St. Jude Children's Research Hospital

ALSAC • Danny Thomas, Founder

Early Mortality in Children with Cancer

Raul C. Ribeiro, MD

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Outline

- Factors associated with an increased early mortality in children with cancer
- Management of selected non-infectious complications during the treatment of hematological malignancies

Definition of Complications Causing Early Mortality

Physiopathological abnormalities caused by the disease or its management which have the potential to cause life-threatening complications during the first two to four weeks from admission

Deaths During Induction: ALL

- 1011 patients (1984-1999) with ALL
- 14 (1.4%) deaths during induction
- Factors associated with early death
  - Age > 10 years
  - WBC count ≥ 100 x 10^9/L

Rubnitz et al., *Cancer* 2004

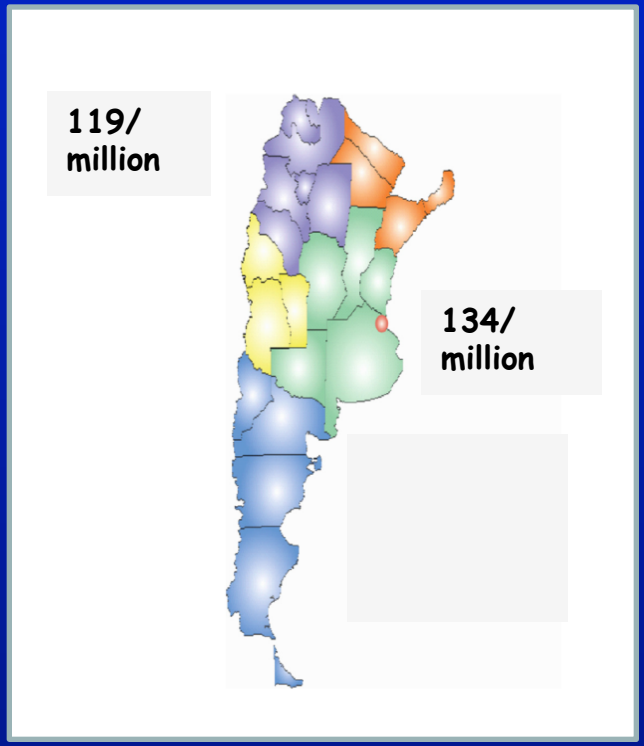
Deaths During Induction: AML

- 259 patients (1984-1999) with AML
- 8 (3.0%) deaths during induction
- Factors associated with early death
  - WBC count ≥ 100 x 10^9/L (3/29; 10%)
  - FAB M5 (4/60; 6.7%)

Rubnitz et al., *Cancer* 2004

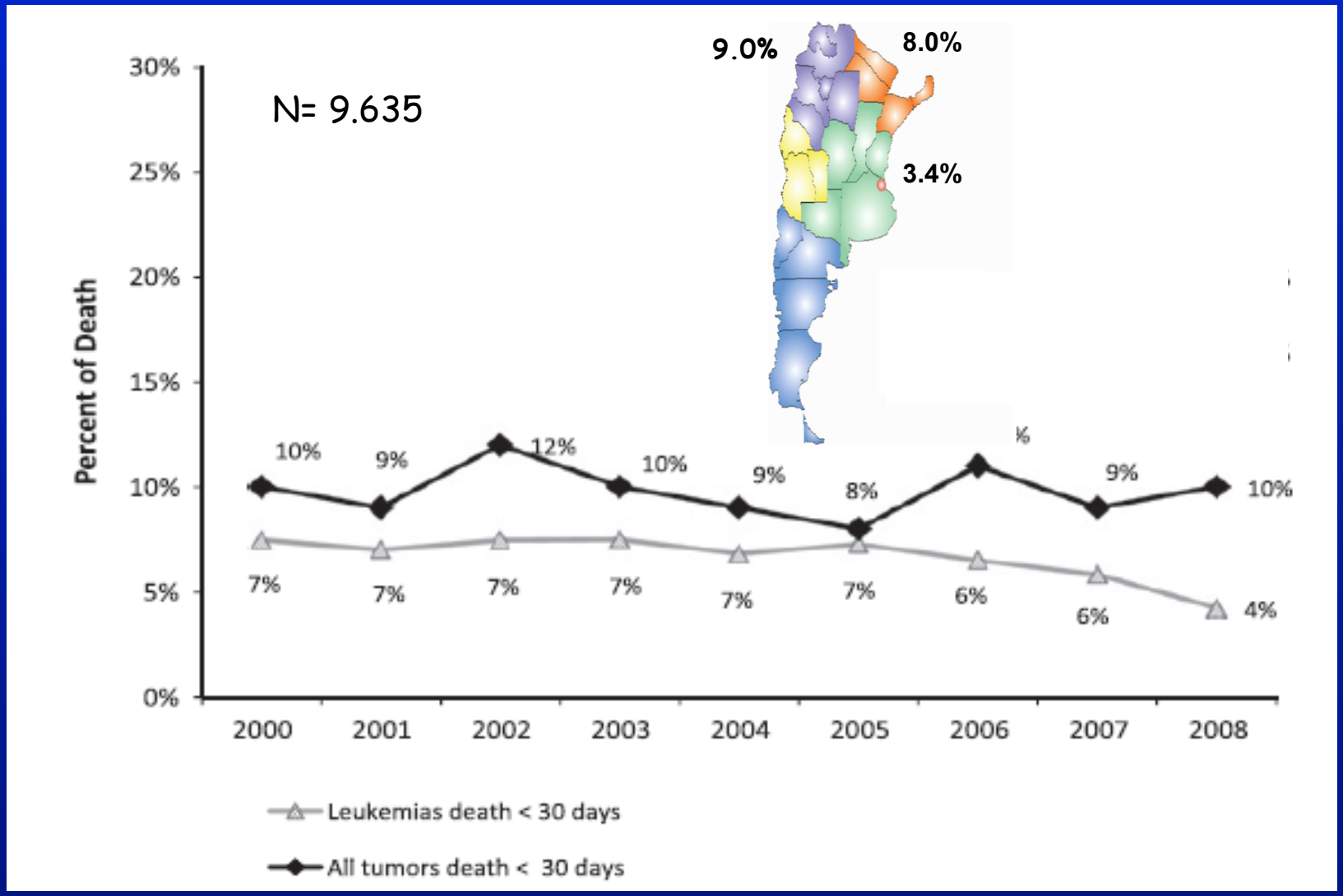
Early Death in Argentina: ROHA study from 2000-2008

- 11.447 children (0-14 years)
- 91% histologically verified
- 80% patients treated in public hospitals
- Overall age standardized
- incidence rates ranged between 119 and 134 per million children



