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Review article

Updates on the diagnosis and Management of tumor lysis syndrome

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Abstract

Tumor lysis syndrome (TLS) represents a serious oncological emergency characterized by hyperuricemia, hyperkalemia, hyperphosphatemia, and hypocalcemia, carrying the potential for life-threatening complications such as arrhythmias, renal failure, and seizures. The diagnostic process relies on serum markers, though limitations in radiological and electrocardiographic assessments necessitate further research. Effective management involves aggressive hydration, electrolyte balance restoration, and hypouricemic agents like allopurinol and rasburicase. Strategies for managing hyperkalemia and hyperphosphatemia include sodium polystyrene sulfonate, glucose and insulin therapy, diuretics, and phosphate binders. In cases of recurrent hypocalcemia, calcium gluconate infusion is recommended, and hemodialysis should be considered for patients with severe metabolic disturbances or acute renal failure. This review discusses the key aspects of TLS, with an emphasis on risk assessment, laboratory-based diagnosis, and management strategies. The diagnostic process is based on serum markers, although limitations in radiological and electrocardiographic studies require further investigation.

Keywords: *Tumor Lysis Syndrome, Hyperuricemia, Hyperkalemia, Hyperphosphatemia, Hypocalcemia, Oncological Emergency, Risk Assessment, Diagnosis, Management Strategies.*

Introduction

Tumor lysis syndrome (TLS) is a well-known hematological-oncological emergency that affects people of all ages, including adults and children [1-3]. TLS was initially observed in patients with non-Hodgkin's lymphoma and acute leukemia, but gradually became more common and extended to a wide range of malignancies [4-6]. This syndrome is caused by the sudden release of tumor cell contents, including potassium, phosphate, and nucleic acids, into the blood, significantly disrupting the body's systemic circulation [7]. This biochemical disturbance triggers a cascade of effects, with nucleic acids being broken down into uric acid, potentially leading to the precipitation of uric acid in renal tubules. Consequently, renal vasoconstriction, impaired autoregulation, reduced renal blood flow, and an inflammatory response can occur [7-10].

TLS can manifest under various circumstances. Patients with high-grade lymphomas and acute lymphoblastic leukemia are particularly susceptible. Additionally, tumors with heightened sensitivity to cytotoxic therapy or those characterized by a high proliferative rate are more likely to experience cell rupture, thus increasing the risk of TLS [1,2,7]. Based on their susceptibility to TLS, patients affected with malignancies are broadly classified into three risk categories: high risk group, intermediate risk group, and low risk groups (Table 1). Factors associated with increased susceptibility of the patients to TLS, include older age, volume depletion, use of nephrotoxic medications, and general comorbid conditions such as cardiac disease, diabetes mellitus, and renal disease [7]. On the other hand, the risk factors for developing acute TLS after initiation of chemotherapy in all tumors are uric acid level > 7.5 mg/dL at initiation of treatment, underlying renal insufficiency, creatinine > 1.6 mg/dL,

hypercalcemia, leukocytosis > 50,000/µl, bulky disease, high LDH, high tumor growth fraction [7-11].

Table 1. Stratification of patients and tumors based on their susceptibility to tumor lysis syndrome

Degree of risk	Type of tumor
High-Risk	Advanced Burkitt lymphoma Advanced leukemia Early-stage leukemia or Burkitt lymphoma with elevated lactate dehydrogenase Acute lymphocytic leukemia with a white cell count of more than 100,000/microliters, or if the increase of lactate dehydrogenase from the baseline is two times the upper limit of normal Diffuse large B-cell lymphoma (DLBCL) and bulky disease with a baseline lactate dehydrogenase two times the upper limit of normal Acute myeloid leukemia (AML) with a white cell count more than or equal to 10,000/microliters
Intermediate-Risk	AML with A white cell count between 25,000 and 100,000/microliters Acute lymphocytic leukemia (ALL) with a white cell count of less than 100,000/microL and LDH of less than twice the upper limit of normal DLBCL with a baseline increase in lactate dehydrogenase of twice the upper limit of normal but the non-bulky disease Early-stage leukemia and Burkitt lymphoma with a lactate dehydrogenase of less than twice the upper limit of normal
Low-Risk	Solid cancers Multiple myelomas Indolent lymphomas Chronic lymphocytic leukemia Chronic myeloid leukemia AML with a WBC count of less than 25,000/microliters and a lactate dehydrogenase elevated to less than two times the upper limit of normal

New therapeutic options have been introduced to treat chronic lymphocytic leukemia (CLL) conditions, including B-cell lymphoma-2 protein inhibitors like venetoclax and oral kinase inhibitors such as idelalisib and ibrutinib [12]. While promising, these treatments carry a potential risk of triggering TLS due to their sensitivity and ability to reduce tumor burden rapidly. This review details the pathophysiology, clinical features, and laboratory diagnostic criteria of TLS to establish a profound understanding of the condition and its risks, ultimately guiding more effective management and intervention strategies.

