Chronic Lymphocytic Leukaemia 4.02

Detailed History of Presenting Illness – Leukaemia in general

HPI:

- Fatigue
- Weakness
- Malaise
- Fever
- Nightsweats
- Weight loss
- Jaundice
- Lymphadenopathy
- Bone pain
- Excessive bruising
- Abdominal pain/swelling/"fullness"

PI:

- Frequent Infections
- Past Radio/Chemotherapy
- Past Cancers

Family/Social:

- Leucaemia
- Smoking
- Alcohol
- CURRENT MEDICATIONS

Patient's AGE speaks volumes:

- **The YOUNG get ALL**
- **The OLD get CLL + AML**
- **Everyone gets everything else**

!! IMPORTANT: get IMMUNISATION history !!

Differential Diagnoses (DDx)

- Chronic Infection
- Non-leukaemia cancer
- Hypersplenism
- Paraneoplastic GM-CSF production
- Lymphoma
- Anaemia
- Depression

Pertinent findings on Examination Leukaemia in General

Any Leukaemia

- Pallor or Jaundice
- **splenomegaly**
- **hepatomegaly**
- abdominal swelling.
- **Lymphadenopathy**

Advanced: Mets → Brain

- central nervous system effects:
- headaches
- seizures
- weakness
- blurred vision
- balance difficulties
- vomiting

AML Only

- swollen, painful, and bleeding gums - mets to the oral tissue;
- pigmented (colored) rash-like spots - mets to the skin; or
- **chloromas** (granulocytic sarcomas; collections of tumorous cells within the skin or other body parts)
- ecchymoses, epistaxis, or menorrhagia

The T-cell variety of (ALL) may cause the thymus to enlarge and press on the **trachea** or the **superior vena cava**.

Tests and Investigations: Making sense of weird blood counts

FBC:

1

Look Carefully. **Whats Different?** Are the…

→ **WBCs Absurdly high? →WHICH KIND?**

Is there a cytopenia? Which cells are missing?

High WBC is NOT DIAGNOSTIC

BLOOD FILM: SHOULD ALWAYS FOLLOW A SUSPICIOUS FBC

2

If the FBC is bizzarre, what do the cells look like?

! LOOK FOR TYPICAL CELL MORPHOLOGIES !

eg: **BLAST CELLS DON'T BELONG IN PERIPHERAL BLOOD**
then order BM biopsy, as the peripheral blood is often an inaccurate reflection of what is going on

A few stray smudge cells are NOT DIAGNOSTIC

Bone Marrow Biopsy:

3

- **looking for the extent of infiltration;**

keyword: "HOMOGENOUS HYPERCELLULARITY"

ASPIRATE: sucking a sample of bone marrow through a needle looking for **abnormality of individual cells**

TREPHINE: drilling a core sample of the bone marrow
Architecture is preserved: best for overview

Looking for: **Fat Spaces Replaced by Homogenous Cells**

Rough Guide: 20% of cells have to be neoplastic before you call it LEUCAEMIA (and if they are)

A marked bone marrow infiltration by an unrecognisable clone of homogenous uniform-looking cells is OBJECTIVELY DIAGNOSTIC

Lymph Node Biopsy: relevant if there is lymphadenopathy

BUT no bone marrow involvement (which makes one think of lymphoma)

Both LN and BM biopsies should be performed if lymphadenopathy is present

Immunophenotyping, Immunocytochemistry, Antigen-Expression Cytometry

4

- is the classification of cell types according to their immunologic characteristics.
- **keyword: "MONOCLONAL PROLIFERATION"**

Using CD markers it is possible to track down the origin of the rogue cells to a particular known subvariety of neoplasm

How? use PCR to look at Immunoglobulin and receptor proteins → then look at PCR bands.
Monoclonal= one band for whole population
Normal (polyclonal) = smeared wide band, reflecting a variety of phenotypes

This study is ALMOST DIAGNOSTIC
Cells clonally expanded for a fight with infection are as a rule **POLYCLONAL; thus a monoclonal swarm is highly distressing**

!!BUT!! → MONOCLONAL does NOT mean MALIGNANT!