Moreno F. et al European Journal Cancer 49, 465 2013

Death in Children with Cancer in Argentina



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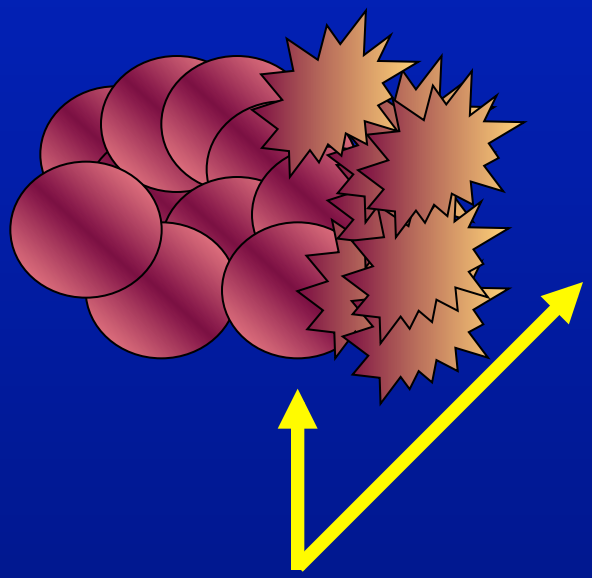
Pathobiologic Interactions

Tumor-Related

Tumor type
Infiltration
Compression
Secretion



Host-Related

Constitutional
Renal
Hemodynamic
Respiratory
Gastrointestinal
Neurologic
Metabolic
Inflammatory

Event

(spontaneous or intentional)

Hematopoietic Malignancies
Early Life-Threatening Complications

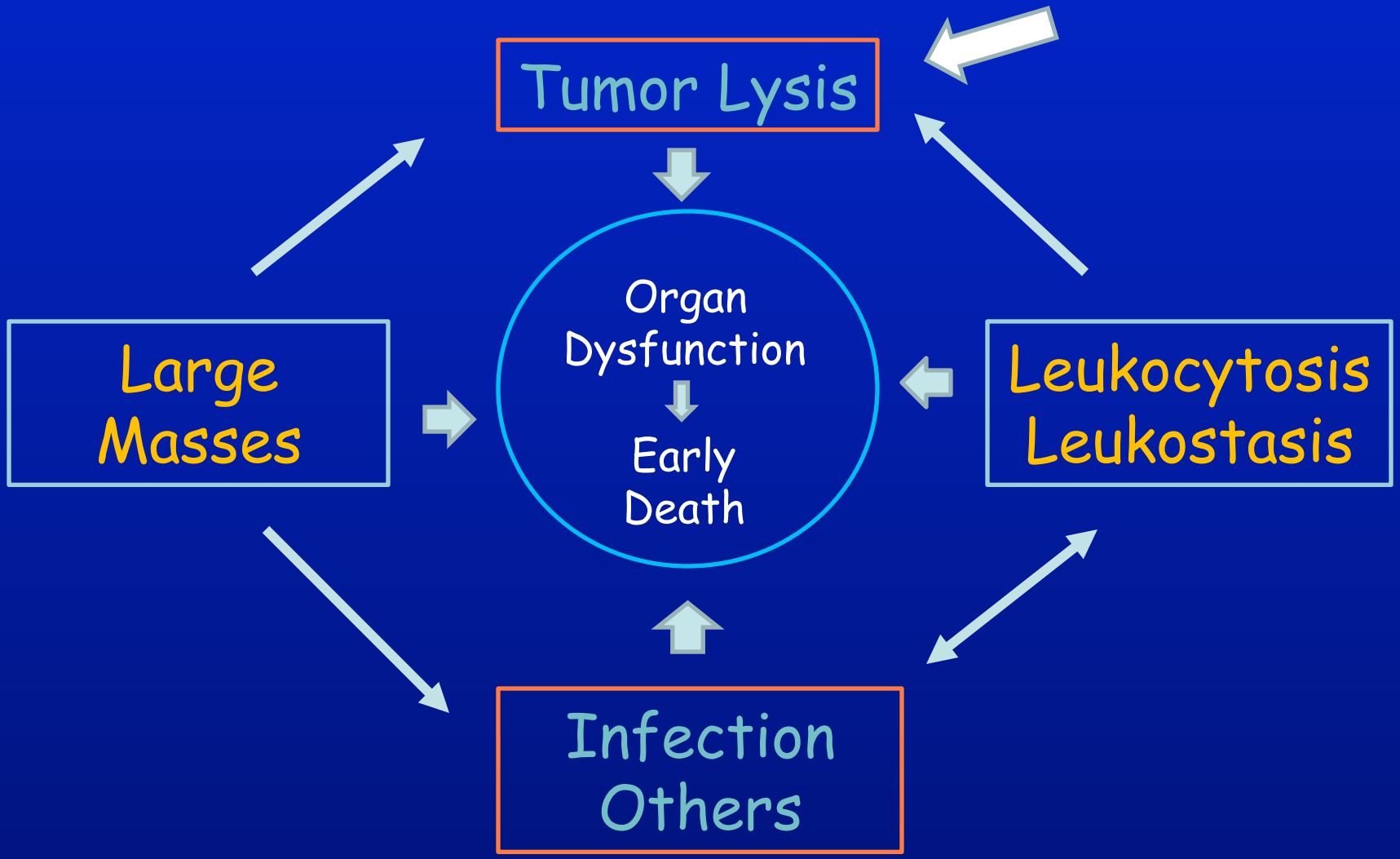
- Tumor Lysis Syndrome
  - Metabolic
  - Others
- Compartment compression syndrome
  - Mediastinum (airways/SVC)
  - Abdomen
- Leukostasis syndrome
- Coagulopathy (Bleeding/Thrombosis)
- Infectious complications

Supportive Care of Leukemia and Lymphomas in Children

Consider all patients with newly diagnosed leukemia or lymphoma to be at risk of life-threatening complications therefore a medical emergency

"Assume all non-identified fish to be sharks!"

A Pathological Conspiracy



Tumor Lysis: Type of Malignancy

- Lymphoproliferative
  - Lymphoblastic Leukemia
  - Non-Hodgkin Lymphoma
- Myeloproliferative
  - Promyelocytic Leukemia
  - Monoblastic
  - Myelomonoblastic

