

# Oncologic Emergencies in Children

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# Oncology in PICU

- At the time of the diagnosis:
  - Tumor bulk causing metabolic disturbances
  - Tumor bulk causing obstructive problems
- After intensive chemotherapy:
  - Metabolic complications
  - Infectious complications

# Complications of oncologic diseases

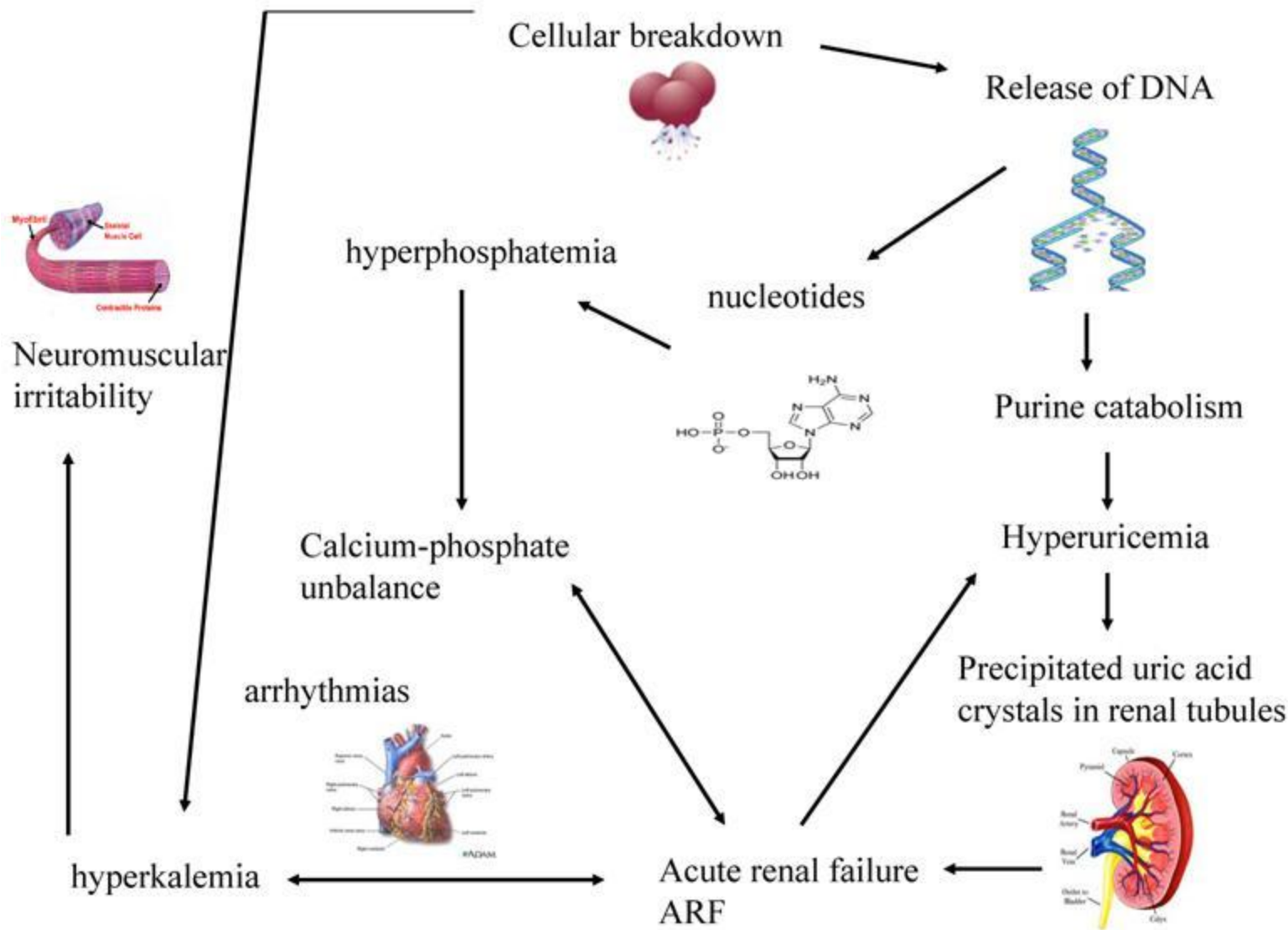
- Tumor lysis syndrome
- Hyperleukocytosis
- Mediastinal masses/superior vena cava syndrome
- Spinal cord compression
- Septic shock
- Acute hypoxemic respiratory failure
- Outcome?

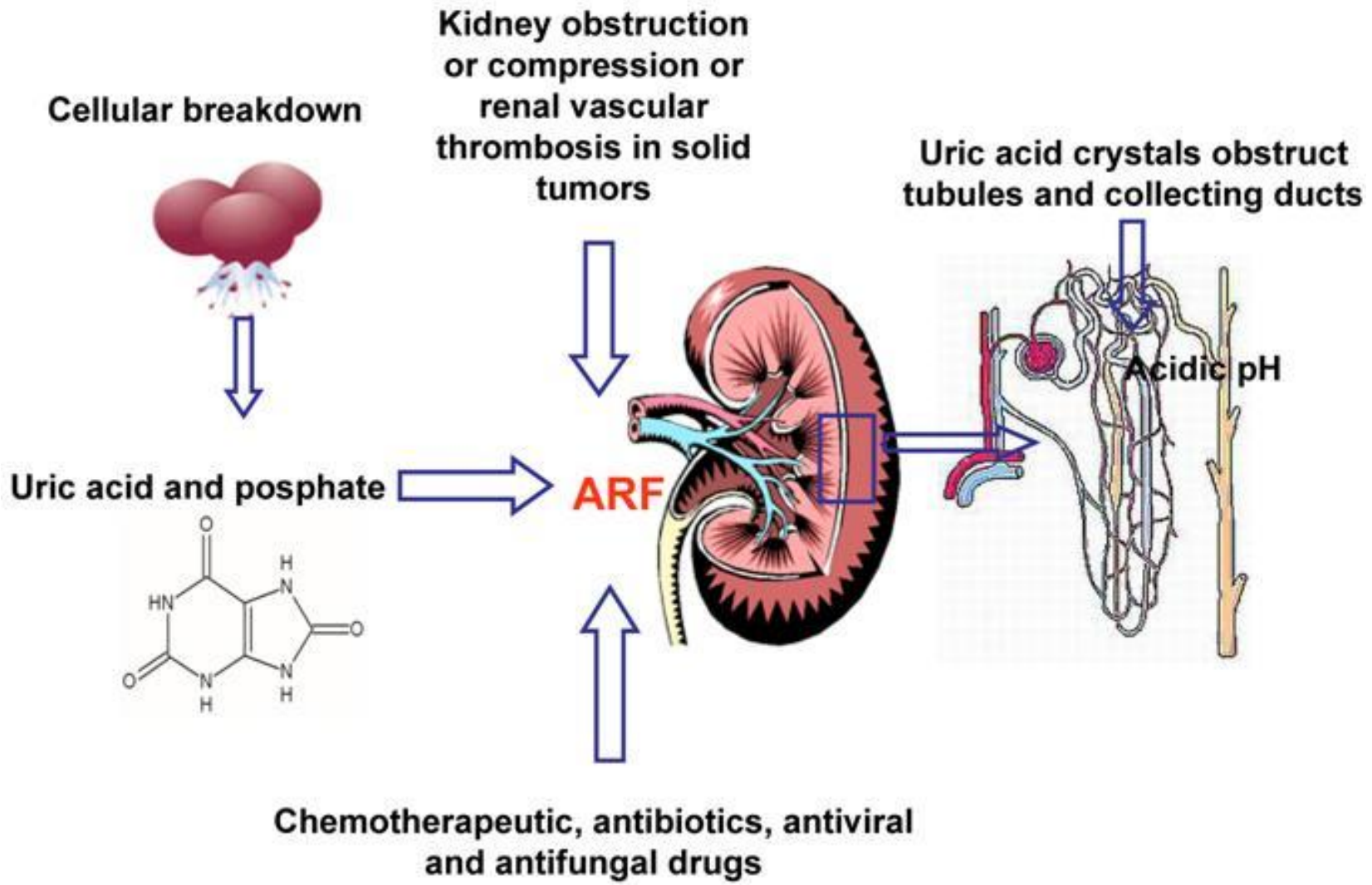
# Tumor Lysis Syndrome

# Tumor Lysis Syndrome

- Patients with rapidly growing tumors, bulky disease and chemo sensitive tumors
- Most common with B-cell leukemia (26.4%), Burkitt's lymphoma (with LDH  $\geq$  500 U/l 14.9%), and T-cell leukemia/lymphoma
- Risk of rapid lysis of tumor cells and release of intracellular contents overwhelming kidney's ability to excrete those products

Wossmann W, et al. Incidence of tumor lysis syndrome in children with advanced stage Burkitt's lymphoma/leukemia before and after introduction of prophylactic use of urate oxidase. *Ann of Hemat.* March 2003





# Tumor Lysis Syndrome

- Can occur at presentation
- More common early after start of chemotherapy (within 12-24 hrs)
- Risk of:
  - Renal failure and
  - life-threatening electrolyte disturbances

