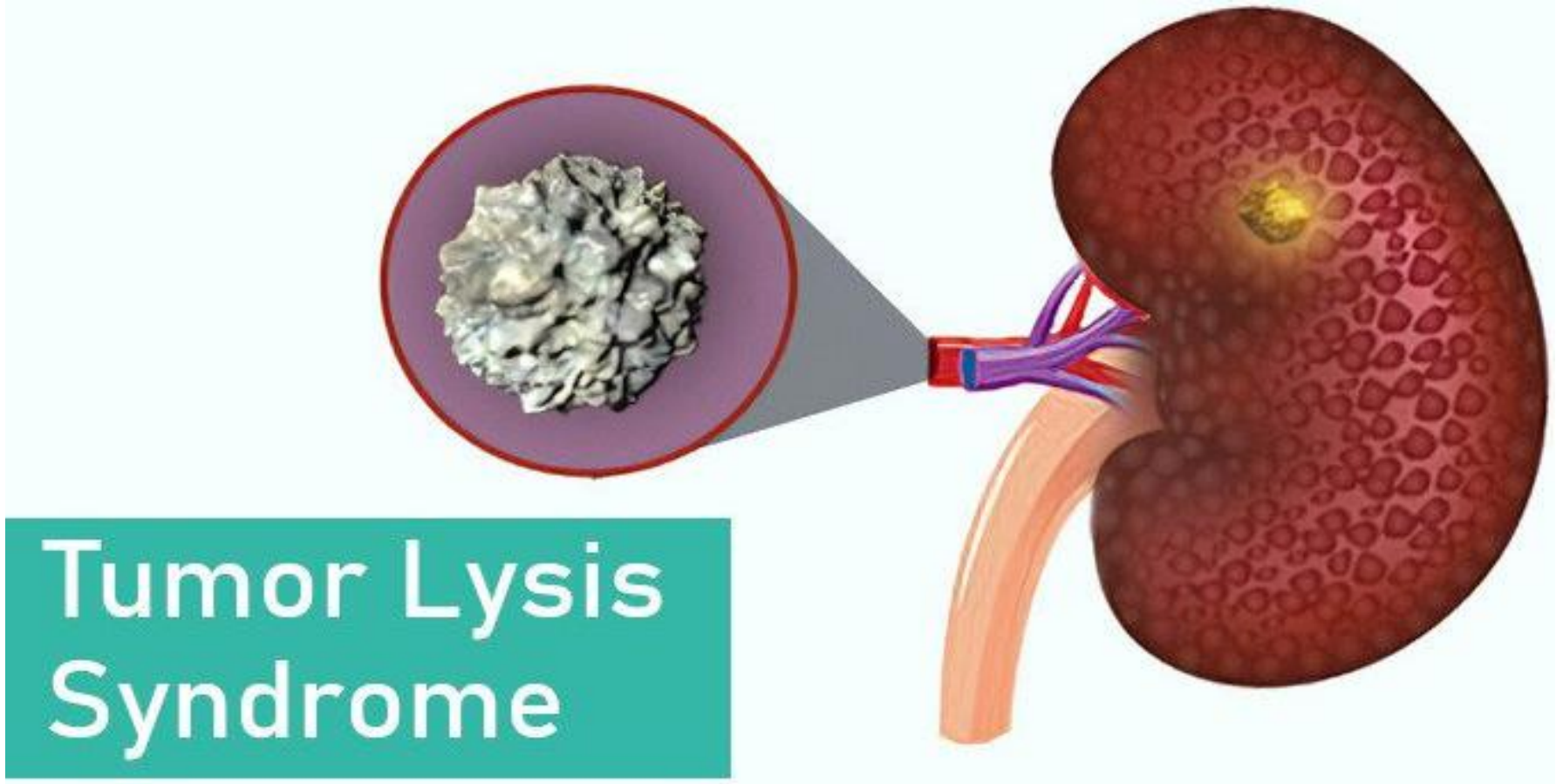

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History

- First described by Bedrna and Polcak (١٩٢٩) in patients with chronic leukaemia treated with radiotherapy, tumour lysis syn- drome (TLS) is a metabolic syndrome caused by the break-down of malignant cells.

