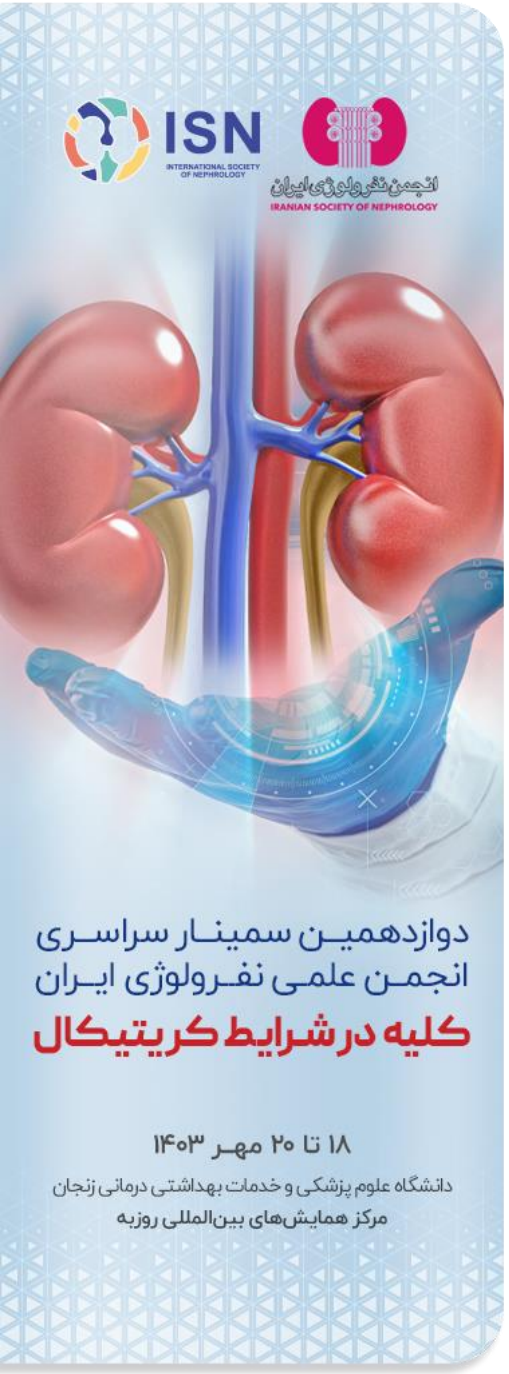

Tumor lysis syndrome (TLS)

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Case Reports in Oncology

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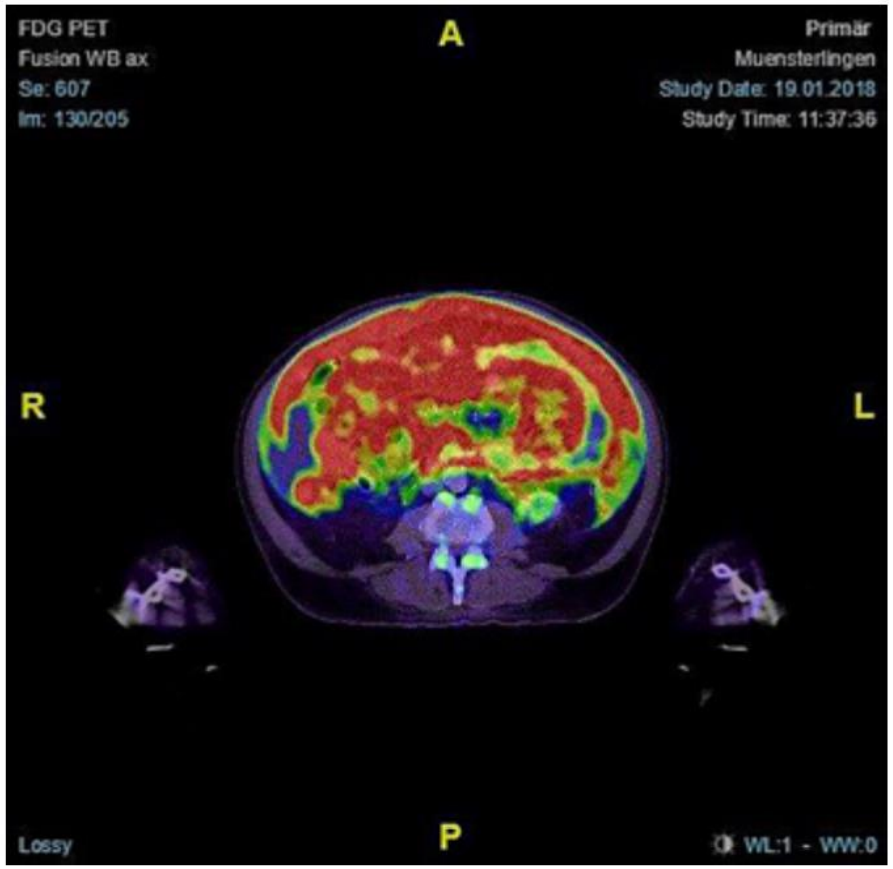
A 75-y/o pts , metastatic malignant disease with unknown primary tumor was referred for further investigation and therapy.

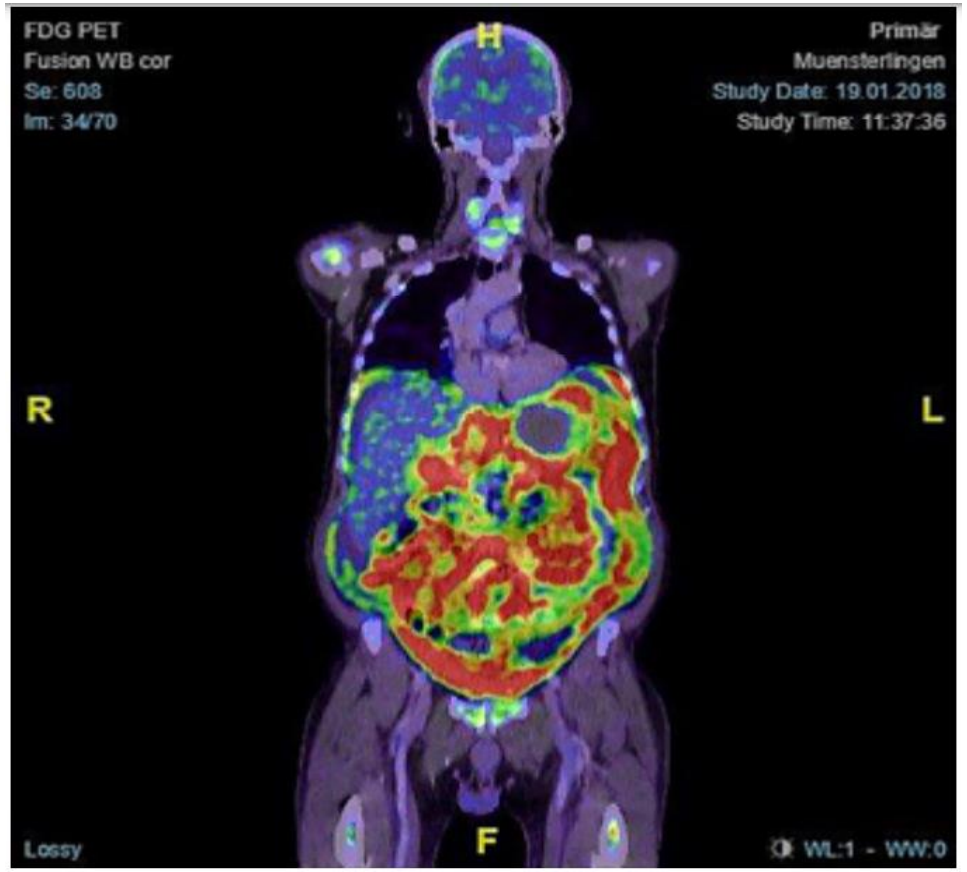
Anorexia, increase in abdominal circumference, 4-kg wt loss in 3wks, heartburn , night sweats and thirst, and progressive dyspnea.

CT of the chest and abdomen January 19, 2018, revealed the clinical picture of malignant metastatic disease.

Münsterlingen, Münsterlingen, Switzerland

The PET-CT examination revealed pronounced FDG depositions in the peritoneum, mesentery, and pleura





Leukocytosis, Hb =12.7
Creatinine=1.4mg/dl
LDH ×10 times, Uric acid × 2 times
All other electrolytes in the normal range(Ca .Ph .K .Na. Mg)
CT-guided biopsy → high-grade B-cell lymphoma

7/days after, hyperkalemia, and hyperuricemia, cr 2.92mg/dl, further increase of LDH, in parallel to the worsening clinical condition

First reported by Cohen et al. in 1980

Massive tumor cell lysis with the release of large amounts of

Potassium,

Phosphate,

Nucleic acids

into the systemic circulation

afflicting 5%-20% of cancer patients.

