When Cells Die: Recognition and Management of Tumour Lysis Syndrome (TLS)

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CancerCare Manitoba
Action Cancer Manitoba

Disclosures

Research support	Lundbeck, BioCanRx
Employee	-
Consultant	Lundbeck, Janssen, Pfizer
Stockholder	-
Speaker	-
Scientific advisory board	Otsuka, Lundbeck, Amgen, Pfizer, Shire

Proposals for definition of MRD terms in ALL. Data from Brüggemann et al16 with permission.

Successful Supportive Care in Oncology

	Early	Late
Anti-emesis	+++	+
TLS	+++	-
Antimicrobials & Vaccinations	++	++
GCSF	+	-
Blood Transfusion	++	+
VTE	+	+
Psycho-social	+++	+++
Tobacco d/c	++	++

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Successful Supportive Care in Hematoligical Malignancy

	Early	Late
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TLS	+++	-
Antimicrobials/ Vaccinations	++	++
GCSF	++	-
Blood Transfusion	++	+
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Psycho-social	+++	+++
Tobacco d/c	++	++

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Objectives:

1. Describe the pathophysiology of TLS
2. Summarize risk factors and clinical consequences of TLS
3. Provide an approach to prevention and management of TLS
4. Differentiate TLS from other metabolic emergencies in oncology

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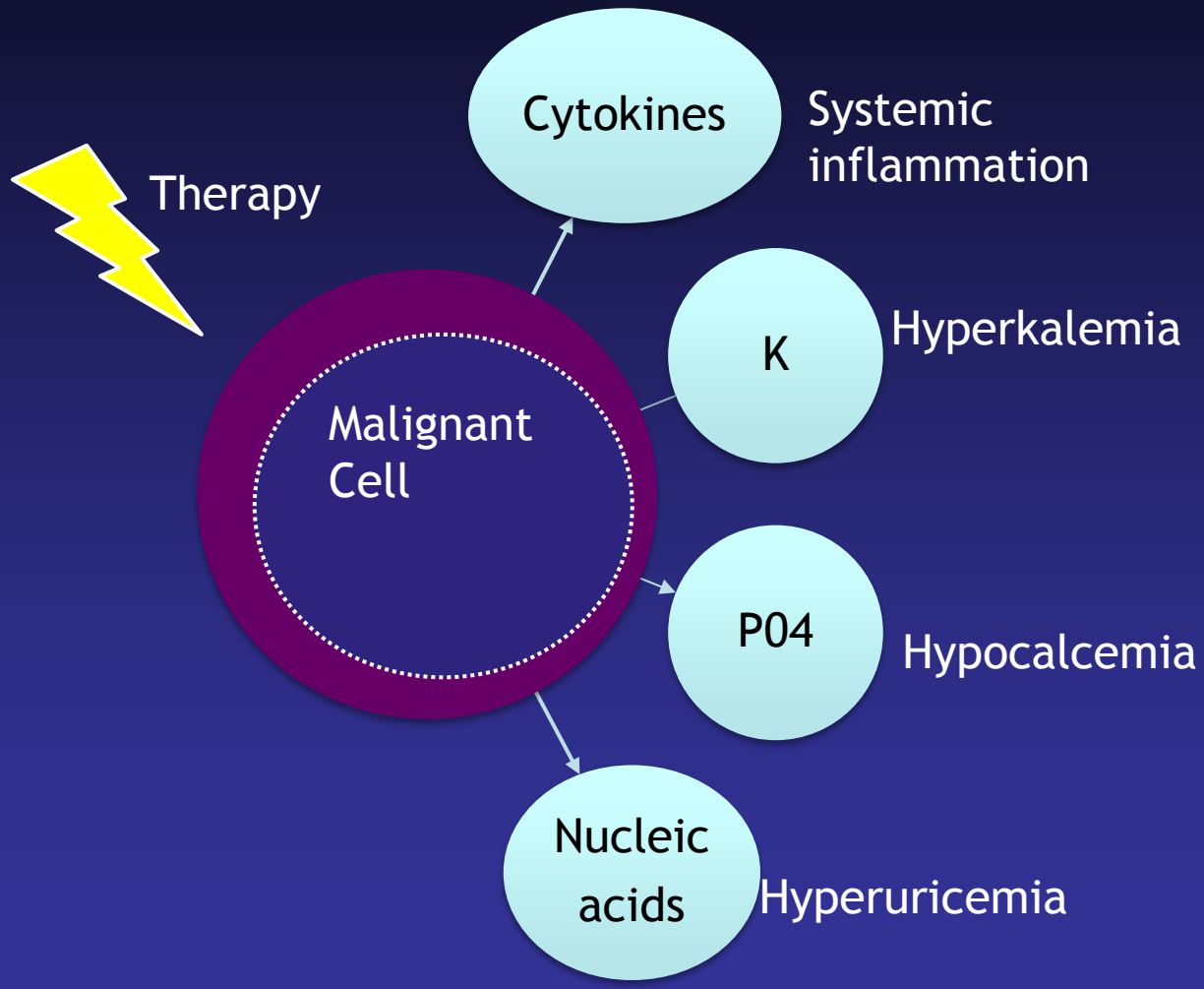
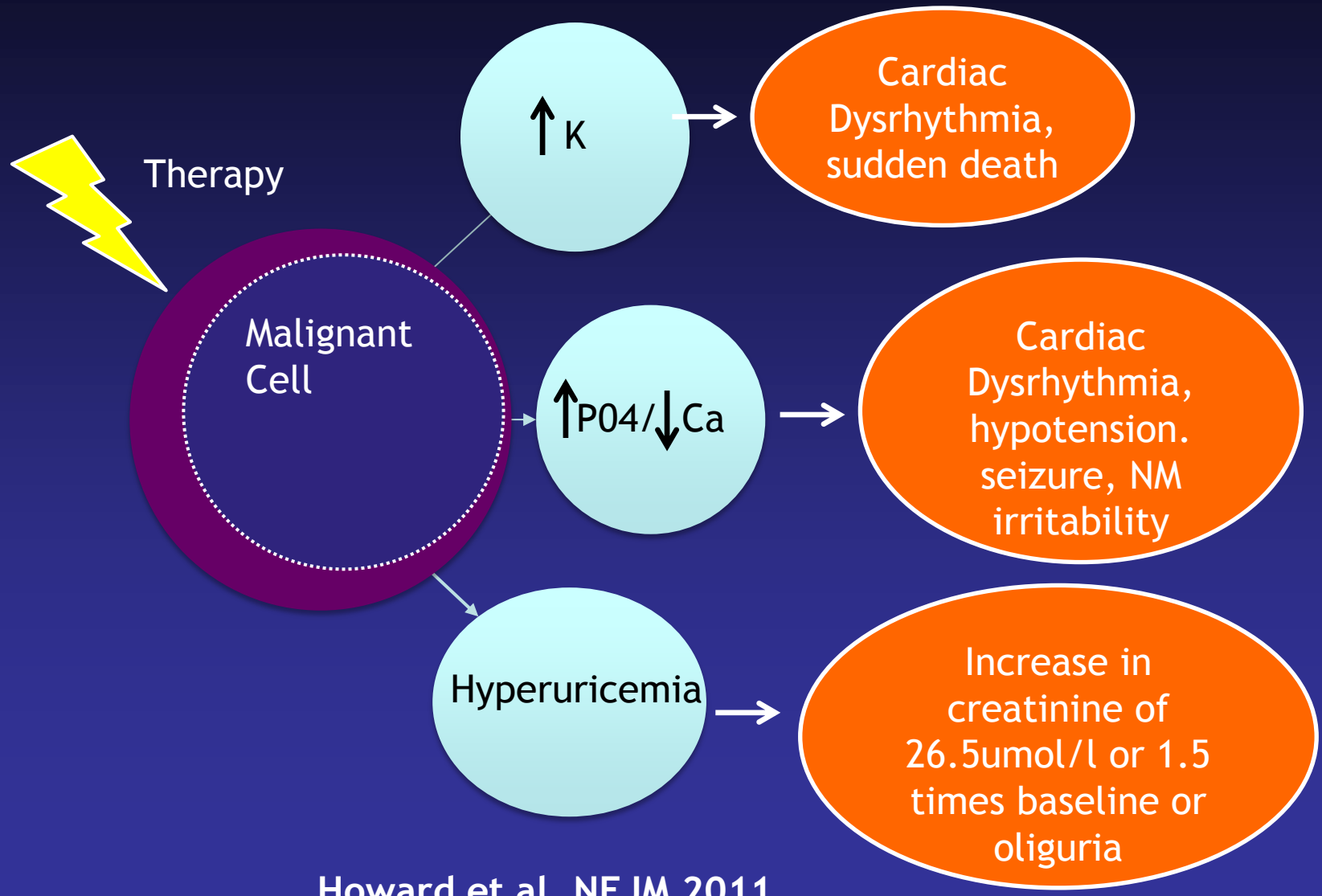
Pathophysiology of TLS

