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Tumor lysis syndrome

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TUMOR LYSIS SYNDROME

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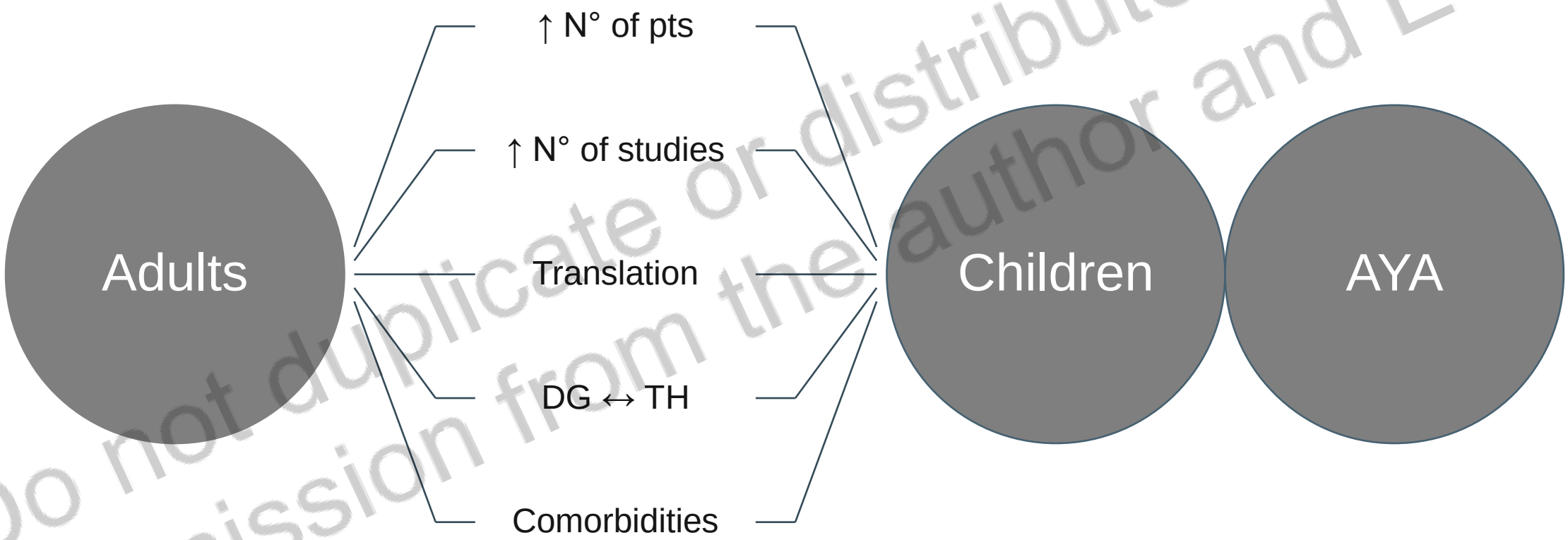
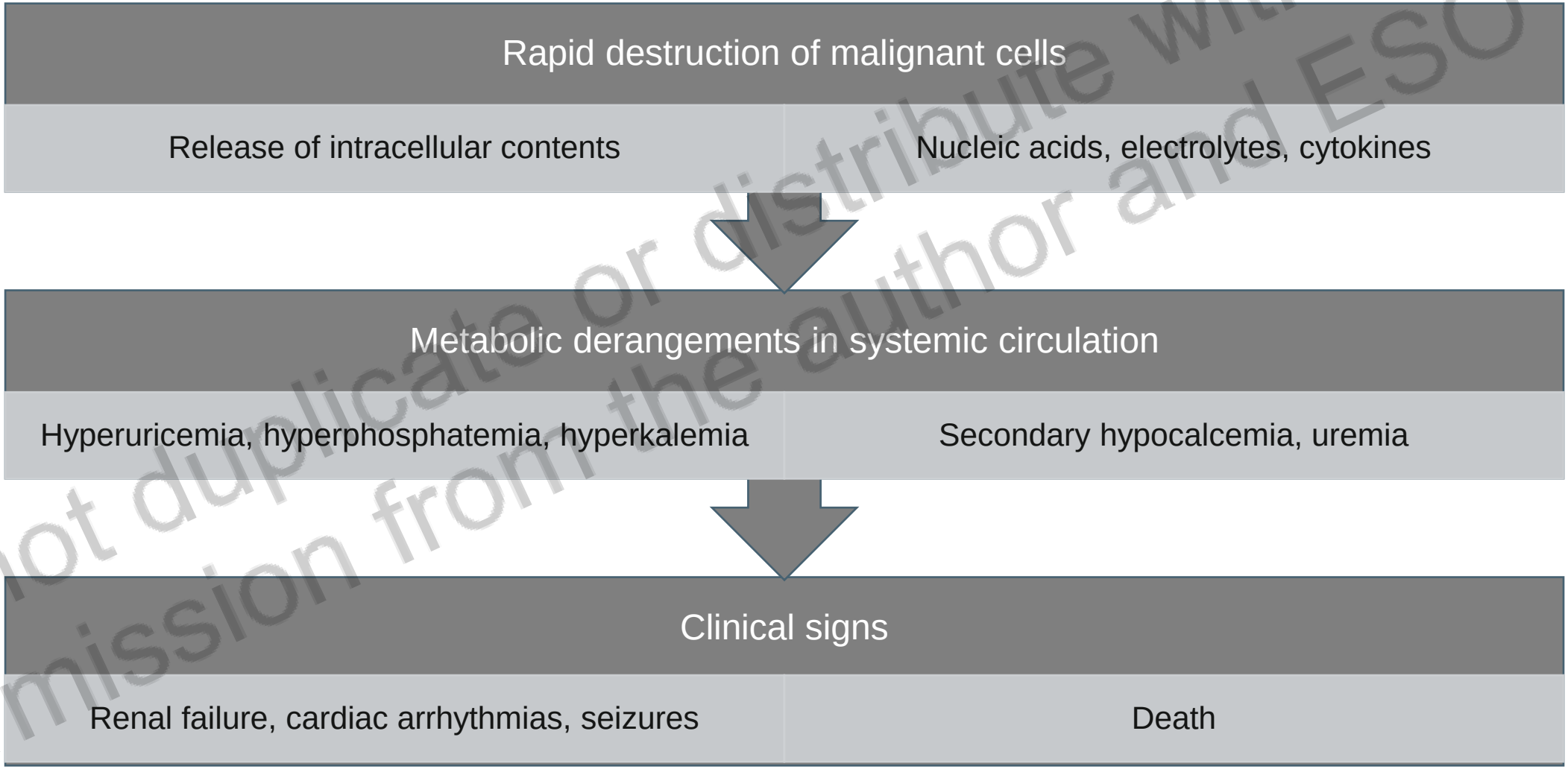
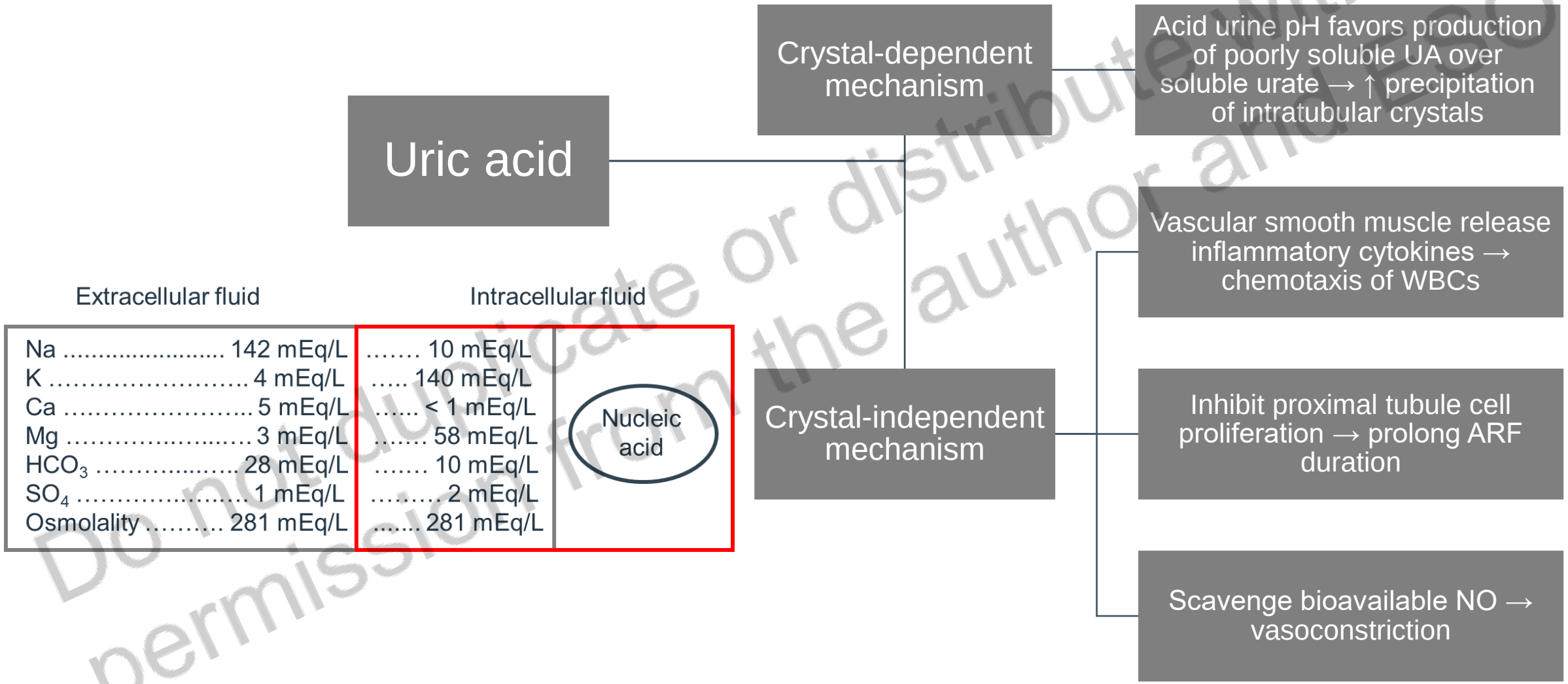
THE MOST COMMON ONCOLOGICAL EMERGENCY