AN ONCOLOGIC EMERGENCY

The phosphorus concentration in malignant cells is up to four times higher than in normal cells

Hyperphosphatemia

1. precipitation of calcium phosphate
2. metastatic calcification(soft tissues, kidney)
3. AKI

$Ca \times pi > 60\ mg_2/dL_2$

Precipitation in the
renal tubules →AKI
heart →cardiac arrhythmias

Hypocalcemia

1. Paresthesia (fingers, toes, circumoral regions)
2. increased neuromuscular irritability
3. carpopedal spasm, bronchospasm, laryngospasm
4. seizures

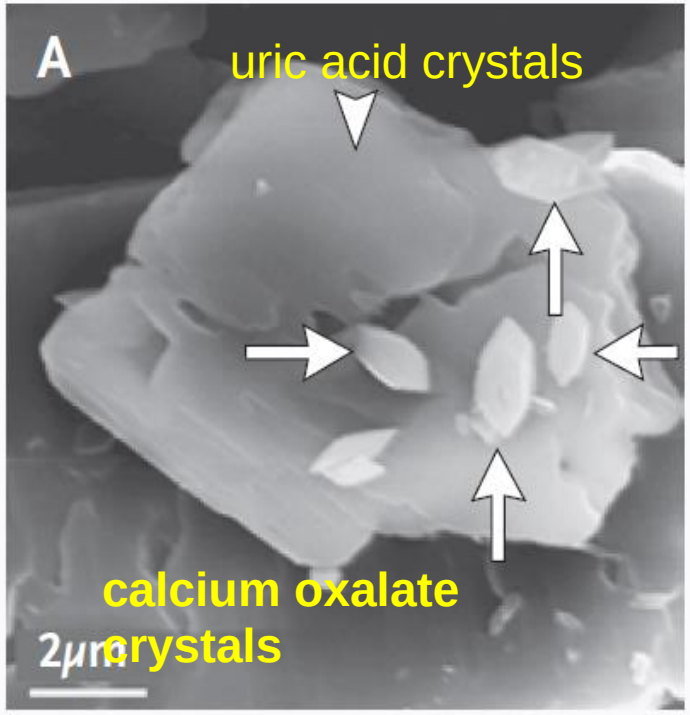
Hyperkalemia

1. sinus bradycardia.
2. Heart block,
3. cardiac arrest ,
4. Skeletal muscle paralysis

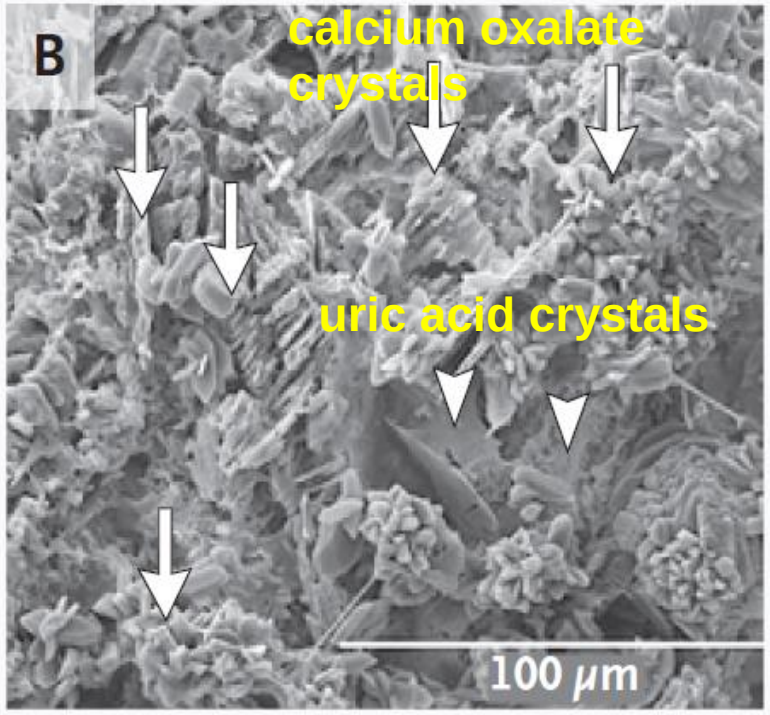
HYPERURICEMIA

1. **precipitation in the renal tubules,**
2. *Induce renal vasoconstriction*
3. *Impaired autoregulation,*
4. *Decreased renal blood flow*
5. *Inflammation,*

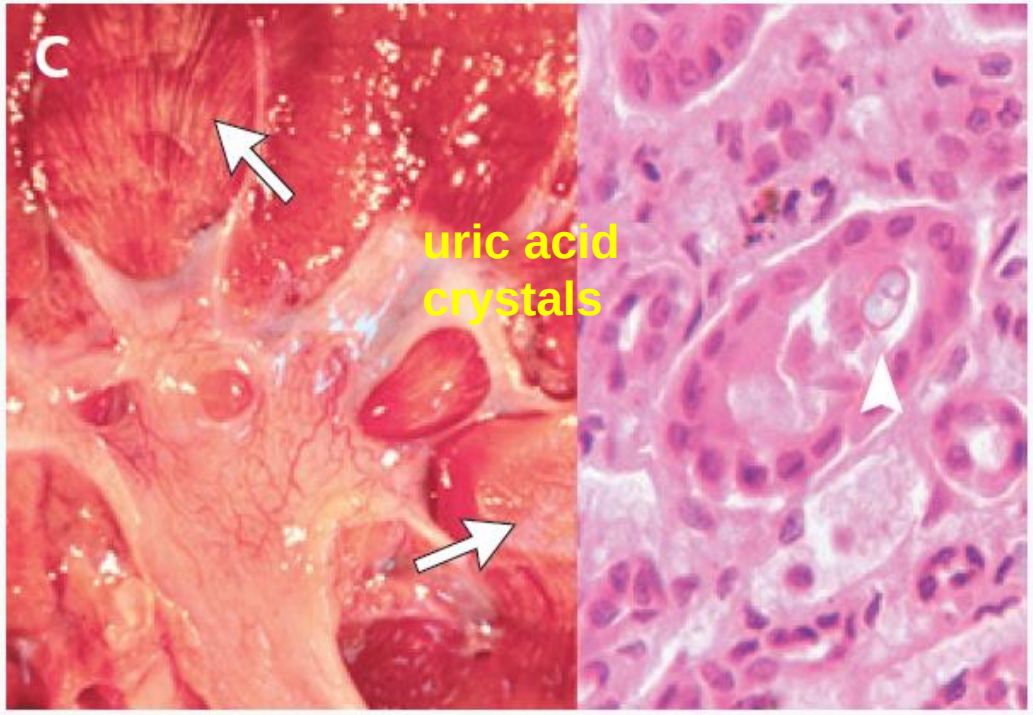
resulting in AKI



large uric acid crystals (arrowhead), which served as seeds for the formation of calcium oxalate crystals (arrows)

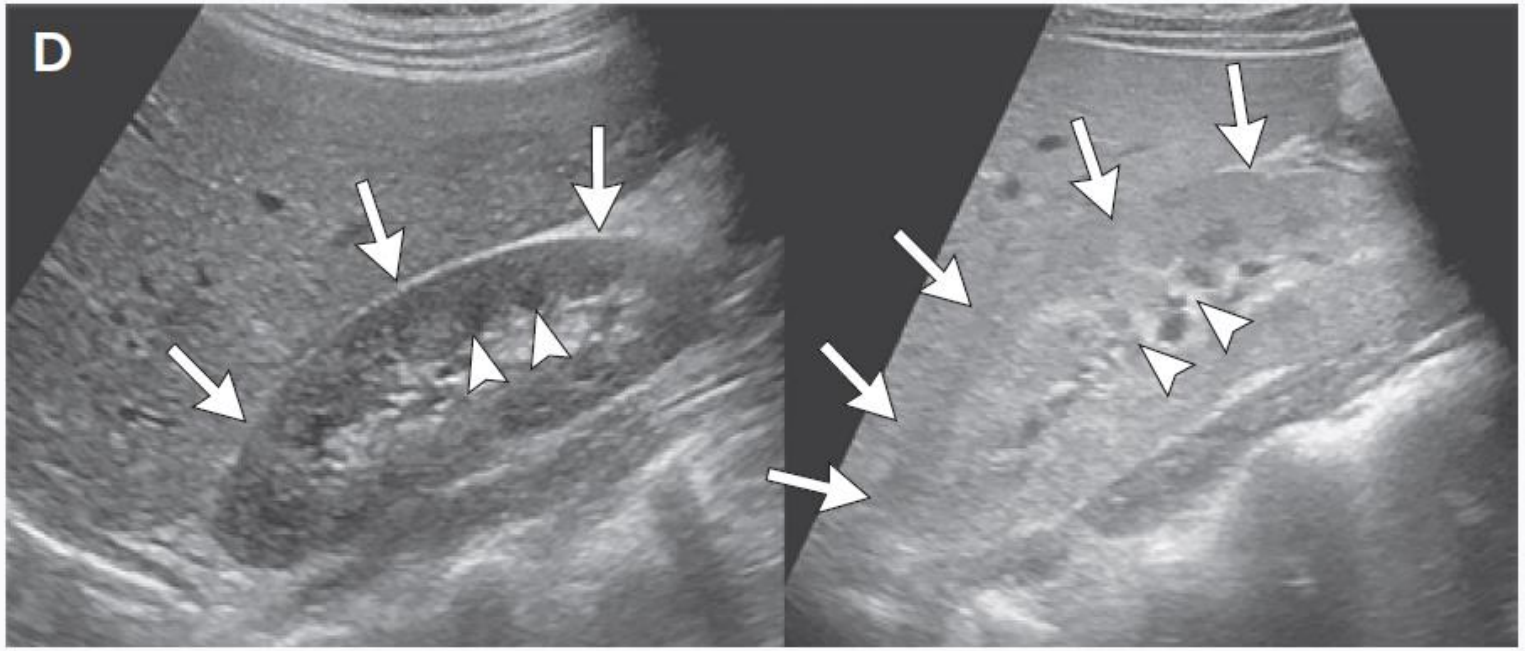


numerous small calcium oxalate crystals (arrows) formed on larger uric acid crystals (arrowheads).

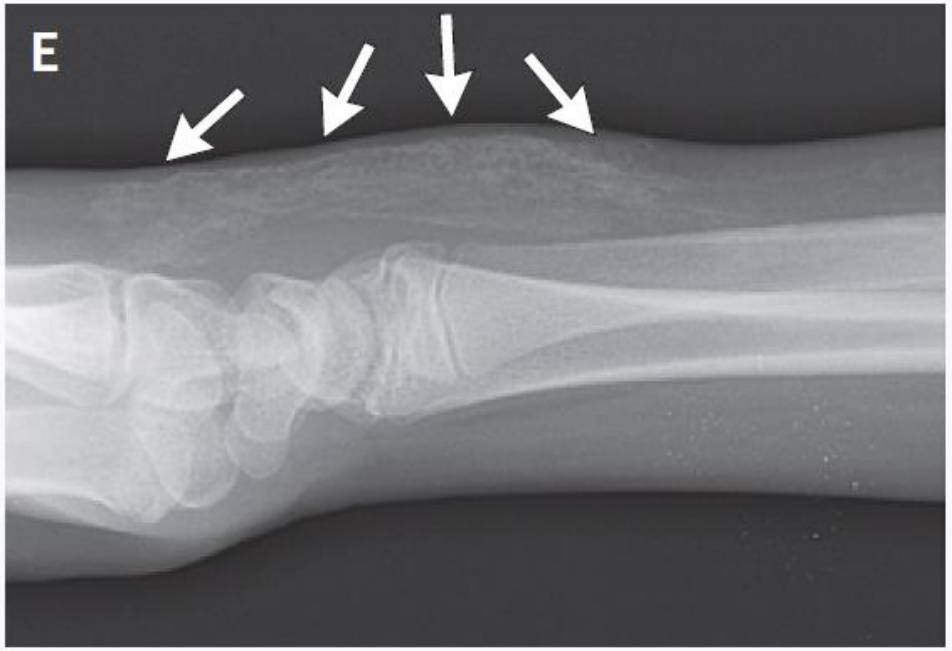


Linear yellow streaks of precipitated uric acid in the renal medulla are shown in the left panel (arrows); a single tubule containing a
uric acid crystal (arrowhead) is shown in the right panel.

