Tumor Lysis Syndrome

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Learning Objectives

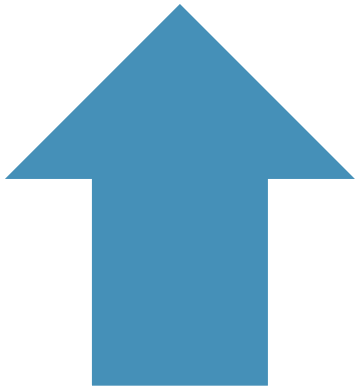
1) Describe the **pathophysiology** of tumor lysis syndrome
2) Identify **risk factors** for development of tumor lysis syndrome
3) Formulate an appropriate pharmacotherapeutic regimen/ monitoring strategy for the **prevention and management** of tumor lysis syndrome

Tumor Lysis Syndrome

- Life-threatening oncologic emergency
- Abrupt release of intracellular contents overwhelming the body's ability to metabolize and excrete adequately
- May be spontaneously induced by tumor prior to treatment or as result of anti-neoplastic therapy
- Prevalence of TLS varies, depending on the tumor type, the type of anticancer treatments used, and the use of prophylactic procedures.

Coiffier B, et al. J Clin Oncol. 2008;26:2767-2778.

Hallmark Laboratory Findings



Uric acid

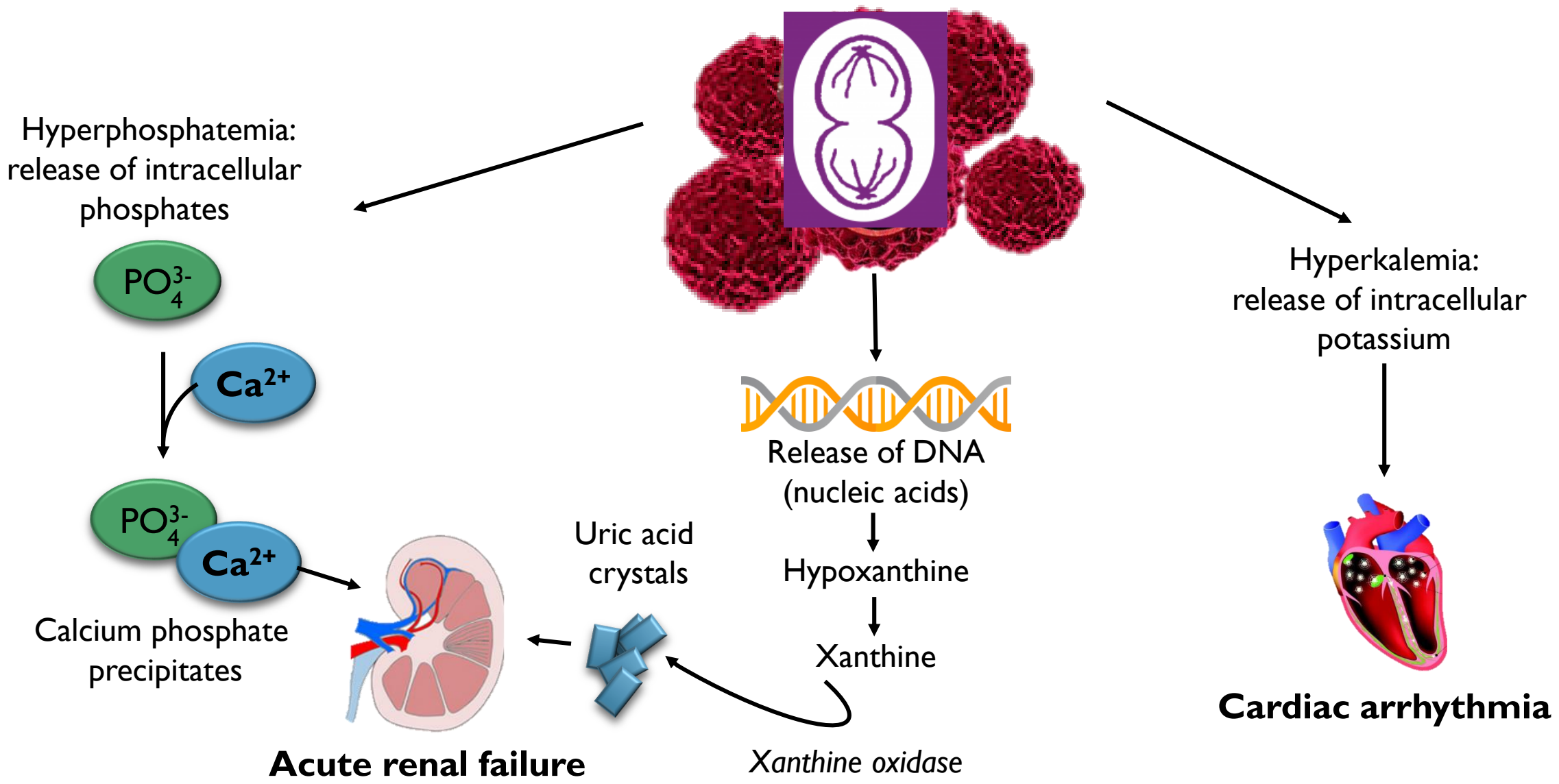
Potassium

Phosphorous

Calcium

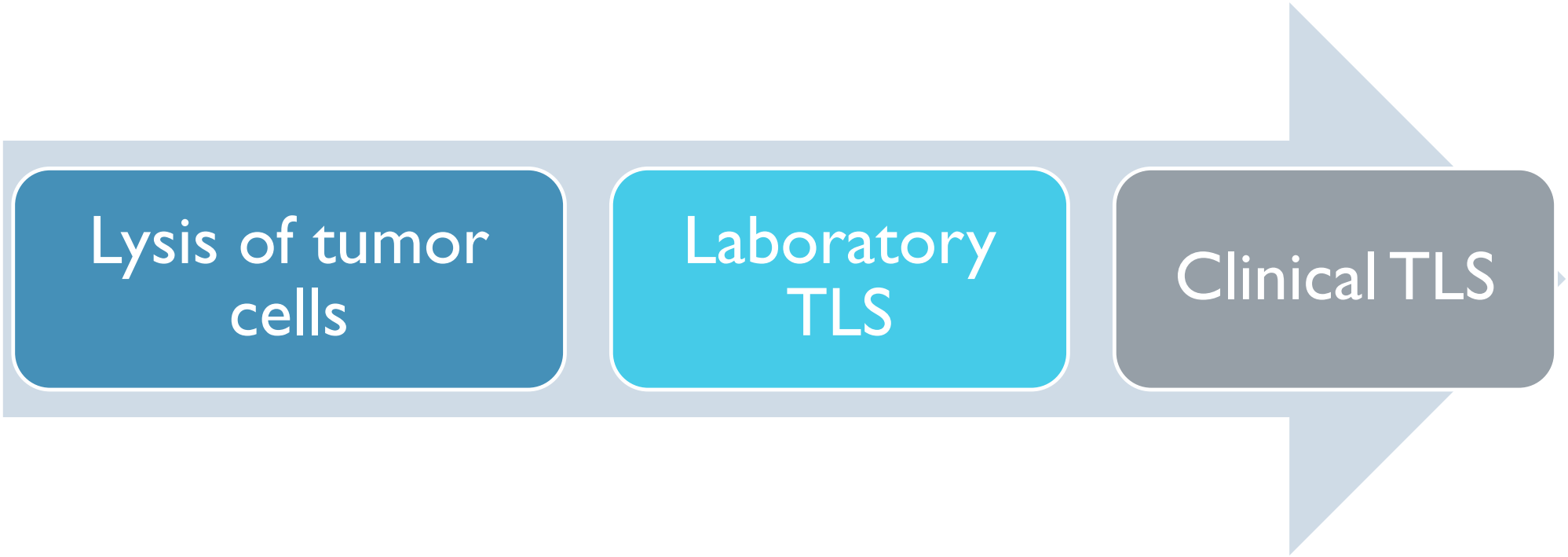
- Observed 12-72 hours after starting chemotherapy
- May continue up to 3 days after start of chemotherapy

Coiffier B, et al. J Clin Oncol. 2008;26:2767-2778.


