NB ALL/CCL (immunologically incompetent) vs Myeloma (immunologically competent)

Acute Lymphoblastic Leukemia (ALL)

- Stain: PAS
- RFs
  - Idiopathic (most common)
  - Genetic: Down Syndrome, Klinefelter's Syndrome, Chromosomal Instability Syndromes (Fanconi, Bloom, NF-1, AT), MTHFR Polymorphisms
  - Infections: HIV, HTLV-1, EBV, CMV, HepB, Varicella?, Influenza? (many often get titers)
  - Why ALL? for the immune system to fxn a lymph must exist for every Ag, to accomplish this feat innumerable DNA rearrangements must occur (which occurs during gestation and early childhood) and in doing so mutations become more common
- Epidemiology
  - bimodal age distribution (~5yo and ~50yo)
- Unique S/S
  - Extra-Medullary Leukemia (EML)
    - Testicular Mass
    - Ant Mediastinal Mass resulting in tracheal narrowing, pleural effusions, SVC syndrome, et al
    - LAD/HSM so big that it looks like lymphoma
    - CNS dz w/ CN neuropathies, leptomeningeal involvement, increased ICP w/ N/V/HA, et al
    - Lytic bone lesions w/ hypercalcemia (esp at chin resulting mental nerve involvement and thus numb chin)
  - Bone pain b/c of BM involvement
- Classification
  - Childhood ALL used to be classified under the FAB Morphology System into one of three types: L1 (85% children, 25% adults), L2 (10% children, 65% adults), L3 (5% children, 10% adults) now ALL is classified via Flow Cytometery
    - B-Cell Lineage 75%
    - T-cell Lineage 25% (NB In general T-Cell ALL usually have unfavorable RFs (occur in older pts, have higher WBC counts, and unfavorable cytogenetics) and thus have poorer prognosis)
- Treatment
  - Induction (4wks): Cyclophosphamide + Vincristine + Adriamycin + Dexamethasone **(CVAD)** ± L-Asparaginase (if child), Rituximab+Methotrexate (if mature B-Cell), Cytarabine (if T-Cell), et al (50% achieve complete remission)
  - Consolidation (4mos): low risk pts (intense chemo meds that are typically different than those used during induction followed by maintenance below) vs high risk pts (HSCT)
  - Maintenance (4yrs): daily 6-mercaptopurine, weekly methotrexate, monthly vincristine and prednisone
  - Other
    - CNS Prophylaxis: all ALL pts need an LP, intrathecal chemo (methotrexate, cytarabine, dexamethasone), systemic chemo (methotrexate, cytarabine, L-asparaginase), and craniospinal radiation (b/c of the high morbidity of radiation most oncologists do not give radiation and studies have found that it has no effect on prophylaxis), begin during induction phase and continues throughout chemo
    - New Meds: hypomethylating agents (Decitabine), histone deacetylase inhibitors (SAHA), ubiquitin proteasome inhibitors (Bartezomib), deoxyadenosine analogues (Clofarabine), anti-CD20 (Rituximab), anti-CD52 (Almtuzumab)
    - L-asparaginase (Elspar), Pegaspargase (Oncaspar) Mech: cleaves asparagine to aspartic acid and ammonia and b/c certain neoplastic cells (specifically ALL) have low levels of asparagines synthetase these cells die, SEs: N/V, F, allergic rxn, hepatotoxicity, bleeding diathesis, pancreatitis, hypoinsulinemia, neurotoxicity
- Prognosis
  - Good: 1-10yo, low initial WBC <30k(B)<100k(T), favorable cytogenetic abnormalities, good response to induction Tx by looking at BM Bx (80% survival in children, overall dramatic increase in survival since the 1980s)
  - Bad: <1yo or >10yo, adults, high initial WBC >30k(B)>100k(T), unfavorable cytogenetic abnormalities, poor response to induction Tx, CNS involvement (NB 25% survival in adults, not as many advances as in children and adults typically more of the bad prognostic RFs esp Ph+ Chromosome)
- Relapse
  - 25% relapse rate esp in BM, CNS, Testes
  - Tx: HSCT