Studies refer to *"transient monoclonal lymphocytosis"*, talking about the over 65 year olds
→ **"watchful waiting"** ensues if the number of monoclonal cells is below a threshold;
for B-CLL a lymphocyte count of 10,000/mm^3 was once required but today we are happy with 5000/ mm^3

Serum Biochemistry, LFTs, Urinalysis, UAC, etc ← Accessory studies

- Major role: looking for **haemolysis, liver and renal function**
- **(13% of CLL gets autoimmune hemolytic anaemia → !! COOMBS TESTS !!)**
- **Urine cultures** also looking for **INFECTION** which is waiting to go out of control

X-rays and Tomography

Imaging to see if there are

- **enlarged lymph nodes** in the chest,
- **a localized mass** in the lungs,
- or **evidence of spread** to the outer bones or joints.

USEFUL FOR STAGING

RULES OF THUMB:
ACUTE = immature (…blastic)
CHRONIC = mature (…cytic)

Imaging with Radionuclides

- **If malignacy is a certainty**, radionuclide studies help determine the extent of metastasis by marking tumour cells with a radioactive marker, thus singling out sites of abnormal hemopoiesis and metastatic involvement. SHOWS RADIATION ONCOLOGISTS+THERAPISTS WHAT TO SHOOT.

How is this diagnosis made ?→ Clinical Pictures, painted by blood and marrow tests

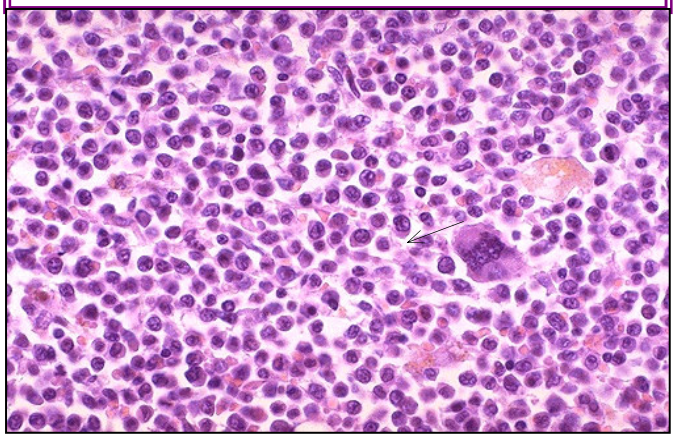
Acute	Chronic:
- Rapid onset symptoms - Severe marrow failure - (pancytopenia)	- Slow + progressive - Anaemia/cytopenia precedes by years - Marrow failure may never occur
Myeloid	**Lymphoid**
- **Granulomocytosis**	- **Lymphocytosis**

Acute Myeloid Leukaemia: *most common leukemia in children less than 1 year of second peak of incidence occurs among adults 40 years of age: Most common acute L. of adults !!*

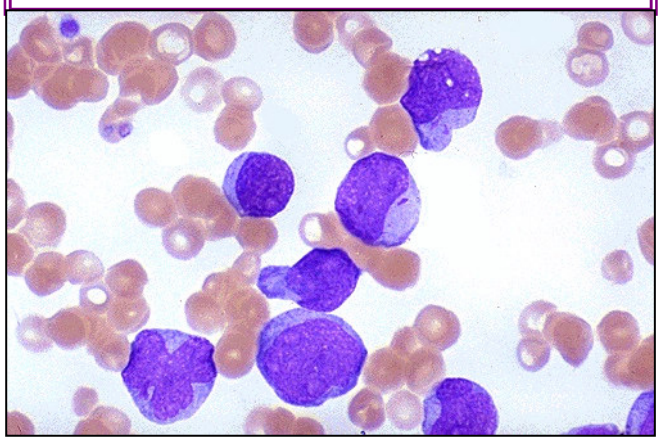
WBCS high but not always
Hemoglobin + latelets LOW
Blast Cells on Film
Marrow heavily infiltrated with **blasts**

Enlarged spleen is seen in 50% of all AML
BUT lymphandenopathy is Rare

At high power, the bone marrow of a patient with acute myelogenous leukemia is seen here. There is one lone megakaryocyte at the right center.