Uric acid precipitates readily in the presence of calcium phosphate crystals, and calcium phosphate precipitates readily in the presence of uric acid crystals.



loss of the normal corticomedullary differentiation (arrowheads) and poor visualization of the renal pyramids. The brightness is similar to that of the adjacent liver (arrows), and the kidney is abnormally enlarged



Several weeks after the treatment of hypocalcemia with multiple doses of IV
calcium carbonate, Soft-tissue calcification of the dorsum of the distal forearm

CLINICAL MANIFESTATIONS

- Nausea, vomiting, diarrhea, anorexia,
- Lethargy, muscle cramps, tetany, syncope, seizures
- Hematuria,
- Heart failure, cardiac dysrhythmias
- Flank pain
- Sudden death

DEFINITION

1. The Hande-Garrow Criteria
2. The Cairo-Bishop Criteria
3. The Expert TLS Panel Consensus

	Hande and Garrow 1993
Clinical criteria	L-TLS + one or more of the following: • K >6 mmol/L • Cr >221 μmol/L • Ca <1.5 mmol/L • The development of a life-threatening arrhythmia or sudden death
Laboratory criteria	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the upper limit of normal, or • 25% decline in serum Ca below the lower limit of normal within 4 days of chemotherapy

	Hande and Garrow 1993	Cairo and Bishop 2004
Clinical criteria	L-TLS + one or more of the following: • K >6 mmol/L • Cr >221 µmol/L • Ca <1.5 mmol/L • The development of a life-threatening arrhythmia or sudden death	L-TLS + one or more of the following: • Kidney injury with serum Cr ≥1.5× upper normal limit • Cardiac arrhythmias/sudden death • Seizures
Laboratory criteria	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the upper limit of normal, or • 25% decline in serum Ca below the lower limit of normal within 4 days of chemotherapy	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the baseline, or • 25% decline in serum Ca below the baseline within 3 days before or 7 days after the initiation of chemotherapy

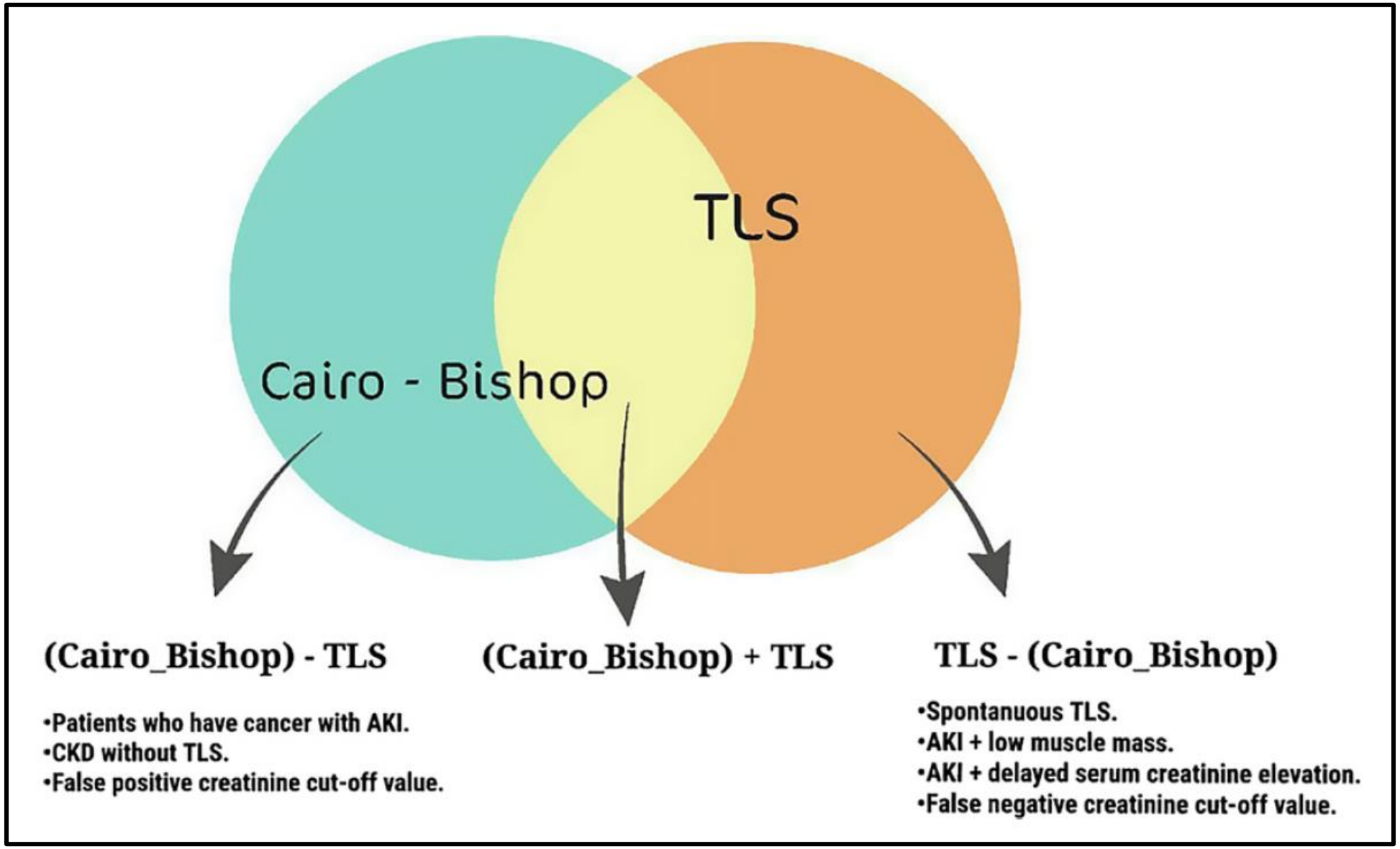
CAIRO-BISHOP DEFINITION

Element	Value	Change from baseline
Uric acid	≥476 micromol/L (8 mg/dL)	25% increase
Potassium	≥6.0 mmol/L (or 6 mEq/L)	25% increase
Phosphorus	≥2.1 mmol/L (6.5 mg/dL) for children or ≥1.45 mmol/L (4.5 mg/dL) for adults	25% increase
Calcium	≤1.75 mmol/L (7 mg/dL)	25% decrease

In the setting of adequate volume expansion

CAIRO-BISHOP GRADING

Organ dysfunction	Stage		
	1–3	4	5
Serum creatinine	1: 1.5× ULN 2: >1.5–3.0× ULN 3: >3.0× ULN	>3.0–6.0× ULN	Death
Cardiac arrhythmias	1: No intervention required 2: Asymptomatic, drug intervention required 3: Symptomatic, cannot be controlled with medication, controlled with defibrillator	Life-threatening, arrhythmias with signs of cardiac decompensation	
Seizures	1: None 2: Short generalized seizure, seizures controlled by medication, focal seizures 3: Seizures with impaired consciousness, generalized seizures	Seizures of any kind that are prolonged, repetitive	

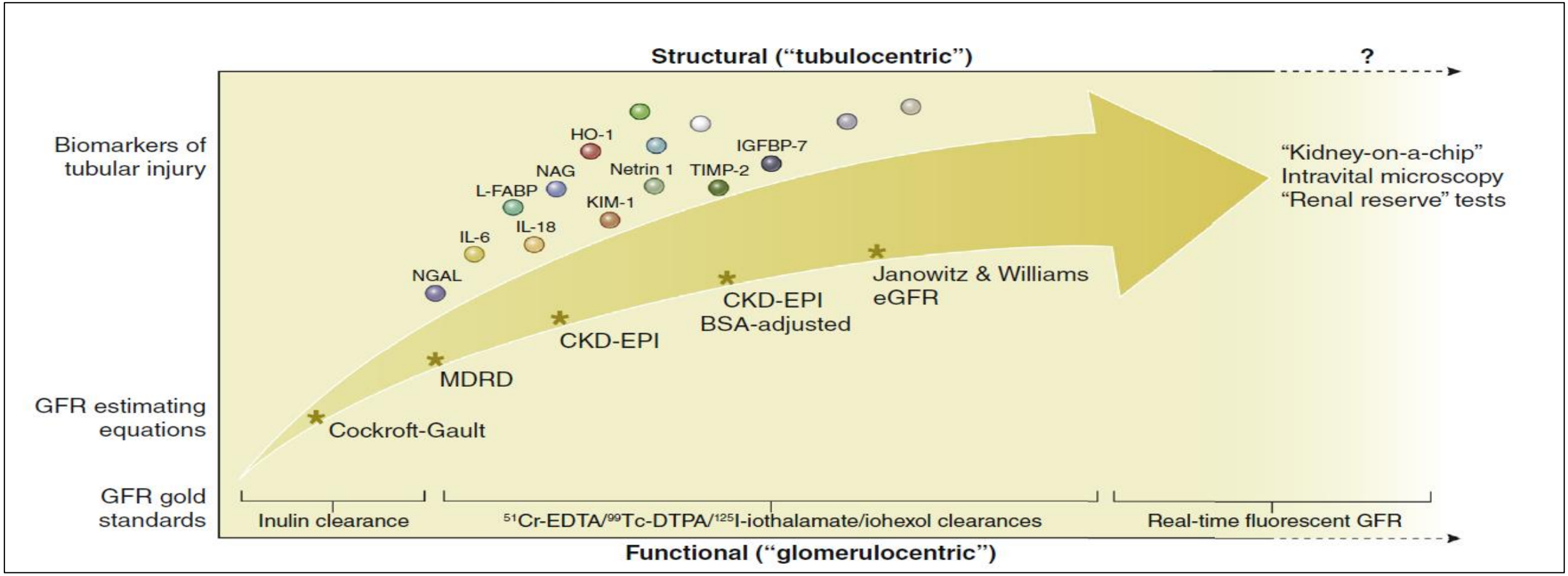

TLS
Cairo - Bishop
(Cairo_Bishop) - TLS
•Patients who have cancer with AKI.
•CKD without TLS.
•False positive creatinine cut-off value.
(Cairo_Bishop) + TLS
TLS - (Cairo_Bishop)
•Spontanuous TLS.
•AKI + low muscle mass.
•AKI + delayed serum creatinine elevation.
•False negative creatinine cut-off value.

