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RESEARCH **REVIEW ARTICLE**

Tumor Lysis Syndrome: Pathophysiology, Risk Factors, Management Strategies, and Prognostic Indicators

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ABSTRACT

Tumor lysis syndrome (TLS) is an oncological emergency that occurs when cancer cells are rapidly destroyed, leading to metabolic disturbances and potentially life-threatening complications. Prompt recognition and prevention of TLS are essential to ensure effective management. TLS can lead to endothelial dysfunction, hyperuricemia, and/or acute renal failure. Additionally, it commonly manifests as metabolic imbalances such as hyperkalemia, hyperphosphatemia, and hypocalcemia. In this review, we aim to offer a comprehensive understanding of TLS, including its epidemiology, pathophysiology, risk factors, and clinical presentation.

KEYWORDS - Tumor lysis syndrome; oncological emergencies; tumor lysis.

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INTRODUCTION

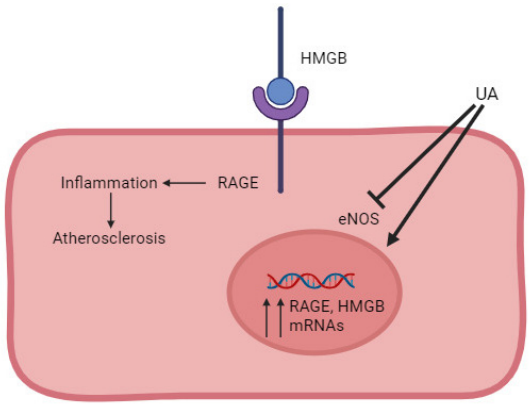
Tumor lysis syndrome (TLS) is an oncological emergency that occurs when cancer cells are rapidly destroyed, often due to chemotherapy or targeted therapies. In some rare cases, TLS can also occur spontaneously in patients with rapidly growing tumors. This process leads to the release of cellular components, causing disruptions in metabolic balance. These disruptions commonly include elevated levels of uric acid, potassium, and phosphates, and decreased calcium levels. These imbalances can have severe clinical consequences, such as acute renal failure, irregular heart rhythms, seizures, and even death. Prompt recognition and effective management of TLS are essential to minimize these risks and improve patient outcomes.

PATHOPHYSIOLOGY

ACUTE RENAL FAILURE - When uric acid (UA) concentrations are high, it can trigger the formation of crystals within the tubular cells of the kidneys. This happens when there is an excessive amount of UA in the tubular fluid. These crystals inside the renal tubules cause an elevation in hydrostatic pressure within Bowman's capsule (Pb). As a result, this increased pressure counteracts the normal vascular hydrostatic pressure, hindering the glomerular filtration rate (GFR). The sudden decrease in GFR can then lead to the development of acute renal failure. [1,2].

ENDOTHELIAL DYSFUNCTION - UA affects endothelial function through various mechanisms. Primarily, it reduces the activity of nitric oxide synthase, which impairs renal autoregulation and accelerates the formation of atherosclerotic plaques (Figure 1).

Figure 1. UA effects on endothelial cells.



At the transcriptional level, UA enhances the expression of the receptor for advanced glycation end products (RAGE) and its ligand, high-mobility group box 1 (HMGB1). RAGE has recently been recognized as a crucial contributor to the formation of atherosclerotic plaques. By upregulating RAGE, UA significantly amplifies the inflammatory processes involved in the development of these plaques [3].

ACUTE KIDNEY INJURY (AKI) AND ITS INDUCTION OF APOPTOSIS IN PROXIMAL CONVOLUTED TUBULAR (PCT) CELLS - UA exerts its pro-apoptotic effects on renal cells through multiple mechanisms [4] (Figure 2)

Firstly, UA enhances the activity of caspase 9, a key mediator of apoptotic signaling pathways. This activation sets off a cascade of events that ultimately leads to cellular apoptosis [4].

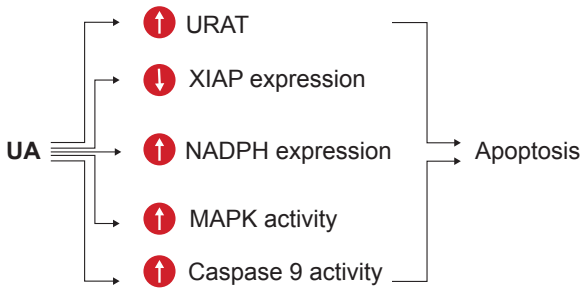
In addition, UA upregulates the expression of Nicotinamide Adenine Dinucleotide Phosphate oxidase 4 (NADPH oxidase 4), also known as NOX 4, a component of the NADPH oxidase complex. The increased levels of NOX 4 contribute to the production of reactive oxygen species (ROS), which can induce oxidative stress and activate apoptotic pathways in renal cells [4].

