcium can be used as a measurement; however, this may not be as accurate as total calcium[155,156]. In cases of symptomatic hypocalcaemia, characterized by tetany, seizure, muscular fasciculation, bronchospasm and laryngospasm, calcium infusion is employed when calcium levels drop to ≤7 mg/dl or ionized calcium falls below ≤3.2 mg/dl (≤0.8 mmol/l). This infusion may be repeated hourly until symptoms abate or calcium levels normalize[104,111]. When hyperphosphataemia coexists with symptomatic hypocalcaemia, it is prudent to administer the lowest effective dose of calcium necessary to alleviate symptoms. The aforementioned strategies aimed at reducing phosphorus levels can also aid in restoring normal calcium levels.

Management of hyperkalaemia

Patients are advised to steer clear of potassium-rich foods as even asymptomatic cases of hyperkalaemia can pose a risk of sudden death. Expert consensus suggests considering pharmacological intervention when serum potassium levels are ≥5.5 mmol/l with continuous cardiac monitoring recommended for levels ≥6 mmol/l, particularly in patients with AKI and TLS or those with rapidly escalating potassium levels[104]. A nationwide inpatient analysis in the USA found that arrhythmia was present in 24% of hospitalized adults with TLS, with significantly higher in-hospital mortality rates observed amongst those with arrhythmia than amongst those without (32.0% versus 21.3%; $P < 0.001$)[61].

Initial treatment for patients diagnosed with LTLS and hyperkalaemia often involves oral potassium-lowering binders such as sodium zirconium cyclosilicate, patiromer or sodium polystyrene sulfonate, supplemented with crystalloid volume expansion and diuretics as needed[104]. Adequate hydration is vital, with higher fluid rates recommended for patients with hyperkalaemia. Increasing tubular flow with crystalloid not only enhances renal blood flow and glomerular filtration rate but also activates flow-dependent Big potassium channels, promoting kaliuresis (excretion of potassium in the urine)[157]. When oral agents are ineffective or symptomatic hyperkalaemia is present, intravenous administration of insulin and glucose infusion is recommended[112,151]. Sodium bicarbonate may be considered; however, its use is generally limited to cases with concurrent metabolic acidosis and is not a primary component of TLS management, considering the potential for exacerbating phosphorus precipitation, especially in the kidneys[104]. Decisions regarding the initiation of renal replacement therapy or dialysis for hyperkalaemia typically fall under the purview of nephrologists or intensive care unit physicians.

When substantial ECG changes are evident, emergency measures to stabilize the cardiac membrane with calcium gluconate should be promptly considered. Whilst raising calcium levels may increase the risk of calcium phosphate crystal precipitation in the kidneys and cardiac conduction system, the imperative to address cardiac dysrhythmias and sudden cardiac death associated with hyperkalaemia outweighs this concern. Management should involve calcium gluconate infusion and/or insulin and glucose administration, complemented by ECG monitoring as per established guidelines[112,151].

Quality of life

Immediate effects of TLS on quality of life

TLS poses a life-threatening risk, substantially diminishing the quality of life for affected patients and prolonging their hospital stay. It heightens the likelihood of admission to the intensive care unit, increases the incidence of AKI and exacerbates the probability of subsequent AKI when exposed to nephrotoxins later in therapy. The potential for subsequent AKI emerges as a particularly critical factor in the deterioration of the quality of life of patients, influencing decisions regarding chemotherapy choice selection and necessitating dosage reduction. Consequently, this increases the risk of relapse and the need for aggressive salvage therapies[158]. For example, patients with TLS face an increased risk of delayed elimination of methotrexate following high-dose administration, leading to a decrease in dose intensity of subsequent treatment while awaiting its elimination and recovery of renal function[158–160].