TUMOR LYSIS SYNDROME (TLS)



URIC ACID AND ELECTROLYTES



INCIDENCE

- Not well defined:
  - Historical lack of standardized diagnostic criteria
  - Variability of:
    - Patient populations
    - Treatment regimens
- Variety of data:
  - Incidence: 4.4 – 53.6%
    - Majority: LTLS
    - L/MIC: CTLS (15.9%)
  - Mortality: 21.4% (children)
  - Uncommon in relapsed and chemo-resistant malignancies

CRITERIA

- Original criteria: 1993, Hande & Garrow
  - Classification
    - Change of 25% from baseline (ULN / LLN)
    - Within 4 days after the initiation of CT
  - Distinction of LTLS and CTLS
- 1st revision: 2004, Cairo & Bishop
  - LTLS
    - At least 2 isolated metabolic derangements
    - 3 days prior to and up to 7 days after the CT initiation
  - Spontaneous vs CT-induced
    - Most often seen 48 – 72h after CT initiation

LABORATORY TLS (LTLS)

Element	Value	Change from the baseline
Uric acid (UA)	≥ 476 µmol/L (≥ 8 mg/dL)	↑ 25%
Potassium (K)	≥ 6 mmol/L (≥ 6 mEq/L)	↑ 25%
Phosphorus (P)	≥ 2.1 mmol/L (≥ 6.5 mg/dL)	↑ 25%
Calcium (Ca)	≤ 1.75 mmol/L (≤ 7 mg/dL)	↓ 25%

Cairo MS, Bishop M. Tumor Lysis Syndrome: new therapeutic strategies and classification . Br J Haematol. 2004;127(1):3-11. .