Hyperphosphatemia: release of intracellular phosphates
PO_4^{3-}
Ca^{2+}
PO_4^{3-}
Ca^{2+}
Calcium phosphate precipitates
Acute renal failure
Uric acid crystals
Release of DNA (nucleic acids)
Hypoxanthine
Xanthine
Xanthine oxidase
Hyperkalemia: release of intracellular potassium
Cardiac arrhythmia

Life-threatening *hyperkalemia* and *permanent acute kidney injury* are the most-feared complications of TLS

Progression of TLS



Cairo MS, et al. Br J Haematol. 2004;127:3-11.

Cairo–Bishop: Definition of TLS

Laboratory TLS

Element	Value	Change From Baseline
Uric acid	≥ 475 µmol/L	> 25% increase
Potassium	≥ 6.0 mmol/L	
Phosphorus	≥ 1.45 mmol/L	
Calcium	≤ 1.75 mg/dL	> 25% decrease

- ≥ 2 of the listed metabolic abnormalities within 3 days before or 7 days after initiation of treatment

Clinical TLS

- Laboratory TLS plus any of the following:
  - Creatinine ≥ 1.5 x ULN
  - Cardiac arrhythmia or sudden death
  - Seizure

Cairo MS, et al. Br J Haematol. 2004;127:3-11.

All patients receiving anti-cancer therapy should be assessed for risk of TLS

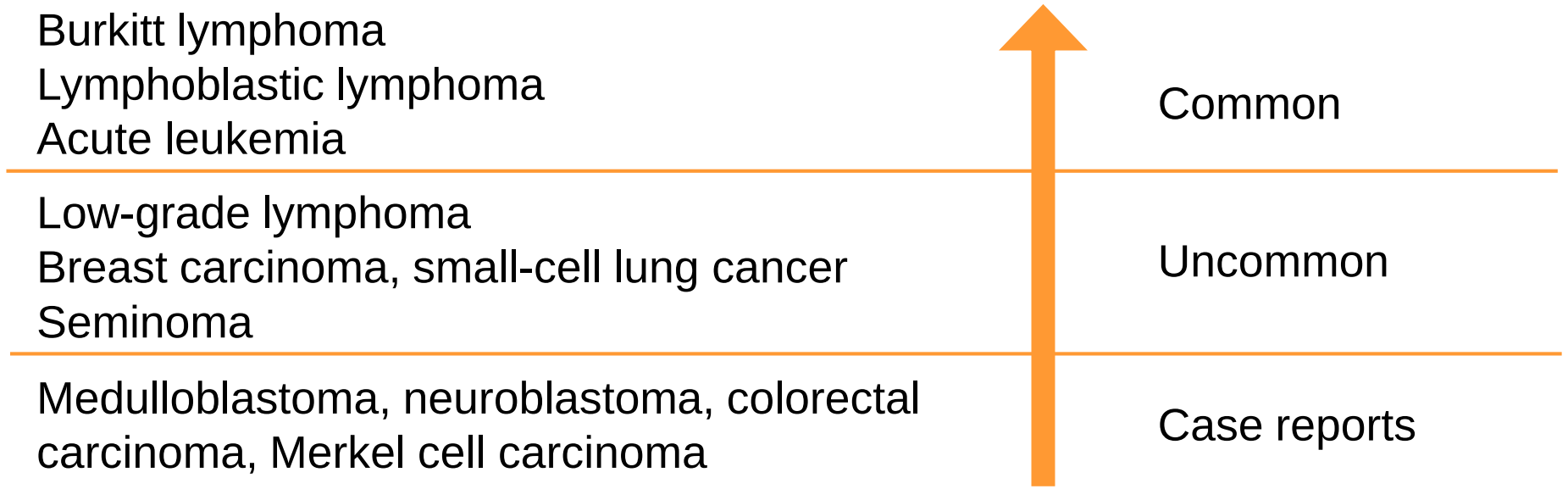
Coiffier B, et al. J Clin Oncol. 2008;26:2767-2778.