## Patients at high risk of TLS who could benefit by rasburicase

<b>Tumor factors</b>	<b>Patients factors</b>	<b>Biochemical factors</b>
High tumor burden	Hyperleukocytosis	High uric acid levels
High tumor growth rate	Pre-existing renal impairment	High LDH levels
High sensitivity to chemotherapy, especially during early treatment phase	Dehydration	High phosphoremia levels
Advanced stage of tumor	Poly-pharmacology	Low pH of urine
Kind of tumor (haematological malignancies more than solid tumors)		High creatinine levels
Lymphoma infiltration of kidney		
Use of monoclonal antibodies and targeted therapies		

# Cairo-Bishop definition of laboratory tumor lysis syndrome

**Table 1.** Cairo-Bishop definition of laboratory tumor lysis syndrome (LTLS).<sup>17</sup>

Uric acid	$\geq 476 \mu\text{mol/L}$ (8 mg/dL) or 25% increase from baseline
Potassium	$\geq 6.0 \text{ mmol/L}$ (6mEq/L) or 25% increase from baseline
Phosphorous	$\geq 2.1 \text{ mmol/L}$ (children) or $\geq 1.45 \text{ mmol/L}$ (adults) or 25% increase from baseline
Calcium	$\leq 1.75 \text{ mmol/L}$ or 25% decrease from baseline

Hochberg, J. et al. Haematologica 2008;93:9-13

# Cairo-Bishop grading system for tumor lysis syndrome

**Table 3.** Cairo-Bishop grading system for tumor lysis syndrome.

	Grade 0*	Grade I	Grade II	Grade III	Grade IV	Grade V
LTLS	-	+	+	+	+	+
Creatinine <sup>†</sup>	1.5 x ULN	1.5 x ULN	>1.5-3.0 x ULN	>3.0-6.0 x ULN	>6.0 UNL	Death <sup>‡</sup>
Cardiac arrhythmia <sup>†</sup>	None	Intervention not indicated	Non-urgent medical intervention indicated	Symptomatic and incompletely controlled medically or controlled with device (e.g. defibrillator)	Life-threatening (e.g. arrhythmia associated with CHF, hypotension, syncope, shock)	Death <sup>‡</sup>
Seizure <sup>†</sup>	None	---	One brief generalized seizure; seizure(s) well controlled by anti-convulsants or infrequent focal motor seizures not interfering with ADL	Seizure in which consciousness is altered; poorly controlled seizure disorder; with breakthrough generalized seizures despite medical intervention	Seizure of any kind which is prolonged, repetitive or difficult to control (e.g. status epilepticus, intractable epilepsy)	Death <sup>‡</sup>

\*No laboratory TLS; <sup>†</sup>Not directly or probably attributable to a therapeutic agent; <sup>‡</sup>Attributive probably or definitely to CTLS. TLS=tumor lysis syndrome; LTLS=laboratory tumor lysis syndrome; ULN=upper limit of normal; CHF=congestive heart failure; ADL=activities of daily living; CTLS=clinical tumor lysis syndrome. ©Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification (2004). Originally published in British Journal of Haematology, Blackwell Publishing Ltd. 127, 3-11.

Hochberg, J. et al. Haematologica 2008;93:9-13



**haematologica**  
the hematology journal

# Consequences of TLS

- Hyperkalemia → weakness, dysrhythmias
- Hyperphosphatemia → hypocalcemia, renal failure
- Hypocalcemia → tetany, seizures  
mental status changes
- Hyperuricemia → "uric acid nephropathy"  
oliguria, renal failure

# Management

- Monitoring:

- Serum creatinine, blood urea nitrogen
- sodium, potassium, calcium, phosphorous
- LDH and uric acid levels

Before therapy and every 4-6 hours for the first 48-72 hours after the initiation of tumor therapy.

- A baseline ECG

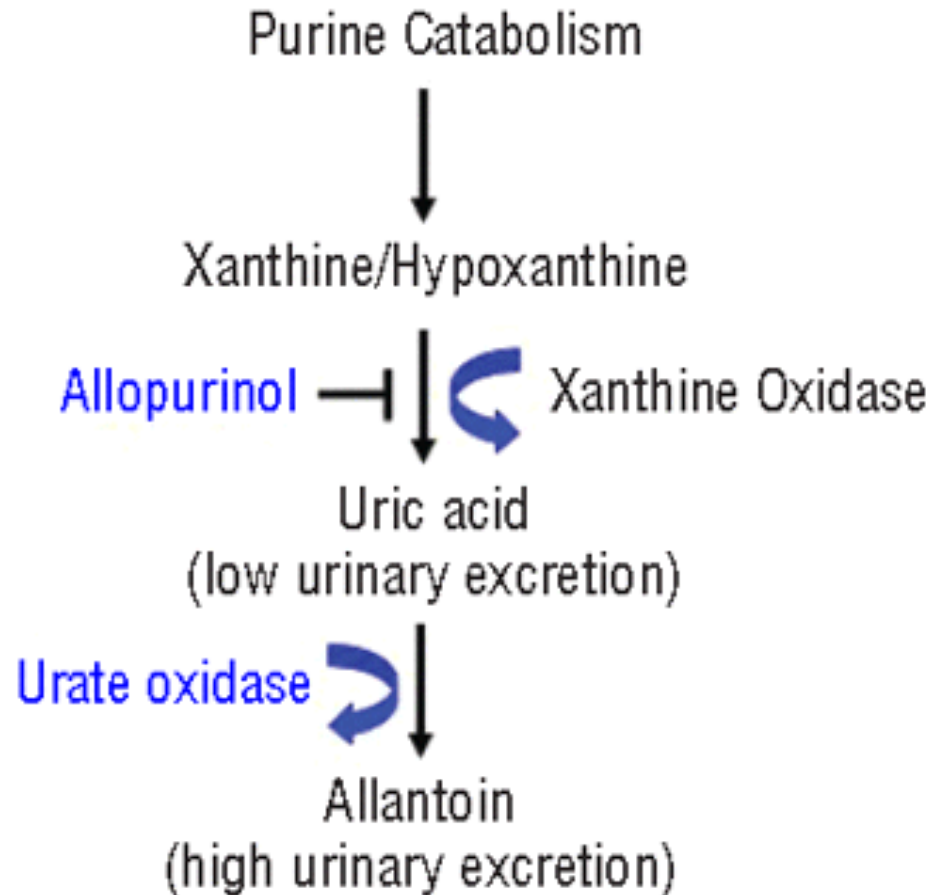
- Continuous cardiac monitoring until the completion of treatment.

- Ideally, intravenous hydration 24-48 hours before the initiation of tumor therapy

# "The best treatment is prevention"

- Hydration
  - Fluid intake = 2-3 L/m<sup>2</sup>/day enhances uric acid excretion, phosphate excretion
  - Goal of urine specific gravity  $\leq 1.010$
- Urine alkalization - add NaHCO<sup>3</sup> to IVF not recommended anymore
  - Hypoxanthine crystals in renal tubules
  - Alkalosis and Ca-PO<sub>4</sub> stones possible

# Purine Catabolism Pathway



# Prevention



## Decrease production of uric acid

- Allopurinol inhibits xanthine oxidase
  - 300 mg/m<sup>2</sup>/day divided tid P.O./I.V.
  - Dose reduction in renal insufficiency
  - Long time standard Rx
  - 24-48 hrs before chemo

## Conversion of uric acid to more water soluble

- Rasburicase (Recombinant urate oxidase)
- Catalyzes conversion of uric acid to allantoin
- Allantoin more soluble, easily excreted by kidneys
- Urine alkalinization unnecessary if used

# Recombinant Urate Oxidase

- Rasburicase is more effective than allopurinol in prevention and treatment of hyperuricemia
  - IV at doses up to 0.1-0.2 mg/kg daily 30 minutes infusion for 1-7 days
  - Contraindicated with G-6-PD deficiency

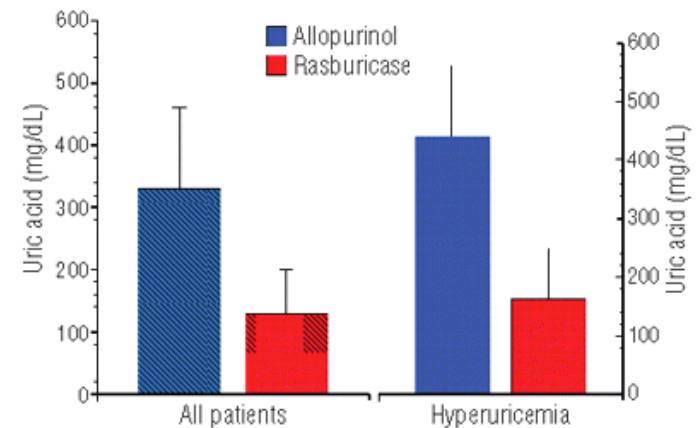


Figure 2. Uric acid AUC 0-96hr mg/dL/hr by treatment comparing all patients versus a subgroup with hyperuricemia.