EPIDEMIOLOGY AND Pathophysiology of TLS

The exact incidence of TLS is not known. However, this depends on the number of risk factors present at presentation and the treatment of potentially at-risk patients [11]. The predisposition to TLS is not related to race or sex [11]. Risk factors for clinical tumor lysis syndrome include a large cancer mass, high cell lysis potential (chemosensitivity), and patient factors (e.g., preexisting nephropathy, dehydration, acidosis, hypotension, and nephrotoxin exposure) [7-11]. Historically, TLS was most commonly reported in patients with high-grade non-Hodgkin's lymphoma (NHL) and acute leukemias, but it was later recognized that it can occur in patients with all types of cancer. According to a study [11], the most common malignancies associated with TLS were non-Hodgkin lymphoma (30%), solid tumors (20%), acute myeloid leukemia (19%), and acute lymphocytic leukemia (13%). The overall in-hospital mortality rate was approximately 21% [13].

TLS is most commonly associated with initiation of cytotoxic chemotherapy. However, there are case reports of tumor lysis syndrome induced by radiation therapy, dexamethasone therapy, and the use of newer chemotherapeutic agents such as rituximab and bortezomib [11,14, 15]. In addition, it must be taken into account that TLS can occur spontaneously [16]. The pathophysiology of TLS is characterized by a cascade of biochemical events that begins when cancer cells lyse and release various cellular components, including potassium, phosphorus, nucleic acids, and cytokines [17-22]. Hyperkalemia can lead to severe and sometimes fatal arrhythmias, whereas hyperphosphatemia can cause secondary hypocalcemia, which in turn can lead to neuromuscular irritability (tetany), arrhythmias, and seizures. Calcium phosphate crystals, which are formed by the precipitation of high levels of phosphorus, together with uric acid crystals, which are formed by the breakdown of nucleic acids, can lead to acute kidney injury [18]. This may be due to intrarenal crystallization and crystal-independent mechanisms, including renal vasoconstriction, impaired autoregulation, decreased renal blood flow, oxidation, and inflammation [25-27]. Furthermore, tumor lysis can release cytokines, triggering a systemic inflammatory response syndrome and often resulting in multi-organ failure [19-22].

TLS occurs when the amount of potassium, phosphorus, nucleic acids, and cytokines released during cell lysis overwhelms the body's homeostatic mechanisms. The kidneys play a crucial role in eliminating uric acid, xanthine, and phosphate. However, due to the kidneys' great ability to excrete these solutes, clinical TLS is unlikely to manifest without nephropathy initially developing. Nephropathy affects the kidney's ability to rapidly excrete solutes to cope with the metabolic load. Crystal-induced tissue injury occurs when calcium phosphate, uric acid, or xanthine precipitates in renal tubules, leading to inflammation and obstruction [23,24]. Calcium phosphate can precipitate throughout the body, especially when the calcium-phosphate product exceeds a certain threshold (more than 60). The risk of ectopic calcification is particularly high when patients require intravenous calcium, and it can lead to serious and occasionally fatal dysrhythmias when calcium phosphate precipitates in the cardiac conduction system [22-24].

Clinical Features of TLS

The clinical presentation of TLS is directly linked to the biochemical derangements detected during laboratory work up of this disorder. However, the severity of these metabolic alterations, particularly when uric acid levels exceed 594.8 μmol/l (10 mg/dl), serum potassium levels surpass 6 mmol/l, and serum phosphorus levels exceed 1.62 mmol/l (5 mg/dl), is influenced by several factors, such as the chemotherapy dose, tumor mass size, the number of lysed cells, and the patient's state of hydration and renal function state [1-7].

