Tumor Lysis Syndrome and AKI

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Disclosure Information

- “No financial relationships to disclose”

Case Discussion

- A 62-year-old female presented with a several week history of general malaise, intermittent febrile episodes for several months, and development of both anorexia and acute metabolic encephalopathy 48 to 72 hours prior to admission.
- A mammogram study performed earlier that month cited ominous appearing masses of the breast and axilla, with recommendations for biopsy and flow cytometry.
- Physical exam was significant for encephalopathy, tachycardia, jaundice, and palpable masses in the axilla.
- Acute kidney, lactic acidosis, hyperuricemia, and leukocytosis with numerous immature forms were noted on admission.

Case: Diagnosis

- Right axillary node core biopsy, bone marrow biopsy, and cerebrospinal fluid analyses confirmed diagnosis of diffuse aggressive large B cell non-Hodgkin's lymphoma with central nervous system involvement.

Case: Laboratory Values

Laboratory Value	Reference Range	72 Hour Pre-Admit	Admission
Sodium	135-145 mmol/L	140 mmol/L	133 mmol/L
Potassium	3.5-5.0 mmol/L	4.7 mmol/L	6.8 mmol/L
Bicarbonate	22-33 mmol/L	24 mmol/L	16 mmol/L
Calcium	8.4-10.5 mg/dL	10.5 mg/dL	10.4 mg/dL
Phosphorus	2.5-4.5 mg/dL	3.8 mg/dL	5.5 mg/dL
Urea nitrogen	6-24 mg/dL	10 mg/dL	50 mg/dL
Creatinine	0.6-1.1 mg/dL	1.54 mg/dL	7.04 mg/dL
Uric acid	2.6-7.2 mg/dL	-----	20.4 mg/dL
White blood cells	4.0-10.5 (1000's/ul)	17.7 (1000's/ul)	29.9 (1000's/ul_
Hemoglobin	12.1-15.8 g/dL	10.4 g/dL	9.1 g/dL

Tumor Lysis Syndrome

- Medical emergency of patients with cancer in which breakdown of tumor cells, either spontaneously or in response to treatment, releases intracellular contents into the circulation, resulting in:
  - **Hyperuricemia**
  - **Hyperkalemia**
  - **Hyperphosphatemia (less common in spontaneous TLS as tumor cells which are rapidly growing reuse phosphate)**
  - **Secondary hypocalcemia**
  - **Metabolic Acidosis**
- Often associated with secondary AKI, and other end-organ dysfunction (seizures and arrhythmias)

TLS: Epidemiology

- Most common malignancies
  - Non-Hodgkin lymphoma: 30%
  - Solid tumors: 10%
  - Acute myeloid leukemia: 19%
  - Acute lymphocytic leukemia: 13%
- In-hospital mortality: 21%
- Median hospital length of stay: 10 days but increases to 21 days if dialysis is needed
- 69% of patients experience severe complication: sepsis (22%), dialysis (15%), acute respiratory failure (23%), mechanical ventilation (16%), cardiac arrest (2%), seizures (1%).

Durani U et al. Oncologist 2017; 22: 1506-1509

Tumor Lysis Syndrome—Cairo-Bishop Definition (Laboratory Only)

No universally accepted diagnostic criteria or classification system

- Hyperuricemia
  - ≥ 8 mg/dl or 25% increase
- Hyperkalemia
  - ≥ 6 mmol/L or 25% increase
- Hyperphosphatemia
  - ≥ 4.5 mg/dl (6.5 mg/dl in children) or 25% increase
- Hypocalcemia
  - < 7 mg/dl (corrected) or 25% decrease