	Hande and Garrow 1993	Cairo and Bishop 2004
Clinical criteria	L-TLS + one or more of the following: • K >6 mmol/L • Cr >221 μmol/L • Ca <1.5 mmol/L • The development of a life-threatening arrhythmia or sudden death	L-TLS + one or more of the following: • Kidney injury with serum Cr ≥1.5× upper normal limit • Cardiac arrhythmias/sudden death • Seizures
Laboratory criteria	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the upper limit of normal, or • 25% decline in serum Ca below the lower limit of normal within 4 days of chemotherapy	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the baseline, or • 25% decline in serum Ca below the baseline within 3 days before or 7 days after the initiation of chemotherapy

	Hande and Garrow 1993	Cairo and Bishop 2004	The expert TLS panel consensus 2008
Clinical criteria	L-TLS + one or more of the following: • K >6 mmol/L • Cr >221 μmol/L • Ca <1.5 mmol/L • The development of a life-threatening arrhythmia or sudden death	L-TLS + one or more of the following: • Kidney injury with serum Cr ≥1.5× upper normal limit • Cardiac arrhythmias/sudden death • Seizures	The same in Cairo-Bishop criteria, but they exclude hypocalcemia as a criterion for diagnosing L-TLS
Laboratory criteria	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the upper limit of normal, or • 25% decline in serum Ca below the lower limit of normal within 4 days of chemotherapy	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the baseline, or • 25% decline in serum Ca below the baseline within 3 days before or 7 days after the initiation of chemotherapy	

Any symptomatic hypocalcemia should constitute clinical TLS

	Hande and Garrow 1993	Cairo and Bishop 2004	The expert TLS panel consensus 2008
Clinical criteria	L-TLS + one or more of the following: • K >6 mmol/L • Cr >221 µmol/L (2.5mg/dl) • Ca <1.5 mmol/L • The development of a life-threatening arrhythmia or sudden death	L-TLS + one or more of the following: • Kidney injury with serum Cr ≥1.5× upper normal limit • Cardiac arrhythmias/sudden death • Seizures	The same in Cairo-Bishop criteria, but they exclude hypocalcemia as a criterion for diagnosing L-TLS
Laboratory criteria	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the upper limit of normal, or • 25% decline in serum Ca below the lower limit of normal within 4 days of chemotherapy	Two of the following changes: • 25% increase in serum P, K, UA, or BUN concentrations above the baseline, or • 25% decline in serum Ca below the baseline within 3 days before or 7 days after the initiation of chemotherapy	
Limitations	• They did not explain the basis by which they chose the diagnostic value of metabolic derangements to be below or over 25% ? • They did not include spontaneous TLS	• They did not exclude patients with CKD who had a serum creatinine more than 1.5 times the upper limit of normal and did not include patients with AKI who had small muscle mass that will lead to creatinine increase in the range lower than the 1.5 times of the upper limit of normal • They did not include spontaneous TLS	• They depended mainly on the Cairo-Bishop criteria, so it carries the same limitations • They added renal failure as a risk factor for developing TLS



kidney function not only is limited to GFR changes but also tubular and vascular, urinalysis and kidney imaging studies should also be considered before therapeutic decisions are taken

DESPITE THE PROPHYLACTIC TREATMENT

1. Approximately 3 to 5 percent of patients develop lab / clinical TLS

2. Uric acid and calcium-phosphate crystals are rare during TLS-induced AKI

Tumor Lysis Syndrome and AKI: Beyond Crystal Mechanisms

JASN 33: 1154–1171, 2022

Characteristic	TLS (*n*=94)	Patients with TLS-AKI (*n*=83)	Patients with Non-AKI TLS (*n*=11)	*P* Value
Male sex, *n* (%)	65 (69.1)	58 (69.9)	7 (63.6)	0.42
Age (yr), mean±SD	58±12	61±14	50±20	0.67
Past history of CKD, *n* (%)	6 (6.4)	5 (6.0)	1 (9.0)	0.69
Baseline serum creatinine levels (μmol/L), median (IQR)	88.0 (80.0–97.0)	88.0 (80.0–97.0)	97.0 (80.0–106.0)	0.71
Past history of hypertension, *n* (%)	35 (37.2)	33 (39.7)	2 (18.2)	0.16
Chronic cardiac dysfunction, *n* (%)	11 (11.7)	11 (13.3)	0	0.19
Diabetes, *n* (%)	12 (12.7)	11 (13.3)	1 (9.0)	0.69
Underlying malignancy, *n* (%)				
AML	30 (31.9)	27 (32.5)	3 (27.3)	0.73
Acute lymphoid leukemia	13 (13.8)	10 (12.0)	3 (27.3)	0.17
Lymphoma	44 (46.8)	39 (46.9)	5 (45.5)	0.92
Chronic lymphocytic leukemia	4 (4.3)	4 (4.8)	0	0.46
Myeloma	1 (1.1)	1 (1.2)	0	0.71
Nephrotoxic drugs	19 (20.2)	19 (22.9)	0	0.08
Laboratory findings at admission				
Phosphates (mmol/L), median (IQR)	2.1 (1.9–2.3)	2.1 (1.9–2.3)	2.2 (2.1–2.3)	0.7
Calcium (mmol/L), median (IQR)	1.6 (1.2–2.1)	1.6 (1.3–2.2)	1.2 (0.9–1.5)	0.02[a]
Potassium (mmol/L), median (IQR)	4.2 (3.6–4.9)	4.3 (3.6–5.1)	4.1 (3.6–4.7)	0.70
LDH (× normal) at admission, median (IQR)	4.0 (2.8–15.5)	4.0 (3.3–8.0)	20.0 (2.0–38.0)	>0.99
Serum creatinine (μmol/L), median (IQR)	157.5 (106.8–289.8)	170.0 (124.0–298.0)	78.0 (51.0–105.0)	<0.001[a]
Uric acid (mmol/L) (before rasburicase), median (IQR)	503.0 (155.0–788.0)	539.0 (165.8–862.0)	200.0 (61.0–383.0)	0.009[a]
Lactatemia (mmol/L), median (IQR)	3.9 (1.8–9.2)	4.2 (1.9–9.4)	2.4 (1.6–3.1)	0.39
Diuresis (ml/24 h), median (IQR)	665 (382–1125)	750 (400–1300)	1200 (1000–2370)	0.007[a]
SOFA at admission, median (IQR)	6 (3–10)	6 (3–10)	3 (1–3)	0.0001[a]
AKI stage 1, *n* (%)		16 (19.3)		
AKI stage 2, *n* (%)		11 (13.3)		
AKI stage 3, *n* (%)		56 (67.5)		
Treatments				
Hypouricemic therapy, *n* (%)	90 (95.7)	80 (96.4)	10 (90.9)	0.39
Need for RRT, *n* (%)		67 (80.7)	0	<0.001[a]
RRT duration (d), median (IQR)		4 (2–13)		
Need for vasopressors, *n* (%)	33 (35.1)	33 (39.8)	0	0.009
Need for mechanical ventilation, *n* (%)	46 (48.9)	44 (53.0)	2 (18.2)	0.03[a]
ICU mortality, *n* (%)	34 (36.2)	33 (39.8)	1 (9.0)	0.04[a]
28-Day mortality, *n* (%)	38 (40.4)	37 (44.6)	1 (9.0)	0.02[a]