Hyperkalemia:

Onset: Occurs 6–72 hours after chemotherapy initiation.
Symptoms: Patients with hyperkalemia, if symptomatic, present with generalized fatigue, muscle weakness, paresthesia or paralysis, and electrocardiographic (ECG) abnormalities such as peaked T waves, PR interval prolongation, flattening or absence of the P wave, QRS complex widening, and a 'sine wave' appearance [25, 26]. Hyperkalemia Can lead to ventricular arrhythmias and sudden death, especially when accompanied by low serum calcium and acidosis.

Hyperphosphatemia and Hypocalcemia

Onset: Typically 24–48 hours after chemotherapy initiation.
Symptoms: Typically, most patients with hyperphosphatemia are asymptomatic. Signs and symptoms of acute hyperphosphatemia result from the effects of hypocalcemia, with patients occasionally reporting symptoms such as muscle cramps, tetany, and perioral numbness or tingling. Other symptoms include bone and joint pain, pruritus, and rash. Moreover, prolongation of QT interval on the ECG, and cardiac dysrhythmias can occur [27,28].

Hyperuricemia

Onset: Develops within 48–72 hours of chemotherapy.
Symptoms: Hyperuricemia itself has no symptoms. However, over time, uric acid crystals can form, with gout and uric acid nephrolithiasis being the two most common complaints. An increase and precipitation of uric acid in the renal tubules can lead to obstructive uropathy and acute kidney injury, manifested by an increase in serum creatinine and a decrease in urine output. [29-31].

Acute kidney injury (AKI)

AKI is a critical outcome associated with TLS, and it may lead to multiple organ failure and death [45]. The principal cause of AKI linked to TLS is phosphate and uric acid precipitation, which can lead to renal calculi, metabolic acidosis, and other end-organ dysfunction. AKI is characterized by a sudden loss of renal function, manifesting as an increase in serum creatinine concentration, the accumulation of nitrogenous waste products, and often a decrease in urinary output [9, 24,32]. It perturbs extracellular fluid balance, acid–base equilibrium, electrolyte levels, and divalent cation regulation. In turn, AKI can lead to other complications, such as acute respiratory distress syndrome [32,33].
Monitoring specific electrolytes and renal function can provide valuable insights into the condition and guide appropriate intervention. Therefore, it is essential to be highly suspicious if any of the above clinical presentations arise in patients with cancer, especially those with tumors in a high-risk group. In rare instances TLS may present prior to the diagnosis of cancer.

Diagnosis of TLS

TLS is diagnosed based on the criteria established by Cairo and Bishop [34]. The major limitation of this criterion is that it requires initiation of chemotherapy, although in clinical practice TLS can develop after radiotherapy [14] or spontaneously and without initiation of chemotherapy [16].

TLS is categorized into two distinct forms: laboratory TLS and clinical TLS (Table 2).

Laboratory Diagnosis of TLS

To diagnose TLS, at least 2 of the following criteria must be met in the same 24-hour period within 3 days before or 7 days after chemotherapy initiation (Table 2):

- Uric acid ≥ 8 mg/dL (476 μmol/L) or 25% increase
- Potassium ≥ 6 mEq/L (6 mmol/L) or 25% increase
- Phosphate ≥ 4.5 mg/dL (1.45 mmol/L) (adults) or 25% increase (children) –
- Calcium ≤ 7 mg/dL (1.75 mmol/L) or 25% decrease

Clinical Diagnosis of TLS

TLS is clinically diagnosed when laboratory TLS criteria are met along with at least one of the following clinical features (Table 2):

- Creatinine is greater than 1.5 times the upper limit of normal based on an age-adjusted reference range. Other potential causes of AKI should be excluded during the evaluation of TLS.
- Seizure
- Cardiac arrhythmia or sudden death

In the diagnostic evaluation of TLS, the following studies and tests are essential [1,7,13,24]:

- **Imaging:**
- Chest X-Ray and computed tomography (CT) scans to assess for the presence of a mediastinal mass and concomitant pleural effusion. Abdominal and retroperitoneal CT scans and ultrasounds if the mass lesion is in the abdomen or retroperitoneum. Special care is required when using intravenous (IV) contrast due to the presence of AKI in TLS.
- Electrocardiography (ECG): ECG is used to identify findings associated with hyperkalemia and hypocalcemia, as hyperkalemia can lead to fatal arrhythmias in TLS.
- Complete Blood Count (CBC): CBC aids in diagnosing malignancies associated with TLS. Most malignancies present with leukocytosis, anemia, and thrombocytopenia.
- Comprehensive Metabolic Panel (CMP): CMP helps identify metabolic derangements related to TLS, such as hyperkalemia, hypocalcemia, hyperphosphatemia, and hyperuricemia. Elevated blood urea nitrogen (BUN) levels, creatinine, and lactate dehydrogenase also indicate TLS. CMP should be monitored two to three times daily before and after therapy initiation, with elevated laboratory values suggesting the onset of TLS.
- Urine analysis is crucial for identifying the precipitation of uric acid salts, which can lead to obstructive uropathy. In the treatment of TLS, urine alkalization with sodium bicarbonate is standard. Regular urine analysis assessing urine pH, specific gravity, and output is mandatory for TLS management.

Table 2. Clinical and Laboratory Diagnosis of Tumor Lysis Syndrome

Type of TLS	Clinical TLS	Laboratory TLS
Definition	Clinical signs and symptoms directly related to TLS, including renal dysfunction, cardiac arrhythmias, neurological manifestations (seizures, tetany, muscle twitching, Trousseau's sign, carpopedal spasm, Chvostek's sign, and bronchospasm or laryngospasm)	Biochemical abnormalities in the absence of clinical symptoms.
Diagnostic Criteria	- Presence of at least two of the following within 3 days before or 7 days after initiation of cancer treatment: - Uric acid level > 8 mg/dL (476 μmol/L) or 25% increase - Potassium level > 6 mEq/L (6 mmol/L) or 25% increase - Phosphate level ≥ 4.5 mg/dL (1.45 mmol/L) (adults) or 25% increase (children)	At least two of the following biochemical abnormalities within 3 days before or 7 days after initiation of cancer treatment without clinical symptoms: - Uric acid ≥ 8 mg/dL (476 μmol/L) or 25% increase - Potassium ≥ 6 mEq/L (6 mmol/L) or 25% increase - Phosphate ≥ 4.5 mg/dL (1.45 mmol/L) (adults) or

	- Calcium ≤ 7 mg/dL (1.75 mmol/L) or 25% decrease - Plus, one of the following clinical signs and symptoms attributed to TLS: Seizure, Cardiac arrhythmia or sudden death, Creatinine greater than 1.5 times the upper limit of normal based on an age-adjusted reference range*.	25% increase (children) - Calcium ≤ 7 mg/dL (1.75 mmol/L) or 25% decrease

**Other potential causes of Acute Kidney Injury should be excluded during the evaluation of TLS.*

Prevention of TLS

The principal of TLS treatment is prevention. Unfortunately, this is inaccessible in spontaneous TLS. Preventing TLS requires a comprehensive strategy to reduce associated risks, which can be summarized in three steps (Table 3). The first step is to identify patients with risk factors for TLS development, the second is to implement adequate prophylactic measures that reduce the risk, and the third is a cautious laboratory and clinical monitoring [35]. Subjects at intermediate and high risk of TLS should be monitored in a hospital setting [7]. It is crucial to address underlying medical conditions and potential hypovolemia before initiating cancer-targeted therapies. Conventional preventive measurements includes aggressive intravenous hydration initiated three days before chemotherapy, diuretic therapy, and inhibition of urate production using high-dose allopurinol [7,35,36].

Active hydration through intravenous (IV) fluids, maintaining a minimum urine output of 2 mL/kg per hour, is a central aspect of prevention [37]. IV fluids should be chosen based on the patient's needs, considering calcium and potassium content. Allopurinol prophylaxis is essential for intermediate-risk patients to mitigate uric acid nephropathy. Allopurinol, available in oral or intravenous forms, inhibits the xanthine oxidase enzyme [35,36]. For patients with allopurinol intolerance or underlying renal disease, febuxostat, a newer xanthine oxidase inhibitor, is an alternative. High-risk patients or those with baseline uric acid levels exceeding 7.5 mg/dL may benefit from rasburicase, which mimics urate oxidase [36, 37]. However, it should be avoided in pregnant or lactating patients and individuals with glucose 6-phosphate dehydrogenase deficiency [36]. Diuretics facilitate the renal excretion of potassium and may also be necessary to maintain adequate urine output, but are contraindicated in patients with hypovolemia or obstructive uropathy [37]. Phosphate binders should be considered case-by-case and discussed with the patient [38]. Urine alkalization, though theoretically appealing, has limited value in routine TLS prevention [7,36]. Regular monitoring of serum markers is essential, and TLS prophylaxis can be discontinued when levels consistently fall within normal limits after completing cancer-related treatment.