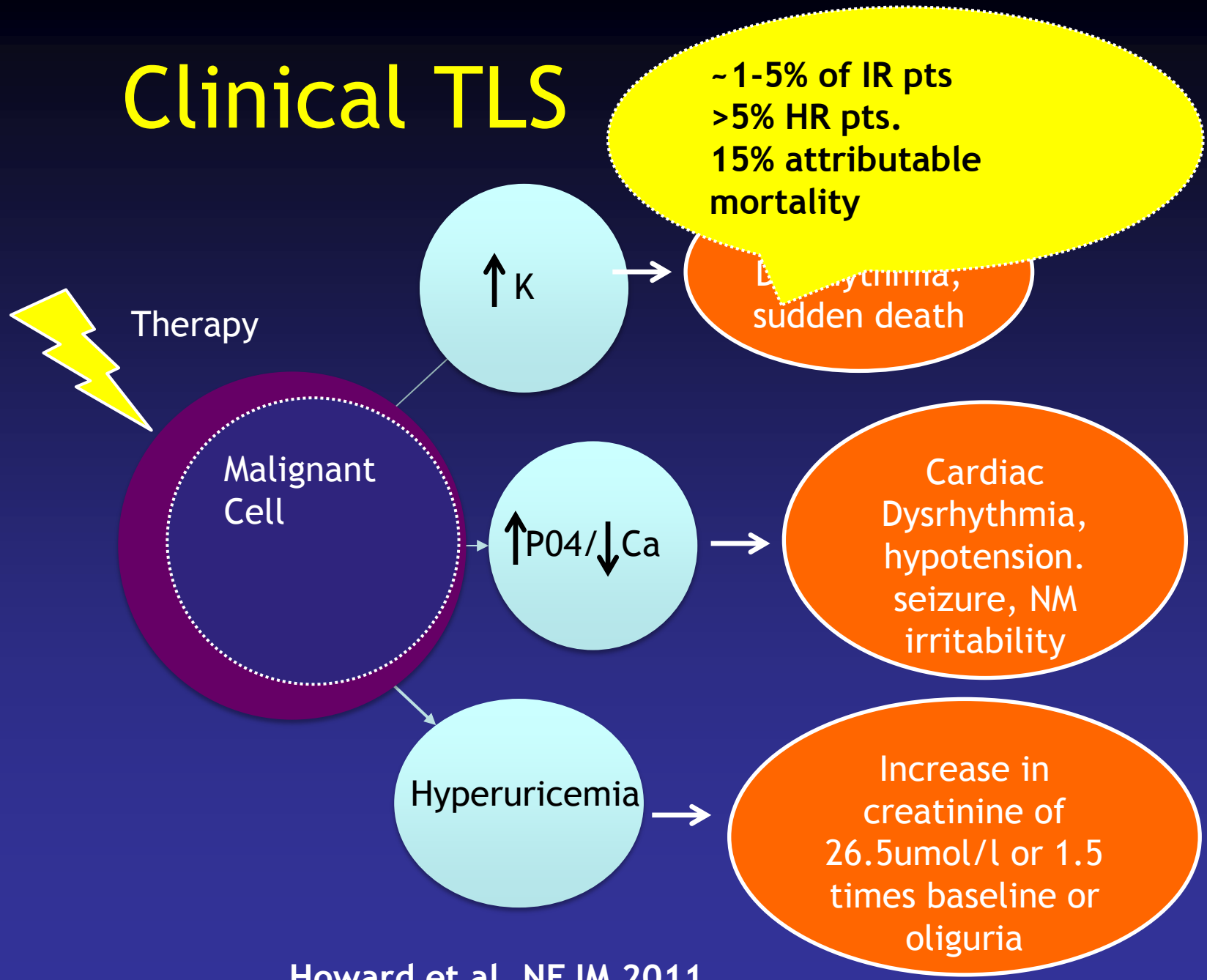


Clinical TLS



Howard et al. NEJM 2011

Clinical TLS



Howard et al. NEJM 2011

Laboratory TLS

Cairo-Bishop criteria	
	25% change or out of normal range for ≥2 values within 3d before or 7ds after Rx
Uric acid	≥476umol or 25% increase from baseline
K	≥6 or 25% increase from baseline
P04	≥1.45 or 25% increase from baseline
Ca	≤1.45 or 25% decrease from baseline