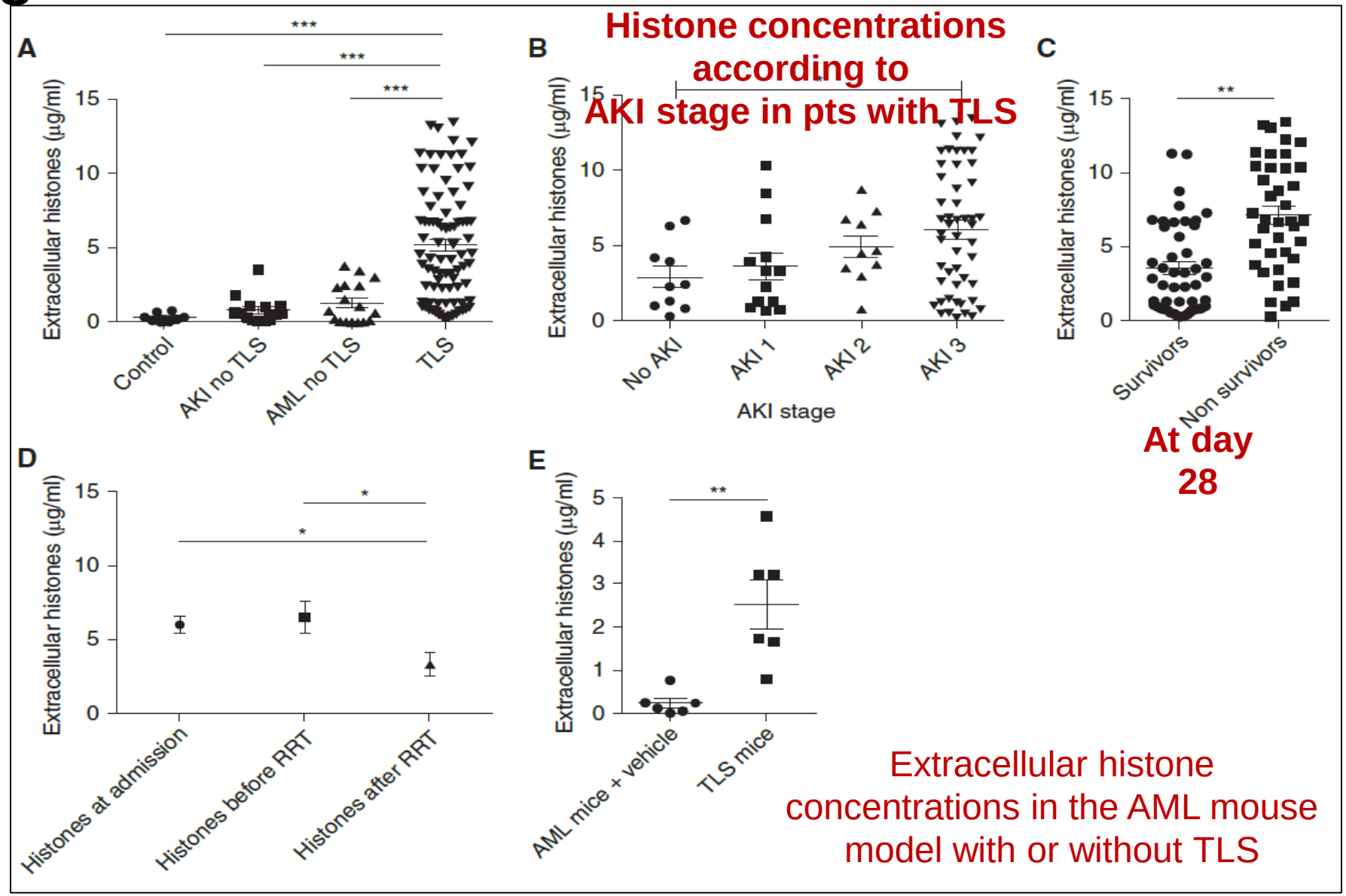
Multicenter cohort of pts with TLS plus and in vivo/ in vitro model of chemotherapy-induced TLS

doi: https://doi.org/10.1681/ASN.2021070997

Characteristics	TLS (*n*=55)	Patients with TLS-AKI (*n*=46)	Patients with Non-AKI TLS (*n*=9)	*P* Value
Male sex, *n* (%)	40 (72.7)	36 (78.3)	4 (44.4)	0.09
Age (yr), mean±SD	57±17	59±15	44±20	0.25
Past history of CKD, *n* (%)	1 (1.8)	0 (0.0)	1 (11.1)	0.16
Baseline serum creatinine levels (μmol/L), median (IQR)	75.5 (61.0–90.8)	76.5 (62.5–90.3)	67.5 (58.3–94.5)	0.71
Past history of hypertension, *n* (%)	15 (27.3)	14 (30.4)	1 (11.1)	0.42
Chronic cardiac dysfunction, *n* (%)	2 (3.6)	2 (4.3)	0 (0.0)	>0.99
Diabetes, *n* (%)	8 (14.5)	8 (17.4)	0 (0.0)	0.33
Underlying malignancy, *n* (%)				
AML	10 (18.2)	9 (19.6)	1 (11.1)	>0.99
Acute lymphoid leukemia	7 (12.7)	5 (10.9)	2 (22.2)	0.59
Lymphoma	35 (63.6)	30 (65.2)	5 (55.5)	0.71
Chronic lymphocytic leukemia	1 (1.8)	1 (2.3)	0 (0)	>0.99
Others	2 (3.6)	1 (2.3)	1 (11.1)	0.30
Nephrotoxic drugs	25 (45.5)	21 (45.7)	4 (44.4)	>0.99
Laboratory findings at admission				
Phosphates (mmol/L), median (IQR)	4.4 (4.1–5.2)	4.6 (4.1–5.2)	4.2 (3.7–4.6)	0.25
Calcium (mmol/L), median (IQR)	2.2 (2.0–2.3)	2.2 (2.0–2.3)	2.1 (1.9–2.3)	0.34
Potassium (mmol/L), median (IQR)	4.4 (4.1–5.2)	4.6 (4.1–5.2)	4.2 (3.7–4.6)	0.25
LDH at admission (UI/L), median (IQR)	2764 (1431–6750)	2764 (1431–6750)	2883 (1191–7344)	0.95
Serum creatinine (μmol/L), median (IQR)	124.0 (89.0–190.5)	124.0 (94.5–195.0)	83.5 (64.5–138.0)	0.04[a]
Uric acid (mmol/L) (before rasburicase), median (IQR)	497.0 (226.0–615.0)	520.0 (270.5–696.5)	404.0 (220.9–511.3)	0.27
AKI stage 1, *n* (%)		15 (32.6)		
AKI stage 2, *n* (%)		6 (13.0)		
AKI stage 3, *n* (%)		25 (54.4)		
Delay between ICU admission and AKI (d), median (IQR)		1 (0–1)		
Positive crystalluria, *n* (%)[b]	7 (12.7)	5 (10.8)	2 (22.2)	0.46
Weddellite crystals (calcium oxalate dihydrate)	0	0	0	>0.99
Whewellite crystals (calcium oxalate monohydrate)	2 (3.6)	2	0	>0.99
Calcium-phosphate crystals	1 (1.8)	0	1	0.16
Uric-acid crystals	3 (5.5)	2	1	0.42
Struvite (magnesium ammonium phosphate hexahydrate)	1 (1.8)	1	0	>0.99

Urine pH (day 1), median (IQR)	6.2 (5.7–6.5)	6.2 (5.3–6.5)	6.2 (5.9–6.3)	0.94
Calcium urinary excretion, median (IQR)	0.1 (0.0–0.5)	0.13 (0.0–0.5)	0.1 (0.0–0.5)	0.76
Calcium-creatinine urinary ratio, mmol/mmol (day 1)				
Phosphate urinary excretion (Ph/creat), mmol/mmol (day 1) median (IQR)	5.6 (3.2–7.2)	4.9 (3.1–7.1)	7.1 (3.4–7.9)	0.39
Uric acid excretion (Uric/creat), mmol/mmol (day 1) median (IQR)	0.5 (0.1–0.9)	0.4 (0.1–1.0)	0.5 (0.0–0.7)	0.49
Uric acid supersaturation index (day 1), median (IQR)	1.5 (0.1–4.3)	1.3 (0.1–3.5)	1.4 (0.1–2.6)	0.94
Calcium phosphate supersaturation index (day 1), median (IQR)	0.21 (0.10–0.45)	0.20 (0.08–0.47)	0.28 (0.18–0.61)	0.36
Treatments				
Rasburicase use, *n* (%)	46 (83.6)	38 (82.6)	8 (88.9)	>0.99
Delay between ICU admission and first rasburicase administration (d), median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.82
Allopurinol use, *n* (%)	9 (16.4)	8 (17.4)	1 (11.1)	>0.99
Need for RRT, *n* (%)	25 (45.5)	25 (54.4)	0	0.03[a]
RRT duration (d), median (IQR)	2 (1–4)	2 (1–4)		
Need for vasopressors, *n* (%)	9 (16.4)	8 (17.4)	1 (11.1)	>0.99
Need for mechanical ventilation, *n* (%)	11 (20)	10 (21.7)	1 (11.1)	0.67
ICU mortality, *n* (%)	9 (16.4)	7 (15.2)	2 (22.2)	0.63
28-Day mortality, *n* (%)	20 (36.4)	16 (34.8)	4 (44.4)	0.71

Circulating histones are elevated in patient plasma during TLS and in a mouse model of TLS



1. Endothelial dysfunction participates in TLS-induced AKI;

2. Plasma levels of extracellular histones are hugely increased during TLS,

3. Extracellular histones induce renal endothelial dysfunction in vitro and in vivo

4. Nonanticoagulant heparin can neutralize extracellular histones and prevent endothelial damage.

Intrinsic tumor-related risk factors

1. High tumor cell proliferation rate
2. Chemosensitivity of the malignancy
3. Large tumor burden, manifested as bulky disease >10 cm in diameter and/or WBC count >50,000/ microl,
4. pretreatment serum LDH >2 times UNL
5. Organ infiltration,
6. Bone marrow involvement

Clinical features risk factors

1. Pretreatment hyperuricemia (>7.5 mg/dL [446 micromol/L]) or hyperphosphatemia (>4.5 mg/dL [1.44 micromol/L])
2. A preexisting nephropathy or exposure to nephrotoxins
3. Oliguria and/or acidic urine
4. Volume depletion or inadequate volume expansion during treatment

NONHEMATOLOGIC SOLID TUMORS

Breast cancer, Melanoma

Small cell carcinoma (mostly the lung)

Neuroblastoma, Medulloblastoma , Germ cell tumors

Ovarian cancer, Squamous cell carcinoma of the vulva

Metastatic colorectal cancer, GIST Hepatocellular carcinoma

Renal cell treated with pazopanib, Urothelial cancer, prostate cancer

Medullary thyroid cancer treated with selpercatinib

MEDICATIONS

1. Combination cytotoxic chemotherapy
2. Glucocorticoids alone in patients with NHL and ALL(Case reports)
3. Rituximab in NHL, Obinutuzumab (anti-CD20)diffuse large B-cell lymphoma
4. Bortezomib in MM
5. Imatinib for CML
6. Venetoclax, a BCL-2 inhibitor for CLL or AML,
7. Radiation therapy alone for NHL and ALL
8. CAR T-cell therapy for lymphoid malignancy
9. Docetaxel
10. Pazopanib, a tyrosine kinase inhibitor(highly albumin bound)

Spontaneous TLS

NHL and acute leukemia, ?inflammatory breast cancer

Spontaneous TLS is associated with hyperuricemia but frequently without hyperphosphatemia