Cammalleri, L et al. Rasburicase represents a new tool for hyperuricemia in tumor lysis syndrome and in gout. Int J Med Sci, March 2007

# Dialysis for Tumor Lysis Syndrome

- Indications:
  - Oliguria,
  - Hyperkalemia
  - Azotemia
  - Hyperphosphatemia  
(correct only symptomatic hypocalcemia)
  - Refractory hyperuricemia
- Hemodialysis or continuous venovenous hemofiltration with dialysis most effective

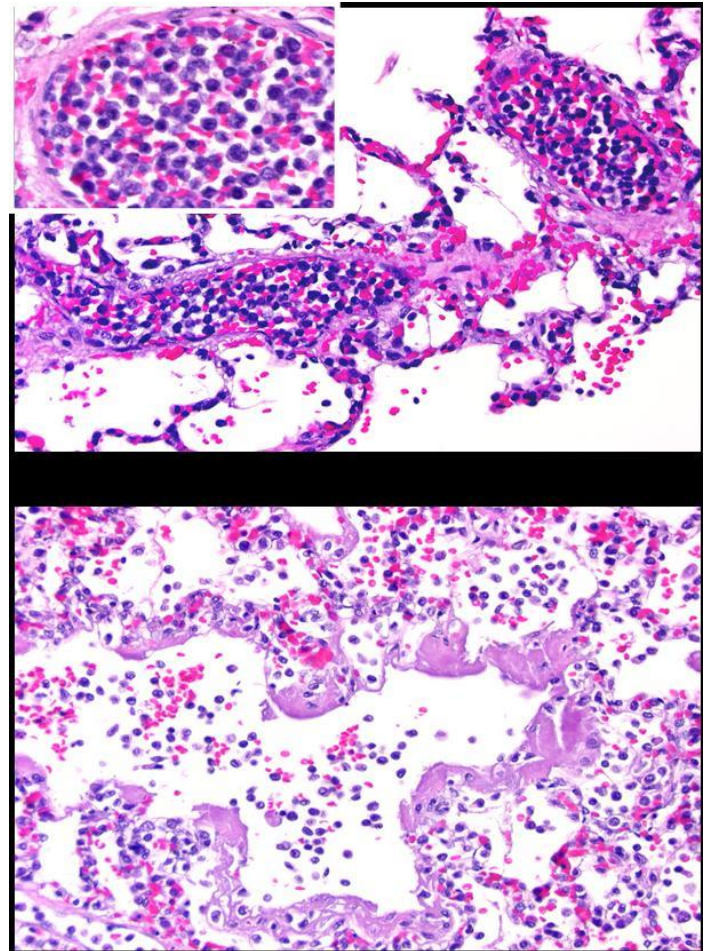
Coiffier, B. et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. J Clin Oncol 2008

# Hyperleukocytosis

# Hyperleukocytosis

5-20% of children with new Dx of leukemia have WBC count  $> 100,000/\text{mm}^3$

These patients at risk of severe complications from hyperviscosity of blood



# Early complications in children with acute lymphoblastic leukemia presenting with hyperleukocytosis

Lowe EJ, et al. Department of Hematology-Oncology,  
St. Jude Children's Research Hospital, Memphis, Tennessee

**Pediatr Blood Cancer. 2005 Jul**

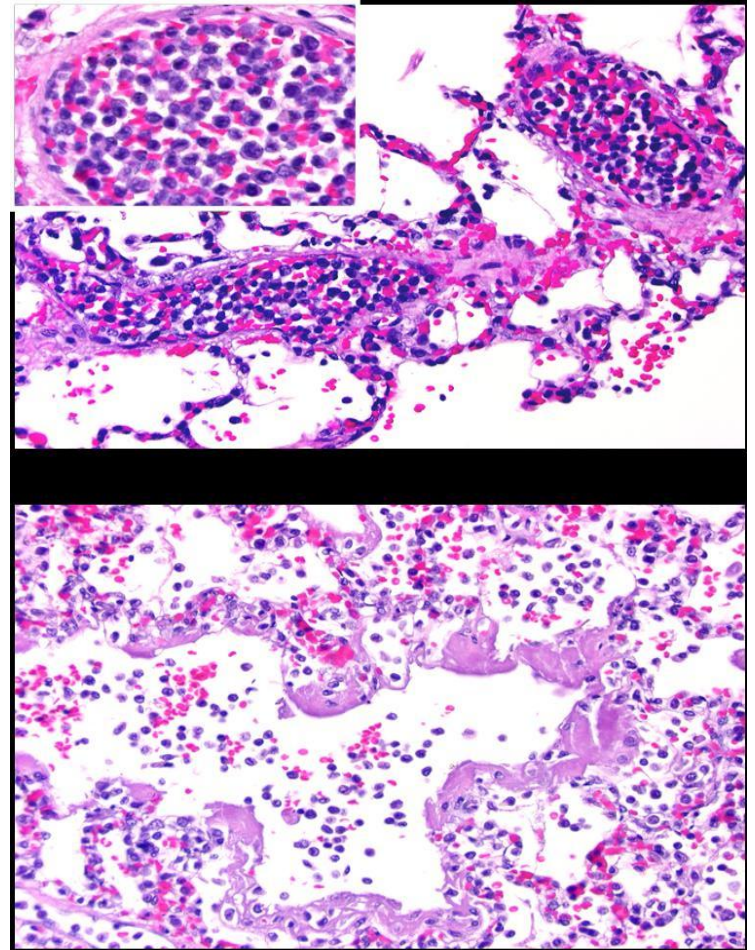
- 178 children, representing 8% of all children with ALL (2288), had an initial leukocyte count  $>200 \times 10^9/L$
- 67 (37.6%) patients had a leukocyte count  $>400 \times 10^9/L$ .
- Sixteen patients (9%) had neurological complications
- Four patients (2%), all with initial leukocyte counts  $>400 \times 10^9/L$ , suffered a CNS hemorrhage.
- Pulmonary leukostasis occurred in 11 patients (6%).
- The degree of hyperleukocytosis was significantly predictive of neurological ( $P=0.006$ ) and respiratory ( $P=0.014$ ) complications.
- The majority of complications occurred at presentation.

# Hyperleukocytosis - Complications

- Blasts interact with endothelium to form aggregates, thrombi in microcirculation
- Most problems in CNS and pulmonary circulation
- Complications more common with AML than ALL (Myeloblasts and monoblasts larger, less deformable, "stickier")

# Pulmonary leukostasis

Pulmonary arteriole with leukostatic thrombus in patient with AML and hyperleukocytosis