Risk Stratification

1) Bulky, chemotherapy-sensitive malignancy
   - Lymphoproliferative malignancy
   - Elevated lactate dehydrogenase (LDH)
   - WBC > 25 x 10^9/L
   - Extensive bone marrow involvement
   - Extensive extramedullary involvement on imaging
2) Volume depletion or dehydration at baseline (or on medications known to cause dehydration)
3) Elevated baseline serum uric acid
4) Pre-existing renal dysfunction
5) Highly effective treatment
   - Venetoclax
   - Ibrutinib

Coiffier B, et al. J Clin Oncol. 2008;26:2767-2778.

Frequency of TLS by Tumor Type



Barton JC. Cancer. 1989;64:738-740. Boisseau M, et al. Eur J Cancer. 1996;32:737-738. Chasty RC, et al. Br J Hosp Med. 1993;49:488-492. Dillman RO. Cancer Metastasis Rev. 1999;18:465-471. Dirix LY, et al. Cancer. 1991;67:2207-2210. Hussein AM, et al. Am J Clin Oncol. 1990;13:10-13. Lorigan PC, et al. Ann Oncol. 1996;7:631-636. Stark ME, et al. Cancer. 1987;60:762-764. Tomlinson GC, et al. Cancer. 1984;53:1783-1785. Vogelzang NJ, et al. JAMA. 1983;249:513-514.

TLS Guidelines: Risk Stratification

	Low Risk	Intermediate Risk	High Risk
ALL	WBC < 50,000/µL	WBC 50,000-100,000/µL *and* LDH < 2 x ULN	WBC ≥ 100,000/µL *or* LDH ≥ 2 x ULN
AML	WBC < 25,000/µL LDH < 2 x ULN	WBC 25,000-100,000/µL *or* LDH ≥ 2 x ULN	WBC ≥ 100,000/µL
Burkitt lymphoma/ leukemia	--	Early stage *and* LDH < 2 x ULN	Advanced or early stage with LDH ≥ 2 x ULN
CLL if treating with **venetoclax**	All LN < 5 cm and ALC < 25,000/µL	Any LN 5-10 cm *or* ALC ≥ 25,000/µL	Any LN ≥ 10 cm *or* LN ≥ 5 cm and ALC ≥ 25,000/µL
DLBCL	--	LDH ≥ 2 x ULN *and* nonbulky disease	LDH ≥ 2 ULN *and* bulky disease
Indolent lymphomas	LDH < ULN	LDH ≥ ULN	--

MM, CML-CP, CLL if treating with alkylating agent, MM, and solid tumors typically considered low risk.

Coiffier B, et al. J Clin Oncol. 2008;26:2767-2778. Mirrakhimov AE, et al. World J Crit Care Med. 2015;4:130-138. Venetoclax [package insert]. 2016.

Mr Tan is a 65-year-old man with relapsed chronic lymphocytic leukemia (CLL) after first-line treatment with ibrutinib. He presented with a high peripheral blood lymphocyte count of 80,000/μL. Imaging studies showed that he had multiple enlarged lymph nodes above and below the diaphragm, with the largest one measuring 8 cm in diameter. Molecular analysis revealed del(17p) mutation but no other cytogenetic abnormality. His haematologist is considering treatment with the BCL-2 inhibitor - venetoclax.