Malignancies at high risk for developing tumor lysis syndrome

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

RISK STRATIFICATION SYSTEM

Low risk disease (LRD)	Intermediate risk disease (IRD)	High risk disease (HRD)
Most solid tumors	Rare, highly chemotherapy-sensitive solid tumors (eg, neuroblastoma, germ cell tumor, small-cell lung cancer) with bulky or advanced stage disease	N/A
MM	Plasma cell leukemia	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, rituximab, or lenalidomide, or venetoclax and lymph node ≥5 cm **or** absolute lymphocyte count ≥25 x 10^9/L, and/or those with high WBC ≥50 x 10^9/L	CLL treated with venetoclax and lymph node ≥10 cm, **or** lymph node ≥5 cm **and** absolute lymphocyte count ≥25 x 10^9/L and elevated baseline uric acid.
AML and WBC <25 x 10^9/L and LDH <2 x ULN	AML with WBC 25 to 100 x 10^9/L	AML and WBC ≥100 x 10^9/L
	AML and WBC <25 x 10^9/L and LDH ≥2 x ULN	
Adult intermediate grade NHL and LDH within normal limits	Adult T cell leukemia/lymphoma, diffuse large B-cell, transformed, and mantle cell lymphomas with LDH > ULN, non-bulky	Adult T cell leukemia/lymphoma, diffuse large B-cell, transformed, and mantle cell lymphomas 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
		Other ALL and WBC ≥100 x 10^9/L and/or LDH ≥2 x ULN
N/A	Burkitt lymphoma and LDH <2 x ULN	Burkitt lymphoma stage III/IV and/or LDH ≥2 x ULN
N/A	Lymphoblastic lymphoma stage I/II and LDH <2 x ULN	Lymphoblastic lymphoma stage III/IV and/or LDH ≥2 x ULN
N/A	N/A	Intermediate risk disease with renal dysfunction and/or renal involvement
		Intermediate risk disease with uric acid, potassium, and/or phosphate > ULN

Prevention and treatment

Low risk disease (LRD)	Intermediate risk disease (IRD)	High risk disease (HRD)
Most solid tumors	Rare, highly chemotherapy-sensitive solid tumors (eg, neuroblastoma, germ cell tumor, small-cell lung cancer) with bulky or advanced stage disease	N/A
MM	Plasma cell leukemia	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, rituximab, or lenalidomide, or venetoclax and lymph node ≥5 cm **or** absolute lymphocyte count ≥25 x 10^9/L, and/or those with high WBC ≥50 x 10^9/L	CLL treated with venetoclax and lymph node ≥10 cm, **or** lymph node ≥5 cm **and** absolute lymphocyte count ≥25 x 10^9/L and elevated baseline uric acid.
AML and WBC <25 x 10^9/L and LDH <2 x ULN	AML with WBC 25 to 100 x 10^9/L	AML and WBC ≥100 x 10^9/L
	AML and WBC <25 x 10^9/L and LDH ≥2 x ULN	
		ULN
N/A	N/A	Intermediate risk disease with renal dysfunction and/or renal involvement
		Intermediate risk disease with uric acid, potassium, and/or phosphate > ULN
Prophylaxis recommendations		
Monitoring	Monitoring	Monitoring
Hydration	Hydration	Hydration
±Allopurinol	Allopurinol	Rasburicase*

Routine prophylaxis of TLS intermediate or high risk
IV hydration & hypouricemic agents

INTRAVENOUS HYDRATION

- Aggressive IV hydration is the cornerstone in all pts at intermediate or high risk for TLS

2 to 3 L/m^2 daily of IV fluid ,

5 percent dextrose one-quarter normal saline,

isotonic saline →if hyponatremia or volume depletion

Urine output: 80 to 100 mL/m^2/h (2 mL/kg per hour)

- Diuretics (furosemide) to maintain the urine output,

contraindicated in patients with hypovolemia or obstructive uropathy.

optimal duration of hydration

- Depend on the drug sensitivity of tumor, it's burden, the patient's ability to drink, and renal function.
- IV hydration should be continued at least until tumor burden is largely resolved,

Urinary alkalinization

Solubility of purine analogs and calcium phosphate at pH 5.0 and 7.0.

Metabolite	pH 5.0	pH 7.0
Uric acid (mg/l)	150	2,000
Xanthine (mg/l)	50	130
Hypoxanthine (mg/l)	1,400	1,500
Calcium phosphate (mg/l)	104.47	16.55

The potential disadvantage of promoting calcium phosphate deposition in the kidney, heart, and other organs in hyperphosphatemia

Urinary alkalinization

Saline alone is as effective as alkalinization in minimizing uric acid precipitation (Acetazolamide / sodium bicarbonate)

1. Initiate when the serum uric acid level is high and discontinued when hyperphosphatemia develops.

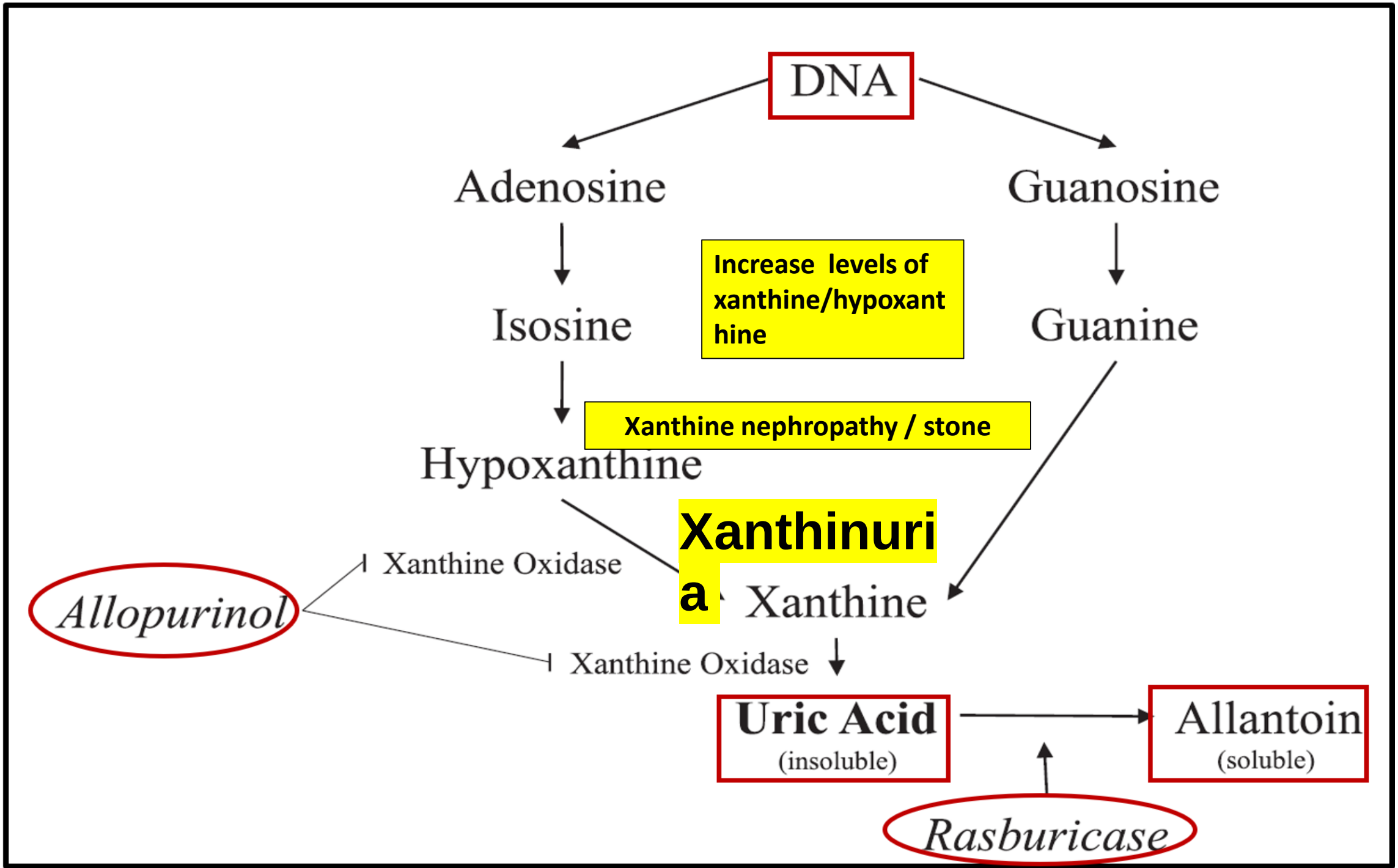
2. Not required in patients receiving rasburicase.

HYPOURICEMIC AGENTS

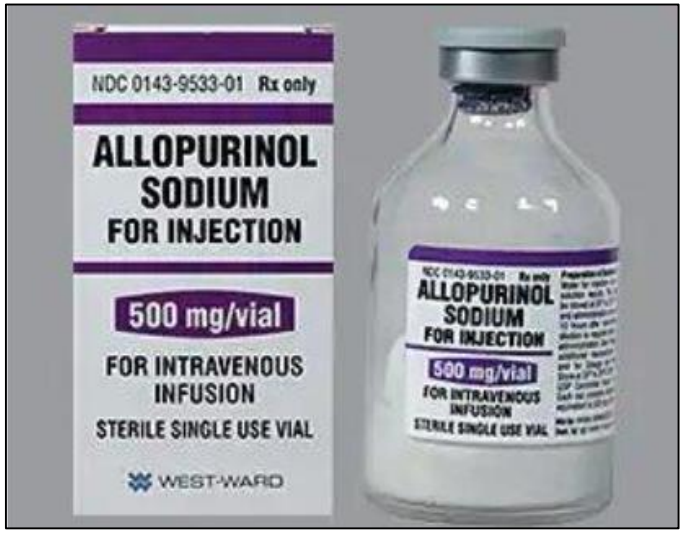
Allopurinol

Rasburicase

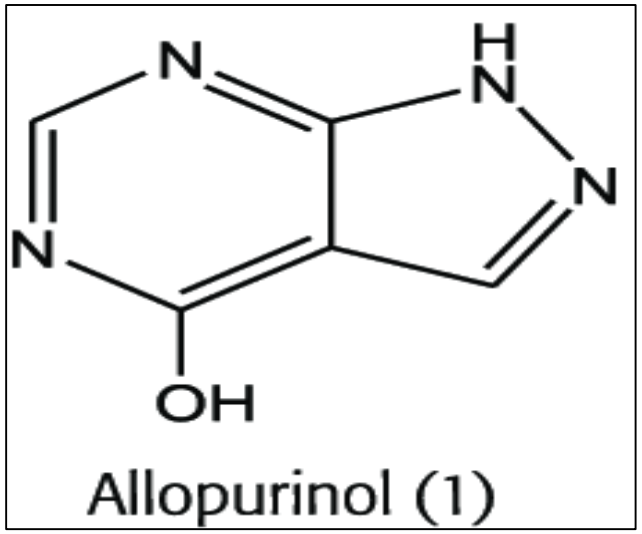
Febuxostat


DNA
Adenosine
Guanosine
Isosine
Guanine
Increase levels of xanthine/hypoxanthine
Xanthine nephropathy / stone
Hypoxanthine
Xanthinuria
Xanthine Oxidase
Allopurinol
Xanthine
Xanthine Oxidase
Uric Acid
(insoluble)
Allantoin
(soluble)
Rasburicase