Long-term effects of TLS on quality of life

TLS, by itself, should not directly influence long-term quality of life. However, diminished renal function resulting from TLS can have enduring effects on a patient's overall health and renal well-being[161,162]. Some patients can lose half of their renal function due to TLS, placing them at very high risk of subsequent AKI upon exposure to additional nephrotoxic substances such as chemotherapy agents like high-dose methotrexate or supportive care medications like vancomycin[163–171]. In certain scenarios, patients can encounter multiple AKI episodes, including an initial episode due to TLS, followed by subsequent episodes triggered by factors such as bacteraemia treated with vancomycin or high-dose

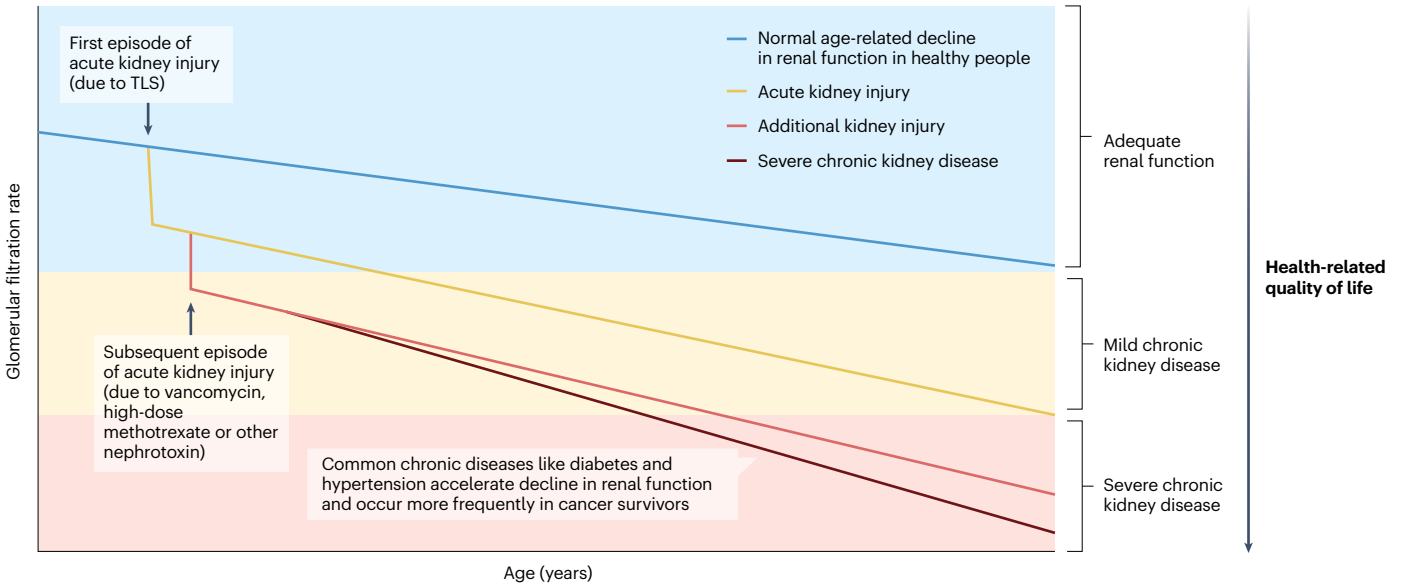


Fig. 4 | Age-related decline in renal function accelerates after loss of renal function due to acute kidney injury. Healthy people lose renal function at a predictable rate starting at birth but have sufficient renal function reserve that such losses do not affect their health or quality of life (blue line). Tumour lysis syndrome (TLS) can cause acute kidney injury at the time of diagnosis of cancer, which is associated with increased length of hospital stay, higher rates of intensive care unit admission, higher 30-day mortality and permanent loss of nephrons (yellow line)[161,162,173,174]. Most patients recover from the acute episode but permanently lose renal function, which puts them at risk of subsequent episodes of acute kidney injury with further loss of renal function (pink line)[175–177]. Age-related decline in renal function occurs at an accelerated rate in people with lower glomerular filtration rates and those with other chronic diseases like diabetes or hypertension (brown line). Health-related quality of life declines with worsening renal function and declines very steeply in those with severe chronic kidney disease (dark blue line on the right)[178–182].