His past medical history is significant for hypertension, and is currently well controlled with PO enalapril 10mg BD. He has no known drug allergy but has G6PD deficiency. Pertinent laboratory results are as follow:

(Renal Panel)			**(Liver panel)**		
Na	(135-145)	135	**Alb**	(38-48)	41
K	(3.5-5)	4.8	**Bil, total**	(5-30)	8
Cl	(95-110)	103	**Conjugated**	(0-5)	3
			Unconjugated	(5-25)	5
CO2	(22-31)	22	**AST**	(10-50)	26
sCr	(65-125 M) (50-90 F)	98	**ALT**	(10-70)	**7**
GFR	(>60)	100	**ALP**	(40-130)	55
Urea	(2.0-6.5)	2.6	**LDH**	(250-580)	**1200**
Glucose	(4-7.8)	4.5	**(FBC)**		
c.Ca	(2.15-2.55)	**1.9**	**WBC**	(3.84-10.01)	5.8
PO4	(0.85-1.45)	1.2	**Hgb**	(11.4-14.7)	12.0
Mg	(0.75-1.07)	0.8	**Platelet**	(164-387)	240
Uric acid	(150-370)	264	**ANC**	(1.56-6.27)	5.5

What would you do next?

1) Is Mr Tan at risk for TLS?
2) What are the risk factors?
3) What risk stratification for TLS does he fall under?
4) What would be your prevention strategies?
    a) Admit the patient for initial dose ramp up of venetoclax, start IV hydration, allopurinol, and administer 1 dose of rasburicase
    b) Admit the patient for initial dose ramp up of venetoclax and start IV hydration and allopurinol
    c) Instruct the patient to begin oral hydration by drinking 1-2 L of water per day prior to first dose of venetoclax in the clinic
    d) Instruct the patient to begin oral hydration and start prophylactic allopurinol prior to first dose of venetoclax in the clinic
    e) Do not begin treatment with venetoclax due to bulky disease and high lymphocyte count
5) Should we correct his electrolyte abnormalities – hypocalcemia?

Ms Lee is a 21-year-old female with newly diagnosed primary mediastinal large B cell lymphoma. She presented to the emergency department with syncope and a routine chest X-Ray revealed a mediastinal mass. Imaging studies showed that the mass was 5.0 x 10.3 x 8.2 cm. Immunhistochemistry reported neoplastic cells positive for CD20 and Ki67 proliferation index of 80-90%. Her haematologist is considering treatment with REPOCH.

She has no past medical history and chronic medication. She has an episode of allergic reaction to honey (angioedema) in 2015. Otherwise, her G6PD level is normal. Pertinent laboratory results are as follow:

