



HEMATOLOGIC MALIGNANCIES IN CHILDREN: EARLY DIAGNOSIS AND MANAGEMENT

MARCH 5, 2019




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LEARNING OBJECTIVES

- Describe childhood blood cancers, including ALL, AML, and rare lymphomas such as Burkitt.
- Identify signs and symptoms of childhood blood cancer and diagnostic tests.
- Assess appropriate referral to a pediatric hematologist-oncologist and patient care during and post-cancer treatment.
- Explain treatments, including the role of clinical trials, and management of short- and long-term side effects.

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FACULTY

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DISCLOSURES

Hematologic Malignancies in Children: Early Diagnosis and Management

Dr. Dyer has no affiliations to disclose.

Dr. Rheingold has research funding from Pfizer, Inc.

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CASE 1: BRUISING ON THE PLAYGROUND

3-year old presents to your office with a new rash. She recently started pre-school and parents have noted that she complains of intermittent leg pain and has a lot of lower extremity bruises. She is napping more but they think it's just due to how active she is at her new pre-school.

- What other questions are important to ask the parents to delineate the full history for the patient?

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CASE 1: FURTHER QUESTIONS TO FILL IN HISTORY

- How long have they noted the bruising? The rash?
- Has she been generally well with respect to appetite and sleep?
- When they report her as being tired, is she taking naps or sleeping longer? Does she seem physically weak, or just tired?
- Has she been sick or running any fever?
- Has she had any nosebleeds, bleeding from the gums, or minor cuts and scrapes that seemed to take a long time to stop bleeding? Any history of pink or red urine or blood in her stool?
- Is she taking any medication?
- Are there medications in the house she might have ingested?

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CASE 1: BRUISING ON THE PLAYGROUND

3-year old presents to your office with a new rash. She recently started pre-school and parents have noted that she complains of intermittent leg pain and has a lot of lower extremity bruises. She is napping more but they think it's just due to how active she is at her new pre-school.

- What parts of your physical exam are especially important?

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CASE 1: FOCUSED PHYSICAL EXAM

- General appearance, well being: Does she look sick? Pale? Icteric?
- Vitals are each important: Temperature, BP, HR, RR, pulse ox if concerned.
- Examine bruises then look over from head to toe for presence of petechiae or purpura in unusual places—flexor surfaces usually spared from trauma. Focus on the pattern of distribution of any unusual findings. Significant hematomas underlying ecchymoses?
- Palpable liver or spleen? Lymph nodes?
- Any signs of trauma or physical abuse?

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CASE 1: BRUISING ON THE PLAYGROUND

Physical Exam:

You notice on your exam that the girl has petechiae all over with bruises on her arms and legs. She also has a palpable spleen tip and a palpable liver edge.



- Differential Diagnosis?

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DIFFERENTIAL DIAGNOSIS FOR PETECHIAL RASH AND BRUISING: THINK BROAD CATEGORIES

Infections: meningococemia, RMSF, sepsis, strep, endocarditis, CMV, other viral infections (TORCH) – would likely be ill appearing and +/- fever

Hematologic: Idiopathic Thrombocytopenia Purpura (ITP), aplastic anemia

Oncologic: Leukemia, Lymphoma, Neuroblastoma

Medications: anticonvulsants, quinine, aspirin, warfarin, sulfa drugs

Vasculitis: Henoch Schoenlein Purpura (HSP) SLE (unlikely for age)

Vitamin Deficiency: C or K

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CASE 1: WHAT LABORATORY STUDIES WOULD YOU ORDER?

Start simple. You really just want to know the platelet count, as well as the white cell count and the hemoglobin. And the differential would be nice if there is an abnormality in the WBC.

The rest of the things which may be running through your head can be ordered based on the results of the CBC.

CBC results:

WBC- 4.2

Hgb- 7.3

Platelets -22,000

Automated differential – 30% atypical lymphocytes

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Beware the Automated Differential

Machine generated differentials that have a high percentage of

Atypical Lymphocytes or Monocytes

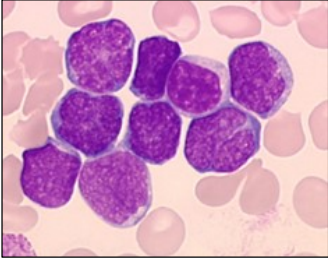
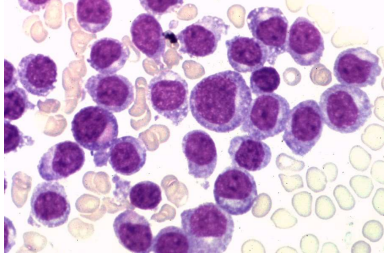
should be regarded with a high level of suspicion.

