# Prevention in
# TUMOR LYSIS SYNDROME

Hemato-Oncology Department

# 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

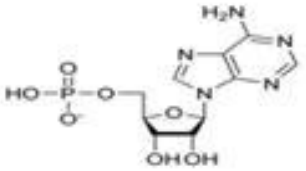
Cellular breakdown

Release of DNA

hyperphosphatemia

nucleotides

Neuromuscular irritability



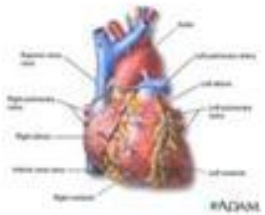
Purine catabolism

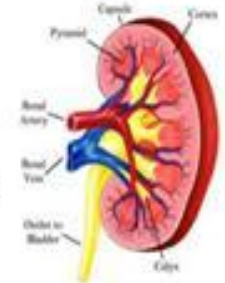
Calcium-phosphate unbalance

Hyperuricemia

Precipitated uric acid crystals in renal tubules

arrhythmias





hyperkalemia

Acute renal failure ARF

# Common Tumors Associated with TLS

- ALL 63%
- Non-Hodgkin’s Lymphoma 18%
- AML 11%
- Solid Tumors 5% - Neuroblastoma; Medulloblastoma; germ cell tumors; sarcoma

# Risk Factors

- Patients with highly proliferative tumors and/or high tumor burden (>10cm diameter; WBC>50,000)
- Pretreatment LDH > 2x upper limit of normal
- Pre-existing renal insufficiency
- Tumor with high sensitivity to treatment

# Cairo Bishop Grading System

- Laboratory TLS requires 2 or more abnormal serum values be present 3 days before  or 7 days after instituting chemotherapy in the setting of adequate hydration and use of a hypouricemic agent

# Cairo Bishop Grading System

- Laboratory tumor lysis syndrome:

  Uric acid ≥8 mg/dL (≥476 mol/L) or 25% increase from baseline

  Potassium ≥6.0 mEq/L (≥6 mmol/L) or 25% increase from baseline

  Phosphorus ≥6.5 mg/dL (≥2.1 mmol/L) or 25% increase from baseline

  Calcium ≤7 mg/dL (≤1.75 mmol/L) or 25% decrease from baseline

# Clinical TLS

- Clinical TLS constitutes laboratory TLS plus at least one of the following:
  - serum Creatinine > 1.5 x ULN
  - cardiac arrythmia/sudden death
  - seizure