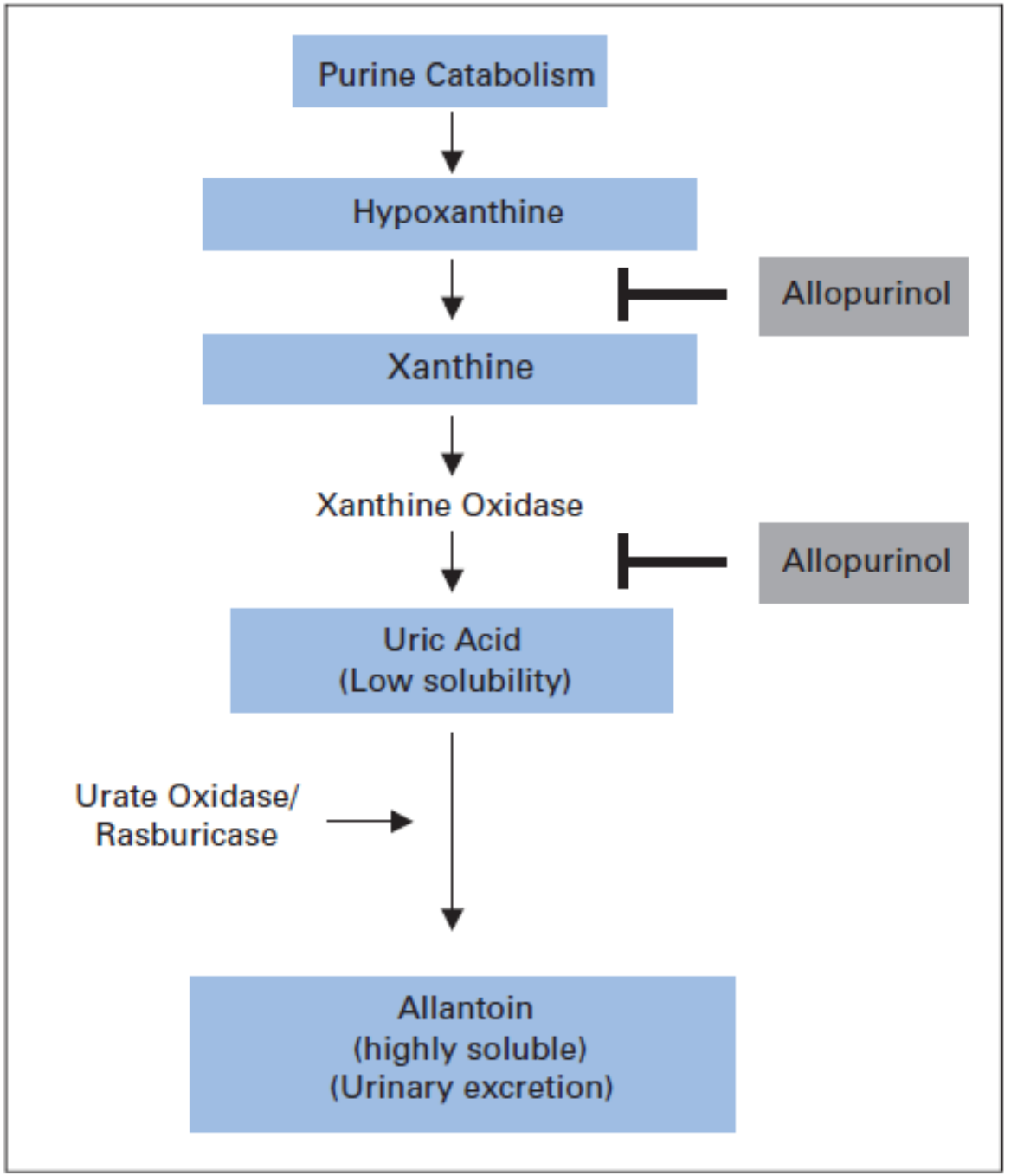
(Renal Panel)			**(Liver panel)**		
Na	(135-145)	135	**Alb**	(38-48)	41
K	(3.5-5)	3.7	**Bil, total**	(5-30)	8
Cl	(95-110)	103	**Conjugated**	(0-5)	3
			Unconjugated	(5-25)	5
CO2	(22-31)	22	**AST**	(10-50)	26
sCr	(65-125 M) (50-90 F)	51	**ALT**	(10-70)	**7**
GFR	(>60)	132	**ALP**	(40-130)	55
Urea	(2.0-6.5)	2.6	**LDH**	(250-580)	**864**
Glucose	(4-7.8)	4.5			
c.Ca	(2.15-2.55)	2.2	**WBC**	(3.84-10.01)	6.2
PO4	(0.85-1.45)	0.74	**Hgb**	(11.4-14.7)	11.9
Mg	(0.75-1.07)	0.82	**Platelet**	(164-387)	283
Uric acid	(150-370)	290	**ANC**	(1.56-6.27)	4.77

What would you do next?

1) Is Ms Lee at risk for TLS?
2) What are the risk factors?
3) What risk stratification for TLS does she fall under?
4) What would your prevention strategies be?
    a) Start IV hydration, allopurinol, and administer 1 dose of rasburicase
    b) Start IV hydration and allopurinol
    c) Start IV hydration and 1 dose of rasburicase
    d) Start IV hydration and consider dialysis
5) Is there any special handling for blood sample in patients who received rasburicase?

