Topic: Tumor Lysis Syndrome

Title Options:

1. Redefining Care for Tumor Lysis Syndrome in Oncologic Emergencies: Emerging Therapies, Protocol Gaps, and the Pharmacist's Role

2. Mitigating Gaps in Tumor Lysis Syndrome Protocols: A Needs Assessment on Advancing Pharmacist-Driven Prophylaxis, System-Level Stewardship, and Managed Care

3. Bridging the Gap in Tumor Lysis Syndrome Protocols: A Needs Assessment on System-Level Strategies for Pharmacist-Driven Prevention, Stewardship, and Managed Care Alignment

Section 1: Why this topic is needed

Tumor lysis syndrome (TLS) is a critical oncologic emergency in hematologic malignancies that can lead to acute kidney injury, arrhythmias, seizures, and death if not prevented or recognized early. The Cairo–Bishop criteria, published in 2004, serve as the principal framework for defining both laboratory and clinical TLS.[1] Subsequent consensus statements, such as those by Cairo et al and Coiffier et al,[2,3] outline approaches to TLS risk assessment and management in patients with hematologic malignancies. Although recent guidelines by the National Comprehensive Cancer Network® (NCCN®)[4] and the European Society for Medical Oncology (ESMO)[5] address disease-specific considerations for TLS, inconsistencies in risk assessment and preventive interventions persist across institutions. The absence of a harmonized TLS guideline further elevates the risk associated with novel therapeutics such as chimeric antigen receptor (CAR) T-cell therapy,[6] proteasome inhibitors,[7] and agents such as venetoclax.[8] Furthermore, substantial variability exists in the intensity of treatment, hydration regimens, and the selection of uric acid–lowering agents in routine clinical practice.

As integral members of the interdisciplinary oncology team, pharmacists are uniquely positioned to standardize supportive care for TLS; however, considerable practice gaps currently hinder optimal delivery. Foremost is the application of true risk-based TLS assessment in daily workflows. Although many educational resources describe the pathophysiology of TLS and the Cairo–Bishop criteria, pharmacists require practical training and education to independently perform and document TLS risk stratification. Following risk stratification, it is also imperative to translate these assessments into real-time adjustments to treatment regimens, hydration protocols, and laboratory monitoring schedules in both inpatient and outpatient settings.

Adding to these challenges, a knowledge gap persists regarding the optimal use of uric acid–lowering agents, specifically concerning the differentiation between prophylactic and therapeutic applications and risk-stratified selection, thereby limiting guideline-concordant practice. Guidelines advocate for selective rasburicase use in high-risk or established TLS[4], balancing rapid uric acid control against cost and safety considerations (eg, glucose-6-phosphate dehydrogenase [G6PD] deficiency)[4]; however, many centers still lack clear, pharmacist-authored criteria and order sets. Educational needs include understanding single- vs repeat- dose strategies, determining when to switch from allopurinol to rasburicase, and interpreting postdose laboratory results. Structured TLS education for pharmacists and interprofessional teams could address this gap. Finally, many centers lack standardized institutional protocols at the system level, such as electronic health record (EHR) order sets, pharmacy verification processes, and pathway integration. Evidence from pharmacist-led TLS and oncologic emergency initiatives demonstrates that pharmacists can safely reduce variability and improve outcomes when they own these stewardship processes, but many pharmacists have not been trained or empowered to do so.

Section 2: Learning Objectives

Set 1: Risk Assessment and Emerging Therapies

Educational Gaps Addressed: Implementation of risk-based assessments in daily workflows and recognition of risks associated with novel therapies.

Upon completion of this educational activity, pharmacists will be able to:

1. **Stratify** distinct TLS risk profiles and specific trigger factors associated with emerging therapies, such as venetoclax and high-grade lymphoma induction regimens (*Cognitive Level: Knowledge/Comprehension)*
2. **Apply** validated, risk-based TLS assessment tools (case studies) to accurately drive real-time adjustments to hydration, monitoring, and therapy regimens within daily clinical workflows (*Cognitive Level: Application)*
3. **Analyze** the clinical and economic impact of predictive TLS risk-stratification models to inform managed care coverage policies and prior authorization criteria for high-risk novel therapeutics *(Cognitive Level: Analysis - Managed Care Focus)*

Set 2: Optimal Utilization of Uric Acid–Lowering Agents

Educational Gaps Addressed: Appropriate selection and administration of prophylactic versus active treatment strategies.