Chronic Lymphocytic Leukemia (CLL)

- Mech
  - monoclonal proliferation of immunologically incompetent but mature B-cells (if polyclonal than infection)
  - CLL and SLL are the same thing, it all depends on the Dx was made: CLL (BM Bx) and SLL (LN Bx)
  - recent NEJM confirmed the hypothesis that 98% of pts w/ CLL were preceded by a Monoclonal B-cell Lymphocytosis (conversion rate of 1%/yr) characterized by certain flow cytometery suggesting its use as a screening tool
- Epidemiology
  - 10k/yr

- ~65yo
- most common leukemia of the elderly

- RFs
  - 1st degree relatives
- S/S
  - usually pts are seen by PCP for normal checkups and initially there is a mild lymphocytosis and overall leukocytosis which is often ignored or attributed to some transient infectious process, only after several visit and climbing leukocytosis/lymphocytosis is CLL entertained
  - always must rule out (1) Infectious/Reactive Processes (eg virus, mono, pertussis, toxo, et al) which can give you a lymphocytosis by checking levels Qmo for 3mo and (2) Non-CLL Neoplasms (eg SLL, Mantle Cell, Hairy Cell, et al) by flow cytometery
  - can be asymptomatic w/ dx on PBS or pts can have classic "B" symptoms and LAD
  - Well's Syndrome (hypersensitivity to bees stings)
  - AIHI or ITP (paradoxic b/c there is hypogammaglobulinemia)
  - Hypogammagloblulinemia w/ increased infections
  - increased incidence of lung/skin cancer
- Complications
  - Richter's Syndrome (5%) occurs when there is isolated LN transformation into DLBCL and sudden clinical deterioration w/ more LAD and B-Sx
- Dx
  - Smear: lymphocytosis (>10k/µL with nl <2.5/µL) with most being mature appearing while others being smudge cells b/c lymphocytes are delicate and thus susceptible to mechanical disruption from making smear

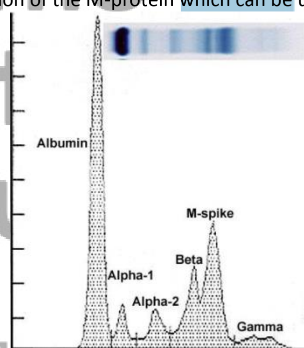
  - BMx: normal or 30% have infiltration w /B-cells
- Unique Type
  - **Hairy Cell Leukemia** (rare, seen in old males, mycobacterial infection + pancytopenia + very large SM + dry fibrotic aspirate w/ + TRAP stain)
- Tx

Rai Staging System		Binet Staging System		Median Survival	Tx
0	Lymphocytosis	A	≤2 Lymphoid areas involved	~10-13yrs	NO treatment just follow pt b/c no cure b/c indolent course, pts typically live a long time and die from other causes, NB also consider Tx if recurrent infections, Dz Related Sx, doubling time <1yr, >300k, young age, etc
I	+ LAD	B	>3	~7-8yrs	
II	+ HSM				
III	+ anemia (<33) not AIHA rather 2/2 BM involvement	C	Anemia or Thrombocytopenia	~1-3yrs	• Chemo: Alkylating Agent (cyclophosphamide-C, et al), Nucleoside Analogue (fludarabine-F, pentostatin-P, et al), MAB (Rituxan-R) usually FR, FC, FCR, PCR, etc • Steroids if AIHA/ITP • Anti-CD (rituxamb = anti-CD20, alemtuzumab = anti-CD52, et al) • Radiation if symptoms due to mass effect of lymphoid tissue • IVIG if infection and IgG <0.3g/dL • HSCT
IV	+ thrombocytopenia (<100) not ITP rather 2/2 BM involvement				

Plasma Cell Dyscrasias aka Monoclonal Gamma-opathies aka Paraproteinemias

- Definition
  - Plasma Cell Neoplasm in BM producing monoclonal Ig (either or both or neither light/heavy chains)
    - +SPEP/-UPEP (are not filtered by kidney and thus collect in blood)
      - 60% IgG
      - 17% IgA
      - 13% IgM
      - 2% Biclonal
      - 0.5% IgD
      - Rare IgE
    - -SPEP/+UPEP (are filtered by kidney and thus collect in urine and light chains are called "Bence Jones" proteins)
      - 5% Only Light Chains (kappa/lambda)