Management of TLS

- Hyperhydration ± alkalinization
- Allopurinol
- Rasburicase
- Dialysis


Purine Catabolism
Hypoxanthine
Allopurinol
Xanthine
Xanthine Oxidase
Allopurinol
Uric Acid
(Low solubility)
Urate Oxidase/
Rasburicase
Allantoin
(highly soluble)
(Urinary excretion)

Xanthine Oxidase Inhibitors

- Prevent the metabolism of xanthine and hypoxanthine into uric acid
- Reduces the formation of uric acid and the incidence of TLS
  - Most effective when used 24-48 hrs prior to initiation of cytotoxic therapy
- Allopurinol: primary agent to correct hyperuricemia for decades
  - Adverse events: hypersensitivity reactions and rash
  - Drug interactions: mercaptopurine, thiazide diuretics, antibiotics
  - Most effective at alkaline pH; however, alkaline pH increases calcium phosphate deposition in the kidneys
- Febuxostat: not FDA approved for use in TLS

Cairo MS. Clin Lymphoma. 2002;3:S26. Davidson MB, et al. Am J Med. 2004;116:546-554. DeConti RC, et al. N Engl J Med. 1966;274:481-486.
Becker MA, et al. N Engl J Med. 2005;353:2450-2461. Allopurinol [package insert]. 2003.

