

SIOP PODC Supportive Care Education (ICON 2016)

Presentation Date: 23rd January 2016

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Managing patients with bulky cancers

Scott Howard, MD, MSc

Professor, University of Memphis

Chair, World Child Cancer USA

Email: scotth1375@gmail.com

Outline

- Tumor bulk affects early mortality
- Patients with acute leukemia and hyperleukocytosis are highly curable
- Management of early toxicities is critical
 - Hyperleukocytosis
 - TLS

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- **Tumor bulk affects early mortality**
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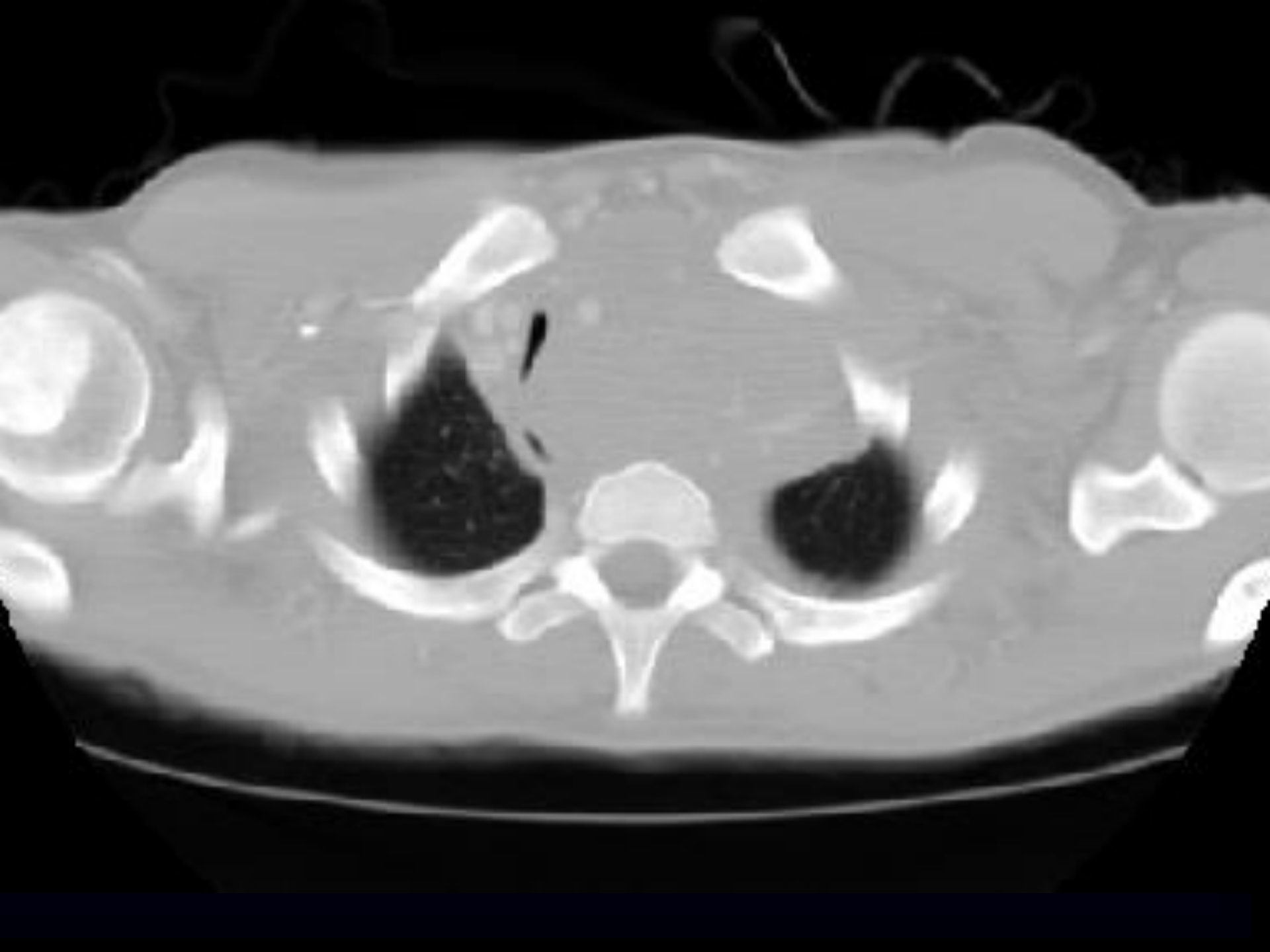
Chest X-ray - Ratio of transverse diameters



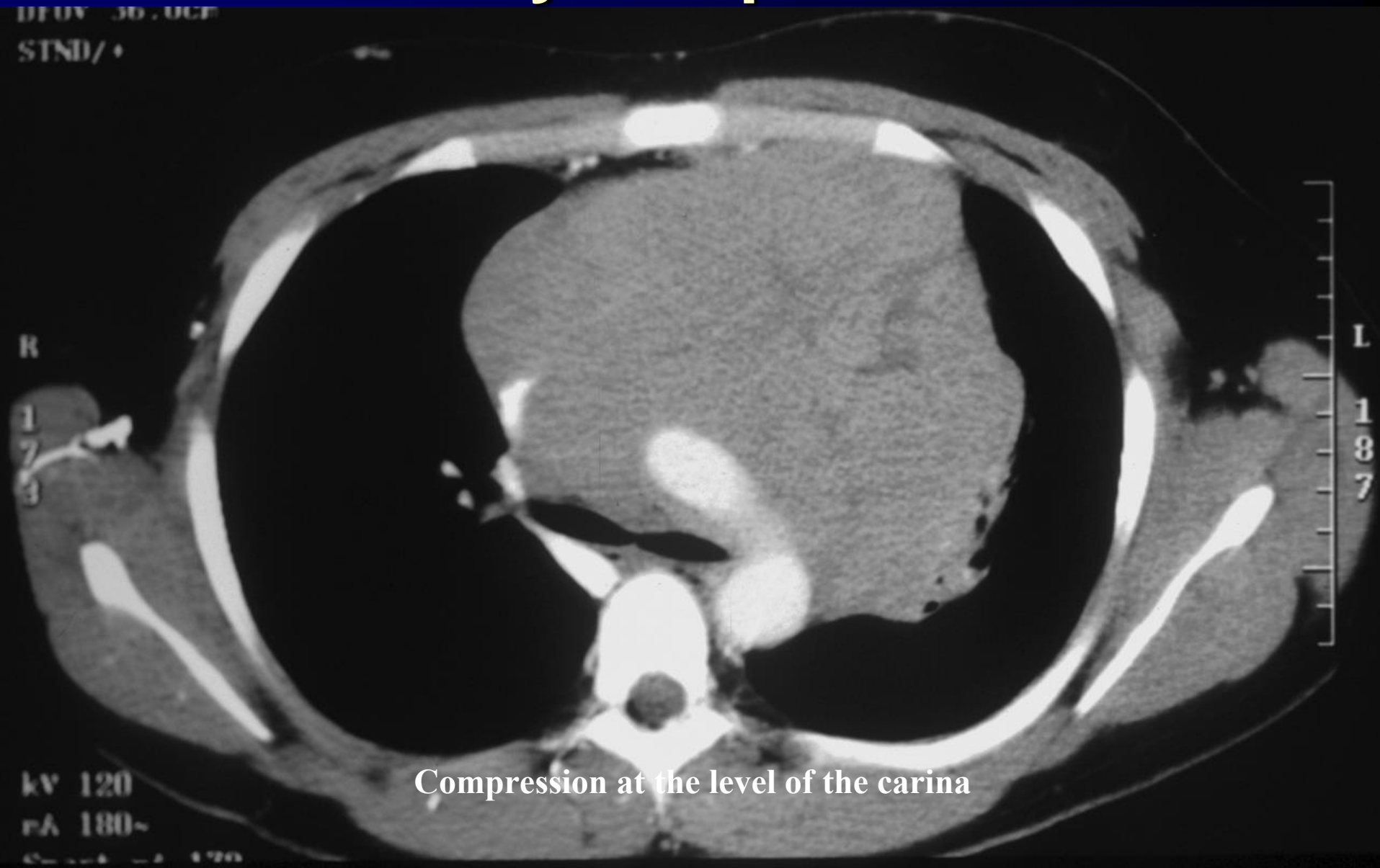
A grayscale chest X-ray image showing the thoracic cavity. The lungs are visible on either side of the central mediastinum. A yellow double-headed arrow is positioned horizontally across the middle of the image, spanning the width of the lung fields. A green double-headed arrow is positioned horizontally below the yellow one, spanning the entire width of the chest. The text 'Diameter of mass' is centered above the yellow arrow, and 'Diameter of chest' is centered above the green arrow.