METABOLIC
Uric Acid
Calcium

COAGULOPATHY
DS

SISTEMIC
INFLAMMATORY
RESPONSE

Metabolic Cell Lysis Syndrome

Hallmark

Rapid increase of uric acid plasma levels

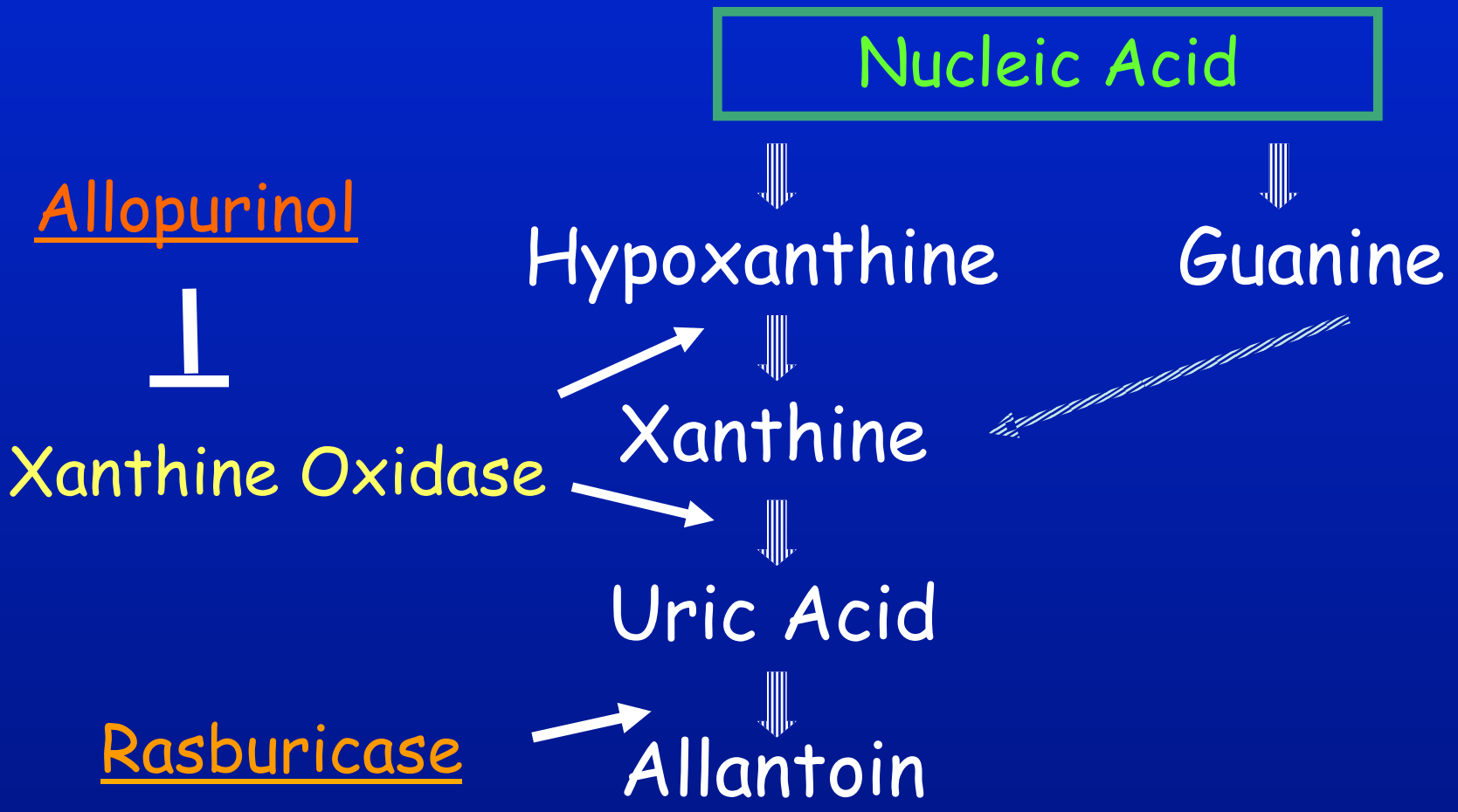
Primary Target Organ: Kidney

- Hyperleukocytosis/high tumor burden
  - Compression of the genitourinary tract
- Highly chemotherapy-sensitive tumor (lymphoid leukemia and Burkitt lymphoma)
- Co-morbid conditions
  - Dehydration, infection, metabolic acidosis

Management of Metabolic Cell Lysis
Fluid Management

- Begin immediately
  - 3 L/m^2/day or 125 mL/m^2/hr
  - Fluid balance every 6 hours (retain no more than 150 ml/m^2 in 6 hours)
  - Maintain urine output at 100 mL/m^2/hr and specific gravity <1.010
  - Forced diuresis (furosemide)
  - NaHO3 if necessary (urinary pH ~ 7.0-7.5)
- No potassium or calcium in IV solution
- Phosphate binder (renagel, lanthanum)
- Adjust sodium load per age and Na^+

Specific Management: Hyperuricemia



Non-Metabolic Tumor Lysis: Acute Myelomonoblastic Leukemia

- 4-year-old girl with a sore throat
- WBC: 30,700/µL with 14% blasts; Hgb: 9.6 g/dl; Platelets 75,000/µL
- BMA/Bx: AML-M4eo, inv(16)
- CXR: Increased interstitial markings with diffuse haziness and coarse reticulonodular pattern; peribronchial thickening

Non-Metabolic Tumor Lysis Clinical Course (cont.)

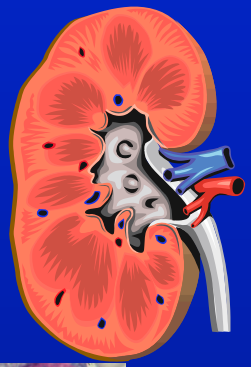
- 2 hrs after start of chemotherapy, O_2 saturation fell; 100% O_2 required
- 6 hrs after, hypotension requiring fluid resuscitation; mechanical ventilation
- Steroids
- Chemotherapy was held

Non-Metabolic Tumor Lysis Clinical Course (cont.)

- Dopamine and norepinephrine
- Steroids
- On day 5, chemotherapy restarted
- By day 8 all pressors were discontinued and she was extubated
- Tolerated further therapy well

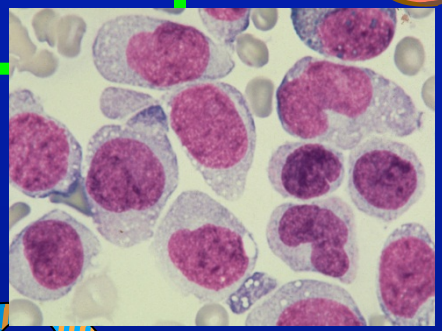
Abnormalities Associated with Myelomonoblastic Leukemia Lysis