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Refer to ED or a dedicated pediatric oncology clinic
 Please tell the family your concerns and say the word
 “cancer” or “leukemia”

At CHOP we will repeat the CBC

Not normal!

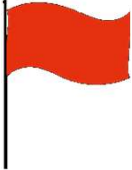




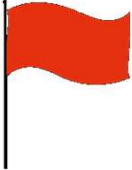
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IN ANY CHILD WITH SUSPECTED LEUKEMIA
AVOID STEROID USE!



Steroids will treat the leukemia
 delaying or obscuring the diagnosis
 and may cause life threatening tumor
 lysis syndrome.



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Leukemia is rare



It presents like many other childhood illnesses that are much more common

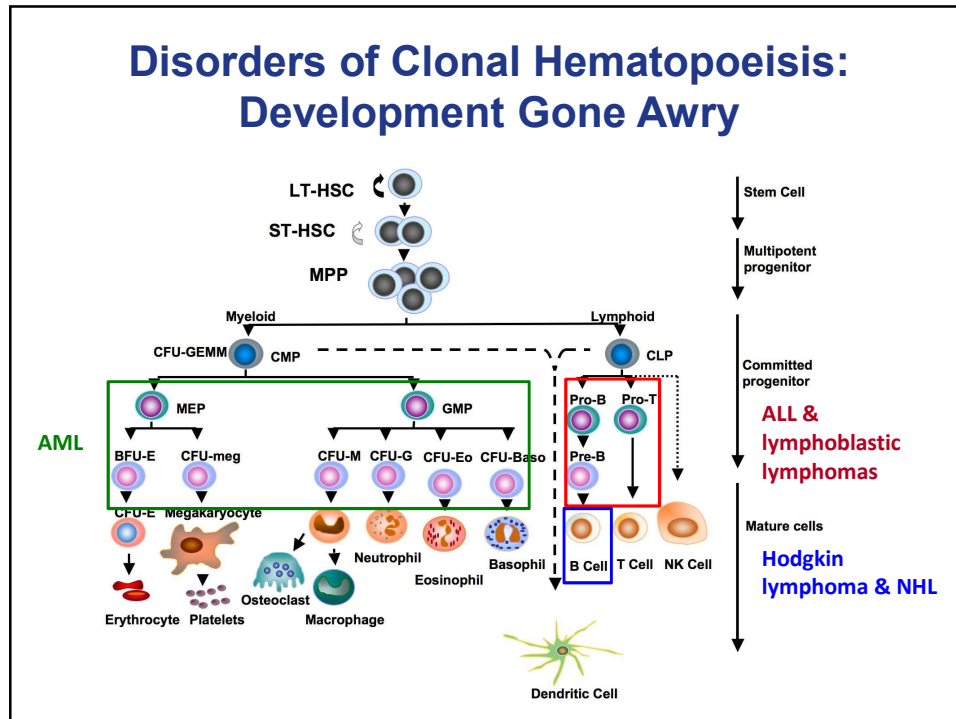
- ▶ ITP (Immune thrombocytopenia purpura)
- ▶ JRA (Juvenile Rheumatoid Arthritis)
- ▶ Hand Foot Mouth (Parvo, Fifth's)
- ▶ EBV (Ebstein-barr virus) / Mononucleosis
- ▶ CMV (Cytomegalovirus)
- ▶ Lymphadenopathy

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Disorders of Clonal Hematopoiesis: Development Gone Awry



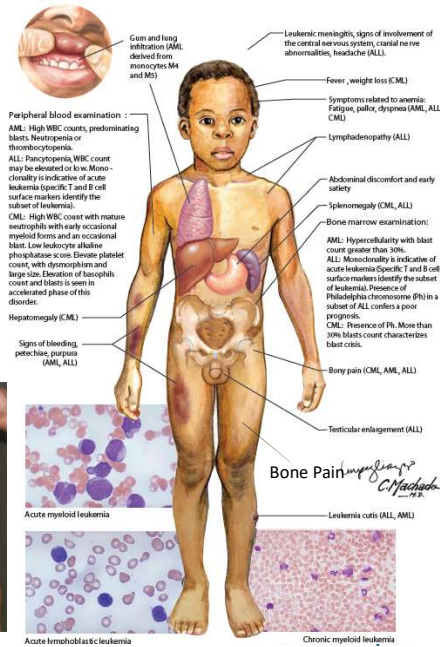
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Clinical Presentation of Leukemia

- Anemia** - pallor, fatigue, headaches, murmur
- Thrombocytopenia** - bruising, petechiae, "rash"
- Neutropenia** - persistent fevers, infection



