Childhood Acute Lymphoblastic Leukemia

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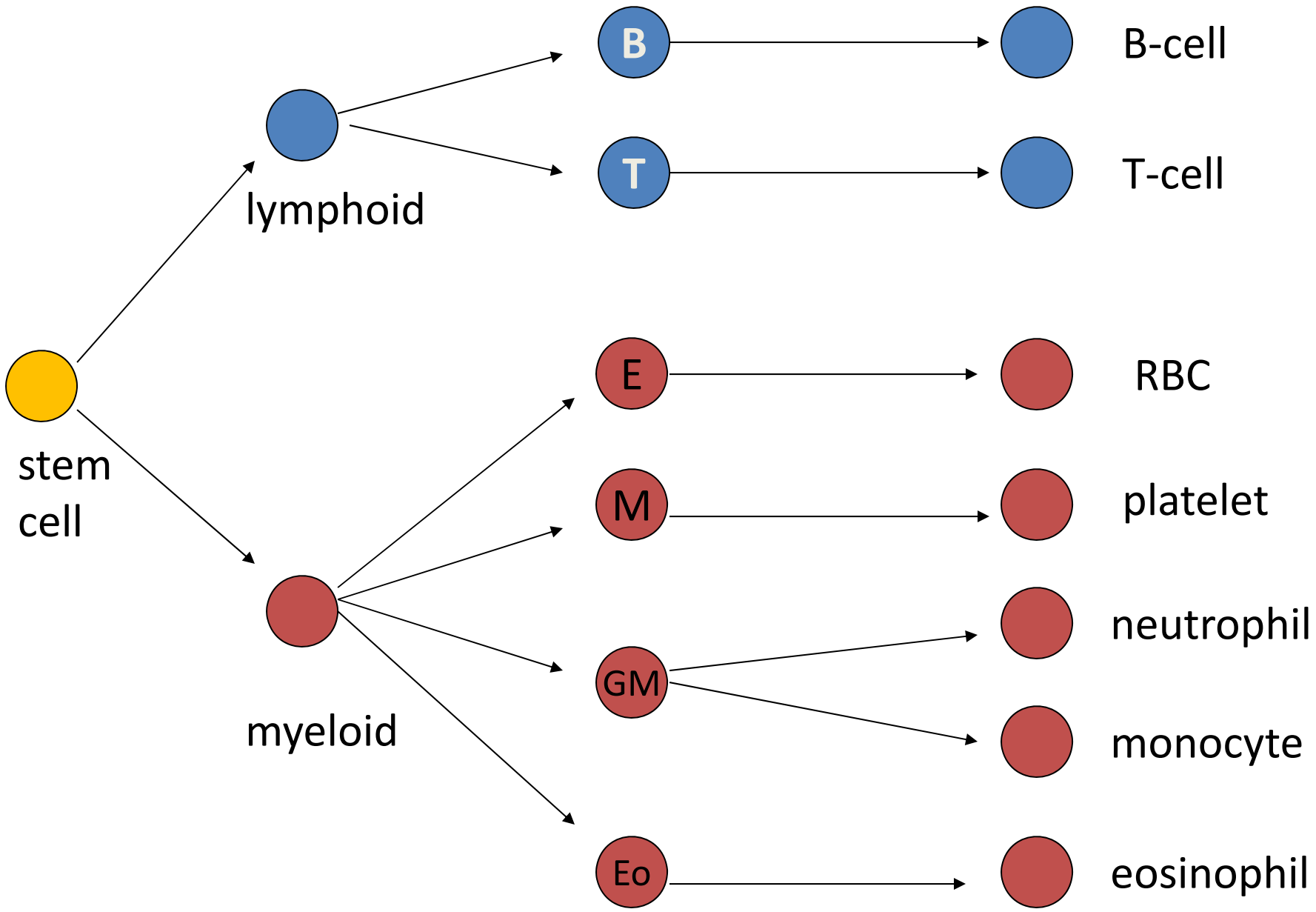
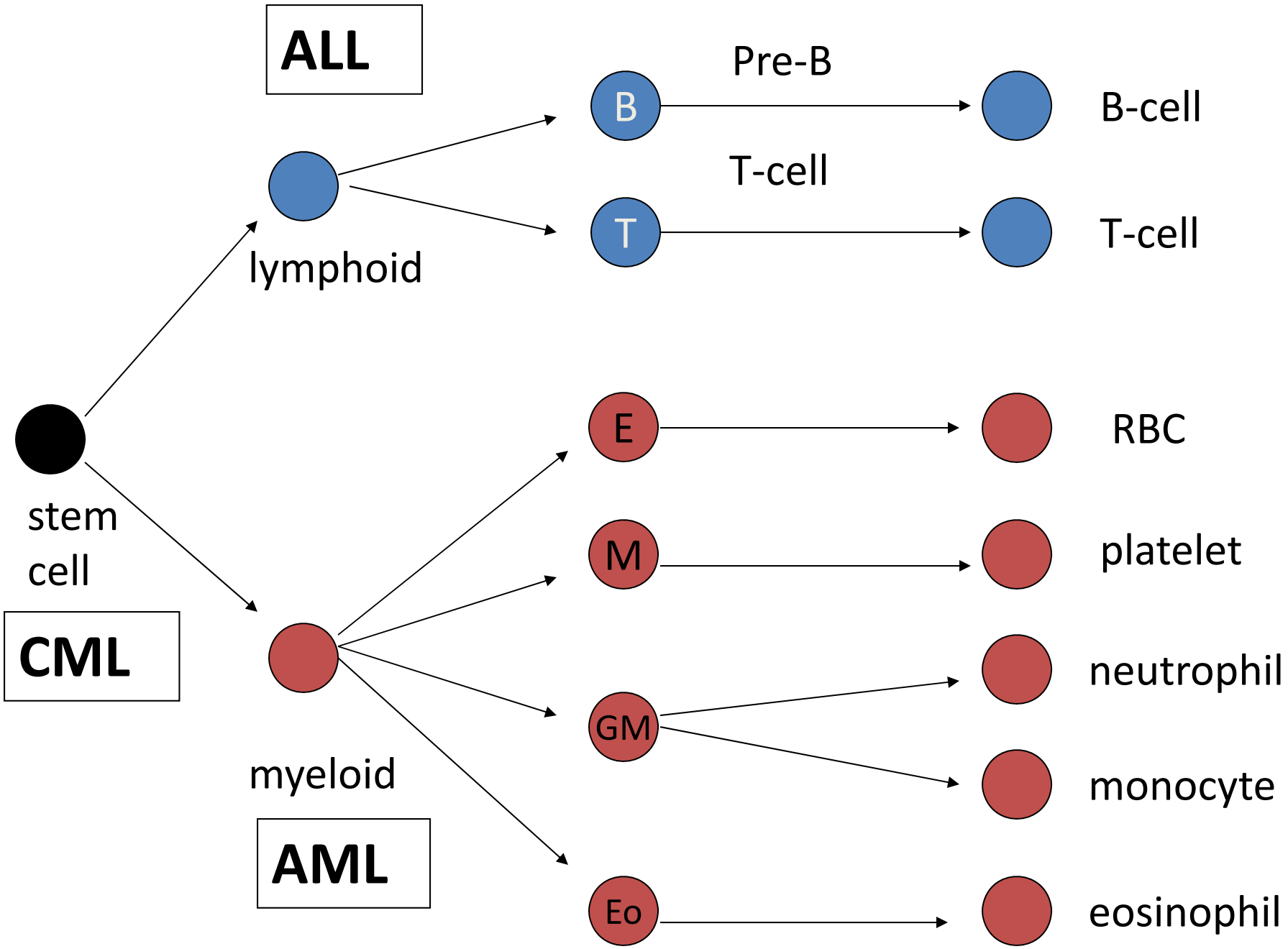
Leukemia: Definition