    - -SPEP/-UPEP
        - 5% Non-Secretors
- Epidemiology
    - 15k cases/yr (1% of all cancers), 10k deaths/yr (2% of all cancer deaths) pretty high mortality
    - ~70yo, African American, Female
    - RFs: unclear but there are associations w/ low income, radiation, diesel/gas/oil, farmers, miners, sheet metal workers, lumberers (NOT smoking)
- S/S
    - Primary (due to the presence of the actual neoplasm in BM)
        - **BM**: pancytopenia due to BM replacement aka myelophthisis, seen on MRI as reduced BM fat
    - Secondary (due to secretion of monoclonal paraprotein, etc)
        - **Bone**: multiple "punched out" lytic lesions in calvarium, vertebra, long bones due to osteoclastic activating and osteoblastic inhibitory factors secreted by neoplastic plasma cell onto overlying bone resulting in ostalgia/fractures (long bones), back pain/vertebral collapse/cord compression (vertebra), and diffuse osteoporosis, not osteoblastic hence bone scans not helpful rather look for lytic bone lesions on plain radiographic skeletal survey
        - **CNS:** various neurologic disease due to hypercalcemia, spinal cord or cranial nerve compression from plasmacytomas, et al
        - **Renal:** A/CKD due to formation of proteinaceous casts of filtered light chains (Bence Jones proteins) in interstitium causing RTA2 and nephrotic syndrome aka "myeloma kidney", metastatic calcification due to hypercalcemia/calciuria, urate nephropathy, type I cryoglobulinemia, renal plasmacytoma, recurrent pyelo, et al
        - **ID:** recurrent infections esp encapsulated bugs due to suppressed normal Ig production (most common cause of death usually pyelo or pulmonary)
        - Other: Rouleaux formation (Ig stimulates RBC to aggregate together forming a "stack of poker chips), coagulopathy (unknown but not clinically significant), amyloidosis (not clinically significant), low quantitative immunoglobulins, low AG
- Diagnosis
    - Serum/Urine Protein Electrophoresis (S/UPEP): only shows you that there is a monoclonal "M" spike in the gamma section, also gives you a crude quantification of the M-protein which can be used to monitor disease



    - Serum/Urine Immunofixation (S/UIF): actually identifies and quantifies the type of Ig that makes up the "M" spike (eg. 5g/dL of IgG) you can also order "Quantitative Immunoglobulin" to asses levels of the normal immunoglobulins
    - "Free Light Chain Assay": new test which is more sensitive than above thus able to diagnose non-secretors as oligosecretors
- Types
    - **Monoclonal Gamma-opathy of Unknown Significance (M-GUS)**
        - Mod BM Bx Clonal Plasma Cell (<10%)
        - Mod M-Protein (<3g/dL)
        - No Evidence of Organ Damage
        - NB prevalence ~3% in >50yo population, ~5% in >70yo population, ~7% in >85yo population, **~1%/yr** or ~10% in 10yrs or ~20% in 20yrs convert to Smoldering MM, WM, amyloidosis, or malignant lymphoproliferative disorder (**[paraprotein]** with 0.5 (low) vs 3.0 (high) is the most imp RF for conversion) therefore f/u w/ SPEP in 6mo and Qyr thereafter
    - **Smoldering Multiple Myeloma (MM)**
        - High BM Bx Clonal Plasma Cell (>10%)
        - High M-Protein (>3g/dL)
        - No Evidence of Organ Damage
        - NB **~2%/yr** convert to Symptomatic MM
    - **Symptomatic Multiple Myeloma (MM)**
        - High BM Bx Clonal Plasma Cell (>10%)
        - High M-Protein (>3g/dL)
        - Evidence of Organ Damage
    - **Solitary Plasmocytoma**
        - a distinct collection of plasma cells without significant BM involvement (<5%) usually found in the UR or GI tract
    - **POEMS** (Polyneuropathy, Organomegaly, Endocrinopathy, M protein, Skin changes)