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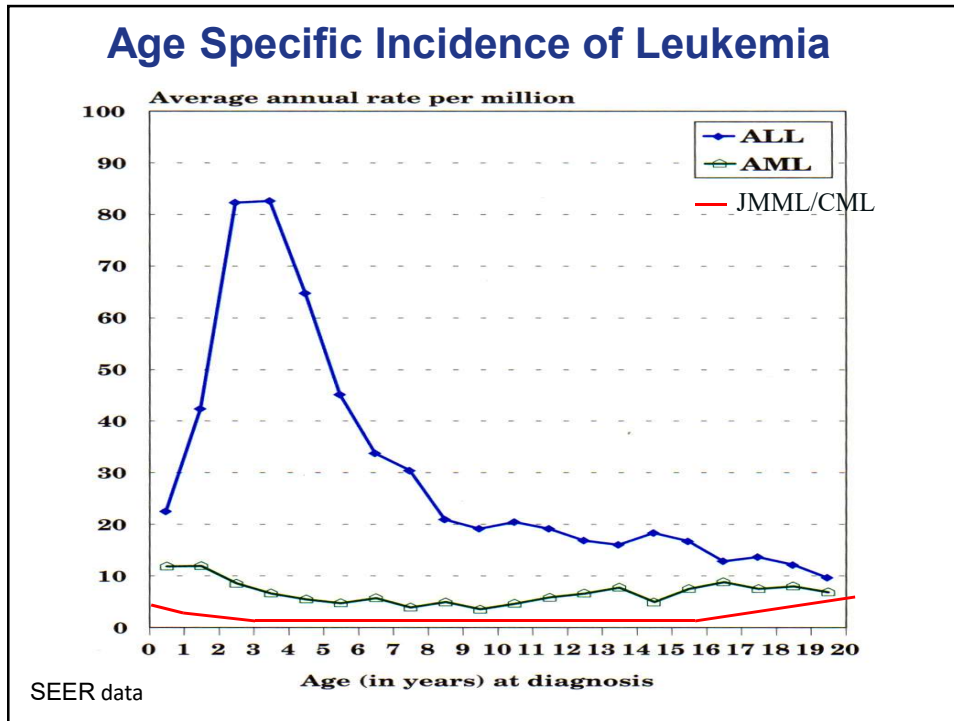
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CHILDHOOD LEUKEMIA

- Leukemia is the most common malignancy of childhood: ~4000 cases/year in North America
 - ~80% is acute lymphoblastic leukemia (ALL)
 - ~85% of these are B-cell ALL
 - ~15% of these are T-cell ALL
 - ~19% is acute myeloid leukemia (AML)
 - ~1% is chronic myeloid leukemia (CML) or rare others
- Etiologies of childhood leukemias remain largely unknown with exception of some genetic predisposition syndromes, trisomy 21, or prior chemotherapy or radiation exposure.

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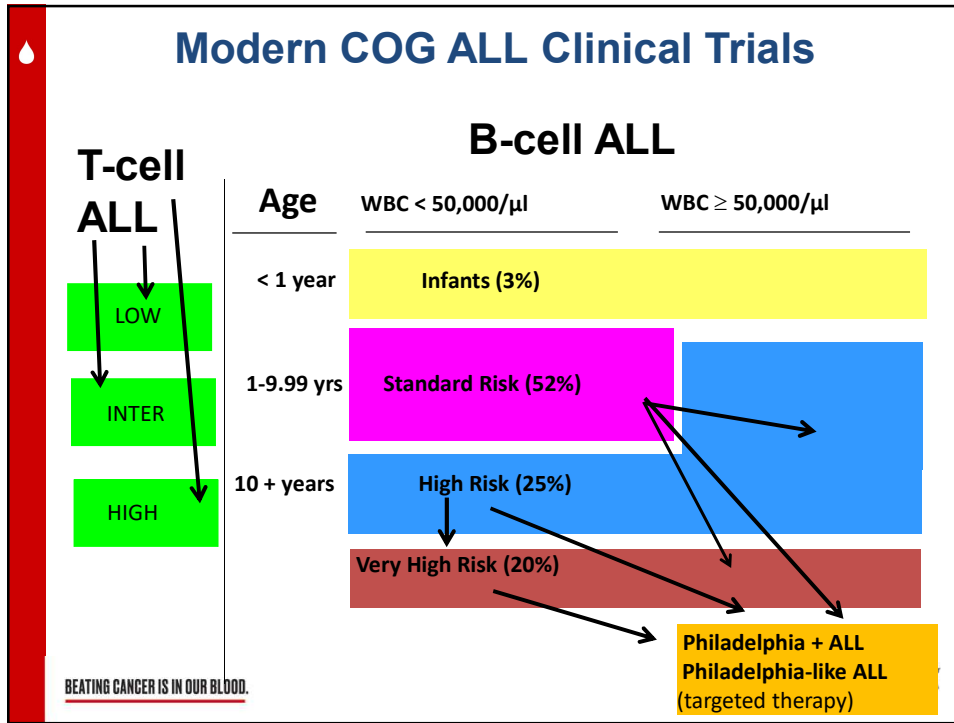
DIAGNOSTIC WORK-UP