Tumor Lysis Syndrome (TLS): Key Features

•Biochemical hallmarks:

•↑ Uric acid (Hyperuricemia)
•↑ Phosphate (Hyperphosphatemia)
•↑ Potassium (Hyperkalemia)
•↓ Calcium (Hypocalcemia)

•Potential consequences:

•Acute kidney injury
•Cardiac arrhythmias
•Seizures
•Death

(Will & Tholouli, ٢٠٢١)

When Does TLS Occur?

- Typically in **first few days** after chemotherapy
- Can also occur after:
- Radiotherapy (Yamazaki et al, ٢٠٠٤)
- Steroids (Sparano et al, ١٩٩٠; Coutinho et al, ١٩٩٧)
- Immunotherapy (Yang et al, ١٩٩٩)
- **Spontaneously** in high tumor turnover (Jasek & Day, ١٩٩٤)

Pathophysiology

- **Massive tumor cell breakdown** → release of:
- Nucleic acids
- Proteins
- Intracellular metabolites
- Overwhelms homeostatic mechanisms. Leads to:
- ↑ Uric acid, phosphate, potassium
- ↓ Calcium

(Locatelli & Rossi, ٢٠٠٥)

Early Effect: Hyperkalemia

- **First metabolic change** in TLS
- May appear **within ۶ hours** after starting chemotherapy
- Can be **immediately life-threatening**

(Flombaum, ۲۰۰۰; Locatelli & Rossi, ۲۰۰۵)

Uric Acid Nephropathy

- Hyperuricemia → uric acid crystal precipitation in renal tubules
- Worse in acidic environment (distal tubules)
- Leads to reduced excretion of cellular breakdown products

Phosphate–Calcium Effects

- ↑ Plasma phosphate → calcium phosphate crystal deposition
- Sites: soft tissues, renal tract
- Worsens renal function

Vicious Cycle

- Acute kidney injury → ↓ potassium clearance → worsening hyperkalemia

- Acidosis → accelerates uric acid crystallization in tubules

- Cascade to clinical TLS

TLS Classification

- **Laboratory TLS:**
- Electrolyte abnormalities only
- **Clinical TLS:**
- Laboratory TLS **+** clinical symptoms/organ failure
- Laboratory TLS often precedes clinical TLS
- **Appropriate therapy can prevent progression**

Cairo–Bishop Definition (٢٠٠٤)

- **Laboratory TLS:**
- Specific electrolyte changes **before/during/after treatment**
- **Clinical TLS:**
- Organ dysfunction **due to** electrolyte imbalance
- Debate: ٢٥% change from baseline — often not calculated in practice

Cairo-Bishop clinical tumor lysis syndrome definition* and grading

Complication	Grade					
	0	1	2	3	4	5
Creatinine ¶Δ	≤1.5 × ULN	1.5 × ULN	>1.5-3.0 × ULN	>3.0-6.0 × ULN	>6.0 × ULN	Death
Cardiac arrhythmia ¶	None	Intervention not indicated	Nonurgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (eg, defibrillator)	Life-threatening (eg, arrhythmia associated with HF, hypotension, syncope, shock)	Death
Seizure ¶	None	–	One brief, generalized seizure; seizure(s) well controlled by antiseizure medications or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which are prolonged, repetitive or difficult to control (eg, status epilepticus, intractable epilepsy)	Death

Risk Factors for TLS

- **High tumor burden → >١٠ cm in diameter or WBC> ٥٠٠٠٠**
- **High-grade tumors** with rapid turnover
- **Pre-existing renal impairment** or renal infiltration by tumor
- **Older age**
- **Pre-existing hyperuricemia or hyperphosphatemia**
- **Elevated LDH> ٢ ULN**
- **Oliguria and/or acidic urine**
- **Volume depletion**
- **Extensive bone marrow involvement**
- **Highly active, cell-cycle–specific agents**
- **Concomitant drugs** that ↑ uric acid:
- Alcohol, ascorbic acid, aspirin, caffeine
- Cisplatin, diazoxide, thiazides, adrenaline, ethambutol
- Levodopa, methyldopa, nicotinic acid, pyrazinamide
- Phenothiazines, theophylline