Here are very large, immature myeloblasts with many nucleoli. A distincitve feature of these blasts is a linear purple "Auer rod" (**arrow)** composed of crystallized granules. These findings are typical for acute myelogenous leukemia (AML) that is most prevalent in young adults.



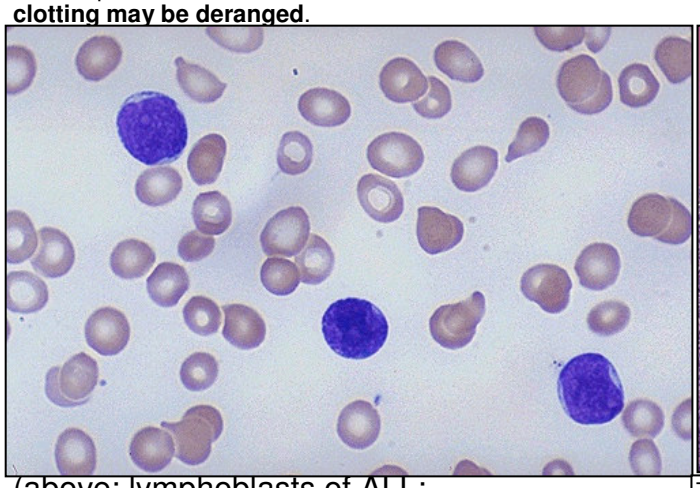
Myeloblasts of AML have
- **Little cytoplasm**
- **MASSIVE nuclei** with prominent nucleoli
- Dispersed nuclear chromatin

Auer rods are elongated, bluish-red rods composed of fused lysosomal granules.
Seen an AUER ROD → its AML FOR SURE.

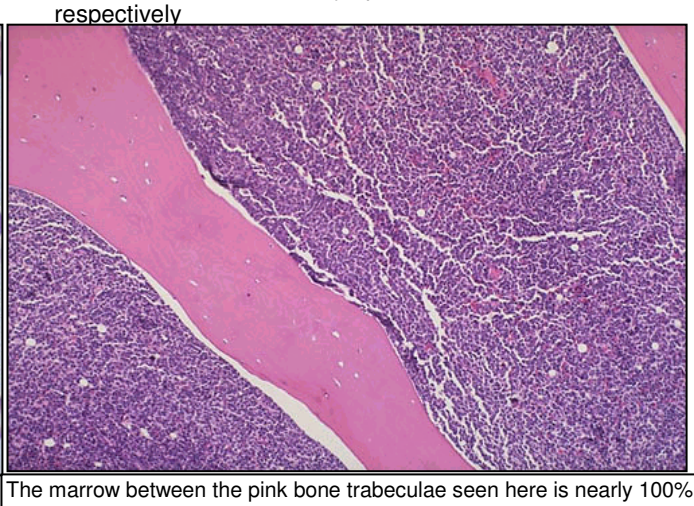
Acute Lymphoblastic Leukaemia *usually strikes children between the ages of 2 to 10. A second peak in incidence is seen in elderly patients*

FBC:
Total **WCC usually high** but May be low ("aleukaemic leukemia")
blast cells on film
Hb and platelets often low
clotting may be deranged.

Bone marrow (BM) heavily infiltrated with blasts- **immunophenotyping and karyotyping is needed on blood and marrow.**
Chest x-ray and CT needed if B or T cell phenotype for abdominal or mediastinal lymph nodes respectively



(above: lymphoblasts of ALL; almost no cytoplasm)



The marrow between the pink bone trabeculae seen here is nearly 100% cellular, and it consists of leukemic cells of acute lymphocytic leukemia (ALL) that have virtually replaced or suppressed normal hematopoiesis.