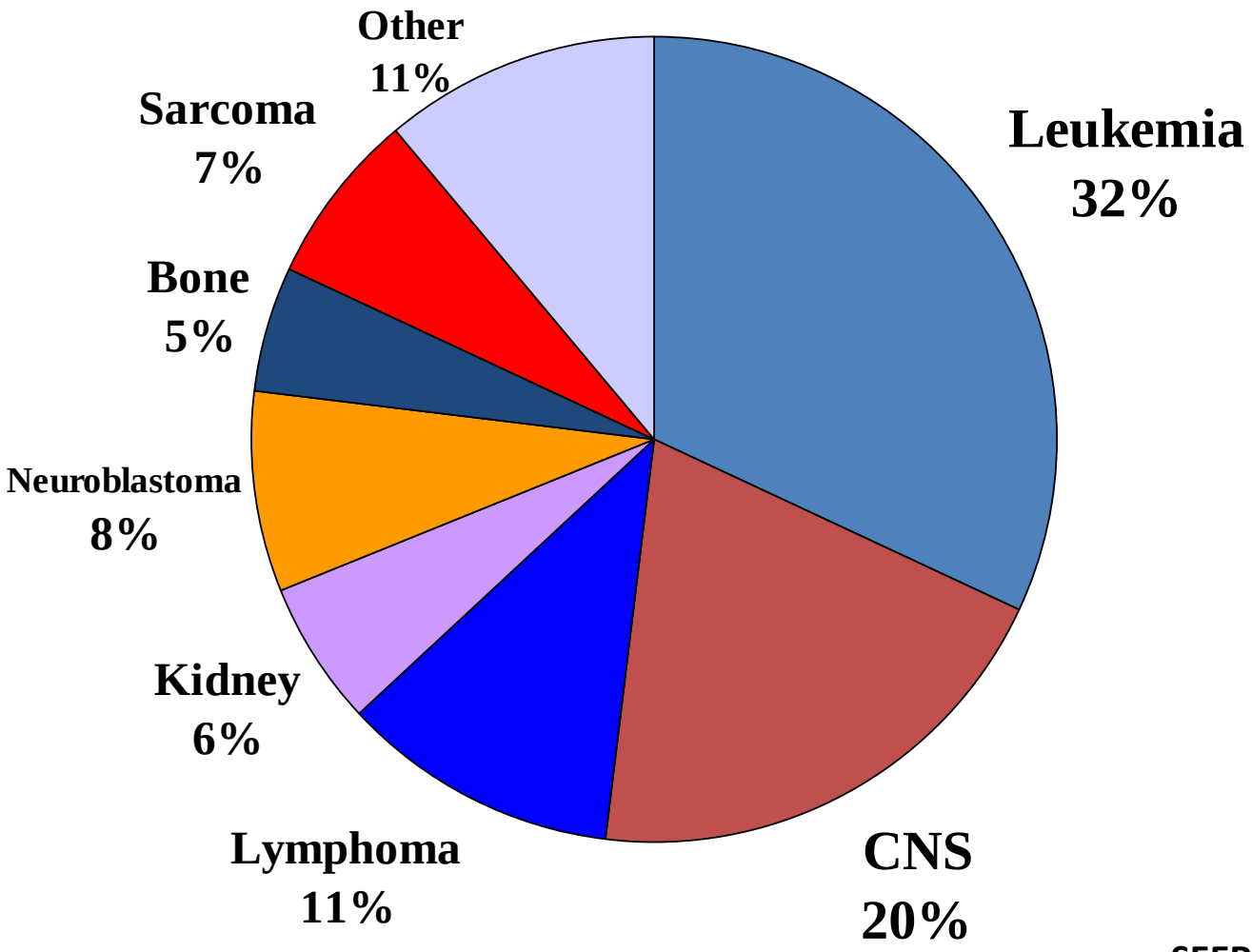
- Clonal malignancy (cancer) of blood precursor cells
- Leukemia cell: blast
- Acute leukemia: >25% malignant blast cells in bone marrow
  - Usually “packed”: > 80-90% blasts

Normal Hematopoiesis



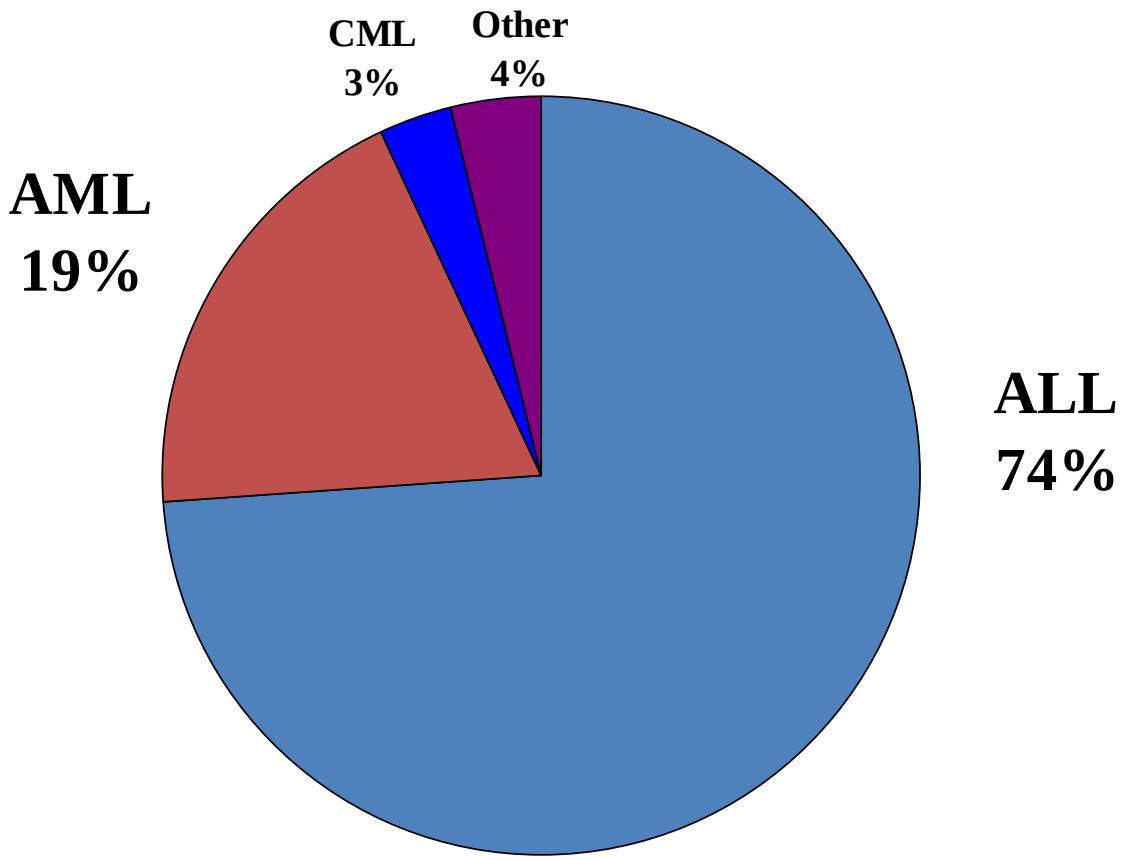

ALL
Pre-B
B
B-cell
T-cell
T
T-cell
lymphoid
stem
cell
CML
E
RBC
M
platelet
GM
neutrophil
monocyte
myeloid
AML
Eo
eosinophil

Childhood Cancer in U.S.