Furthermore, UA activates the mitogen-activated protein kinase (MAPK) pathway, which plays a critical role in cellular responses to stress and apoptosis. The activation of MAPK pathways, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), and p38 MAPK, promotes apoptotic processes in renal cells [4].

Moreover, UA affects the transport of urate and modulates the expression of X-linked inhibitor of apoptosis protein (XIAP). Changes in urate transport can impact intracellular UA levels and contribute to apoptotic signaling. Decreased levels of XIAP, an anti-apoptotic protein, further increase the susceptibility of renal cells to undergo apoptosis [4].

In summary, the upregulation of caspase 9 activity, increased ROS production through NOX 4 upregulation, activation of the MAPK pathway, modulation of urate transport, and decrease in XIAP expression collectively contribute to the pro-apoptotic effects of UA on renal cells. Understanding these mechanisms is crucial for unraveling the intricate pathways involved in UA-induced renal cell apoptosis and may assist in the development of targeted therapeutic interventions.

Figure 2. UA various mechanisms of inducing apoptosis in Proximal convoluted tubular (PCT) cells.



NADPH: Nicotinamide Adenine Dinucleotide Phosphate; MAPK: mitogen-activated protein kinase; XIAP: X-linked inhibitor of apoptosis protein

HYPERKALEMIA - It is a significant and dangerous abnormality in the context of TLS. What makes TLS-related hyperkalemia particularly hazardous is the rapid increase in serum potassium levels, highlighting the importance of temporal fluctuations in potassium rather than its absolute value as a critical prognostic factor. While hyperkalemia often presents without symptoms, when symptoms do occur, they can be nonspecific, including nausea, vomiting, and muscle weakness. However, the most life-threatening consequences arise from electrocardiogram (ECG) abnormalities, such as QRS widening, absence of P waves, and significant elevation of T waves. These cardiac disturbances can lead to ventricular fibrillation and sudden cardiac death [5]. Therefore, prompt diagnosis and careful management of hyperkalemia in the context of TLS are of utmost importance.

HYPERPHOSPHATEMIA AND HYPOCALCEMIA - Phosphate plays a crucial role in the complex metabolic pathways of the body. When phosphate levels rise, a condition known as hyperphosphatemia, can result in hypocalcemia due to the sequestration of free calcium ions. Clinical manifestations of hyperphosphatemia and concurrent hypocalcemia may include muscle twitching, Chvostek's sign, Trousseau's sign, coma, and seizures. These symptoms, particularly in individuals at risk for TLS, require immediate attention as they may indicate the presence of TLS and necessitate urgent management [5].

A comprehensive understanding of the pathophysiology of TLS is essential for identifying high-risk patients and monitoring relevant laboratory parameters to classify patients based on electrolyte imbalances. Recognizing clinic-features also assists in accurate classification. This knowledge of the pathophysiology optimizes treatment plans and improves outcomes by predicting treatment response and minimizing complications.

CLASSIFICATION

TLS, according to the Cairo-Bishop criteria [6], is categorized into two main groups: Laboratory Tumor Lysis Syndrome (LTLS) and Clinical Tumor Lysis Syndrome (CTLS). This classification was established to enhance our understanding of the different aspects and presentations of TLS. LTLS focuses on the metabolic abnormalities detected in laboratory tests, such as elevated levels of uric acid (UA), potassium, phosphate, and decreased levels of calcium. LTLS provides valuable information about the biochemical changes that occur during TLS. On the other hand, CTLS encompasses not only the laboratory abnormalities but also clinical manifestations such as impaired renal function, reduced urine output, cardiac abnormalities, and even neurological symptoms like seizures and altered mental status. This classification assists healthcare professionals in evaluating the severity and clinical impact of TLS in patients. Table 1 offers an overview of the classification, summarizing the specific metabolic abnormalities and clinical symptoms associated with LTLS and CTLS, thereby aiding in the accurate diagnosis and management of TLS.