- **Plasma Cell Leukemia**
  - plasma cell count >2000/mcL
- **Lymphoplasmacytic Lymphoma aka Waldenstrom's Macroglobulinemia**
  - Definition
    - Acts more like a low-grade NHL (lymphoplasmacytic lymphoma) that secretes IgM than a true plasma cell dyscrasia
      - 90% IgM
      - 5% IgA
      - 5% IgG
  - Diagnosis
    - High BM Bx Clonal Plasma Cell (>10%)
    - High M-Protein specifically IgM (>3g/dL)
    - Specific/Unique evidence of organ damage
      - YES BM
      - NO Bone
      - NO CNS
      - NO Renal
      - NO ID
      - Other
        - **Hyperviscosity Syndrome**: b/c IgM is big it can increase blood viscosity
          - S/S: visual impairment w/ "sausage" veins on fundoscopy, headache, dizziness, AMS, CHF, pulmonary infiltrates, mucosal bleeding due to abnormalities in plt fxn, Type I cyroglobulinemia
          - Dx: relative serum viscosity of >5 (relative serum viscosity defined as the ratio of viscosity of serum to H_2O w/ normal being 1.8)
          - Tx: requires emergency plasmapharesis
        - **HSM/LAD**: not typically seen in MM
        - **Peripheral Neuropathy**: IgM deposits against myelin-associated glycoprotein
  - Treatment
    - treated more like a lymphoma than MM

- Prognosis
  - Labs: refer below but it has been found that increased beta2-microglobulin is the MOST important poor prognostic factor
    - Beta2-microglobulin is a transmembrane glycoprotein that sheds from surface membranes
  - Cytogenetics: k-RAS, aneuploidy, del13q, t(4:14 or 14:16) (poor prognosis)

International Staging System (ISS)
(the current staging system but newer ones are being developed which incorporate cytogenetics)

Stage	beta2-microglobulin (mg/L)	Albumin (g/dL)	Survival
I	<3.5	>3.5	62mo
II	3.6-5.4	<3.5	44mo
III	>5.5	Any	29mo

Durie-Salmon Staging System
(used less after the emergence of the ISS, also fails to incorporate renal function or cytogenetics)

Stage	Criteria	Survival
I	Hb ≥10g/dL Ca ≤12mg/dL ≤1 Lytic Bone Lesions IgG ≤5g/dL or IgA ≤3g/dL or Urine Light Chain ≤4g/d	61mo
II	Hb 8.5-10g/dL Ca 12mg/dL 1-5 Lytic Bone Lesions IgG 5-7g/dL or IgA 3-5g/dL or Urine Light Chain 4-12g/d	55mo
III	Hb ≤8.5g/dL Ca ≥12mg/dL ≥5 Lytic Bone Lesions IgG ≥7g/dL or IgA ≥5g/dL or Urine Light Chain ≥12g/d Cr <2mg/dL then Stage IIIA vs ≥2mg/dL then Stage IIIB	30mo (Stage IIIA) 15mo (Stage IIIB)

- Treatment
  - MGUS / Smoldering MM
    - no Tx as studies show that early Tx does not improve survival
  - Symptomatic MM

- General: 4 cycles of various regimens of chemo (usually all three below) then HSCT (can be done in <1/2 of pts) w/ subsequent chemo, assess response by following M-protein level and BM, relapse is common and when it occurs use a different chemo regimen, in general MM is incurable but good remissions can be achieved
- Adjuvant
    - Bisphosphonates/Ortho Surgery/Analgesics for bone pain
    - Local radiation for symptomatic plasmacytomas
    - Plasmapharesis for hyperviscosity syndrome
    - IVIG for recurrent infections
    - Hydration, etc for hypercalcemia
    - Erythropoietin for anemia
- Chemo
    - Angiogenesis Inhibitors: lenalidomide (Revlimid)
        - Mech: these drugs used to be used as anti-emetics in pregnant women but was found to cause significant limb deformities in fetuses b/c of anti-angiogenic effects, it was theorized that it would be helpful in treating cancer b/c tumors require new vessels for survival
        - SEs:
        - NB thalidomide (Thalomid) was the first drug created but has many SEs
    - Proteasome Inhibitors: bortezomib (Velcade)
        - Mech: proteasomes normally "eat" up proteins in cells hence their effectiveness in a paraproteinemia
        - SEs: peripheral neuropathy
    - Steroids
    - Old: melphalan (Alkeran)