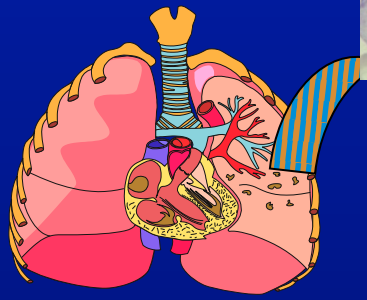
Lysozyme
Inflammatory
cytokines



Tubular
Dysfunction

Hypoalbuminemia
Hypokalemia
Hypophosphatemia
Hyponatremia





Respiratory Failure
Hemodynamic
instability

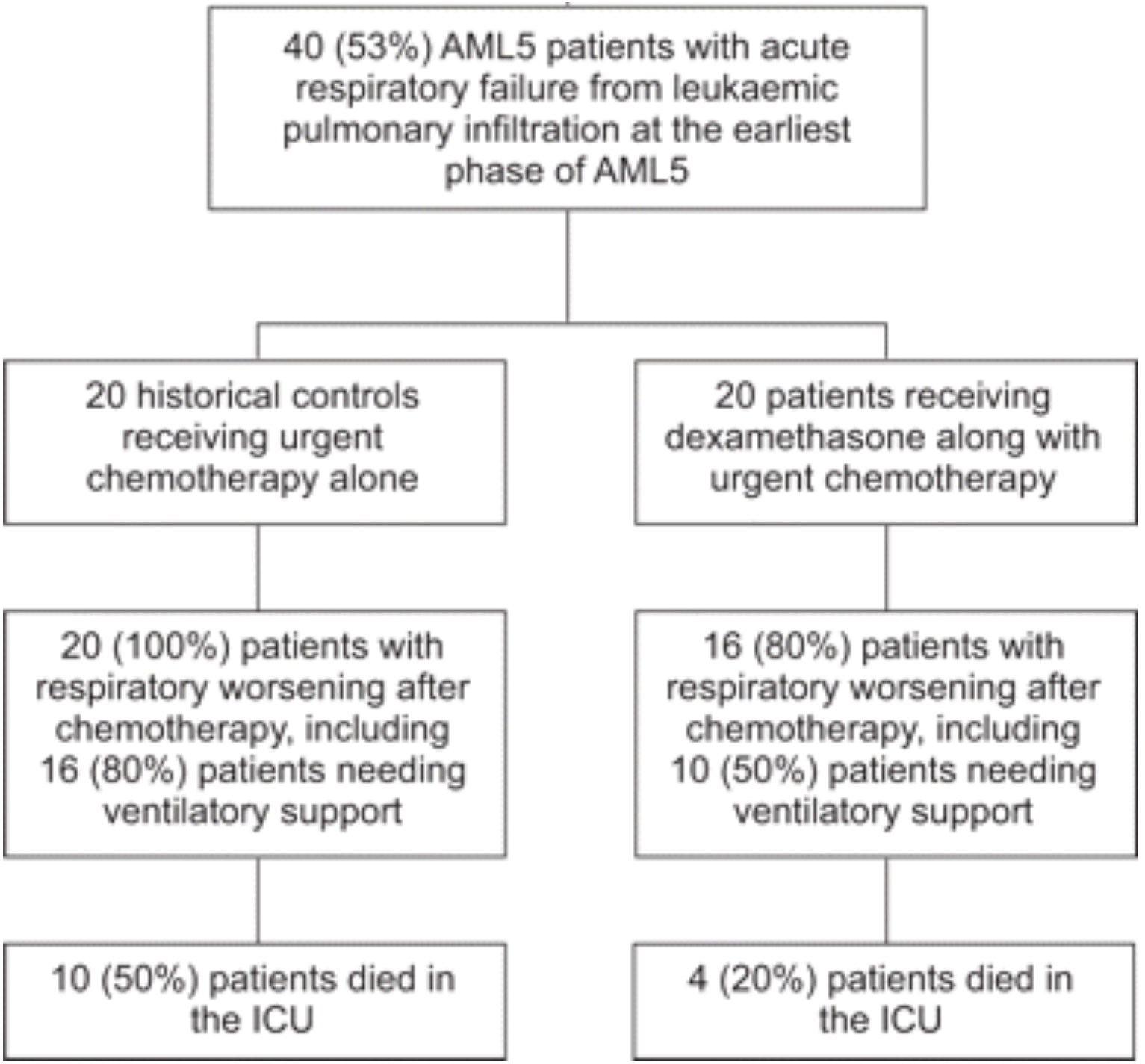
Initial Management of Myelomonoblastic leukemia

- Low-dose cytarabine
- Carefully fluid balance
- Stop chemotherapy if abrupt cell lysis occurs
- Corticosteroids
- Vasopressors
- Lung protection

Dexamethasone Use in Monocytic Leukemia

- 45 patients with AML M5 (2005-2008)
- 20 required ICU before chemotherapy for respiratory manifestations
- None had prior comorbidity
- Dexamethasone (10 mg q 6 h) until WBC < $1 \times 10^9/L$
- Control a historic group

Azoulay E et al Eur Respir J 39:648, 2012



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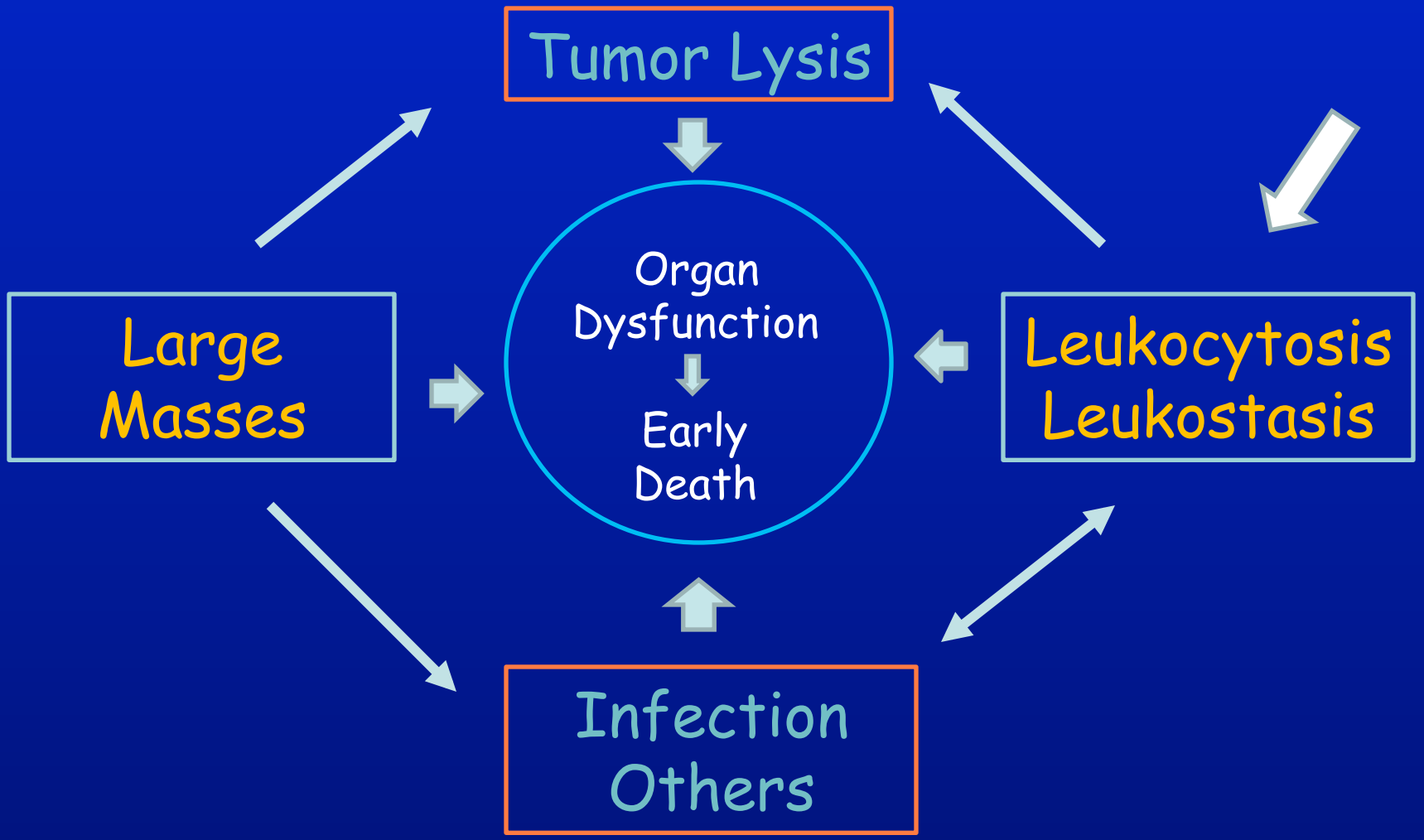
A Pathological Conspiracy