SEER Data, 1975-95

Childhood Leukemia in U.S. (Age < 20 years)

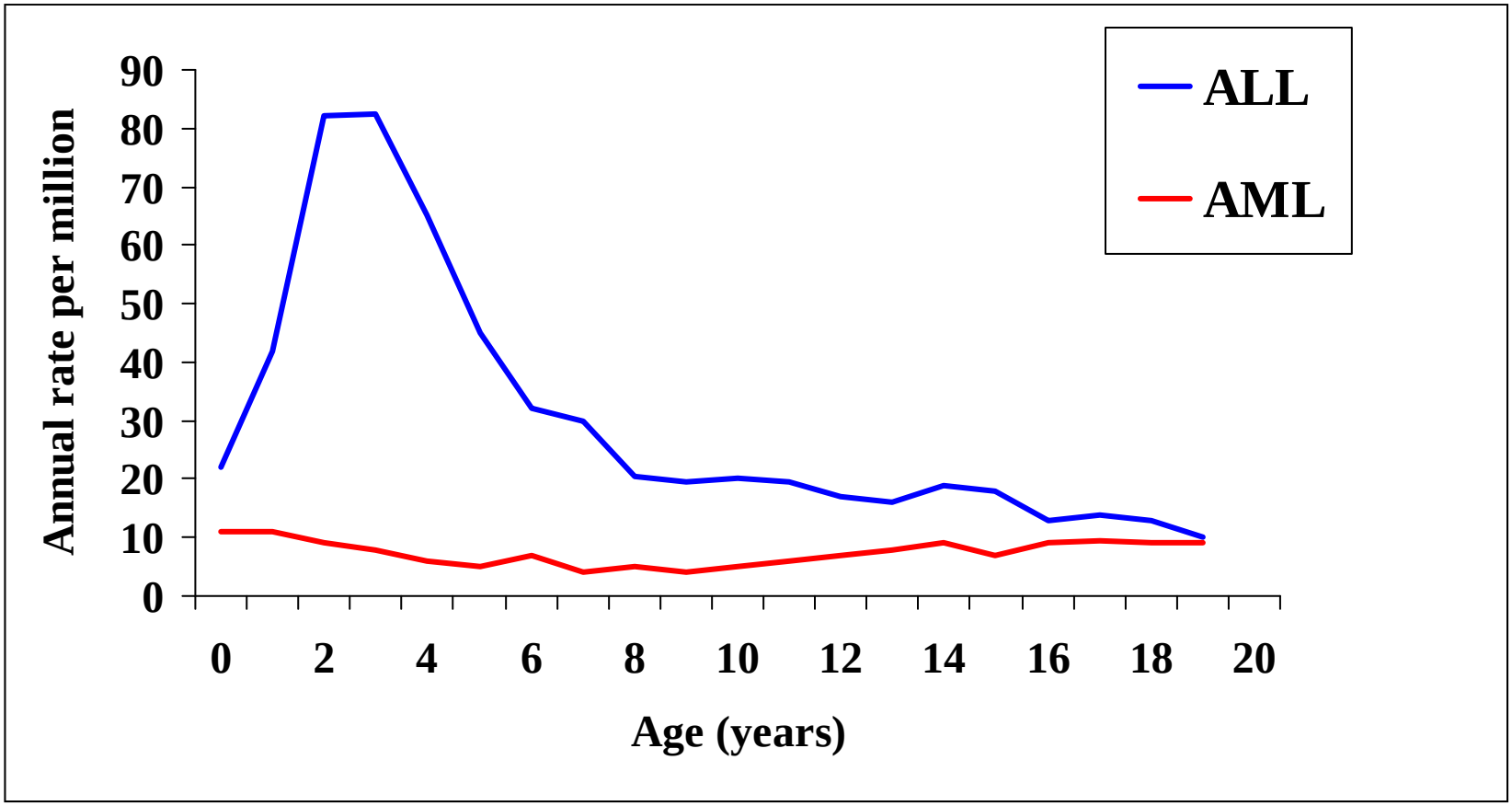


SEER data, 1975-95

Leukemia: Epidemiology

- ~3250 new cases in US/year
  - ~2500 new cases of ALL/year
- Annual incidence 39.5/million (age <20 yrs)

Leukemia: Age-Specific Incidence



Childhood ALL: Etiology

- **No known cause for vast majority of cases**
- **Down Syndrome**
  - ~10-20 x increased risk of developing childhood leukemia
    - 50-75% of leukemia cases are ALL
  - Cumulative incidence of leukemia
    - ~2% by age 5 years
    - ~3% by age 30 years
  - Almost always have B-ALL (not T-ALL)
  - Higher risk of treatment-related complications (infections, mucositis)
  - Overall ALL outcome similar to non-Down Syndrome patients

Signs and Symptoms

- Replaced Marrow
  - Anemia: Pallor, decreased energy
  - Thrombocytopenia: petechiae, bruising, bleeding (rare)
  - Neutropenia: severe infection
  - Bone pain: limp, back pain

Signs and Symptoms

- Extramedullary Disease
  - Organomegaly: hepatosplenomegaly
  - Lymphadeonpathy
  - CNS disease: h/a, meningismus, cranial nerve palsies
  - Skin: Leukemia cutis (AML, infants)
  - Testicular masses (ALL)
  - Ocular: retina, cornea

- Fever

- Exceedingly rare to pick up leukemia as incidental finding on routine CBC in asymptomatic patient

CBC at Presentation

Leukocyte count (/mm^3)	%
< 10,000	53
10-49,000	30
>50,000	17
Hemoglobin (g/dL)	
<11.0	88
Platelets (/mm^3)	
<20,000	28
20,000-99,000	47
>100,000	25

Differential Diagnosis

- Rheumatologic: JRA
- Infections: EBV
- Non-malignant Heme: aplastic anemia, ITP, leukemoid reaction
- Other malignancies: Neuroblastoma, Lymphoma

Leukemia: Initial Management

- Stabilize Patient
- Assess for Leukemia-related “emergencies”

Leukemia: Initial Management

1. Assess for Possible Infection

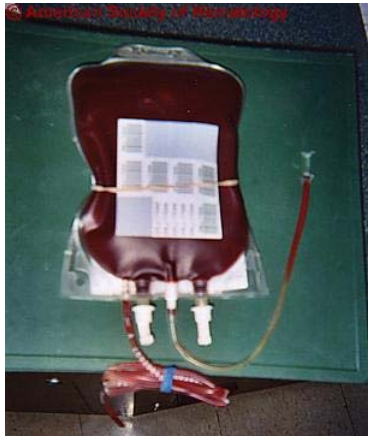
If febrile:

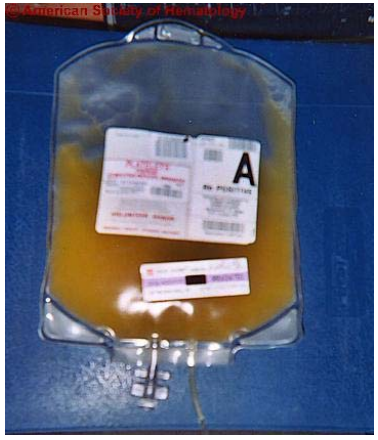
- Blood culture, regardless of age
- Begin broad spectrum antibiotics, regardless of ANC
  - Cefepime (with 48-hour vanco rule-out)

Leukemia: Initial Management

2. Assess for Need for Transfusions

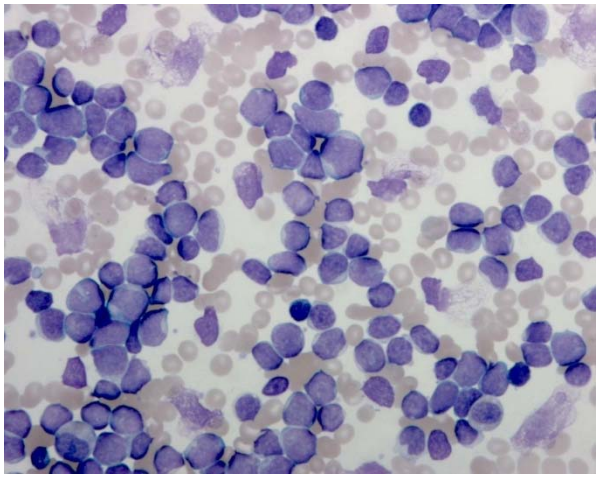
- Transfuse PRBC's, platelets (leukodepleted, CMV-negative, irradiated)