- 2 or more occurring 3 days before or 7 days after therapy

Cairo MS, Bishop M. Br J Hematol 2004; 127: 3-11

TLS—Cairo and Bishop Clinical Syndrome

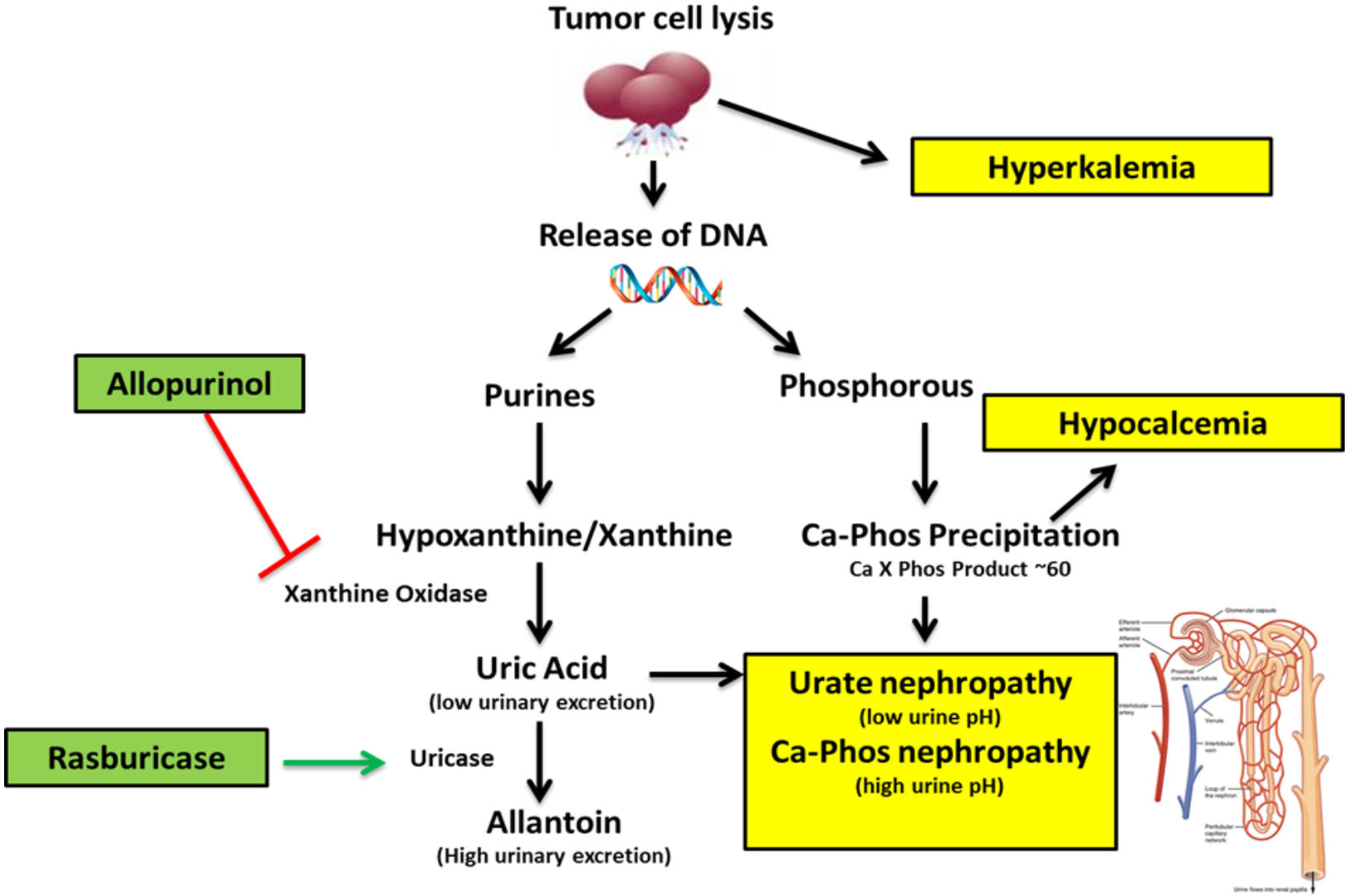
- Serum creatinine > 1.5 X upper limit of normal
- Cardiac arrhythmia, sudden death
- Seizure