Hyperleukocytosis

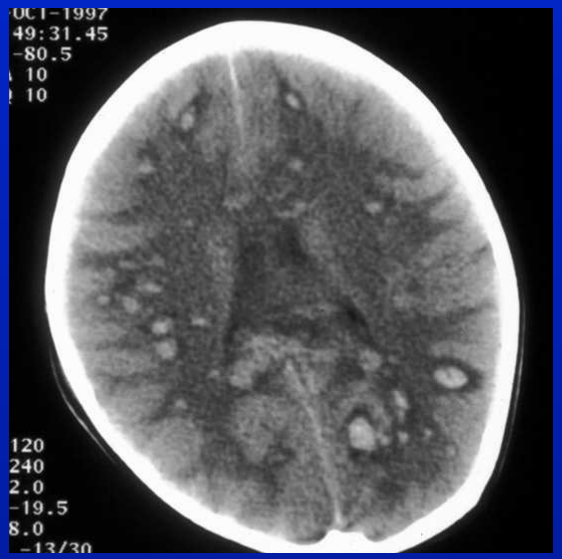
- Associated with both ALL and AML
- Defined as WBC > 100 $x10^9/L$
  - 15% lymphoblastic leukemia
  - 20% myeloid leukemia
- Associated with an increased mortality rate
- Complications: Neurologic, Pulmonary and Metabolic

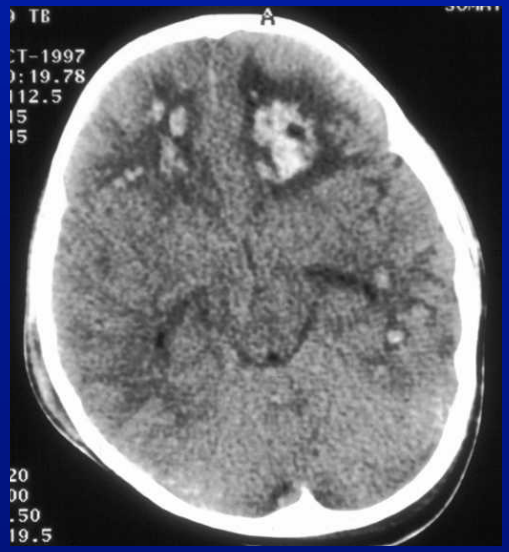
Factors Associated with Hyperleukocytosis

- Age < 1
- T-cell, monoblastic
- Large liver and spleen
- Elevated LDH
- Cytogenetics
  - 11q23
  - Ph-positive

CNS Leukostasis

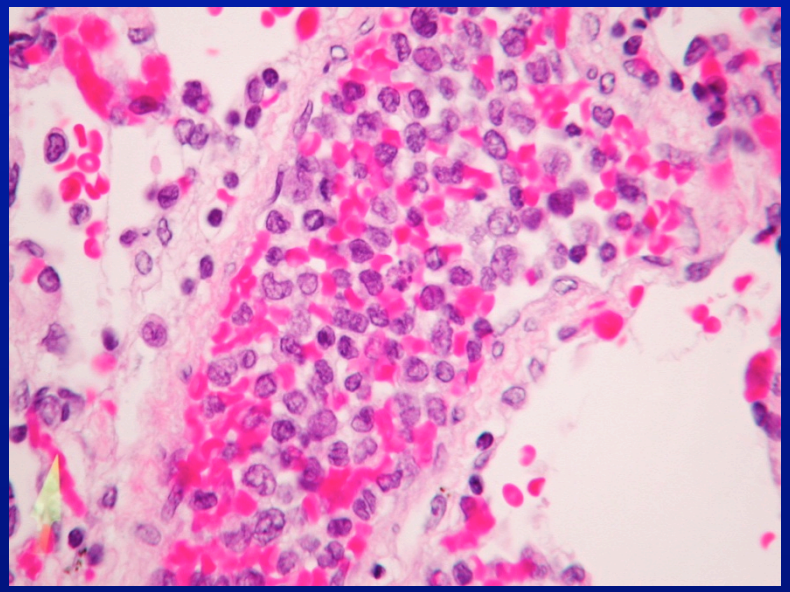
- Symptoms include: headache, mental status changes, vision changes, seizures, coma, death
- Intracranial hemorrhage

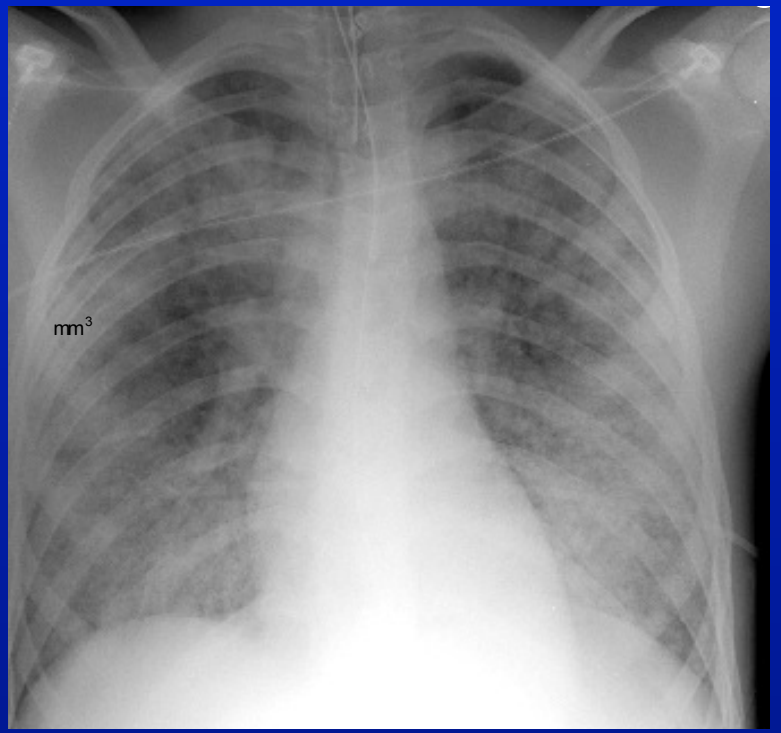




Pulmonary Leukostasis Syndrome

- Triad: respiratory symptoms, hypoxia, infiltrates on CXR
- Pulmonary hemorrhage



