Common Pediatric Tumors

By
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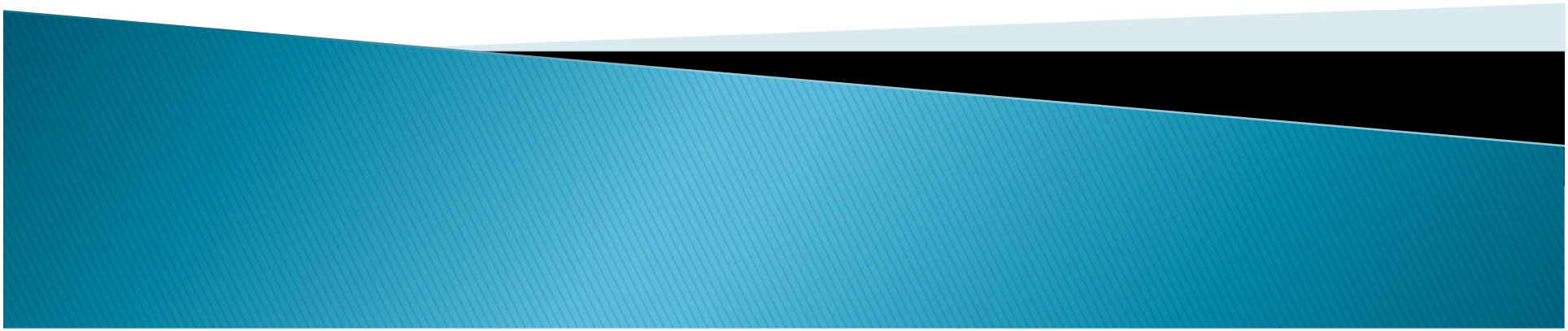
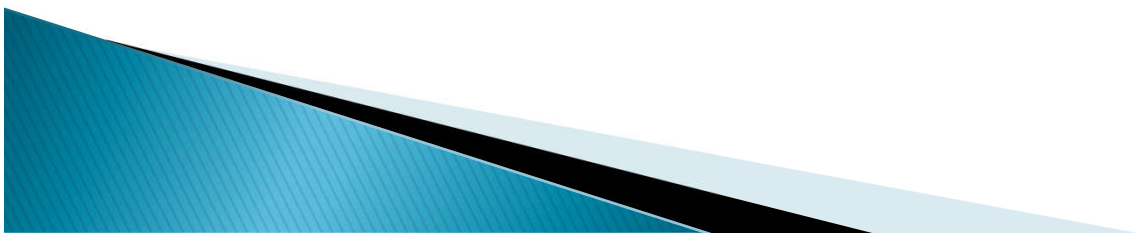


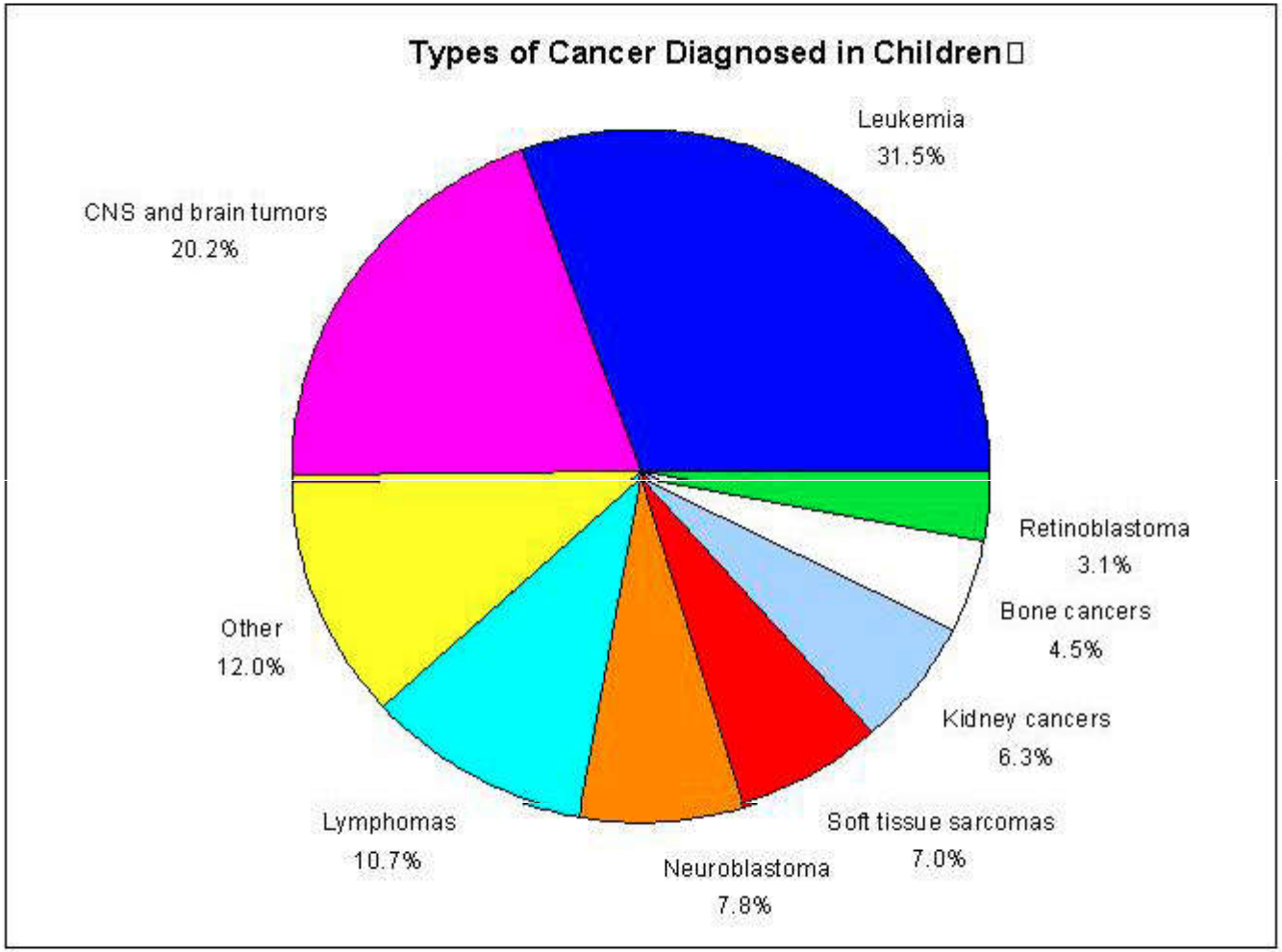
Introduction

- Childhood Cancer is not common disease.
- However One in every 330 children develops cancer before age 20.
- Over 20 children die of cancer yearly.
- Earlier diagnosis and referral can still improve outcome.

Distribution of Childhood Cancer

- Leukemia is the most common childhood cancer
- Brain tumors are second most common
- Lymphomas are the third most common
- Then solid tumors outside the CNS
  - Neuroblastoma – neural crest derived
  - Wilms – renal tumors and syndromes
  - Bone tumors
  - Rhabdomyosarcoma – soft tissue sarcomas




Types of Cancer Diagnosed in Children
Leukemia
31.5%
CNS and brain tumors
20.2%
Retinoblastoma
3.1%
Bone cancers
4.5%
Kidney cancers
6.3%
Soft tissue sarcomas
7.0%
Neuroblastoma
7.8%
Lymphomas
10.7%
Other
12.0%

Common risk factors of cancer in children

- Down's syndrome : ALL*20
- Undescended testis : germinal tumour*40, even after surgical correction
- Retinoblastoma : in 40% of cases, there is a mutation in the RB1 gene – autosomic dominant transmission – prenatal counselling if both parents are heterozygotes
- With advances in molecular biology and genetics, better understanding in the role oncogenes and tumor suppressor genes in the future.