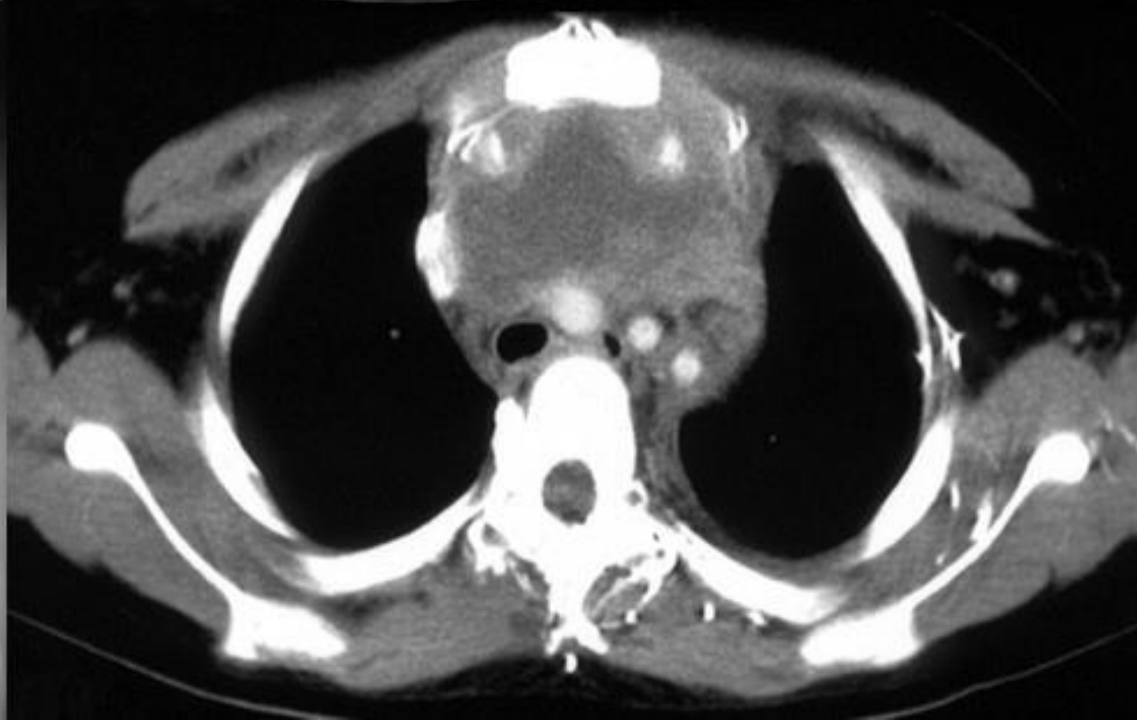
Diameter of mass

Diameter of chest



Mediastinal mass with central airway compression





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Leukocyte count at diagnosis of acute lymphoblastic leukemia (ALL)

WBC	n (%)	Event-free survival
<10,000		87%
10,000 to 49,000		86%
50,000 to 99,000		84%
100,000 to 300,000		86%
≥300,000		73%
All patients	498	86%

**What percentage of children with ALL
present with WBC count $> 100,000$?**

A. 2%

B. 5%

C. 8%

D. 10%

E. 13%

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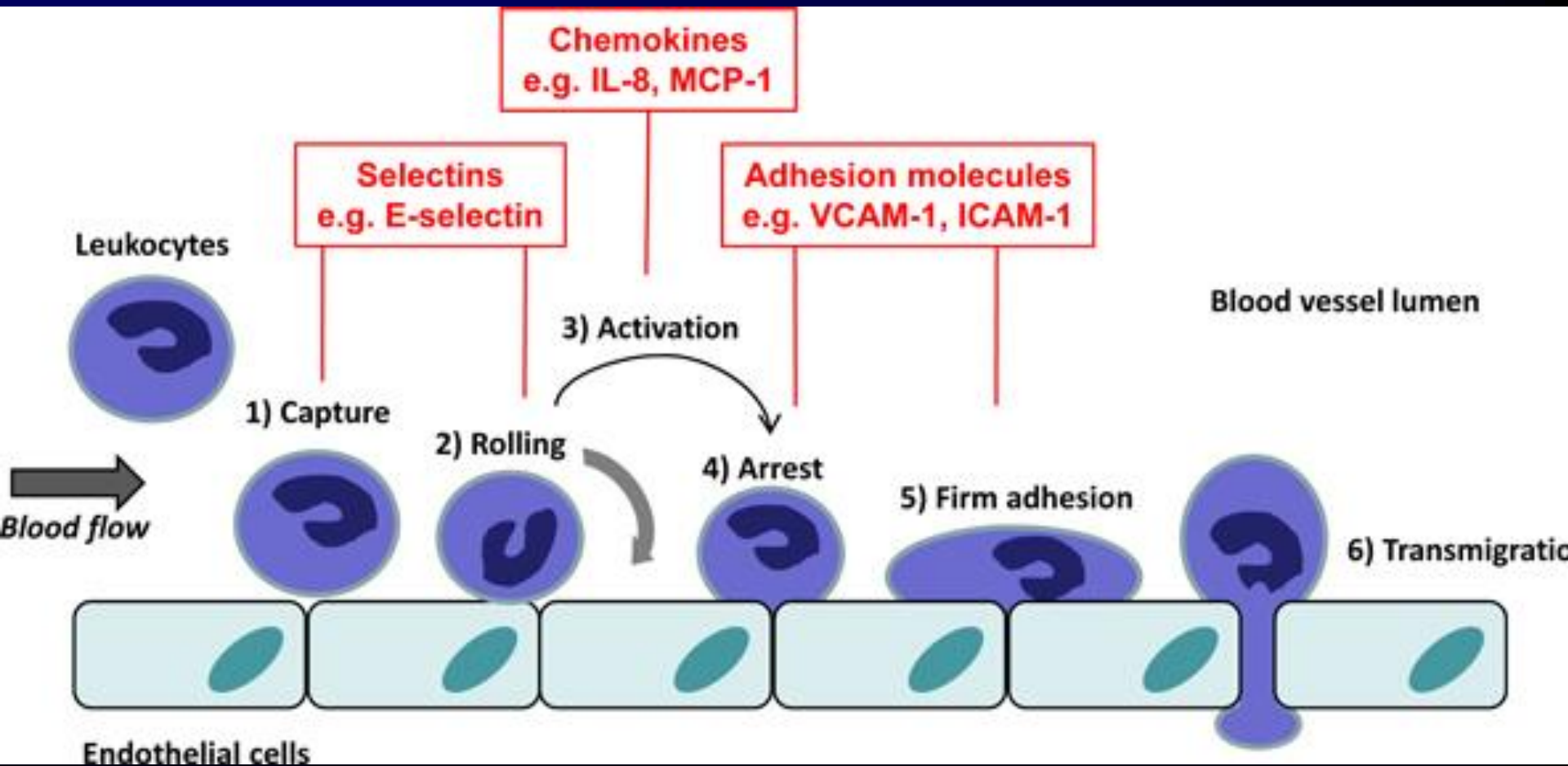
Leukocyte count at diagnosis of acute lymphoblastic leukemia (ALL)