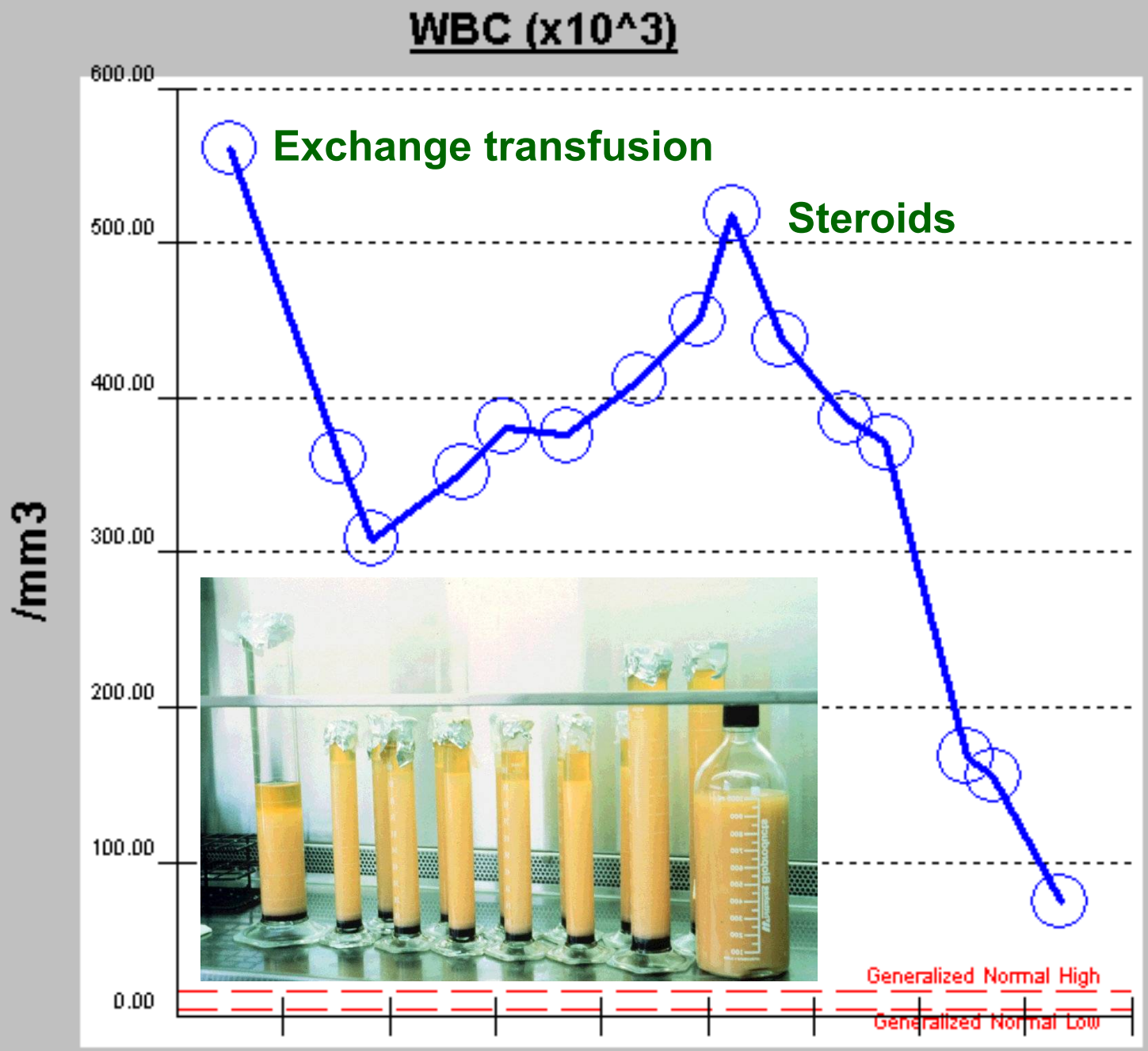


Leukemic infiltrates throughout
Alveolar exudate & hyaline membranes
Alveolar hemorrhage
Leukostatic plugs in pulmonary vessels
Enlarged right ventricle

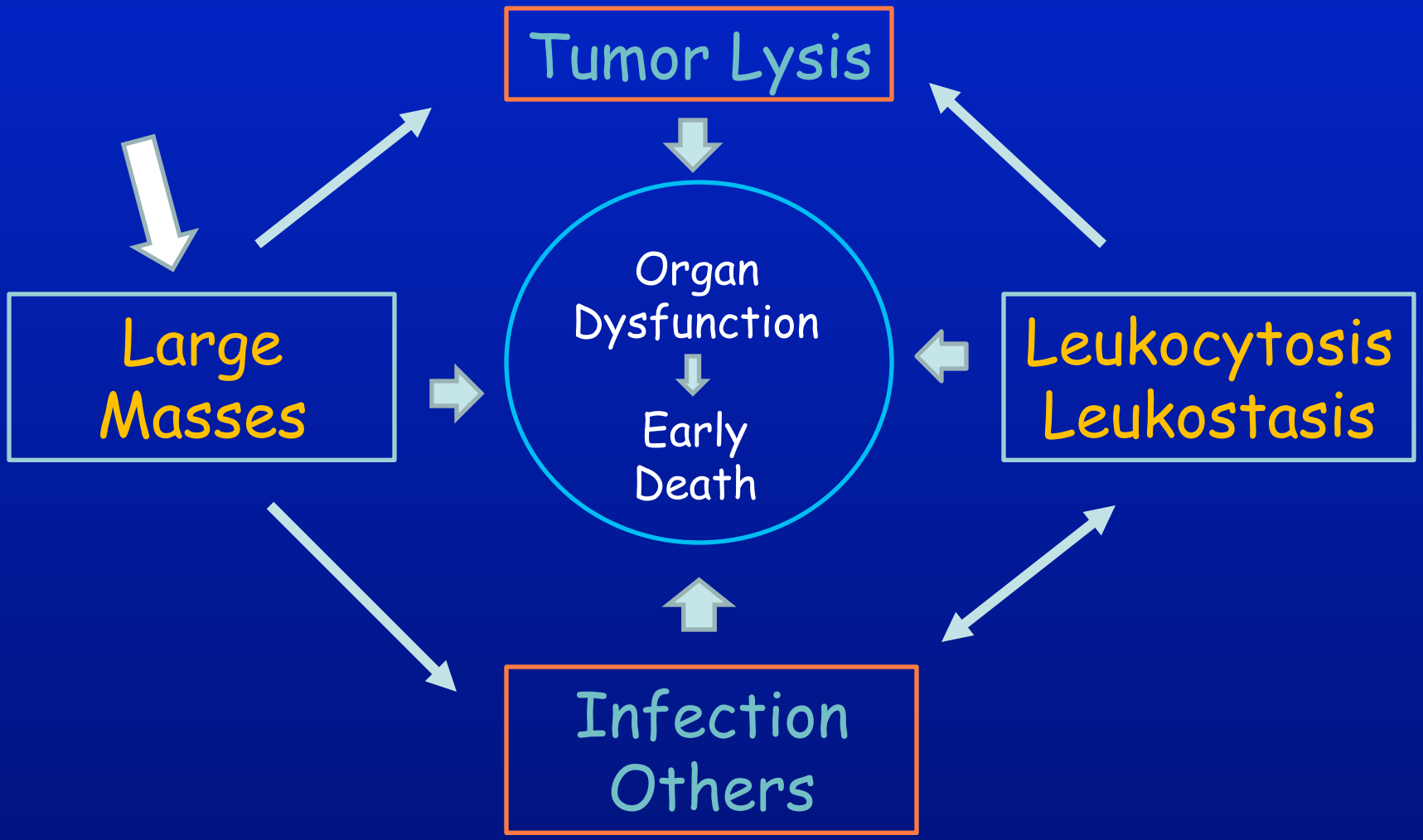
Specific Management of Hyperleukocytosis