Cairo et al BJH 2004; Howard et al NEJM 2011

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Risk Factors for TLS

Risk Factor	Example
Tumor Burden	Lymph Nodes WBC Organ infiltration BM involvement
Cell Lysis Potential	Sensitivity to chemo (hem) Chemo intensity (hem) LDH
Other features on Presentation	Impaired Renal function/age Dehydration Other nephrotoxins Hypotension
Supportive Care	Hydration Exogenous K or Ca Thiazides; ASA; Caffeine; Vit C; Alcohol; Cisplatin Allopurinol/rasburicase

Howard et al. NEJM 2011

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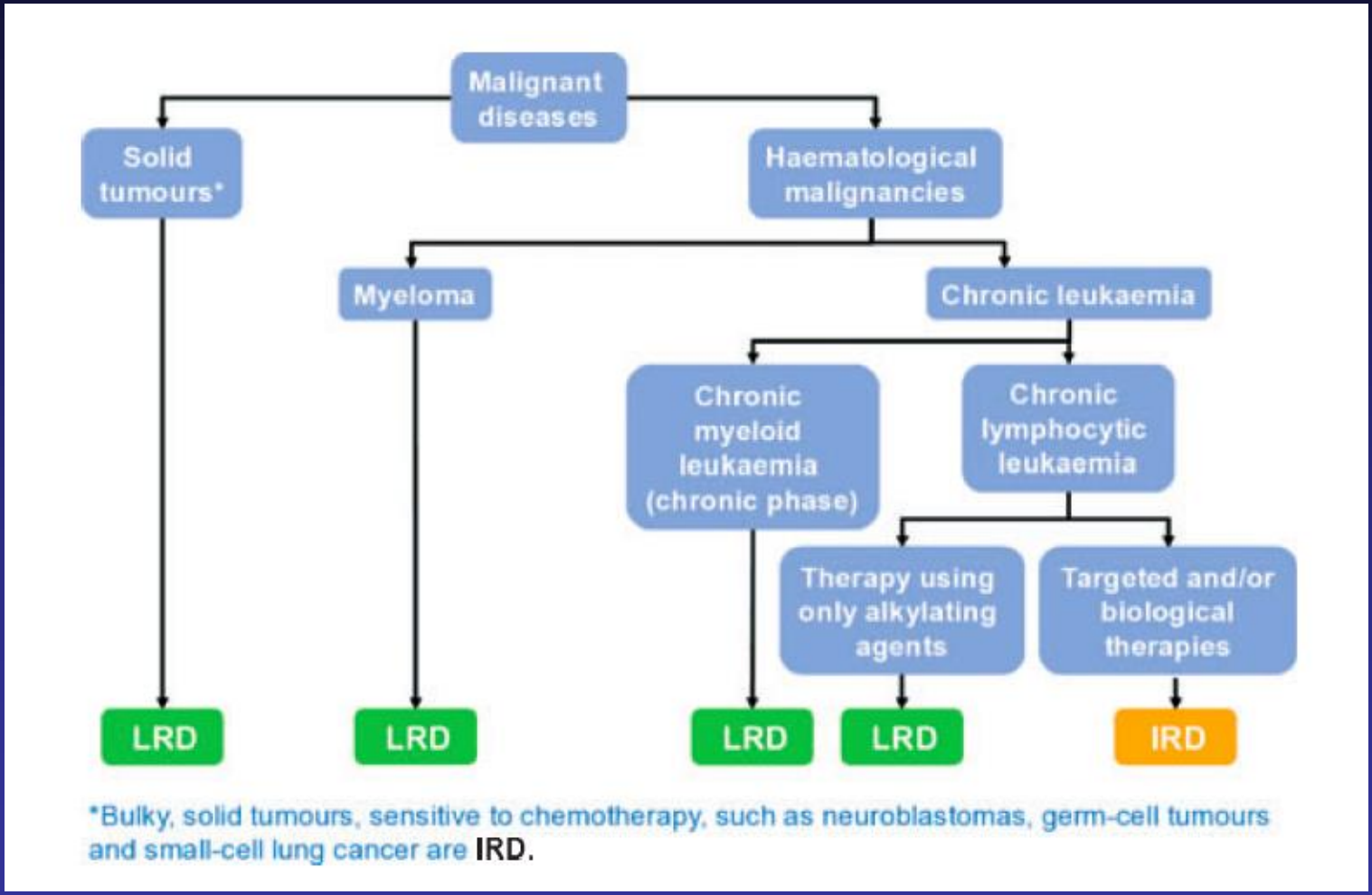
Risk Factors for TLS
Solid tumours and "indolent" HM



Cairo et al BJH 2010

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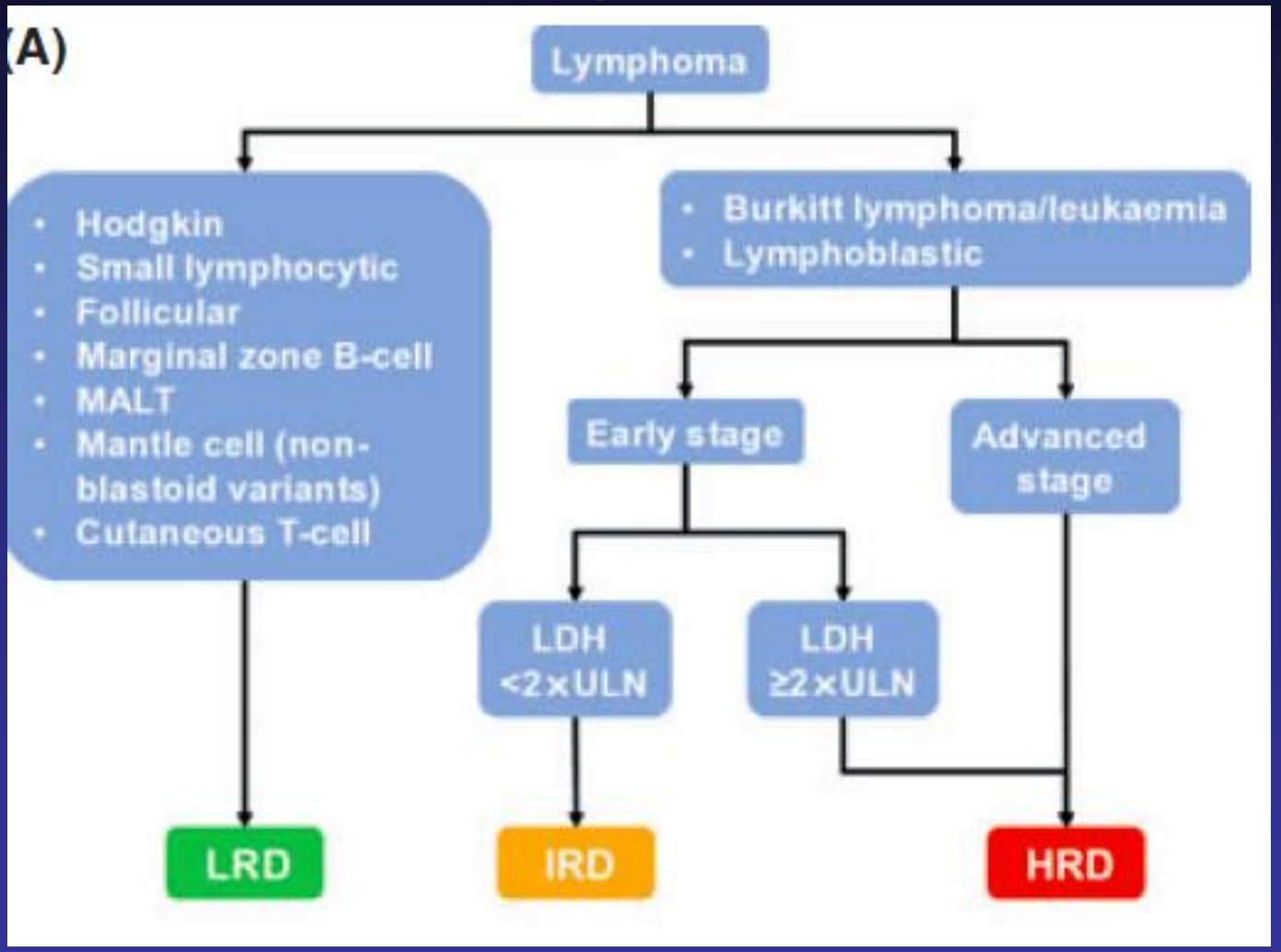
Risk Factors for TLS Lymphomas



