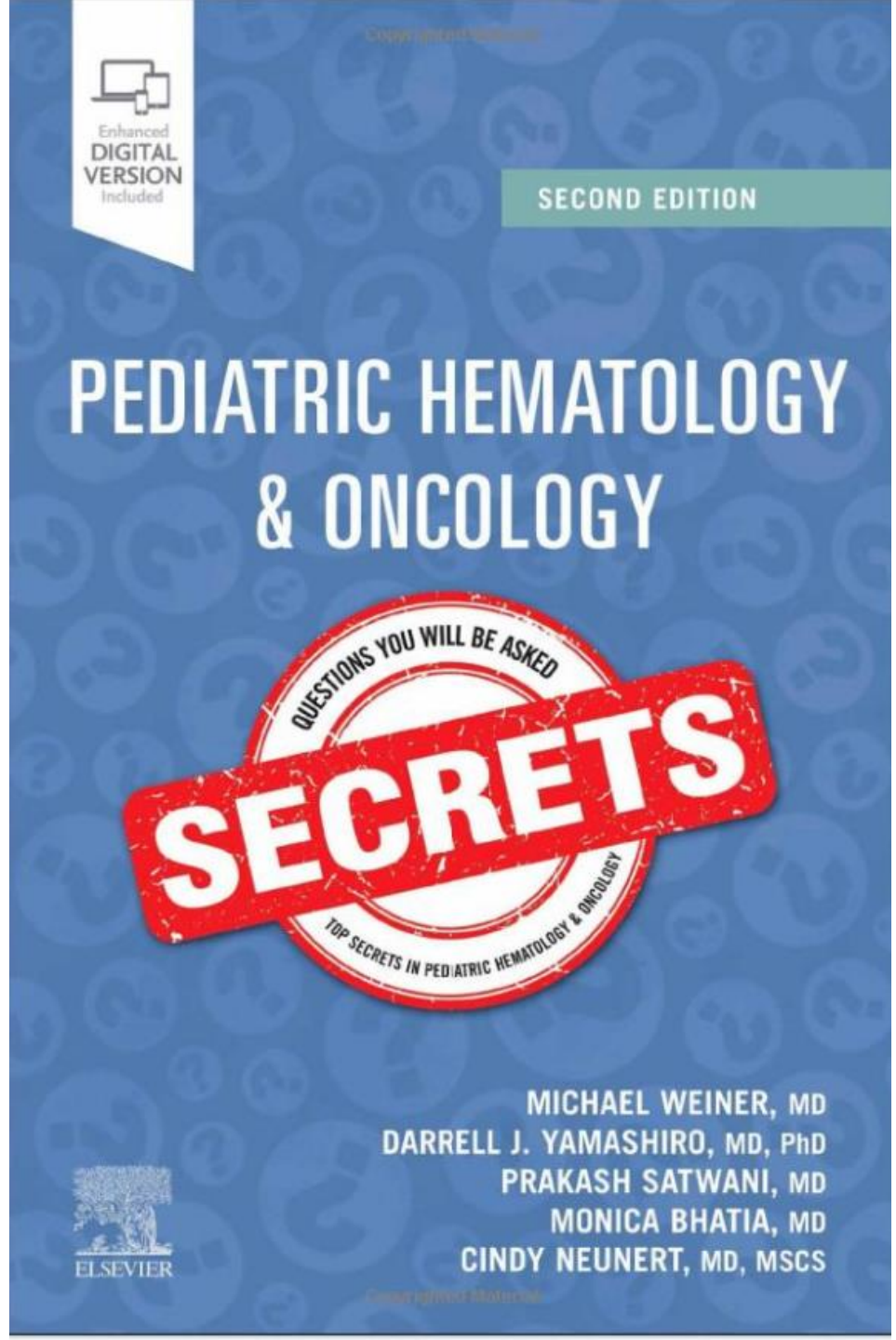
Pediatric Hematology-Oncology Series


Enhanced
DIGITAL
VERSION
Included
SECOND EDITION
PEDIATRIC HEMATOLOGY
& ONCOLOGY
QUESTIONS YOU WILL BE ASKED
SECRETS
TOP SECRETS IN PEDIATRIC HEMATOLOGY & ONCOLOGY
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Hematologic Malignancies

Amr Qudeimat

How is malignancy defined?

- atal?
- currence?
- M

No single criterion

Clonality

Maturity/differentiation.

How does it evolve?

Many overlapping pathways. Remember malignancy is not a single disease!

- Genetic factors.
- Mutagens (chemicals, radiation etc.).
- Immune factors + random mutations+ tolerance (failure of surveillance)

When to suspect it?

