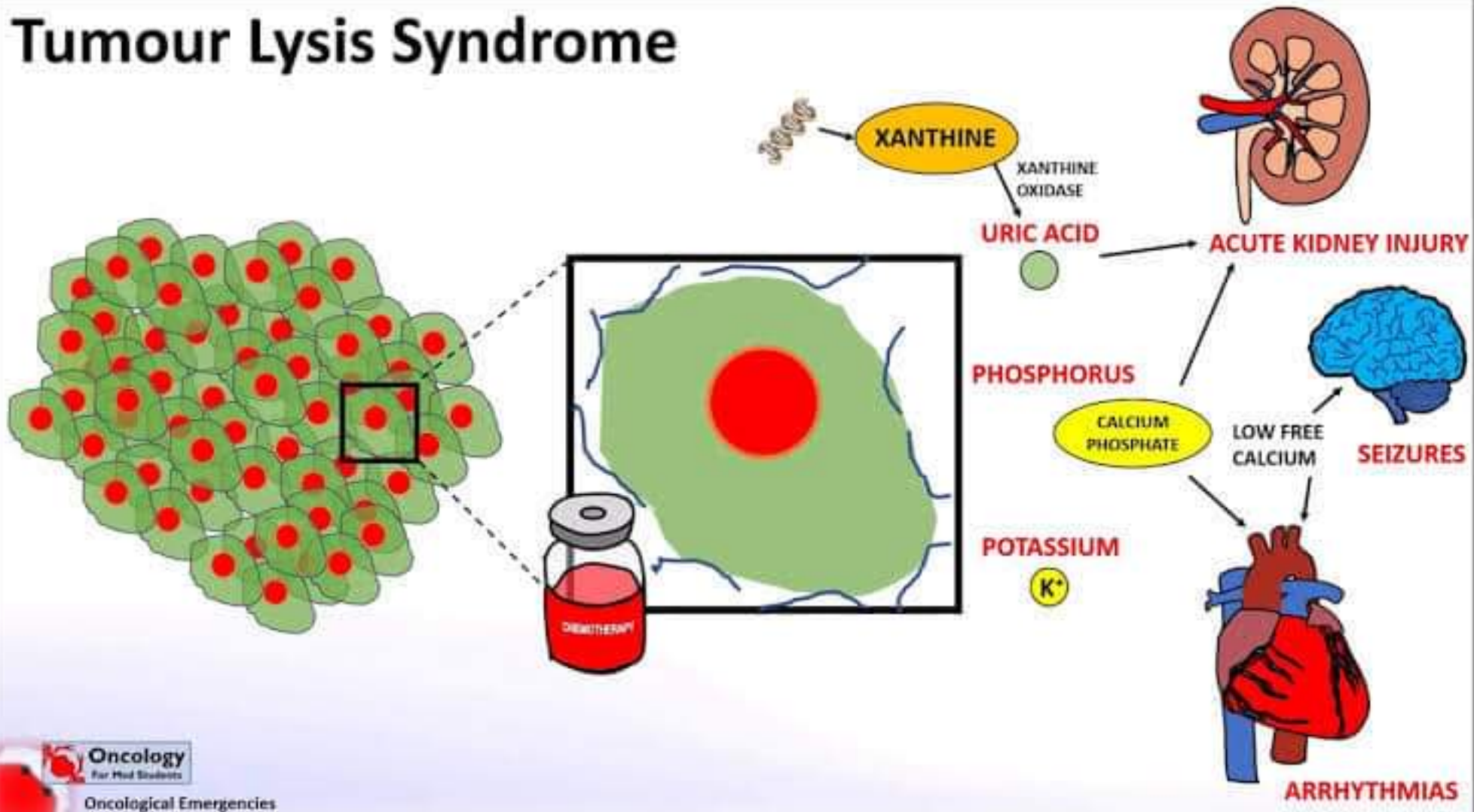
Tumour Lysis Syndrome



What Is Tumor Lysis Syndrome?