Lymphoma

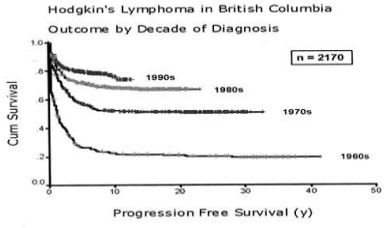
- Lymphoma (solid tumor of lymphocytes involving LNs, spleen, etc) vs leukemia (liquid tumor of lymphocytes involving blood and BM) but in general each has a component of the other
- NB WHO has recently modified the Revised European and American Lymphoma (REAL) Classification dividing lymphomas into (1) B-cell lymphomas (80%) (2) T/NK- cell lymphomas (10%) (much more aggressive than B-cell, worse prognosis, involve skin, usually require HSCT) (3) Hodgkin's lymphomas

	Hodgkin's Lymphoma (HL)	**NON-Hodgkin's Lymphoma (NHL)**
Epidemiology	• Incidence: 7,800/yr • M>F (except Nodular Sclerosis Type) • Bimodal Age Distribution (20s and >50) much worse the older the patient • Despite all of our advances we still do not know the etiology of HL	• Incidence: 66,000/yr • M=F (except Mantle Cell) • Unimodal Age Distribution (>50yo)
Pathology	LN • Other Cells: Inflammatory Milieu w/ Lymphocytes, Eosinophils, Plasma Cells, etc that spills over into blood (majority) • Neoplastic Cell: Reed-Sternberg (RS) Cells (minority) ○ non-neoplastic cells outnumber neoplastic cells ○ *** severity ∝ RS cells ∝ 1/lymphocytes *** ○ Diagnostic feature of HL ○ giant cells with bilobed nucleus w/ prominent eosinophilic nucleoli w/ surrounding clear space called "owl's eyes" ○ arise from B-cells (2% T-cells) but lack certain CD markers including 15, 30, 70	LN • Neoplastic Cells (majority) ○ neoplastic cells outnumber non-neoplastic cells ○ >85% B Cells • Other Cells: ? (minority)

Signs/Symptoms Lymphadenopathy • Reactive/-itis: <2cm, TTP, soft, mobile, cervical/axillary/inguinal, <40yo, lasting <4wks, benign context, viral (HIV, EBV, CMV, HSV, VZV, Hepatitis, Measles, Rubella), bacteria (staph, strept, various atypicals), fungi, parasites, infiltration (amyloid, sarcoid) • Neoplasm: >2cm, non tender unless massive, hard, fixed, supraclavicular is always abnl, >40yo, lasting >4wks, worrisome context, leukemia/lymphoma, mets • NB do not empirically give abx to see if reactive vs malignant	• LAD: superficial and regional (usually cervical/supraclavicular and occasionally mediastinal) begins at a single group of LNs and then spreads with orderly, anatomic spread to contiguous adjacent LNs with rare extranodal involvement but if it is it is usually mediastinum, lung, liver, bone, BM • S/S: B Symptoms (F>38C w/o evidence of infection that is often called Pel-Epstein Cyclic Fever, drenching night sweats, weight loss >10% of body weight the past 6 months, can be seen in other cancers but classically associated w/ HL), Pruritus, LNs hurt following EtOH, Cough, Dyspnea, Hoarseness, SVC Syndrome, eventually spreads to BM w/ leukemic Sx	• LAD: deep and generalized (usually intraabdominal) begins at many LNs all at once and spreads to other distant LNs in addition to extranodal involvement most commonly GI, skin, thyroid, breast • S/S: B Symptoms are less common, Extreme Fatigue, Waldeyer's Ring (oropharyngeal LAD), Testicular Enlargement, HSM, Ab Fullness, Coomb's + autoimmune cytopenias, agammglobulinemia, eventually spreads to BM w/ leukemic Sx
Prognosis	If not treated then <5% live after 5yrs with most dead at 3yrs BUT if treated regardless of type and stage 80% can be cured RFs: EBV	RFs: Post-Transplant LPDs (PTLPDs) • 5% of pts w/ solid organ transplants • Highest risk during first year • EBV+ • Often more aggressive than nl lymphomas • Tx: lower degree of immunosuppression allowing pts own immune system to attack EBV and if this doesn't work then Tx w/ chemo HIV • Often more aggressive than nl lymphomas • HIV imparts 60-100x increased r/o NHL • NHL is considered an AIDS defining malignancy • Concurrent HARRT and chemo likely provides additional benefit • 67% DLBCL, 20% American Burkitt's, 16% Primary CNS Lymphoma, 5% Primary Effusion Lymphoma (HHV-8), etc EBV (HL, African Burkitt's, etc) HCV (Waldenstrom's Macroglobulinemia, Nodal Margin/Splenic Zone B-Cell Lymphoma, etc) H. pylori (Gastric MALT Lymphoma) Sjogren's