Delayed diagnosis is a challenge. Nonspecific complaints common

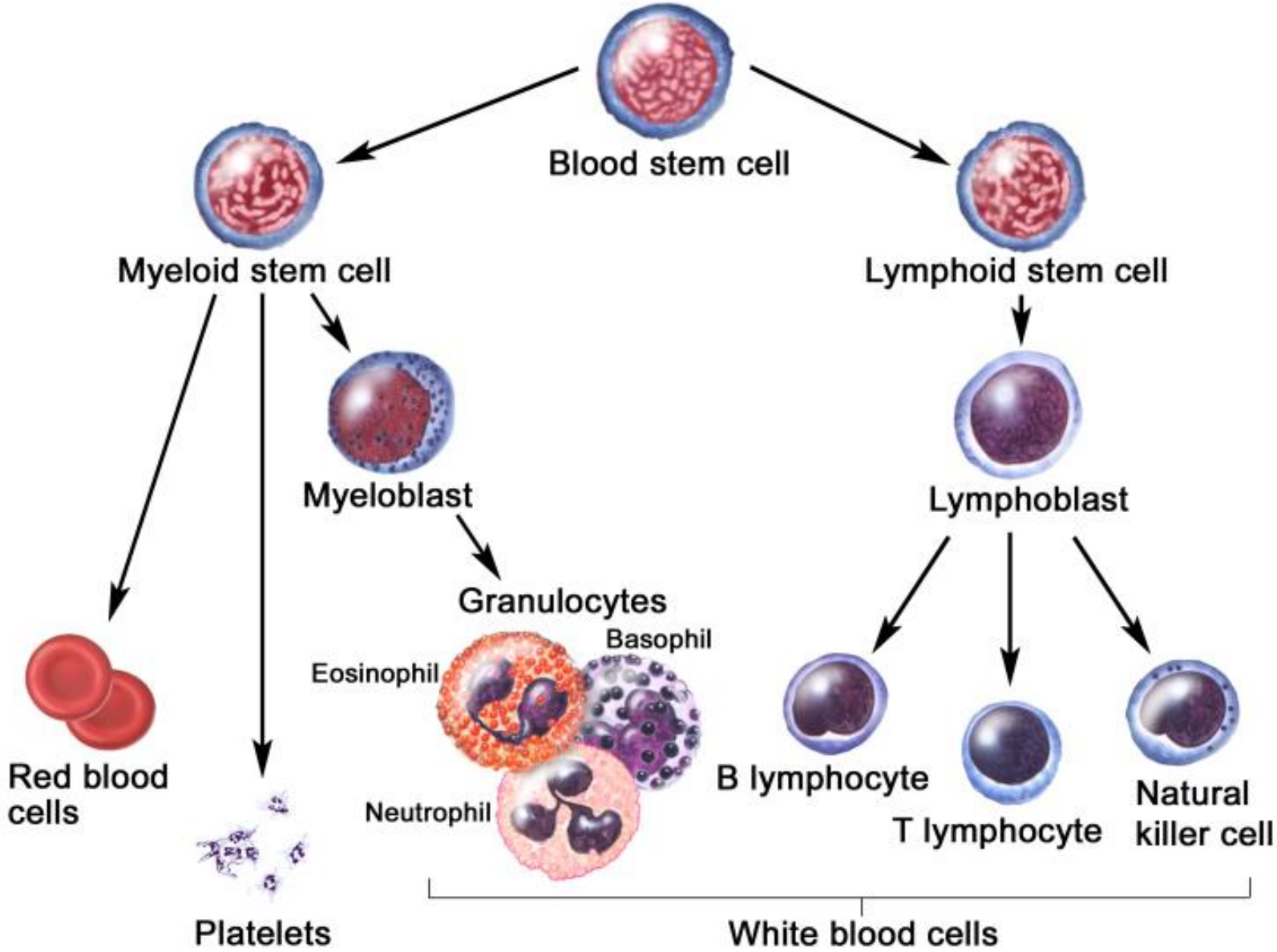
- Unexplained fevers lasting longer than typical viral infections.
- Cranial nerve palsies, abnormal gate, loss of coordination.
- Abdominal distention.
- Fatigue, weight loss.
- Anemia in a post pubertal male.