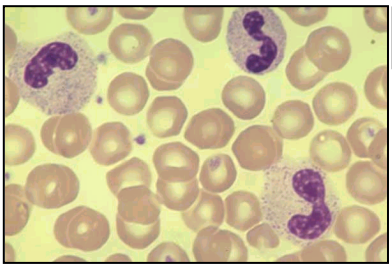
Chronic Myelogenous Leukaemia

Peak Incidence at ages 30 to 50 years old

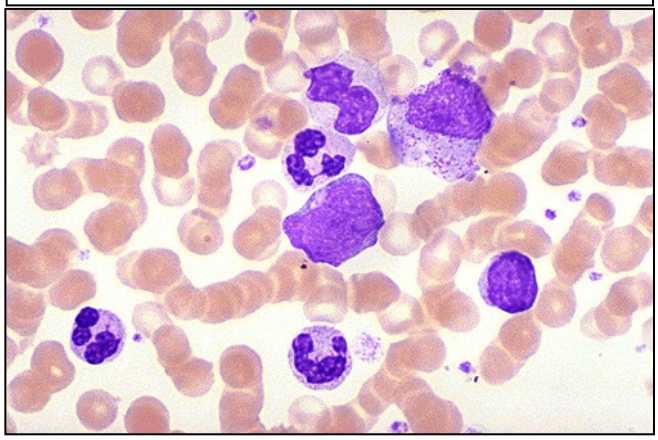
FBC: Increased WCC (**mainly neutrophils and myelocytes plus excess basophils and eosinophils)**
Platelets may be raised and clumped.
ESR low in absence of secondary infection.
LDH and urate levels increased.
BM- gross hypercellularity

Philadelphia chromosome +ve on chromosomal analysis
Blast count rises with blast crisis transition.
There is usually massive spleen enlargement

A peripheral blood smear in a patient with CML. Often, the numbers of basophils and eosinophils, as well as bands and more immature myeloid cells (metamyelocytes and myelocytes) are increased. Unlike AML, there are not many blasts with CML. There are numerous granulocytic forms seen here, including immature myeloid cells and band neutrophils. A useful test to help distinguish this disease is the leukocyte **alkaline phosphatase (LAP) score, which should be low with CML** and high with a leukemoid reaction to infection



← *band neutrophils*



Chronic phase (Mild, indolent course)
1. Excessive Granulocyte (Neutrophils) proliferation

Blastic phase (Malignant, leukemic course)
2. Increased blasts and Promyelocytes

Chronic Lymphocytic Leukaemia *is the most common type of leukemia*

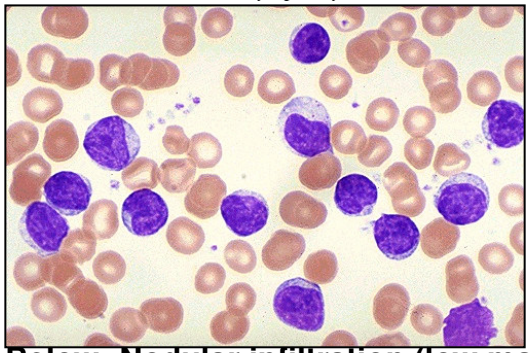
usually occurs in older patients; it is rare in patients less than 40 years of age.

FBC: Lymphocytosis > 5 x 10^9 /L with mature appearance **← 90% of the time its B-cell dominant**
(a % of cells more friable leads to **smear cells**- a mutation of actin and spectrin)
anaemia, thrombocytopenia + neutropenia usually absent in early stage CLL;
autoimmune haemolysis +/- thrombocytopenia can occur at any stage.

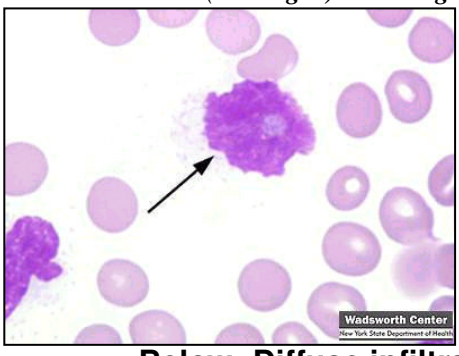
!!SMUDGE CELLS!!
= pathognomic for CLL

Bone Marrow- lymphocytosis >25% with **characteristic immunophenotypic marker pattern.**
Trephine biospy - infiltration prognositically informative: nodular (faviourable) or diffuse (unfavourable)