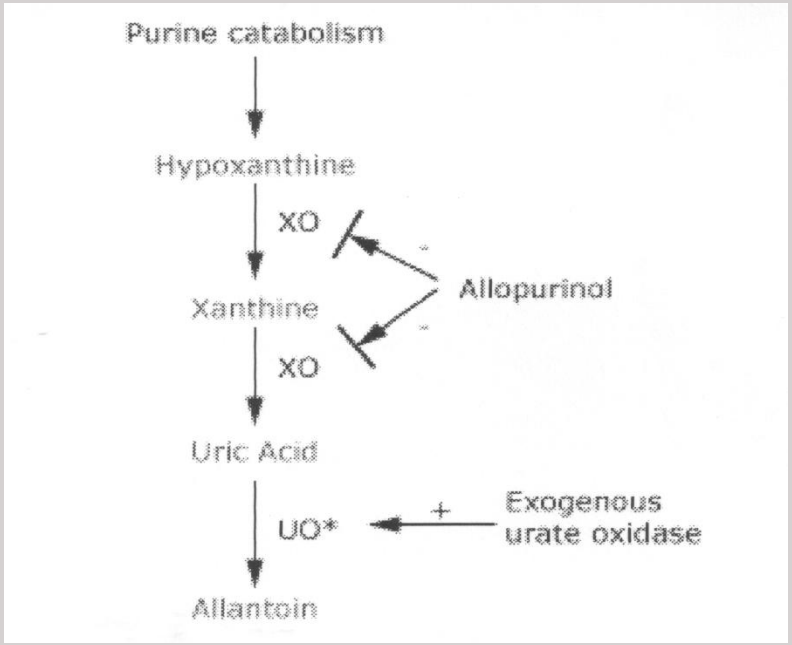
# Clinical TLS

| | Grade 0‡ | Grade I | Grade II | Grade III | Grade IV | Grade V |
|---|---|---|---|---|---|---|
| LTLS | No | Yes | Yes | Yes | Yes | Yes |
| Creatinine‡ | ≤1.5 × ULN | 1.5 × ULN | >1.5–3.0 × ULN | >3.0–6.0 × ULN | >6 × ULN | Death§ |
| Cardiac arrhythmia‡ | None | Intervention not needed | Nonurgent intervention needed | Symptomatic and incompletely controlled medically or controlled with a device | Life-threatening (eg, arrhythmia associated with CHF, hypotension, or shock) | Death§ |
| Seizures‡ | None | None | One brief, generalized seizure, seizures controlled with anticonvulsant drugs, or infrequent motor seizures | Seizures with impaired consciousness, poorly controlled seizures, generalized seizures despite medical interventions | Status epilepticus | Death§ |

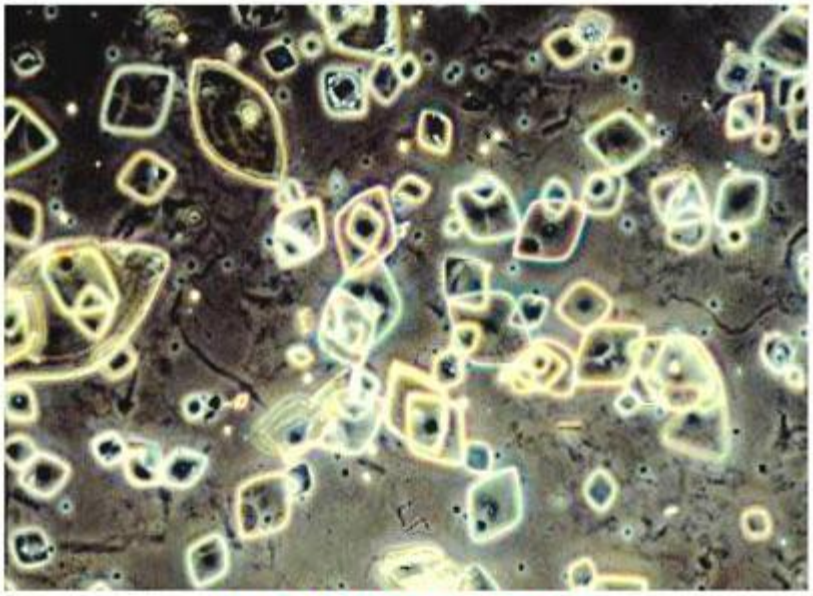
# Clinical Manifestations of TLS

- Nausea/Vomiting, diarrhea, anoxeria
- Hyperkalemia → weakness, dysrhythmias
- Hyperphosphatemia → hypocalcemia, renal failure
- Hypocalcemia → muscle cramps, tetany, mental status changes, seizures
- Hyperuricemia → "uric acid nephropathy" = oliguria, renal failure

# Hyperuricemia



# Hyperuricemia



URIC ACID (U-pH ≤5.4)

# Hyperphosphatemia

- Malignant cells contain higher concentration of phosphorus
- Hyperphosphatemia causes hypocalcemia (precipitation in renal tubules/heart is increased when phos*ca product > 60 mg/dL)
- More common cause of renal failure since the use of Allopurinol and UO

## Table 1: Patient Classification for Tumor Lysis Syndrome

| | |
|---|---|
| High risk | Burkitt's lymphoma, lymphoblastic lymphoma, B-cell ALL, ALL if WBC >100 K, AML if WBC >50 K, monoblastic AML |
| Intermediate risk | DLBCL, ALL if WBC 50-100 K, AML if WBC 10-50 K, CLL if 10-50 K and treated with fludarabine, other malignancies with rapid proliferations and expected rapid response to therapy |
| Low risk | Indolent NHL, ALL if WBC >50 K, AML if WBC >10 K, CLL if WBC >10 K, other malignancies |

ALL=acute lymphoblastic leukemia; WBC=white blood cell count; AML=acute myelogenous leukemia; DLBCL=diffuse large B-cell lymphoma; CLL=chronic lymphocytic leukemia; NHL=non-Hodgkin's lymphoma.