Metabolic derangement produced by rapid tumor breakdown as a consequence of therapy.

Characterized by:

- hyperuricemia (DNA breakdown)
- hyperkalemia (cytosol breakdown)
- hyperphosphatemia (protein breakdown)
- hypocalcemia (2^0 to hyperphosphatemia)

Which can lead to:

- acute **renal failure** 2^0 to urate nephropathy and calcium phosphate
- cardiac dysrhythmias 2^0 to hyperkalemia and hypocalcemia
- neuromuscular symptoms (cramps and tetany) 2^0 to hypocalcemia
- sudden death from hyperkalemia or hypocalcemia

Tumor Lysis Syndrome

- Caused by rapid & massive tumor cell lysis and release of intracellular contents (potassium, phosphate and nucleic acids) into the bloodstream that overwhelms the kidney's ability to excrete those products
- Can occur at presentation or more commonly after initiation of chemo for high grade lymphomas (*e.g.*, Burkitt's) and leukemia
- Can also be precipitated by radiation, steroid or antibody therapy
- Risk of renal failure and life-threatening electrolyte disturbances is caused by the breakdown of nucleic acids -> uric acid, which can precipitate in the renal tubules
- Hyperphostatemia with deposition of calcium phosphate in the renal tubules can also cause renal failure

Table 3: Risk factors for developing a tumour lysis syndrome[37]

Cancer-Related Risk factors
• Large burden of tumour
• Neoplastic infiltration of the bone marrow, liver, spleen, kidneys
• Tumour with high mitotic rate
• Tumour highly chemosensitive
• Haematologic malignancy
Patient-Related Risk Factors
• Pre-existing nephropathy
• Hyperuricemia
• Hypotension
• Dehydration
• Nephrotoxins (drugs, contrast)
• Exogenous potassium or phosphorus intakes

Risk for Tumor Lysis Syndrome by Tumor Type

- Burkitt's lymphoma — Frequent cases
- Lymphoblastic lymphoma
- Acute leukemia
- Large cell lymphoma
- Low-grade lymphoma treated with chemotherapy, radiotherapy or steroids — Recognized complication but few occurrences
- Breast carcinoma treated with chemotherapy or hormonal therapy
- Small cell lung carcinoma
- Seminoma
- Neuroblastoma
- Low-grade lymphoma treated with interferon — Case reports only
- Merkel's cell carcinoma
- Medulloblastoma
- Adenocarcinoma of the gastrointestinal

Criteria for Classification of Laboratory Tumor Lysis Syndrome

Metabolic Abnormality	Criteria for Classification of Lab TLS
Hyperuricemia	> 8.0 mg/dl (475.8 μmol/liter) in adults or above the upper limit of the normal range for age in children
Hyperphosphatemia	> 4.5 mg/dl (1.5 mmol/liter) in adults or > 6.5 mg/dl (2.1 mmol/liter) in children
Hyperkalemia	> 6.0 mmol/liter
Hypocalcemia	Corrected calcium <7.0 mg/dl (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter)†

Two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before the start of therapy or up to 7 days afterward

† The corrected calcium level in milligrams per deciliter = measured calcium level in milligrams per deciliter + 0.8 × (4 − albumin in grams per deciliter)

Cairo-Bishop definition of laboratory tumor lysis syndrome

- Uric acid : 476 mmol/L (8 mg/dL) or 25% increase from baseline
- Potassium : 6.0 mmol/L (6mEq/L) or 25% increase from baseline
- Phosphorous :2.1 mmol/L (children) or ³1.45 mmol/L (adults) or 25% increase from baseline
- Calcium : 1.75 mmol/L or 25% decrease from baseline

Table 1. Cairo-Bishop classification of tumor lysis syndrome in adults

Laboratory TLS	Clinical TLS
Uric acid: ≥8.0 mg/dl	AKI (defined as creatinine >1.5× the upper limit of normal for patient age and sex)
Potassium: ≥6.0 mEq/dl	Cardiac arrhythmia
Phosphorus: ≥4.6 mg/dl	Seizure, tetany, or other symptomatic hypocalcemia
Calcium: ≤7.0 mg/dl	

Patients must meet more than two of four laboratory criteria in the same 24-hour period within 3 days before to 7 days after chemotherapy initiation. A >25% increase from "baseline" laboratory values is also acceptable (13). Other causes of AKI (*e.g.*, nephrotoxin exposure, obstruction) should be excluded. TLS, tumor lysis syndrome.