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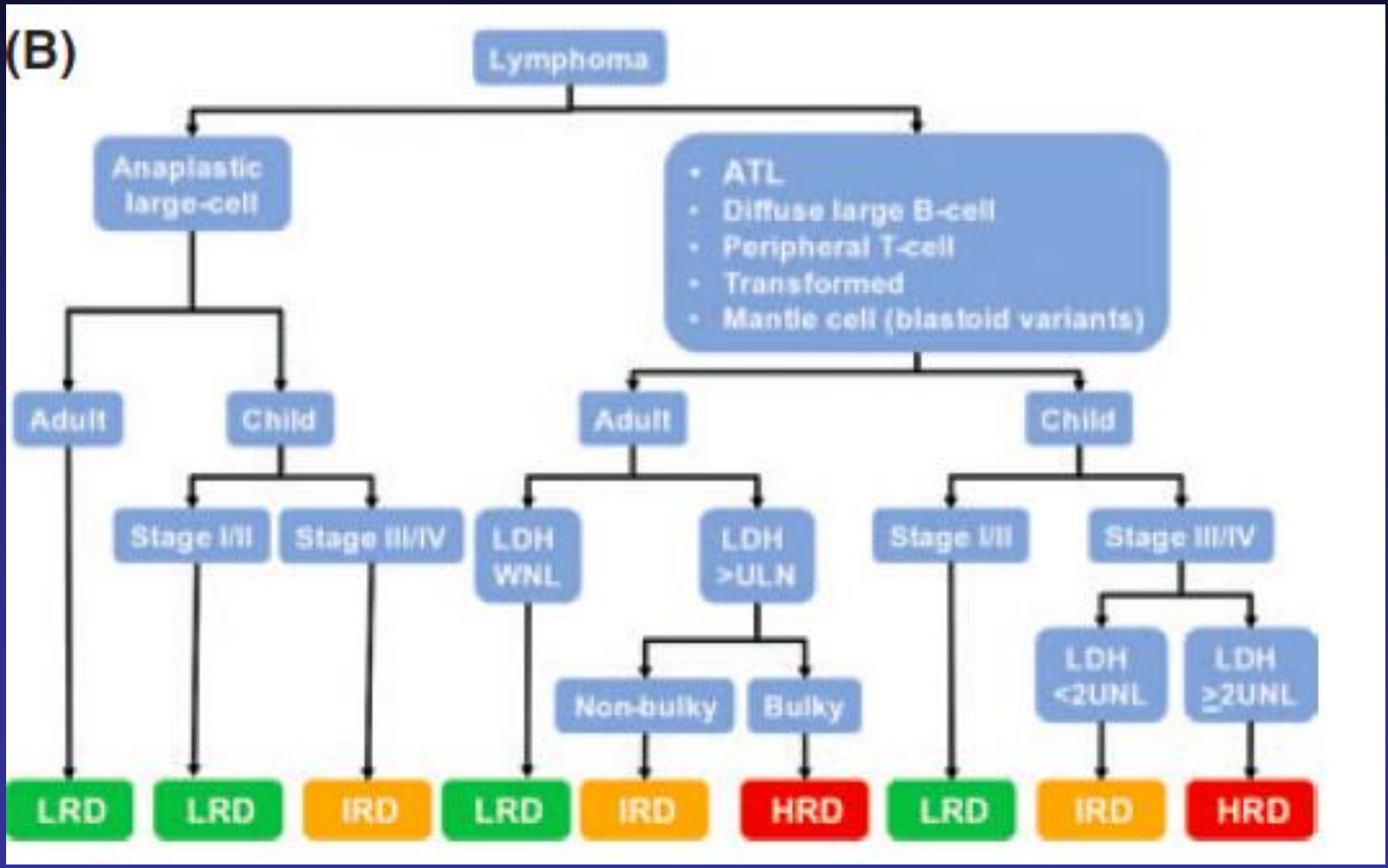
Risk Factors for TLS
Lymphomas