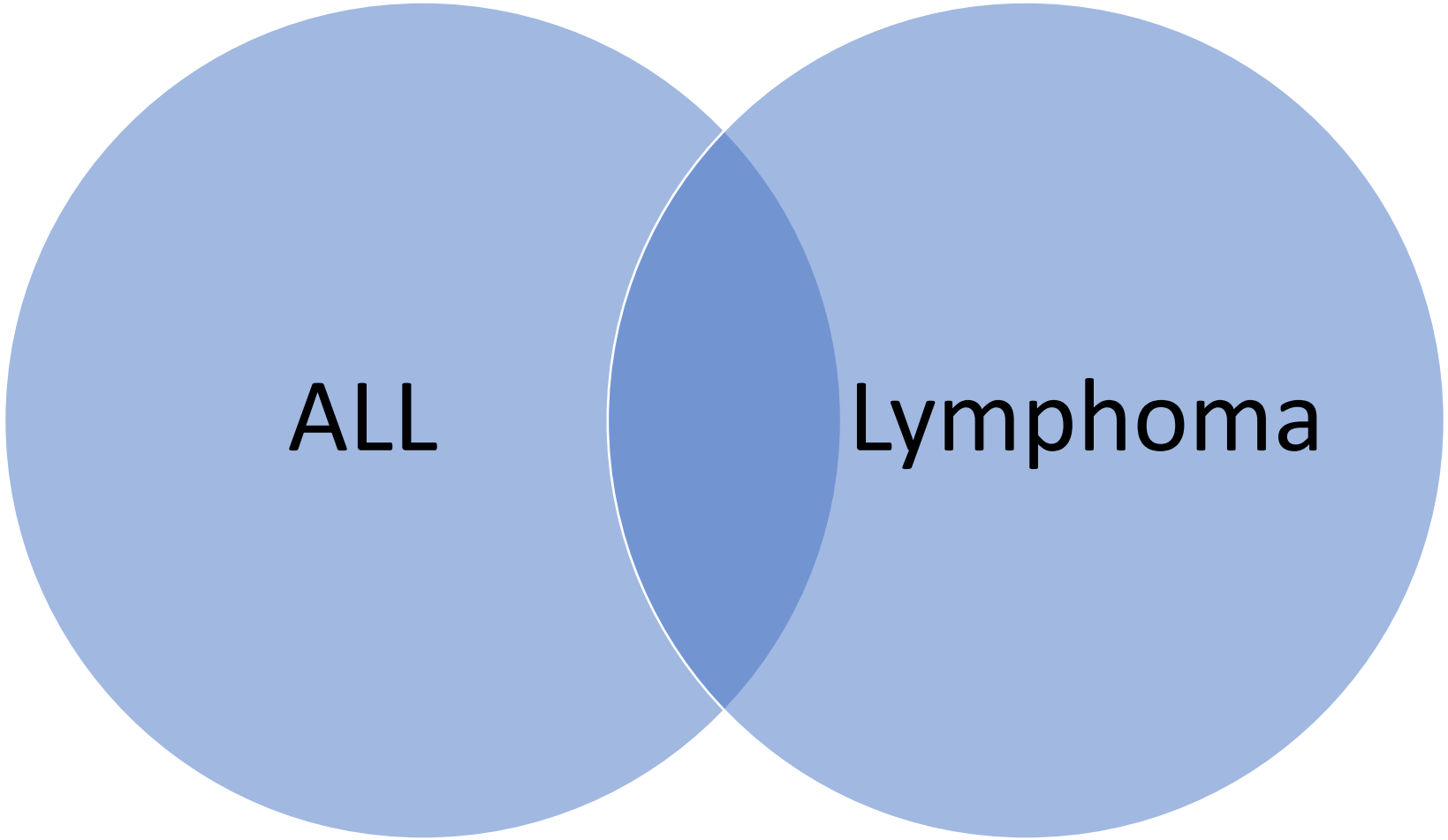
Hematologic malignancies


Acute: ALL,
emia
ic: CLL, CM
Lym

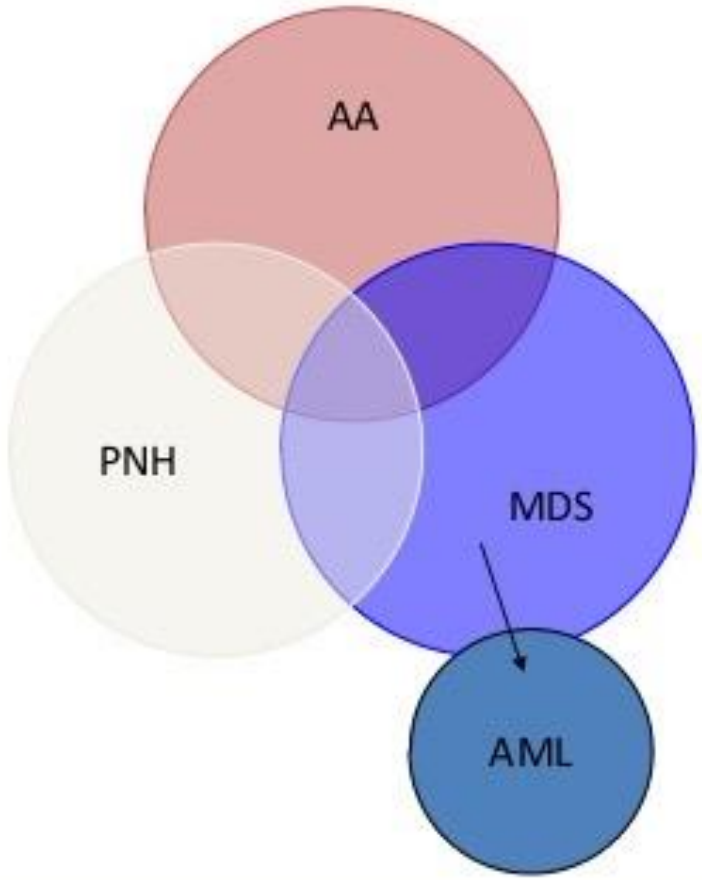
Blood cell lines

Lymphoid vs myeloid




ALL
Lymphoma

Bone Marrow Failure Syndromes



Venn diagram of the relationship among BM failure syndromes.
Overlapping features of MDS with aplastic anemia, AML, and PNH suggest a shared pathophysiologic mechanism of marrow failure.

lymphoblastic Leukemia vs Lymphoma

Location

Phenotype.

Relationship between increased blast population and leukemia.

- Causes of increased blast population.
- Morphology.
- Immunophenotype.
- Cytogenetics and molecular pathology.

MDS

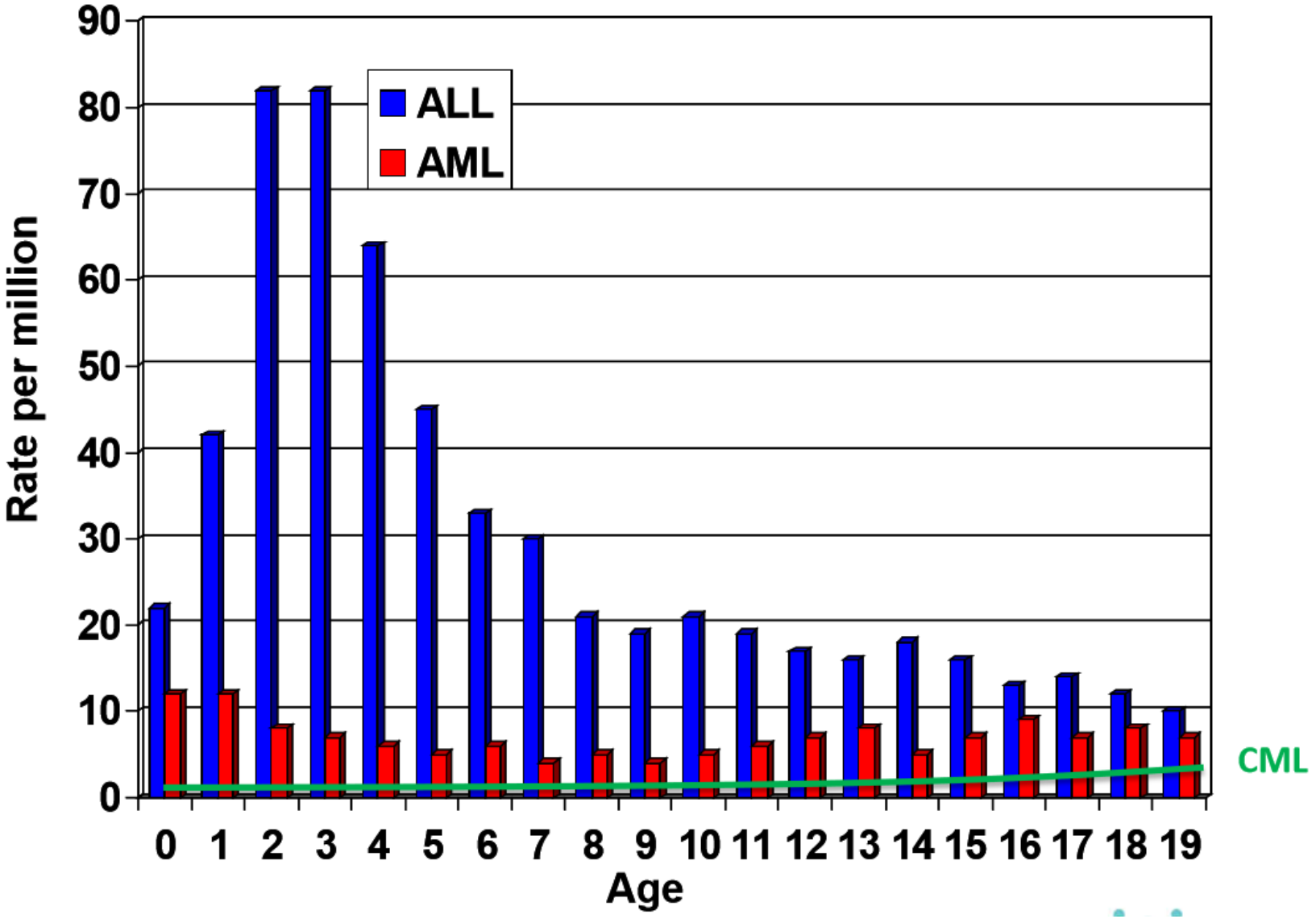
Defined by:

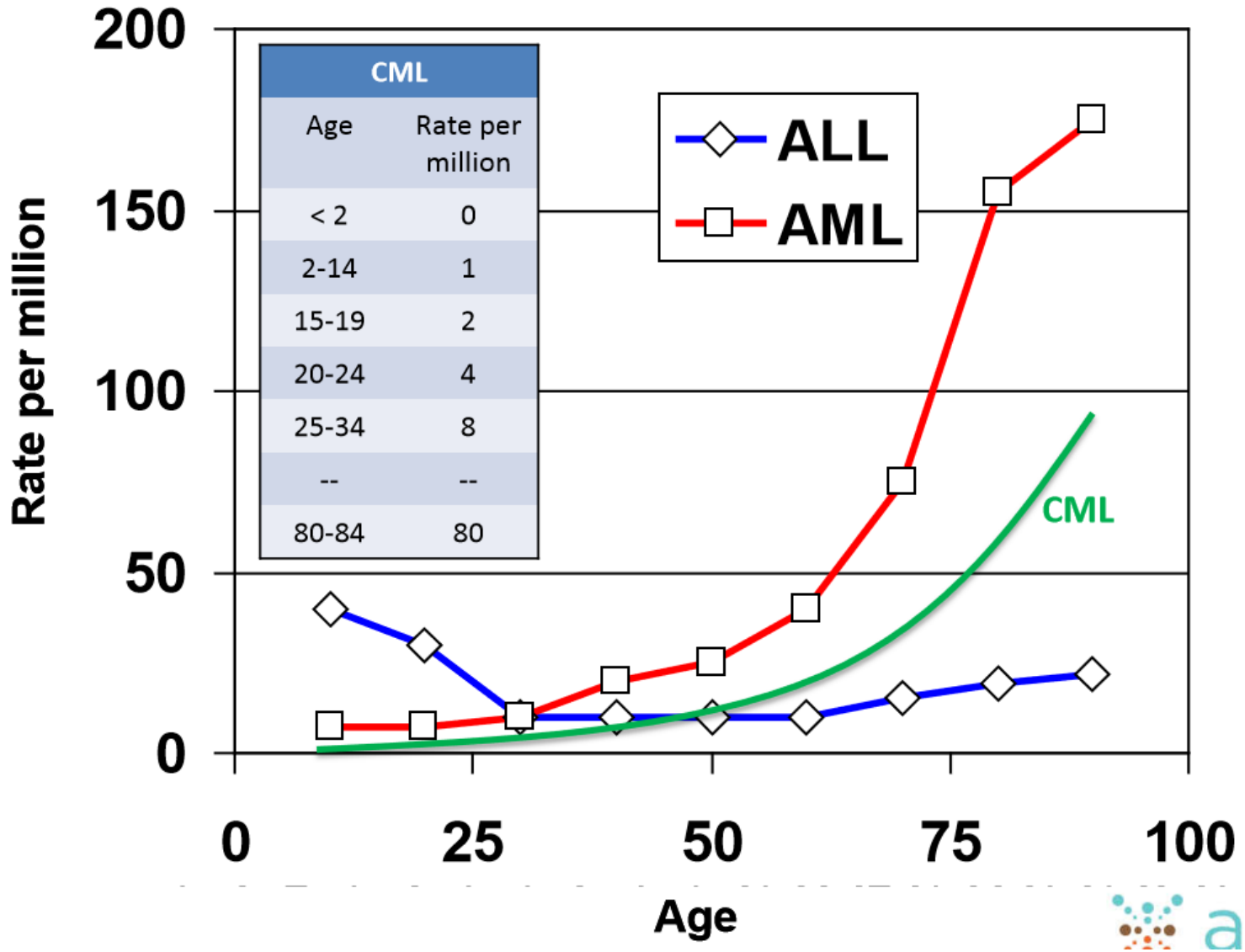
- Dysplastic bone marrow changes.
- Increased blast population.
- MDS defining Cytogenetic abnormalities.

MDS

- De-novo vs Secondary.
- Natural history.
- Treatment.

AML


90
80
70
60
50
40
30
20
10
0
Rate per million
ALL
AML
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
Age
CML


CML
Age
Rate per million
< 2
0
2-14
1
15-19
2
20-24
4
25-34
8
--
--
80-84
80
ALL
AML
CML
Rate per million
200
150
100
50
0
0
25
50
75
100
Age