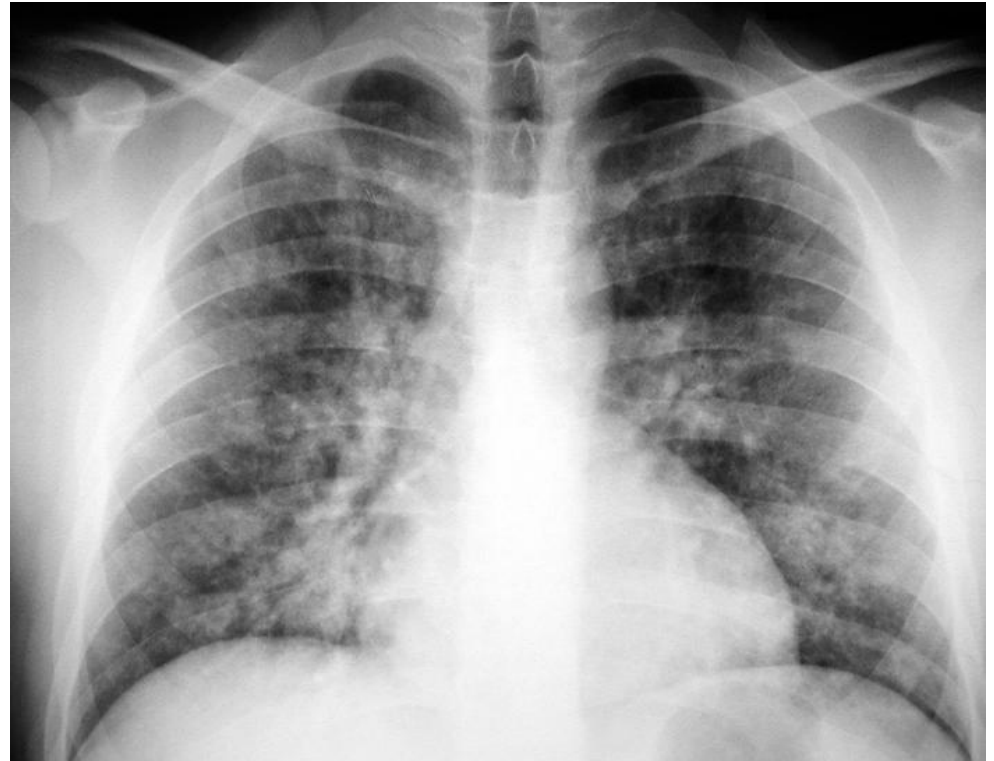


# Pulmonary leukostasis

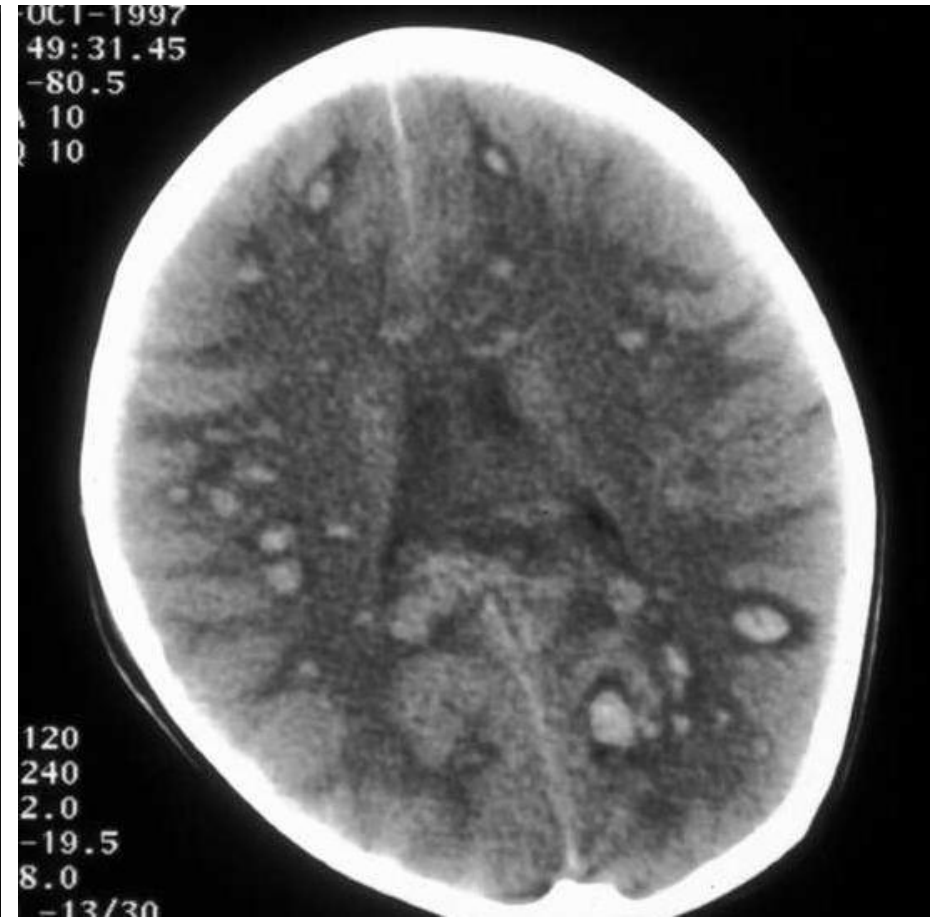
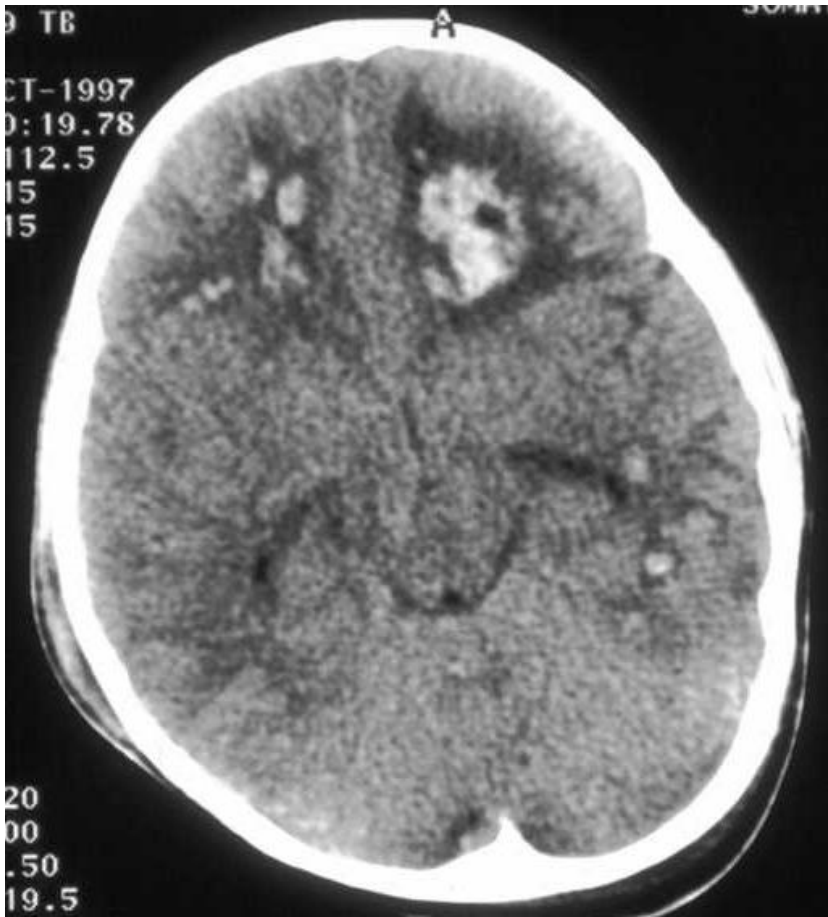
- Symptoms:

- Dyspnea
- Tachypnea
- Hypoxemia
- Acidosis
- Cor pulmonale

- CXR: diffuse interstitial infiltrates



# CNS leukostasis



# CNS leukostasis

- Headache, blurred vision, agitation, mental status changes, seizures, coma
- High risk of intracranial hemorrhage, especially with AML and thrombocytopenia

# Therapy for hyperleukocytosis

- Decrease blood viscosity  
(directly related to morbidity)
  - Hydration
  - AVOID use of diuretics
  - AVOID PRBC transfusion  
(Hb goal < 10 gm/dL for viscosity)
- Transfuse platelets to keep > 20,000/mm<sup>3</sup> and treat coagulopathy (common with AML) to decrease risk of intracranial hemorrhage

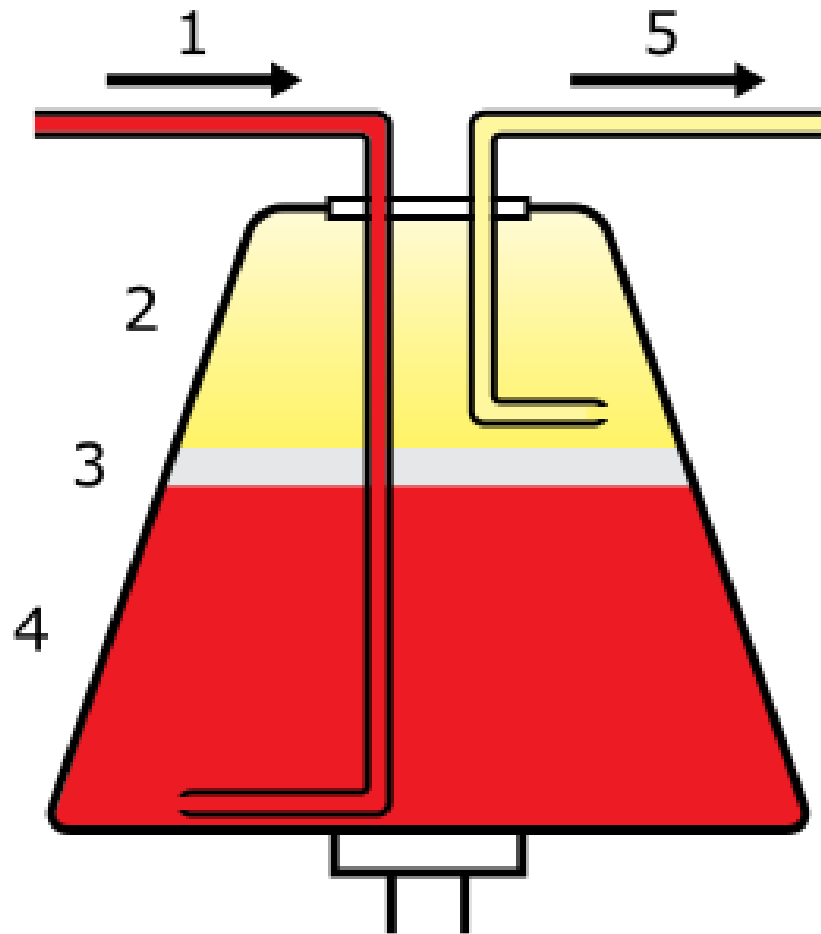
# Therapy for hyperleukocytosis

- Hydration, as with tumor lysis syndrome
- Consider leukopheresis or exchange transfusion (WBCs > 300,000 in ALL)
- PICU supportive care - mechanical ventilation, hemodynamic support, etc

# Leukopheresis



Whole blood enters the centrifuge (1)  
and separates into plasma (2), leukocytes (3), and  
erythrocytes (4).  
Selected components are then drawn off (5).