- CBC** - manual differential
- Tumor Lysis Labs**
Lytes (Ca/Phos), Uric Acid, LDH
- PT/PTT, fibrinogen**
- CXR** - mediastinal mass, effusions

- Spinal Tap** - CNS leukemia
- Bone Marrow aspirate/biopsy**
 - Flow cytometry of marrow – antigens to ID subtype
 - Cytogenetics of Leukemia ^A

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MOST PEDIATRIC LEUKEMIA IS TREATED ON CLINICAL TRIALS

A standard chemotherapy regimen exists for every type of leukemia (and lymphoma)

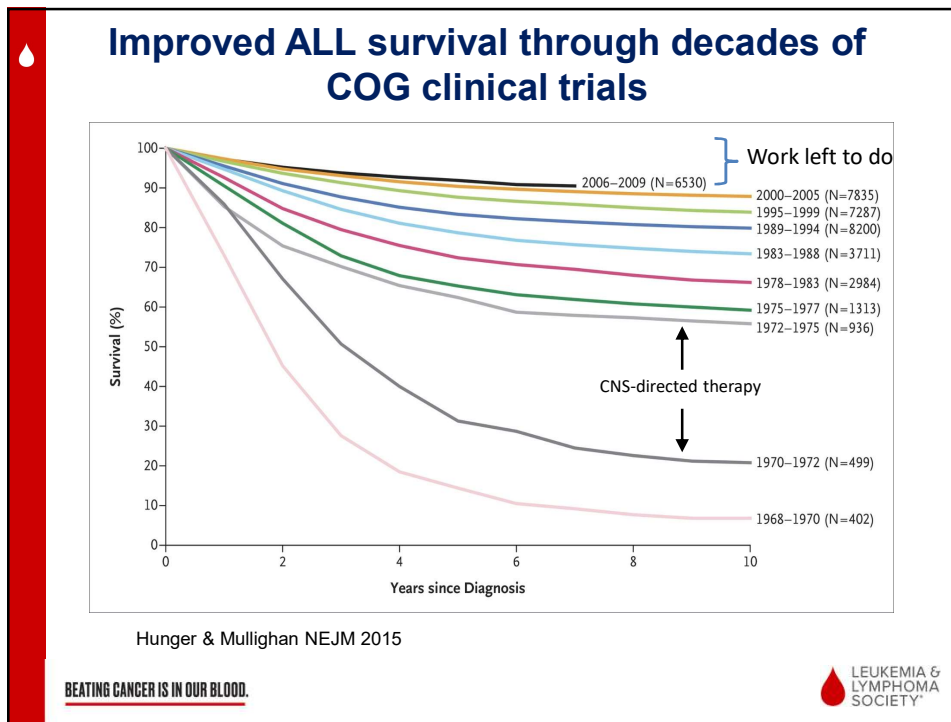
To improve survival pediatric oncologists compare the standard to a “new” regimen.

New=

- Higher Dose of Current Drug
- More (or less) Intensive Therapy
- New Drugs
- New Risk Stratification
- New Biology

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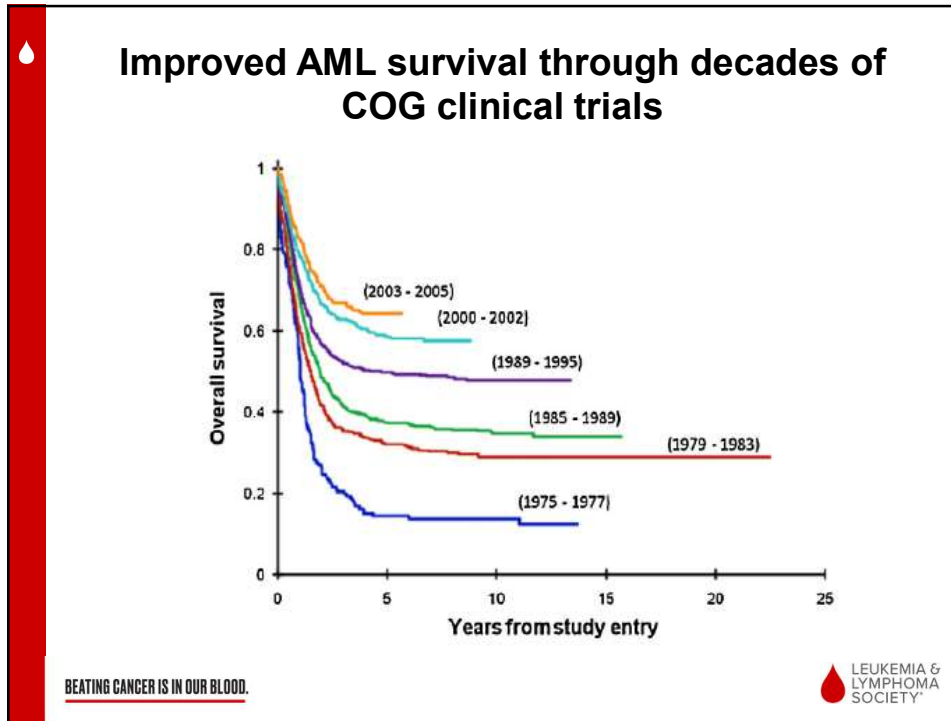
AML THERAPY SUMMARY