methotrexate administration[158]. Many cancer therapies and supportive care agents possess nephrotoxic properties, potentially exacerbating renal damage initiated by TLS during the initial treatment phase[158]. Moreover, ageing individuals commonly experience renal senescence, characterized by measurable declines in glomerular filtration rate after the age of 50 years, rendering them more susceptible to renal injury[172]. An increasing number of studies suggest that inadequate renal adaptation after AKI can lead to CKD[161,162,173,174]. The loss of renal function due to TLS sets in motion an accelerated decline in kidney function, laying the groundwork for the premature onset of clinically significant CKD[175–177] (Fig. 4). Health-related quality of life is intricately intertwined with renal function, with notable declines observed in patients as CKD progresses, particularly in advanced stages (stages 4 and 5), and is further compromised in those requiring maintenance dialysis[178–182].

Outlook

Several important knowledge gaps exist in the management of TLS that warrant further investigation[183]. First, there is ongoing debate regarding the utility of xanthine oxidase inhibitors, such as allopurinol and febuxostat, in enhancing renal and clinical outcomes compared with standard care. Allopurinol is commonly used to reduce the formation of new uric acid in patients at risk for TLS, though it has never been shown to improve outcomes. The controversy stems from concerns regarding xanthine accumulation, which increases the risk of xanthine nephropathy. Second, there is an urgent need for a simplified risk classification system that clinicians can rapidly and effectively apply at the bedside of patients potentially at risk of TLS. Third, the intermediate-term and long-term effects of TLS on subsequent AKI risk and long-term renal function have not been evaluated. Finally, access to rasburicase at an appropriate dose remains problematic for people in countries with limited resources and those who lack adequate health-care coverage.

Should the xanthine oxidase inhibitors allopurinol and febuxostat play any role in patients at risk of TLS?

In regions where rasburicase is not available, the use of allopurinol emerges as a pragmatic choice. However, the question 'Is allopurinol better than nothing?' frequently arises, particularly in LMICs[184]. Hyperuricaemia, a hallmark of TLS, has conventionally been addressed with allopurinol[185,186]. Unfortunately, the mechanism of action of allopurinol, involving the inhibition of xanthine oxidase and the resultant accumulation of xanthine, poses challenges[130–132] (Fig. 3). This accumulation of xanthine molecules, at the expense of reduction of new uric acid in a one-to-one ratio, often goes unnoticed due to infrequent measurement of serum and urine xanthine levels, potentially leading to xanthine nephropathy[139,140,187–189]. This phenomenon explains the frequent clinical observation of patients with bulky disease treated with allopurinol who develop AKI despite well-controlled uric acid levels. It should come as no surprise that enabling an extremely insoluble molecule (xanthine) to accumulate would lead to crystallization in the renal tubules and induce crystal-induced renal injury. Depending on urine pH, xanthine is anywhere from 2% to 30% as soluble as uric acid, and therefore much more prone to crystallizing in the renal tubules and to cause crystal-induced renal injury[2,189–192]. Thus, enabling the accumulation of an unmeasured, extremely insoluble molecule like xanthine to avoid the accumulation of a measurable, more soluble molecule like uric acid is likely counterproductive[140]. This issue may be inevitable in

settings where rasburicase is not available but is completely preventable in countries with access to rasburicase since avoiding xanthine oxidase inhibitors enables all purines to be metabolized to uric acid, which can be both measured and managed[130–132,139,140,187–189]. In settings where rasburicase is not available, a randomized trial of best supportive care plus allopurinol versus best supportive care without allopurinol could provide valuable insights. This research would contribute to the refinement of TLS management strategies, particularly in resource-constrained environments. The proposal of this randomized trial in these settings has been controversial: some argue that allopurinol has been used for almost a century and that many patients have good outcomes with its use, and therefore it would be unethical to withhold it, even though it has never been shown to reduce TLS or AKI. Others suggest that xanthine nephropathy is a known complication of allopurinol use in this setting and that it represents a potentially harmful therapy with no proven benefit, and therefore its use is not ethical. The strong objection in both directions suggests that a randomized trial is warranted and ethically obligatory. Universal access to rasburicase would be preferable and is discussed below.