<table>
<tr><td>Staging</td><td colspan="2">New: Ann Arbor Staging System w/ Cotswolds Modifications
NB mainly used for HL not so much NHL b/c most are automatically generalized

Stage 1: 1 LN group (aka contiguous = LNs side by side) OR extra-lymphatic organ (except liver or BM)
Stage 2: ≥2 LN groups (aka non-contiguous) OR extra-lymphatic organs on same side of diaphragm
Stage 3: >2 LN groups (aka non-contiguous) OR extra-lymphatic organs on both sides of diaphragm
Stage 4: extranodal tissue including liver and BM
• x = bulky disease where greatest diameter of mediastinal mass / max diameter of chest wall is >1/3 OR greatest diameter of ab mass is >10cm
• A = no B symptoms vs B = any B symptoms (worse prognosis)
• E = involves a single contiguous extranodal site (pts can have for example Stage IE where only 1 LN group is involved but they also extranodal tissue involvement, in this case they are not automatically Stage IV)
• H = hepatic involvement
• S = splenic involvement
• Eg. Stage IIxAEHS

Old: Staging Laparotomy
• where you perform liver resection biopsy, splenectomy, periaortic LN dissection, and iliac crest BM biopsy
• rarely performed these days
• mortality of 1.5% and morbidity of 6% w/ abscesses, obstruction, etc</td></tr>
<tr><td>Tx</td><td>• Stage I/II and NO RFs 2cycles of ABVD (some just do IFRT if small)
• Stage I/II and YES RFs: 4 cycles of ABVD + RT
• Stage III/IV: 8 cycles of ABVD or BEACOPP/StanfordV + RT
• Refractory/Relapsed: HSCT
• RFs: >50yo, B Sx, high ESR, bulky dz, E stage
• ABVD (Adriamycin aka doxorubicin + Bleomycin + Vinblastine + Dacarbazine) each cycle takes 4d, can be done outpt, 2-3wks b/t cycles
• Other: Stanford V (Doxorubicine + Bleomycin + Vinblastine but NO Dacarbazine rather Cyclophosphamide + Vincristine + Procarbazine + Prednisone), BEACOPP (Bleomycin + Etoposide + Adriamycin aka doxorubicin + Cyclophosphamide + Vincristine + Procarbazine + Prednisone)
• some just do chemo alone given the long term toxicity of RT and while there is slightly worse disease free state overall survival time is the same
• NB MOPP used to be the original chemo but is no longer used
• IFRT (Involved Field Radiotherapy)
• NB historically RT was “Mantel Field” (cervical, supraclavicular, mediastinal, axillary) and “Inverted Y Field (peri-aortic, spleen, iliac, inguinal, femoral) (developed at Stanford) but there was high (1%/yr) r/o solid tumors and hypoTH, MI, breast cancer
• now wide RT is used for bulky disease (>10cm)
• NB pts are at increased risk for second malignancies: AL, NHL, Lung Cancer, Breast Cancer (1% lifetime) along w/ infertility and hypothyroidism
 