Common High-Risk Malignancies

- B-cell non-Hodgkin lymphoma (esp. **Burkitt leukemia/lymphoma**)
- Acute lymphoblastic leukemia (ALL)
- Rarely: low TLS-risk malignancies can cause TLS unexpectedly

Malignancy	Pediatric (n = 682)		Adult (n = 387)		Total (n = 1069)	
	Number	Percent	Number	Percent	Number	Percent
Acute lymphoblastic leukemia	433	63	73	19	506	47
Acute myeloid leukemia	74	11	104	27	178	17
Chronic lymphocytic leukemia	0	0	37	10	37	3.5
Chronic myeloid leukemia	6	0.9	36	9	42	4
Non-Hodgkin's lymphoma	122	18	109	28	231	22
Hodgkin's disease	8	1.2	6	1.6	14	1.3
Multiple myeloma	0	0	15	3.9	15	1.4
Other hematologic malignancies	5	0.7	3	0.7	8	0.7
Solid tumors	34	5	4	1	38	3.6

TLS in Solid Tumors

- Reported in breast cancer, SCLC, neuroblastoma, GCT, sarcoma, ovarian cancer, …

- Agents implicated include docetaxel, pazopanib

TLS associated with Treatment modalities

- Common with cytotoxic chemotherapy combinations
- Also seen with:

✓Glucocorticoids alone

✓Monoclonal antibodies(rituximab, Obinutuzumab)

✓Targeted agents: venetoclax, imatinib

✓Radiation therapy alone

✓CAR T-cell therapy

Spontaneous TLS

- Occurs prior to therapy, associated with high uric acid and AKI

- Seen in aggressive NHL and acute leukemia

Prophylaxis: Why It Matters

- Clinical TLS: **~۳–۶%** of patients with high-grade tumors
- Serious outcomes:
- ۱/۳ require **dialysis**
- Mortality > **۱۵%**

Key Prevention Principle

- Identify high-risk patients early
- Implement prophylactic measures before therapy starts
- Complete prevention not always possible:

  Small % develop spontaneous TLS before treatment

Cairo et al. (٢٠١٠) TLS Risk Model

Low risk:

- Active monitoring
- Hydration ± allopurinol

Intermediate risk:

- Active monitoring
- Hydration + allopurinol

High risk:

- Active monitoring
- Hydration + rasburicase

High-Risk TLS Criteria

- **Planned for intensive chemotherapy +** any of the following:
- **ALL or AML** with WBC > ١٠٠ × ١٠^{9}/L
- **Burkitt lymphoma** or **lymphoblastic lymphoma**
- **High-grade lymphoma** (DLBCL, T-cell NHL) **with bulky disease:**
  - LDH > ٢ × ULN
  - Mass > ١٠ cm (adults)
- Any hematologic malignancy **with renal impairment** or **allergy to allopurinol** → consider rasburicase

Timing of Prophylaxis

- Most useful during first treatment course
- Also indicated for re-induction or salvage chemotherapy
- Not indicated for consolidation (including BMT) if patient is in/near remission

Hydration in TLS Prophylaxis

- Target: **~٣ L/٢٤ h in adults**
- Traditionally combined with allopurinol + **alkaline diuresis**
- **Alkaline diuresis NOT recommended**:
- ↑ Uric acid solubility at alkaline pH, but…
- Xanthine & hypoxanthine ↓ solubility → crystal precipitation

Allopurinol Prophylaxis

- **Adults:** ٢٠٠–٤٠٠ mg/m²/day (١–٣ doses), max ٨٠٠ mg
- Common practice: ٣٠٠ mg/day
- **Children:** ٣٠٠–٤٥٠ mg/m²/day (max ٤٠٠ mg)
- **Infants <١٠ kg:** ٣,٣ mg/kg every ٨ h
- Adjust dose in **renal failure**
- Duration: up to ٧ **days** post-chemotherapy
- Switch to **rasburicase** if biochemical/clinical markers worsen