Caveats with Definitions

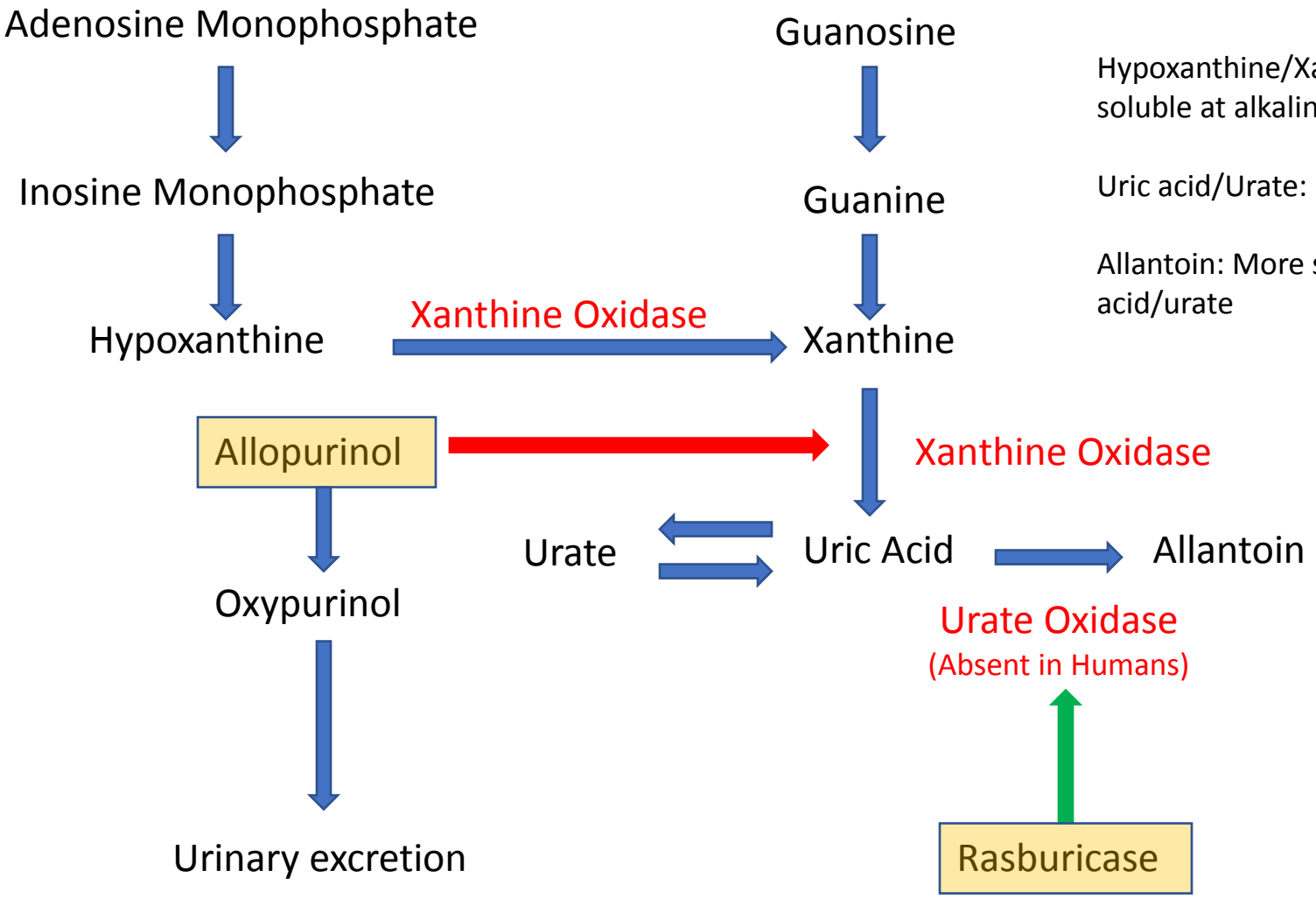
- Patients with TLS may not have > 2 laboratory manifestations present at the same time
- 25% change from baseline may or may not be significant and many have advocated dropping this from the definition (Howard Modification in 2011)
- No matter what, the present of clinical and/or laboratory manifestations of TLS requires emergent therapy

Howard SC et al. New Engl J Med 2011; 364: 1844-1854

Pathophysiology of TLS



Key Pathways in Purine Metabolism



Hypoxanthine/Xanthine : Less soluble at alkaline pH

Uric acid/Urate: Poorly soluble

Allantoin: More soluble than uric acid/urate

Risk Factors: Tumor Related

- **Acute lymphocytic/lymphoblastic leukemia**
  - **WBC ≥ 100,000**
- **Acute myeloid leukemia**
  - **WBC ≥ 50,000**
- **Burkitt, lymphoblastic, diffuse large B-cell lymphoma**
- **Large tumor burden**
- **LDH > 1500 IU (incidence < 13% in those with LDH < 2 x ULN v. 45% with in those with LDH > 2 x ULN)**
- **Chemotherapy responsive tumor**
- **Extensive BM involvement**
- **Can occur spontaneously**
- **Has been seen with XRT, interferon, rituximab, tyrosine kinase inhibitors and novel/targeted therapies including CAR-T cells**

Risk Factors: Patient Related

- Older age
- Reduced GFR
- Dehydration/volume depletion
- Baseline hyperuricemia
- Splenomegaly
- CNS/Renal involvement by tumor
- Mediastinal mass

Belay Y, et al, J Oncology 2017

Clinical Presentation

- Typically, 24 hours or later post-therapy
- Clinical presentation depends on the combination and severity of the biochemical abnormalities
  - Hyperkalemia: muscle weakness, cardiac arrhythmias
  - Uric acid: uric acid nephropathy which is the most common manifestation of TLS
  - Hyperphosphatemia: calcium phosphate precipitation leading to AKI and hypocalcemia