Leukemia: Initial Management

3. Assess for signs/sx of Hyperleukocytosis:
   - WBC >100, 000/mm^3
   - Signs/Symptoms of sludging in CNS, Lung
   - IV fluid, anti-leukemic therapy
   - Pheresis (AML more often than ALL)



Leukemia: Initial Management

4. Assess for possible DIC:
   - Risk for life-threatening bleeding
   - AML > ALL
     - For ALL patients: T-ALL > B-ALL
   - Check PT/PTT/fibrinogen in all patients
   - Transfuse FFP, cryoprecipitate as needed

Leukemia: Initial Management

5. Assess and Treat Acute Tumor Lysis Syndrome
   - High uric acid, high potassium, high phosphate (low calcium)
   - Can result in renal failure (uric acid precipitates)
   - Should check electrolyes, BUN/Cr, uric acid in all patients
     - G6PD in case rasuburicase needs to be used
   - Prevention/treatment:
     - IV hydration (no K in IVF)
       - Bicarbonate no longer routinely used
     - Allopurinol (Rasburicase)

Leukemia: Initial Management

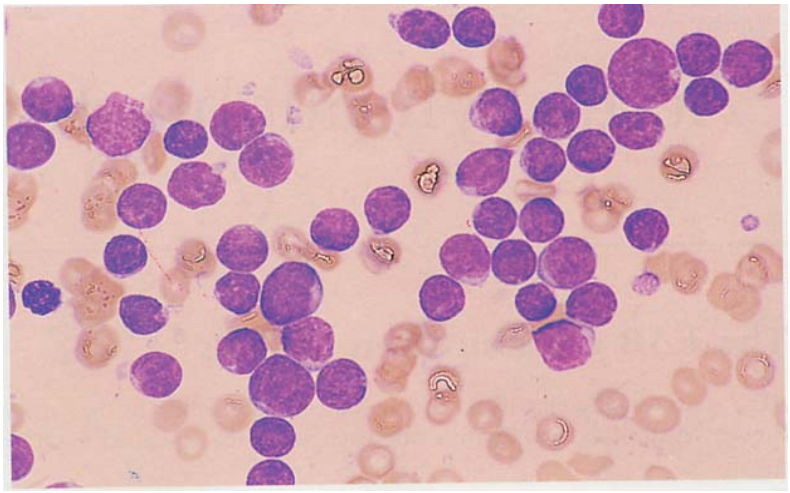
4. Assess for Anterior mediastinal mass:
   - T-cell ALL (almost exclusively)
   - Range of symptoms may be present
   - Obtain CXR in all patients at initial diagnosis
   - Consider CXR in new asthmatic prior to treating with steroids

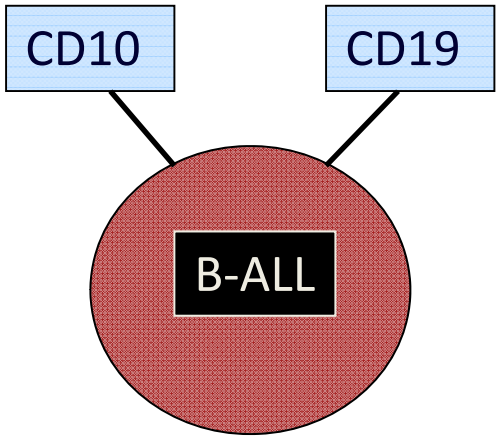
Summary of Initial Management

- CBC with differential
- DIC screen
- Clot to blood bank
- “Tumor Lysis Labs”: Lytes, BUN/Cr, Ca, Mg, Phos, Uric Acid
  - G6PD (in case rasburicase is needed)
- Chest x-ray

Diagnostic Evaluation

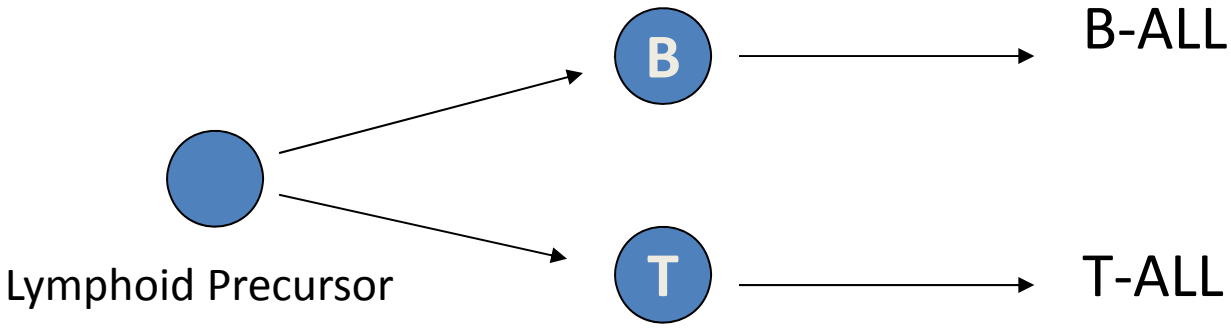
- Bone Marrow Aspirate/Biopsy
  - Morphology
  - Flow cytometry
  - Cytogenetics: Karyotype, FISH, PCR





- Spinal Fluid (with IT therapy—<u>after</u> diagnosis is made)