Upon completion of this educational activity, pharmacists will be able to:

1. **Differentiate** between the appropriate prophylactic and treatment indications using specific uric acid–lowering agents based on disease state, tumor burden, and baseline renal function. *(Cognitive Level: Comprehension)*
2. **Select** the optimal, risk-stratified uric acid–lowering therapy (e.g., determining the appropriate threshold for allopurinol versus single-dose rasburicase) for patients presenting with or at high risk for clinical TLS. *(Cognitive Level: Evaluation)*
3. **Evaluate** institutional data to design cost-effective, managed care–aligned formulary pathways that ensure the safe use of high-cost uric acid–lowering agents. *(Cognitive Level: Evaluation, Managed Care Focus)*

Set 3: System-Level Standardization and Protocol Integration

Educational Gaps Addressed: Lack of standardized institutional protocols and the need for pharmacist-driven interventions.

Upon completion of this educational activity, pharmacists will be able to:

1. **Illustrate** the essential components required to construct standardized electronic health record (EHR) order sets and structured pharmacy verification pathways for TLS prevention. *(Cognitive Level: Application)*
2. **Design** pharmacist-driven intervention protocols that integrate standardized TLS patient counseling, interprofessional education, and proactive laboratory monitoring into routine oncology care. (*Cognitive Level: Synthesis)*
3. **Formulate** value-based care initiatives that align standardized institutional TLS protocols with health plan payer requirements to reduce network-wide practice variability and prevent costly hospital admissions associated with oncologic emergencies. (*Cognitive Level: Synthesis - Managed Care Focus)*

SECTION 3: AGENDA (ONLY OVERVIEW AS PER CLIENT'S REQUEST)

Bridging the Gap in Tumor Lysis Syndrome Protocols: A Needs Assessment on System-Level Strategies for Pharmacist-Driven Prevention, Stewardship, and Managed Care Alignment	
10 min	**Welcome & Program Overview**
TLS Pathophysiology and the Central Role of Hyperuricemia	
20 min	
Clinical Trials Evidence and Real-World Data in TLS Management	
15 min	
30 min	**Managed Care and Oncology Pharmacy Strategies to Operationalize TLS Best Practices**

Section 4: Clinical Gaps Table

Identified Practice Gap	Learning Objective	Outcomes
Gap#1: Risk recognition and stratification. Pharmacists lack guidance in accurately stratifying patients into low-, medium-, high- risk categories.	**Stratify** distinct TLS risk profiles and specific trigger factors. **Apply** validated, risk-based TLS assessment tools (case studies) to accurately drive real-time adjustments. **Analyze** the clinical and economic impact of predictive TLS risk-stratification models to inform managed care coverage policies and prior authorization criteria.	**Demonstrate** ability to integrate TLS risk stratification assessment into daily workflow.
Root Cause Analysis: The dynamic nature of TLS management in hematologic malignancies poses a substantial challenge for pharmacists, especially in stratifying TLS risk and integrating it into routine workflows. TLS risk assessment is multifaceted; the risk level is frequently influenced by tumor burden, chemosensitivity, baseline kidney function, and treatment regimens. Decisions are often made under time constraints during treatment initiation or regimen adjustments. The absence of standardized prompts and documentation fields in many practice settings leads to inconsistent and, at times, implicit risk stratification. Moreover, initiating treatment in outpatient settings and transitioning between different levels of care can fragment accountability for monitoring frequency and escalation. This increases the likelihood that risk-based decisions are not consistently implemented.		