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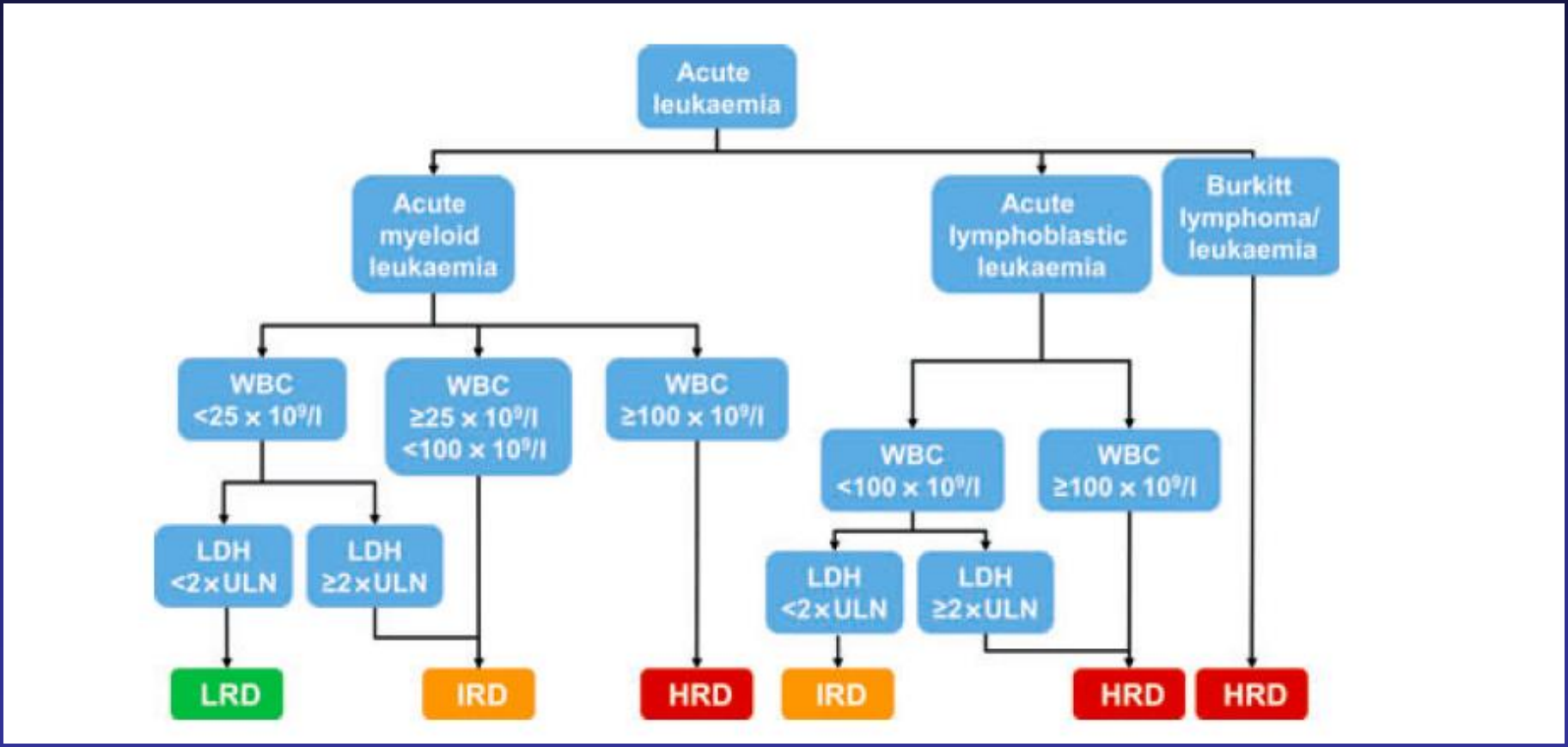
Risk Factors for TLS
Acute Leukemias



Cairo et al BJH 2010

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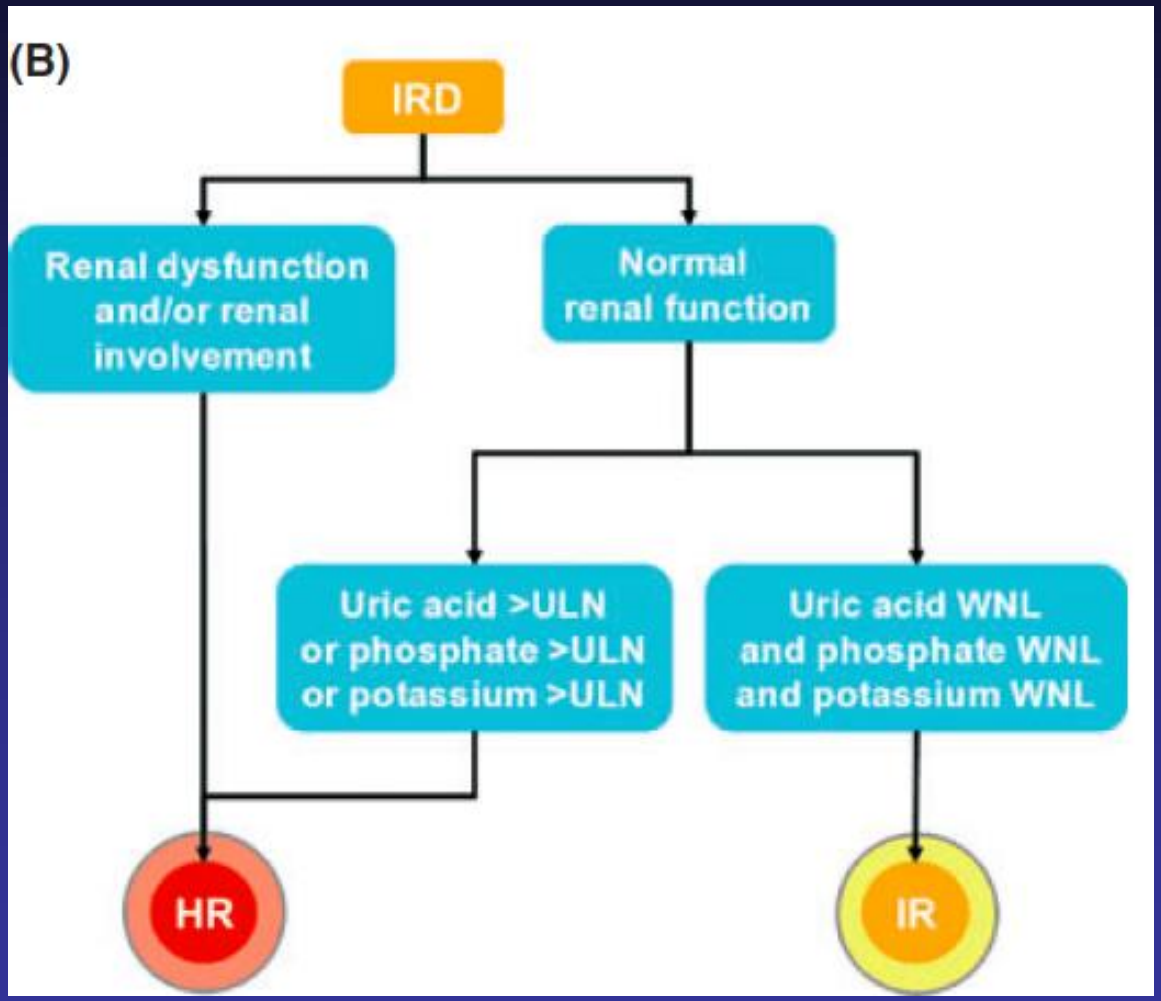
Risk Factors for TLS: The role of renal impairment