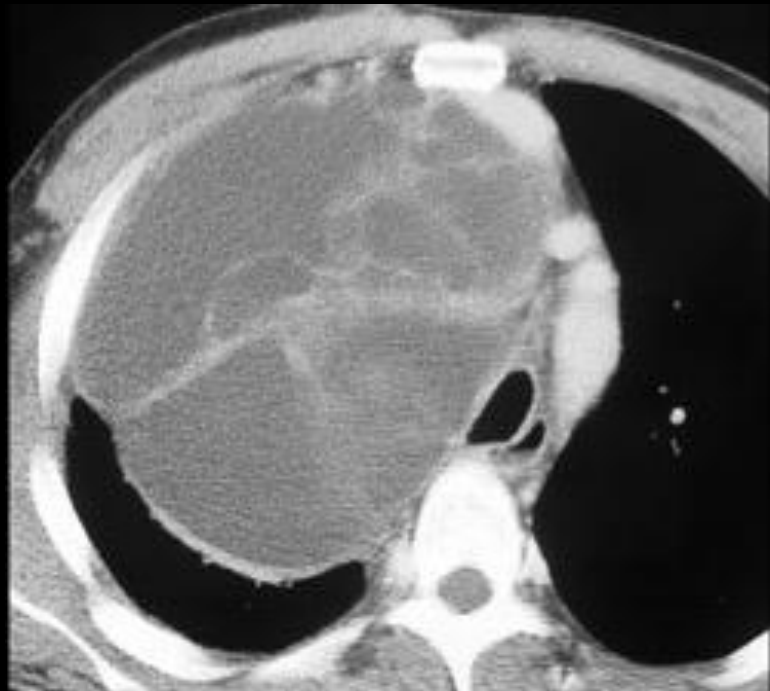
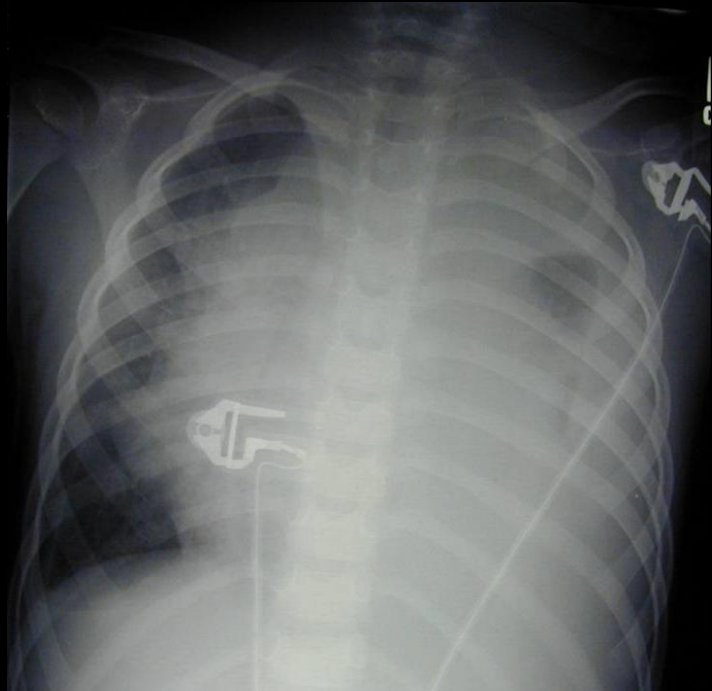


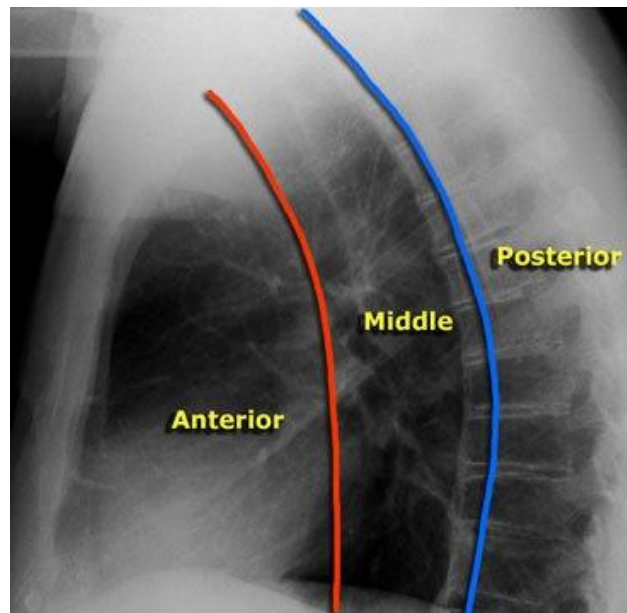
## Leukapheresis and exchange transfusion in children with acute leukemia and hyperleukocytosis. A single center experience.

Hasse R, et al. Germany. *Klin Padiatr.* 2009 Nov-Dec

- At diagnosis 11 (14 % ) of 77 children with acute leukemia had hyperleukocytosis.
- 4 patients (2 ALL, 2 AML) received exchange transfusion
- 2 others (1 ALL, 1 AML) underwent leukapheresis.
- Marked cytoreduction was achieved in all patients within 24 h after therapy initiation.
- There were no procedure-related adverse events.
- Symptoms due to hyperleukocytosis markedly improved after cytoreduction.

# Mediastinal Masses

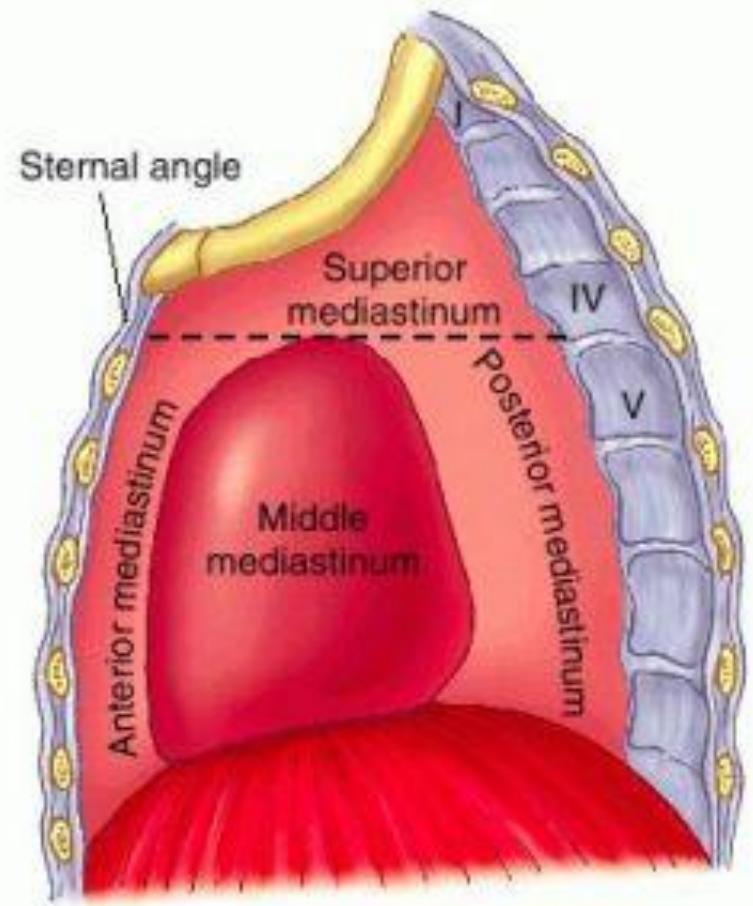




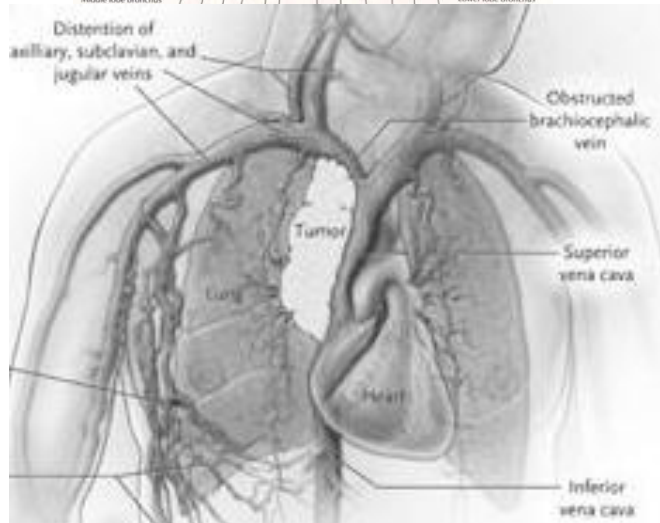
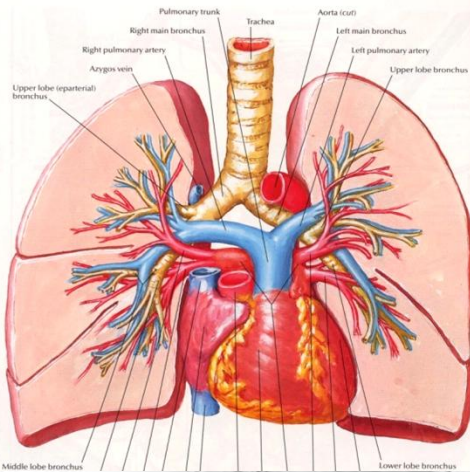
	Lesions	Fluid	Fat	Vascular
Anterior	Thymic Lymphoma Germ Cell Goiter	Thymic C Thymoma Pericardial C Germ Cell Lymphoma	Germ cell-b Thymolipoma Fat Pad	Thyroid Cardiac Coronary
Middle	Lymph nodes Duplication C Arch anomaly	Duplication C Necrotic nodes Pericard recess Retroperitoneal	Lipoma Esophageal FV polyp	Arch anomaly Azygous Vein Vascular nodes
Posterior	Neurogenic Bone and marrow	Neuroenteric C Schwannoma Meningocele	Extramedullary Hematopoiesis	Desc Aorta
>1 comp	Infection Hemorrhage Lung Cancer	Lymphangioma Mediastinitis	Liposarcoma	Hemangioma

# Mediastinal tumors in children

- Anterior
  - Non-Hodgkin's lymphoma
  - Hodgkin's disease
  - Teratoma
- Middle
  - Lymphoma
- Posterior
  - Neuroblastoma



# Pathophysiology of large mediastinal tumors



- Displacement or obstruction of:
  - Tracheobronchial tree
  - Heart and great vessels
  - SVC
- Superior mediastinal syndrome