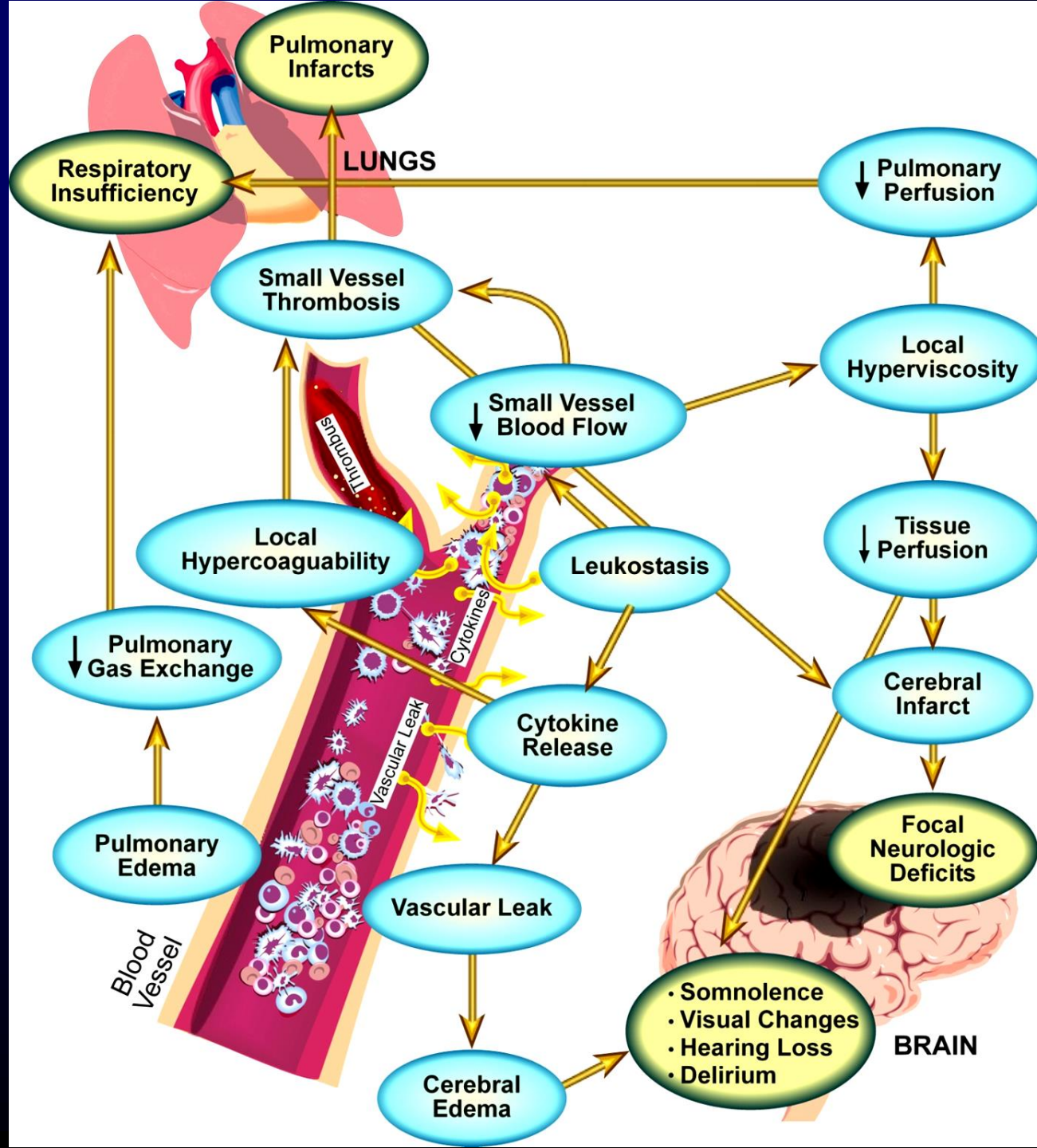
WBC	n (%)	Event-free survival
<10,000	227 (46)	87%
10,000 to 49,000	144 (29)	86%
50,000 to 99,000	64 (13)	84%
100,000 to 300,000	44 (9)	86%
≥300,000	19 (4)	73%
All patients	498 (100)	86%

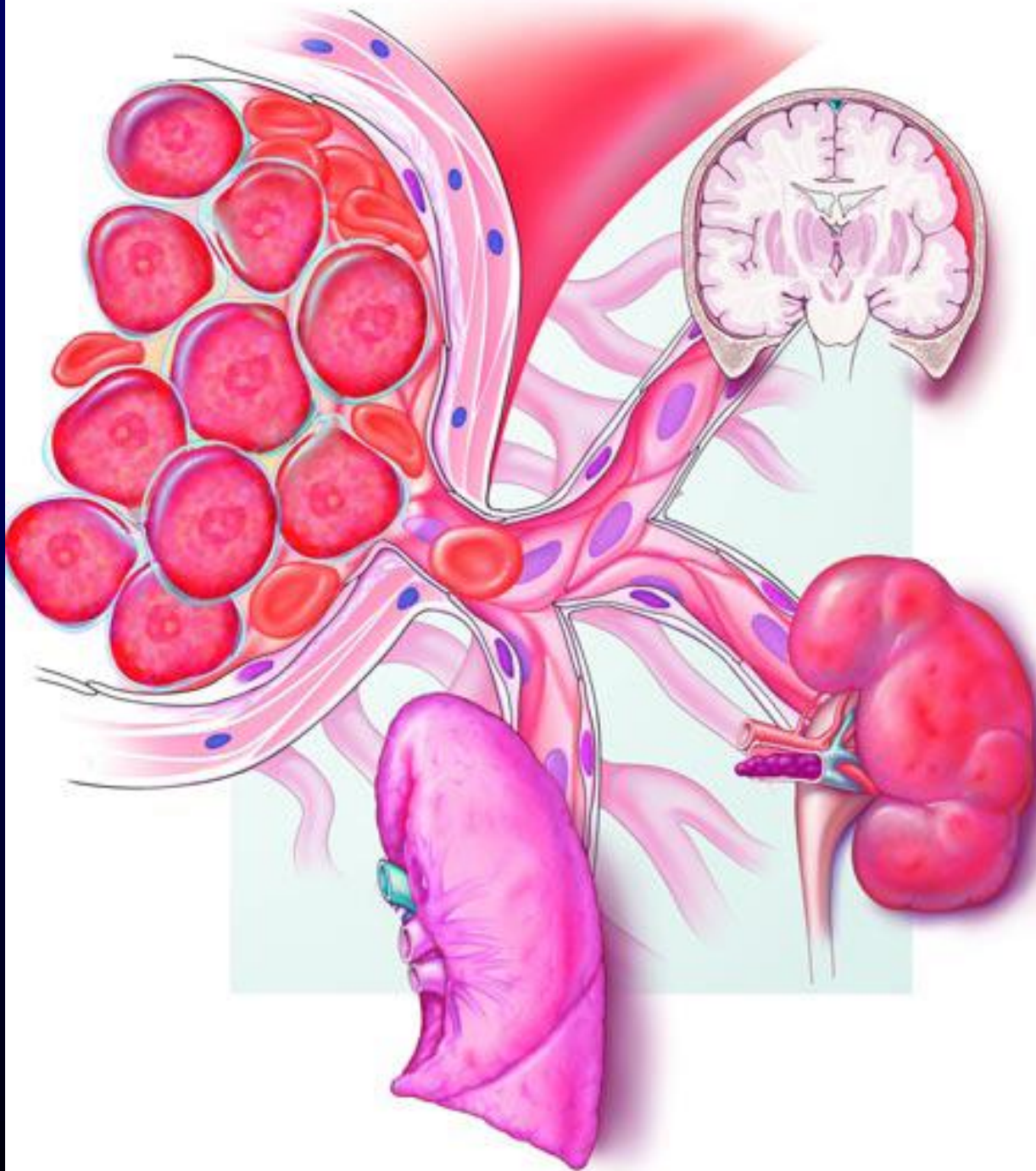
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Pathophysiology of leukostasis