AML

- Concordance studies

- Congential Bone marrow failure syndromes predispose to AML

FAB: morph/phenotype; 30% blasts

AML Subtype		Comments
M0	**AML without differentiation**	Difficult to distinguish from ALL; diagnosis requires expression of surface markers such as CD13, CD33 and CD117 (c -kit) in the absence of lymphoid differentiation
M1	**AML with minimal differentiation**	Myeloperoxidase detectable by special stains/flow cytom etry
M2	**AML with differentiation**	Auer rods; common t(8;21) -> AML1 -ETO fusion, good prognosis , chloromas
M3	**Acute promyelocytic leukemia (APL), hypergranular type**	Auer rods; DIC/bleeding;; t(15;17) -> PML-RARα fusion, good prognosis with ATRA therapy
M3v	**APL, microgranular variant**	Cytoplasm of promyelocytes demonstrates a fine granularity, and nuclei are often folded. Same clinical, cytogenetic and therapeutic implications as FAB M3.
M4	**Acute myelomonocytic leukemia (AMML)**	Mixture of myeloblasts (at le ast 20%) and monocytic blasts; often with peripheral monocytosis
M4Eo	**AMML with eosinophilia**	AMML with >5% abnormal eosinophil precursors in marrow (with basophilic granules), common inv(16), good prognosis
M5	**Acute monocytic leukemia**	>80% of bone marrow non-erythroid cells are monocytic; M5a: monoblastic; M5b: monocytic (more differentiated); ***for both M4 and M5***: infant age, MLL 11q23 rearrangements, CNS involvement, chloromas, gingival hyperplasia
M6	**Acute erythroblastic leukemia**	Rare in children
M7	**Acute megakaryoblastic leukemia**	Seen mostly in children with Down syndrome (good prognosis if ≤ 2 years old; GATA1 mutations) or mosaicism for trisomy 21; rare in normal children (poor prognosis , t(1;22) -> OTT-MAL fusion, often infants); myelofibrosis commo n

WHO: clinical/molecular; 20% blasts

- Is the AML due to prior XRT/chemo?
  - If yes: Dx is Therapy-related AML (t-AML)
- Is the AML in a child with Down syndrome?
  - If yes: Dx is DS-related AML
- Is major ("Big 4") recurring abnormality present?
  - If yes: Dx is AML w/ t(8;21); inv(16); t(15;17); MLL-r
  - *NOTE: No minimum blast % needed*
- Is there dysplasia, prior MDS and/or MDS-related mutation (-7, del(5q), etc.)?
  - If yes, Dx is AML with MDS-related changes
  - ***If no to all: Dx is AML, NOS - use FAB to subclassify***

t-AML

T-AML vs relapse?