Hematological malignancies

Childhood leukemia

Non-Hodgkin lymphoma (NHL)

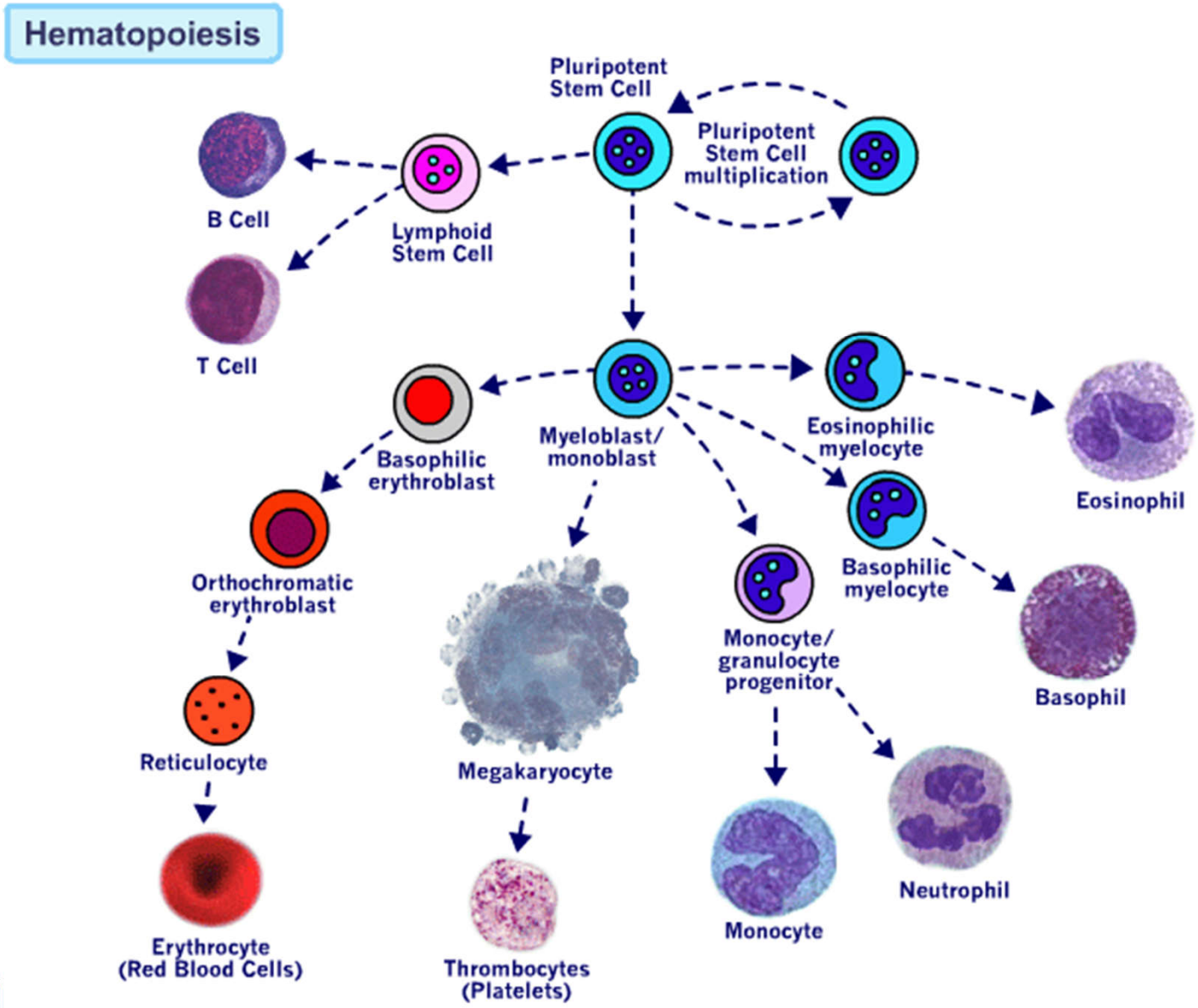
Hodgkin Disease

Childhood leukemia

- Definition:

  Uncontrolled proliferation of **immature blood cells** with a different immunological subtypes which is lethal within 1 -6 months without treatment

  The disorder starts in the bone marrow, where normal blood cells are replaced by leukemic cells


Hematopoiesis
Pluripotent Stem Cell
Pluripotent Stem Cell multiplication
B Cell
Lymphoid Stem Cell
T Cell
Myeloblast/ monoblast
Basophilic erythroblast
Eosinophilic myelocyte
Eosinophil
Orthochromatic erythroblast
Basophilic myelocyte
Basophil
Monocyte/ granulocyte progenitor
Reticulocyte
Megakaryocyte
Neutrophil
Monocyte
Erythrocyte (Red Blood Cells)
Thrombocytes (Platelets)

- **Incidence:**

  Most frequent neoplasm in children (28 – 33%)

  45/ 1 million children under the age of 16 years

  Incidence peak at 2 – 5 years

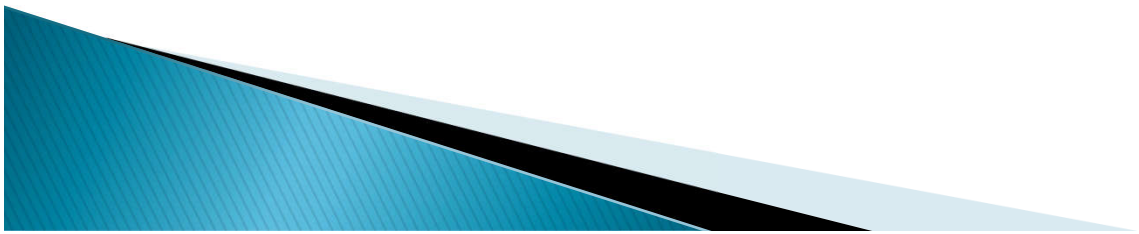
  M:F = 2:1

- Classification

  75-80%- acute lymphoblastic leukemia (ALL)

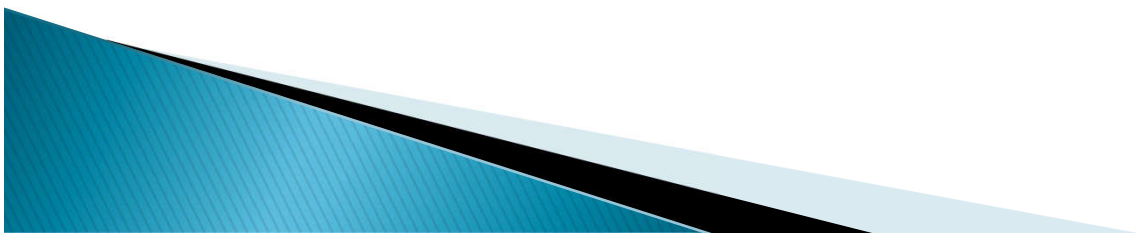
  15-20% - acute myelogenous (non-lymphoblastic) leukemia (AML/ ANLL)

  <5% - undifferentiated acute leukemia and chronic myelogenous leukemia -CML



- **Ethiology:**
- Unknown

- Higher risk in certain chromosomal disorders:
  -Trisomy 21 (14-20 times higher) and other trisomies
  -Turner syndrome
  -Klinefelter syndrome
  -monosomy 7



- Some diseases risk for leukemia:
  - Neurofibromatosis type 1
  - Fanconi anemia ,Bloom syndrome, Kostmann S., Shwachman- Diamond S., ataxia-teleangiectasia(chromosomal breakage syndromes)

  -Congenital agammaglobulinemia(XLA)
  -Wiskott- Aldrich S.