Spontaneous TLS

- Current definitions are not sensitive nor specific for spontaneous TLS
- Recommendation:
- *Patients with hyperuricemia (UA ≥ 8.0 mg/dL) in the presence of suspected malignancy with elevated lactate dehydrogenase (>2 × ULN), acute oliguric or anuric kidney injury despite adequate volume resuscitation without evidence of post-obstructive cause, and urinary uric acid to creatinine ratio greater than 1.0 be considered spontaneous TLS until proven otherwise.*

J Investig Med High Impact Case Rep. 2015 Jul-Sep; 3(3): 2324709615603199

Pathophysiology of AKI

- Volume depletion
- Uric acid
- Phosphate-calcium precipitation
  - Intratubular crystals
  - Nephrocalcinosis
- Xanthine crystalluria

Role of Uric Acid in TLS AKI

- Degradation product of DNA and RNA in liver
- Micro- and macrocrystal formation in distal tubules and collecting ducts
  - Acid urine pH favors urate (soluble)→uric acid (less soluble)
  - Tubulo-glomerular feedback reduces RPF and GFR
- Crystals induce active inflammatory response, induce cytokine release: MCP-1, interleukins, TNF-α
- Possible direct vascular effects via AII, NO, vasoconstriction, anti-angiogenic effects

Prophylaxis

- Prophylaxis recommended to all patients with hematological malignancies undergoing chemotherapy
- Prophylaxis also recommended for all high and moderate risk patients
- However, exact regimen for prophylaxis is not detailed in guidelines but relies on a combination of:
  - Decreasing uric acid level
  - Adequate hydration
  - Management of electrolyte levels
- Highest risk patients should receive hydration and rasburicase in an in-patient setting

Prevention and Treatment of TLS

- **Volume expansion**
- **Hyperuricemia**
  - **Urine alkalinization**
  - **Allopurinol/feboxustat**
  - **Rasburicase**
  - **Hemodialysis**
- **Hyperkalemia**
  - **Potassium binding resins**
  - **Hemodialysis**
- **Hyperphosphatemia**
  - **Phosphate binders**
  - **Hemodialysis**
- **Hypocalcemia**
  - **Treat only if symptomatic**

Risk Stratification is Critical in Deciding the Prophylactic Regimen

Hydration Regimens

- Decreases extracellular uric acid, phosphorus and potassium concentrations
- Enhanced renal blood flow and maintains GFR
- Ideally, started 24-48 hours pre-therapy
- Monitor for volume overload and use diuretics only when indicated for volume overload.
- Generally, 1-2 ml/kg/hr of IVF and particular fluid guided by laboratory values and clinical circumstances (avoid lactated ringers)
- Goal urine output: 2 ml/kg/hour
- Continue IVF until TLS resolved

Use for ALL patients independent of risk

Urine Alkalinization

- Favors uric acid → urate
  - Solubility of urate = 200 mg/dl at pH 7
  - Solubility of uric acid = 15 mg/dl at pH 5
- Increases calcium-phosphate precipitation risk
- Reduces ionized calcium
- Xanthine and hypoxanthine have low solubility even at pH 7
  - Risk of xanthine crystal uropathy with allopurinol
- Rasburicase use makes urinary alkalinization obsolete

- **NOT RECOMMENDED**

Allopurinol

- Isomer of hypoxanthine—inhibits xanthine oxidase
  - Reduces uric acid synthesis but does not directly reduce uric acid levels
  - Rapidly metabolized to oxypurinol by xanthine oxidase
- Increases plasma concentrations of the uric acid precursors hypoxanthine and xanthine
  - These inhibit enzymes involved in purine synthesis
- RISK: Xanthine and hypoxanthine can form crystals and deposit in the kidney leading to xanthine nephropathy
- Side effects: fever, rash, eosinophilia, systemic hypersensitivity reactions, Stevens-Johnson syndrome, hepatitis, AIN, bone marrow suppression
- Begun 2-3 days prior to therapy and continued for 10-14 days
- DOES NOT reduce preexisting uric acid levels