***BELOW**: These mature lymphocytes are increased markedly in number.*

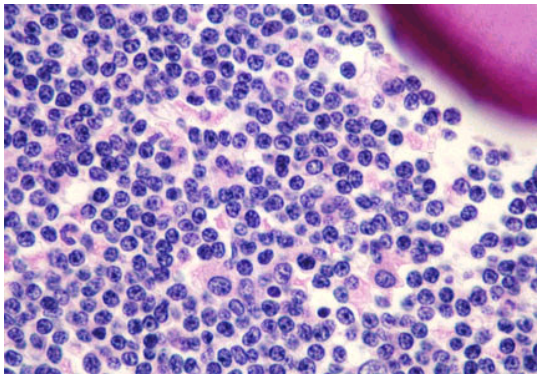


BELOW: a smear ("smudge") cell at high magX



Below: Nodular infiltration (low mag)

Below: Diffuse infiltration



PROGRESSION of CLL = NEWLY DISCOVERED- MOST COMMONLY DETECTED ON ROUTINE BLOOD TEST (or sometimes a painlessly swollen node)

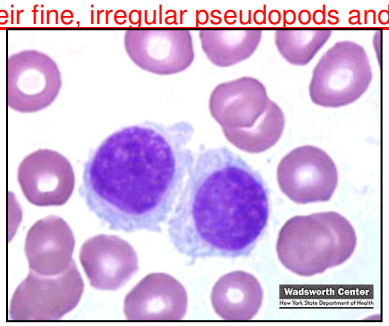
- organomegaly,
- pancytopenia,
- anaemia,
- lymphadenopathy

ASSORTED HEMATOLOGICAL NEOPLASTIC CONDITIONS:

Large granular lymphocyte leukaemia:

Hb and platelets normal,
mild anaemia may be present.
Mild - mod lymphocytosis with large cells (abundant cytoplasm and distinct granules)

Hairy cell leukaemia: Hairy cells are characterized by their fine, irregular pseudopods and immature nuclear features. ***They are seen only in hairy cell leukemia.*** →
pancytopenia (mod-severe),
circulating **'hairy cells'** in low numbers
(kidney shaped nuclei, clear cytoplasm
and irreg cytoplasmic projections),
neutropenia <1 x 10 9/L, monocytopenia usual.
BM biopsy often unsuccessful as 'dry tap'
due to increased myelofibrosis



Non Hodgkins lymphoma

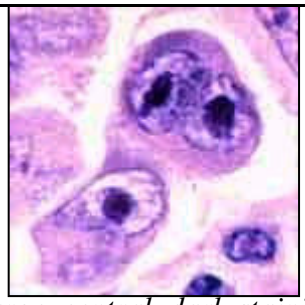
normocytic normochromic anaemia common,
lecoerythroblastic film with BM infiltration +/- pancytopenia,
occasional hypersplenism,
LFTs abnormal in hepatic infiltration
Film may show lymphoma cells
(cleaved buttock cells in follicular lympoma
and blasts in high grade disease),
serum LDH useful in prognosis

DIFFERENCE BETWEEN HODGKINS AND NON-HODGKINS

Hodgkins= T cell	Non-Hodgkins= B cell
Localised process	Systemic
Neoplastic cells <1% of mass Most of mass = inflammatory exudate stimulated by cytokines	Most of mass = neoplastic lymphoid cells
significant marrow involvement	Almost nil marrow involvement
prone to viral infection (+ myco, fungal, protozoan)	prone to bacterial infection

Hodgkins:

painless supradiagphragmatic lymph node enlargement,
FBC may be normocytic, normochromic anaemia,
reactive leucocytosis,
eosinophilia and /or reactive mild thrombocytosis.
BM may be reactive.
Serum ALP may be increased
non specifically or in assoc with bone or liver involvement, increased LDH
indicator of bulky disease



Reed-Sternberg cells: PATHOGNOMIC for H's L → → → → →
a bizarre, gigantic cell with more than one large nuclei, each enclosing a large, central, dark-staining nucleolus with clear space around it