- Environmental factors

  Ionizing radiation (atomic bomb developed high incidence of leukemia)

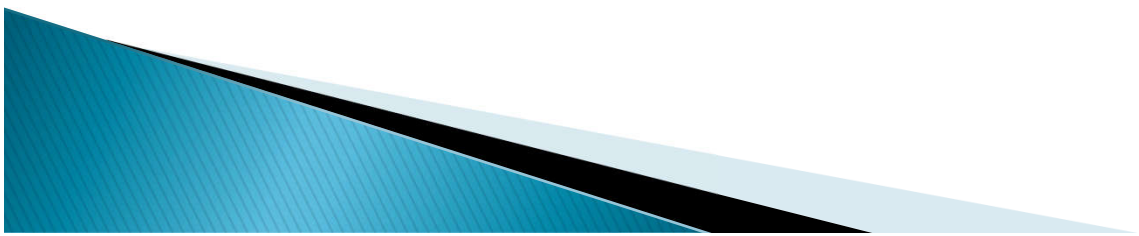
  Chemical and drugs:

  -benzene

  -chloramphenicol

  -alkylating agents

  - Infection (viral -HTLV, EBV, HIV)



Acute lymphoblastic leukemia

Acute lymphoblastic leukemia

- 80% of leukemias
- Girl – to- boy ratio is 1: 1.2
- Peak incidence 2 – 5 years
- Incidence in white children is twice as high as in nonwhite children

- Clinical manifestations depend on :

The degree of bone marrow infiltration by leukemic cells

The extramedullary involvement of the disease

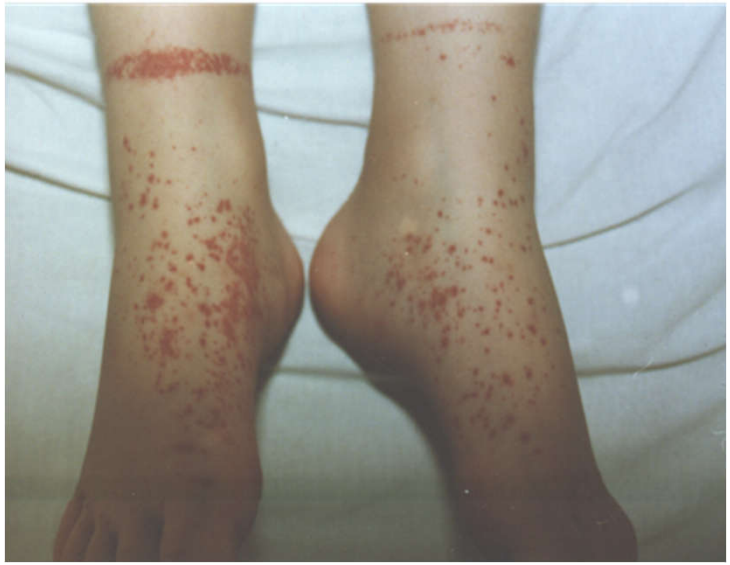
General manifestation due to abnormal metabolic state

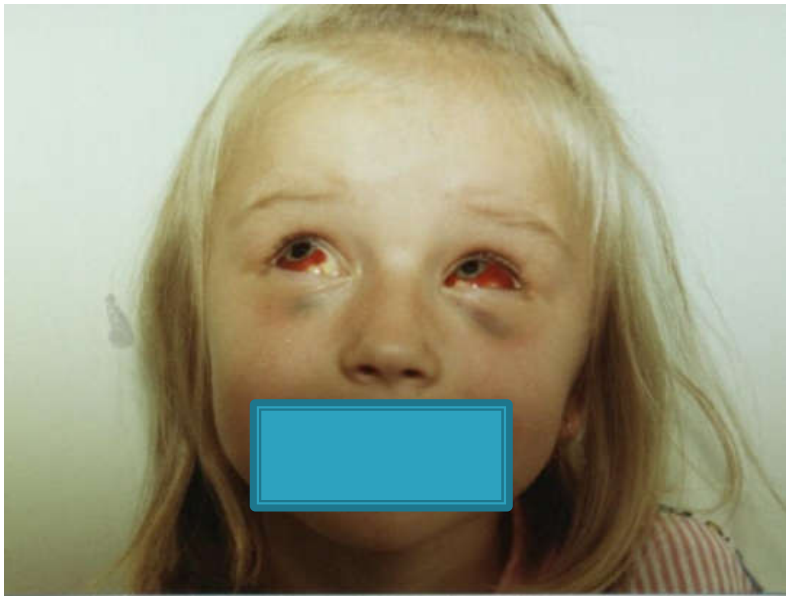
Degree of bone marrow infiltration by leukemic cells

- **Anemia**: pallor, fatigue, tachycardia, dyspnea, occasionally- cardiovascular decompensation

- **leukopenia**:infections, temperature elevation

- **Thrombocytopenia**: petechiae, mucosal bleeding, epistaxes, prolonged menstrual bleeding





The extramedullary involvement of the disease

- Lymphadenopathy
- Hepato- and/or splenomegaly
- Mikulicz syndrome (infiltration of salivary glands and/or tear glands)
- **Cardiac involvement**:
  -leukemic infiltration or hemorrhage
  -occasionally cardiac tamponade due to pericardial infiltration
  -Tachycardia, low blood pressure or other signs of cardiac insufficiency

- **Mediastinum:**

  enlargement due to leukemic infiltration by lymph nodes and /or thymus (observed in T-cell leukemia)

- **Pleura/and pericardium**: effusion
- **Kidney enlargement**
- **Skin**: maculopapular skin infiltration, often of deep red color (infants)

- **Testicular involvement**: enlargement of one or both testes without pain , hard consistency
- **Penis**: priapism is occasionally associated with elevated WBC

- **Bone and joint involvement:**

  bone pain initially present in 25 % to 50% of patients !

  bone or joint pain, sometimes with swelling and tenderness due to leukemic infiltration of the periosteum.

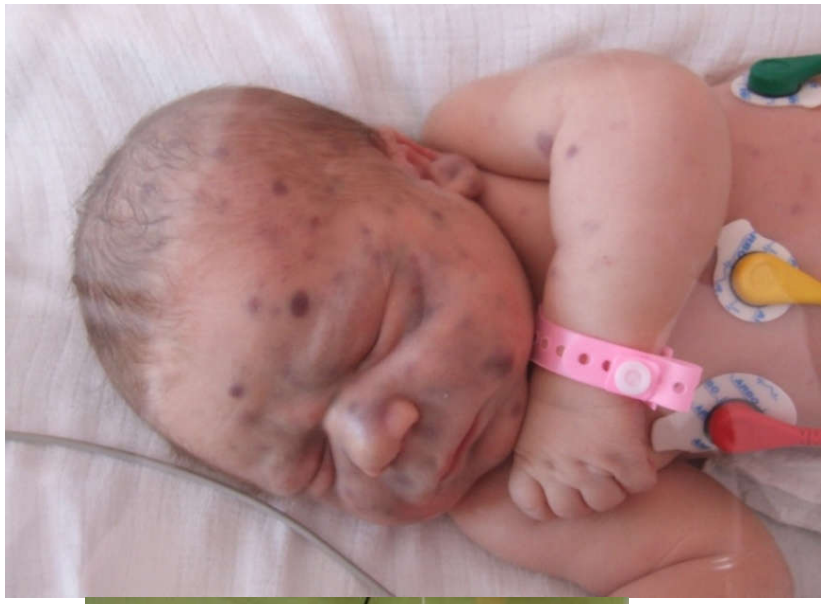
  Differential diagnosis:
Rheumatic fever, Rheumatoid arthritis