CLINICAL TLS (CTLS)

Complication	Grade					
	0	1	2	3	4	5
LTLS	Absent	Present	Present	Present	Present	Present
Creatinine (Cr)	< 1.5 x ULN	1.5 x ULN	> 1.5-3 x ULN	> 3-6 x ULN	> 6 x ULN	Death
* Oliguria	Urine output < 0.5 ml/kg/h for 6h					
Arrhythmia	None	Intervention not indicated	Non-urgent medical intervention	Symptomatic, incompletely controlled medically; Controlled with device	Life-threatening (CHF, hypotension, syncope, shock)	Death
Seizures	None	Not applicable	One, brief, generalized; Well controlled; Infrequent local motor	Altered consciousness; Poorly controlled; Tetany	Prolonged, repetitive (status epilepticus; intractable EPI)	Death

Cairo MS, Bishop M. Tumor Lysis Syndrome: new therapeutic strategies and classification . Br J Haematol. 2004;127(1):3-11. .

IN THE CURRENT ERA

- 2nd revision: pending
  - ≥ 2 metabolic abnormalities can be present simultaneously – **tumor unrelated**
    - Hypocalcemia associated with sepsis
  - 25% change from baseline
    - Not clinically significant, unless the value is already outside normal – **removal proposed**
  - Hypocalcemia – **debate**
    - Secondary phenomenon to hyperphosphatemia
    - Indicator of calcium phosphate binding and precipitation in tissues
  - ↑ LDH
    - Surrogate biomarker for rapid cell turnover
    - Important for TLS risk assessment
- Targeted therapies:
  - Rapidly evolving, highly effective
  - Tumors previously rarely associated – increasingly described in the literature
  - Morbidity and mortality may be higher:
    - Lack of recognition
    - Inadequate prophylaxis
    - Delayed treatment

Agent	Class	Malignancies	Incidence: single/combined (%)
Monoclonal Ab			
Brentuximab	Anti-CD 30	ALCL	1.7
Obinutuzumab	Anti-CD 20	NHL, R/R DLBCL	3/5
Rituximab	Anti-CD 20	NHL, PTLD	Case reports
Kinase inhibitors			
Alvocidib	CDK inhibitor	AML	4.2/42.2
Dasatinib	Bcr-Abl/Src TKI	Ph+ ALL, CML	3.4/4.2
Dinaciclib	CDK inhibitor	ALL, AML	15
Imatinib	Bcr-Abl TKI	Ph+ ALL, GIST	Case reports
Nilotinib	Bcr-Abl TKI	CML	Case reports
Sorafenib	VEGFR TKI	HCC, RCC	Case reports
Sunitinib	VEGFR TKI	GIST, RCC	Case reports
Chimeric immunoreceptors			
CAR-T	CD19 targeted	B-cell malignancies	10
Immunomodulatory agents			
Lenalidomide	Analog of Thalidomide	NHL	4/1.7 (+ Rituximab)
Thalidomide	Unknown mechanism	HCC	Case reports

Characteristics	Risk factors
Malignancy	Burkitt
	LBL
	DLBCL
	ALL
	Solid tumors: ↑ proliferative rates + rapid response to TH
Burden / extent of disease	Bulky disease (> 10 cm) / widely metastatic disease
	↑ LDH (> 2 x ULN)
	↑ WBC (> 25 x 10^9/L)
Patient - related	Preexisting renal disease (uremia, nephropathy, RF, UT obstruction)
	Oliguria, hypovolemia, hypotension
	Pre-TH hyperuricemia / hyperphosphatemia
	Concurrent use of nephrotoxic drugs
	Baseline UA > 450 µmol/L (7.5 mg/dL)
Effective / rapid cytoreductive TH	Sensitivity to disease-specific TH (steroids, etoposide) + anesthesia / surgery

TLS & LEUKEMIAS

Type of malignancy	Risk	
Leukemia – Burkitt	High	
ALL	Intermediate	WBC < 100 x 10^9/L+ LDH < 2 x ULN
	High	WBC < 100 x 10^9/L+ LDH > 2 x ULN
		WBC > 100 x 10^9/L
AML	Low	WBC < 25 x 10^9/L+ LDH < 2 x ULN
	Intermediate	WBC < 25 x 10^9/L+ LDH > 2 x ULN
		WBC = 25 – 50 x 10^9/L

TLS & LYMPHOMAS

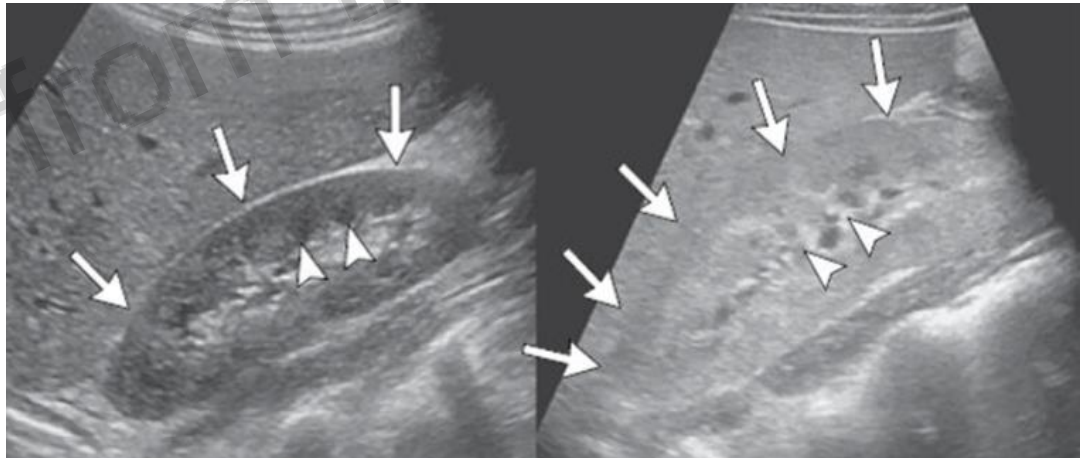
Type of malignancy		Risk	
Solid tumor		Low (* **Exception: GCT and NBL**)	
CML		Low	
Lymphoma – Burkitt type		Intermediate	Early stage + LDH < 2 x ULN
		High	Early stage + LDH > 2 x ULN
			Advanced stage
Lymphoma – non Burkitt type	ALCL	Low	Early stage
		Intermediate	Advanced stage
	LBL	Intermediate	Early stage + LDH < 2 x ULN
		High	Early stage + LDH > 2 x ULN
			Advanced stage
	HL, MZL, MALT, CTL	Low	
	DLBCL, PTL	Low	Early stage
		Intermediate	Advanced stage + LDH < 2 x ULN
		High	Advanced stage + LDH > 2 x ULN