Table 3. Practical steps in prevention of tumor lysis syndrome (TLS)

Step	Preventive measurements
Step 1: Identify patients with risk factors for TLS development	Address underlying medical conditions and potential hypovolemia before initiating cancer-targeted therapies Identify degree of risk
Step 2: Implement adequate prophylactic measures that reduce the risk for TLS	Aggressive intravenous hydration initiated three days before chemotherapy, Diuretic therapy Inhibition of urate production using high-dose allopurinol
Step 3: Cautious laboratory and clinical monitoring	Regular monitoring of serum markers is essential, and TLS prophylaxis can be discontinued when levels consistently fall within normal limits after completing cancer-related treatment.

Management of established TLS

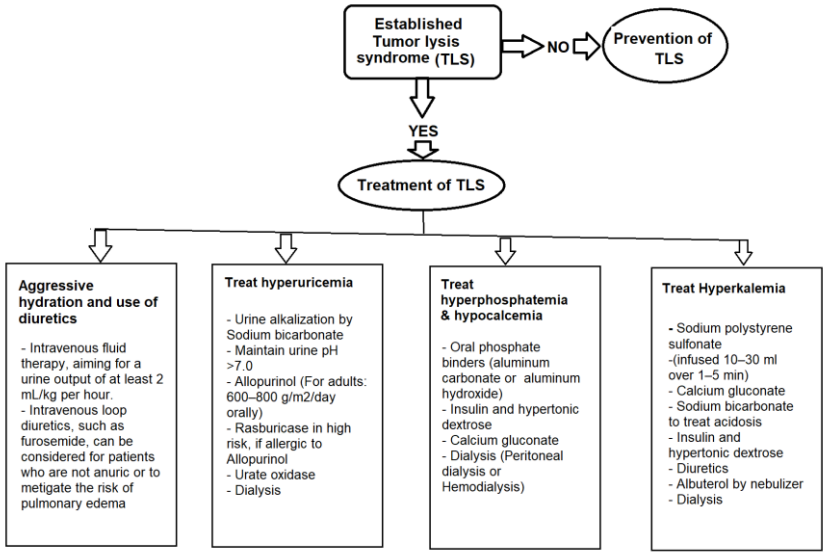
Patients with laboratory evidence of TLS and those who present with clinical TLS, especially those with cardiorenal comorbidities, should be promptly admitted to an intensive care unit (ICU) [7]. It is essential to initiate aggressive intravenous (IV) fluid therapy, aiming for a urine output of at least 2 mL/kg per hour. IV loop diuretics, such as furosemide, can be considered for patients who are not anuric. Loop diuretics not only help mitigate the risk of pulmonary edema but may also aid in controlling hyperkalemia. However, their use should be decided on a case-by-case basis described below. Figure 1, describes TLS treatment algorithm.

Intravenous Fluid administration

Intravenous hydration plays a central role in the prophylaxis against TLS. It is recommended for patients at risk of TLS, excluding those prone to volume overload, such as the elderly or

those with cardiac and baseline renal diseases [7]. Aggressive intravenous hydration increases intravascular volume, thereby correcting electrolyte imbalances by diluting extracellular fluids. This, in turn, reduces the concentration of serum potassium, uric acid, and phosphate. Increased intravascular volume resulting from hydration can enhance renal blood flow, glomerular filtration rate, and urinary volume, potentially reducing the risk of requiring dialysis [33,36,37].

Figure 1. Tumor lysis syndrome treatment algorithm



Diuresis

Diuretic therapy plays a vital role in managing TLS by enhancing diuresis, the process of increased urine production, which can help eliminate excess waste products from the body. Several diuretics, such as Mannitol, can be utilized when hydration alone is insufficient to maintain adequate diuresis [39]. It induces osmotic diuresis, which involves water movement from the body into the renal tubules, increasing the excretion of waste products like uric acid. Furosemide is another diuretic option. However, its effectiveness can be limited if the renal tubules are impacted by urate precipitation, a common concern in TLS. In such cases, alternative diuretics like mannitol may be preferred [39]. Thiazides are contraindicated because they increase the blood levels of uric acid [18].