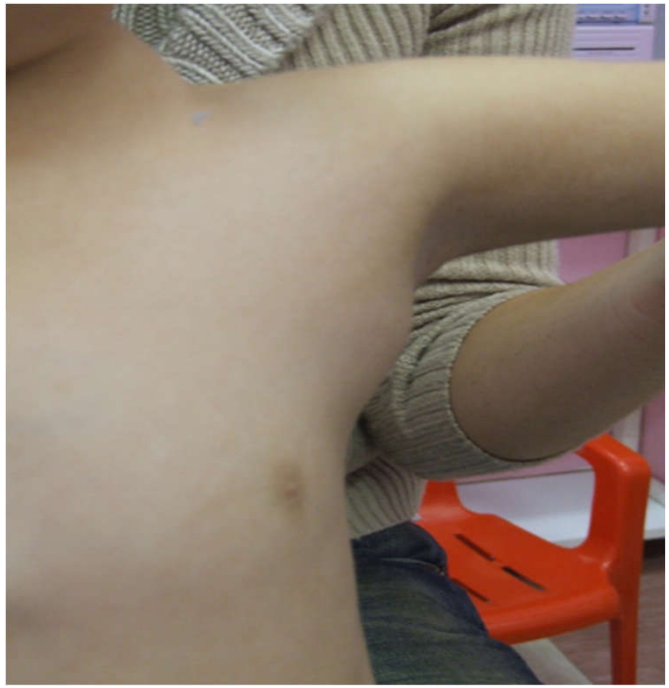
- **CNS involvement :**

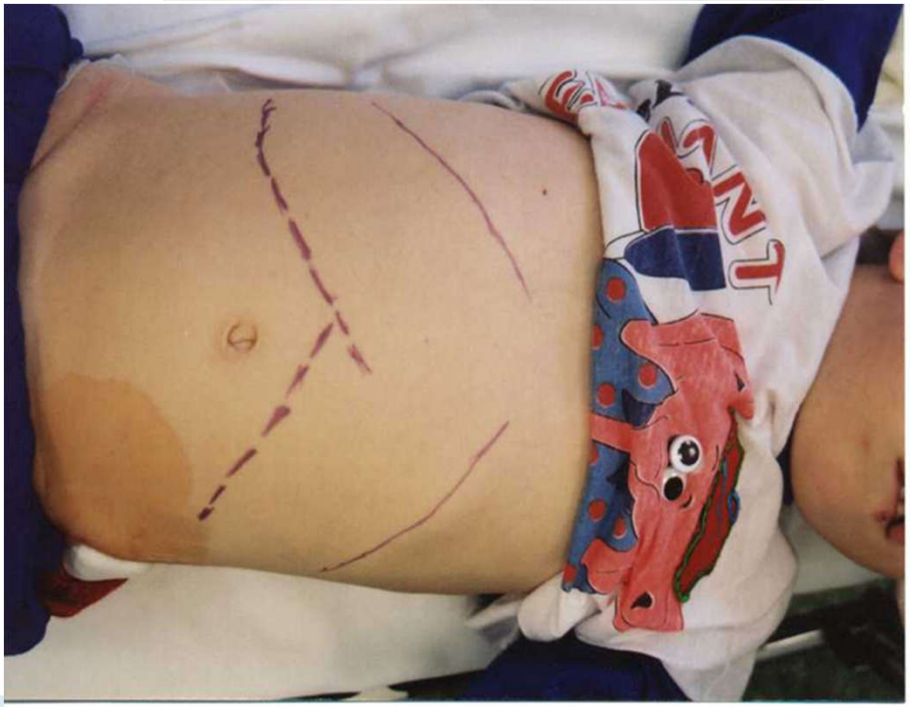
  At time of diagnosis less than 5% have CNS leukemia with meningeal signs (morning headache, vomiting, papilla edema, focal neurological signs)

General manifestation due to abnormal metabolic state

Anorexia
Weight loss
Low grade fever

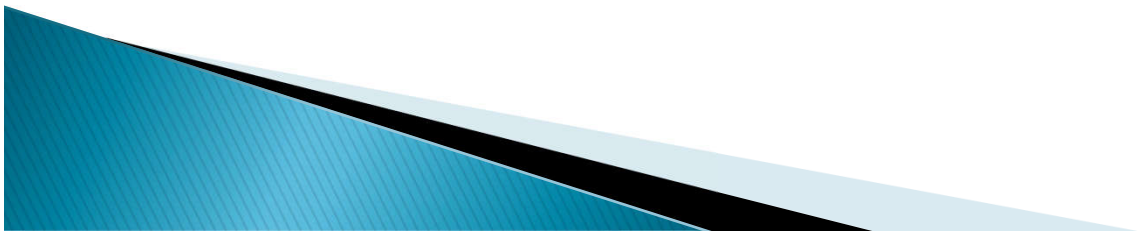




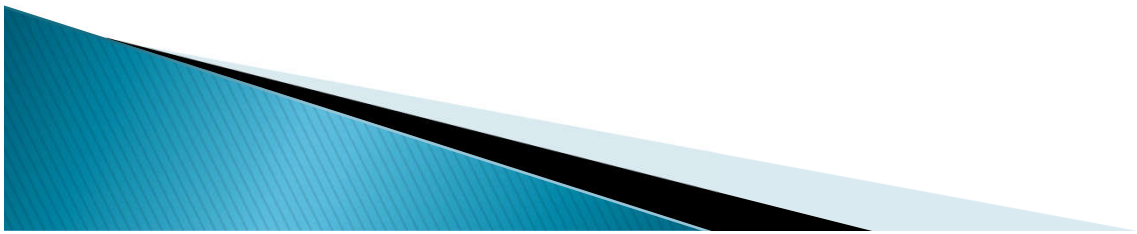


Classification of ALL

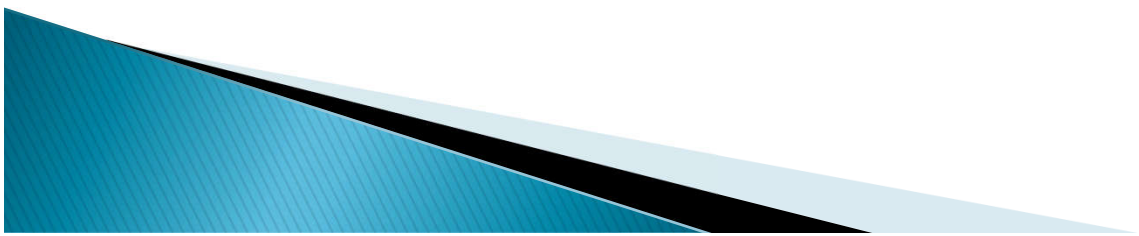
- Morphologic
  - French American British Classification
    - L1: small uniform blasts (pediatric ALL)
    - L2: larger, more variable sized blasts (adult ALL)
    - L3: uniform cells with basophilic and sometimes vacuolated cytoplasm (mature B cell ALL)
- **L1 - 85% of childhood ALL**
- **L2 - Majority of adult ALL**
- **L3 - Includes Burkitt's. < 5% of ALL**



Classification of ALL			
Immunologic Subtype	**FAB Type**	**% of Cases**	**Cytogenetic Abnl**
Pre-B cell ALL	L1, L2	75	t(9:22) t(4:11) t(1:19)
T-cell ALL	L1, L2	20	14q11 or 7q34
B-cell ALL	L3	5	t(8:14) t(8:22) t(2:8)