Elimination of the intermediate-risk category and the imperative for simplified bedside risk stratification

Since the introduction of risk stratification systems, the definition of 'intermediate risk' has sparked intense debate. Despite ongoing discussion, the optimal management of patients classified as being at intermediate risk remains challenging. Adding to the complexity facing clinicians is the intricacy of applying multiple risk strata, often characterized by elaborate lists and flow charts of risk factors. In response to these challenges, a simplified risk stratification system is needed that considers only the two independent risk factors for TLS: chemosensitivity and cancer bulk. Non-bulky disease is generally associated with a low risk of TLS, whereas bulky disease poses a high risk of TLS regardless of the cancer type or other factors. With effective frontline therapies now available for almost all cancers, most patients with bulky disease are consequently at risk of TLS (Fig. 2). Given that the 'intermediate-risk' category for TLS has never been adequately defined and treatment of patients in this risk group remains controversial, the most obvious simplification would be a division into two risk groups: 'at risk' (high risk) or 'not at risk' (low risk). Those at risk would receive a TLS care bundle with standard interventions. Implementing a straightforward trigger tool wherein clinicians simply assess cancer bulk and determine whether the patient has bulky disease (≥500 g of cancer in adults or 300 g/m^2 of body surface area in children) and then applies a standardized package of interventions based on the 'trigger' of documented bulky disease has the potential to greatly simplify and standardize TLS management. To make the application of a simplified system even more practical, bulky disease can be estimated based on the presence of cancer in the bone marrow, liver or spleen, or of tumours at any site that are 10 cm in diameter or larger. We have previously advocated a more nuanced assessment of cancer bulk that carefully estimates the bulk of disease at these four sites and combines them for a total bulk score; however, this is more suitable in a research environment since precise estimation requires time and specific expertise. For rapid, practical application, each site can be assessed as bulky or not and, if any site is bulky, it identifies the patient as being at high risk of TLS. The TLS care bundle for patients at risk includes inpatient care, continuous cardiac monitoring, measurement of electrolytes every 4–8 h, hyperhydration, rasburicase administration, and reduction of potassium and phosphate. Further research is warranted to ascertain whether such an approach would make high-quality TLS management more practical across diverse health-care settings, like the success of trigger tools in other areas of health care[193–196].

Effect of TLS on the risk of subsequent AKI during cancer therapy and on long-term renal function

Beyond risk stratification, there is a pressing need for comprehensive analyses of the ramifications of TLS on subsequent AKI episodes, chemotherapy delays, dose reductions, relapse risk, long-term renal function and cancer prognosis. This research is indispensable for elucidating the cost-effectiveness of rasburicase and other interventions since their benefits can be both short-term and long-term, particularly in preserving renal function and avoiding clinically relevant nephropathy as patients age. It has been shown that patients treated initially with allopurinol (versus rasburicase) have a higher risk of subsequent delayed elimination of high-dose methotrexate despite the fact that it is administered 6 weeks later, indicating subclinical persistent nephropathy[158]. However, the effect of initial TLS management on the tolerance of other chemotherapy agents and on long-term renal function is not known.

Access to essential medications for TLS management

Cancer care and outcomes in LMICs differ radically from those in high-income countries but many efforts are under way to reduce disparities[197–207]. The essential medicines list (EML) of the WHO serves as a guiding framework for many governments in making procurement and reimbursement decisions pertaining to cancer care[208]. Currently, allopurinol is listed in the WHO EML whilst rasburicase is not. This discrepancy may have contributed to delays in rasburicase availability in LMICs, thereby increasing the risk of TLS-associated morbidity. Advocacy for the inclusion of rasburicase in the EML is imperative not only for potential cost savings but also for preservation of kidney function and the preservation of lives in settings where managing TLS complications, including intensive care and haemodialyses, may be particularly challenging[22,209–211].

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