TLS & RENAL FUNCTION

Renal dysfunction	Risk		
Absent	Low risk disease	No change	
	Intermediate risk disease	UA, P, K – N	No change
		UA, P, K > ULN	Upstage – high TLS risk
Present	Low risk disease	Upstage – intermediate TLS risk	
	Intermediate risk disease	Upstage – high TLS risk	

RENAL FAILURE (RF)

- Poor prognostic factor
- Preclusion of initial CT
- Long-term complications



PROPHYLAXIS ACCORDING TO TLS RISK

Minimal	Low	Intermediate	High	CTLS
None	Hydration	Hydration	Hydration	Hydration
	Allopurinol	Allopurinol / Rasburicase	Rasburicase	Rasburicase
	Close monitoring	Lab tests on 8-12h	Cardiac monitoring	Cardiac monitoring / ICU
			Lab tests on 6-8h	Lab tests on 4-6h

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

FLUID MANAGEMENT IN TLS

- Isotonic solution:
  - 2000 – 3000 ml/m^2/d IV (1.2 – 2 x maintenance)
  - 200 ml/kg/d in children ≤ 10 kg
- Urine output:
  - 80 – 100 ml/m^2/h (2 – 4 ml/kg/h)
    - 4 – 6 ml/kg/h in children ≤ 10 kg
  - Diuretics:
    - If necessary, to maintain diuresis
    - Usually not needed in pts with normal cardiac and renal function
    - Contraindicated in pts with hypovolemia or obstructive uropathy
    - Preferable loop diuretics (Furosemide):
      - Induce diuresis and may also increase potassium secretion
      - 0.5 – 2 mg/kg IV

International Expert Panel on TLS 2008

URINE ALKALINIZATION – TO ALKALINIZE OR NOT?

- In the past:
  - Acetazolamide and/or sodium bicarbonate
  - Alkalinization to a urine pH of 6.5 to 7 or even higher
  - Recommended to increase uric acid solubility
- Novel findings:
  - No data demonstrating efficacy
  - Likelihood of uric acid precipitation in the tubules
  - Promotion of calcium phosphate deposition in kidneys in pts with marked hyperphosphatemia
  - Favors calcium binding to albumin, decreasing ionized Ca concentration

ELECTROLYTE MANAGEMENT

Abnormality	Recommendation
Hyperphosphatemia ≥ 2.1 mmol/L (6.5 mg/dL)	
Moderate	Avoid IV / PO phosphate administration
Severe	Aluminum hydroxide (50-150 mg/kg/d/on 4-6h (avoid in pts with renal insufficiency)
	Dialysis
Hypocalcemia ≤ 1.75 mmol/L (7 mg/dL) or ionized Ca ≤ 0.8 mmol/L (3.2 mg/dL)	
Asymptomatic	No TH
Symptomatic	ECG
	Ca gluconate (30-100 mg/kg IV) Ca chloride (10 ml/kg IV)
Hyperkalemia	
Moderate (asymptomatic) ≥ 6 mmol/L	Avoid potassium IV and PO
	ECG + cardiac monitoring
	Sodium polystyrene sulphonate (1 g/kg/PD/on 6h)
Severe (symptomatic) ≥ 7 mmol/L	Ca gluconate (100-200 mg/kg IV, slowly)
	Insulin (0.1 U/kg IV) + D25% (2 ml/kg IV)
	Salbutamol per nebulisation (0,1 mg/kg)
	NaHCO3 (1-2 mEq/kg IV), not concomitantly with Ca!
	Dialysis