Prognosis in ALL



parameters	Good	poor
WBC	Low < 10x10 ^{9} /l)	High(>50x10 ^{9} /l)
Gender	Girls	Boys
Immunophenotype	Pre B-ALL	T- B ALL
Age	Child(2-7year)	Adult or infant.
Cytogenetic	Normal,hyperdiploid 50 ,t (12:21)	Ph+,hypodiploid,11q23rearrangements,T(9:22),(4:11)
Time to clear blast from blood	< 1week	>1week
Time to remission	<4weeks	>4weeks
CNSdisease at presentation	Absent	Present
Minimal residual disease.	Negative at 1-3 months	Still positive at 3-6 months.
LDH	Not high	high

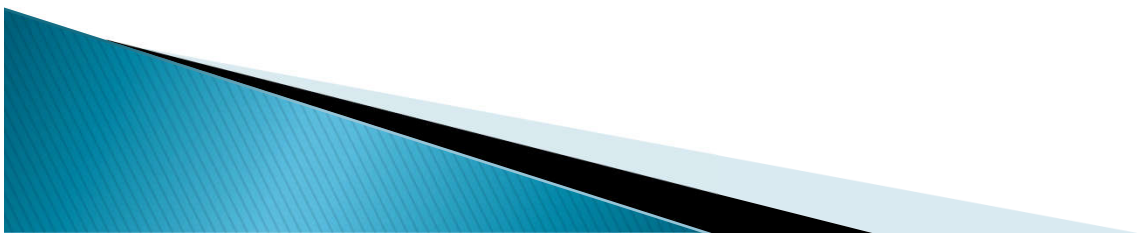
Diagnosis of ALL

- Investigations:
- CBC:
  - 60% of pts have an elevated WBC.
  - Most are anemic
  - Most are thrombocytopenic
  - 90%have blast in the periphral blood film.
- electrolytes:
  - Hypo/hyper kalemia
  - Hypomagnesimia
  - hyperphosphatemia
- Hypermetabolism:
  - ↑LDH.
  - ↑uric acid.

- Bone marrow biopsy and aspirate:
  - 30%or more of all nucleated cells are blast.
- Radiology:
  - CXR: mediastinal mass(T-cell ALL)
  - Osteopenia or lytic lesion 50% of patients with ALL.(intractable pain).

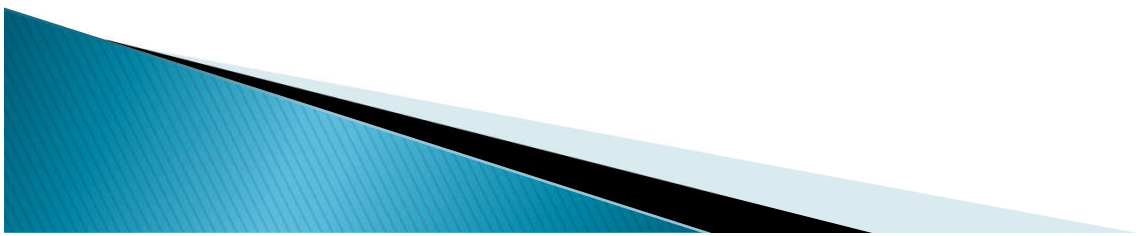
ALL specificTreatment

- 1-Remission Induction
- 2 – Intensification (Consolidation) Therapy
- 3 – Maintenance Therapy
- 4 – CNS Prophylaxis
- 5 – Allogeneic Stem Cell Transplant



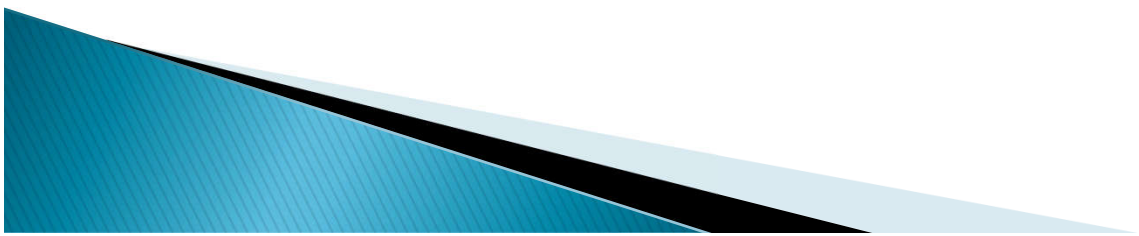
- ***Remission Induction***
  - Goals: restore normal hematopoiesis, induce a complete remission rapidly in order to prevent resistance to drugs
  - Standard induction regimen
    - 4 or 5 drugs: vincristine, prednisone, anthracycline, L-asparaginase, +/- cyclophosphamide
  - 80-90% complete remission

- ***Intensification***
  - High doses of multiple agents not used during induction or re-administration of the induction regimen

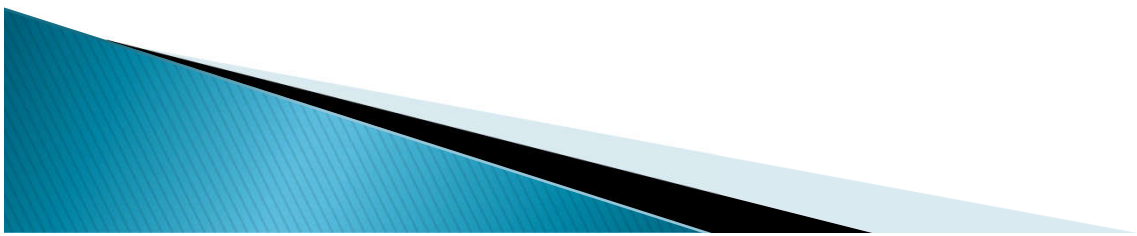


- ***Maintenance Therapy***
  - Daily po 6MP, weekly MTX, monthly pulses of vincristine and prednisone for 2-3 yrs

- ***CNS Prophylaxis***
  - Given during induction and intensification
  - Intrathecal: MTX, Cytarabine, corticosteroids
  - Systemic: high dose mtx, cytarabine, L-asparaginase
  - +/- Cranial Irradiation



- Stem Cell Transplant
  - Indications:
    - Ph Chromosome
    - t(4;11) mutation
    - Poor initial response to induction therapy



COMPLICATION OF TREATMEN

- 1-short term complication:
- Bone marrow suppression
- Nutrational problems(gut mucosal damage)
- Alopecia
- Tumor lysis syndrome
- 2-long term complication
- Infertility
- Hormonal disorders
- Growth disorders
- Psychological problems
- Recurrence of tumor

Complications Treatment

- Tumor Lysis Syndrome

Release of intracellular proteins →catobilized to hypoxanthine → xanthine → uric acid → Crystalization of uric acid and in renal tubules → impaired renal function

Release of phosphate from malignant cells → calcium phosphate precipitation and further renal impairment along with hypocalcemia and resultant symptoms from ↓Ca

- Hyperphosphatemia: nausea, vomiting, diarrhea, seizures, lethargy
- Hypocalcemia: arrhythmia, hypotension, tetany, cramps
- Hyperkalemia: arrhythmia, cramps, paresthesia