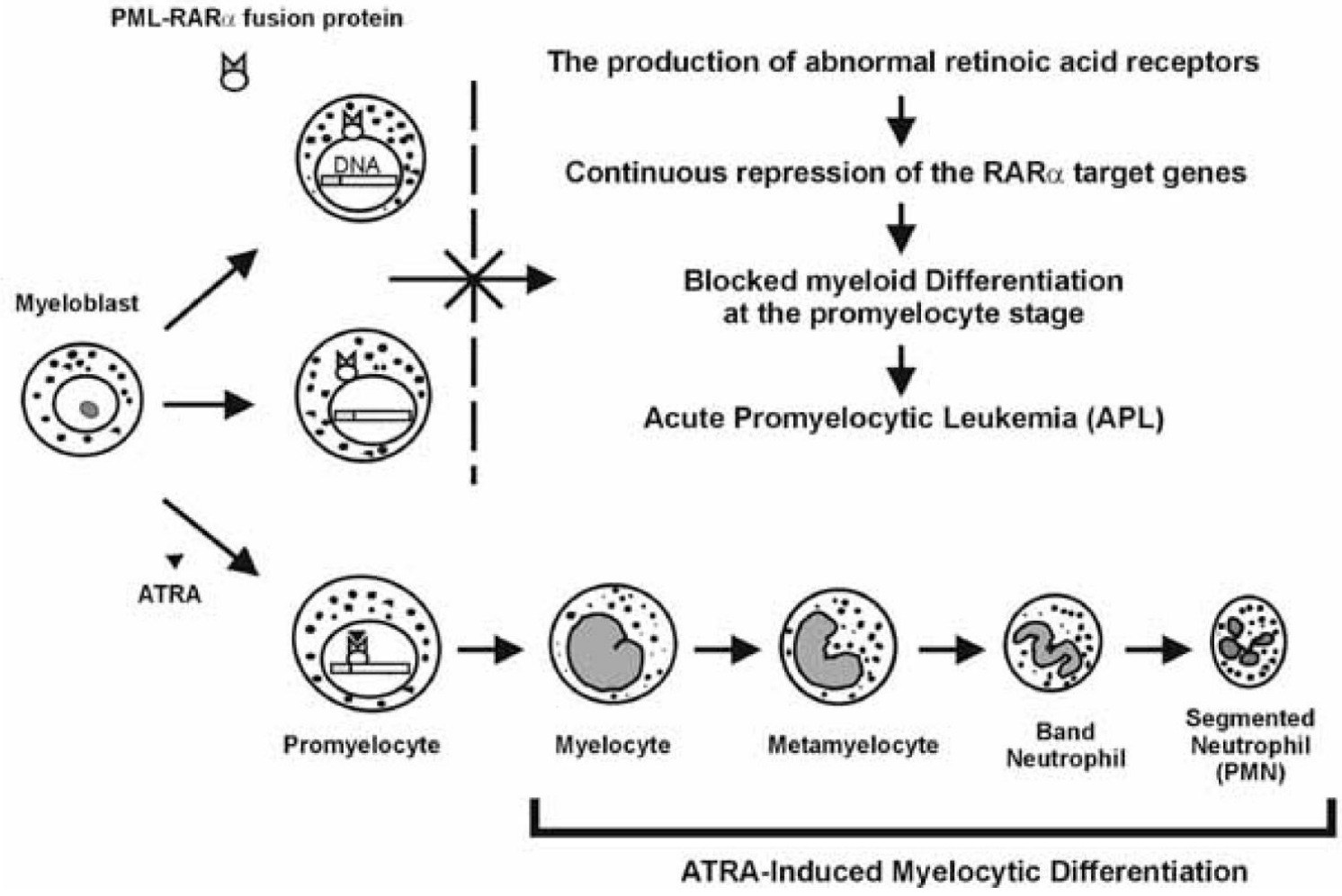
APML or AML M3

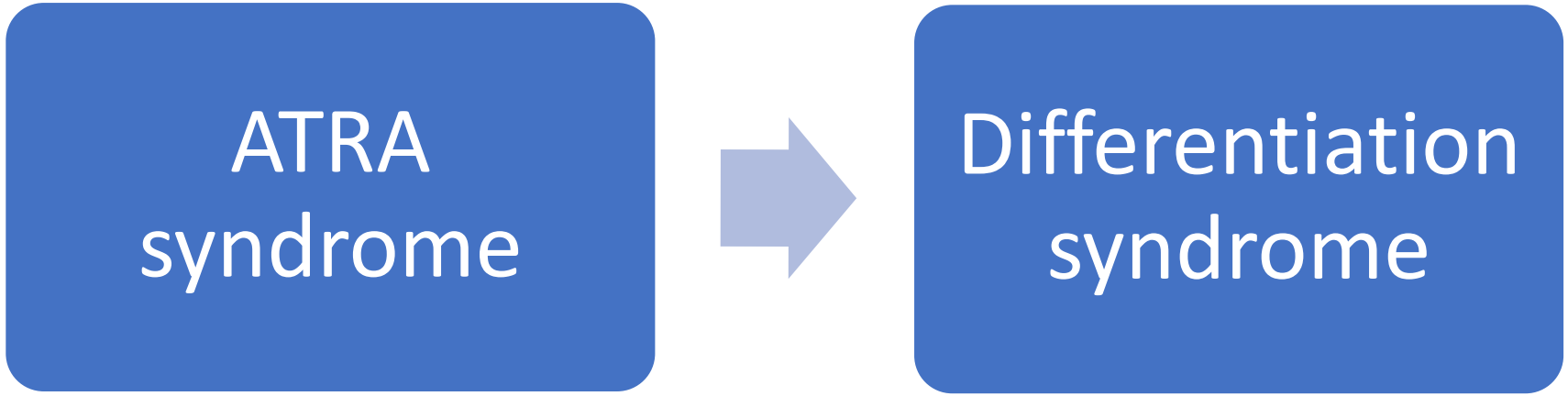
Unique type of AML, showing diversity of this disorder.

Can be cured with ATRA (all trans retinoic acid).

t(15;17) and ATRA

- Understand the significance of rearrangements of the ATRA receptor gene in M3 AML




ATRA syndrome
Differentiation syndrome

Cytogenetic	Molecular	FAB	Characteristics
t(8;21)	*AML1-ETO (RUNX1-RUNX1T1)*	M2	Auer Rods Chloromas Good px
t(15;17), variants	*PML-RARA* *{variant}-RARA*	M3	Granules/Auer rods DIC/bleeding Good px (with ATRA/Arsenic)
inv(16)/ t(16;16)	*CBFB-MYH11*	M4Eo	Eos w/ baso granules Chloromas Good px
abnormal 11q23	*MLL-{partner}*	M4 M5	Infant WBC/skin/CNS/gums t-AML after topo II inh

Treatment

Chemotherapy Vs BMT

CML

Ph+ (9;22) BCR-ABL

Chronic, accelerated and blast crisis phases.

Treatment options.

ALL

- AML vs ALL
- Predisposing conditions: TP53 mutations, immunodeficiencies.
- May involve CNS or testis.
- Ph+ ALL.
- Mainstay of treatment is chemotherapy with overall long term survival over 90%.
- Some high risk patients proceed to BMT.

Lymphomas

In 5 minutes!

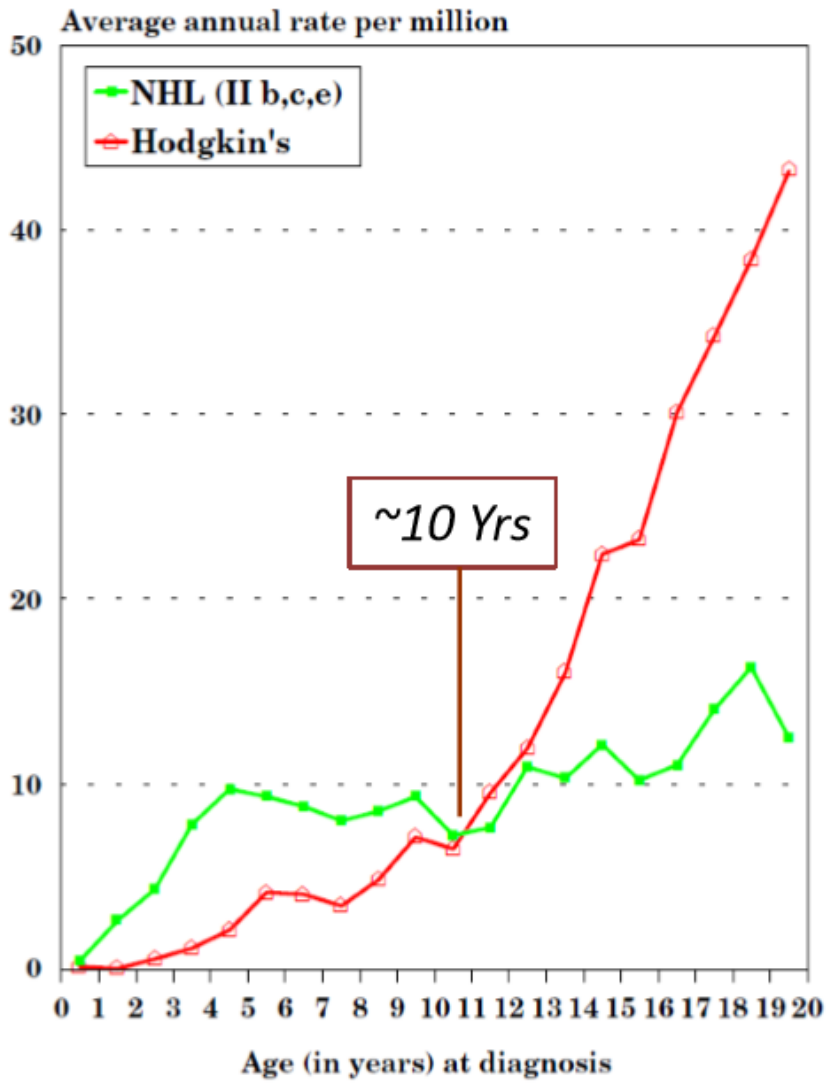
Age 0-14

Leukemia	32%
CNS	20
Lymphoma	11
Neuroblastoma	8
Rhabdo/STS	7
Kidney	6
Bone	6
Germ-cell	4
Retinoblastoma	3
Liver	1

Age 15-19

Lymphoma	25%
Germ cell	14
Leukemia	12
CNS	10
Soft-tissue Sarcoma	8
Bone	8
Thyroid carcinoma	7
Melanoma	7

	T cell derived	B cell derived
Immature	T-lymphoblastic	B-lymphoblastic
Mature	Anaplastic Large Cell	Burkitt Diffuse Large B cell Hodgkin


Average annual rate per million
50
40
30
20
10
0
NHL (II b,c,e)
Hodgkin's
~10 Yrs
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
Age (in years) at diagnosis

Hodgkin Lymphoma

Most commonly presents with painless neck or chest adenopathy.