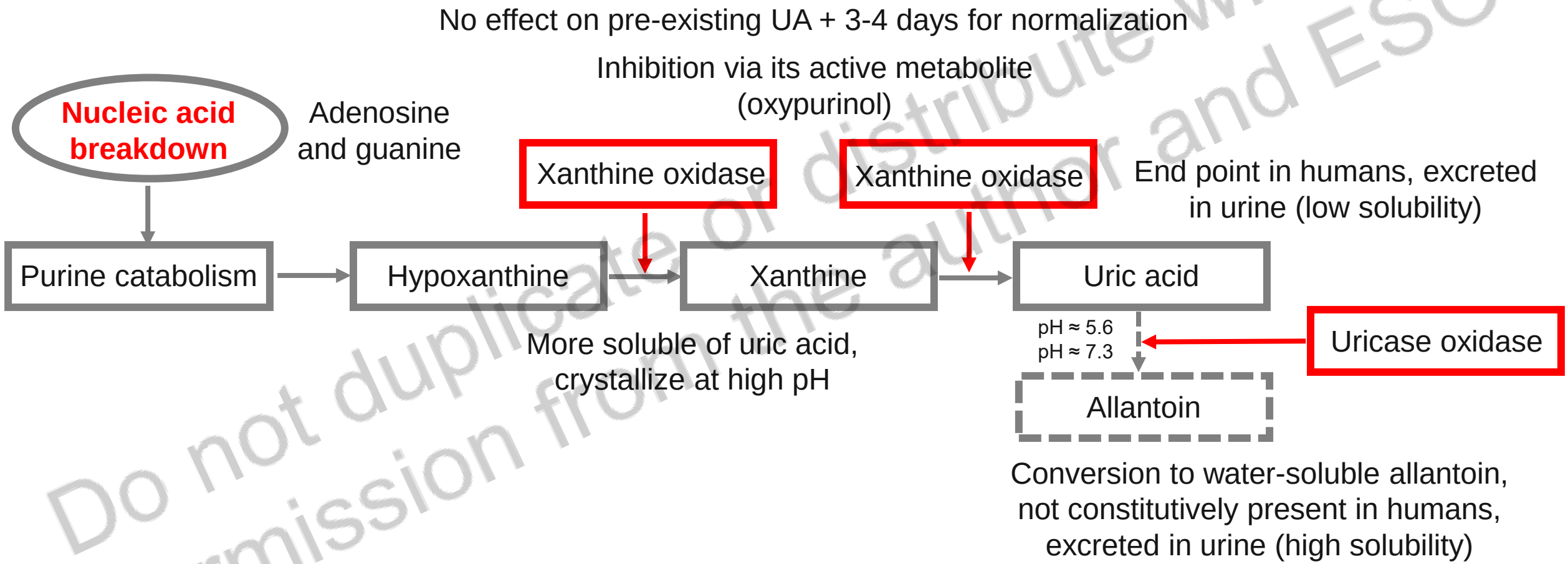
ALLOPURINOL

Recommendation		
PO	300 (200-400) mg/m^2 or 10 mg/kg	
	Divided in 3 doses, every 8h	
	Duration 3-8 days	
	Max 800 mg/d	
IV	Same dose/regime/duration	
	Reconstitution with 5% Glucose or 0.9% NaCl	
	Incompatible with 8.4% NaHCO3	
	Max 600 mg/d	
Reduce in RF	**GFR = CL_{Cr} (ml/min/1.73 m^2)**	**Dosage (% per day)**
	> 20	100
	≤ 20	50-66 (1/2-2/3)
	≤ 10	10-25-33 (1/5-1/4-1/3)
	< 3	10-25 q 36-48h
Reduce if concomitant	6-MP and/or AZA by 65-75%	
Adjust if concomitant	Thiazide / loop diuretics, CPM, HD-MTX, CsA, ampicillin, amoxicillin, carbamazepine	
Caution	Hypersensitive reactions (vasculitis, SJS); HLA-B*58:01 allele in certain Asian populations	

RASBURICASE

TLS profile	Baseline UA		Dose (mg/kg)	Duration
	mmol/L	mg/dL		
HR	460	> 7.5	0.2	Based on UA levels
IR	460	< 7.5	0.15	Based on UA levels
LR	460	< 7.5	0.1	Clinical judgement
Clinical trial			0.05	
Administration	IV over 30 min			
Duration	Average: 2 days (1-7 days)			
Contraindications	Contraindicated: G6PD deficiency*, anaphylaxis, hypersensitive and hemolytic reactions (* due to hydrogen peroxide, byproduct of uric acid breakdown)			
Caution	Ab formation in 10%, methemoglobinemia, teratogenicity (?)			

PURINE METABOLISM



FEBUXOSTAT?

- A xanthine oxidase inhibitor (as Allopurinol)
  - Not purine base analog (as Allopurinol)
  - Minimal effects on other enzymes involved in purine and pyrimidine metabolism
  - Relatively new, a bit more expensive (no generic preparations)
  - Not causing hypersensitivity reaction (associated with Allopurinol)
- Clinical trial FLORENCE (Febuxostat for TLS prevention in hematologic malignancies)
  - Randomized: Febuxostat vs Allopurinol in adults
  - Better control of hyperuricemia, good safety profile, preservation of renal functions
  - No lowering of creatinine level
  - Greater incidence of liver dysfunction, nausea, joint pain
- Pediatric reports
  - 10 mg daily (lowest dose) vs up to 120 mg in adults (dose adjustment?)
  - Preliminary results similar as in adults

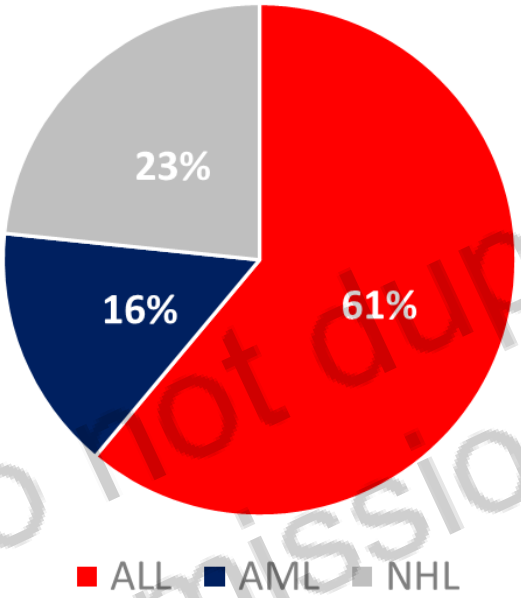
Kishimoto K, Kobayashi R, Hori D, Sano H, Suzuki D, Kobayashi K. Febuxostat as a Prophylaxis for Tumor Lysis Syndrome in Children with Hematological Malignancies. Anticancer Res. 2017;37(10):5845-5849.

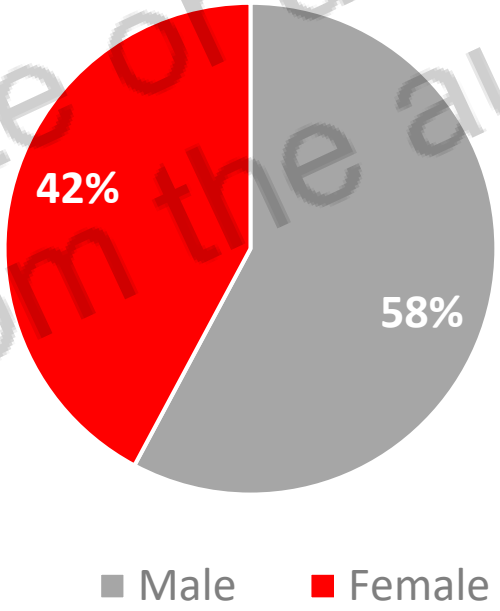
GUIDELINES FOR DIALYSIS USE

- Around 3% of pts
  - 1.5% children, 5% AYA and adults
  - Reduced – Rasburicase!
- Indications:
  - Severe oliguria or anuria / Intractable fluid overload
  - Persistent hyperphosphatemia / hyperkalemia
  - Symptomatic hypocalcemia
  - A calcium-phosphate product ≥ 70 mg^2/dL^2
- HD – efficient in removing UA:
  - Clearance ≈ 70 – 100 ml/min
  - Decrease UA ≈ 50% with each 6h course