# Presentation and symptoms

- Often a subacute hx of cough, low-grade fever, dyspnea,  $\pm$  orthopnea,  $\pm$  weight loss
- Signs/symptoms of airway obstruction and/or SVC syndrome demand emergency evaluation
  - Airway obstruction - - stridor, wheezing, dyspnea, anxiety, "position of comfort"
  - SVC syndrome - - plethora, engorgement of face & upper extremities; dilatation of veins in area ; CNS (in 95% of children it is due to malignancy)

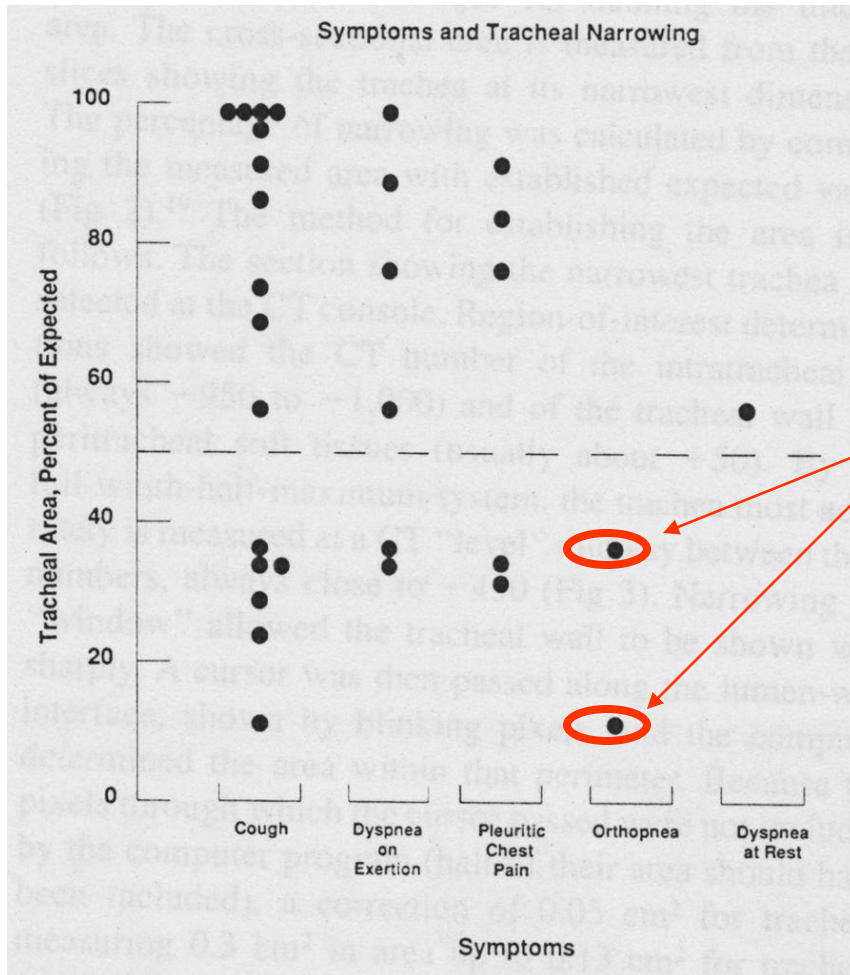
# Evaluation of the child with mediastinal mass

- Management/diagnostic decisions difficult and controversial - - emergency treatment vs definitive Dx
- Significant stridor, dyspnea usually not present unless airway cross-sectional area narrowed by >50%
- Some authors recommend CT scan to evaluate tracheal compression prior to decisions regarding sedation/anesthesia

# Evaluation

- Inability to tolerate supine position of grave significance with anterior mediastinal mass
- May result from weight of tumor compressing not only airway, but great vessels and heart (especially RV outflow tract)
- If can tolerate supine position, CT and PFT's may help indicate which children will tolerate anesthesia
  - Shamberger, 1991 and 1995

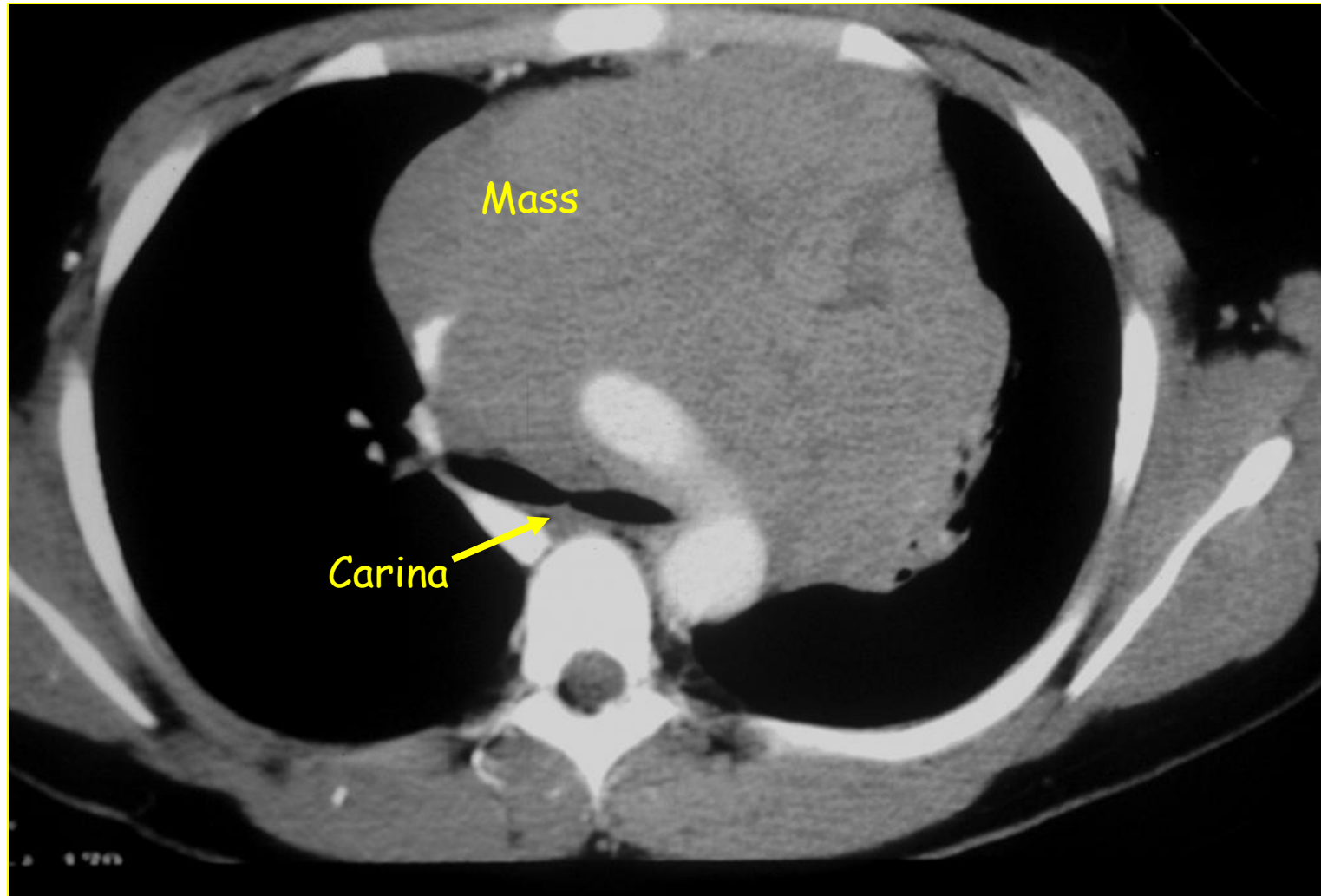
# Respiratory symptoms and tracheal area



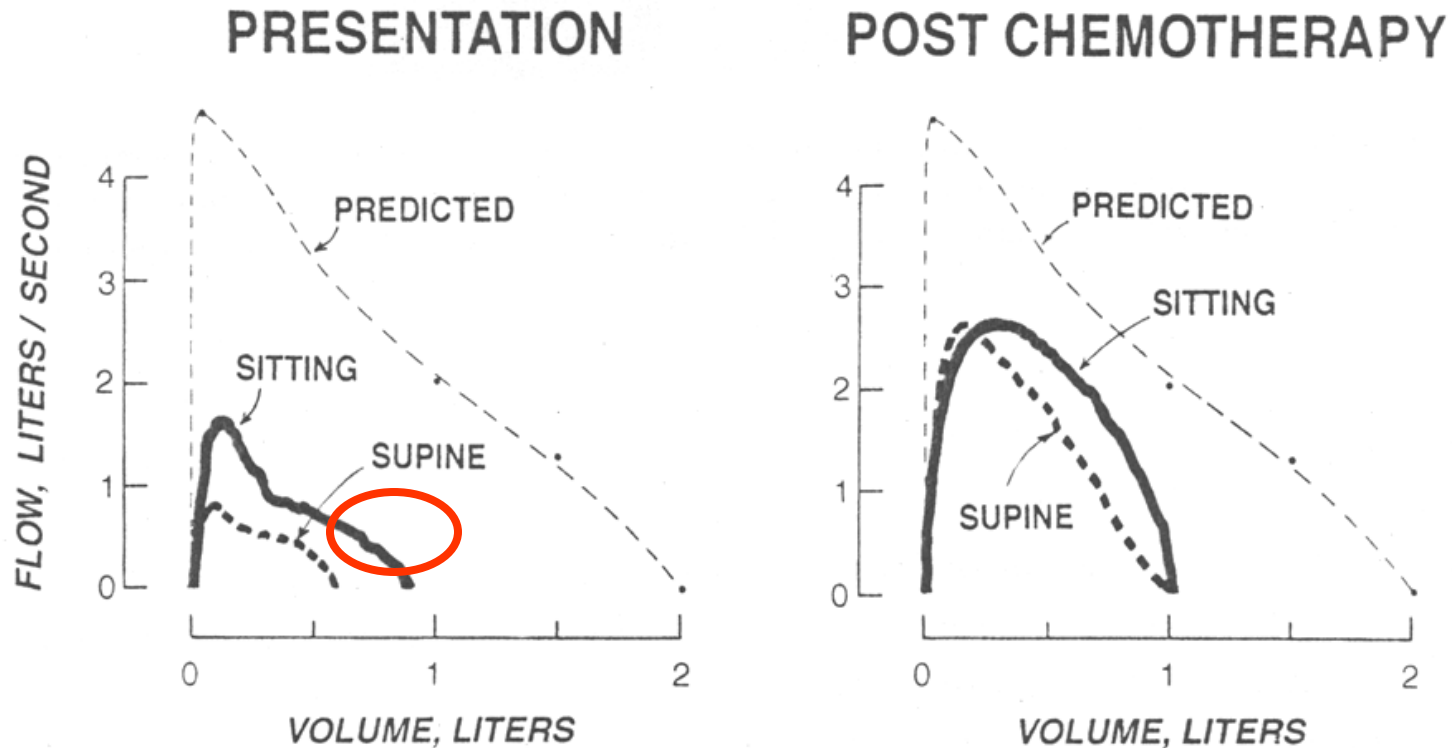
Note severe tracheal narrowing in patients with orthopnea