Allopurinol



In intermediate risk If pretreatment uric acid <8 mg/dL although + single dose of rasburicase



Allopurinol (1)

IV 200 to 400 mg/m^2 / day, in 1-3 divided doses (max 600 mg/day)

PO 300 mg/m^2 /day every 8hours (max 800 mg / day)

CREATININE CLEARANCE

10 to 20 mL/minute,	200 mg daily
3 to 10 mL/minute,	≤100 mg daily
<3 mL/minute	≤100 mg/dose at extended intervals

ACUTE KIDNEY INJURY →50% dose reduction

- ↑ed concentration of purines and promote formation of active thioguanine nucleotides →6-MP, azathioprine reduced to $\frac{1}{3}$ TO $\frac{1}{4}$ of the usual dose

- Hypersensitivity reactions, including vasculitis and Stevens-Johnson syndrome strong genetic association between HLA-B*58:01 allele and severe cutaneous adverse events .

Rasburicase

Dose-related responses,
In adults, a flat dose of 3 mg, 0.2 mg/kg once – twice daily up to 7 days,

High-risk pts or a baseline uric acid ≥8 ➔ 0.2 mg/kg
Intermediate-risk pts ➔ 0.15 mg/kg

Allopurinol start once the serum uric acid is brought down to adequately low or normal levels.

Contraindications, ADR

- Hemolysis in G6PD deficiency, hydrogen peroxide,(byproduct of uric acid breakdown)→severe hemolysis
- Anaphylaxis may occur with the initial dose but is more common with repeated courses of rasburicase
- Methemoglobinemia
- Spuriously low uric acid sample be collected in a pre-chilled tube and should be immediately placed on ice, and the assay should be completed within four hours

Febuxostat

Selective inhibitor of xanthine oxidase

May be used in pts who cannot tolerate allopurinol in a setting in which rasburicase is either not available or contraindicated.

No needed to dose adjustment in mild to moderate renal impairment

Less drug-drug interactions than allopurinol, A bit more expensive

TREATMENT OF ESTABLISHED TUMOR LYSIS SYNDROME

1. Supportive care urine output and cardiac, measurement of electrolytes, creatinine, and uric acid every 4 to 6 hours
2. treating electrolyte abnormalities(k.ca.p)
3. Wash out the obstructing uric acid
4. **Renal replacement therapy**
5. **Early consultation with an expert in renal medicine**

INDICATIONS FOR RENAL REPLACEMENT THERAPY

- Similar to those in patients with other causes of AKI
- Lower thresholds to start RRT with TLS

rapid potassium release and accumulation, particularly if urine output is low.

RENAL REPLACEMENT THERAPY

1. Severe oliguria or anuria
2. Intractable fluid overload
3. Persistent hyperkalemia
4. Hyperphosphatemia-induced symptomatic hypocalcemia
5. A calcium-phosphate product ≥70 mg^2/dL^2

Recovery of renal function is excellent

if dialysis is initiated early

IHD

- uric acid clearance =70 to 100 mL/min(50% fall with each 6h treatment)
- Pi clearance= 60 to 100 mL/min

CVVH/CVVHD

- Well tolerate, effective
- Pi clearance =40 mL/min

In CAVHD dialysate flow rate of 4L/h

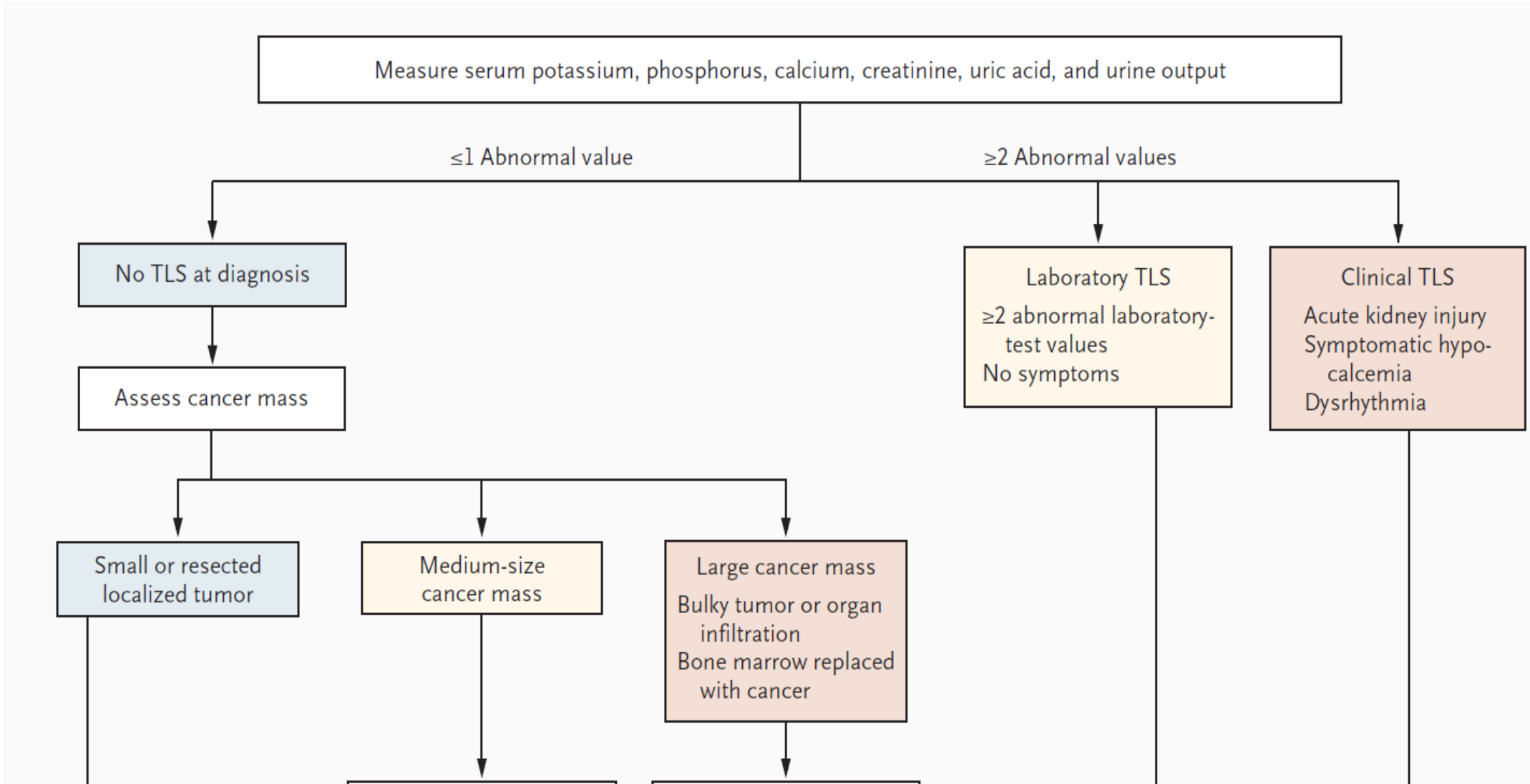
PD

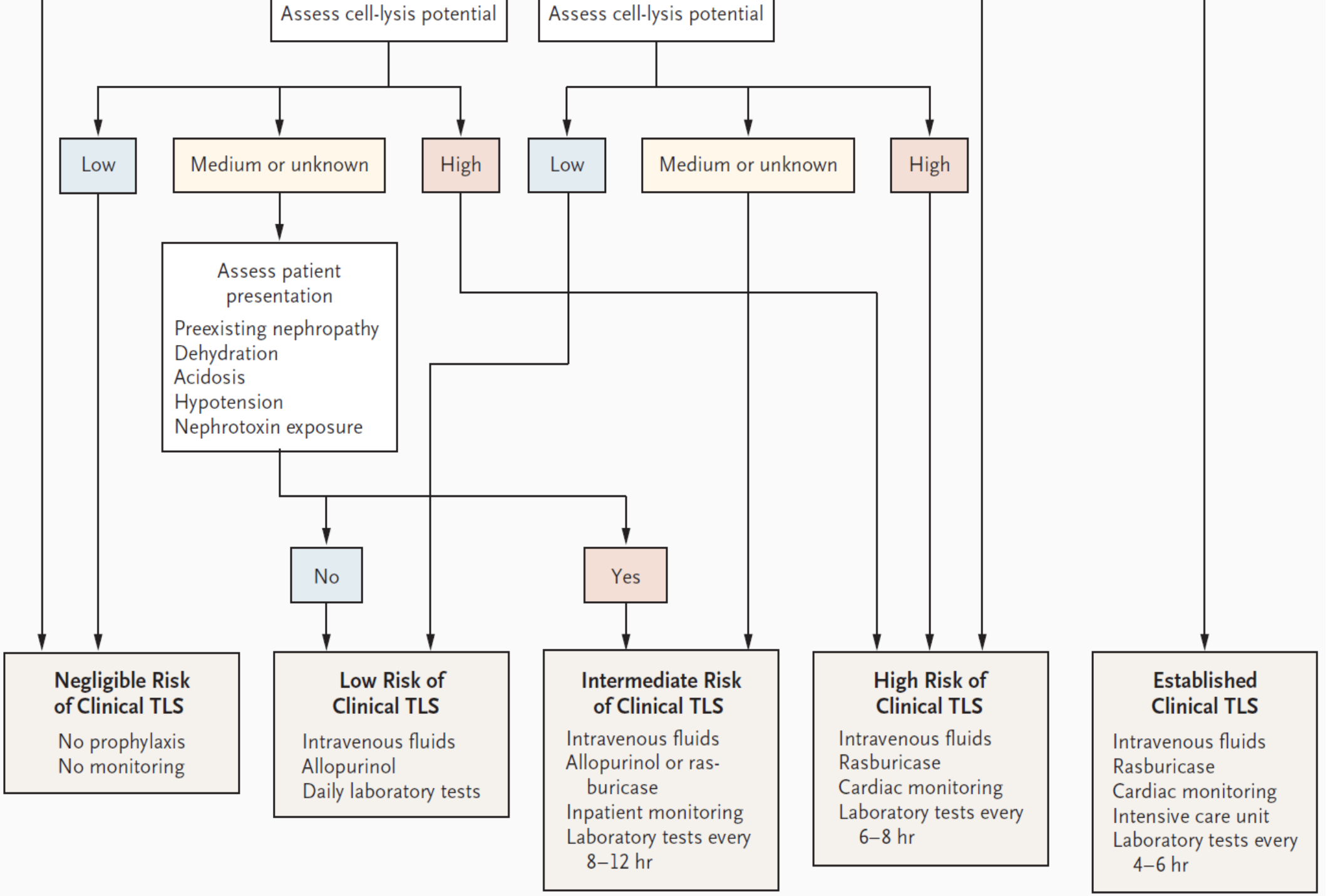
- uric acid clearances below 10 mL/min
- NOT RECOMENDED