SINGLE CENTER EXPERIENCE

- January 2015 – January 2020: 167 pts
- Age – average 8.1, median 6.6 years

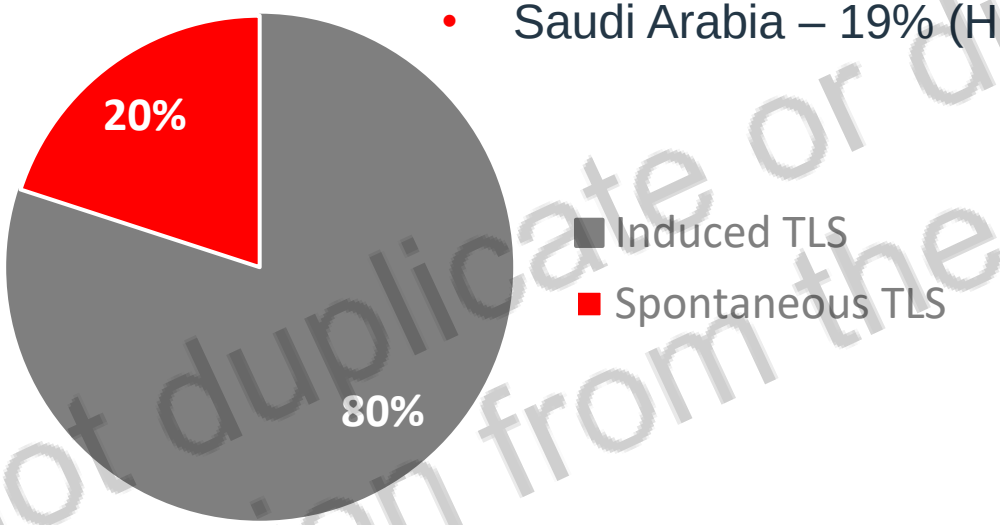


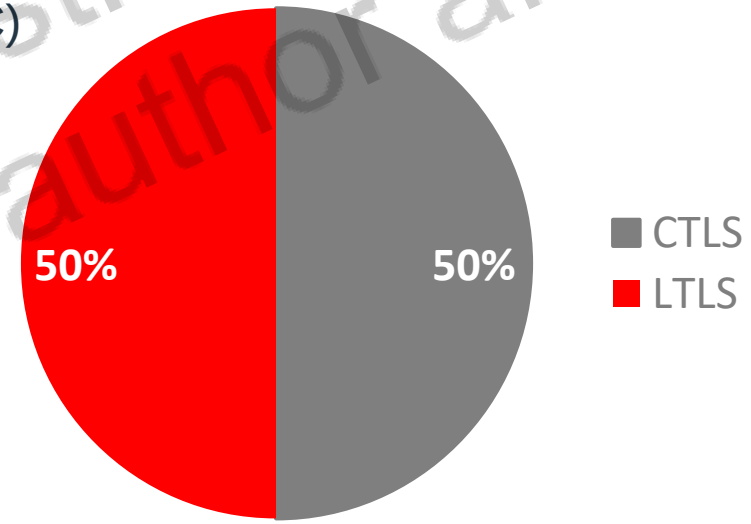


- <u>Risk stratification / Staging</u>:
  - ALL
    - SR – 8
    - **IR – 66**
    - **HR – 39**
  - AML
    - SR – 2
    - **IR/HR – 21**
  - NHL
    - I – 1
    - II – 2
    - **III – 17**
    - **IV – 11**

TLS INCIDENCE

- TLS: 20/167 – 11.98% (U-MIC)
  - Pakistan (2 studies) – 37.1% and 62.6% (L-MIC)
  - Ethiopia – 29.5% (M-MIC)
  - Saudi Arabia – 19% (HIC)