Prevention and management

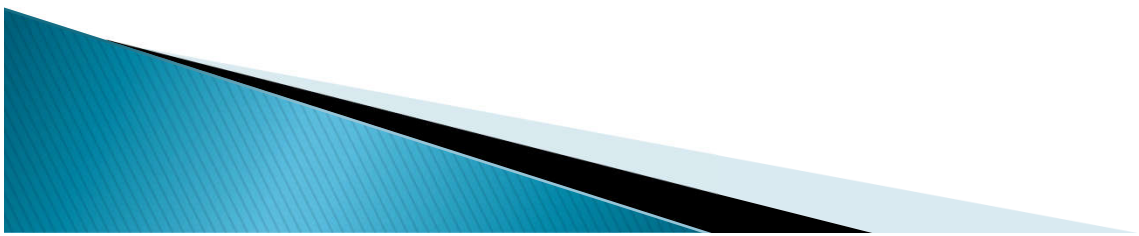
- IV hydration : promotes excretion of uric acid and phosphate; improves renal blood flow/GFR
- Allopurinol → competitive inhibitor for xanthine oxidase. Therefore, ↓ conversion of purine metabolites to uric acid
- Recominant urate oxidase (rasburicase)
  - Promotes conversion of uric acid to allantoin (highly soluble; urinary excretion)
  - Indicated in patients at high risk of TLS (Burkitt's Lymphoma, B-ALL, ALL (WBC >100,000), AML (WBC >50,000)
  - Also indicated in patients that develop hyperuricemia despite allopurinol

- Dialysis can be used in severe cases
- Urine alkalization is NOT recommended – does not increase solubility of xanthine/hypoxanthine with an increased propensity to develop xanthine-obstructive uropathies (esp with allopurinol use

Lymphomas

Childhood Lymphomas

- Lymphoma subtype
  - Hodgkin's Disease (HD)
  - Nonhodgkin's Lymphoma (NHL)
    - * **Burkitt's**
    - * **Lymphoblastic**
    - * **Anaplastic Large Cell**



Presentation of Hodgkin's Disease

- **Age: adolescents >> young child**
- Painless lymphadenopathy
- Progresses over weeks → months
- **Location** 95%

  Cervical/ supra clavicular ↑ LNS unilateral or bilateral

  Mediastinum ± hilum

  LNs below diaphragm and spleen

  Liver, lung, bone marrow

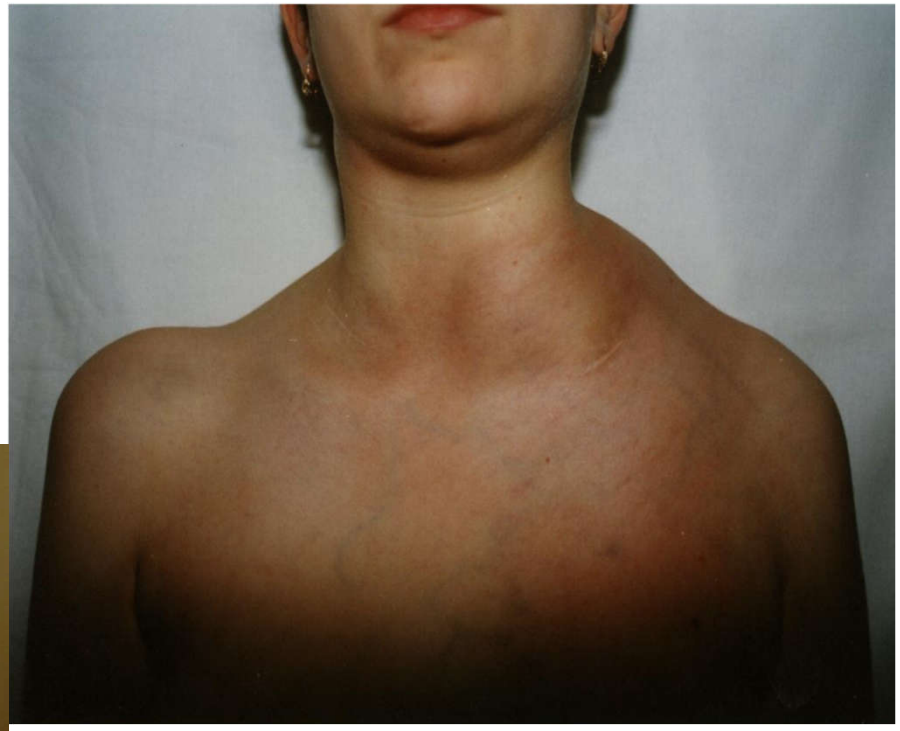
- Pathogmonic histologically :**Reed-Sternberg cells**
- Incidence: 5-7% of all neoplasia in childhood
- Boys more than girls
- Rare before 5 years; increasing until the age of 11 years
- Peak incidence between 15 and 35 years of age
- High incidence in patients with LE, rheumatoid disorders, ataxia teleangiectasia, agammaglobulinemia

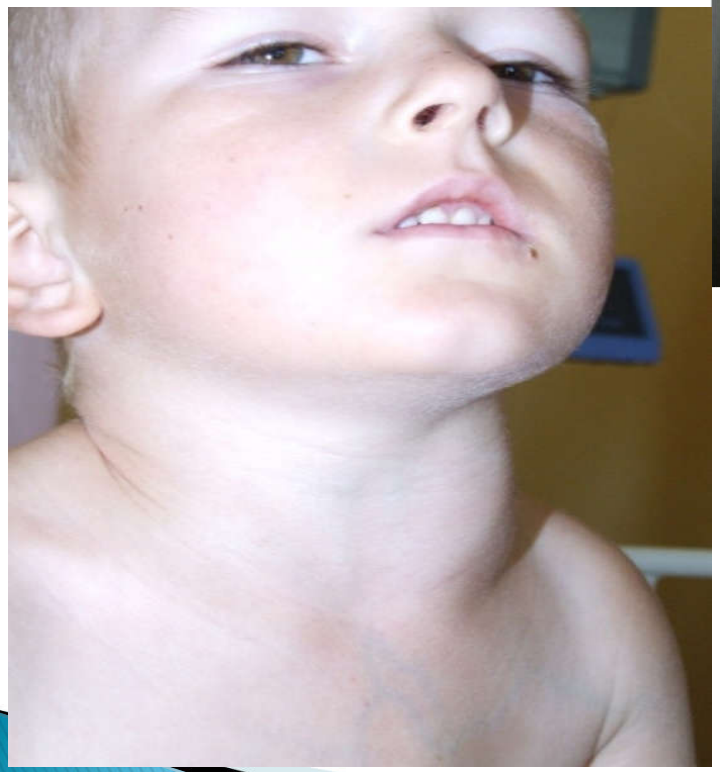
Presentation of Hodgkin's Disease

- Systemic symptoms ''B" symptoms 25%
- Fevers
- Night sweats
- Weight loss
- Pruritus
- Superior Mediastinal Syndrome (SMS)

  Orthopnea, SOB, stridor, hypoxia

  = Oncologic Emergency: compression on
  - Tracheal
  - Bronchial
  - Cardiac





Histological classification:

- Lymphocyte predominance
- Nodular sclerosing
- Lymphocyte-depleted
- Mixed cellular

Staging classification

- I: involvement of a single lymph node region(I) or a single extralymphatic organ (IE)
- II:two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site one or more lymph node regions on the same side of the diaphragm
- III: involvement of lymph node regions on both sides of the diaphragm (III) which may be accompanied by involvement of an extralymphatic organ (IIIe) or site, or both (IIIES)
- IV: diffuse or disseminated process
- A: absence of B symptoms
- B: presence of:loss of 10% or more body weight in 6 months preceding diagnosis, unexplained fever, drenching night-sweat, pruritus

Differential diagnosis

- Toxoplasmosis, tuberculosis, atypical infections
- NHL
- Mononucleosis
- Metastatic disease
- Thymus hyperplasia
- Rheumatoid arthritis, LE
- Sarcoidosis