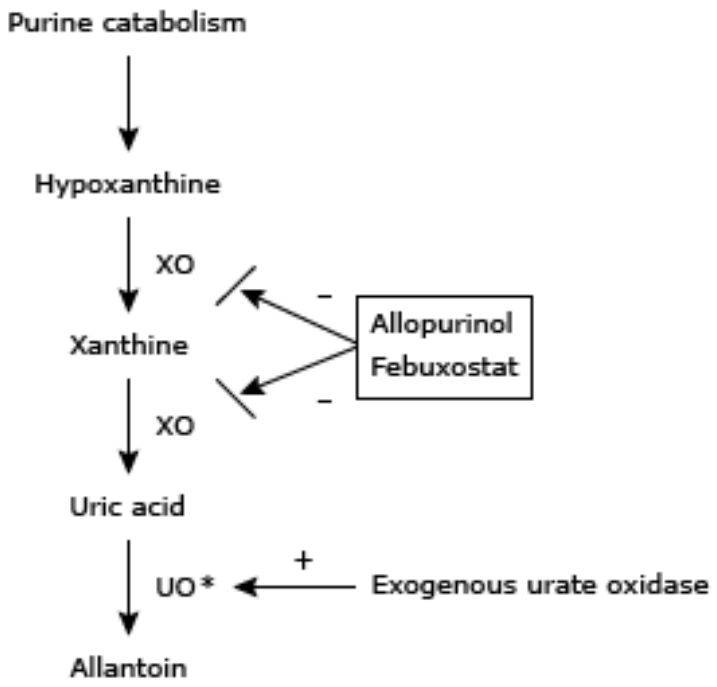
Allopurinol Side Effects

- There is a strong genetic association between inheritance of the HLA-B*58:01 allele and severe cutaneous adverse events with allopurinol, particularly in certain Asian populations (Han Chinese, Thai, Korean).
- Screening is advised by several expert groups for high-risk patients, with avoidance of the drug in those with the inherited high-risk allele
- However, the widespread application of screening in other populations is less clear because not all patients with allopurinol-induced severe cutaneous adverse events carry the allele
- Given the time it takes to carry out HLA testing, Asian patients who are in need of urgent chemotherapy for a tumor at high or moderate risk of TLS should probably receive rasburicase instead of allopurinol

BMJ. 2015;351:h4848. Epub 2015 Sep 23

Xanthinuria

- Allopurinol increases levels of hypoxanthine and xanthine
- Xanthine is much less soluble than uric acid
- Risk for xanthine precipitation in the tubules, resulting in xanthine nephropathy or xanthine stone formation
- Because the serum xanthine level is not routinely measured, its effect on the risk of acute kidney injury is not certain
- Not an issue with rasburicase



Rasburicase

- Recombinant urate oxidase which catalyzes uric acid formation to soluble allantoin
- Rapid onset (within 4 hours)
- Indicated for a **single course** of treatment for the management of plasma uric acid levels in pediatric and adult patients with leukemia, lymphoma, and solid tumor malignancies who are receiving anti-cancer therapy expected to result in tumor lysis and elevation of plasma uric acid.
  - 0.15-0.2 mg/kg/d as 30 min IV infusion for up to 7 days guided by uric acid levels
  - 1-2 lower fixed-dose doses (3-7.5 mg) also effective—and much less expensive
  - Average duration of therapy is 2 days
- Recommended if:
  - Baseline pre-chemotherapy uric acid > 8 mg/dL
  - Baseline kidney dysfunction
  - Heart failure- inability to tolerate aggressive hydration regimens