TUMOR CELL LYSIS

Efflux of K+

Release of nucleic acid

Hyper phosphatemia

Purine catabolism
see Figure 1

Hyperuricemia

Hyperkalemia

Precipitation of uric acid crystals

Calcium-phosphate imbalance

Arrythmias EKG abnorm.

Acute renal failure

Fluid depletion
Fever, vomiting, diarrhea
poor intake

Arrows=activation or consequences

Clinical manifestations

- *Hyperuricemia: lethargy, nausea, vomiting & renalfailure*
- *Hyperphosphatemia may precipitate hypocalcemia and cause tissue damaga due to ca.phosphate precipitation in tissues*
- *Tissue damage may present as pruritic skin or gangrenous skin lesions, arthritis, eye inflammation or as renal failure*
- *Hypocalcemia can present as tetany, carpopedal spasm, cramps, seizures, alteration in sensorium or as cardiac arrest*
- *Arf, arrythmias, neuromuscular symptoms duw to hyperkalemia and hypocalcemia may lead to sudden death*

Table 2
Prophylactic Management of TLS

- Central venous access and on an oncology or intensive care unit
- Baseline electrocardiogram
- Rigorous hydration – approximately 3 liters/m2/day to maintain urine output of at least 100 ml/m2/day. If necessary, diuretics such as furosemide and/or mannitol may be used to maintain urine output.
- Baseline lab values including: LDH, uric acid, sodium, potassium, creatinine, BUN, phosphorus and calcium. These labs should be checked every 6 to 8 hours for the first 48 to 72 hours after therapy, and then tapered according to risk.
- Administer allopurinol 200-300 mg/m2/day or rasburicase 0.20mg/kg/day, intravenously over 30 minutes for 3 to 7 days.
- (Optional) Alkalinization of urine with sodium bicarbonate in IV fluids.

Prevention - Urinary Alkalinization

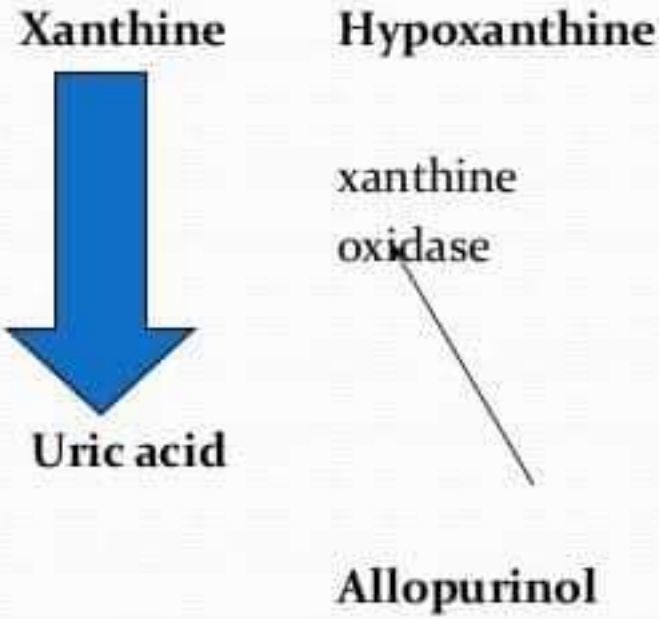
- Urine alkalinization - add $NaHCO_3$ to IVF
  - Uric acid more soluble at urine pH = 7.0 vs 5.0
  - Goal of urine specific gravity ≤1.015 and pH 7.0-7.5
  - Caution -- hypoxanthine and Ca-PO_4 stones possible if urine pH >7.5
- Fallen out of favor as no demonstrated advantage; may be appropriate for patients with underlying metabolic acidosis