Gap#2 Optimal Use of Uric Acid–Lowering Agents Guidelines call for selective rasburicase use in high risk or established TLS, but many centers still lack clear pharmacist-authored criteria and order sets.	**Differentiate** prophylaxis vs treatment of hyperuricemia in TLS and select an appropriate uric acid–lowering strategy based on risk tier, baseline renal function, and clinical status. **Identify** regimens and scenarios with heightened or commonly under-recognized TLS risk (e.g., venetoclax initiation/ramp-up; high-grade lymphoma induction; high tumor burden/chemosensitive disease) and adjust prophylaxis and monitoring accordingly. **Implement** a patient-specific plan that includes timing, monitoring targets, and safety/operational checks (e.g., contraindication screening considerations and response assessment).	**Demonstrate** the ability to choose and justify optimal uric acid–lowering therapy using a risk-stratified approach and regimen-specific risk modifiers.
Root Cause Analysis: This gap indicates variability in the application of evidence-based practices at the point of care. The differentiation between xanthine oxidase inhibitors (XOIs), which prevent uric acid formation, and uricolytics, which promote rapid uric acid degradation, is not consistently translated into risk-stratified decision-making by pharmacists. This results in both undertreatment (delayed control in high-risk patients) and nonstandardized utilization (variable agent selection and timing). This is further complicated by the introduction of emerging therapies and intensified induction regimens, leading to abrupt tumor lysis, often in outpatient settings. In these settings, pharmacists play a crucial role in communicating prophylactic and treatment strategies to patients. Variations in local practice norms, stewardship policies, and operational constraints further contribute to inconsistent agent selection, delayed laboratory follow-up, and downstream risks, such as AKI and escalation of care.		

Gap#3: Lack of standardized institutional TLS protocols (EHR order sets, verification rules, pathway integration) (Managed Care):	**Assess** current-state workflow and identify failure points that drive TLS variation (risk documentation gaps, missing labs, unclear monitoring ownership, outpatient follow-up failures). **Design or refine** an institutional TLS protocol/order set that links risk tier to prophylaxis, labs/monitoring cadence, and escalation actions, including defined responsibilities across disciplines. **Select and track** metrics to evaluate adoption and impact (e.g., adherence to risk-based prophylaxis, timely lab monitoring, AKI incidence, ICU transfer, length of stay [LOS]) and propose iterative improvements.	**Demonstrate** the ability to implement and sustain standardized TLS workflows.
Root Cause Analysis: System-level variability persists when evidence-based TLS management is not integrated into the medication-use process. Without standardized protocols and EHR support, TLS prevention and monitoring are subject to individual clinician practices, leading to inconsistent prophylaxis selection, laboratory ordering, and responses to early abnormalities. Cross-setting transitions further exacerbate this problem by obscuring accountability for laboratory monitoring frequency and escalation. Limited informatics resources, competing priorities, and a lack of consensus regarding regimen governance impede implementation. Consequently, the system does not consistently enable pharmacists to function at their highest professional capacity in preventing TLS-related complications and ensuring timely interventions.		

Section 5: Needs Assessment

Analysis and Literature Search

Despite often being predictable and preventable, tumor lysis syndrome (TLS) remains a high-mortality oncologic emergency in hematologic malignancies.[3,9,10] Pharmacists are critical to TLS risk assessment, prophylaxis selection, acute management, and protocol implementation. However, gaps in knowledge, performance, and systems limit their ability to consistently prevent and manage this emergency. These gaps highlight distinct but interrelated educational needs, including (1) accurate TLS risk recognition and stratification; (2) optimal use of uric acid–lowering agents and other prophylactic and treatment measures; and (3) development and implementation of standardized institutional TLS protocols and order sets.

GAP#1 Risk Recognition and Stratification

Tumor lysis syndrome (TLS) is a life-threatening oncologic emergency resulting from the rapid release of intracellular components such as potassium, phosphate, and nucleic acids into the bloodstream following the lysis of malignant cells. This sudden influx can cause severe metabolic imbalances, potentially leading to AKI,[11] cardiac arrhythmias,[12] seizures, and even death.[12,13] TLS incidence rate varies widely, ranging from 5% to 70%, depending on cancer type and other factors.[13–20] The increasing use of targeted therapies and immunotherapies in hematologic malignancies, while transforming treatment, has also increased the incidence of TLS. Consequently, current guidelines stress the importance of careful, individualized risk assessment and timely intervention to ensure patient safety in the face of these powerful new treatments.

Despite these advances in treatment, TLS is associated with substantial in-hospital mortality, with reported rates ranging from 14% to 21%.[9,19] Mortality risk varies considerably depending on the clinical context and the specific malignant neoplasm. For example, while overall mortality may be low in some groups, patients with acute myeloid leukemia (AML) who develop clinical TLS (CTLS) can face induction mortality rates as high as 79% (30 of 38).[21] In high-grade non-Hodgkin lymphoma, CTLS is associated with a 37% mortality rate.[19] Spontaneous TLS carries a particularly poor prognosis; historical data indicate that in-hospital mortality can reach 100% despite treatment (case report).[22] Immune checkpoint inhibitor–associated TLS has been reported with mortality rates of approximately 44%, indicating substantial risk with certain novel agents.[23] These outcomes underscore why

early recognition and accurate risk stratification are essential to prevent progression from laboratory abnormalities to clinical TLS.