Rasburicase

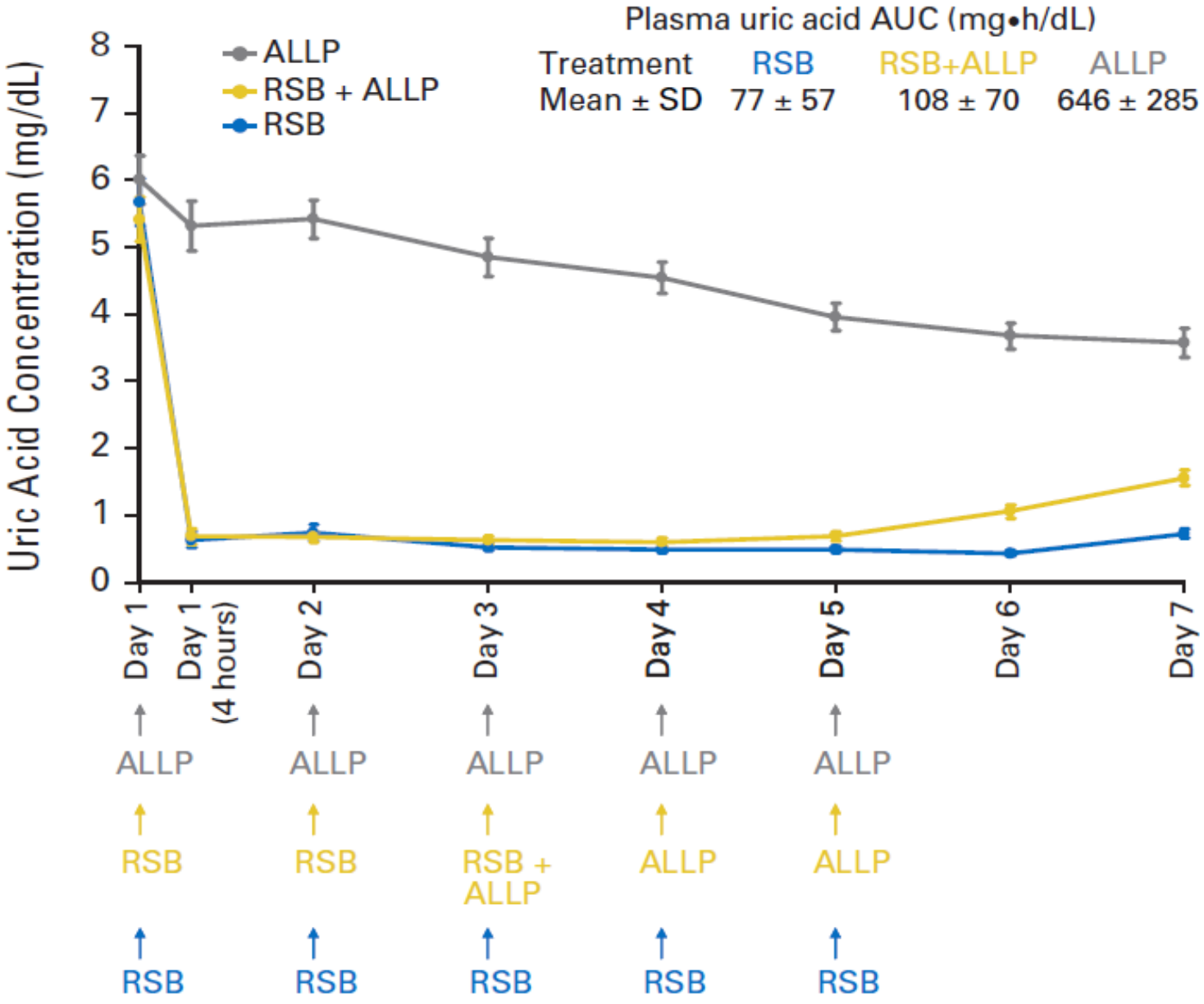
- No drug interactions
- Response rate is essentially 100%
- 10-20% of patients develop anti-rasburicase antibodies
  - Some IgE
  - Some IgG—neutralizing

- Cost--~$390 for 1.5 mg vial; ~ $4000 per day for adult at recommended dose o f 0.2 mg/kg

Rasburicase: Data

- In adults, one phase 3 trial comparing allopurinol and rasburicase:
  - 280 adults with hematologic malignancies at risk for TLS (mainly AML) randomly assigned to rasburicase alone (on days 1 to 5), rasburicase (on days 1 to 3) plus oral allopurinol (300 mg daily on days 3 to 5), or allopurinol alone (300 mg daily on days 1 to 5)
  - Compared with allopurinol alone, normalization of serum uric acid (≤7.5 mg/dL) at days 3 to 7 was achieved by a **significantly higher percentage of patients receiving rasburicase alone (87 versus 66%)**
  - Both rasburicase groups were also superior to allopurinol alone in time to control serum uric acid (**median time, 4 hours with rasburicase with or without allopurinol versus 27 hours with allopurinol alone**).
  - The incidence of laboratory TLS was significantly lower with rasburicase as compared with allopurinol alone (41 versus 21 %), and tended to be lower with the addition of rasburicase to allopurinol (27 versus 21 %with allopurinol alone).
  - No difference in clinical TLS

J Clin Oncol. 2010;28(27):4207. Epub 2010 Aug 16


Plasma uric acid AUC (mg•h/dL)
Treatment RSB RSB+ALLP ALLP
Mean ± SD 77 ± 57 108 ± 70 646 ± 285
ALLP
RSB + ALLP
RSB
Uric Acid Concentration (mg/dL)
0
1
2
3
4
5
6
7
8
Day 1
Day 1 (4 hours)
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
ALLP
ALLP
ALLP
ALLP
ALLP
RSB
RSB
RSB + ALLP
ALLP
ALLP
RSB
RSB
RSB
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Rasburicase: Outcomes