</td><td>Stage I (rare)
Stage II (rare)
Stage III: (rare)
Stage IV: (almost all)
• Hence treatment is based on histopathologic classification (indolent vs aggressive vs very aggressive) NOT stage b/c almost all are already Stage IV
• In general XRT is not helpful b/c the disease is usually so diffuse
• Indolent: goal is symptom management w/ IFRT for bulky disease, transfusions for cytopenias, etc, some use single chemo agents (purine nucleoside analogues, oral alkylating agents, rituximab, radio-labeled monoclonal antibodies), others just leave it alone b/c they are so slow growing, watch for FL to transform into DLBCL
• Aggressive: R ± CHOP (Cyclophosphamide + Hydroxydaunorubicin aka doxorubicin + Oncovorin aka vincristine + Prednisone) add Rituximab if CD20+ (NB also add RT for bulky disease) add methotrexate if CNS, paranasal sinus, testicular, breast, periorbital, paravertebral or BM involvement, NB prednisone is lympholytic and many times are already on partial Tx b/c they are often on steroids for other reasons
• Very Aggressive: CODOX-M ± R (Cyclophosphamide + Oncovorin aka vincristine + DOXorubicin + Methotrexate) add Rituximab if CD20+, add IVAC (Ifosfamide + Etopoisde? + ? + Cytarabine) if high risk (high LDH and multifocal dz or single but >10cm), all pts get CNS prophylaxis, lymphoblastic leukemias treat like ALL, following remission the HSCT, watch for TLS
• Relapsed Disease: Salvage High Dose Chemo ± HSCT</td></tr>
</table>

Prognosis	IPS (International Prognostic Score) • Albumin <4 g/dL • Hb <10.5 g/dL • Male • Age >45yo • Stage IV • WBC >15k/mcL • Lymph <600/mcL or <8% • 0,1,2,3,4,≥5 = 84,77,67,60,51,42% 5yr survival rate	IPI (International Prognostic Index) • Age >60yo • Stage III/IV • ECOG Performance Status >2 • ≥2 extranodal areas • LDH >ULN • Tumor Burden (systemic Sx, >3LNs >3cm, >1LN >7cm, Plt <100k, etc) • 1,2,3,≥4 = 87,67,55,44% 5yr survival rate
Work-Up	Immunophenotyping and Cytogenetics: Leukemia & Lymphoma Panel Pathology: FNA (rarely done b/c you need histology but sometimes you can't help it if the only LN is hard to get to like retroperitoneal and avoid incisional b/c just better for pathology if they have the whole LN) → Core → Excisional Bx and BM Bx but some argue not doing for Stage I/II HL (± LP if neuro symptoms, etc) • Bx if depending on your suspicion of a malignant LN • BM Bx + means metastatic disease and is highly prognostic for the presence of CNS disease Imaging: CT chest/ab/pelvis but not entirely sensitive therefore also get a PET scan (± MRI Head if neuro symptoms, ± Bone Scan if bony pain or elevated alkphos, etc) Labs: CBC, LFTs, Albumin, LDH, Uric Acid, Phos, Ca Serology: HIV, HB/CV, EBV and connective tissue disorders Flow Cytometry (tells you CD) FISH (tells you gene rearrangements) Do an LP for the aggressive lymphomas and if lymphomas already involve testicle, paranasal sinus, or eye NB lymphagiograms were the diagnostic test of choice in the past but they are no longer done b/c very difficult to do (you have to inject contrast in lymphatic vessels b/t toe webs which then travels up body lighting up all LNs thereby showing which ones were enlarged!!!) and PET/CT is much better	