Alkalization

Urinary alkalization is a critical component of TLS management, aiming to reduce the risk of uric acid crystallization in the kidneys, a condition known as uric acid nephropathy. This is achieved by increasing the urinary pH to create an environment where uric acid remains soluble and does not form harmful crystals [7,18, 36].

There are several methods to achieve urinary alkalization. One approach is to add sodium bicarbonate to a hydrating physiologic solution. Intravenous administration of isotonic 0.45% sodium bicarbonate in normal saline with 5% dextrose can be performed at a specific rate to achieve effective diuresis and maintain urinary alkalization within the optimal pH range of 7.0–7.3 [39-41]. This pH range ensures the efficient excretion of uric acid in soluble form. However, it's important to recognize that the methods used to achieve urinary alkalization can be a subject of debate. Some studies have questioned the effectiveness of alkalization in improving TLS-induced abnormalities, as it may lead to the increased precipitation of calcium phosphate in the renal microvasculature and tubules, especially in patients with hyperphosphatemia [30,42]. This can result in obstructive nephropathy, further decreasing glomerular filtration rates and increasing the risk of AKI [43].

Moreover, systemic alkalization with sodium bicarbonate can influence calcium-phosphate bonding, reducing ionized calcium concentration and potentially causing hypocalcemia [10,36]. Urinary alkalization may also decrease the solubility of xanthine, raising the risk of xanthine nephropathy [10,36,39]. If alkalosis occurs during urinary alkalization, it's im-

portant to discontinue bicarbonate administration and manage the patient based on the degree of alkalosis [18,36]. Depending on the severity of alkalosis, treatment may involve intravenous solutions like 0.9% sodium chloride and potassium chloride if hypokalemia is present. Severe alkalosis may manifest as hyperirritability or tetany, which can be managed with calcium gluconate. In some cases, acidifying agents like ammonium chloride may be required [27,28].

Allopurinol Treatment

Allopurinol is a well-established method for managing hyperuricemia associated with TLS. It is a synthetic compound structurally similar to hypoxanthine and competitively inhibits xanthine oxidase, thereby preventing the conversion of hypoxanthine and xanthine into uric acid. Since 1966, allopurinol has been the standard treatment for malignancy-associated hyperuricemia and is also used in managing patients at risk for TLS [44]. Allopurinol reduces renal uric acid load, effectively preventing its further production, although it doesn't impact existing uric acid [45]. The recommended intravenous dosage of allopurinol is usually 200 to 400 mg/m2/day. Allopurinol requires a delay in chemotherapy initiation, may result in undesirable drug interactions, and often needs dose adjustments for patients with impaired renal function. Common side effects include skin rashes and hypersensitivity reactions, with rare, severe symptoms [46]. Additionally, long-term allopurinol use can lead to xanthine nephropathy, emphasizing the importance of maintaining urinary pH and excretion rates to prevent complications [47-50].

Urate Oxidase Treatment

Urate oxidase, particularly the recombinant form known as rasburicase, represents a modern and rapid method for managing TLS-induced hyperuricemia [18,39, 51-55]. Due to its swift reduction of serum uric acid levels, rasburicase is more effective than allopurinol, as evidenced by lower blood urea nitrogen and creatinine levels [46,52]. An advantage of urate oxidase treatment is the prompt initiation of chemotherapy, eliminating the need for delays. Furthermore, urate oxidase doesn't require urine alkalization, simplifying the treatment process. However, vigilance is necessary to monitor potential complications, such as calcium phosphate deposition. The pegylated form of urate oxidase, PEG-uricase, further reduces plasma uric acid levels without antigenicity and has a longer duration of action. While the cost of rasburicase can be a concern, its advantages in treating TLS in high-risk patients, particularly those unable to ingest oral allopurinol or allergic to it, make it a valuable addition to the TLS management options [56,57]. The primary objective of urate oxidase treatment is to rapidly reduce uric acid levels, thus minimizing the risk of renal dysfunction requiring dialysis and mitigating TLS-related complications [58,59].