- 1) **AML therapy is intensive,**
 - Mostly done as an inpatient as more toxicity
 - Higher infection risk
- 2) **AML therapy is shorter**
 - 4 courses of chemotherapy
 - 3 courses + Bone Marrow Transplant (BMT)
- 3) **25-50% of patients will undergo BMT**
 - Intermediate Risk with matched sibling
 - All High Risk AML go w/ best donor
- 4) **No planned radiation unless emergent**
- 5) **Some targeted therapy studies underway**
- 6) **Patients with Trisomy 21 get reduced chemotherapy**

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PEDIATRICIANS ROLE

- 1) **Generally the oncologists takes over much of the general pediatric care during therapy**
 - May need to do some care if child is far from an oncology center (western states)
 - We have psych support, but not as much ADHD, ASD, delay
- 2) **During less intensive care may be sent to PCP office for simple issues**
 - R/O strep throat, URI with no fever, hurt finger
- 3) **PCP needs to help keep the siblings healthy and immunizations UTD**
 - Siblings can get most any immunization now and they should get the flu vaccine every year
- 4) **Once therapy is completed care will resume at PCP but with planned follow-up in Oncology**
 - Restart missed immunizations until 6 months off therapy
 - For most part treat like a normal child, education challenges
 - Oncologists follows for late effects, but any concerns = CALL

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CASE 2: SWOLLEN GLANDS

13-year old otherwise healthy boy presents to your office because of “swollen glands” of the neck that do not seem to be going away after a cold 2-3 weeks prior.

- What other questions are important to ask the parents to delineate the full history for the patient?

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CASE 2: ADDITIONAL HISTORY QUESTIONS FOR PARENTS AND PATIENT

- Have the glands been growing in size or getting smaller?
- Have they noticed any other swollen glands?
- Tender to touch?
- Associated symptoms: Sore throat? Fever? Runny nose? Rash? Fatigue? Pallor? Weight loss? Night sweats?
- Abdominal distention or abdominal pain?

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CASE 2: SWOLLEN GLANDS

13-year old otherwise healthy boy presents to your office because of “swollen glands” of the neck that do not seem to be going away after a cold 3-4 weeks prior.

Physical Exam:

- What parts of your physical exam are especially important?

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CASE 2: PARTICULARLY PERTINENT PHYSICAL EXAM:

- **General appearance, well being:** Ill appearing? Pale? Level of energy.
- **Vitals,** as always
- **HEENT:** Scalp, ears, throat/tonsils, dentition
- **Neck:** masses which they are asking about as well as any others, range of motion, discomfort or tenderness
- **Abdomen:** appearance, size of liver/palpable edge? Spleen? Other masses? Distention?
- **Skin:** rash, ecchymoses, hematomas, other skin masses?
- **Lymph nodes:** scalp, esp. occipital, anterior and posterior cervical, supraclavicular, axillary, inguinal, epitrochlear, popliteal. Look in all these places, noting size, symmetry.


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CASE 2: SWOLLEN GLANDS

Node exam and location helps with Differential Diagnosis




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CASE 2: SWOLLEN GLANDS

Node exam and location helps with Differential Diagnosis



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Benign or Malignant

	Benign	Concern
Location	Anterior or Posterior Cervical , Inguinal	Supraclavicular, Epitrochlear
Symptoms	Viral, Rhinorrhea	Weight loss, night sweats
Node	< 1-1.5cm, soft, mobile, erythema	> 3cm, hard, matted
Exam	Other signs of Infection	Hepatosplenomegaly, Facial swelling, Respiratory Distress

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LYMPHADENOPATHY PEDIATRICIAN APPROACH AND TREATMENT: LIKELY BENIGN

- Serial exams/observation (no intervention)—start weekly
- Treat any underlying infection
- Antibiotic trial if red, tender (lymphadenitis)
- Avoid steroids (prednisone) as can treat leukemia and lymphoma
- and obscure diagnosis
- **This is particularly important if you have a child who you think has mono and is having trouble swallowing or tremendous pain, and you are considering a short course of prednisone!**
- If not sure consider laboratory and radiology evaluations