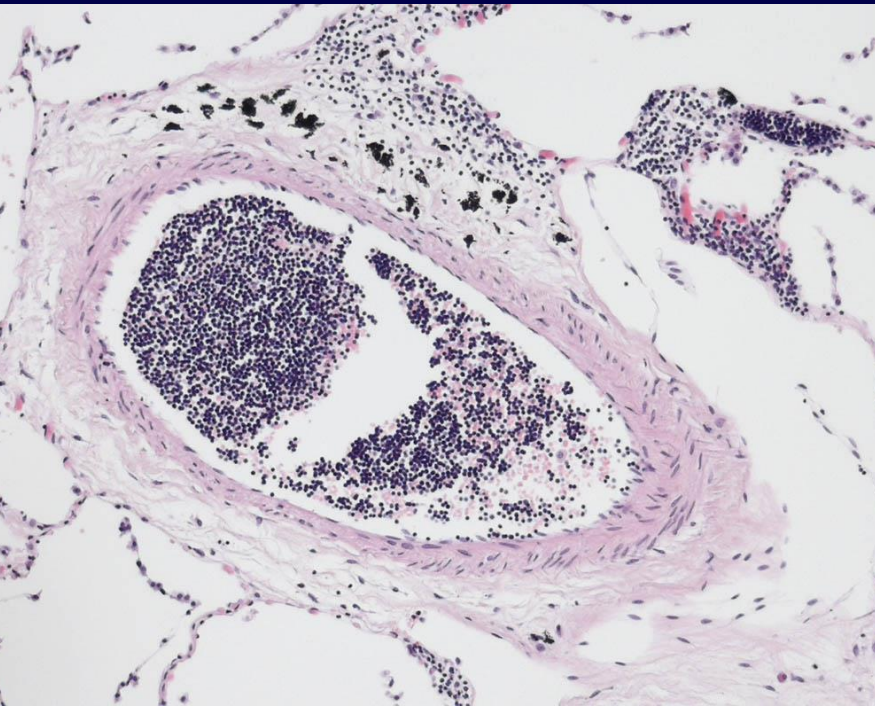






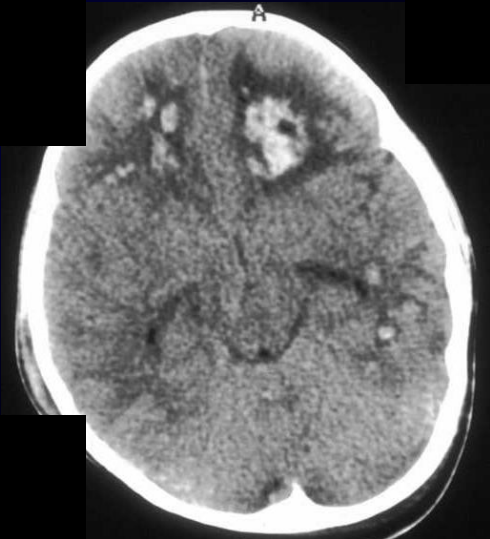
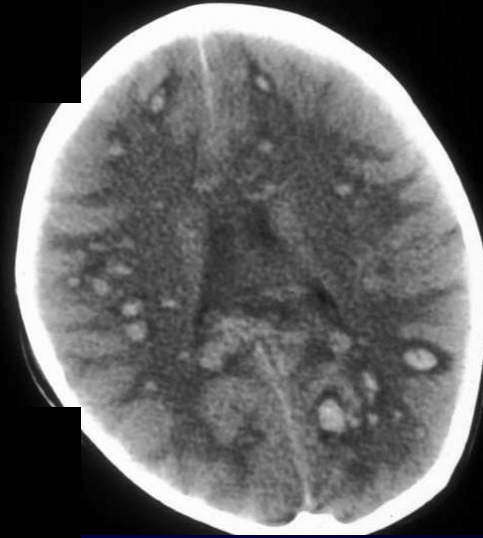
Pulmonary leukostasis

- Symptoms: dyspnea, tachypnea, hypoxemia
- CXR – bilateral interstitial or alveolar infiltrates
- Risk for pulmonary hemorrhage



CNS Leukostasis

- Symptoms include: headache, mental status changes, seizures, coma, death
- Risk of intracranial hemorrhage
 - Thrombocytopenia
 - Coagulopathy



Neurological Complications

Complications in 178 children with ALL and WBC > 200,000	Number (%)
Ophthalmologic only	9 (5%) 1 required XRT
CNS leukostasis (seizure, altered mental status, cranial nerve palsy)	6 (3.4%)
Intracranial hemorrhage	4 (2.2%) 2 died

Therapy for hyperleukocytosis

- Blood viscosity relates directly to morbidity
- Hydration
- *AVOID* use of diuretics
- *AVOID* red blood cell transfusion
- Transfuse platelets to keep $> 20,000/\text{mm}^3$ and treat coagulopathy (platelets do not contribute to viscosity)
- Rapid diagnosis and initiation of prednisone (ALL) or hydroxyurea (AML)
- Cyto reduction by leukapheresis or exchange transfusion NOT necessary

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Modified Cairo-Bishop Definition of TLS

Table 1. Definitions of Laboratory and Clinical Tumor Lysis Syndrome.*

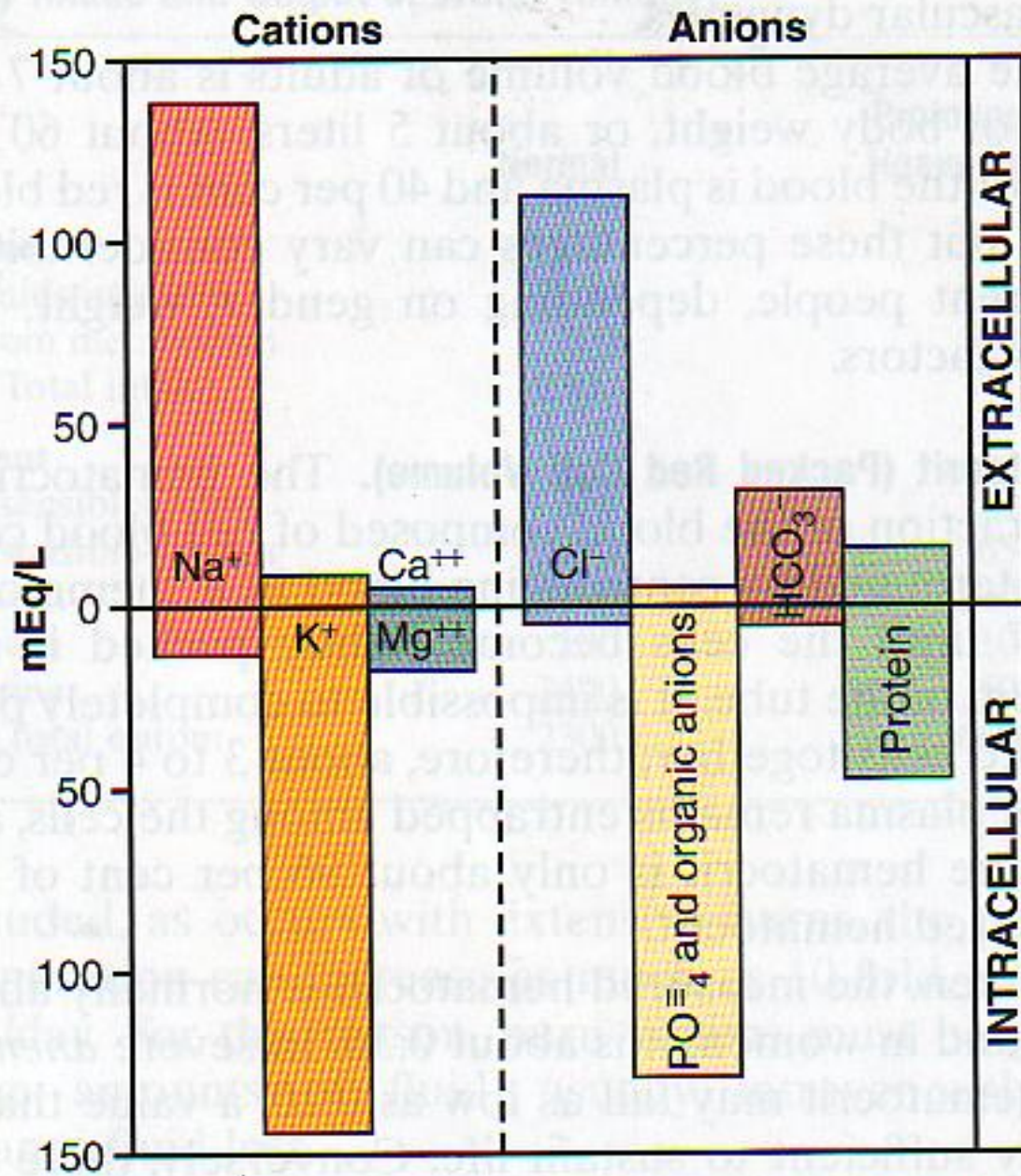
Metabolic Abnormality	Criteria for Classification of Laboratory Tumor Lysis Syndrome	Criteria for Classification of Clinical Tumor Lysis Syndrome
Hyperuricemia	Uric acid >8.0 mg/dl (475.8 μ mol/liter) in adults or above the upper limit of the normal range for age in children	
Hyperphosphatemia	Phosphorus >4.5 mg/dl (1.5 mmol/liter) in adults or >6.5 mg/dl (2.1 mmol/liter) in children	
Hyperkalemia	Potassium >6.0 mmol/liter	Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia
Hypocalcemia	Corrected calcium <7.0 mg/dl (1.75 mmol/liter) or ionized calcium <1.12 (0.3 mmol/liter) [†]	Cardiac dysrhythmia, sudden death, seizure, neuromuscular irritability (tetany, paresthesias, muscle twitching, carpopedal spasm, Trousseau's sign, Chvostek's sign, laryngospasm, or bronchospasm), hypotension, or heart failure probably or definitely caused by hypocalcemia
Acute kidney injury [‡]	Not applicable	Increase in the serum creatinine level of 0.3 mg/dl (26.5 μ mol/liter) (or a single value >1.5 times the upper limit of the age-appropriate normal range if no baseline creatinine measurement is available) or the presence of oliguria, defined as an average urine output of <0.5 ml/kg/hr for 6 hr