Within the interprofessional team, oncology pharmacists are uniquely positioned as medication experts responsible for optimizing prophylactic regimens, identifying drug interactions, and providing essential patient education. However, documented knowledge and performance gaps exist among pharmacists regarding TLS management and risk stratification.[8] Conversely, evidence from pharmacist-led clinics demonstrates that pharmacists are highly capable of independently performing TLS risk stratification and prophylaxis when provided with structured education and institutional protocols.[24] This discrepancy suggests that the issue is not a lack of inherent ability, but a critical need for specialized education to address identified gaps in professional practice.

TLS risk stratification is a prerequisite to initiating therapy, as it dictates the clinical pathway, including the selection of prophylactic agents, the intensity of laboratory monitoring, and the potential need for hospitalization. With appropriate training, pharmacists and clinicians can categorize patients into low-risk (< 1%), intermediate-risk (1%–5%), or high-risk (> 5%) groups based on disease histologic findings, tumor burden, and patient-specific factors.[1,8] High-risk malignant neoplasms typically include Burkitt lymphoma, acute lymphoblastic leukemia (ALL) with white blood cell (WBC) counts ≥ 100 000/μL, and acute myeloid leukemia (AML) with WBC counts ≥ 100 000/μL.[3] Moreover, the emergence of novel targeted therapies such as venetoclax,[6] obinutuzumab,[25] and CAR T-cell therapy[4] can elevate a patient's risk level, frequently triggering TLS in diseases previously considered low-risk, such as chronic lymphocytic leukemia (CLL).

Although guidelines provide a framework for risk assessment, a poll conducted during a case roundtable with Targeted Oncology indicated that only 12.5% (2 of 16) of participants were extremely confident about TLS risk assessment and prevention; 75.0% (12 of 16) reported moderate confidence and 12.5% (2 of 16) were somewhat confident.[26] This highlights the disparity between theoretical knowledge and practical experience.

Lastly, TLS associated with some newer therapies for hematologic malignancies might be overlooked. As Matthew David, MD, discussed in his case roundtable, "obinutuzumab [Gazyva] is one that I wanted to highlight because I think it gets overlooked. It is becoming a more commonly used anti-CD20 monoclonal antibody in CLL, and we see TLS commonly in those first couple of doses." In these cases, he indicated that observing trends in electrolyte changes early on (6 to 8 hours after therapy initiation vs 24 hours) helped diagnose laboratory TLS (LTLS) and usually prevented CTLS.[26]

Taken together, TLS risk stratification is a complex process that requires educational initiatives and independent practice. Pharmacist-focused education, designed to anticipate TLS development, enables pharmacists to accurately perform risk stratification and can prevent a potentially reversible condition from becoming irreversible.

GAP#2 Optimal use of uric acid–lowering agents and other prophylactic measures

TLS prophylaxis and treatment regimens are initiated based on the initial risk stratification; therefore, inaccurate risk assessment can create a cascading effect that compromises the selection, timing, and escalation of uric acid–lowering agents.

Patient safety analyses conducted following a reported incident of delayed rasburicase ([Elitek], a uric acid–lowering agent for TLS management) identified 64 incidents of delayed or omitted TLS treatments—16 of 64 resulted in patient harm.[8] These incidents were attributed to a critical lack of knowledge among health care staff, including pharmacists, regarding the urgency of administering these medications. Because such delays can transform a potentially reversible clinical condition into an irreversible one, pharmacist-focused education is essential to address these documented knowledge gaps and ensure the prompt delivery of time-critical interventions for hematologic emergencies.

While direct studies explicitly detailing pharmacists' understanding of TLS pathophysiology and treatment as a primary outcome of educational initiatives are lacking, the extensive impact of pharmacist-led programs strongly suggests that education is crucial for standardizing and enhancing their expertise.