Prognosis

- Stage I/II EFS >90%
- Stage III/IV EFS 70-80%

Non-Hodgkin lymphoma (NHL)

- Neoplasia of the **lymphatic** system and its precursor cells with genetically disturbed regulation, differentiation and apoptosis
- If marked bone marrow involvement is present the clinical condition is equal of leukemia
- Incidence 5 -7 % of all neoplasias in childhood
- Peak incidence between 5 and 15 years
- Ratio of boys to girls 2:1
- Burkitt *lymphoma* (BL): endemic form in Africa 10:100,000 children and sporadic form in Europe and USA

Etiology, pathogenesis and molecular geneticsof (NHL)

Often chromosomal alterations are detecable: in B-cell NHL translocation of chromosome 14 – t(18;14)

Predisposing factors for NHL:

- Acquired immunodeficiency: autoimmune disorders, HIV infection
- EBV infection
- Congenital B-cell defect, congenital T-cell defect with thymus hyperplasia
- Bloom syndrome, Chedak-Higashi syndrome, SCID, ataxia teleangiectasia, Wiskott-Aldrich syndrome
- Exposure to irradiation
- Drug induced, after immunosuppressive treatment

WHO classification

Histology	Rate	Immuno - phenotype	Main occurence
Burkitt lymphoma Burkitt-like lymphoma	50%	B-cell	Abdomen
Large B-cell lymphoma	7-8%	B-cell	
Lymphoblastic lymphoma	30%	Pre-T-cell or pre-B-cell	Thorax, lymph nodes, bone
Anaplastic, large cell lymphoma	7-8%	T-cell	Lymph nodes, skin, soft tissue, bone

Burkitt lymphoma
Burkit-like lymphoma

- About 50% of NHL
- Localization: abdomen, lymphatic tissue of adenoids and tonsils
- 80% with translocation t(8;14) or t(8;2) and t(22;8) with *c-MYC* on chromosome 8q24 which stimulates proliferation
- 40% with a p53 mutation

Large B-cell lymphoma

- 7-8% of NHL
- Localization: abdomen, peripheral lymph nodes, skin, bone

Lymphoblastic lymphoma

- 30% of NHL
- Usually mediastinal localization

Anaplastic Large Cell Lymphoma

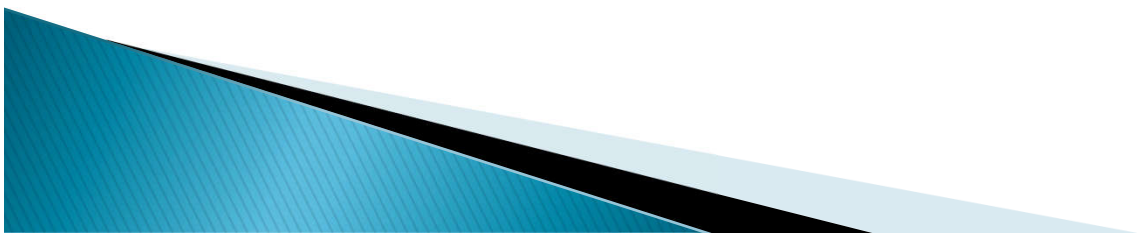
- 7-8% of NHL

Duration of symptoms: usually a few days to weeks

Non-specific symptoms: fatigue, nausea, anorexia, loss of weigth and/or fever

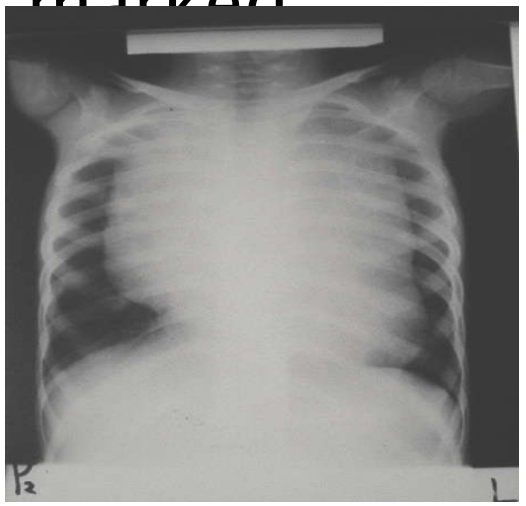
In relation to localisation of NHL:

- **Abdomen**:
- especially the ileocecal region, mesentery, retroperitoneum, ovaries > painfull, spasms, vomiting
- constipation, intussusception
- Apendicitis-like
- Ileus, ascites



Mediastinum:

- Mostly anterior or middle part of mediastinum > cough, stridor, dyspnea, wheezing
- Edema of the neck and face with marked dyspnea may indicate SVCS
- Pain of the back or abdomen
- Pleural effusion



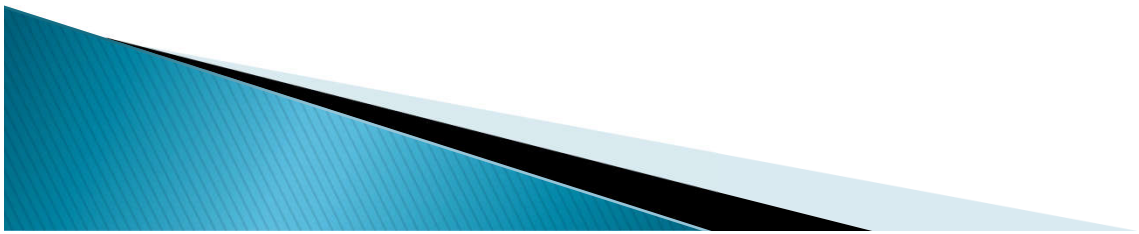
- Involvement of adenoid and tonsils, nasopharyngeal lymph nodes, parotid gland swelling

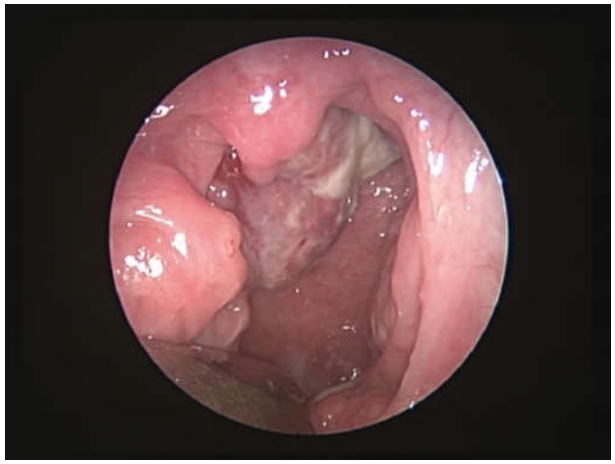
Peripheral lymph nodes:

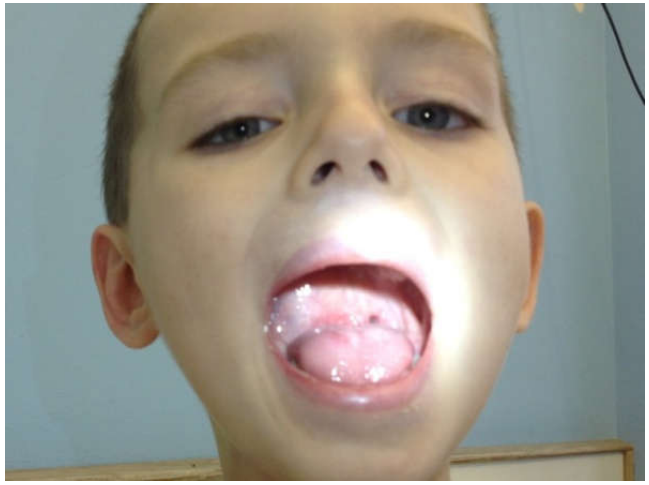
- Mostly cervical, supraclavicular and inguinal
- Lymph nodes are firm, not usually tender, but involving multiple lymph nodes that usually occur unilaterally