- Retrospective cohort study of administrative data
- Clinical and economic outcomes were compared between 26 rasburicase-treated patients and 104 propensity score matched allopurinol-treated controls receiving treatment for cancer between 2005 and 2009
- Rasburicase treatment was associated with a significant 5.3 mg/dL greater reduction in uric acid within two days of treatment initiation ($p<0.0001$), a shorter length of stay in the intensive care unit (by 2.5 days, $p<0.0001$), a shorter total length of hospital stay (by five days, $p = 0.02$), and lower total health care costs per patient per hospitalization (by $20,038, $p<0.02$) as compared with allopurinol treatment.

Clin Lymphoma Myeloma Leuk. 2017;17(3):173. Epub 2016 Nov 21

Rasburicase--Cautions

- Anaphylaxis risk (more common with repeated use)
- Contra-indicated with G6PD deficiency
  - Hydrogen peroxide released: uric acid→allantoin
  - Screen those at high risk
- Methemoglobinemia risk
- Interferes with uric acid measurement
  - Collect blood specimen in chilled heparinized tube, immerse in ice, assay within 4 hours
- Start allopurinol after therapy to control uric acid levels.

< 1% of treated patients

Febuxostat

- **Febuxostat:**
  - **Non-purine analogue xanthine oxidase inhibitor**
  - **Useful in those unable to tolerate allopurinol**
  - **No effect on other purine and pyrimidine metabolic pathways**
  - **One study for prevention of TLS (FLORENCE Trial) showed superior efficacy in lowering uric acid but no difference in outcomes v. allopurinol**
  - **Hepatic metabolism with ~50% excreted in urine**
    - **< 5% excreted as unchanged drug**
  - **No dose adjustment for low GFR**
  - **UA lowering effect is > than allopurinol (demonstrated in gout)**
  - **Concern for higher rate of hepatotoxicity**

Ann Oncol. 2015 Oct;26(10):2155-61. Epub 2015 Jul 27

Treatment Issues

- Despite appropriate prophylaxis: 3-5% of patients develop laboratory and/or clinical TLS
- Can also spontaneously
- Patients who present with or develop TLS during therapy should receive intensive supportive care with continuous cardiac monitoring and measurement of electrolytes, creatinine, and uric acid every four to six hours
- Effective management involves treating electrolyte abnormalities, the use of rasburicase at 0.2 mg/kg (if it was not given initially) with repeated doses as necessary, attempting to wash out the obstructing uric acid crystals with fluids with or without a loop diuretic, and the appropriate use of renal replacement therapy

Treatment: Hypocalcemia

- Symptomatic hypocalcemia should be treated with calcium at the lowest doses required to relieve symptoms.
- To avoid calcium-phosphate precipitation, most symptomatic acutely hypocalcemic patients with hyperphosphatemia due to TLS (particularly if the calcium phosphate product is >60 mg2 per dL^2)should not be treated with calcium until hyperphosphatemia is corrected.
- In most situations, clinicians should use other oral phosphate binders, even though there are no good studies demonstrating efficacy
- However, patients with severe symptoms of hypocalcemia (eg, tetany or cardiac arrhythmia) should be considered for calcium replacement regardless of the phosphate level. Asymptomatic patients with hypocalcemia do not require treatment.

Howard SC, Jones DP, Pui CH. The Tumor Lysis Syndrome. N Engl J Med 2011; 364:1844

Dialysis in TLS

- Much less common since introduction of rasburicase and hyperuricemia seldom indication
- At first sign of TLS
  - Hemodialysis recommended first to gain immediate control of electrolyte/acid-base issues
  - Renal replacement therapy may be needed if the calcium phosphate product is ≥70 mg^2/dL^2.
  - CRRT—some recommend over HD to avoid "rebound" metabolic disturbances seen with HD but would aim for higher clearance levels (30-40 ml/kg/hr)
- Treatment of AKI and metabolic abnormalities
  - When HD required, OR of death 1.98
- Frequent or continuous treatment required for a few days to combat continuous release of cellular constituents