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CASE 2: SWOLLEN GLANDS

Physical Exam:

- Vitals- RR-18, HR 90, Pulse Ox- 99% RA, T- 38C/101F
- Bilateral anterior cervical lad- R>L, tangerine sized
- Nodes are hard and matted nodes
- Palpable supraclavicular node on right
- No axillary, epitrochlear or inguinal nodes
- No hepatosplenomegaly
- Able to lie flat without respiratory distress



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REFER TO A TERTIARY CARE CENTER / PEDIATRIC ONCOLOGY CLINIC

Labs: CBC with a differential
LDH, uric acid, ESR
Other titers- EBV, cat scratch

Imaging:
CXR to assess for a mediastinal mass

Radiologic Work-up
Neck, chest, abdominal, pelvic CT
PET/CT

Do NOT start steroids as an outpatient
It can mask the diagnosis and create resistance

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CASE 2: SWOLLEN GLAND - DIAGNOSTIC EVALUATION

Fine needle aspirate vs excisional node biopsy



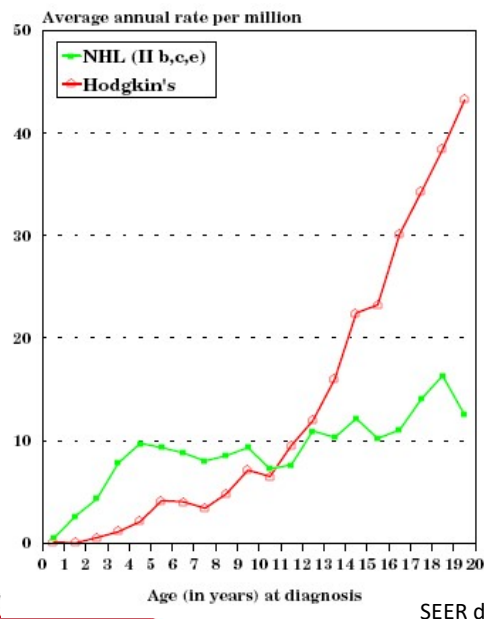
- 1) Oncologists want to meet the child before the ENT biopsies it
- 2) Oncologists always want excisional node biopsy- nodal architecture and diagnostic tissue
- 3) Always send for pathology and culture (good communication with surgeon)

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LYMPHOMA EPIDEMIOLOGY



Hodgkins- incidence rises drastically with age during adolescence
Rarely seen in < 5 year olds
Female & Caucasian predominance

Non-Hodgkins-
Rare in toddlers but level incidence until young adult age



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MALIGNANCY- HODGKINS

LAD: Unilateral enlarged hard matted node or cluster of nodes (neck > other sites), supraclavicular

“B” symptoms: Weight Loss, Fever, Drenching Night Sweats

-Some children with no symptoms

Exam: Pruritis / Rash

Labs: ESR (tumor marker), CBC, LDH

CXR: Assess for mediastinal mass

Staging: Rare spread to bone marrow, no CNS

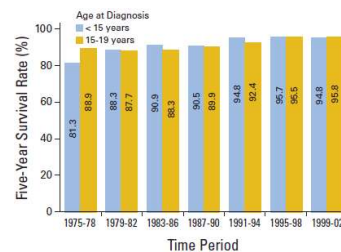
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HODGKINS THERAPY

Hodgkins disease (HD) in childhood is curable in > 95% of patients.



Treatment has evolved over time:

Use of hybrid therapy with 4-6 cycles of chemotherapy and radiation in most patients

Better appreciation of therapy-induced sequelae

- Males- sterility, cardiac toxicity
- Females- breast cancer, cardiac toxicity

Present focus is design of clinical trials with targeted immunotherapy to reduce late effects without compromising survival

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CASE 3: A WHEEZY TEEN

15-year old male presents to your office in spring with a two week history of some 'wheezy breathing' and fatigue. Worse when playing lacrosse. Had mild reactive airway disease as a toddler, no episodes in years.