Prevention - Hypouricemic Agents

- Allopurinol – a hypoxanthine analog that inhibits XO producing more hypoxanthine and xanthine which are more soluble in acidic urine; takes 2-3 days to be effective
- Urate Oxidase/Rasburicase – breaks down uric acid to allantoin which is more soluble in urine; acts within several hours
- UO has significantly reduced the need for rescue dialysis therapy for TLS

Prevention - Allopurinol

- Decrease production of uric acid
  - allopurinol inhibits xanthine oxidase
    - 300 mg/m²/day divided tid PO/IV
    - Dose reduction in renal insufficiency
    - Long-time standard Rx



Allopurinol vs. Rasburicase

Goal: prevention and/or treatment of uric acid nephropathy

- Low risk patients: *Allopurinol*
  - UA: normal
  - certain tumors (namely non-hematologic malignancies, Hodgkin's lymphoma, chronic myeloid leukemia),
  - Tumor burden: lower (WBC < 50 x 10(9)/L and LDH < 2x normal),
  - Intensity of cytoreductive therapy: Low
  - Intravascular volume: adequate
  - Tumor infiltration of the kidney: absent
- High risk patients: *Rasburicase*
  - UA: increased
  - certain tumors (eg, Burkitt's lymphoma, lymphoblastic lymphoma, acute lymphoblastic leukemia, and acute myeloid leukemia),
  - Tumor burden: High (WBC > 50 x 10(9)/L and LDH >2x normal),
  - Intensity of cytoreductive therapy: aggressive
  - Intravascular volume: decrease
  - Tumor infiltration of the kidney: present

Management

Metabolic abnormality	Drug category	Drug name	Dose
Hyperuricemia	Xanthine oxidase inhibitors	Allopurinol	Prophylaxis: 200~600mg/dl Tx: 600~900mg/dl
	Uric acid oxidizers	Rasburicase	0.15~0.2mg/kg/d for 5~7 d
Hyperkalemia	Intracellular potassium transporters	Sodium bicarbonate	1meq/kg IV 50~100meq/L IVF
		Insulin + dextrose	
	Exchange resins	Kayexalate	25~50gm Q6h
Hyperphosphatemia	Phosphate-binding agents	Aluminum hydroxide	10ml Q2h for 12x/day
Hypocalcemia	Mineral	Calcium gluconate; Calcium chloride	10% calcium chloride: K^+ ↑: 2~4mg/kg Q6~8h prn K^+ ↓: 0.5~1gm Q1~3d

Approach to the Management and Treatment of Tumor Lysis Syndrome

	Decreased urine output(<50ml /hr)	hyperkalemia	Uraemia	hypocalcemia	hyperuricemia	hyperphosphatemia
Primary intervention	Mannitol challenge	Potassium binding raisin	Diuretic	Cautious replacement	Allopurinol or Rasburicase	Aluminum hydroxide (200–500 mg/kg)
Clinical manifestation	Renal insufficiency or fluid overload	Arrythmia	Pericarditis or platelet dysfunction	Arrythmia or Tetany	Renal insufficiency	Renal insufficiency
Secondary intervention	haemodialysis	Treat arrythmia	Haemodialysis	Treat arrythmia	haemodialysis	haemodialysis

Summary

- *Successful management and treatment of tumor lysis syndrome is highly dependent on the prompt identication of clinical and laboratory characteristics, signs and symptoms of patients at risk.*
- *Establishment of vascular access and the initiation of prophylactic measures, especially hydration and administration of allopurinol or rasburicase, are vital.*
- *The early recognition and treatment of metabolic abnormalities usually prevents the severe and life-threatening complications associated with tumor lysis syndrome.*