Table 1. A Comparison between Laboratory Tumor Lysis Syndrome (LTLS) and Clinical Tumor Lysis Syndrome (CTLS)

Laboratory Tumor Lysis Syndrome (LTLS)1 *	Clinical Tumor Lysis Syndrome (CTLS)2*
Elevated uric acid (>8 mg/dL)	Elevated uric acid (>7.5 mg/dL)
Elevated potassium (>6 mEq/L)	Elevated potassium (>6 mEq/L)
Elevated phosphate (>4.5 mg/dL)	Elevated phosphate (>4.5 mg/dL)
Decreased calcium (<7 mg/dL) or ionized calcium (<1.1 mmol/L)	Decreased calcium (<7 mg/dL) or ionized calcium (<1.1 mmol/L)
N/A	Impaired renal function, oliguria, anuria, cardiac abnormalities, neurological manifestations (seizures, altered mental status)

1: (2 or more of the following without clinical symptoms).
2: (2 or more of the following + one of the clinical symptoms).
*The symptoms and/or laboratory abnormalities must be within 3 days before and 7 days after the chemotherapeutic agent initiation

The classification of TLS serves as a framework for evaluating the risk factors associated with its occurrence. By categorizing tumors into high, intermediate, and low-risk groups, healthcare professionals can identify individuals who require close monitoring and intensive management.

RISK FACTORS

The risk of developing TLS can be attributed to both patient-related and cancer-related factors [7]. According to the Cairo-Bishop criteria, tumors are classified into high, intermediate, and low-risk categories [5]. Among patient-related factors, renal function plays a crucial role as TLS can lead to AKI, making patients with an already decreased GFR, such as older individuals, more susceptible to TLS. Pre-existing electrolyte imbalances, such as hyperkalemia and hyperuricemia, also indicate an increased risk for TLS and require close monitoring [7].

Hydration status is another important factor to consider, as aggressive hydration is a fundamental preventive measure against TLS. Adequate hydration helps prevent oliguria and maintains serum osmolarity, which is especially important for cancer patients who may experience vomiting and diarrhea, further predisposing them to dehydration. Age also influences the risk of TLS, with older patients generally facing a higher risk and often exhibiting a poorer prognosis.

When considering tumor-related factors contributing to the development of TLS, a stratification has been established to assess the associated risk [8]. It is important to note that the risk of TLS development, in terms of tumor factors, does not necessarily align with the prognosis. For example, even though solid tumors are generally categorized as low risk, the occurrence of TLS within this context is indicative of a poor prognosis. Therefore, this classification system should not be used as a determinant of prognostic implications in TLS among patients with specific tumor types. Instead, its primary purpose lies in the meticulous monitoring of individuals who are at a higher risk of developing TLS. Table 2 provides a summary of the tumor risk stratification for TLS.

Table 2. Tumor Risk Stratification for Tumor Lysis Syndrome (TLS); LDH: Lactate dehydrogenase

Risk Group	Cancers
High risk	-Advanced Burkitt's lymphoma/ leukemia or Early-stage disease with elevated baseline LDH
	-ALL with WBC count ≥ 100,000 (or lower if baseline LDH elevation is twice the upper limit of normal)
	-AML with WBC count ≥ 100,000
	-DLBCL with baseline LDH* twice the upper limit of normal and bulky disease
Intermediate risk	-AML with WBC count ranging from 25,000 to 100,000
	-ALL with WBC count < 100,000 and LDH levels < twice the upper limit of normal
	-Early stage Burkitt lymphoma/leukemia with LDH levels < twice the upper limit of normal
	-DLBCL with baseline LDH increase twice the upper limit of normal but non-bulky disease
Low risk	-Indolent lymphomas
	-CLL
	-CML in the chronic phase
	-AML with WBC count < 25,000 and LDH levels elevated to < twice the upper limit of normal
	-Multiple myeloma
	-Solid cancers

ALL: acute lymphocytic leukemia.
AML: acute myeloid leukemia.
DLBCL: diffuse large B-cell lymphoma.
CLL: chronic lymphocytic leukemia.
CML: chronic myeloid leukemia

EPIDEMIOLOGY

Gaining a comprehensive understanding of the epidemiology of TLS is crucial for assessing the risk, implementing preventive measures, and optimizing management strategies for this potentially life-threatening condition. While TLS can occur in various malignancies, it is most commonly observed in hematologic malignancies such as acute leukemias, high-grade lymphomas, and aggressive solid tumors with a high proliferation rate. The incidence of TLS varies depending on factors such as tumor type, disease stage, treatment modality, and patient-specific characteristics. Certain subgroups, including those with high tumor burden, bulky disease, or rapidly growing tumors, are at a higher risk. TLS can occur spontaneously before treatment initiation or as a result of cancer therapy, including chemotherapy, radiation, or immunotherapy. Improving our understanding of the epidemiology of TLS enables healthcare providers to identify high-risk patients, initiate appropriate preventive measures, and promptly manage this complex syndrome.