*J Clin Oncol.* 2008;28:2767-2778.

**Tumor lysis syndrome (TLS) prophylaxis recommendations based on TLS risk**

| Low risk disease (LRD) | Intermediate risk disease (IRD) | High risk disease (HRD) |
|---|---|---|
| Most solid tumors | Rare, highly chemotherapy sensative solid tumors (eg, neuroblastoma, germ cell tumor, small cell lung cancer) with bulky or advanced stage disease | N/A |
| MM | N/A | N/A |
| CML | N/A | N/A |
| Indolent NHL | N/A | N/A |
| HL | N/A | N/A |
| CLL and WBC <50 x $10^9$/L treated only with alkylating agents | CLL treated with fludarabine or rituximab, and/or those with high WBC ≥50 x $10^9$/L | N/A |
| AML and WBC <25 x $10^9$/L and LDH <2 x ULN | AML with WBC 25 to 100 x $10^9$/L<br>AML and WBC <25 x $10^9$/L and LDH ≥2 x ULN | AML and WBC ≥100 x $10^9$/L |
| Adult intermediate grade NHL and LDH within normal limits | Adult intermediate grade NHL and LDH > ULN, non bulky | Adult intermediate grade NHL with bulky disease and LDH ≥2 x ULN |
| Adult ALCL | Childhood ALCL stage III/IV | N/A |
| N/A | Childhood intermediate grade NHL stage III/IV with LDH <2 x ULN | Stage III/IV childhood diffuse large B cell lymphoma with LDH ≥2 x ULN |
| N/A | ALL and WBC <100 x $10^9$/L and LDH <2 x ULN | Burkitt's leukemia<br>Other ALL and WBC ≥100 x $10^9$/L and/or LDH ≥2 x ULN |
| N/A | BL and LDH <2 x ULN | BL stage III/IV and/or LDH ≥2 x ULN |
| N/A | LL stage I/II and LDH <2 x ULN | LL stage III/IV and/or LDH ≥2 x ULN |
| N/A | N/A | IRD with renal dysfunction and/or renal involvement<br>IRD with uric acid, potassium and/or phosphate >ULN |
| **Prophylaxis recommendations** | | |
| Monitoring | Monitoring | Monitoring |
| Hydration | Hydration | Hydration |
| ±Allopurinol | Allopurinol | Rasburicase* |

# Prevention - Monitoring

- Follow laboratory parameters (UA, phosphate, potassium, calcium, creatinine, LDH) closely, starting 4-6 hours after initiation of chemo & then every 6 hours therafter
- Monitor UOP/Intake; monitor for seizures/cardiac arrthymias
- Monitor for 24-72 hours after intiation of chemo

# Prevention - Hydration

- Hydration to produce high urine output
  - Fluid intake = 2-3 L/$m^2$/day (or 200 ml/kg/day for patients <10kg) enhances uric acid excretion, phosphate excretion
  - Goal UOP of 80-100 ml/m2 per hour (or 4-6 ml/kg/hr if patient < 10kg)
  - Use isotonic fluid: D5 1/4 NS or  NS if hyponatremic
  - Do not add calcium or potassium
- Monitor for fluid overload in patients with underlying cardiac dysfunction or renal insufficiency