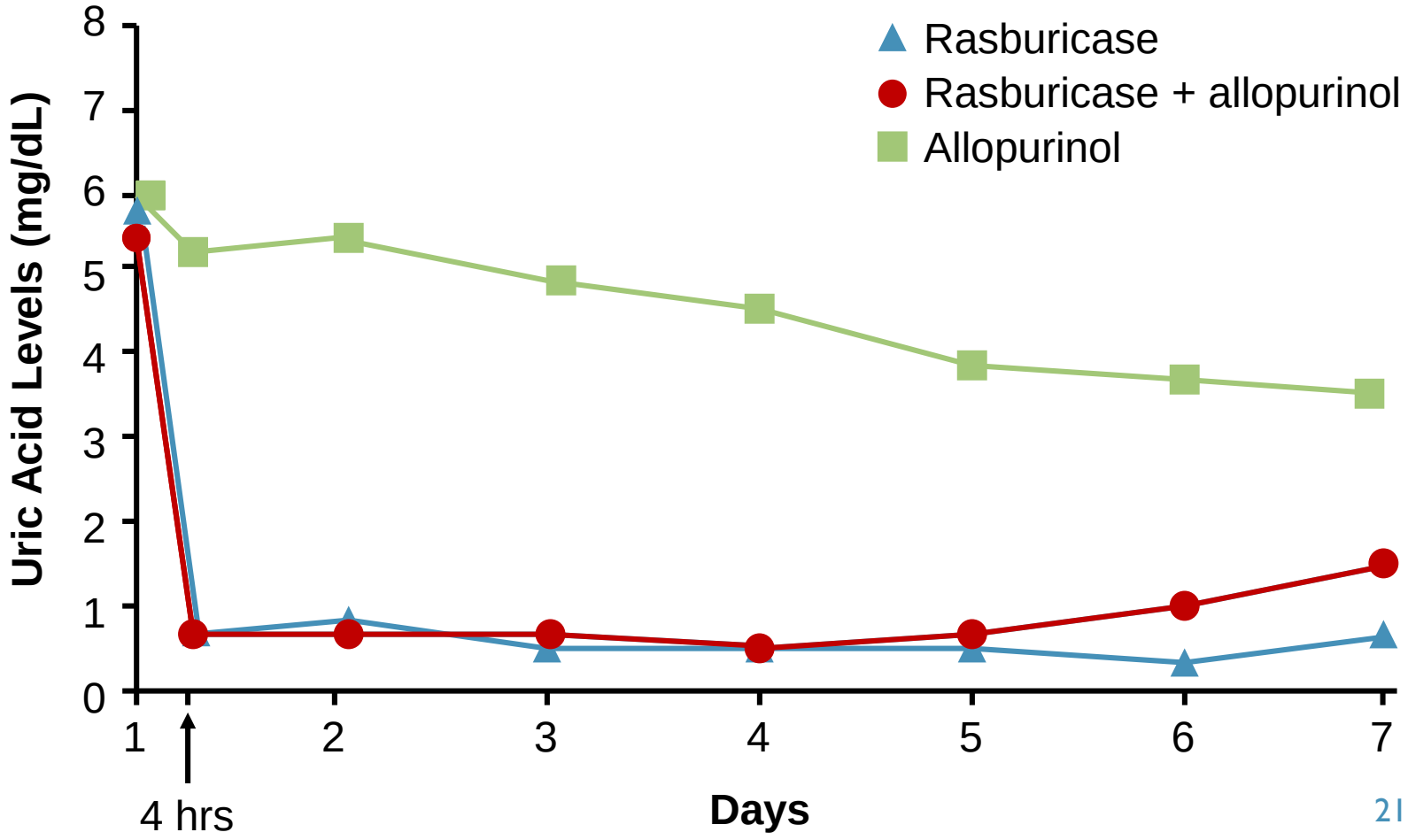
Rasburicase

- Derived from a cDNA clone isolated from *Aspergillus flavus* and synthesized in *Saccharomyces cerevisiae*
- Contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency
- Special handling:
  - Blood must be collected in pre-chilled tubes containing heparin anticoagulant
  - Immediately immersed in an ice water bath and given urgent (STAT) status
  - Plasma samples must be prepared by centrifugation in a pre-cooled centrifuge
  - Plasma must be maintained in an ice water bath and analyzed for uric acid within 4 h of collection

Ribeiro RC, et al. Clin Lymphoma. 2003;3:225-232.
Chiang J, et al. Asia Pac J Clin Oncol. 2011 Dec;7(4):351-6.

Rasburicase vs Allopurinol in Adults With Hematologic Malignancies at Risk for TLS

- Drug-related AEs infrequent in all groups and primarily immunoallergenic in nature: rasburicase, 4%; rasburicase + allopurinol, 5%; allopurinol, 1%
- No life-threatening AEs or deaths occurred



Cortes J, et al. J Clin Oncol. 2010;28:4207-4213.

Do not give allopurinol and rasburicase together.

Allopurinol blocks the conversion of xanthines to uric acid, which reduces the effect of rasburicase.

Cortes J, et al. J Clin Oncol. 2010;28:4207-4213.

Managing TLS: Summary

Minimal Risk	Low Risk	Intermediate Risk	High Risk	Clinical TLS
No prophylaxis indicated	**Prophylaxis: hydration ± allopurinol** Daily lab tests	**Prophylaxis: hydration + allopurinol**; consider rasburicase Lab tests every 8-12 hrs	**Prophylaxis: hydration + rasburicase** Lab tests every 6-8 hrs **Cardiac monitoring**	**Prophylaxis: hydration + rasburicase** Lab tests every 4-6 hrs **Cardiac monitoring in ICU**

- Management of electrolyte abnormalities
- Dialysis

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

Do not treat *asymptomatic* hypocalcemia

It increases risk of calcium phosphate precipitation

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

References

- Coiffier B, et al. Guidelines for the Management of Pediatric and Adult Tumor Lysis Syndrome: An Evidence-Based Review. *J Clin Oncol* 2008; 26:2767-78.
- Howard SC, Jones DP, Pui CH. The tumor lysis syndrome. *The New England journal of medicine*. 2011;364(19):1844-1854.
- Reeves DJ et al. Evaluation of a single fixed dose of rasburicase 7.5 mg for the treatment of hyperuricemia in adults with cancer. *Pharmacotherapy* 2008; 28:685-90.

THE END

THANK YOU!