Shamberger, 1991

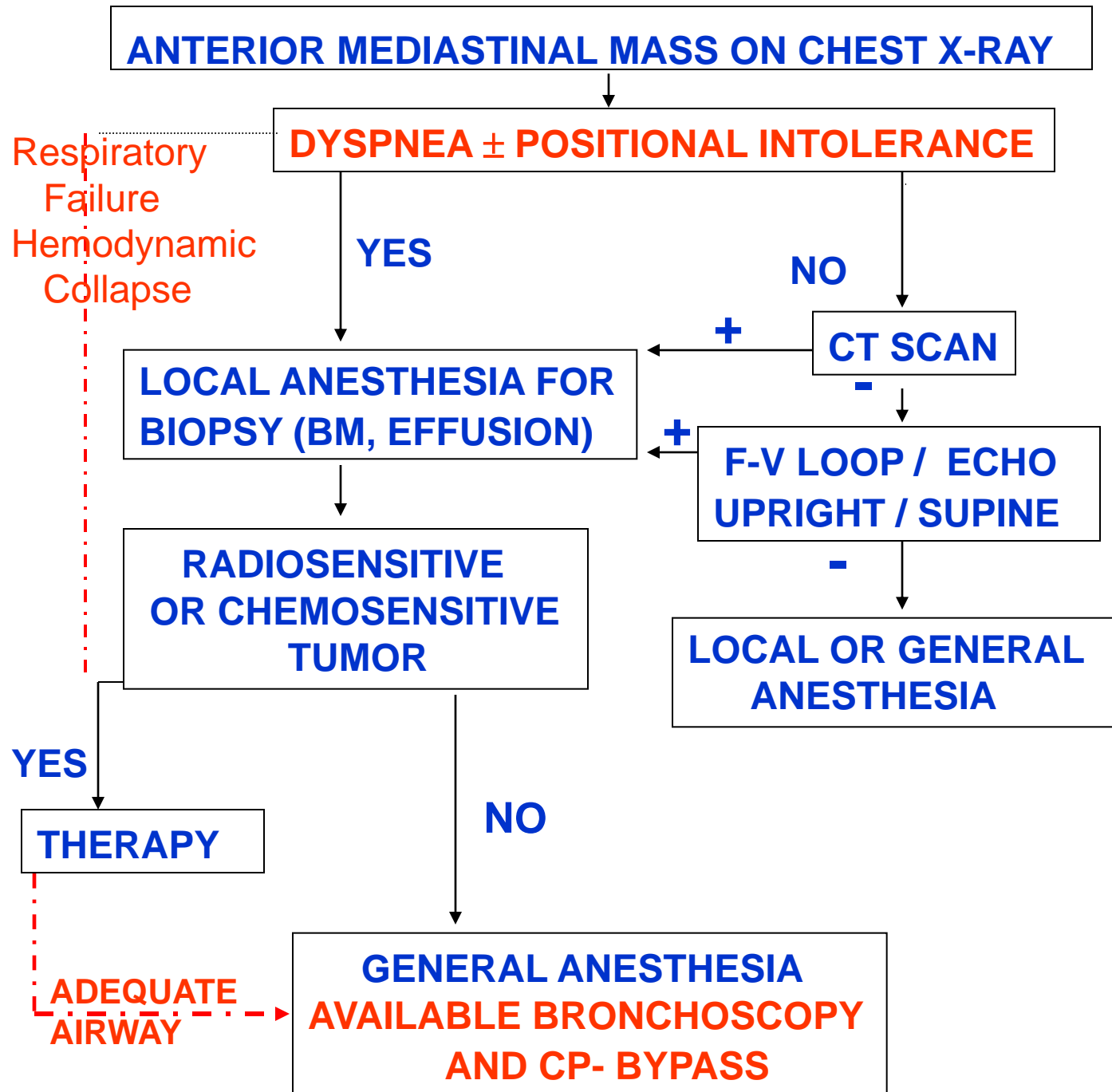
# CT Scan of Mediastinal Mass Showing Tracheal Compression at Carina



# PFT's with large mediastinal lymphoma



Shamberger, 1995 - - note dramatic pre-chemotherapy reduction in flow supine vs upright - - due to weight of mass on airways



# Emergent Management

- Keep child in sitting, left lateral decubitus position - - helps "lift" mass off airway and RVOT
- IV access (lower extremities preferable due to SVC obstruction)
- Face mask  $O_2$ , non-invasive PEEP
  - Heli-ox possibly helpful due to large airway obstruction → decreases airway resistance

# Emergent Management

- AVOID sedation for procedures unless anesthesiologist present and prepared for **VERY difficult intubation**
- If impending respiratory failure and requires intubation . . .
  - Awake, bronchoscopic intubation ideal to maintain airway muscle tone, prevent worsened extrinsic compression
  - Ideally, have cardiopulmonary bypass available
  - **AVOID neuromuscular blockade** - - worsened obstruction even as low as carina

# Therapy

- Urgent radiotherapy since most lymphomas are radiosensitive.
- Chemotherapy, including steroids or cyclophosphamide, is a possible alternative to irradiation.

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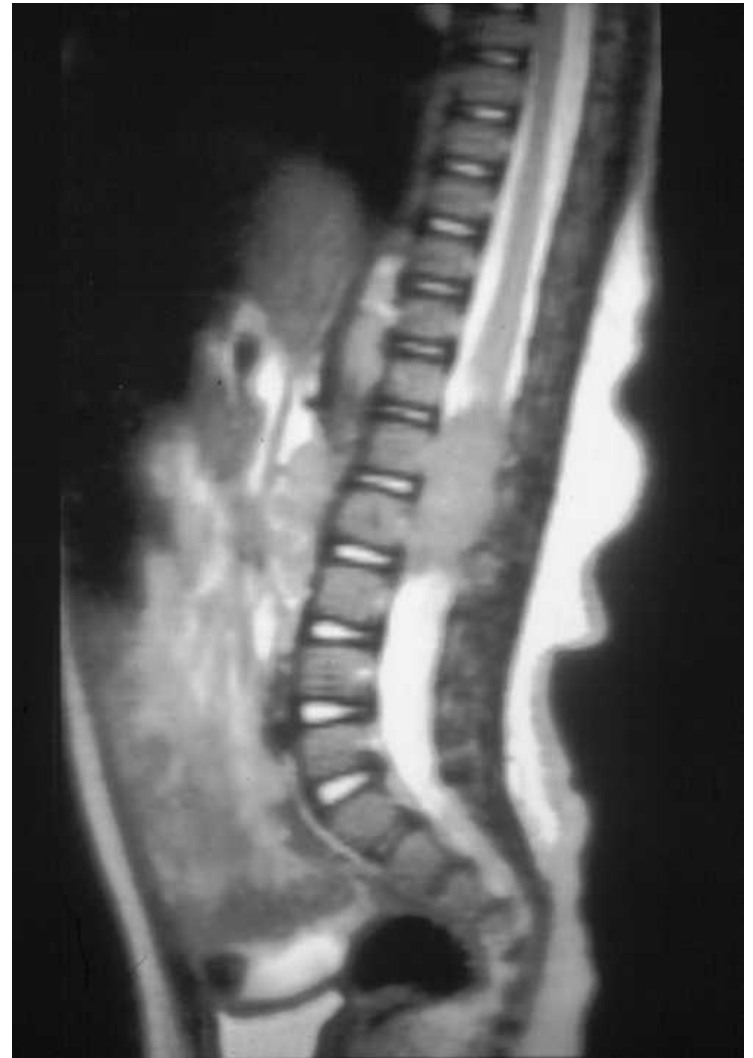
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# Spinal cord compression

# Spinal cord compression

- Occurs in 3-5% of children with cancer, often at diagnosis.
- Can occur with any tumor type, but mostly with neuroblastoma, sarcoma, and Hodgkin's disease.