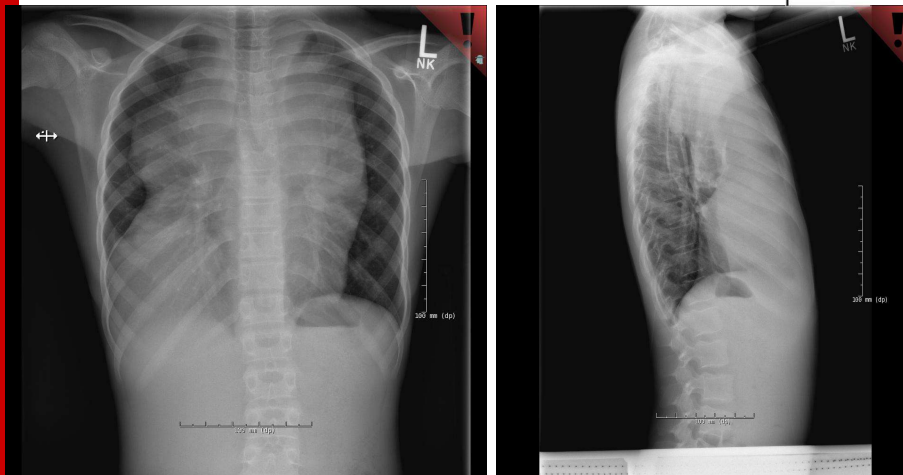
- What other questions are important to ask the patient to delineate the full history for the patient?

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CASE 3: A WHEEZY TEEN

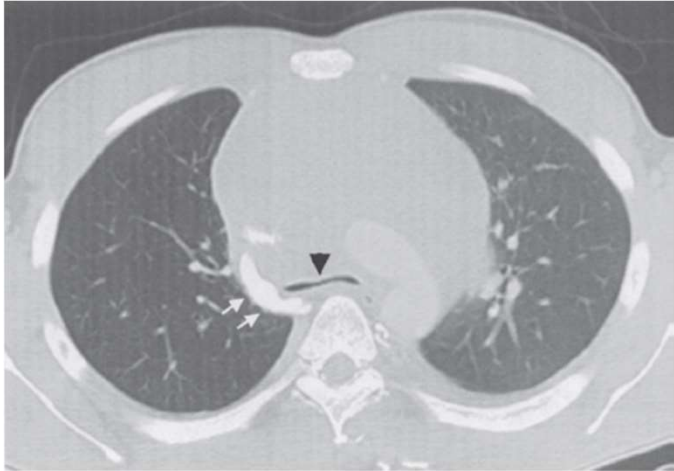


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CT SCAN IF PATIENT CAN LIE FLAT

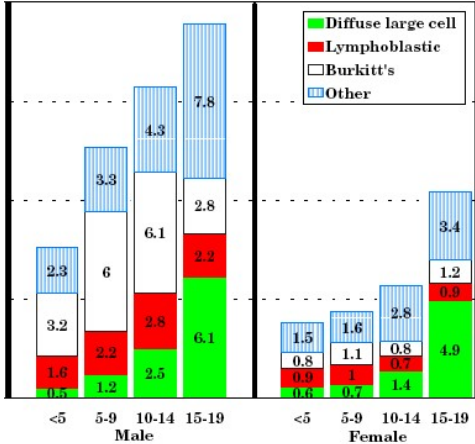


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NON-HODGKINS LYMPHOMA EPIDEMIOLOGY



Sex	Age Group	Diffuse large cell	Lymphoblastic	Burkitt's	Other	Total Incidence
Male	<5	0.5	1.6	3.2	2.3	7.6
	5-9	1.2	2.2	6.0	3.3	12.7
	10-14	2.5	2.8	6.1	4.3	15.7
	15-19	6.1	2.2	2.8	7.8	18.9
Female	<5	0.6	0.0	0.8	1.5	2.9
	5-9	0.7	1.0	1.1	1.6	4.4
	10-14	1.4	0.7	0.8	2.8	5.7
	15-19	4.9	0.5	1.2	3.4	10.0

Incidence is slightly higher in white vs black children

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NON-HODGKINS LYMPHOMA

Symptoms: Well to very ill appearing, respiratory symptoms, fever, pain, can be non specific malaise

Exam: Wheeze/cough, abdominal mass

LAD: Localized or generalized and all over body

Labs: CBC, Uric Acid and LDH elevated

Imaging: CXR: Assess for mediastinal mass,
US : Abdominal mass, Full body CTs and PET for staging
Can spread to CNS and BM- LP and Bone Marrows

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NON-HODGKINS LYMPHOMA SUBTYPE CLINICAL TRIALS

Therapy

Mature B-Cell

Burkitt's (40%)
Diffuse Large B-cell (20%)
Mediastinal B-cell (3%)

Chemotherapy &
Immunotherapy (rituximab)

Lymphoblastic Lymphoma (30%)
T-cell & B-cell

Treat like ALL

Anaplastic Large Cell (10%)

Chemotherapy &
-targeted therapy (crizotinib)
-immunotherapy (brentuximab)