The incidence of TLS varies significantly among different studies and tumor subtypes. For example, a study found that 26.4% of patients with B-cell acute lymphoblastic leukemia (B-ALL) developed TLS [9], with precursor B-cell ALL accounting for 72% of TLS cases [10].

In a retrospective cohort study, TLS cases were distributed among different tumor types. Surprisingly, multiple myeloma, typically considered a low-risk tumor for TLS, had the highest incidence at 18.6%. Acute myeloid leukemia (AML) and diffuse large B-cell lymphoma (DLBCL) accounted for 17.5% of TLS cases each [11].

Another study exploring TLS in hematological malignancies reported an overall TLS occurrence rate of 20%. Among these cases, 12% were classified as laboratory TLS and 8% as clinical TLS. The incidence of TLS varied depending on the specific malignancy, with factors such as tumor type, tumor burden, serum LDH levels, and tumor sensitivity to chemotherapy contributing to the variation [12].

In a prospective multicenter study focusing on high-risk hematological malignancies, the incidence of TLS was 30.7%. Of these cases, 11.1% were classified as laboratory TLS, while 19.6% were clinical TLS. Importantly, all patients with clinical TLS experienced acute kidney injury (AKI) [13].

In the pediatric population, children with acute leukemia predominantly experienced laboratory TLS (93%), with a smaller percentage (7%) developing clinical TLS. Precursor B-cell ALL emerged as the most common subtype associated with TLS [10].

Furthermore, in the case of AML, a study developed prediction models for TLS incidence, reporting an overall incidence of 26.4% for laboratory TLS and 5.4% for clinical TLS [14].

The observed variation in TLS incidence among studies and tumor subtypes can be attributed to multiple factors. Differences in study populations, diagnostic criteria for TLS, disease stage at diagnosis, and treatment regimens all contribute to the heterogeneity. Additionally, variations in patient characteristics, such as age, sex, and underlying comorbidities, may further contribute to the discrepancies. To enhance our understanding of TLS and optimize patient management strategies, further research and standardization of TLS definitions and assessment criteria are warranted across different tumor subtypes.

CLINICAL PRESENTATION

TLS symptoms can vary significantly, ranging from nonspecific manifestations such as nausea, vomiting, diarrhea, and fatigue, to more pronounced symptoms resulting from metabolic disturbances [5]. Hyperuricemia, a hallmark of TLS, can trigger acute kidney injury (AKI) and contribute to uremia and fluid overload, leading to renal dysfunction [15]. Although urinalysis is not commonly performed due to anuria, it may reveal hematuria and the presence of uric acid crystals [15]. Additionally, the development of hyperkalemia can lead to cardiac arrhythmias, necessitating electrocardiogram monitoring in individuals at risk. Seizures, stemming from hypocalcemia, may rarely occur as an initial symptom of TLS. It is important to recognize the occurrence of muscular spasms, such as Trousseau and Chvostek signs, as potential indicators of this syndrome [5]. Therefore, heightened vigilance is crucial when encountering any of these manifestations in patients predisposed to TLS, emphasizing the need for prompt and decisive medical attention.

MANAGEMENT

The management of TLS involves a combination of preventive and therapeutic measures that are closely interconnected. By implementing these strategies, healthcare providers aim to minimize the associated morbidity and mortality. The following table provides a summary of the different approaches that can be taken (Table 3).

Table 3. A summary of the different approaches that can be taken.

Prevention	Treatment
Hydration	Hydration
Alkalization[1]	Urate oxidase (Rasburicase)[2]
Xanthine oxidase inhibitors (allopurinol)	Calcium gluconate[3]
Urate oxidase (Rasburicase)[2]	Cation exchange resins
	Dialysis
	Diuretics[4]

1: not routinely recommended;
2: contraindicated in patients with G6PD deficiency;
3: only if hypocalcemia symptoms are evident (muscle twitching);
4: thiazide and loop diuretics can worsen hyperuricemia

PREVENTION

HYDRATION - It plays a crucial role in the prevention and treatment of TLS by maintaining adequate urine flow and preventing the formation of UA crystals [16,7]. However, caution should be exercised in patients with pre-existing cardiac or renal conditions to avoid the risks of fluid overload and complications such as lower extremity edema, pulmonary edema, and congestive heart failure.