Many cases are associated with EBV infection.

B symptoms.

Classic (most common) and NLPHL

Excellent outcomes in low stage disease.

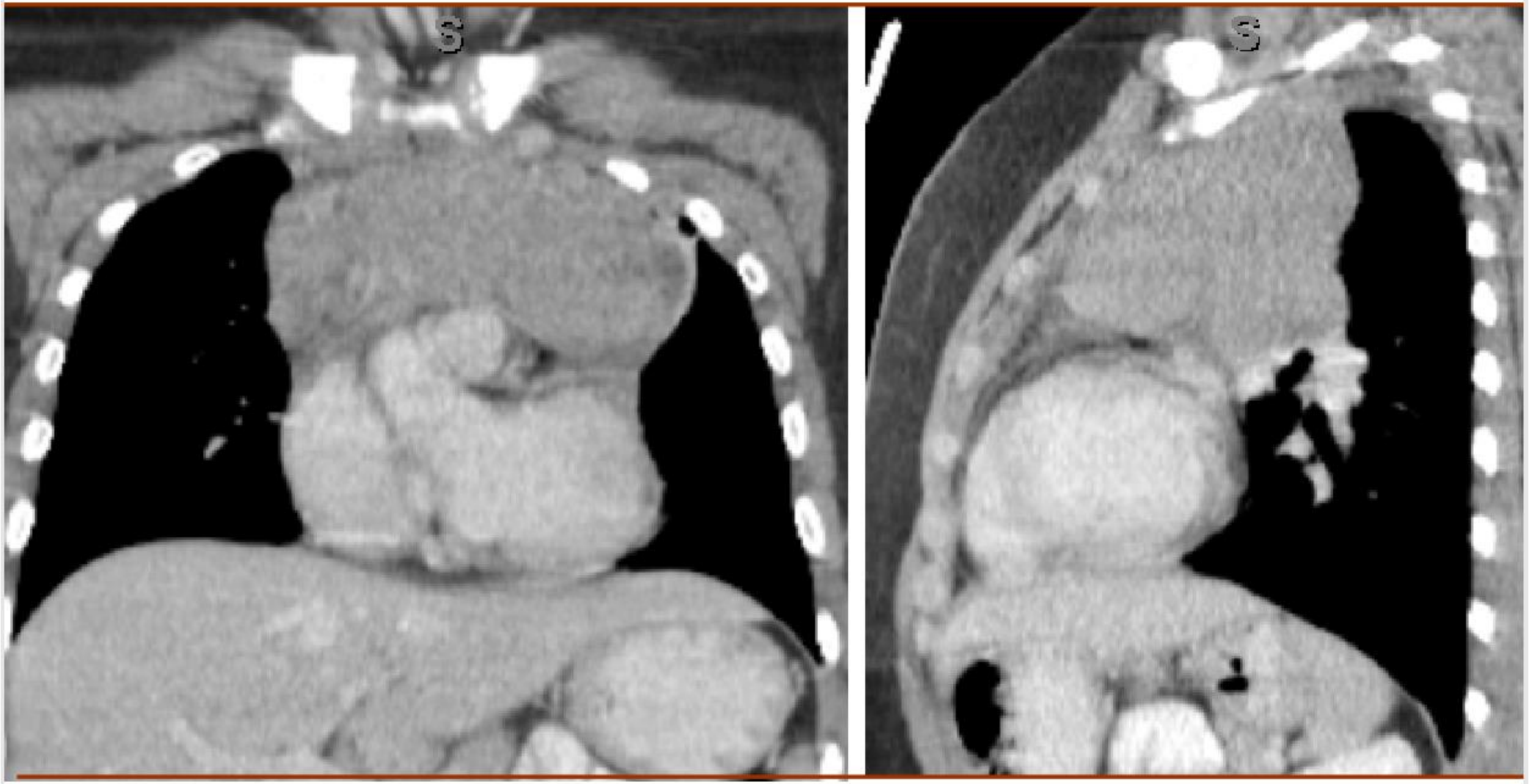
Malignant cell of classic Hodgkin is Hodgkin Reed-Sternberg (owl eye)

Clinical Presentation of Hodgkin Lymphoma

1. Painless lymphadenopathy
2. Mediastinal mass (~2/3)
3. Constitutional symptoms

- B symptoms are prognostic
  - Weight loss of 10% in 6 months
  - Drenching night sweats
  - Unexplained fevers >38°C for 3 consecutive days
- Others are not prognostic
  - Fatigue, anorexia, mild weight loss
  - Pain immediately following alcohol
  - Pruritus: generalized, can be severe, more often in advanced disease

- Markers of inflammation and RES activation (↑CRP, ESR, ferritin, copper)
- Anemia of chronic inflammation
- Immune dysregulation: autoimmune neutropenia, AIHA, ITP, nephrotic syndrome



Burkitt Lymphoma

- Mature NH B cell lymphoma.
- Very high proliferation rate, early diagnosis and treatment matters.
- High risk for tumor lysis syndrome.
- Most famous associated genetic abnormality t(8;14).
- Excellent prognosis if treatment not delayed.