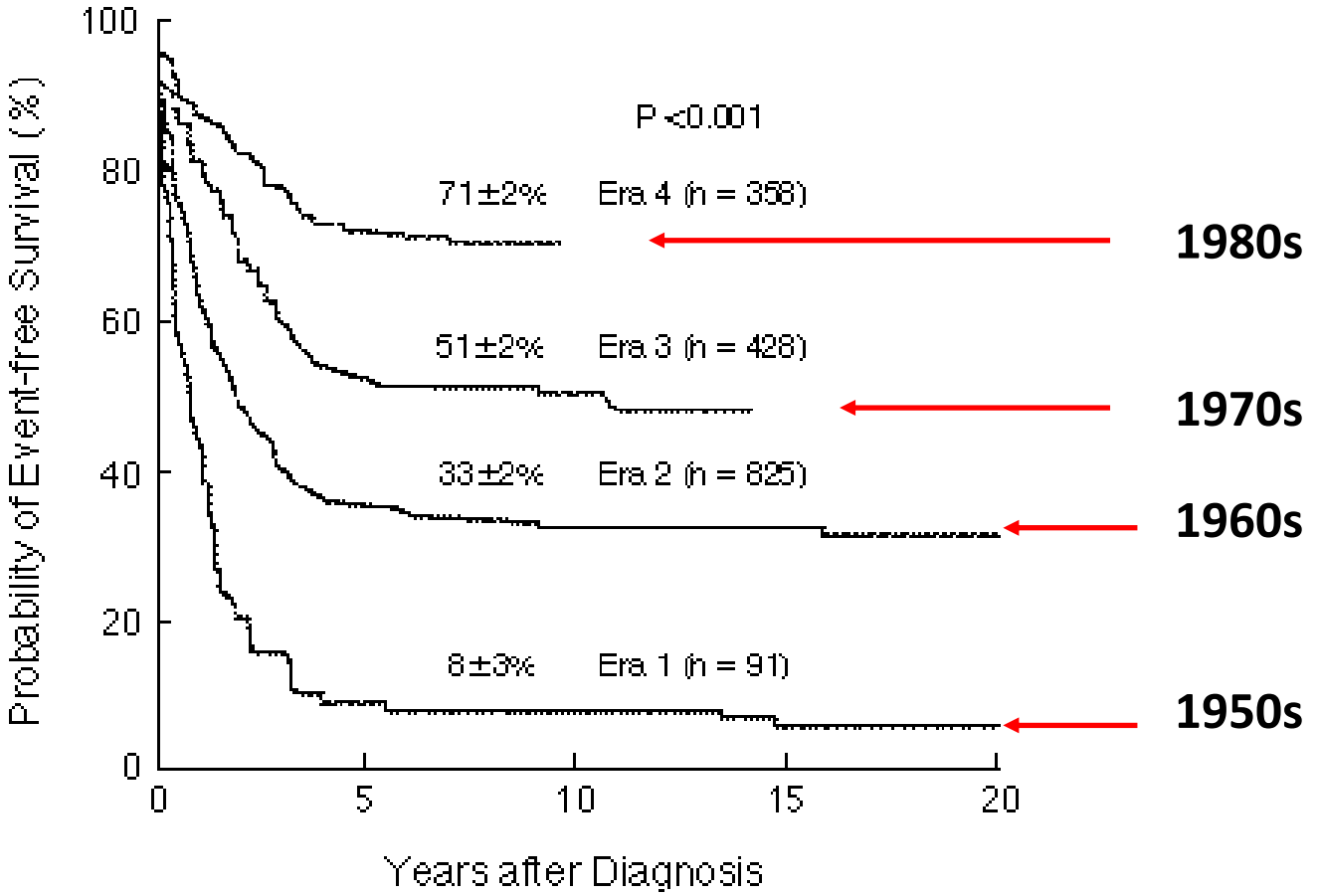
ALL: Immunophenotype



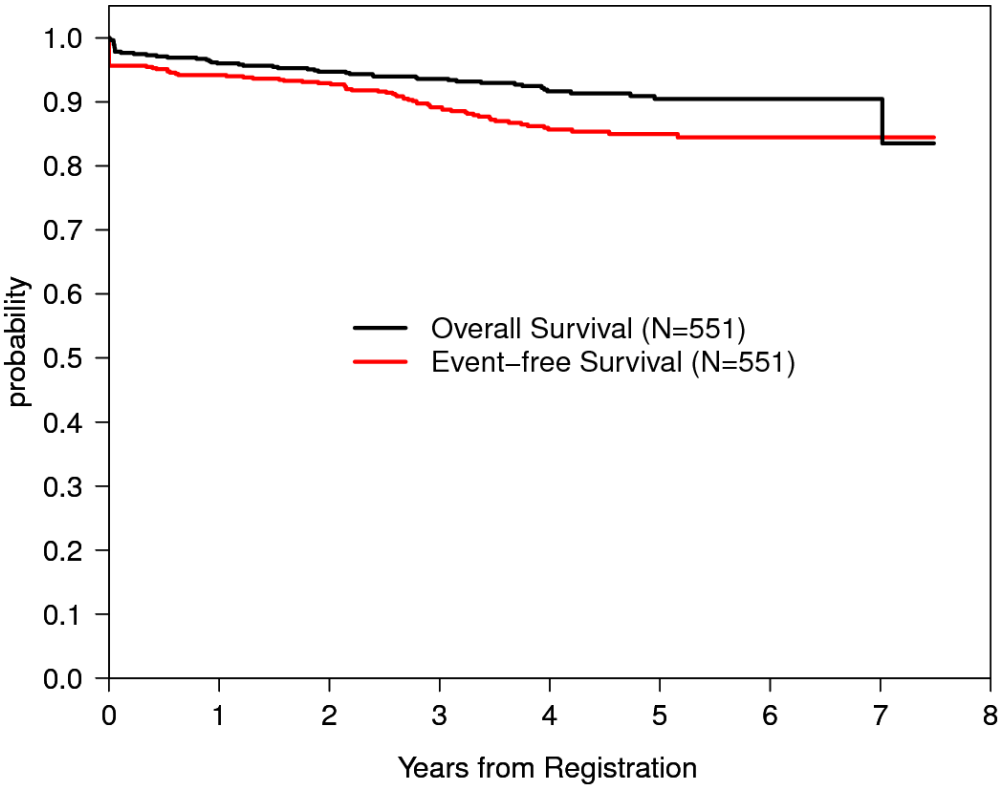
- B-ALL: 85% of patients
- T-ALL: 15% of cases
  - Higher median age at diagnosis (adolescents)
  - Higher presenting leukocyte counts
  - Anterior mediastinal mass
  - Male predominance

Childhood ALL:
Treatment and Outcome

Childhood ALL: Dramatic Improvement in EFS



Childhood ALL Outcome: 2014



CR rate: >95%

4 yr EFS: 86% [95% CI 82-88%]

4-yr OS: 92% [95% CI, 89-94%]

Median f/u: 4.5 years

Why Improvement in Outcome?

- Not a result of new drugs
  - Most of the agents used today were available in 1960s-1970s
- Better supportive care
  - Transfusions
  - Antibiotics
  - Acute tumor lysis syndome
- Recognition of CNS as sanctuary site
- Risk-adapted therapy

Risk-Adapted Therapy

- Intensity of therapy stratified based on patient's risk of relapse
- Patients assigned to "risk group" based on presenting features that have been previously correlated with outcome
  - "High risk" features: more intensive therapy
  - "Low risk" features: less intensive therapy
- Goal of Risk-Adapted Therapy: Treat away the higher risk of relapse

Risk-Adapted Therapy

- Prognostic Factors used to risk-classify patients with ALL
  - Age
  - Presenting WBC
  - Immunophenotype: B-ALL vs. T-cell
  - Presence/Absence CNS Leukemia
  - Leukemia Cytogenetics
  - Early Response to Initial Chemotherapy

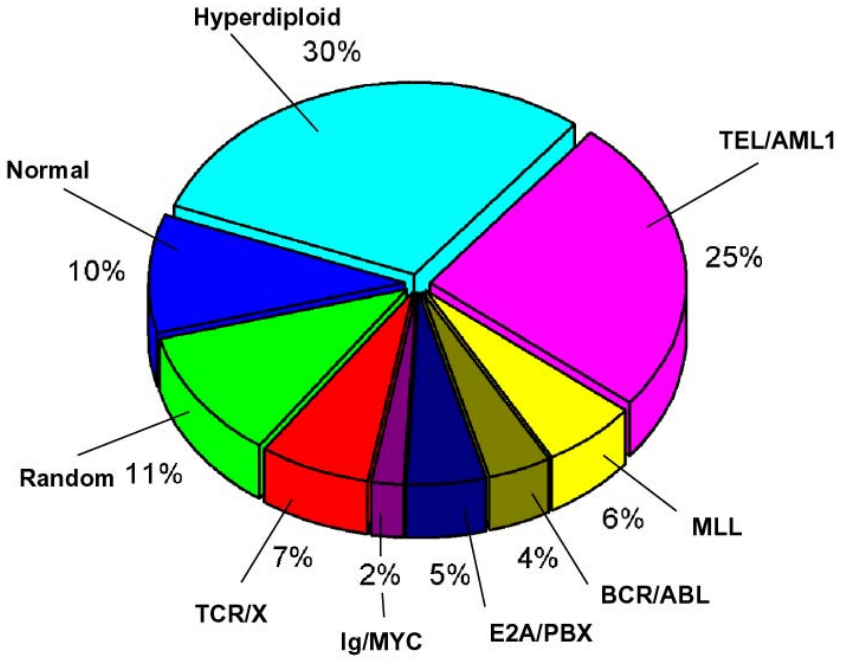
ALL: Prognostic Factors

Age and **Presenting WBC:**
Recognized for decades as strong predictors of outcome

Favorable	Less Favorable
• Age 1- 10 years	• Age < 12 months, or ≥ 10 years
• WBC < 50,000/mm^3	• WBC ≥ 50,000/mm^3