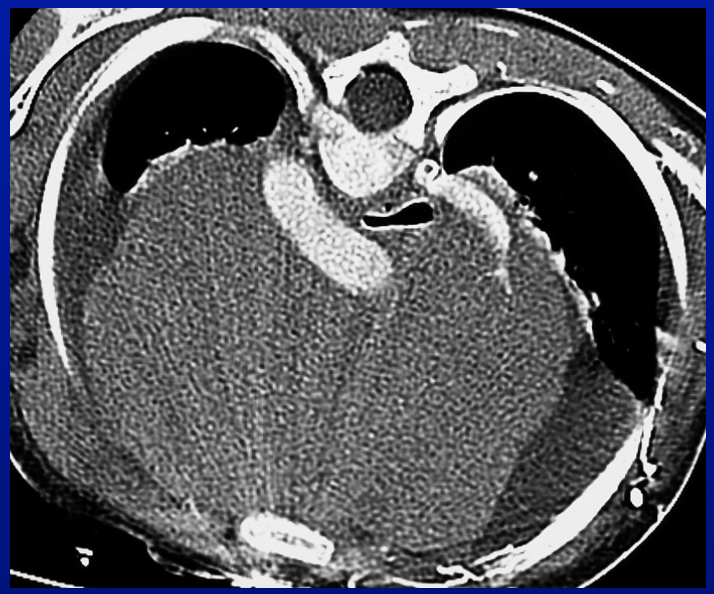
Pathophysiology-directed strategy

- Leukostasis
  - Gentle cytoreduction with chemotherapy
  - Corticosteroids
  - Leukapheresis
  - Avoid PRBC transfusion and diuretics
  - Maintain platelet count > 50 x 10^9/L
- Lung protection
- Correction of Metabolic problems


WBC (x10^3)
/mm3
600.00
500.00
400.00
300.00
200.00
100.00
0.00
Exchange transfusion
Steroids
Generalized Normal High
Generalized Normal Low

A Pathological Conspiracy

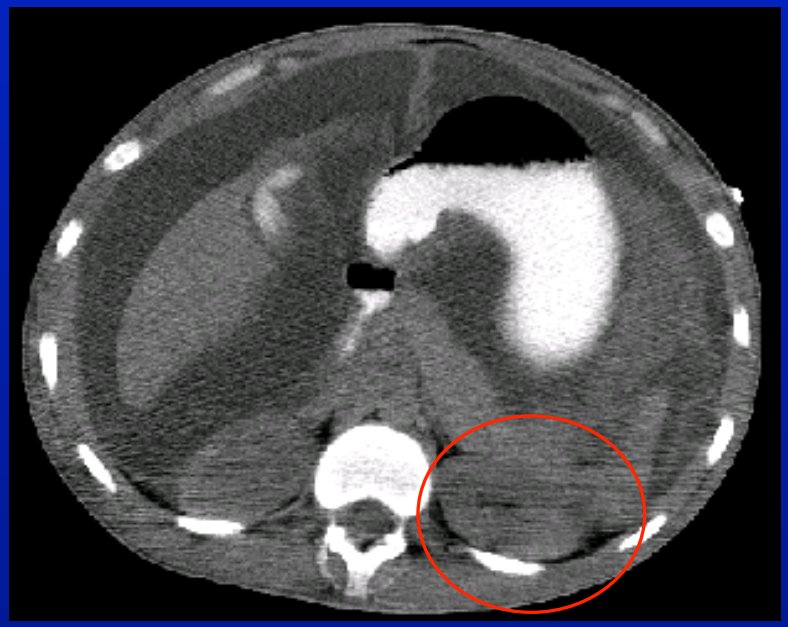




Management of Mediastinum Compartment Syndrome

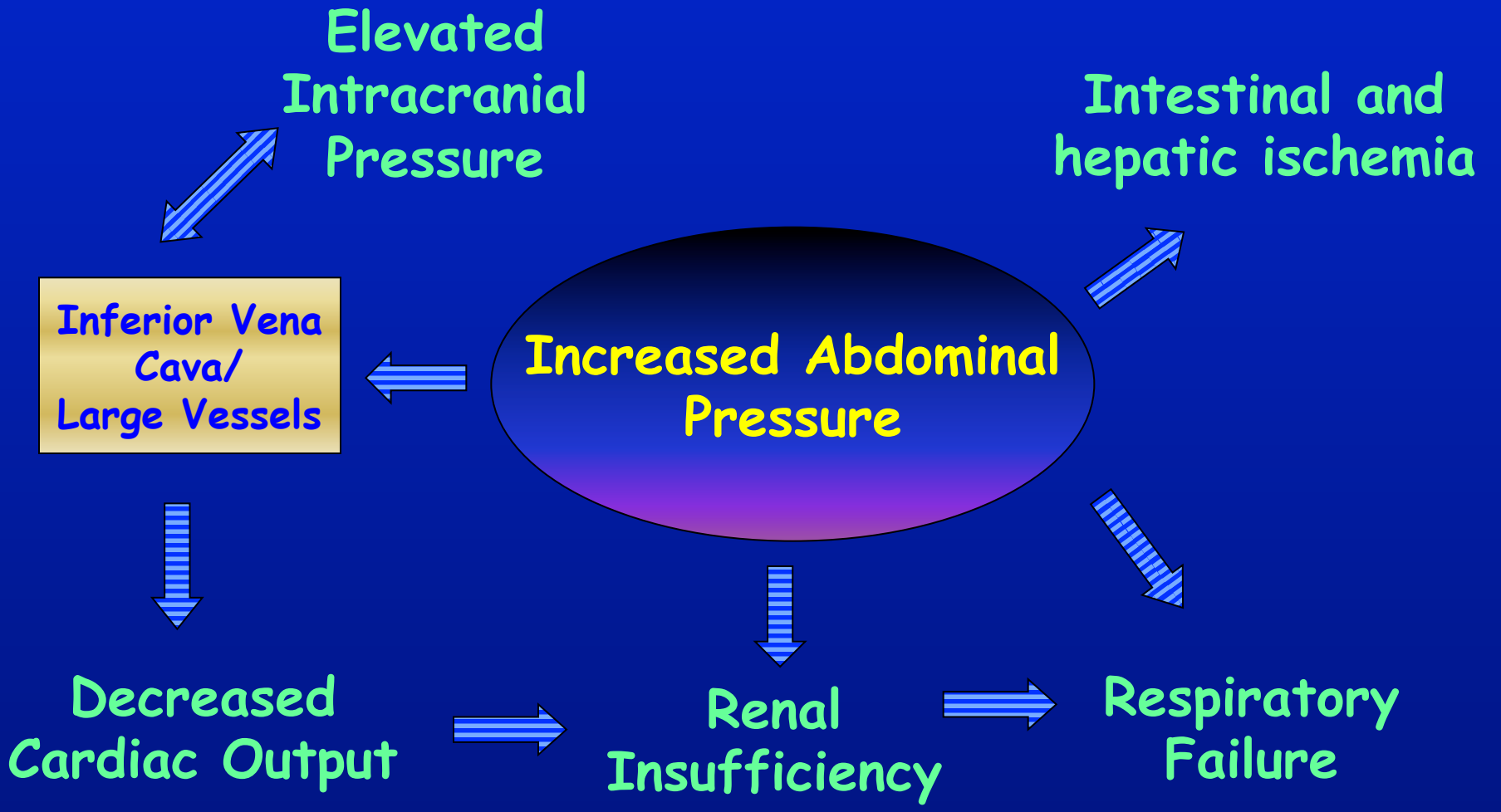
- Avoid hyperhydration
- Minimal manipulation of the patient
- Obtain diagnostic information from the most accessible site
- Multidisciplinary team approach if the patient requires invasive procedure
- Usually very sensitive to steroids