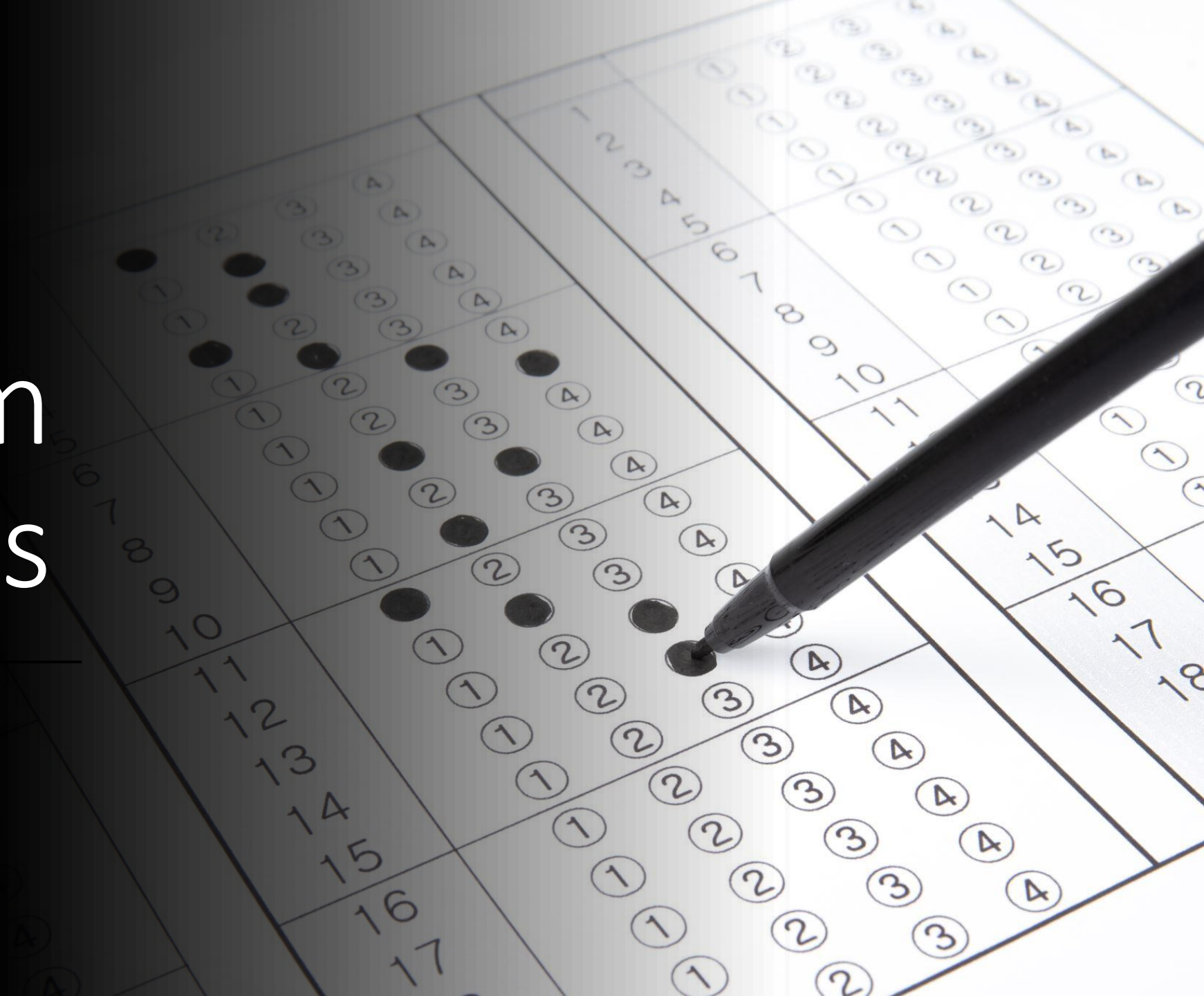
	Sporadic	Endemic
EBV	15%	95%
Geography	North America, Europe	Equatorial Africa, Brazil Turkey, New Guinea
Incidence	0.2/100,000	10/100,000
Location	Abdominal mass LN, Marrow, CNS ovaries	Jaw mass, abdomen, CNS in 1/3

Anaplastic Large cell Lymphoma

Is a mature T cell Lymphoma.

Most common genetic abnormality is t(2;5) or ALK (anaplastic lymphoma kinase)

Past Exam Questions



A 6-month-old girl is brought to the emergency room with high fevers of 39.5 degrees Celsius. A complete blood count shows a total white blood cell count of 16,000 WBCs/microliter, a hemoglobin of 6.7 gm/dl and a platelet count of 11,000 platelets per microliter. Flow cytometry on a bone marrow aspirate is consistent with B cell lymphocytic leukemia.

Which of the following factors carries a higher risk (worse prognosis) in this child?

A) Initial white blood cell count of 11,000/microliter.
B) Female sex.
C) High grade fever.
D) Severe thrombocytopenia.
E) Age of 6 months.

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A 5-year-old girl presents with pan cytopenia. Her CBC shows a total white blood cell count of 800 WBCs/microliter, hemoglobin of 7.1 gm/dl and a platelet count of 40,000 platelets per microliter. Bone marrow aspirate examination shows a blast population of 12% with dysplastic megakaryocytes. Cytogenetic studies reveal monosomy 7 and no other abnormalities.

Which of the following is the definitive treatment for this child?

A) Bone marrow transplant.
B) Chemotherapy.
C) Reassurance and repeating CBC in 6-8 weeks.
D) Radiation therapy.
E) High dose IV vitamin B12.

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7) You round on a 5-year-old male patient who was diagnosed 2 days ago with Burkitt's lymphoma and was started yesterday on his first cycle of chemotherapy. His presentation was with a very large abdominal mass. You review his evening chemistries making sure no abnormalities exist.

Which of the following abnormalities do you need to watch for over the next few days?

A) Hypokalemia.
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12) You are consulted to evaluate a 7-year-old girl with new onset thrombocytopenia. You obtain a bone marrow biopsy on this child and it's consistent with myelodysplastic syndrome. The child's mother asks you what the outcome will be if this condition is left untreated.

Which of the following represents the most accurate response?

A) It will eventually progress to acute myeloid leukemia.
B) It will eventually progress to acute lymphocytic leukemia.
C) It will eventually progress to chronic myeloid leukemia.
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As you are counseling this child's parents. Which is an accurate statement to make?

A) This condition is self-limiting and does not require any intervention or treatment.
B) This condition is much more common at this age than in adulthood.
C) Myelodysplastic syndrome is characterized by associated polycythemia in most patients.
D) Myelodysplastic syndrome is not associated with any cytogenetic abnormalities in the affected hematopoietic cells.
E) Unlike myelodysplastic syndrome in the elderly which usually evolves de novo, childhood myelodysplastic syndrome is usually secondary in nature.

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