Childhood ALL: Cytogenetics

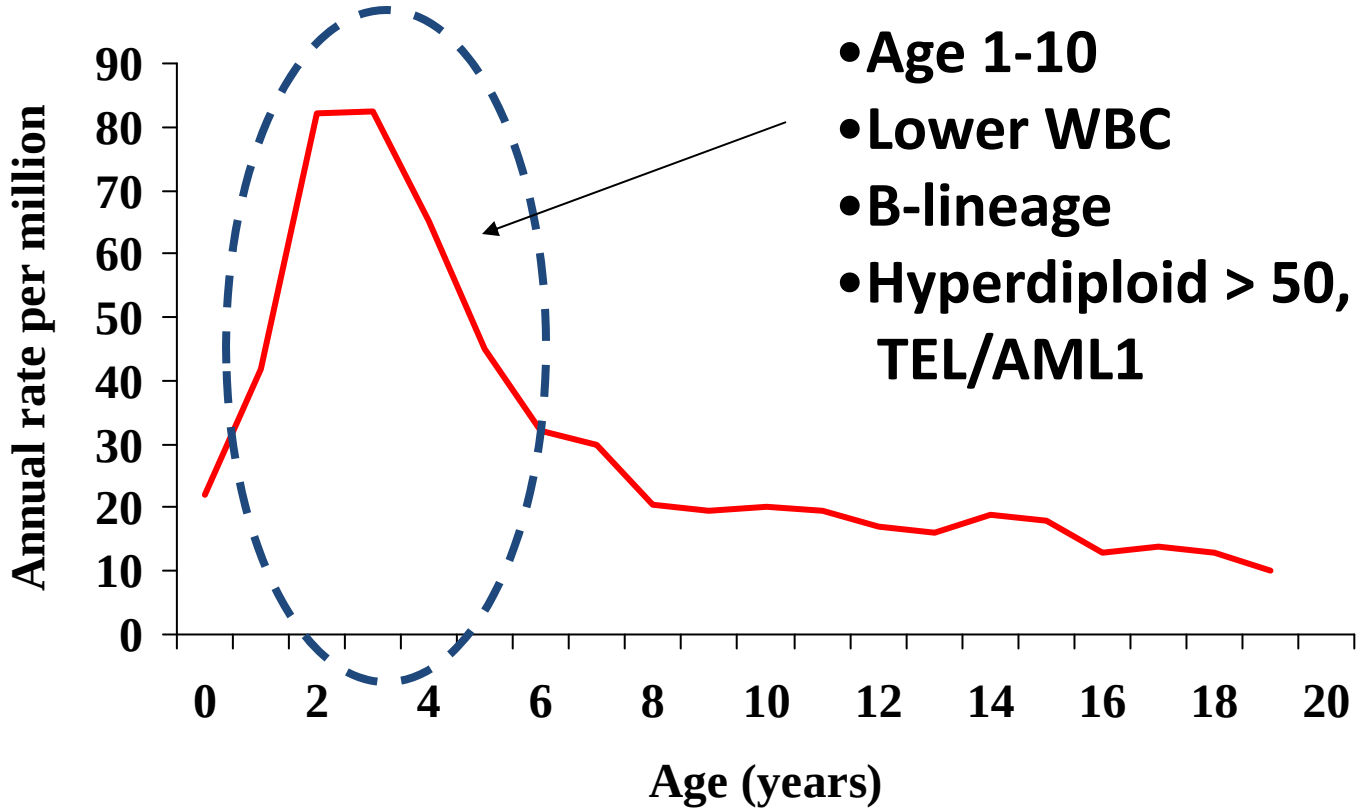
- Multiple recurrent chromosomal abnormalities
  - Ploidy: Number of chromosomes
  - Translocations: Rearrangements of genes



Cytogenetic Abnormalities: Prognostic Signficance

Favorable	Unfavorable
• Hyperdiploidy – 51-65 chromosomes • TEL/AML1 [(t12;21)]	• Hypodiploidy (<45) • MLL translocations – chromosome 11 • Philadelphia chromosome [t(9;22)]
~50% of patients	**~10% of patients**

“Favorable” Risk Group



- Age 1-10
- Lower WBC
- B-lineage
- Hyperdiploid > 50, or TEL/AML1

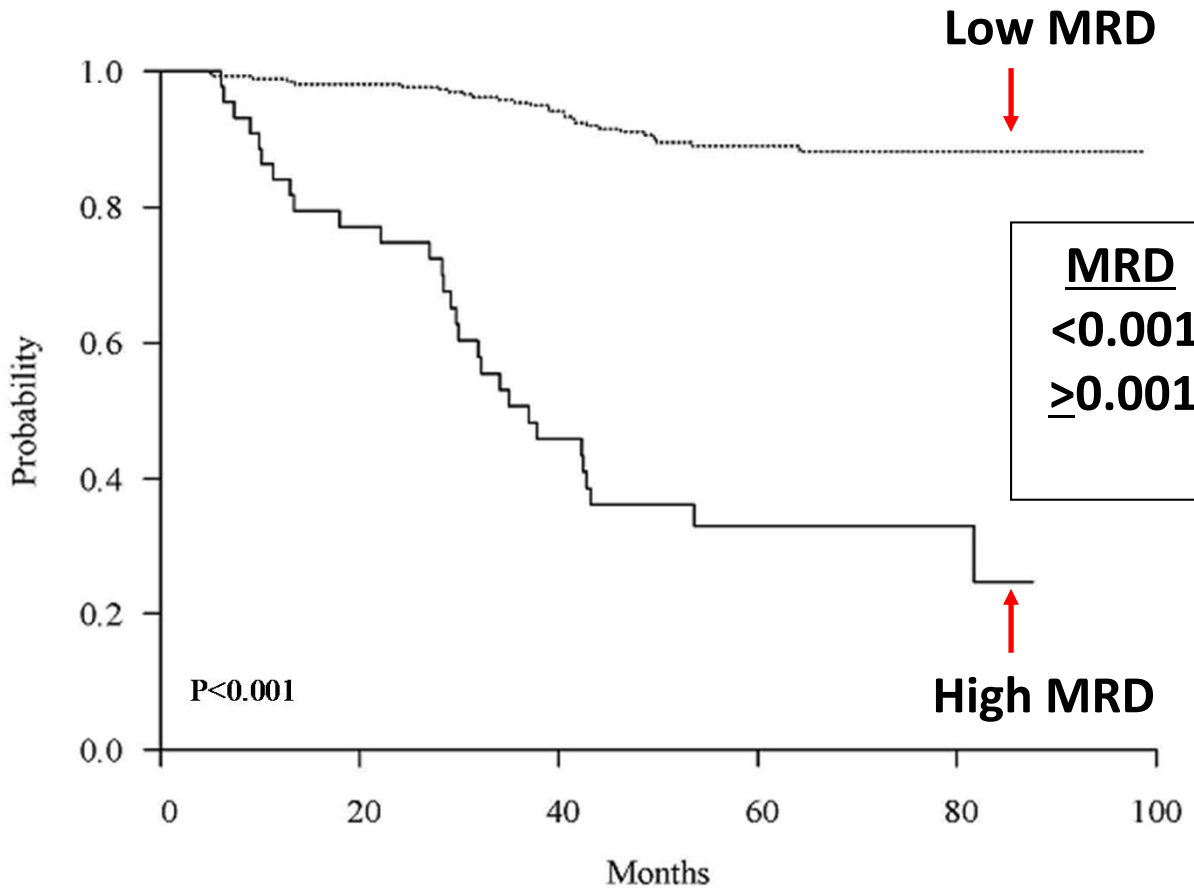
Early Response To Therapy

- Response after a few weeks of therapy strongly correlated with long-term outcome
- End of Induction Minimal Residual Disease (MRD)

What is MRD?