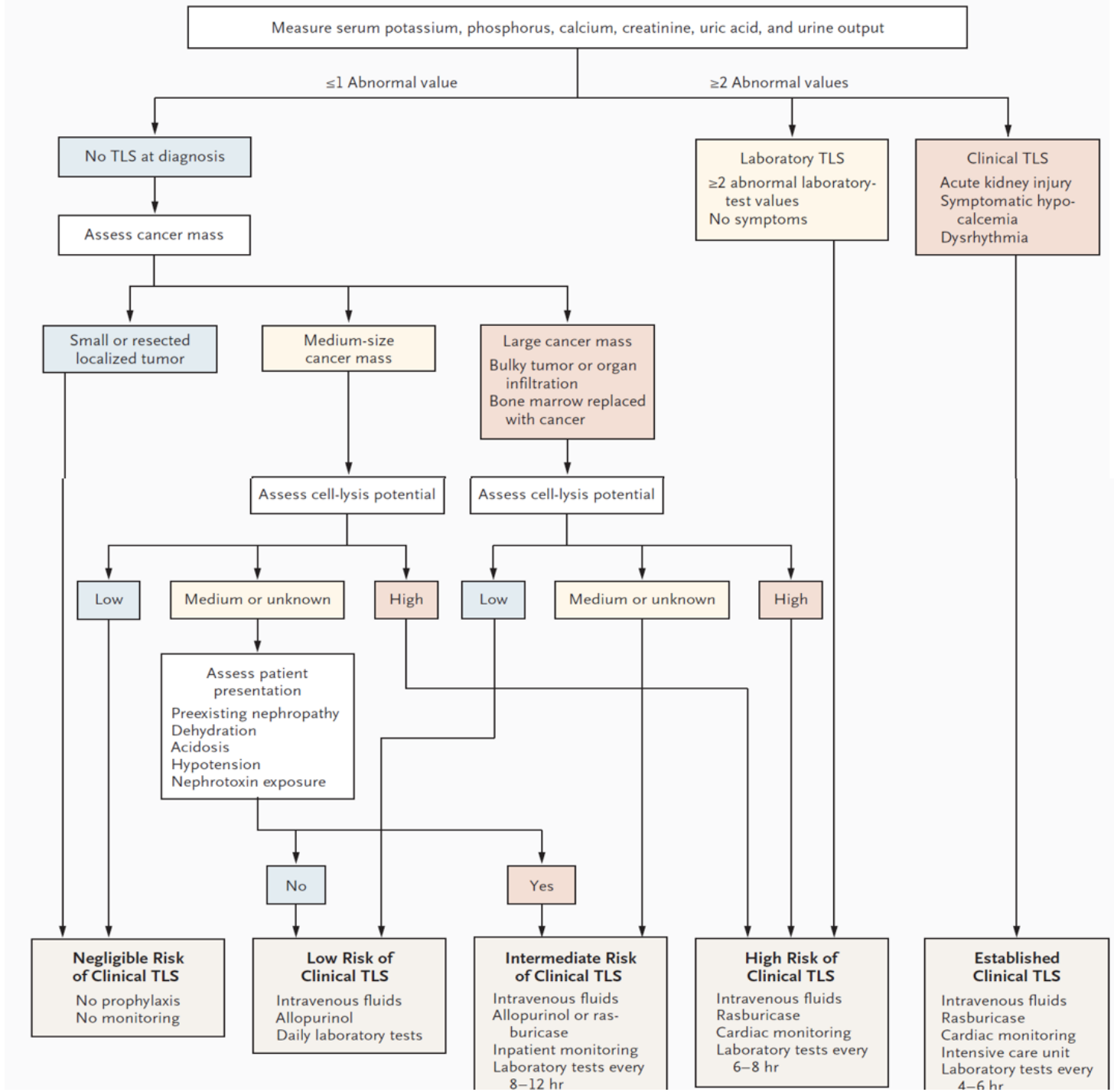
Wang Y, Lu J, Tao Y. Impact of daytime continuous veno-venous haemofiltration on treatment of paediatric tumour lysis syndrome. J Int Med Res. 2018;46(9):3613–20.

Choi KA, Lee JE, Kim YG, Kim DJ, Kim K, Ko YH, et al. Efficacy of continuous venovenous hemofiltration with chemotherapy in patients with Burkitt lymphoma and leukemia at high risk of tumor lysis syndrome. Ann Hematol. 2009;88(7):639–45.

Tan HK, Bellomo R, M'Pis DA, Ronco C. Phosphatemic control during acute renal failure: intermittent hemodialysis versus continuous hemodiafiltration. Int J Artif Organs. 2001;24(4):186–91.


Measure serum potassium, phosphorus, calcium, creatinine, uric acid, and urine output
≤1 Abnormal value
≥2 Abnormal values
No TLS at diagnosis
Assess cancer mass
Small or resected localized tumor
Medium-size cancer mass
Large cancer mass
Bulky tumor or organ infiltration
Bone marrow replaced with cancer
Laboratory TLS
≥2 abnormal laboratory-test values
No symptoms
Clinical TLS
Acute kidney injury
Symptomatic hypocalcemia
Dysrhythmia


Assess cell-lysis potential
Assess cell-lysis potential
Low
Medium or unknown
High
Low
Medium or unknown
High
Assess patient presentation
Preexisting nephropathy
Dehydration
Acidosis
Hypotension
Nephrotoxin exposure
No
Yes
Negligible Risk of Clinical TLS
No prophylaxis
No monitoring
Low Risk of Clinical TLS
Intravenous fluids
Allopurinol
Daily laboratory tests
Intermediate Risk of Clinical TLS
Intravenous fluids
Allopurinol or rasburicase
Inpatient monitoring
Laboratory tests every 8–12 hr
High Risk of Clinical TLS
Intravenous fluids
Rasburicase
Cardiac monitoring
Laboratory tests every 6–8 hr
Established Clinical TLS
Intravenous fluids
Rasburicase
Cardiac monitoring
Intensive care unit
Laboratory tests every 4–6 hr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Assess cancer mass
Laboratory TLS
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Dysrhythmia
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Large cancer mass
Bulky tumor or organ infiltration
Bone marrow replaced with cancer
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Hypotension
Nephrotoxin exposure
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Intravenous fluids
Rasburicase
Cardiac monitoring
Laboratory tests every 6–8 hr
Established Clinical TLS
Intravenous fluids
Rasburicase
Cardiac monitoring
Intensive care unit
Laboratory tests every 4–6 hr

SEVERE HYPOPHOSPHATEMIA ASSOCIATED WITH SPONTANEOUS TUMOR LYSIS SYNDROME (sTLS):

Kamel Gharaibeh, Ziad El-Zoghby. Mayo Clinic, Rochester, Minnesota, USA

A 41-y/o male 69 days post allogenic stem cell transplant, with relapsing Tcell ALL

WBC 53,000(60% blasts)
Cr 2.2 mg/dL(base 1.0)
Uric acid 10 mg/dL (base3.3)
LDH 1404 U/L
K 4.6 mEq/L
Ca 8.8 mg/dL
P <0.3 mg/dL asymptomatic

Hydroxyurea, IV fluid, rasburicase and P replacement (IV and oral)➔days later, Cr and P normalized and WBC decreased to 0.4.

Review of his record 6 months earlier showed initial diagnosis ALL(presented with classical sTLS except for low serum P of 0.3 mg/d)

- ✓ Urine P was less than 2 mg/dl and urine P/creatinine ratio <0.06➔no Urinary waste
- ✓ No Spurious hypophosphatemia
- ✓ PTH was 39 pg/ml.

حسین منزوی

آهای خبردار!
مستی یا هوشیار؟
خوابی یا بیدار؟
خاله یادگار!
تو شبِ سیا
تو شبِ تاریک
از چپ و از راست
از دور و نزدیک
یه نفر داره
جار می‌زنه، جار:
آهای غمی که
مثلِ یه بختک
رو سینه‌ی من
شده‌ای آوار
از گلوی من
دستاتو، وردا

توی کوچه‌ها
یه نسیم رفته،
پی ولگردی
توی باغچه‌ها،
پاییز اومده
پی نامردی
توی آسمون
ماهو دق می‌ده
دردِ بی‌دردی
خاله یادگار!
نمیای بریم
شهرو بگردیم
قدم به قدم؟
نمیای بریم
چراغ وردایم
پرسه بزنیم
دنبالِ آدم؟

THANK FOR YOUR ATTENTION

سکوت میکنم و عشق در دلم جاریست
که این شگفت ترین نوع خویشتن داریست


زنجان شهر جهانی فیلیله