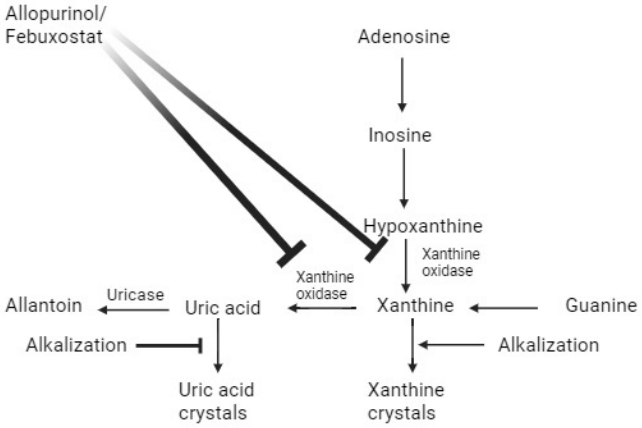
ALKALIZATION OF THE URINE - In the past, sodium bicarbonate (NaHCO3-) was commonly used to alkalinize the urine as a preventive and treatment measure for TLS. The goal was to increase the urine pH using NaHCO3- in order to inhibit the formation of UA crystals and subsequent UA nephropathy. However, this approach has limitations. While it may effectively prevent UA crystal formation due to the relatively low pKa of UA, the metabolites preceding UA in the purine degradation pathway, namely xanthine and hypoxanthine, have reduced solubility at alkaline pH compared to acidic pH [16]. Consequently, simultaneous use of NaHCO3- with inhibitors of the last two steps of the purine degradation pathway, such as allopurinol, can lead to the precipitation of xanthine and hypoxanthine, causing nephropathy [16]. Moreover, NaHCO3- can induce metabolic alkalosis, making its use no longer recommended.

PHARMACOTHERAPY - When considering medication options for managing TLS, it is crucial to have a comprehensive understanding of the purine degradation pathway (Figure 3).

Tumor cells, known for their rapid proliferation, synthesize excessive amounts of purines, specifically adenine and guanine, for DNA synthesis. These purines undergo a complex multistep degradation process. In humans, the final step involves the enzyme xanthine oxidase, which converts xanthine to UA. Xanthine oxidase inhibitors, such as allopurinol and febuxostat, target this last step by inhibiting the production of xanthine and hypoxanthine. It is important to note that while many mammals can further transform UA into a more soluble product called allantoin, humans lack this ability, leading to the accumulation of uric acid in the body.

Allopurinol, a competitive inhibitor of xanthine oxidase, has been widely used as a prophylactic agent and has demonstrated a lower incidence of TLS development. Although it is less effective than rasburicase [17,18], allopurinol remains a common choice for prophylaxis in patients at low to intermediate risk of TLS [17]. It is important to emphasize that allopurinol does not degrade the already formed UA and therefore has a minimal role in treating TLS; rather, its primary use is for prophylaxis.

Figure 3. Showing purines degradation pathway

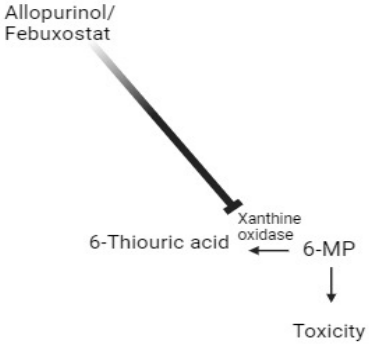


*Only occurs in mammals, and doesn't take place in humans

Febuxostat, a novel inhibitor of xanthine oxidase, has emerged as a distinct therapeutic option with inherent advantages. It has demonstrated efficacy in reducing serum UA levels, showing comparable effectiveness to its predecessor, allopurinol [19]. As a result, febuxostat plays a significant role in the field of pharmacotherapy, particularly for patients who may have difficulty tolerating allopurinol due to hypersensitivity reactions.

It is important to note that xanthine oxidase is involved in the metabolism of several chemotherapeutic agents (Figure 4). For example, azathioprine (AZA) is peripherally converted into its active compound, 6-mercaptopurine (6-MP), which acts as an antineoplastic or immunosuppressive drug in rapidly proliferating tissues. Inhibiting xanthine oxidase with allopurinol or febuxostat can significantly increase the concentrations of 6-MP [20], potentially leading to severe and even life-threatening side effects.

Figure 4. Showing how 6-MP interacts with Xanthine oxidase inhibitors.



INFORMED TREATMENT

The treatment of TLS focuses on correcting the metabolic abnormalities associated with the condition.

The treatment of TLS aims to correct the metabolic abnormalities associated with the condition.