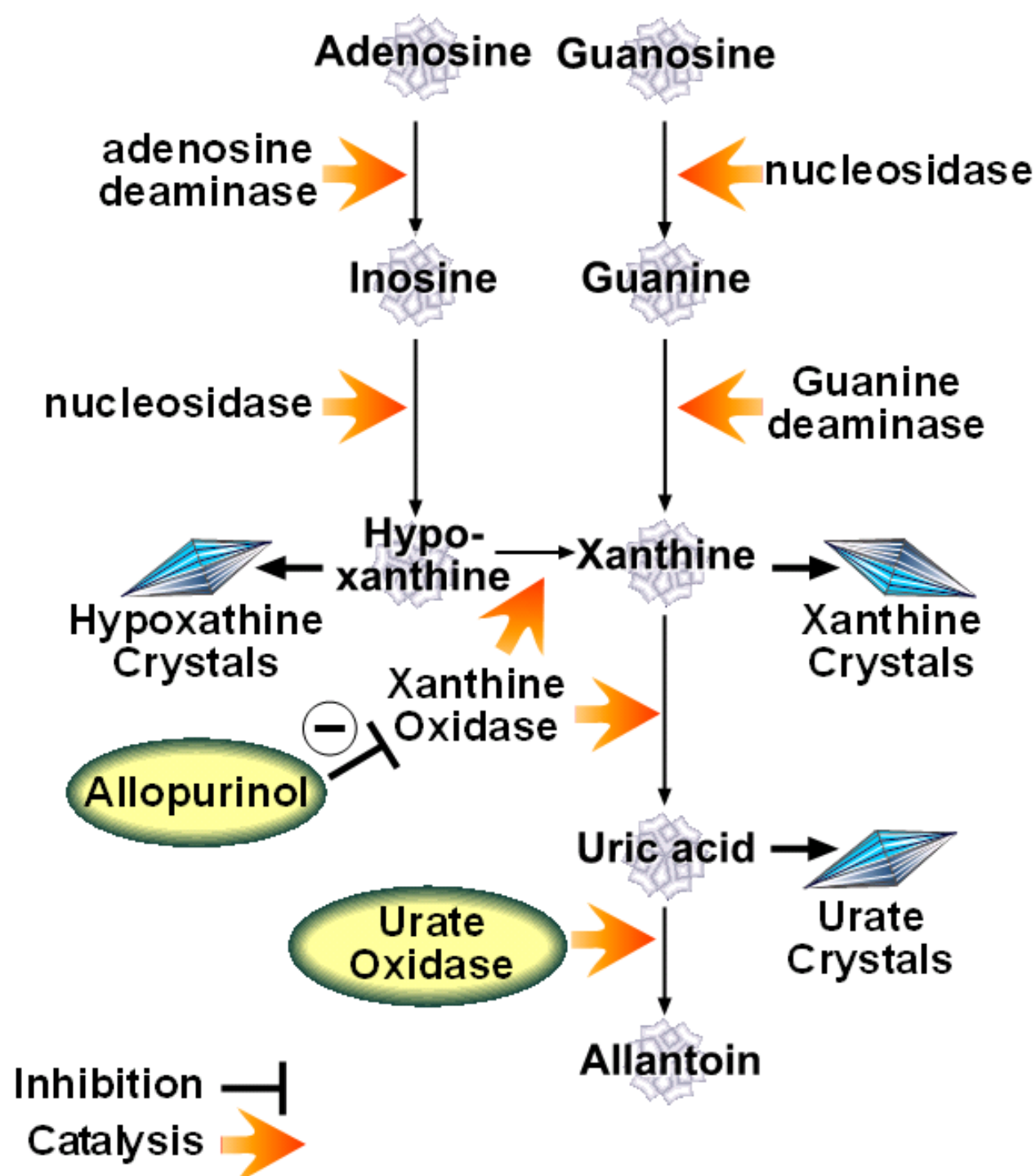
Br J Haematol 2004;127:3-11

N Engl J Med 2011;364:1844-54

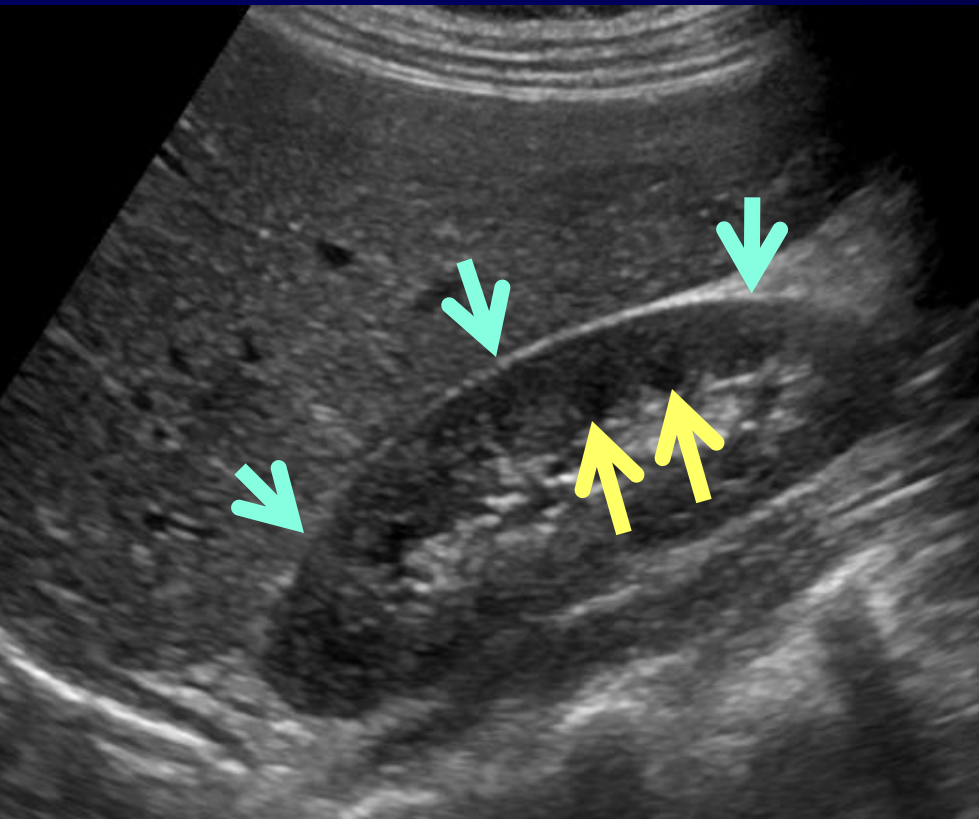
Definition of laboratory TLS

Metabolic abnormality	Criteria for laboratory TLS (2 or more present on same day)
Hyperuricemia	Uric acid > 8 mg/dL (476 μmol/L)
Hyper-phosphatemia	Phosphorus > 4.5 mg/dL (1.5 mmol/L) in adults or >6.5 mg/dL (2.1 mmol/L) in children
Hyperkalemia	Potassium > 6 mmol/L
Hypocalcemia	Corrected calcium < 7 mg/dL (1.75 mmol/L) or ionized calcium < 1.12 mg/dL (0.3 mmol/L)