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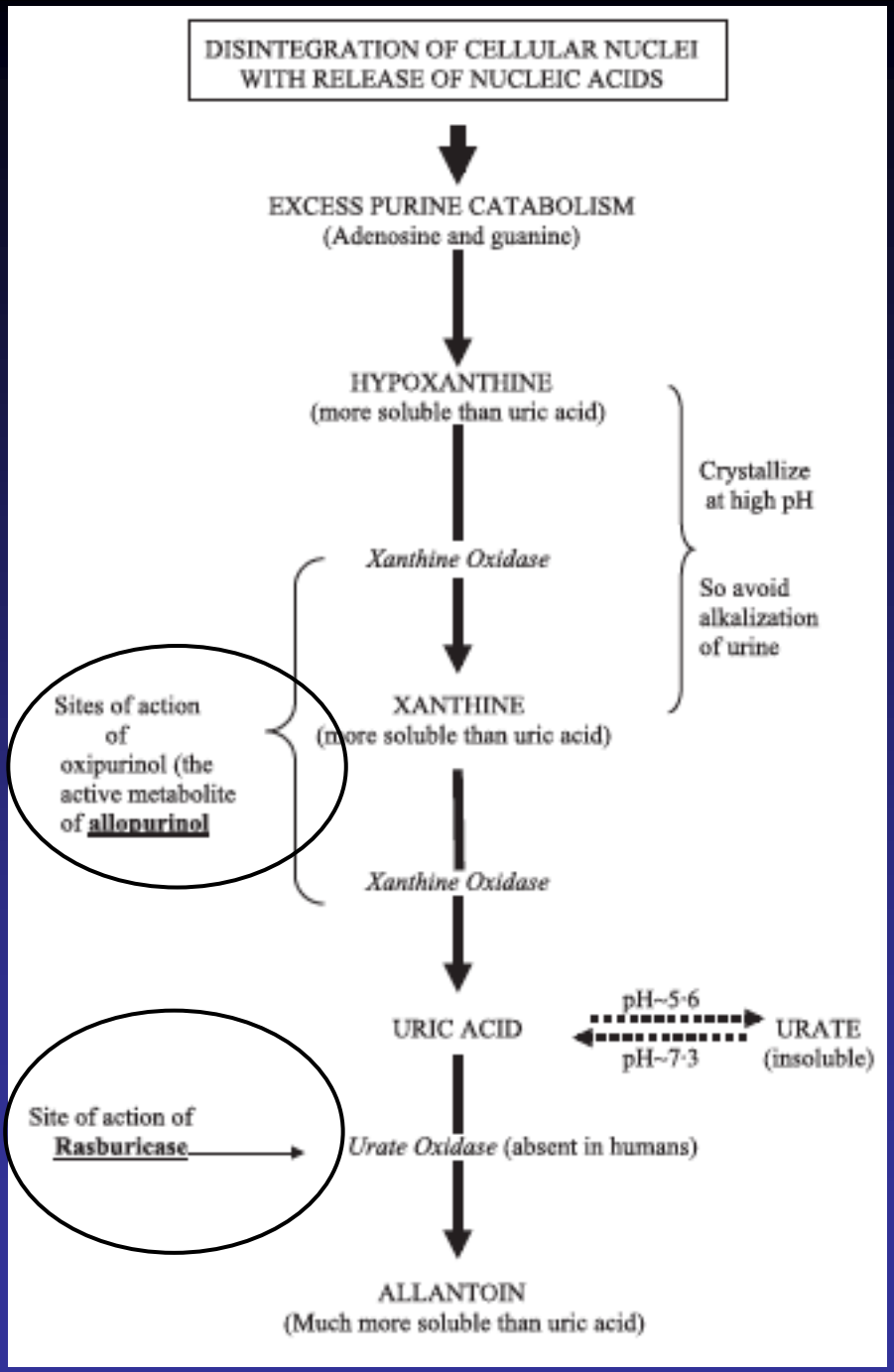

Uric Acid & TLS

Jones et al BJH 2015

TLS prophylaxis: Risk-based

TLS Risk			
	Low	Intermediate	High
Monitoring	Y	Y	Y
Hydration	N	Y	Y
Allopurinol	+/-	Y	Y
Rasburicase	N	+/-	Y

Clinical TLS treatment

Intravenous fluids 3l/m^2/day

Rasburicase 7.5mg x 1, then allopurinol

Frequent ECGs

Laboratory tests q4-6 hrs

+/- Cardiac monitoring/ICU

+/- Hemodialysis

l TLS treatment

Chemistry tube on ice

Caution in G6PD def

venous fluids 3l/m^2/day

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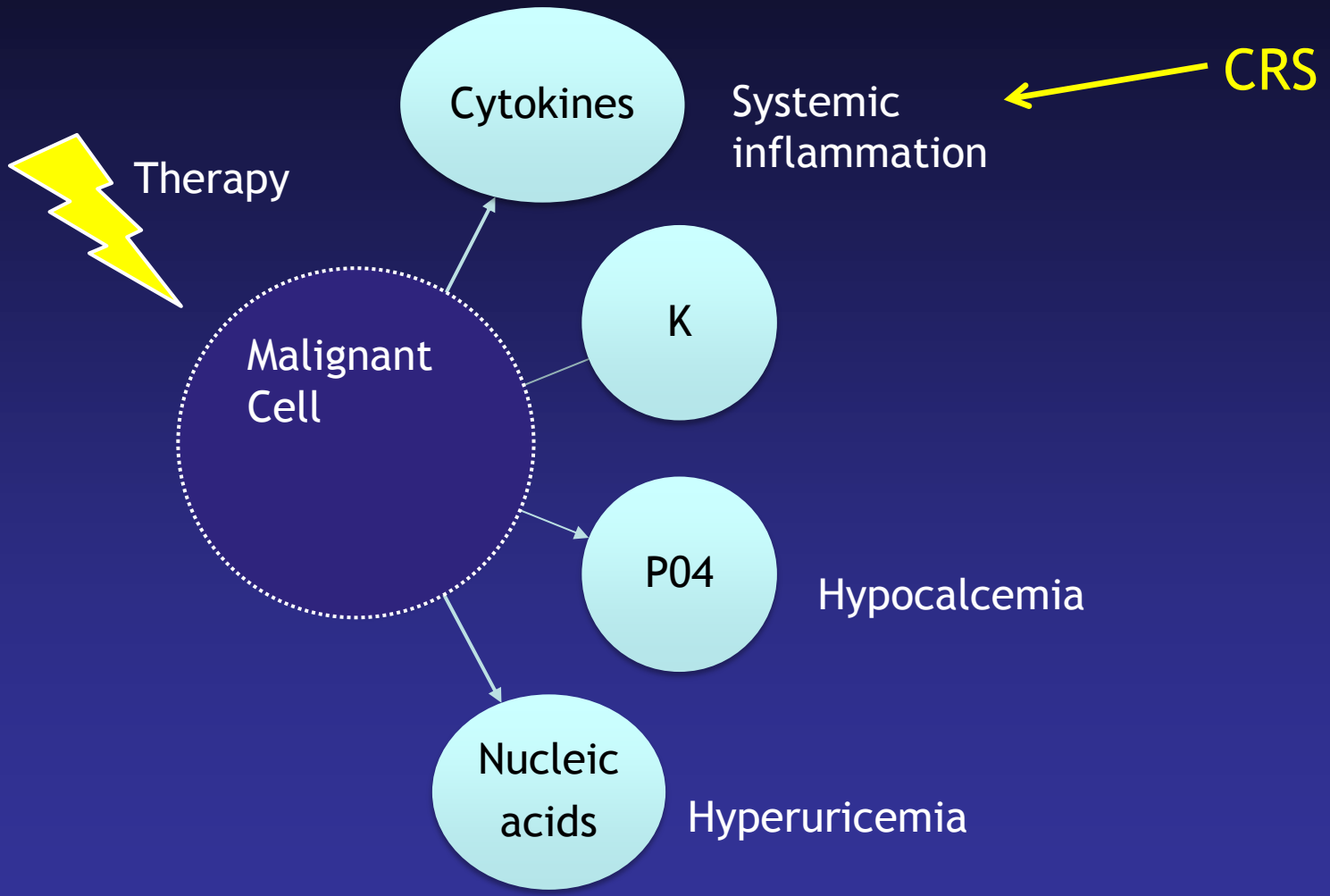