- At end of 1st month of treatment, >95% of children are in complete remission
  - Recovered blood counts
  - Marrow normal in appearance without visible blasts
- However, all patients have submicroscopic ("invisible") disease
- MRD Assays: Quantification of very low levels of leukemia (1 in 1000-100,000 cells)
- Techniques:
  - Flow cytometry
  - PCR: leukemia-specific IgH and/or TCR gene rearrangements

Event-Free Survival Based on Day 30 MRD



MRD	N	5-yr RFS
<0.001	269	89 ± 2%
≥0.001	39	33 ± 8%

p<0.001

Risk Group Stratification

- **Standard Risk**: **All** of the following
  - Age 1-10 years
  - WBC < 50,000/mm3
  - B-cell phenotype
  - No or very few leukemia cells in spinal fluid
  - No VHR features
- **High Risk**: **Any** of the following
  - Age ≥ 10 years
  - WBC > 50,000/mm3
  - T-cell phenotype
  - Spinal fluid with ≥ 5 WBC/hpf and detectable lymphoblasts

And: No VHR features

Very High Risk: Any of the following

- High MRD at end of induction
- Adverse cytogenetics
  - MLL gene rearrangement
  - Hypodiploidy

Risk Group Classification:

	Initial Risk Group N=794	Final Risk Group N=751
SR	462 (58%)	407 (54%)
HR	332 (42%)	260 (35%)
VHR	0	66 (9%)
Ph+	0	18 (2%)

Childhood ALL: Treatment

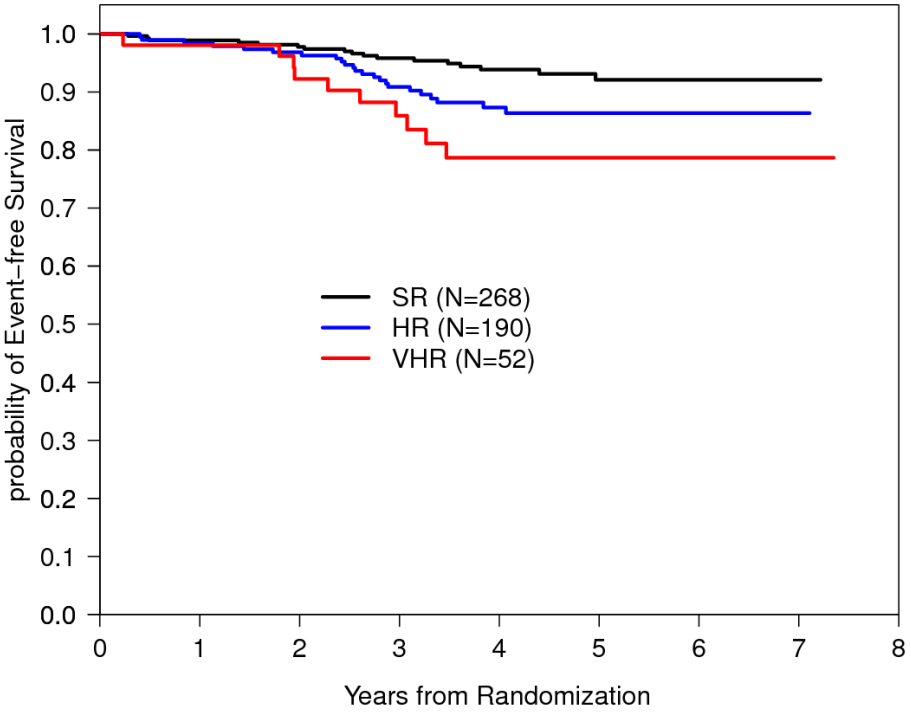
- 2-3 years of chemotherapy
  - Remission Induction: 1 month
    - Multiagent, inpatient
    - Goal: Achieve CR (no visible leukemia)—96% of patients
  - Intensification/Consolidation: 6-9 months
    - Typically outpatient
    - **Intensity of therapy varies by Risk Group**
  - Continuation/Maintenance
    - Low-intensity, outpatient
  - CNS-directed therapy
    - Intrathecal chemotherapy
    - Cranial radiation for subset (10-20%)

- **Stem cell transplant**: Only for relapsed/refractory disease

CNS-Directed Therapy

- Cranial irradiation + IT therapy had been standard for all children with ALL
- Intensification of systemic and intra-thecal chemotherapy effective for standard risk and most high risk patients
- Now protocol-specific use of cranial RT
- Dose for prophylactic RT: 12 Gy in 8 fractions
- Dose for CNS 3 disease : 18 Gy in 10 fx

Outcome by Risk Group



	4-yr EFS
SR	**94%** [90-96%]
HR	**87%** [81-92%]
VHR	**79%** [64-88%]

Toxicities of Therapy

Acute

- Infections
- Asparaginase-related
  - Pancreatitis
  - Clots
- Fractures
- Seizures

Long-term

- Cardiac
- Neurocognitive
- Short stature/obesity
- Cataracts
- Bone (AVN)
- Second Malignancies

Primary Care for the Child with ALL

On Therapy

- Immediate evaluation for any fever
  - Blood culture, antibiotics
  - Admission to hospital if neutropenic or ill-appearing
- Bactrim for PCP prophylaxis (until 6 months off-therapy)
- No vaccines to patient, except annual flu shot (no intranasal!)
  - No restriction on vaccines to siblings (except **no intranasal flu vaccine**)

Primary Care for the Child with ALL

Off-Therapy

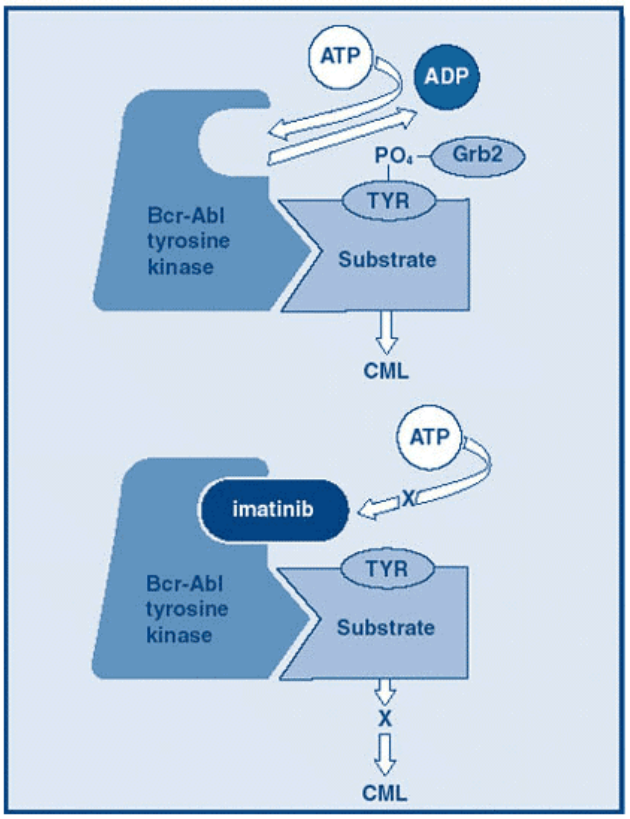
- Routine fever evaluation (once central line removed)
- May resume all vaccines after 6 months
  - No need to repeat vaccines given prior to diagnosis
- Consider possible late effects
  - Growth
  - School performance
  - Cataracts
  - Cardiac (LV dysfunction)
  - Second tumors (if radiation)

Future Directions

- Identify New Prognostic Factors
  - Identification of biologically distinctive subsets
    - eg, Ph-like ALL (~15% of patients)
- Develop New Therapies
  - Targeted Therapy (based on underlying genetics)
  - Immunotherapy
- Minimize Toxicity