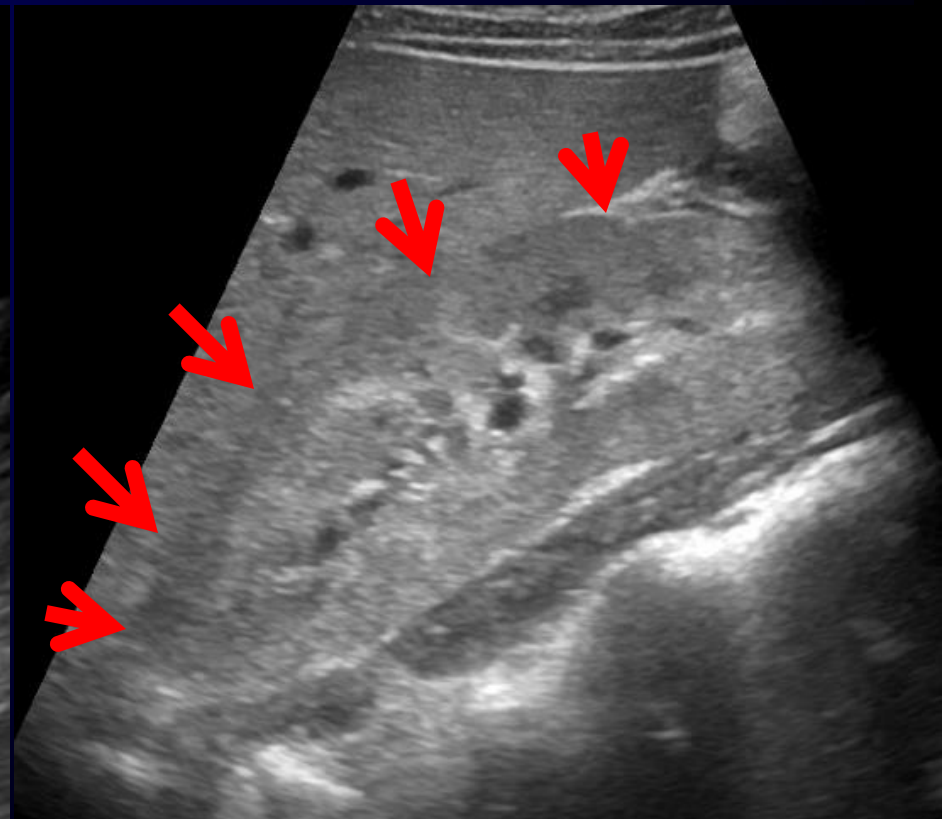




Acute kidney injury in a patient with tumor lysis syndrome

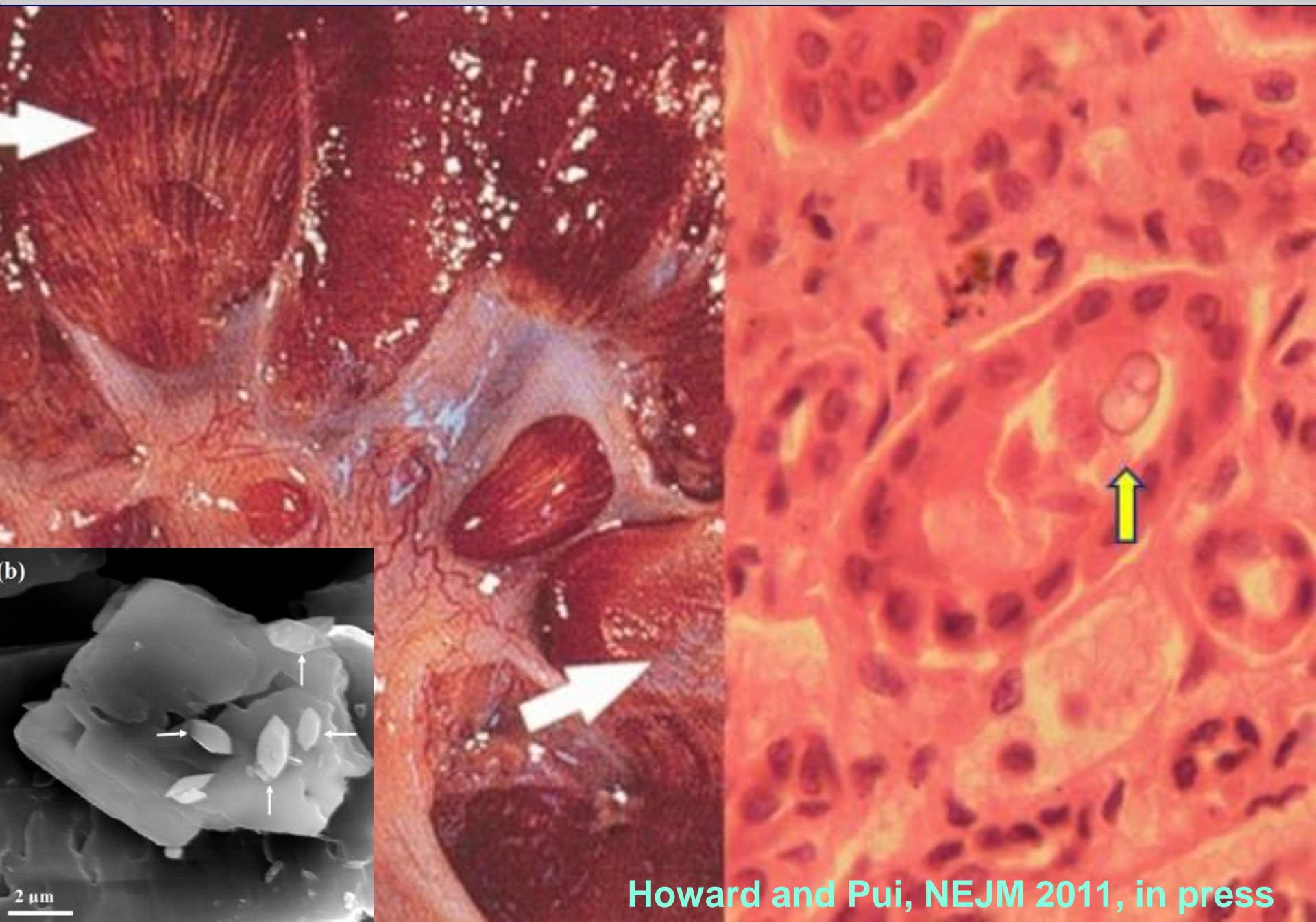


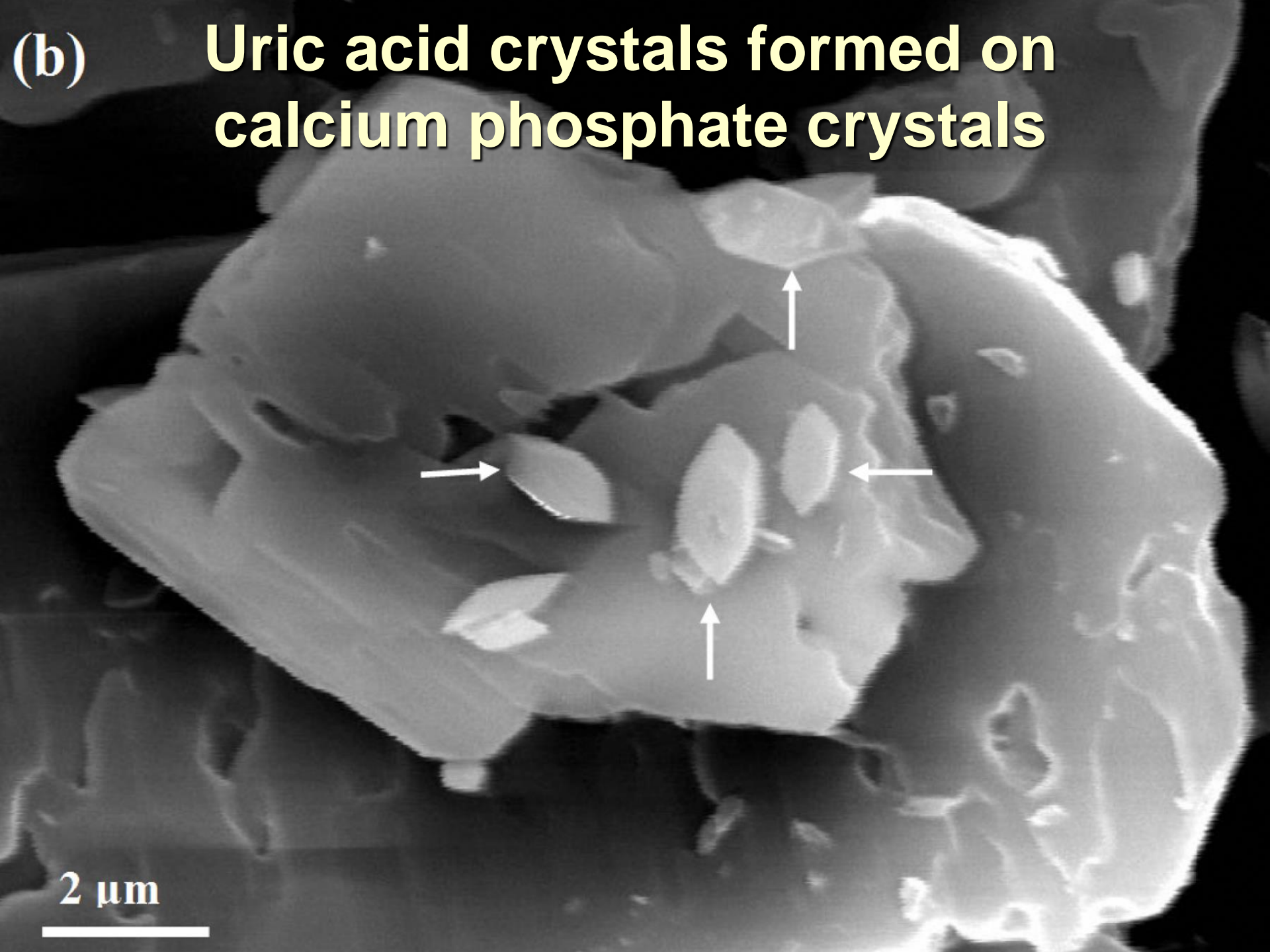
Normal kidney



Kidney in a patient with tumor lysis syndrome

Figure 2. Crystals of uric acid, calcium phosphate, and calcium oxalate