Anthony Perissinotti, PharmD, BCOP, asserts, "It's really best practice to train everybody around you. I want to empower others on my team, my attendings, my fellows, other residents to be able to monitor for, treat and prevent tumor lysis syndrome."[27]

Effective management of TLS requires pharmacists to possess a thorough understanding of its pathophysiology and familiarity with the Cairo–Bishop criteria for identifying laboratory and clinical TLS. Established in 2004, the Cairo–Bishop criteria provide a clinical consensus for identifying and grading TLS by differentiating between biochemical changes and symptomatic organ damage.[28] Laboratory TLS (LTLS) is diagnosed when a patient exhibits 2 or more metabolic abnormalities within 3 days before or up to 7 days after the initiation of therapy.[1,3,8,29] These abnormalities include a 25% change from baseline or meeting the following absolute thresholds: uric acid ≥ 8 mg/dL (476 µmol/L); potassium ≥ 6.0 mmol/L; phosphorus ≥ 4.5 mg/dL (1.45 mmol/L) for adults or ≥ 6.5 mg/dL (2.1 mmol/L) for children; and calcium ≤ 7.0 mg/dL (1.75 mmol/L). [1,3,6,27] Clinical TLS (CTLS) is identified

when LTLS is present in conjunction with at least 1 significant clinical complication not solely attributable to a therapeutic agent, such as kidney failure (creatinine ≥ 1.5 times the upper limit of normal), cardiac arrhythmias [or sudden death], or seizures. [1,3,6,27]

A significant diagnostic refinement, introduced by Howard et al. and now integrated into current practice, stipulates that laboratory abnormalities for LTLS must occur within the same 24-hour period to enhance clinical specificity.[30] In addition, contemporary risk-stratification models now incorporate the upgrading of a patient's risk based on highly potent novel agents, such as venetoclax, or where tumor burden (eg, lymph node size) is relatively high.[31] NCCN guidelines[4] also incorporate these risk-stratification modifications and recommend TLS prophylaxis for patients undergoing treatment for chronic lymphocytic leukemia/small lymphocytic lymphoma, specifically for: (1) drug factors (treatment with venetoclax, chemoimmunotherapy, lenalidomide, and obinutuzumab), (2) progressive disease after small-molecule inhibitor therapy, (3) disease factor (lymph nodes > 5 cm), (4) spontaneous TLS, and (5) laboratory factors (elevated white blood cell count, uric acid, and kidney dysfunction).[4]

Following risk stratification, preventive strategies should be implemented before antineoplastic therapy to anticipate TLS and optimize outcomes. For low-risk patients, management typically involves vigorous oral hydration (2 to 3 L/d) and close monitoring of fluid status and electrolytes.[8,29,32] Some guidelines suggest considering allopurinol for the initial 7 days of the first treatment cycle. For intermediate-risk patients, protocols mandate aggressive hydration (intravenous or oral) and allopurinol (300 to 600 mg/d) or febuxostat (120 mg/d), initiated 2 to 3 days before therapy, with laboratory monitoring every 8 to 12 hours. [8,29,32] These protocols are supported by evidence from a pivotal phase 3 study (FLORENCE trial) showing that febuxostat was significantly superior to allopurinol for uric acid control (mean AUC for serum uric acid [sUA] was 514.0 ± 225.7 vs 708.0 ± 234.4 mg·h/dL; $P < .001$).[33]

Conversely, regimens for high-risk patients are markedly different. These patients require intravenous hydration (2500 to 3000 mL/m^2/d) and prophylactic rasburicase. While the licensed dose for rasburicase is 0.2 mg/kg, evidence indicates that a single fixed 3-mg dose is often sufficient for prophylaxis in adults.[3,10,34] NCCN guidelines[4] recommend testing for G6PD deficiency before rasburicase administration. In patients with G6PD deficiency, allopurinol should be substituted for rasburicase, and monitoring frequency should be increased to every 4 to 8 hours. A phase 3 study by Cortes et al. demonstrated that rasburicase (0.2 mg/kg) provided more rapid and efficient control of plasma uric acid than allopurinol in adults at high risk for tumor lysis syndrome (TLS).[35] Finally, a meta-analysis of

10 studies found that a single dose of rasburicase (3 or 6 mg) is as effective as the 5-day regimen for controlling uric acid in TLS prevention.[36]