# Prevention - Urinary Alkalinization

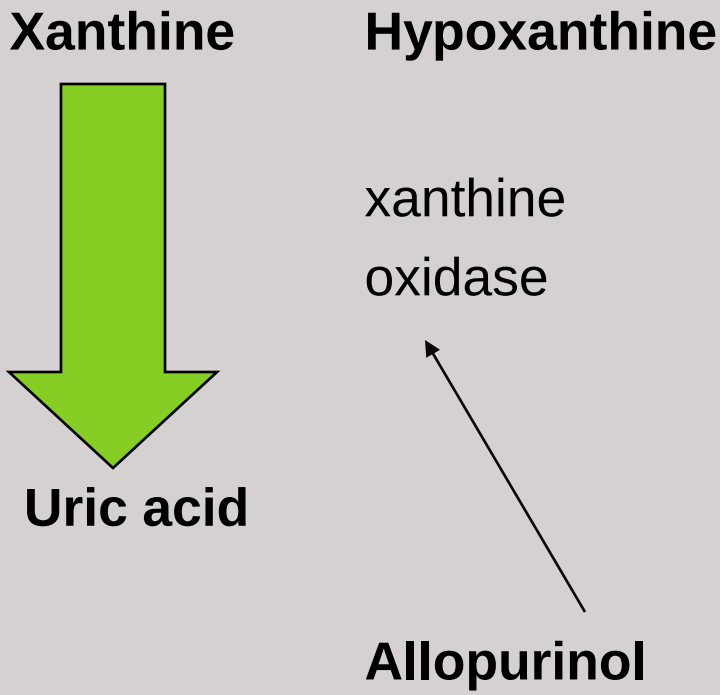
- Urine alkalinization - add $NaHCO_3$ to IVF
  - Uric acid more soluble at urine pH = 7.0 vs 5.0
  - Goal of urine specific gravity $\leq$1.015 and pH 7.0-7.5
  - Caution -- hypoxanthine and Ca-PO4 stones possible if urine pH >7.5
- Fallen out of favor as no demonstrated advantage; may be appropriate 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/m$^2$/day divided tid PO/IV
    - Dose reduction in renal insufficiency
    - Long-time standard Rx



# . . . Tumor Lysis Syndrome Prevention & Management

- **ALLOPURINOL:**

  -Competitive inhibitor of xanthine oxidase which decreases conversion of purine metabolites to uric acid. Used prophylactically for TLS

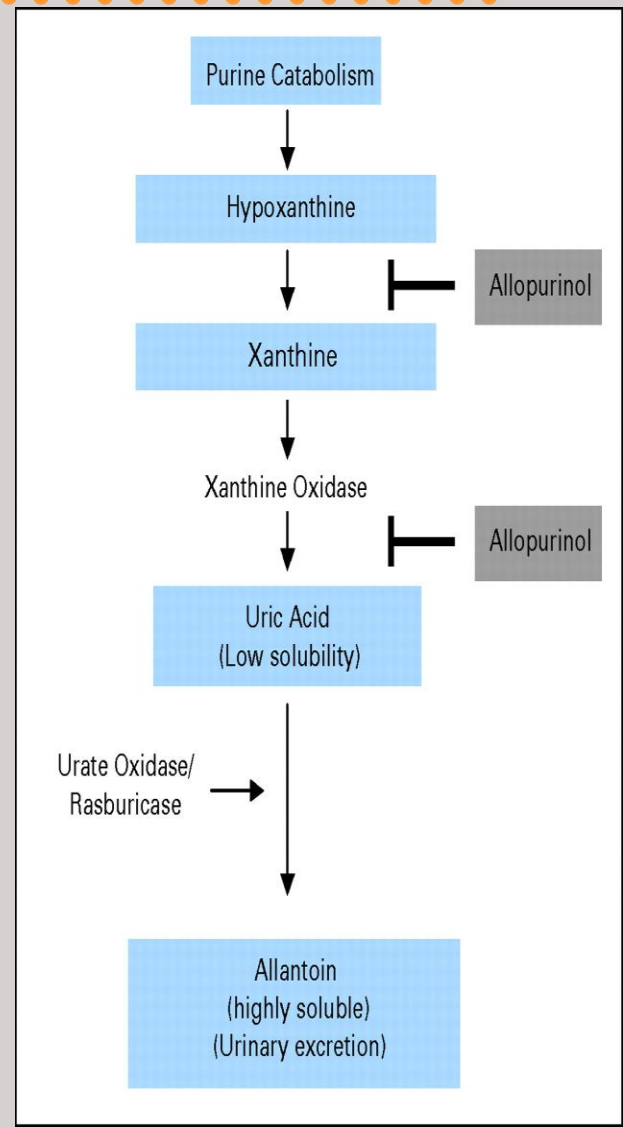
-Prophylactic option for patients with a medium risk of TLS