NK/T lymphoma
Rare others

Radiation rarely used for NHL
except emergencies

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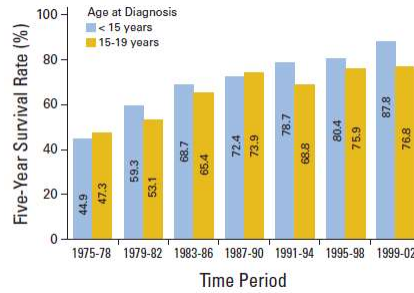
NHL OUTCOMES

Localized disease— 95%

Advanced stage-
Stage III/IV, BM+, CNS+
70-90%

Less favorable - 45-70%

- Burkitts w/ CNS +/- BM disease
- Primary mediastinal DLCL
- Systemic ALCL subset (ALK-negative)
- NK/T Lymphoma



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SIDE EFFECTS OF TREATMENT

SHORT TERM

- Chemotherapy induced N/V
- Anorexia, Malnutrition
- Constipation and/or Diarrhea
- Hair Loss
- Infection, Infection, Infection
- Diabetes
- Hypertension
- Organ toxicity
- Heart, Lung, Kidney, Liver
- Stress/Anxiety

LONG TERM

- Growth and puberty delay
- Educational challenges
- Under and overweight
- PTSD
- Diabetes
- Organ toxicity
- Heart, Lung, Kidney, Liver
- Second malignancies

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Resources for HCPs

- ❑ Online & In-person free CME & CE courses: www.LLS.org/CE
- ❑ **New** Podcast series for healthcare professionals – www.LLS.org/CE:
Listen as we speak with experts about diagnosis, treatment and survivorship to educate HCPs treating with blood cancer.

Clinical Trials and Research

- ❑ Clinical Trials: Learn more about clinical trials:
www.LLS.org/ClinicalTrials
- ❑ Research: Focused on finding cures and driving research:
www.LLS.org/Research

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Resources for Patients

- ❑ Childhood blood cancer resources: www.LLS.org/childhoodcancer
 - ❑ Fact sheet on Long-Term and Late Effects of Treatment for Childhood Leukemia or Lymphoma
- ❑ Telephone and Web Education Programs: www.LLS.org/Programs and www.LLS.org/Educationvideos
- ❑ Support Resources: www.LLS.org/Support
 - ❑ Financial Assistance
 - Co-Pay
 - Travel Assistance
 - Referral to Medication Access programs
 - ❑ LLS Chapters
 - ❑ LLS Community (social media platform)
 - ❑ Patti Robinson Kaufman First Connection Program (peer-to-peer)
 - ❑ One-On-One Nutrition Consultations (PearlPoint)

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FREE GUIDES, BOOKLETS, AND FACT SHEETS

Supporting Patients, Caregivers and Professionals

www.LLS.org/Booklets



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Resources for Patients

Information Resource Specialists and Clinical Trial Specialists:

www.LLS.org/IRC

Assist through treatment, financial & social challenges, and **give accurate treatment and support information.**

Patients & caregivers can also work one-on-one with **clinical trial specialists who are registered nurses** with expertise in blood cancers. RNs will personally assist through the clinical trial process, **providing an additional resource to your HCP team.**

- Phone: (800) 955-4572, M-F, 9 am to 9 pm ET
- Email: infocenter@LLS.org
- Live chat: www.LLS.org/InformationSpecialists

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CDN'S PRIMARY ACTIVITIES

RESEARCH

We accelerate research translation. CDN has over 25 years of experience developing, conducting, implementing and evaluating practice-based research with Community Health Centers and other safety-net practices.

EDUCATION

We provide peer support through training and education that integrates online and on-site didactic and experiential learning. Collaborate with us to meet your training needs.

PARTNERSHIP

We conduct research and educational activities in partnership with government, academic, not-for-profit, and for-profit organizations. CDN has an extensive network of multidisciplinary researchers, clinicians, clinical leaders and policy-makers.

DISSEMINATION

We provide dissemination services through webcasts for public health and clinical research projects. CDN has extensive experience disseminating research and training programs to our extensive network of multidisciplinary researchers, clinicians, clinical leaders and policy-makers.

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DISTANCE LEARNING ACTIVITIES


- ▣ **Online CE-accredited webcasts**
 - ✓ Group-oriented, case-based interactive learning models
 - ✓ On-demand (24x7x365) archived sessions for enduring training materials
- ▣ **Live conference session webcasts (Simul-casts)**
- ▣ **Online class production**
- ▣ **Learning collaboratives**
- ▣ **CE accreditation for-**
 - ✓ Continuing Medical Education (CME)
 - ✓ Continuing Nursing Education (CNE)
 - ✓ Continuing Education for Social Workers (CE-SW)
 - ✓ Continuing Education for Health Educators (CHES)
 - ✓ Continuing Education for Pharmacists (CPE)

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Q & A

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THANK YOU

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