However, given that clinical scenarios often deviate from best-case conditions, the curriculum must also ensure preparedness for managing complex TLS-associated metabolic crises when prophylactic measures are insufficient. Consequently, training should cover treatment protocols for established TLS. Treatment should emphasize: (1) vigorous hydration with intravenous fluids escalated to 3 $L/m^2/d$ (adults) or 4 $L/m^2/d$ (children) to maintain a urine output >100 $mL/m^2/h$; (2) rasburicase 0.2 mg/kg/d, continued for up to seven days based on clinical response; (3) maintenance of electrolyte balance; and (4) renal replacement therapy (RRT), including hemodialysis or continuous RRT for refractory hyperkalemia, severe hyperphosphatemia, or oliguric renal failure.[32,37,38]

Rasburicase is central for TLS prophylaxis and treatment, with strong support from randomized controlled trials, large-scale retrospective cohort studies, and prospective clinical investigations.[39–41] A pivotal phase 3 study (Cortes et al) established that rasburicase provides significantly faster control of plasma uric acid than allopurinol (4 vs 27 hours).[35] The study reported a low 2% incidence of acute kidney failure, although it was not powered to detect differences in clinical end points. A 2017 retrospective analysis of 26 rasburicase- and 104 allopurinol- treated patients matched on propensity score (PS) to evaluate mean changes in uric acid (UA) and economic outcomes, including intensive care unit (ICU) length of stay.[39] The analysis demonstrated that rasburicase was associated with a significant reduction in plasma UA (5.3 mg/dL; $P < .001$) and ICU stays by 2.5 days ($P < .001$).[39]

Additionally, a retrospective cohort study of 150 patients (n = 89, rasburicase with or without allopurinol; n = 61, allopurinol alone) showed similar findings.[41] Mean UA levels were significantly lower in the group receiving rasburicase (2.70 vs 5.82 mg/dL; $P < .01$).[41] However, no significant differences were observed in kidney function recovery (odds ratio [OR], 0.90; $P = .79$), creatinine level at day 7 (1.80 vs 1.66 mg/dL; $P = .51$), and final creatinine level at day 30 (2.08 vs 2.07 mg/dL; $P = .98$).[41] A more recent retrospective, real-world (RW) study by Cairo et al involving 282 patients demonstrated TLS–associated mortality was significantly less likely among patients treated with rasburicase than those treated with allopurinol (2.1% vs 7.1%; $P = .047$).[39]

Despite the widespread use of rasburicase, a study by Darmon et al involving 153 adult patients with acute leukemia (58.0%), aggressive non-Hodgkin lymphoma (29.5%), and Burkitt leukemia/lymphoma (12.5%) indicated that 30.7% of patients in high-risk cohorts developed TLS.[42] Among these patients, 17 of 153 (11.1%) developed laboratory TLS, and 30 of 153 (19.6%) developed clinical TLS accompanied by AKI.[42] Approximately 64% of the

patients who developed TLS experienced AKI, identifying TLS as an independent risk factor for increased 90-day mortality.[42] Collectively, clinical evidence illustrates that TLS presents a complex metabolic challenge, and pharmacists are central to anticipating and managing these issues, requiring readiness to adjust treatment regimens as patient needs evolve.

Lastly, the pharmacists' knowledge must extend to the technical aspects of processing samples from patients with TLS. For example, they must ensure urate assays from patients receiving rasburicase are sent to the laboratory on ice to prevent ex vivo enzymatic degradation that results in falsely low values.[14] They must also maintain awareness of confounding conditions such as pseudohyperkalemia[43,44] in patients with extreme leukocytosis to prevent inappropriate, life-threatening treatments. In clinical practice, pharmacists are responsible for determining the appropriate use of allopurinol, febuxostat, or rasburicase, while monitoring hydration status, kidney function, and potential contraindications like G6PD deficiency. Vigilant monitoring of hydration and management of symptoms related to acute kidney injury are vital components of their oversight.

The high rate of TLS-associated AKI and mortality underscores a critical need for pharmacist-focused education in anticipating metabolic complexities and independently adjusting regimens to prevent irreversible kidney failure.

GAP#3 Lack of standardized institutional TLS protocols

Educational initiatives are needed to empower pharmacists to lead system-level changes and implement standardized institutional protocols that facilitate safe, individualized care for hematologic emergencies. System-level variability persists when evidence-based TLS management is not integrated into the medication-use process. Without standardized protocols and EHR support, TLS prevention and monitoring depend on individual clinician practices, leading to inconsistent prophylaxis selection, laboratory ordering, and delayed responses to early abnormalities. Limited informatics resources, competing priorities, and a lack of consensus regarding pathway governance impede implementation. Consequently, the system does not consistently enable pharmacists to practice at the highest scope of their licensure to prevent TLS-related complications and ensure timely intervention.