# Spinal cord compression

- Spinal cord compression for as little as 24 hours can result in permanent sequelae.

# Presentation

- **Back Pain:** suspect cord compression when:
  - pain not relieved in supine position or
  - back pain has a radicular component.
- Weakness, sensory abnormalities, and paresis.
- Paraplegia and quadriplegia can occur rapidly if there are neurologic abnormalities
- Urinary and fecal incontinence.

# Diagnosis

- MRI is the imaging procedure of choice (with and without gadolinium enhancement)



# Treatment

- Treatment of cord dysfunction:  
give dexamethasone bolus of 1-2 mg/kg and  
obtain MRI
- Decompression:
  - surgery, radiation, chemotherapy.
- Surgery indicated:
  - if tumor type is not known or
  - symptoms progress despite radiotherapy.
- Chemotherapy is appropriate for:
  - lymphoma, leukemia, and neuroblastoma.

# Sepsis & Febrile Neutropenia

# Febrile Neutropenia

## Definitions:

- Absolute neutrophil count  $< 500$  cells/mm<sup>3</sup>
- Fever: Single oral temp  $\geq 38.3^{\circ}\text{C}$  or  $\geq 38^{\circ}\text{C}$  that persist for more than 1 hour
- Non-infectious etiologies for fever should be considered:
  - Blood product transfusion
  - G-CSF
  - Active primary disease
  - Medications

# Risk Factors for Serious Infections (Invasive Bacterial Infections)

- Presence of leukemia as the cancer type
- A temperature of 39°C or higher, occurrence of chills
- $\geq 7$  days since last chemotherapy
- Relapse of leukemia
- Hypotension (diastolic)

Rackoff WR, et al. J Clin Oncol 1996

Lucas KG, et al. Cancer 1996

Jones GR, et al. Pediatr Hematol Oncol 1996

Santolaya, et al. J. Clin. Oncol 2001

## Labs:

- CRP  $\geq 90$  mg/L
- ANC  $\leq 200$ /mm<sup>3</sup>
- AMC  $< 100$ /mm<sup>3</sup>
- Platelet  $\leq 50,000$ /mm<sup>3</sup>
- Gram negative sepsis

# Sepsis in Pediatric Cancer Patients

- Same diagnostic criteria as other pts:

- Fever/hypothermia
- Tachycardia
- Tachypnea
- Hypoperfusion
- Acidosis
- Hypotension
  - (SCCM/ACCP Consensus Conference, 1992)

- Common etiologies:

- Gram + cocci
  - $\alpha$ -hemolytic Strep
  - Staph. Epi
  - Staph aureus
- Gram - rods
  - Pseudomonas
  - Enterobacter
  - E. coli
- Fungi
  - Candida spp
- Viruses

# Therapy for Sepsis in Oncology Patients

- Empiric broad-spectrum Abx
- Early consideration of antifungals
- Usual PICU supportive care
  - Mechanical vent
  - Fluids/inotropes
  - Nutrition/blood products, etc
- Consider aggravated cardiac dysfunction if hx of high-dose anthracyclines, radiation
- Risk of adrenal suppression in pts with steroid Rx hx
- Granulocyte transfusion reportedly helpful in fungal sepsis - - but remains controversial

# Outcome of Oncology Patients in PICU

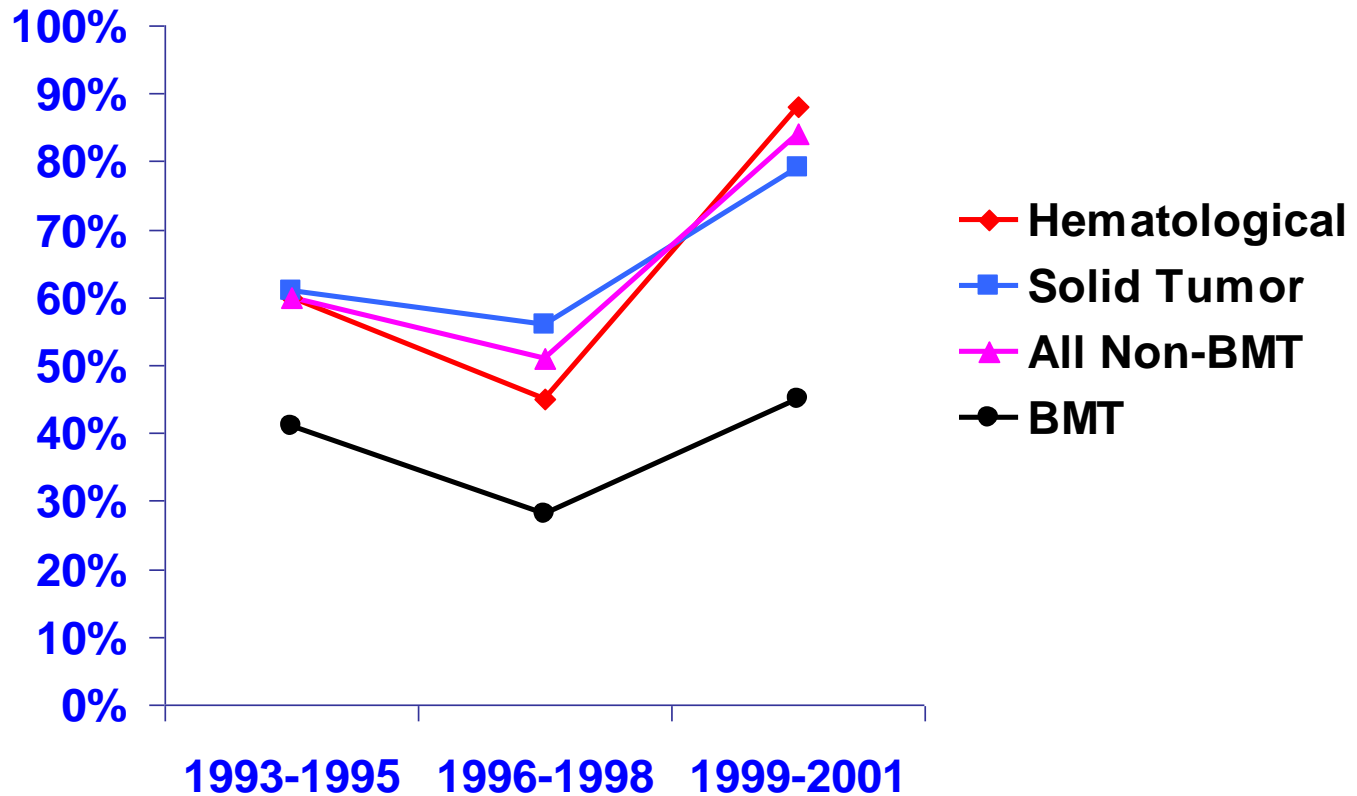
# Outcomes of intensive care in pediatric oncologic patients

- Shock and respiratory disease are the most frequent indications for PICU admission.
- Survival of oncology patients in PICU historically poor, especially for shock, respiratory failure, and if post-BMT
- Recent studies with more encouraging outcomes, however

# Mechanical Ventilation Survival in Pediatric Oncology

Butt	79-87	32 %
Meert	84-88	50 %
Sivan	86-88	26 %
van Veen	83-92	45 %
Hallahan	87-96	72 %
Keengwe	90-97	58 %
Ben-Abraham	89-99	36 %
Heying	95-99	50 %

# ICU Survival of Respiratory Failure in Pediatric Oncology Patients at St Jude Children's Research Hospital (Sillos, 2002)



**OR of ICU Survival 99-01 vs 93-98: 1.45 (95% C.I. 1.09, 1.98)**

# Changes in outcomes (1996-2004) for pediatric oncology and hematopoietic stem cell transplant patients requiring invasive mechanical ventilation.

Tamburro RF, et al. Penn State Children's Hospital, USA.  
Pediatr Crit Care Med. 2008 May;9(3):270-7.

## CONCLUSIONS:

- Hematopoietic stem cell transplant (HSCT) patients who require mechanical ventilation have worse outcomes than non-HSCT oncology patients.
- Outcomes for both groups have improved over time.
- Allogeneic transplant, higher PRISM score, need for repeated mechanical ventilation, and concomitant organ system dysfunction are risk factors for death.

# Predicting Survival

Prognostic factors in pediatric cancer patients admitted to the pediatric intensive care unit.

Dursum O, et al. Turkey

J Pediatr Hematol Oncol. 2009

Assessing the risk of mortality in paediatric cancer patients admitted to the paediatric intensive care unit: a novel risk score?

Meyer S, et al. Germany

Eur J Pediatr. 2005

Introduction of the oncological pediatric risk of mortality score (O-PRISM) for ICU support following stem cell transplantation in children.

Schneider DT, et al.

Bone Marrow Transplant. 2000

## Mortality rate was related to:

- leukemia/lymphoma vs Solid organ (P=0.029)
- The number of organ failures (P<0.0001)
- Neutropenia (P=0.001)
- Septic shock (P=0.025)
- Mechanical ventilation (P=0.01)
- Inotropic support (P=0.01).

The strongest predictor for poor outcome was the number of organ failures (P<0.05).

# Conclusions

- Pediatric oncology patients experience a broad variety of critical illnesses related to both disease and therapy
- Long-term survival for many pediatric cancers is improving
- ICU outcomes for this patient group is improving
- Good ICU care can benefit children with malignancies

Thank You