HYPERURICEMIA - Xanthine oxidase inhibitors have limited effectiveness in treating the hyperuricemic state of TLS since they cannot degrade pre-existing UA. However, rasburicase, a recombinant uricase produced through advancements in recombinant DNA technology, offers a solution by reintroducing ancestral genes that have been lost in humans. Rasburicase, derived from the fungus Aspergillus flavus, has demonstrated superior efficacy in reducing serum UA levels compared to allopurinol, along with improved tolerability [17]. It is considered the preferred treatment option for high-risk TLS cases [17] and established TLS cases. However, caution must be exercised as rasburicase can induce acute hemolysis in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency [22]. Therefore, screening for G6PD should be done prior to rasburicase administration [23].

HYPERKALEMIA - High serum potassium levels, one of the most dangerous manifestations of TLS, require limiting potassium intake before initiating chemotherapeutic agents. To treat hyperkalemia, cation exchange resins such as sodium polystyrene sulfonate and calcium gluconate can be used to promote potassium loss through the gastrointestinal tract [28]. Hypertonic dextrose and insulin, as well as inhaled β-agonists, help shift potassium into the intracellular compartment [28-30]. It's important to note that monotherapy with beta agonists is not recommended in the setting of hyperkalemia; they should be administered with insulin [27]. Diuretics such as loop and thiazide diuretics can enhance renal potassium excretion [27].

It is important to highlight that the use of diuretics in TLS to promote potassium excretion can be challenging due to the potential development of hyperuricemia [24]. Thiazide diuretics, for example, increase serum UA concentrations by enhancing the reabsorption of urate through Organic Anion Transporter 1 (OAT 1) and Organic Anion Transporter 4 (OAT 4) transporters in proximal convoluted tubule (PCT) cells [29]. The implementation of diuretic therapy, despite its advantages in treating hyperkalemia, needs to be carefully considered due to the potential trade-off between its benefits and the exacerbation of hyperuricemia.

HYPOCALCEMIA - Calcium gluconate can be used to replenish low serum calcium levels [24], alleviating muscle twitching symptoms associated with TLS. However, cautious consideration is necessary to avoid administering calcium gluconate solely for correcting asymptomatic hypocalcemia, as it may worsen renal failure and precipitate calcium phosphate deposition [5].

HYPERPHOSPHATEMIA - Oral phosphate binders, such as aluminum hydroxide or aluminum carbonate, have been used to limit phosphate absorption [24]. While the administration of aluminum hydroxide may be useful in reducing serum phosphate levels during TLS, it is important to recognize that in the presence of AKI, kidney function replacement becomes the most effective approach for addressing this profound complication [30]. Among dialysis options, hemodialysis has demonstrated superior phosphate clearance compared to continuous venovenous hemofiltration or peritoneal dialysis [16].

DIALYSIS - It plays a critical role in managing TLS and AKI when other treatment approaches are insufficient, even with the availability of rasburicase [31]. When conservative measures fail to effectively eliminate and treat TLS, initiating dialysis therapy becomes essential. Various dialysis techniques can be used, but it's important to note that peritoneal dialysis (PD) may result in slower clinical improvement and is not recommended as the primary choice for established TLS cases [31]. Hemodialysis, hemofiltration, and other extracorporeal therapies have comparable effectiveness, although no clinical trials have directly compared their efficacy specifically in the context of TLS [31]. Therefore, selecting the appropriate dialysis modality should be based on individual patient characteristics and clinical judgment. To ensure optimal management of TLS in high-risk pediatric and adult patients, cytotoxic chemotherapy should be administered in a healthcare facility equipped with easily accessible dialysis services [16]. While the use of rasburicase has reduced the need for dialysis, a small proportion of patients still require this intervention, highlighting the ongoing importance of dialysis in the comprehensive care of TLS [16].

CONCLUSION

TLS is a critical condition caused by rapid cancer cell destruction, disrupting metabolic balance. TLS involves elevated uric acid, potassium, and phosphates, with decreased calcium levels. It

can lead to renal failure, irregular heart rhythms, seizures, and death. TLS is classified as laboratory TLS or clinical TLS based on metabolic abnormalities and clinical signs. Risk factors include renal dysfunction, electrolyte imbalances, hydration status, and tumor characteristics. Prompt recognition and management are crucial to minimize complications and improve outcomes in TLS, particularly in hematologic malignancies.

REFERENCES

1 Howard, S. C., Jones, D. P., & Pui, C.-H. (2011). The Tumor Lysis Syndrome. New England Journal of Medicine, 364(19), 1844–1854. doi: 10.1056/NEJMra0904569.

2 Perazella, M. A., & Herlitz, L. C. (2021). The Crystalline Nephropathies. Kidney International Reports, 6(12), 2942–2957. doi: 10.1016/j.ekir.2021.09.003.