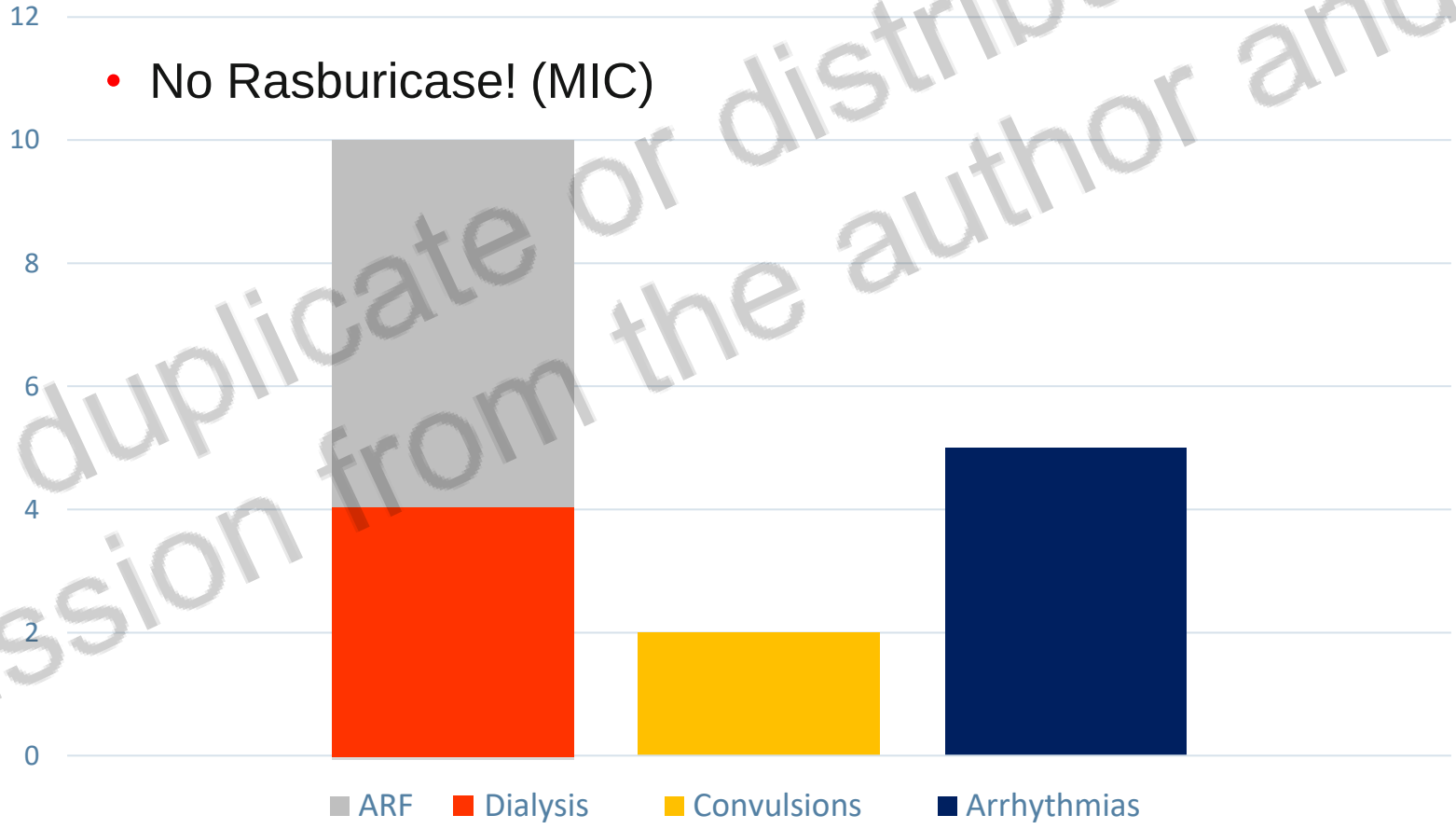




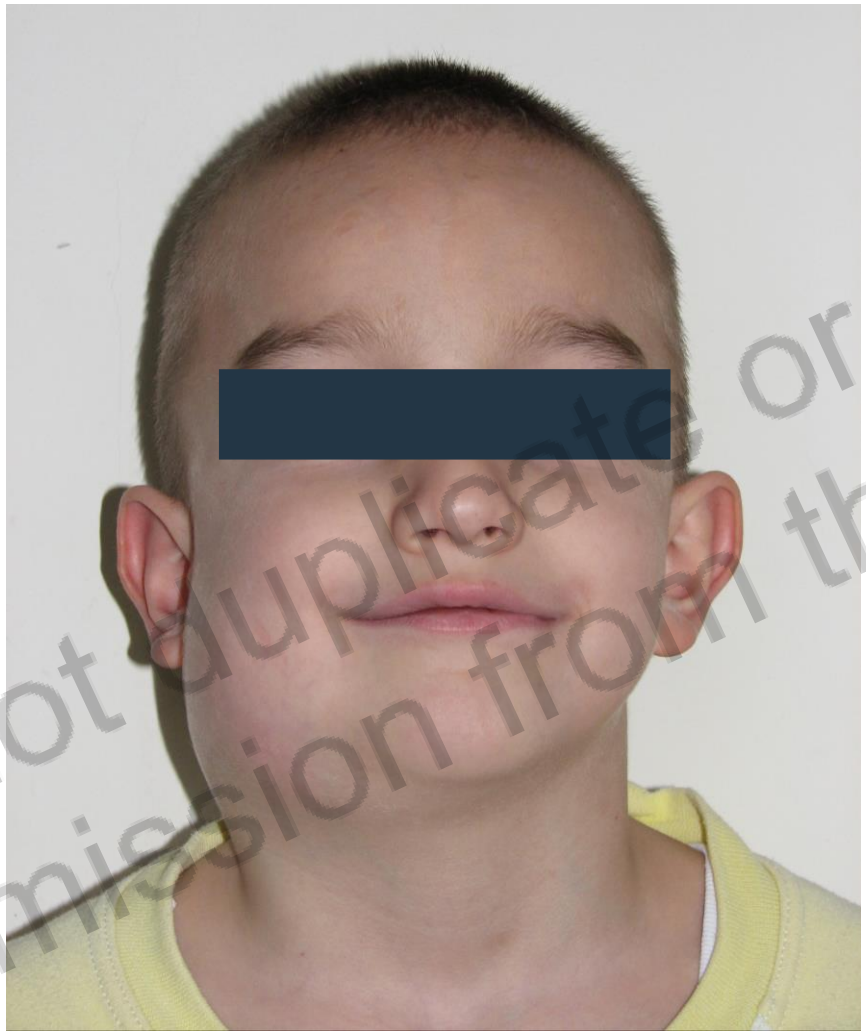
- Induced TLS:
  - Day 1 – 31.3% (5/16), day 2 – 37.4% (6/16), days 3-6 – 31.3% (5/16)
  - Average from CT initiation – 2.44±1.55 days