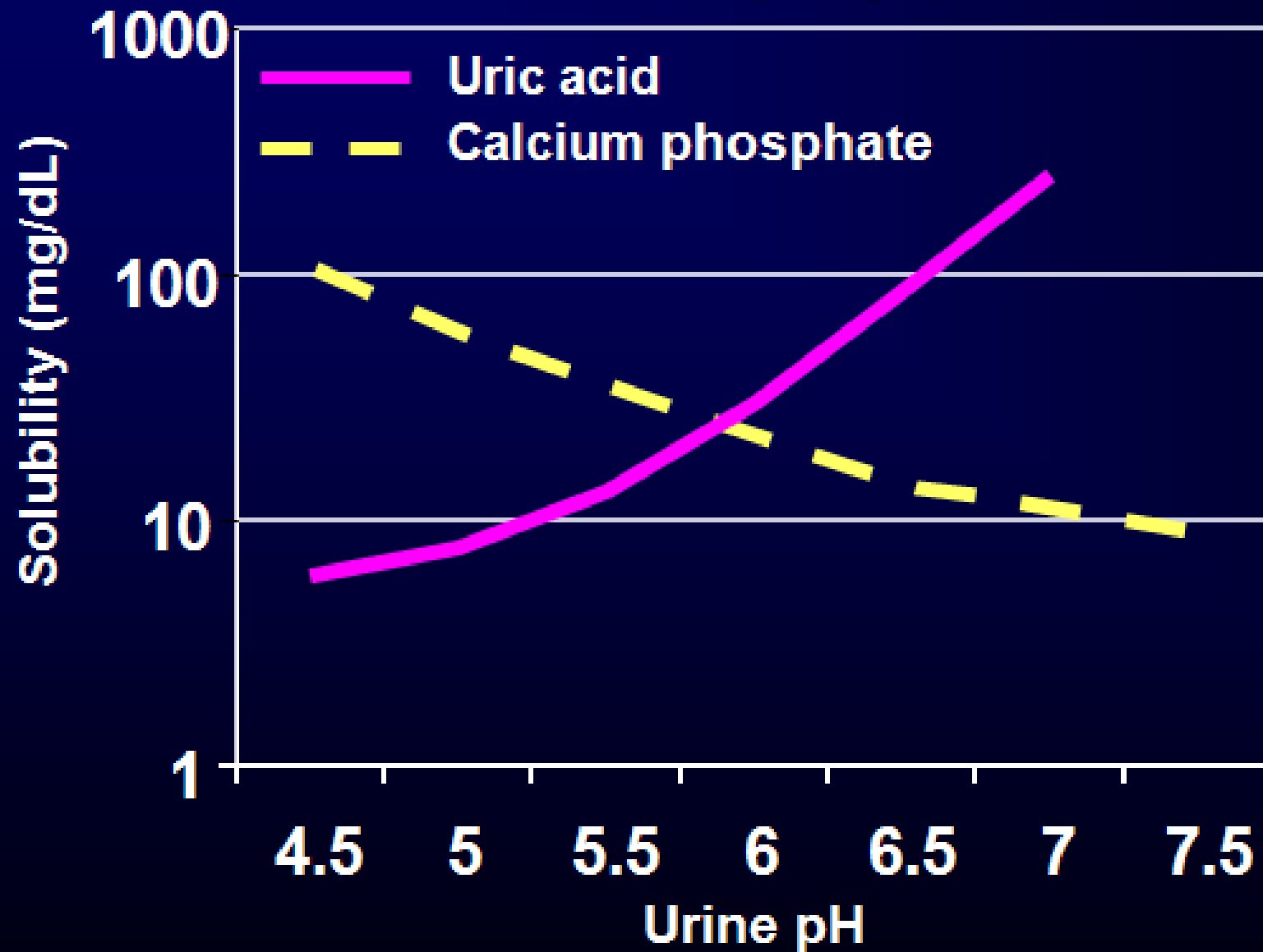




(b) Uric acid crystals formed on calcium phosphate crystals

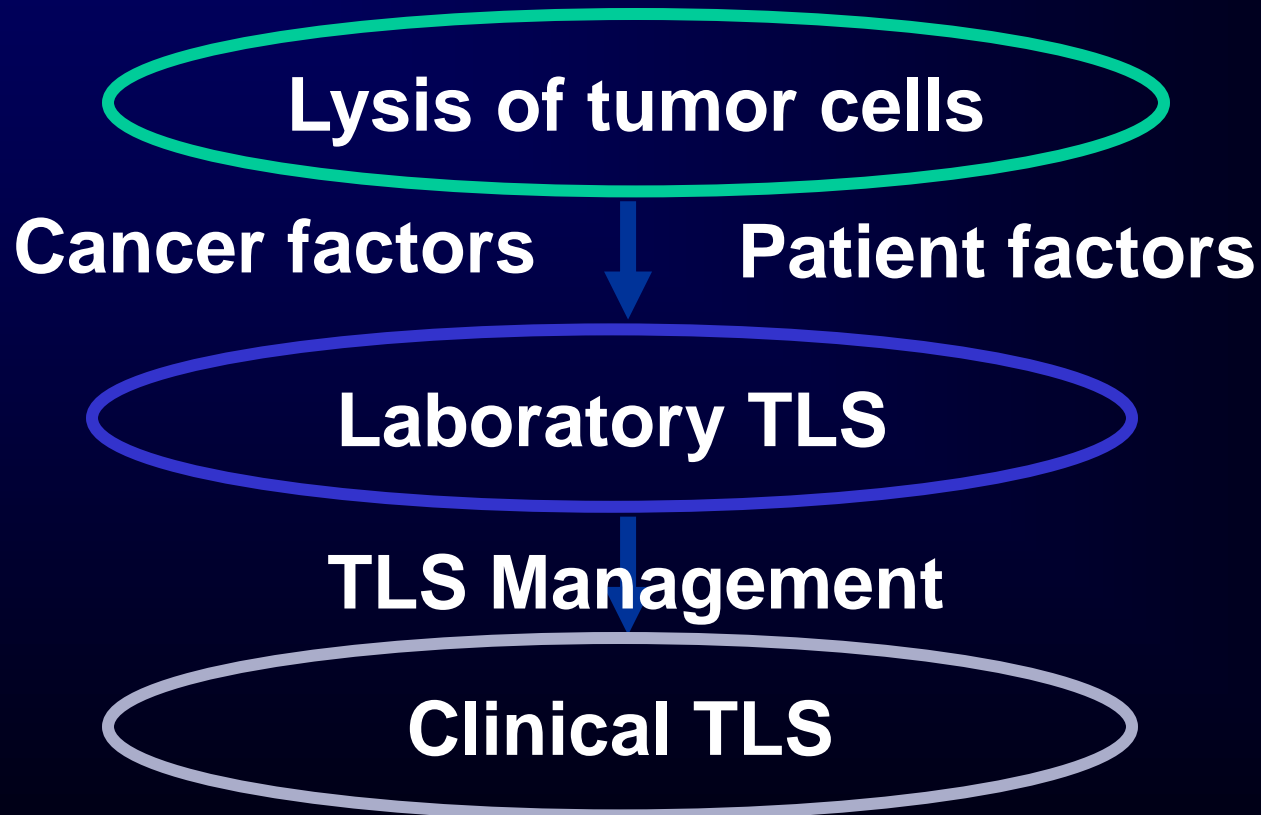
2 μm

Solubility by pH



Howard et al. Acute complications. In: *Childhood Leukemias*. 2nd ed. New York: Cambridge University Press; 2006:709-38