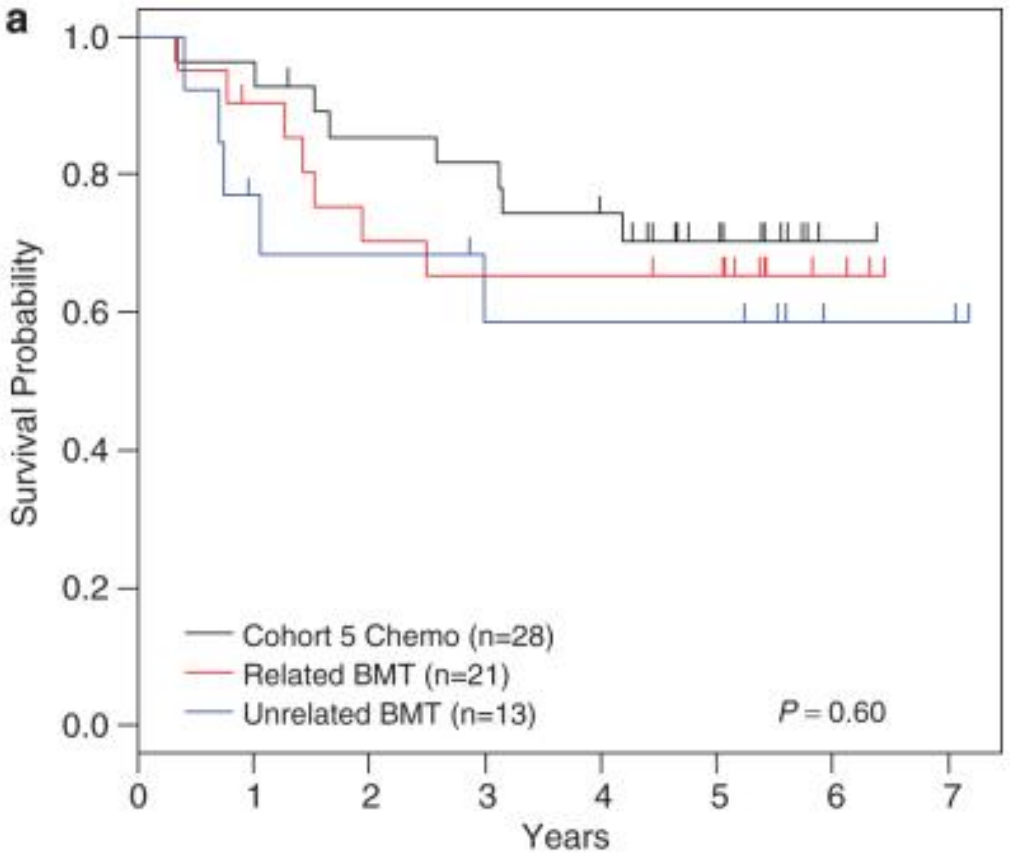
Targeted Therapy: TKI

Figure 2. Inhibition of Bcr-Abl by imatinib. The aberrant phosphorylation and activation of downstream signal transduction by the Bcr-Abl fusion protein is inhibited by the competitive binding of imatinib in the ATP-binding site.[7]

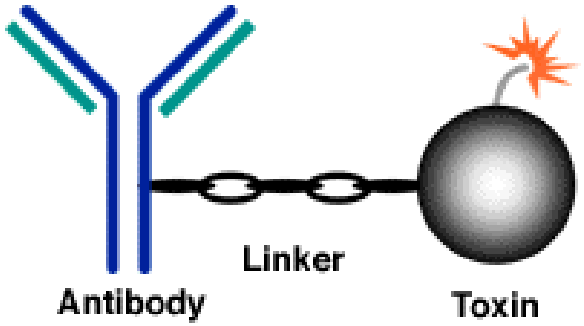


- Ph+ ALL: ~5% of childhood ALL
  - More common in adolescents/adults
- t(9;22) forms bcr-abl fusion kinase
- TKI: tyrosine kinase inhibitor
  - Targets bcr-abl kinase
  - Prolonged responses in CML
  - Transient responses in relapsed, Ph + ALL (weeks-months)

TKI + Chemo Improves Cure Rates for Childhood Ph+ ALL

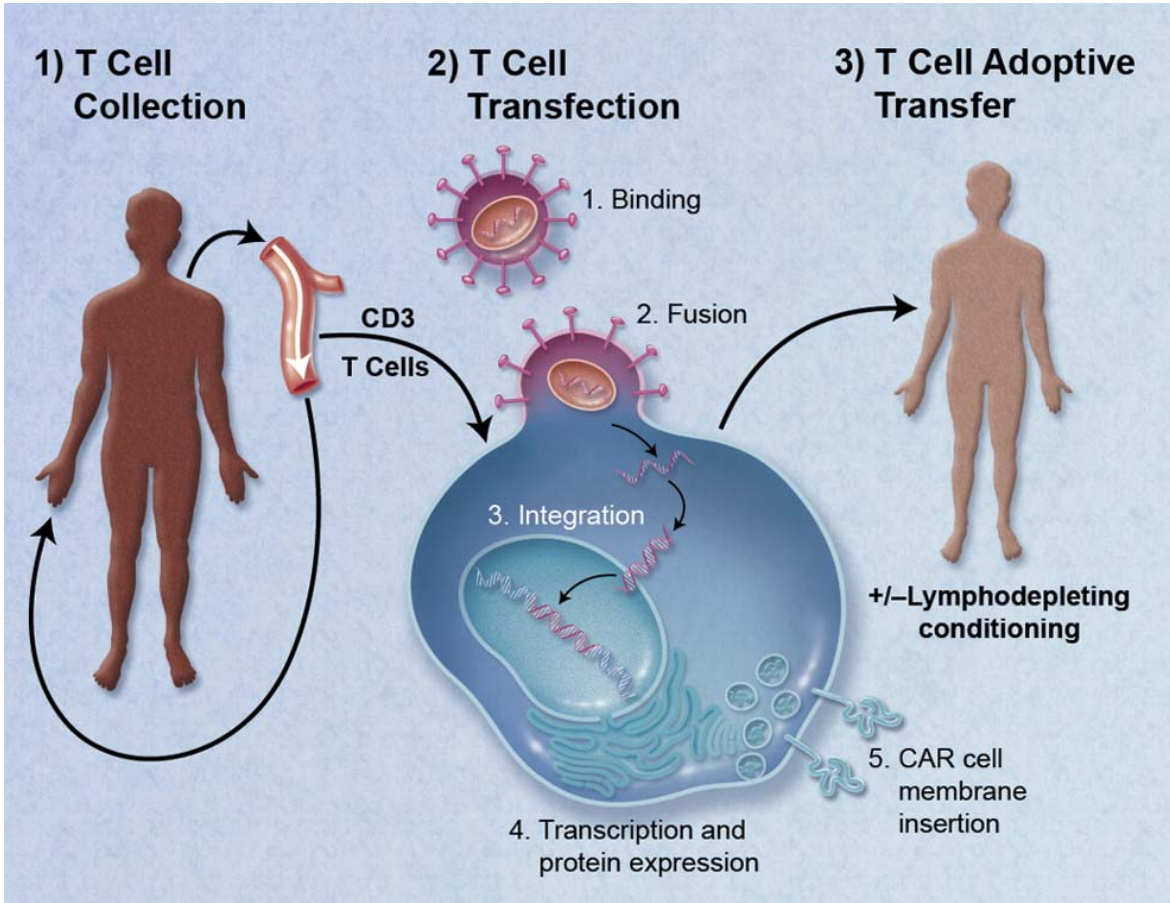


Toxin-Conjugated Monoclonal Antibodies



- Leukemia-specific antibody linked to toxin
- "Targeted" cell kill:
  - Antibody binds to leukemia
  - Toxin internalized into cell
  - Most normal cells are spared
- Several trials open of B-cell ALL-specific antibodies linked to
  - Pseudomonal exotoxin
  - Calicheamicin
  - Monomethyl auristatin (anti-mitotic agent)

CAR T-cells



CAR T-cells

- T-cells harvested from patient
- Harvested cells transfected with genes that allow the T-cells to become specific for tumor (eg, targeting CD19 in B-ALL)
- Transfected cells infused back to patient

- Trials underway in B-ALL (adult and pediatric)

Childhood ALL: Summary

- Most common cancer in children
- >80% event-free survival with 2-3 years of chemotherapy (primarily outpatient)
  - Stem cell transplant only after relapse
  - Overall, 90% are long-term survivors
- Risk-adapted therapy: Intensity of therapy based on risk of relapse
  - Presenting features: age, WBC count
  - Biologic features of leukemia: Chromosomal abnormalities
  - Early Response to therapy: MRD
- Current Treatment Protocols
  - Decrease toxicity, improve QOL
  - Develop new, more effective therapies

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