Garimella PS, et al Nephrology 2017; 22: 85-88

Uric Acid Clearance with Dialysis

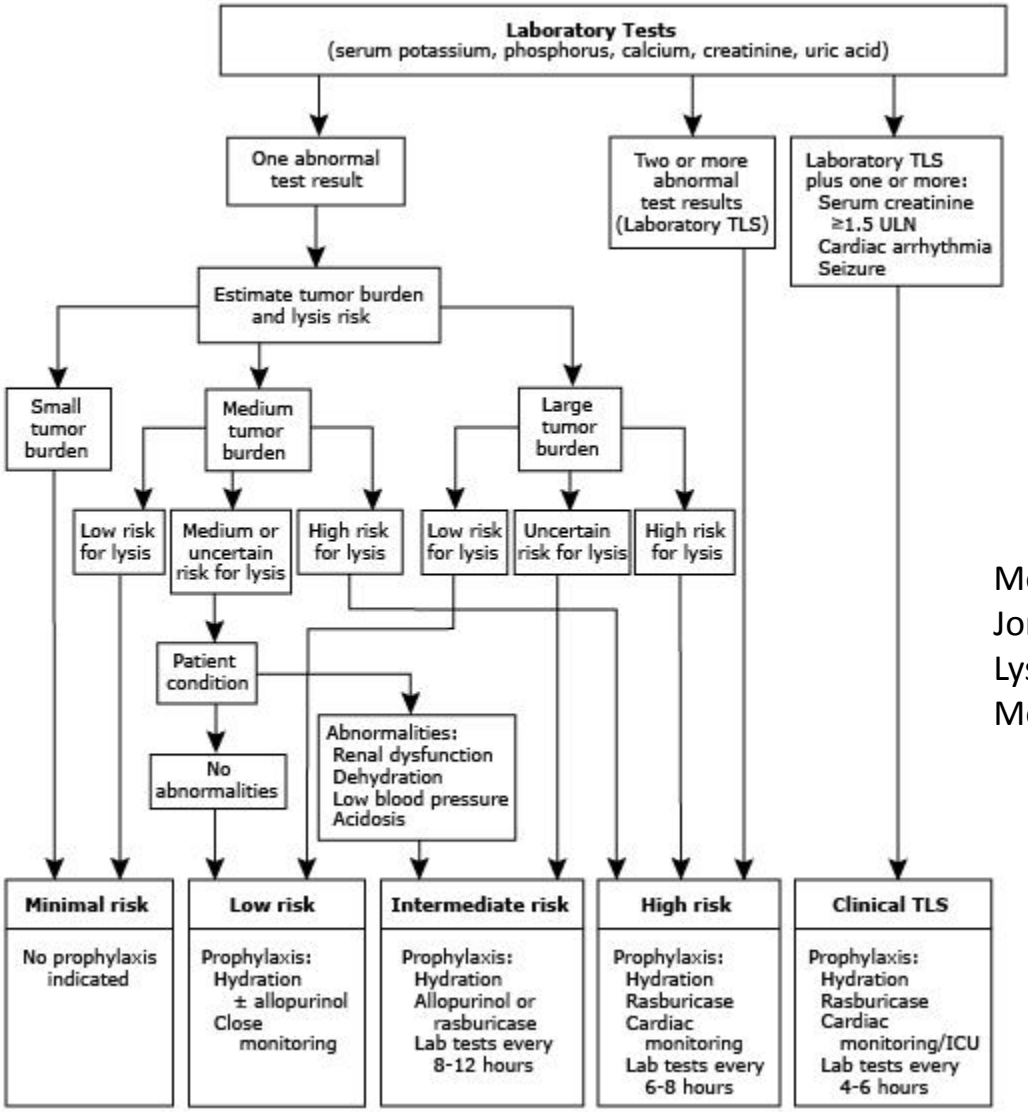
- Oliguria due to acute uric acid nephropathy responds quickly to hemodialysis with initiation of a diuresis usually occurring as the serum uric acid concentration falls below 10 mg/dL.
- Hemodialysis is efficient in removing uric acid; the clearance is approximately 70 to 100 mL/min, and serum uric acid levels fall by approximately 50 percent with each six-hour treatment
- Peritoneal dialysis is much less efficient with uric acid clearances below 10 mL/min.

Arch Intern Med. 1974;133(3):349.

Prophylaxis and Treatment of TLS

- IV fluids (≥ 100 ml/hr)
- Urinary alkalinization NOT recommended
- Allopurinol
  - Prophylaxis in patients with low-moderate risk for TLS
- Rasburicase
  - For patients with TLS or at high risk for TLS
- Treat hyperkalemia and hyperphosphatemia
- Treat only symptomatic hypocalcemia
- Monitor labs frequently

Summary



Modified from Howard SC, Jones DP, Pui CH. The Tumor Lysis Syndrome. N Engl J Med 2011; 364:1844