Hyperkalemia Treatment

Effectively managing hyperkalemia in Tumor Lysis Syndrome (TLS) is pivotal to patient care. The foremost objective is to counteract the detrimental impact on the myocardium and stabilize the cardiac membrane to avert life-threatening cardiac arrhythmias [60]. Typically, this is achieved by administering 10% calcium gluconate, which provides immediate cardiac protection and membrane stabilization, particularly for patients exhibiting significant electrocardiographic changes due to severe hyperkalemia [61-63].

Furthermore, several interventions are employed to mitigate potassium levels. For moderate hyperkalemia, consideration may be given to Kayexalate® (sodium polystyrene sulfonate), even though its effects are not instantaneous since it functions as an ion-exchange resin in the gastrointestinal tract [60]. Notably, recent reports have associated sodium polystyrene sulfonate with colonic necrosis in critically ill patients, rendering it unsuitable for treating acute toxicities such as life-threatening arrhythmias. In severe cases of hyperkalemia with or without significant electrocardiographic changes, alternative treatment modalities encompass hypertonic glucose and insulin, loop diuretics, and bicarbonate. However, the efficacy of bicarbonate primarily lies in cases of severe metabolic acidosis. These interventions collectively address hyperkalemia as part of TLS management [32,64].

Hyperphosphatemia and Hypocalcemia

Addressing hyperphosphatemia and accompanying hypocalcemia is paramount in managing TLS. Hyperphosphatemia treatment is contingent on the extent of phosphorus elevation, typically necessitating intervention when phosphorus levels surpass 1.62 mmol/l (>5 mg/dl)

[60]. In cases of mild asymptomatic hyperphosphatemia associated with chronic renal failure, it is advisable to curtail dietary phosphate intake, and the utilization of phosphate binders, such as aluminum hydroxide or aluminum carbonate (administered four times daily at 30 ml each), may be considered to curtail phosphate absorption. Given their inherent toxicity, it is vital to abstain from the prolonged use of aluminum compounds, especially in individuals with advanced chronic kidney disease.
Severe hyperphosphatemia in patients with end-stage renal failure can be rectified through hemodialysis or peritoneal dialysis, with the concomitant correction of related hypocalcemia. As a general practice, calcium supplements are typically not administered, as they can instigate the precipitation of metastatic calcifications [65]. In the case of hypocalcemia, the preferred course of action encompasses the intravenous administration of parenteral calcium, such as calcium gluconate, typically administered over 10 minutes. However, vigilance is essential when administering calcium gluconate, as it can potentially result in severe arrhythmias. In recurrent hypocalcemia scenarios, adopting a continuous intravenous infusion of calcium gluconate aligns with an effective treatment approach within the broader TLS management framework.

Acute kidney injury (AKI)
AKI within the context of TLS is a crucial aspect of patient care. Studies have indicated that many patients may not survive the acute episode of TLS [45, 66, 67]. Therefore, it is vital to effectively recognize and address TLS-related biochemical and clinical abnormalities. One of the primary strategies for preventing AKI is intravascular volume expansion. This typically involves administering 3 liters/m2/day of hydration and encouraging forced diuresis. However, despite these preventive measures, hemodialysis should be considered for patients with significantly elevated uric acid, phosphate, and potassium levels and those already experiencing AKI [87].
While various dialytic modalities, including hemodialysis, peritoneal dialysis, and continuous dialysis hemofiltration, are available, the choice depends on the patient's requirements and the clinical context. Hemodialysis is generally preferred because of its ability to correct life-threatening electrolyte imbalances rapidly. Dialysis sessions are typically scheduled every 12 hours until renal and hepatic functions are restored, along with the recovery of urinary volume. In specific cases with a substantial phosphate burden, more frequent dialysis (every 12–24 hours) may be necessary [68,69].

Conclusion
TLS is an urgent metabolic complication that can arise from aggressive cancer treatments, or spontaneously. Timely risk assessment and prevention are crucial, with strategies involving proper hydration, uric acid-lowering measures, phosphate binding, and careful potassium management. When TLS manifests, it demands intensive care support, featuring aggressive hydration, potential loop diuretic use (especially in patients at risk of fluid overload), phosphate binding, uric acid-lowering agents like rasburicase, and dialysis for refractory cases. As cancer treatment methods continue to advance, recognizing TLS risk factors and biochemical indicators becomes increasingly vital for clinicians, highlighting the pivotal role of healthcare professionals in patient safety during these high-impact anti-cancer therapies.

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