-Limitations:

----1)ineffective in reducing uric acid levels before chemoTx

----2) Xanthine and hypoxanthine precipitate→obstructive uropathy

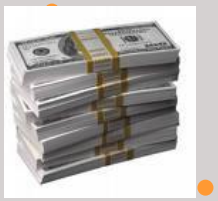
----3)reduces clearance of some chemoTx (azothiopurine & 6-mercaptopurine)



# Prevention - Urate Oxidase

- Present in other mammalian species
- Catalyzes conversion of uric acid to allantoin
  - Allantoin more soluble, easily excreted by kidneys
- Urine alkalinization unnecessary if used

- Recombinant urate oxidase (rasburicase) more effective than allopurinol in prevention and treatment of hyperuricemia
  - Goldman SC et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma or leukemia at high risk for tumor lysis. Blood. 2001;97:2998-3003.
- Contraindicated with G6PD deficiency, asthma



# ...Tumor Lysis Syndrome Prevention & Management

- **<u>RASBURICASE</u>** (recombinant urate oxidase) :

  -promotes catabolism of uric acid:

Uric acid → allantoin (10x more soluble than uric acid)

  -100 adult pt (w/ aggressive NHL) got 3 to 7 days of rasburicase beginning day 1 of chemo:

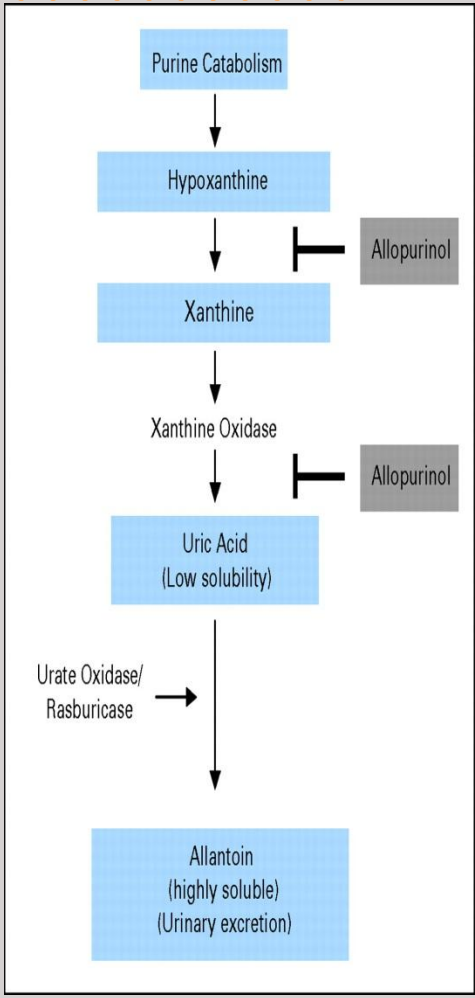
1)Uric acid levels decreased w/i 4 hrs of rasburicase

2)Normalized uric acid levels maintained throughout chemo

3)No increase in creatinine observed

4)No patient required dialysis

-One European and one US study showed that rasburicase prophylaxis resulted in net savings in health care costs ($9,978 for 7 day stay VS. $51,990 for 21 day stay w/ HD)



# Conclusions

- Pediatric oncology patients experience a broad variety of critical illnesses related to both disease and therapy.
- Long-term survival for many pediatric cancers is improving.
- ICU outcomes for this patient group is improving.
- Good ICU care can benefit children with malignancies.