Risk Factors for Development of Tumor Lysis Syndrome



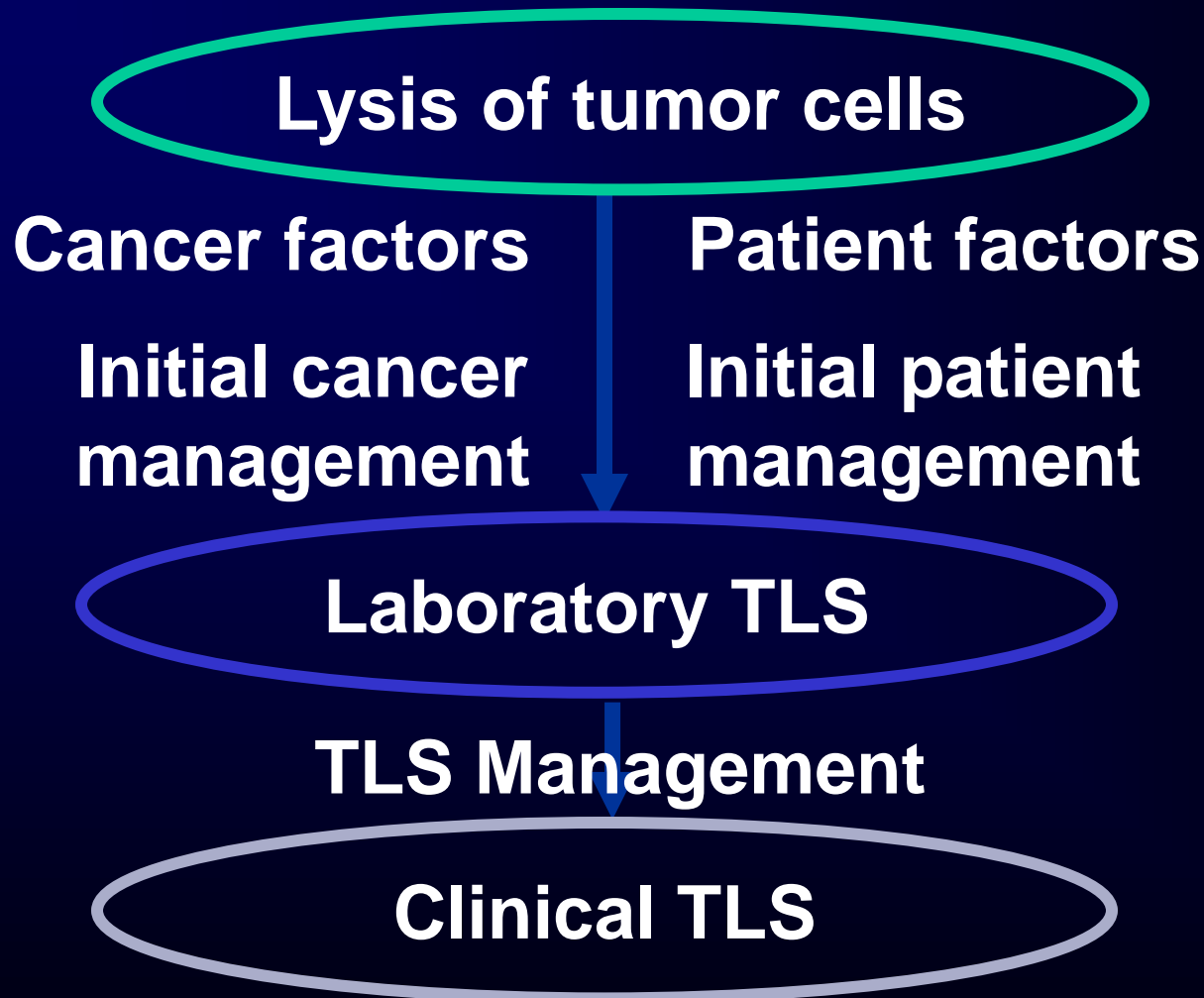
Risk for TLS – Patient Factors

- **Patient factors**
 - **Gout**
 - **Chronic renal insufficiency**
 - **Hypertension**
- **Presentation**
 - **Hyperuricemia**
 - **Dehydration**
 - **Diminished urine output**
 - **Acute renal insufficiency**
 - **Acidic urine**

Risk for TLS – Cancer Factors

- **Bulky tumors**
 - Large tumor mass
 - Organ infiltration
 - Bone marrow involvement (leukemias are bulky)
- **Highly proliferative tumors - LDH is a marker**
- **Chemosensitive tumors**
 - Burkitt lymphoma

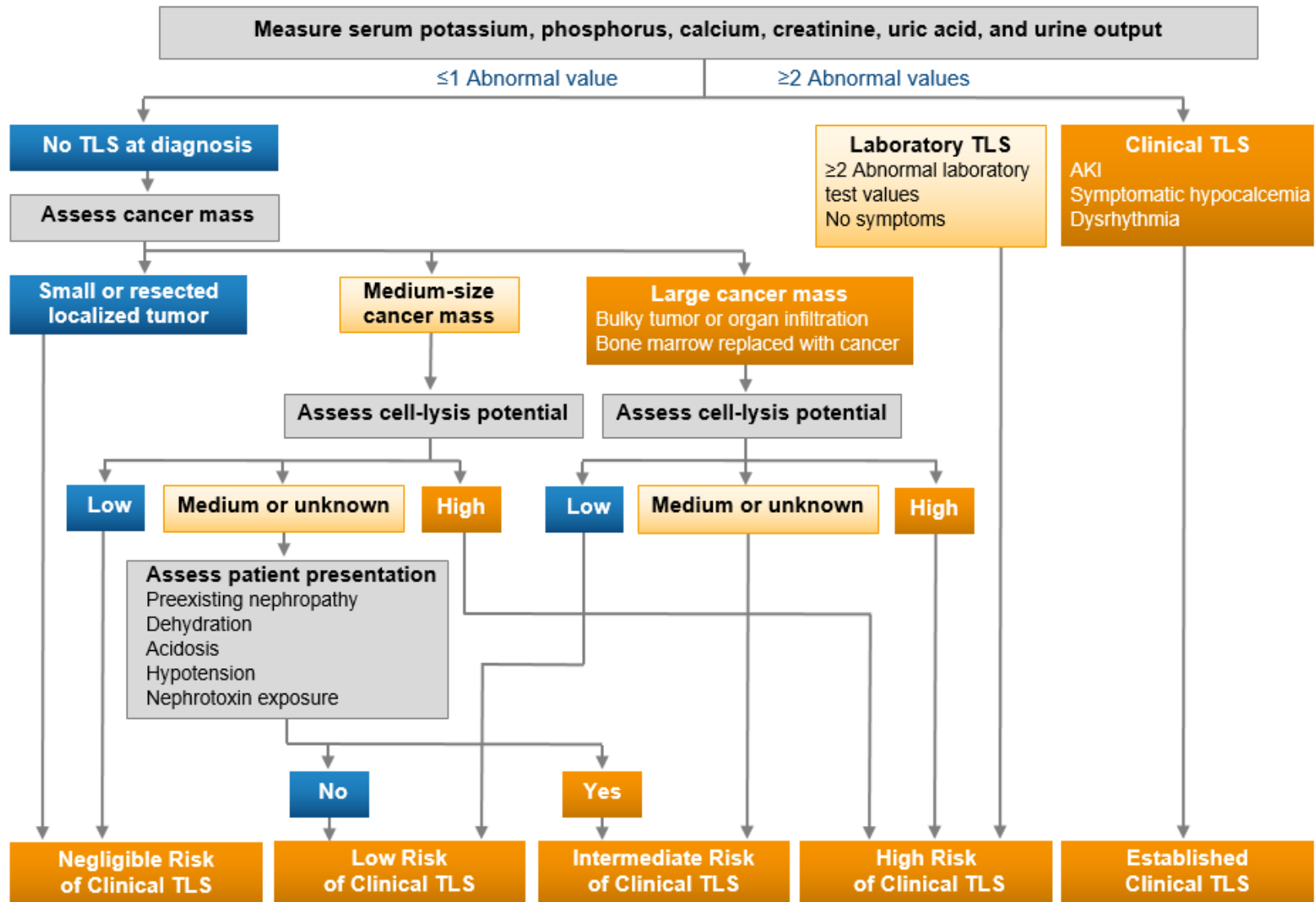
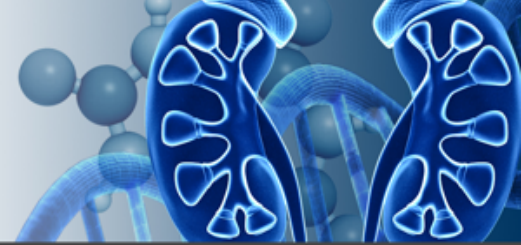
Risk Factors for Development of Tumor Lysis Syndrome



Management and Prevention

- TLS risk stratification
- Monitoring
 - Outpatient vs. inpatient
 - Cardiac monitoring or not
 - Laboratory frequency
- IV fluids
- Potassium
- Phosphorus
- Uric acid

TLS Risk Stratification



From *N Engl J Med*, Howard SC, et al. The tumor lysis syndrome, 364:1844-1854. © 2011 Massachusetts Medical Society. Reprinted with permission from Massachusetts Medical Society.

Stratification according to risk of clinical TLS

Negligible risk

**No prevention,
no monitoring**

Some risk

**IVF, monitoring,
uric acid control**

**Low
risk**

**Interme-
diate risk**

**High
risk**

**Established
clinical TLS**

**Labs daily,
allopurinol**

**Labs q 12 hr,
rasburicase
or allopurinol**

**Labs q 4-8 hr, cardiac
monitor, rasburicase**

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