3 Cai, W., Duan, X.-M., Liu, Y., Yu, J., Tang, Y.-L., Liu, Z.-L., Jiang, S., Zhang, C.-P., Liu, J.-Y., & Xu, J.-X. (2017). Uric Acid Induces Endothelial Dysfunction by Activating the HMGB1/RAGE Signaling Pathway. Oxidative Medicine and Cellular Longevity, 2017, 4391920. doi: 10.1155/2017/4391920

4 Verzola, D., Ratto, E., Villaggio, B., Parodi, E. L., Pontremoli, R., Garibotto, G., & Viazzi, F. (2014). Uric Acid Promotes Apoptosis in Human Proximal Tubule Cells by Oxidative Stress and the Activation of NADPH Oxidase NOX 4. PLOS ONE, 9(12), e115210. doi: 10.1371/journal.pone.0115210

5 Adeyinka, A., & Bashir, K. (2022, October 31). Tumor Lysis Syndrome. StatPearls. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK459262/.

6 Cairo, M. S., & Bishop, M. (2004). Tumour lysis syndrome: new therapeutic strategies and classification. British Journal of Haematology, 127(1), 3-11. doi: 10.1111/j.1365-2141.2004.05094.x

7 Puri, I., Sharma, D., Gunturu, K. S., & Ahmed, A. A. (2020). Diagnosis and management of tumor lysis syndrome. Journal of Community Hospital Internal Medicine Perspectives, 10(3), 269–272. doi: 10.1080/20009666.2020.1761185

8 Cairo, M. S., Coiffier, B., Reiter, A., & Younes, A. (2010). Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. Review, British Journal of Haematology, 149(4), 578-586. doi: 10.1111/j.1365-2141.2010.08143.x.**

9 Baeksgaard, L., & Sørensen, J. B. (2003). Acute tumor lysis syndrome in solid tumors—a case report and review of the literature. Cancer Chemotherapy and Pharmacology, 51, 187-192. doi: 10.1007/s00280-002-0551-2

10 Al Bagshi, M., Sadek, A. O., Hassan, E. S., & Abbas, A. A. (2013). Tumor lysis syndrome in children with acute leukemia: Incidence and outcome. Journal of Clinical Neonatology, 4(3), 100-103. Retrieved from [Al Bagshi: Tumor lysis syndrome in children with... - Google Scholar]

11 Ebellins Tabares Calvache, Allison Dessiret Tabares Calvache, Cristiane Seganfredo Weber, Tumor lysis syndrome in hematological inpatients, experience from a university hospital in Brazil: A retrospective cohort study, Hematology, Transfusion and Cell Therapy, 2023, , ISSN 2531-1379, https://doi.org/10.1016/j.htct.2023.02.005. (https://www.sciencedirect.com/science/article/pii/S2531137923000743)

12 Ansari, M. A. (2012). Tumour lysis syndrome in haematological malignancies. JLUMHS, 11(2), 84.

13 Darmon, M., Vincent, F., Camous, L., Canet, E., Bonmati, C., Braun, T., Caillot, D., Cornillon, J., Dimicoli, S., Etienne, A., et al. (2013). Tumour lysis syndrome and acute kidney injury in high-risk haematology patients in the rasburicase era: A prospective multicentre study from the Groupe de Recherche en Réanimation Respiratoire et Onco-Hématologique. British Journal of Haematology, 161(5), 666-674. https://doi.org/10.1111/bjh.12415

14 Ejaz, A. A., Pourafshar, N., Mohandas, R., Smallwood, B. A., Johnson, R. J., Hsu, J. W., & Kunze, G. (2015). Uric Acid and the Prediction Models of Tumor Lysis Syndrome in AML. PLoS One, 10(3), e0119497. doi: 10.1371/journal.pone.0119497. PMID: 25775138. PMCID: PMC4361475.

15 Rampello, E., Fricia, T., & Malaguarnera, M. (2006). The management of tumor lysis syndrome. Nature Reviews Clinical Oncology, 3, 438–447. doi: 10.1038/ncponc0581.

16 Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol. 2008 Jun 1;26(16):2767-78. doi: 10.1200/JCO.2007.15.0177. Erratum in: J Clin Oncol. 2010 Feb 1;28(4):708. PMID: 18509186.

17 Alakel N, Middeke JM, Schetelig J, Bornhäuser M. Prevention and treatment of tumor lysis syndrome, and the efficacy and role of rasburicase. Onco Targets Ther. 2017 Feb 2;10:597-605. doi: 10.2147/OTT.S103864. PMID: 28203093; PMCID: PMC5295804.