Abdominal Compartment Syndrome



- Pathological elevation of intraabdominal pressure
- Multiple organ dysfunction
- Narrowing of the inferior vena cava
- Direct renal compression or displacement
- Bowel wall thickening
- Rounded appearance of the abdomen

Abdominal Compartment Syndrome

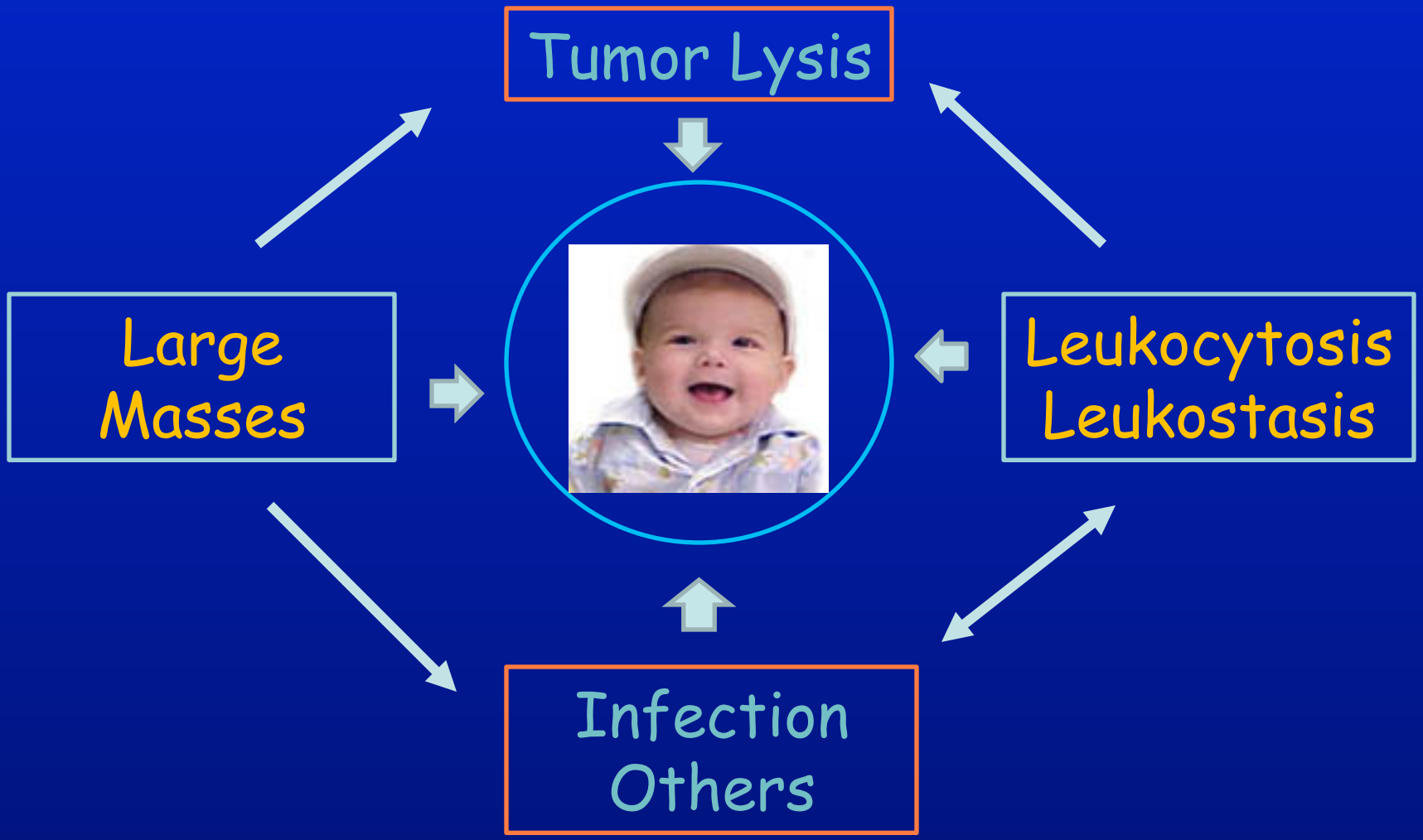


Conclusions

Early mortality can be reduced in newly diagnosed patients with leukemia and lymphoma (<1%)

- Anticipate complications by carefully attention to clinical details
- Treatment based on the pathophysiology and leukemia cell type
- Multidisciplinary approach is essential

Effective Interventions = Happy End!



www.cure4kids.org

- Principles of Treatment in ALL, by Ching-Hon Pui, MD
- Early Complications of Children with Leukemia/Lymphoma: Tumor Lysis Syndrome Revisited by Raul C. Ribeiro, MD
- Early Complications of AML by Monika Metzger, MD, Nobuko Hijiya, MD and Jeffrey Schmidt, MD
- Acute Complications of Childhood Leukemia by Scott Howard
- Infectious complications in AML patients receiving chemotherapy by Beth Kurt, MD, Jeffrey E. Rubnitz, MD, PhD and Patricia Flynn, MD
- Early Complication of Acute Leukemia: Hyperleukocytosis by Eric Lowe, MD
- And many more..... choose "seminars", and type "complications and Leukemia"