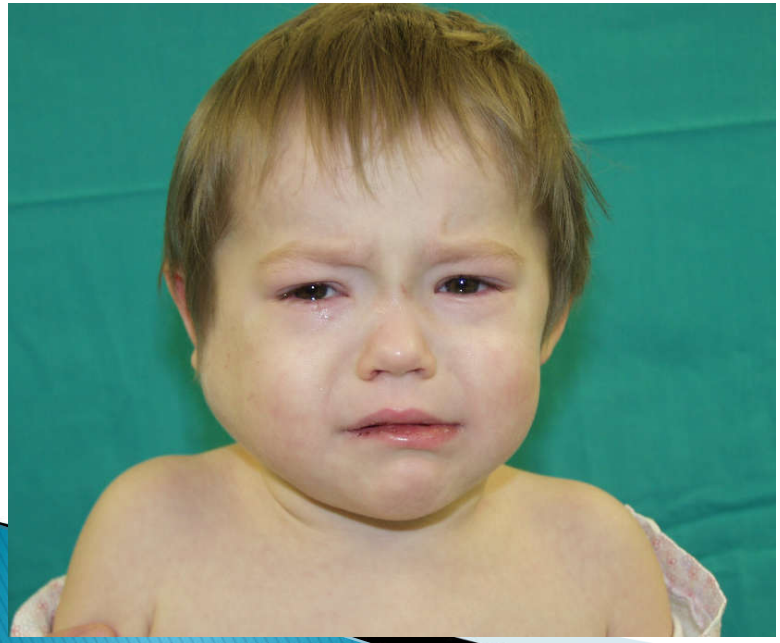
Other locations:

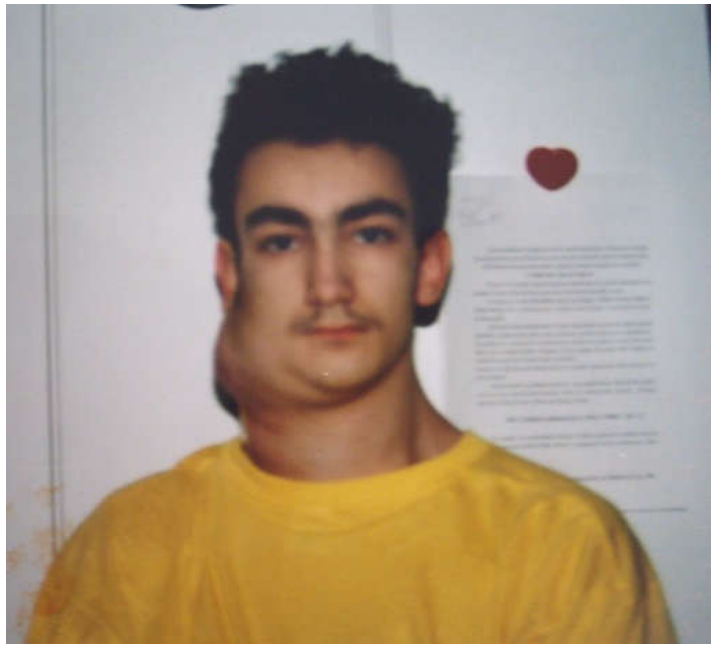
CNS, cranial and peripheral nerves, skin, muscles, bone, thorax, gonads, parotid gland, epidural region→ spinal cord compression











Differential diagnosis

- Lymph node enlargement in infectious diseases
- Autoimmune lymphoproliferative syndrome
- Hodgkin Lymphoma
- metastatic disease of sarcomas or neuroblastomas
- ALL: if more than 25% blasts = ALL, if less= NHL IV stage

CNS TUMORS

- Most common solid tumors in children
- 2nd most frequent (16.6% of all childhood malignancies)
- Incidence has increased over the past 2 decades
- Males > females, white> African American
- Signs & Symptoms (related to the location, histologic grade of tumor & age of child)

* General

-Headache

-Seizures

-Mental status changes

-Increased intracranial Pressure (ICP)

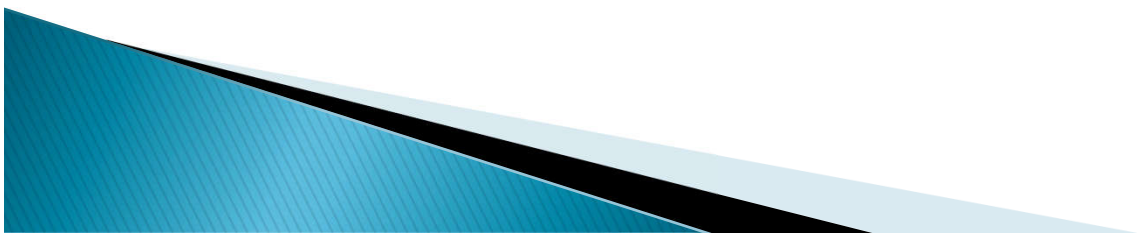
* Posterior Fossa

  - Cerebellum: nausea, vomiting, headache, papilledema, clumsy walk, double vision, dizzyness

  -Brainstem: vomiting, cranial nerve palsies, headache, head tilt, personality changes, hearing loss

* Spinal Cord: depends on location

  - Thoracic-chest pain
  - Cervical or lumbar-neck, arm, back, leg weakness, muscle spasms & wasting, altered bowel, bladder function
  - Progression of symptoms can result in paralysis



* Cerebral Hemisphere
  - Frontal lobe-one-sided paralysis, memory loss, mental changes, urinary changes
  - Occipital lobe-visual changes, seizures
  - Parietal lobe-Language disturbances, seizures, loss of reading, math
  - Temporal lobe-seizures, unable to recognize sounds, visual impairments

  NOTES

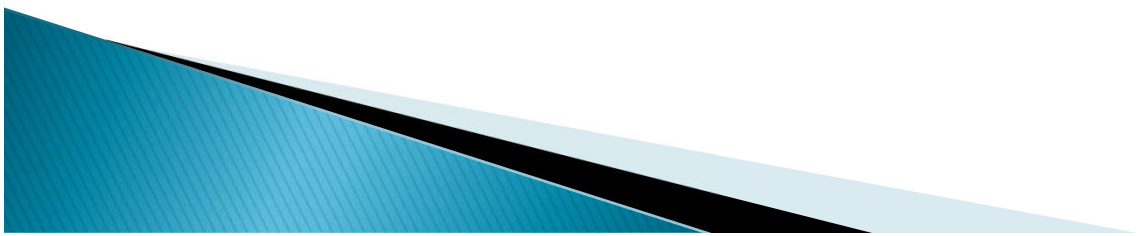
  -infants: delay or loss of dev. Milestones

  -school age-personality changes, decline in school performance, change in handwriting

- Endocrinal

  DI, hypothyroidism, precocious puberty

- Diagnostic Evaluation
  - MRI head:preferred Add spine if required
  - CT head
  - Lumbar puncture
  - Lab work for “tumor markers” for germ cell tumors- AFP & B-hCG



- TREATMENT

  -- Surgery: Most extensive resection feasible

  --Radiation Therapy

  --Chemotherapy
- Prognosis
  - Varies greatly depending on type of tumor, resectability,