Cytokine Release Syndrome

Activated lymphocytes and/or myeloid cells release inflammatory cytokines (eg IL-6)

General	Fever, malaise, fatigue, anorexia, myalgias, arthralgias, nausea, vomiting, headache
Skin	Rash
GI	Nausea, vomiting, diarrhea
CVS	Tachycardia, widened pulse pressure, hypotension, increased cardiac output (early), diminished cardiac output (late)
Coagulation	Elevated D-dimer, hypofibrinogenemia ± bleeding
Renal	Azotemia
Hepatic	Transaminitis, hyperbilirubinemia

Lee DW, et al. Blood. 2014

Cytokine Release Syndrome

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Therapy:
- **General supportive care**
- **Corticosteroids**
- **+/-Tocilizumab**

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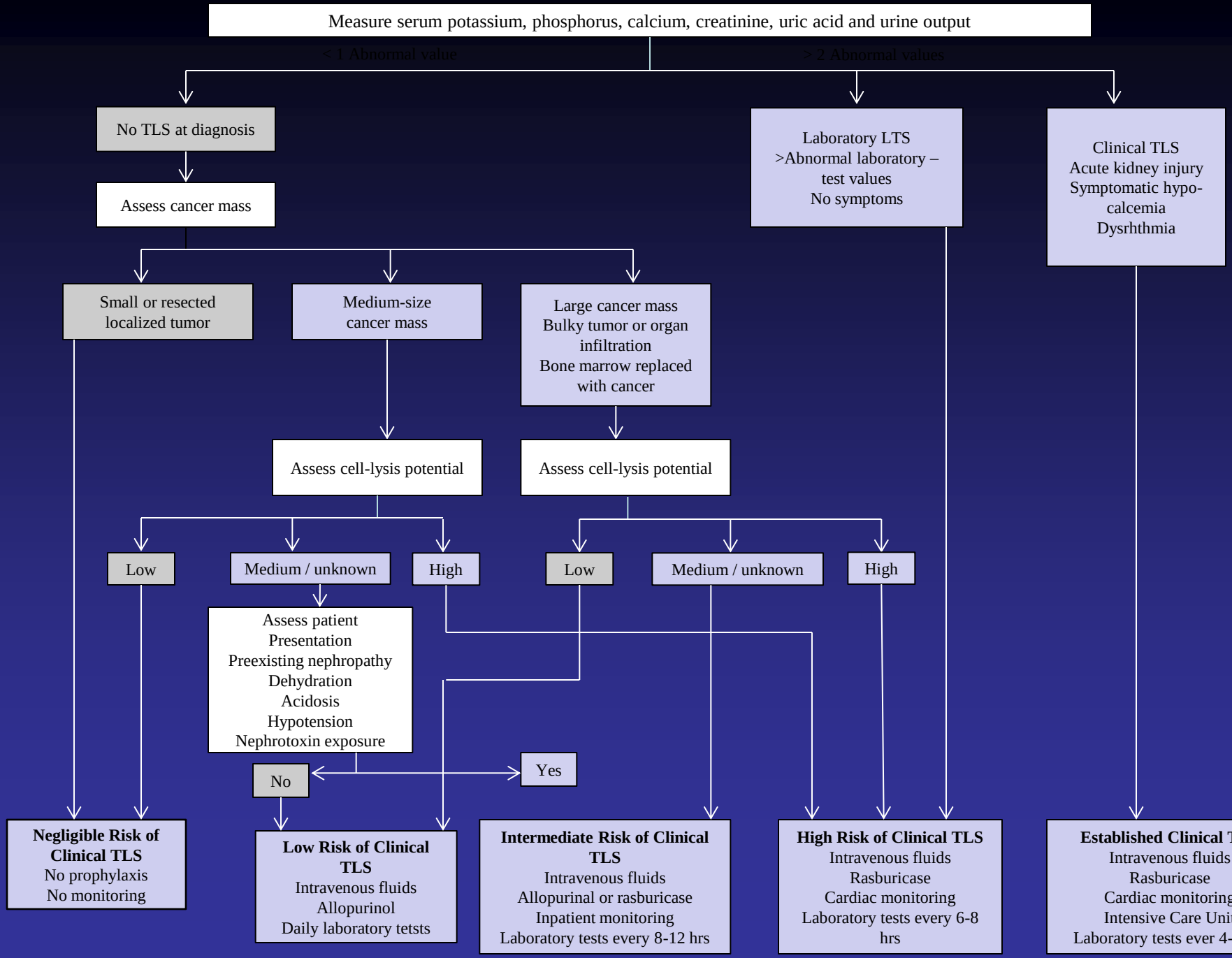
Extra slides