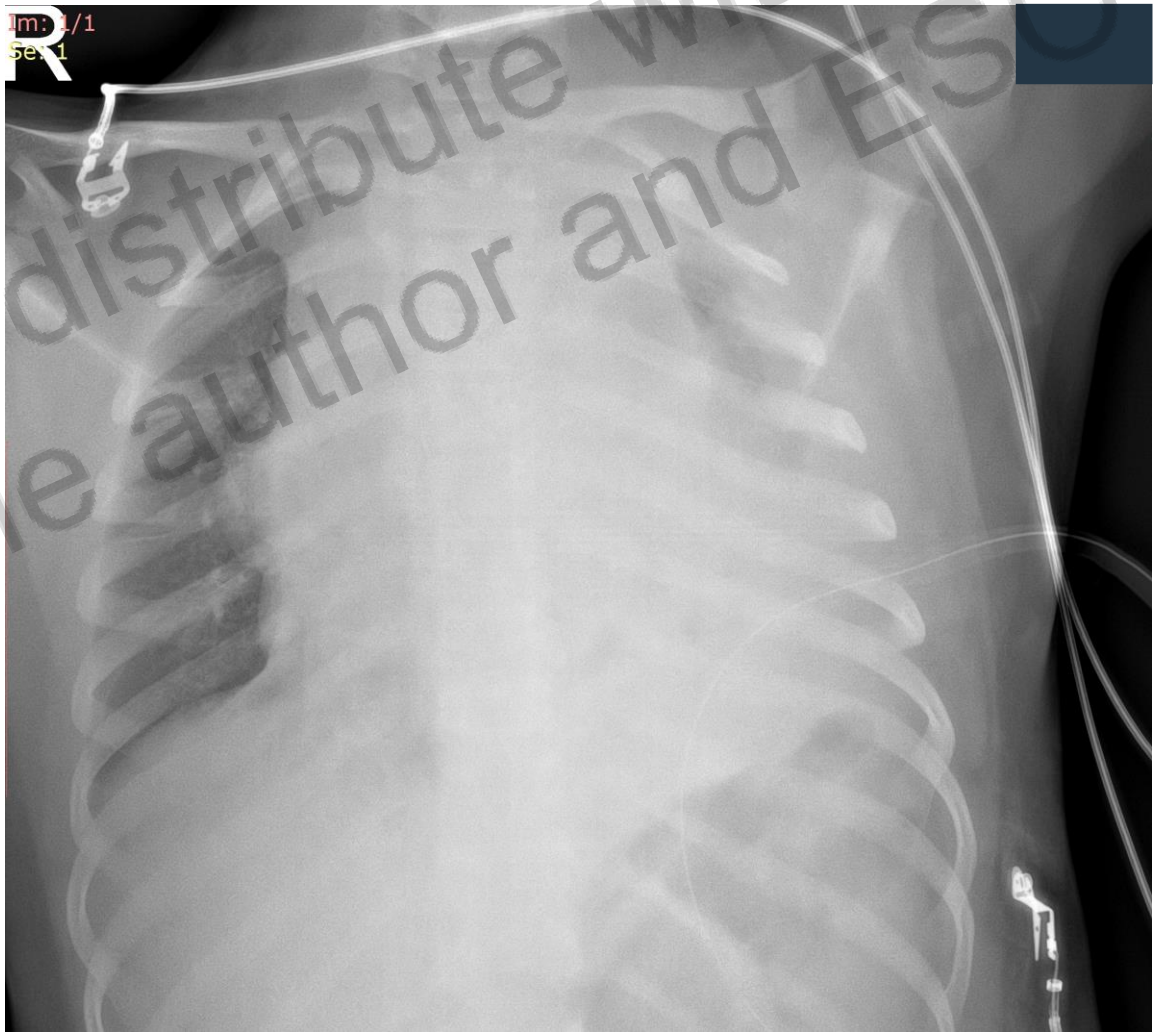
COURSE OF CTLS

- All pts with CTLS developed ARF – RRT in 40% (all alive)
- Choice of RRT: HD – stable pts, HDF – unstable pts (+ MV)
- No Rasburicase! (MIC)

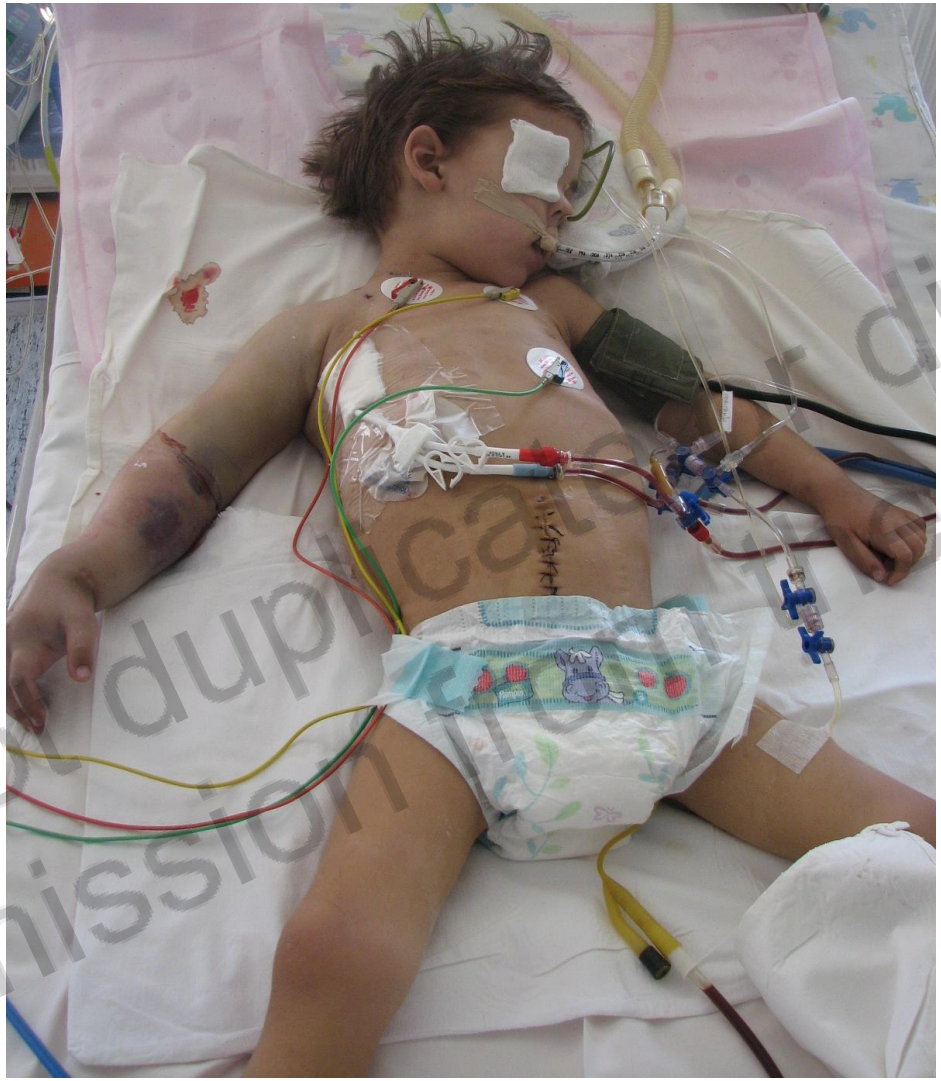


BULKY MASSES: BURKITT & T-LBL





BURKITT: TLS – HDF + COMPARTMENT Sy



KEY POINTS

Prevention	• Awareness + early recognition • Precise TLS risk stratification + adequate prophylaxis
Intervention	• Vigilant laboratory and clinical monitoring • Minimization of TLS and disease complications
Investigation	• CT in HR-TLS: MDT and necessary facilities • Collaboration: clinic + laboratory = predictive algorithms

Recommendations - The British Committee for Standards in Haematology (BCSH)