A primary failure point in current TLS management is the substantial variation in clinical practice, often resulting from a lack of formal institutional guidelines. National patient safety analyses indicate that inadequate staff knowledge (across medical, nursing, and pharmacy disciplines) regarding medication criticality and limited medication availability at the ward level are major contributors to patient harm.[8] In managed care and community

settings, clinicians often report that logistical challenges and delayed laboratory turnaround times are considerable barriers to safe therapy initiation, particularly for high-risk drugs such as venetoclax.[27,45–47] Without standardized protocols, health care teams often develop redundant processes for each new patient, leading to inconsistent risk documentation and failures in outpatient follow-up. Furthermore, systemic risks are heightened when specialist medications are used in unfamiliar clinical settings without the oversight of dedicated hematologic-oncologic teams.

Another critical gap exists in the misalignment between drug acquisition costs and the total cost of care. A comparative study of rasburicase and allopurinol for TLS in pediatric patients showed that rasburicase-treated patients incurred a mean cost of $30 470 compared with $35 165 for allopurinol-treated patients ($P = .43$).[48] This could be attributed to a significantly shorter critical care stay for rasburicase-treated patients (1.4 vs 2.5 days; $P < .001$).[48] A similar economic benefit was seen in another study by Cairo et al.[49] However, managed care organizations must weigh this against the economic burden of established TLS, where hospital costs are more than 5 times higher and lengths of stay are 2 to 3 times longer for patients requiring dialysis.[19,50] Clinical guidelines and real-world studies support the use of rasburicase as the first-line agent for high-risk patients to prevent these complications. Managed care regimens should therefore avoid restrictive step therapy or arduous prior authorization (PA) processes for high-risk patients, as treatment delays can be life-threatening.[51] Furthermore, setting-of-care decisions must be protocol-driven; while low- to intermediate-risk patients can often be managed in outpatient clinics with oral hydration, high-risk patients (eg, those initiating venetoclax with bulky nodes) often require 48-hour inpatient admissions for continuous hydration and frequent laboratory monitoring.

Pharmacists are ideally positioned to anchor these systems by leading the development of standardized ordering templates and electronic prescribing sets. By implementing pharmacist-led clinical models, such as venetoclax ramp-up clinics, institutions have achieved a 94.3% success rate in target dose attainment while minimizing clinical tumor TLS incidents.[24,51,52] These models bridge gaps in care by empowering pharmacists to independently review laboratory data, manage complex drug-drug interactions, and adjust TLS prophylaxis through collaborative practice agreements (CPAs). In managed care, pharmacists coordinate with medication access specialists to create a closed-loop system that ensures patients have timely access to both chemotherapeutic agents and required supportive care, thereby preventing dangerous delays in therapy.

To evaluate the impact of standardized institutional protocols, institutions should integrate features into the electronic health record (EHR) to track specific performance indicators.[53] Key metrics include adherence to risk-based prophylaxis, the frequency of pharmacist

interventions, and the incidence of laboratory vs clinical TLS. Clinical and economic outcomes such AKI incidence, ICU transfer rates, and LOS should be tracked against baseline data to justify resource allocation. Iterative improvements can then be proposed based on patient-reported outcomes (PROs) and risks-avoided data, ensuring the system evolves alongside contemporary treatment paradigms.[53] Regular public reporting on these co-designed outcomes fosters a culture of accountability and clinical excellence within the interprofessional team.

Collectively, these gaps highlight the need for a comprehensive, pharmacist-focused educational initiative that not only strengthens individual clinical competencies in TLS risk stratification and prophylaxis but also equips pharmacists to lead institutional protocol development and continuous quality improvement CQI efforts in TLS management.

Section 6: Bridging the gaps

System-level interventions, such as standardized protocols and specialized clinics, provide essential frameworks for patient safety; however, their effectiveness is contingent on the clinicians and pharmacists who implement them. Therefore, targeted educational initiatives are necessary to cultivate strategic leadership skills in oncology pharmacists, enabling them to independently assess risk and design protocols. By addressing documented knowledge gaps regarding the complexities of TLS and novel therapeutics, focused education ensures that system-level changes translate into standardized care and the elimination of critical therapeutic delays.

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