Measure serum potassium, phosphorus, calcium, creatinine, uric acid and urine output
< 1 Abnormal value
> 2 Abnormal values
No TLS at diagnosis
Assess cancer mass
Laboratory LTS
>Abnormal laboratory – test values
No symptoms
Clinical TLS
Acute kidney injury
Symptomatic hypo-calcemia
Dysrhthmia
Small or resected localized tumor
Medium-size cancer mass
Large cancer mass
Bulky tumor or organ infiltration
Bone marrow replaced with cancer
Assess cell-lysis potential
Assess cell-lysis potential
Low
Medium / unknown
High
Low
Medium / 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 tetsts
Intermediate Risk of Clinical TLS
Intravenous fluids
Allopurinal or rasburicase
Inpatient monitoring
Laboratory tests every 8-12 hrs
High Risk of Clinical TLS
Intravenous fluids
Rasburicase
Cardiac monitoring
Laboratory tests every 6-8 hrs
Established Clinical TLS
Intravenous fluids
Rasburicase
Cardiac monitoring
Intensive Care Unit
Laboratory tests ever 4-6 hrs

Criteria for rasburicase in MB

ALL	**Clinical TLS OR** **• Initial WBC> 100** **• Lymphomatous presentation and high tumor burden**
AML	Clinical TLS, OR • Initial WBC>50
Lymphoma "Very Aggressive" Histology (BL or Lymphoblastic Lymphoma)	Clinical TLS • Stage III /IV disease, OR • Any stage disease with LDH > than 2x ULN and uric acid $\geq$ 476 umol/L
Germ Cell Tumour	Clinical TLS, OR • Stage III/IV disease and LDH greater than 2 times ULN and Uric acid $\geq$ to 476 umol/L

sification	Cairo-Bishop criteria [11]	Howard criteria [12]	Key difference in Howard criteria
ory TLS	25% change or level above or below defined values for any 2 or more serum values defined below within 3 days before or 7 days after initiation of therapy	Two or more metabolic abnormalities must be present during the same 24-hour period within 3 days before to 7 days after initiation of therapy	Removed 25% change and added that both abnormalities be present in 24-hour period
cid	≥476 μmol/L or 25% increase from baseline	≥475.8 μmol/L (adults) or above ULN range for age (children)	Lowered threshold value and removed 25% increase from baseline
sium	≥6.0 mmol/L or 25% increase from baseline	≥6.0 mmol/L	Removed 25% increase from baseline
phorous	≥2.1 mmol/L (children), ≥1.45 mmol/L (adults), or 25% increase from baseline	≥2.1 mmol/L (children), ≥1.5 mmol/L (adults)	Raised threshold value for adults and removed 25% increase from baseline
um	≤1.75 mmol/L or 25% decrease from baseline	<1.75 mmol/L corrected calcium[a] or <0.3 mmol/L ionized calcium	Amended values with distinction between corrected and ionized calcium

Clinical TLS

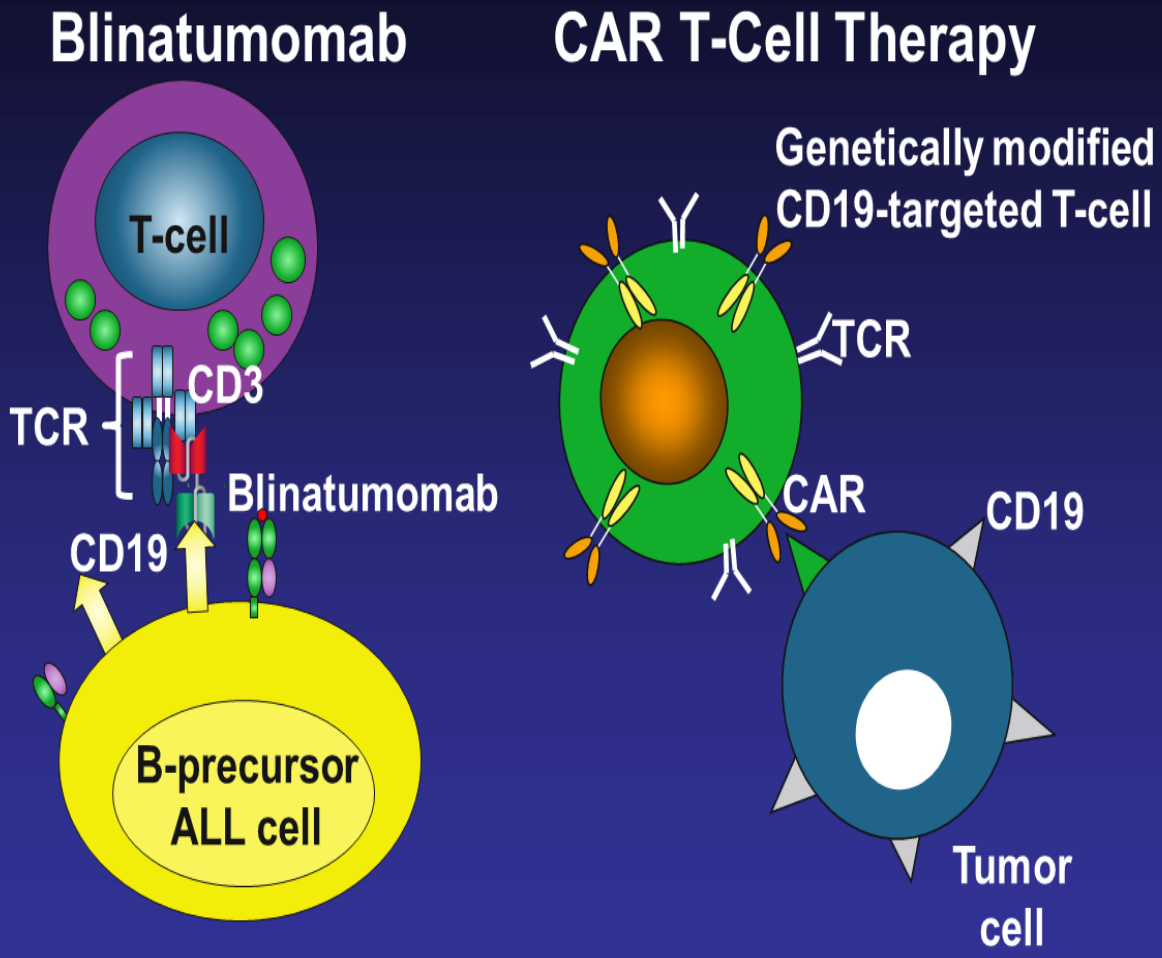
Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia

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

Increase in the serum creatinine level of 0.3 mg/dl (26.5 μmol/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

Howard et al. NEJM 2011

Immunotherapy Targets in ALL/NHL



Maino JE, et al. Exp Rev Hema. 2016;9:563-577.