HL (95%) • More curable w/ 95/65% cure rates if early/advanced	**Incidence**	**Patient**	**Characteristics**
Lymphocyte Depletion	<1%	>50yo Male	• many RS cells • few lymphocytes • diffuse fibrosis • typically retroperitoneal LNs • poor prognosis
Mixed Cellularity	20%	40yo Male	• many RS cells • few lymphocytes • many other cells including eosinophils, histiocytes, plasma cells (hence "Mixed Cellularity") • typically subdiaphragmatic LNs • moderate prognosis
Lymphocyte Predominance	5%	20yo Male	• few RS cells that are atypical called "popcorn cells" b/c they have B-Cell antigens and they look slightly different • many lymphocytes • best prognosis
Nodular Sclerosing	70%	20yo Female	• few RS that are atypical called "lacunar cells" b/c they have clear areas surrounding the cells • many lymphocytes • banding fibrosis creating nodules • typically mediastinal LNs

- NON-Classical HL (5%)
  - Nodular Lymphocyte Predominant (NLP)

NHL these are subsequently divided into indolent (slow/stable cancer, no symptoms, >40yo, advanced stage w/ widespread LAD and BM/liver/spleen involvement, typically incurable but not a big deal, Tx can be deferred until pt becomes symptomatic or when disease progresses, sometimes disease is spontaneously regresses, median survival is 10yrs) vs aggressive (fast/progressive cancer, w/ symptoms, any age, early stage w/ one organ/compartment involvement, chemo/radiation is necessary w/ 50% being cured quickly or 50% dyeing quickly) • Not sure what small vs large and cleaved vs non-cleaved means???	
Indolent Slow Growing but Incurable (35-40%) Survival (years if unTx) Low Grade	• **Follicular Lymphoma** (20%) mixed cleaved, 10% transform into DLBCL • **Small Lymphocytic Lymphoma** (SLL) (5%) (related to CLL, essentially SLL and CLL are one disease and the term that is used is essentially dependent on which tissue (blood or LN) was used to make the diagnosis) • **Various Marginal Zone Lymphomas** (5%) including primarily MALToma, etc, 2/2 chronic antigenic stimulation esp, GI(H.pylori)/Resp(?)/Mouth(?)/Spleen(HCV)

Aggressive
(50%)
Survival (months if unTx)
	• **Diffuse Large B Cell Lymphoma** (DLBCL) (30%)
	  ○ can transform from follicular lymphoma by acquiring t(14;18) resulting in over-expression of bcl-2 protein
	  ○ Richter's Transformation (from CLL/SLL) 10% risk, heralded by F, rapid LAD, rising LDH
	  ○ Life expectancy measured in months if unTx
	  ○ Almost all pts respond to Tx but nearly ½ will become refractory
	• **Various T-cell Lymphomas** (5%) including primarily Peripheral T-Cell Lymphoma Not Otherwise Characterized and Mycosis Fungoides and Sezary Syndrome (these are cutaneous lymphomas which form Pautrier microabscesses in the skin filled with neoplastic lymphocytes, seen in black males), etc
	• NB ALL HODGKIN'S LYMPHOMAS ARE CONSIDERED AGGRESSIVE

Very Aggressive Fast Growing
Curable
(5%)
Survival (weeks if unTx)
High Grade
	• **Burkitt's Lymphoma** (1% adult but 30% child classically <35yo M>F)
	  ○ Resulting from an activating translocation of the c-myc oncogene on chromosome 8 to a promoter t(8;14 or 2;8 or 8;22)
	  ○ Three different types: (1) Sporadic (USA/Europe) ab mass w/ -EBV (2) Endemic (Africa) jaw mass w/ +EBV (3) Immunodeficient (HIV) variable location
	  ○ Extends particularly to BM (35%), CNS (15%), mesentery, gonads, kidney, breast
	  ○ Very rapid tumor growth therefore high r/o TLS
	  ○ Histology: three unique features (1) "starry sky" reflecting macrophages phagocytizing apoptotic tumor cells (2) near 100% MIB-1 score which reflects mitotic activity (3) +c-myc stain
	  ○ No surgery or XRT b/c dz is usually diffuse
	• **Lymphoblastic** (LN involved form of ALL)
	• **Mantle Cell Lymphoma, Large Cell Immunoblastic** (rare)