Rasburicase Prophylaxis

- Indicated in **very high-risk** patients + hydration & monitoring
- **Contraindicated** in G٦PD deficiency
- Licensed dose: ٠,٢ **mg/kg**
- Duration: ٥–٧ **days** for prophylaxis
- Highly effective in both adults & children

Treatment of Established TLS: Principles

- **Multidisciplinary approach**: hematology, nephrology, ICU
- Patient status can change rapidly → **frequent monitoring**
- If high-dependency care not available → transfer to specialized centre Maintain **high index of suspicion**

Fluid Balance Goals

- **First step**: Vigorous hydration + careful monitoring
- Prevent: uric acid crystallization & calcium phosphate deposition in renal tubules
- **Adults:** ~٣ L/m²/٢٤ h
- **Urine output targets:**
- Infants: >٤ mL/kg/h
- Older patients: ١٠٠ mL/m²/h
- Balanced/isotonic solutions; **NO potassium** in fluids

Monitoring Fluid Status

- Measure urine output hourly
- Fluid balance assessment every ۶ h
- Document all losses (vomiting, diarrhoea)
- Daily weights (infants: twice daily)
- Watch for fluid overload in infants, elderly, cardiac/renal disease patients

Reduced Urine Output: Next Steps

- Reassess fluid balance + labs
- Rule out **urinary tract obstruction** by tumour
- **Fluid overload** → nephrology consult
- Use diuretics cautiously:
- Furosemide ٠٫٥ mg/kg IV possible in emergencies
- May worsen uric acid deposition, esp. with tubular blockade

Urine Alkalinization

- **NOT recommended** in TLS
- Risks:
- ↑ calcium phosphate precipitation
- ↓ xanthine solubility
- Evidence of benefit is **equivocal**

Hyperuricaemia Management

- **Allopurinol**: Xanthine oxidase inhibitor

•Prevents new uric acid formation

•**Does NOT break down existing uric acid deposits**

•Role: prophylaxis only — **not first choice in established TLS**

• Rasburicase in Established TLS

- **Mechanism:** Recombinant urate oxidase → converts uric acid to soluble allantoin
- **Advantages over allopurinol:** Breaks down existing uric acid deposits, rapid effect
- Switch from allopurinol if TLS develops (unless: allergy or **G۶PD deficiency**)
- **Dose:** ۰,۲ mg/kg/day IV over ۳۰ min, for ۳–۷ days
- Monitor: Electrolytes daily, clinical response
- EMA/FDA: up to ۵ days daily dosing

Hyperphosphataemia Management

- If hydration + rasburicase fail → control often difficult without dialysis
- **Aluminium hydroxide** (٥٠–١٥٠ mg/kg/day) described but:
- Slow acting
- Poorly tolerated
- **Not routinely recommended**
- Dialysis often required for severe cases

Hypocalcaemia Management

- Asymptomatic: Do not treat (risk of calcium phosphate deposition)
- Cardiac monitoring if:

١. Corrected calcium ≤٧ mg/dl

٢. ≥٢٥% drop from baseline

- Symptomatic (arrhythmia, seizure, tetany):

١. Give calcium gluconate (standard doses) to relieve symptoms

٢. Aim: Treat symptoms, not normalize numbers

Hyperkalaemia Management

- **Cardiac monitoring** if:
- K^+ ≥۶ meq/L
- ≥۲۵% rise from baseline
- **Medical emergency**: K^+ ≥۷ meq/L → urgent dialysis likely
- Temporary measures:
- Calcium gluconate infusion (cardioprotection)
- Nebulized or IV salbutamol
- IV insulin + glucose
- Effects temporary → dialysis often required

Dialysis in TLS

- **Indications:**
- Renal deterioration + fluid overload
- Severe hyperkalaemia, hyperuricaemia, hyperphosphataemia, hypocalcaemia unresponsive to medical therapy
- **Not recommended:** Peritoneal dialysis (slow effect, abdominal pathology risk)
- **Options:** Haemodialysis, haemofiltration, CRRT
- Daily dialysis may be optimal (continuous metabolite release)
- CRRT for haemodynamically unstable patients
- Continue until renal recovery & urine output adequate

THANK YOU