18 Martens KL, Khalighi PR, Li S, White AA, Silgard E, Frieze D, Estey E, Garcia DA, Hingorani S, Li A. Comparative effectiveness of rasburicase versus allopurinol for cancer patients with renal dysfunction and hyperuricemia. Leuk Res. 2020 Feb;89:106298. doi: 10.1016/j.leukres.2020.106298. Epub 2020 Jan 7. PMID: 31945598.

19 Bellos I, Kontzoglou K, Psyrri A, Pergialiotis V. Febuxostat administration for the prevention of tumour lysis syndrome: A meta-analysis. J Clin Pharm Ther. 2019 Aug;44(4):525-533. doi: 10.1111/jcpt.12839. Epub 2019 Apr 10. PMID: 30972811.

20 Kenneth R. Hande, in Encyclopedia of Cancer (Second Edition), 2002

21 Imani M, Shahmohamadnejad S. Recombinant production of Aspergillus Flavus uricase and investigation of its thermal stability in the presence of raffinose and lactose. 3 Biotech. 2017 Jul;7(3):201. doi: 10.1007/s13205-017-0841-3. Epub 2017 Jun 30. PMID: 28667645; PMCID: PMC5493577

22 Lakra, R., Grewal, U. S., Dhaliwal, L., Gaddam, S. J., Master, S. R., & Ramadas, P. (2022). Patients Receiving Rasburicase for Treatment and Prophylaxis of Tumor Lysis Syndrome Are Under-Tested for Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency: A Single Center Retrospective Analysis. Blood, 140(Supplement 1), 11054–11055. https://doi.org/10.1182/blood-2022-170490.

23 Latha SM, Krishnaprasadh D, Murugapriya P, Scott JX. Single dose rasburicase in the management of tumor lysis syndrome in childhood acute lymphoblastic leukemia: A case series. Indian J Nephrol. 2015 Mar-Apr;25(2):91-4. doi: 10.4103/0971-4065.139092. PMID: 25838646; PMCID: PMC4379632.

24 Rampello E, Fricia T, Malaguarnera M. The management of tumor lysis syndrome. Nat Clin Pract Oncol. 2006 Aug;3(8):438-47. doi: 10.1038/ncponc0581. PMID: 16894389.

25 Li T, Vijayan A. Insulin for the treatment of hyperkalemia: a double-edged sword? Clin Kidney J. 2014 Jun;7(3):239-41. doi: 10.1093/ckj/sfu049. PMID: 25852882; PMCID: PMC4377764.

26 Mushiyakh Y, Dangaria H, Qavi S, Ali N, Pannone J, Tompkins D. Treatment and pathogenesis of acute hyperkalemia. J Community Hosp Intern Med Perspect. 2012 Jan 26;1(4). doi: 10.3402/jchimp.v1i4.7372. PMID: 23882341; PMCID: PMC3714047.

27 College of Emergency Physicians. (n.d.). Pharmacology of hyperkalemia [PDF document]. Retrieved from https://www.acep.org/siteassets/sites/acep/media/hyperk/documents/pharmacology.pdf

28 C. Ben Salem and others, Drug-induced hyperuricaemia and gout, Rheumatology, Volume 56, Issue 5, May 2017, Pages 679–688, https://doi.org/10.1093/rheumatology/kew293

29 National Center for Biotechnology Information. (n.d.). Thiazide Diuretics - StatPearls - NCBI Bookshelf. Retrieved from https://www.ncbi.nlm.nih.gov/books/NBK532918/#:~:text=Thiazide%20diuretics%20cause%20hyperuricemia%20and,exchanger%20on%20the%20luminal%20membrane. (Last Update: January 23, 2023)

30 Ñamendys-Silva SA, Arredondo-Armenta JM, Plata-Menchaca EP, Guevara-García H, García-Guillén FJ, Rivero-Sigarroa E, Herrera-Gómez A. Tumor lysis syndrome in the emergency department: challenges and solutions. Open Access Emerg Med. 2015 Aug 20;7:39-44. doi: 10.2147/OAEM.S73684. PMID: 27147889; PMCID: PMC4806807.

31 Jones GL, Will A, Jackson GH, Webb NJ, Rule S; British Committee for Standards in Haematology. Guidelines for the management of tumour lysis syndrome in adults and children with haematological malignancies on behalf of the British Committee for Standards in Haematology. Br J Haematol. 2015 Jun;169(5):661-71. doi: 10.1111/bjh.13403. Epub 2015 Apr 15. PMID: 25876990.