summary of abnormalities that can be seen in FBCs and blood films

Recovering bone marrow following chemotherapy; ,patient may show symptoms of a viral infection etc, low WCC, myelocytes and metamyelocytes, normal RBC and platelets.
Reactive Film or Features - features suggesting that the observed changes are secondary to an external process and not due to a primary haematological disorder. Includes 9eft shift, reactive lymphocytes, toxic features
Left Shift - presence of immature neutrophil precursors. A "mild" left shift with the presence of "band or stab" forms and occasional myelocytes , often accompanied by toxic granulation, is a common consequence of sepsis. A more pronounced left shift, eg with promyelocytes and or blasts are more likely to denote a leucocrythroblastic blood film or leukaemia.
Toxic Changes - characteristic of bacterial infection. Can include the following; heavy dark staining granules (=toxic granulation), vacuolation, Dohle bodies (cytoplasmic RNA)
Megaloblastic Film or Features - the presence of larger red (macrocytosis) and white cells. The neutrophils may demonstrate nuclear hypersegmentation (right shift)
Reactive Lymphocytes – atypical cellular forms classically seen in viral infections (eg EBV). Distinguish from lymphoblasts.
Leukaemoid Reaction - reactive and excessive leucocytosis usually characterised by the presence of immature cells (blasts, promyelocytes, myelocytes) in the peripheral blood. Associated disorders - chronic infections. severe haemolysis and metastatic cancers. Needs to be distinguished from true leukaemia
Pancytopenia- anaemia, leucopenia and thrombocytopenia.
Blasts/Blast Cells - the most primitive recognisable haemopoietic precursor cell recognisable by light microscopy. Typically have large nuclei with little cytoplasm (high nuclear:cytoplasmic ratio) and nucleoli - Myeloblasts/Monoblasts/Lymphoblasts
Leucoerythroblastic Film or Feature - the constellation of features that suggests marrow infiltration or replacement. Defined as the presence of immature white cells, immature (nucleated) red cells and Poikiloocytosis characterised by fragmented cells and tear drop forms. Megakaryocyte fragment may also be present and there are often 1-3 cytopenias. (see myeloproliferative film)

Circulating Plasma Cells - rarely seen in normals. Present in plasma cell leukaemia (>2x10?/1) and to a lesser extent myeloma and other lymphoproliferative diseases. Also occasionally seen in reactive states.
Circulating Lymphoma Cells - abnormal lymphoid cells seen in the blood of patients with lymphoporliferative diseases (also called "blood spill")
Smear/Smudge Cells - characteristic of chronic lymphocytic leukaemia. Bare and smeared nulclei that have been damaged in the process of film spreading.
Mveloproliferative Film or Features - those that suggest the presence of an underlying (chronic) myeloproliferative disease or disorder. May include; thrombocytosis, and large platelets. neutrophilia and left shit in neutrophil lineage, eosinophilia, basophilia,,and red cell changes such as tear drop poikilocytes and circulating nucleated red blood cells. Frequently have leucocrythroblastic characters.

Staging:

Stage	Description
0	Absolute lymphocytosis >$15*10^9$
I	0 + enlarged lymph nodes (adenopathy)
II	0 + enlarged liver and/or spleen +- adenopathy
III	0 + anaemia +- adenopathy +- organomegaly
IV	0 + thrombocytopenia (platelets <$100*10^9$/l) +- adenopathy +- organomegaly

Disease Definition of CLL: neoplasm of monoclonal B cells

Management of CLL:

Contrary to popular belief, MOST ILLNESSES HAVE NO CURE.

→ **NO CURE:** same lifespan, treatment or not

CURABLE	INCURABLE
AML + ALL	CLL
CML	Indolent non Hodgkins lymphoma (sometimes called low grade)
Large cell non Hodgkins lymphoma	
Hodgkins lymphoma	

CURABLE:

Means that

- **intensive chemo IMMEDIATELY FOLLOWING DIAGNOSIS has positive effect** (while the patient is still healthy and the cells are not resistant)

INCURABLE:

FOR THE INCURABLES, intensive chemo means a **slightly longer remission**

BUT!! Recurring disease will be MORE AGGRESSIVE

Thus, patients will still die at the same rate no matter the treatment:

THEREFORE : give

- **single chemo drugs orally to control symptoms**
- **radiation to affected sites**
- **watchful waiting**

EVENTUALLY the disease will become resistant to this half-assed treatment and thus **AGGRESSIVE CHEMO WILL BECOME NECESSARY IN THE END.**

CHEMOTHERAPY:

If its being administered to CLL, its

- Usually **ORAL**
- Usually **ALKYLATING AGENTS:**

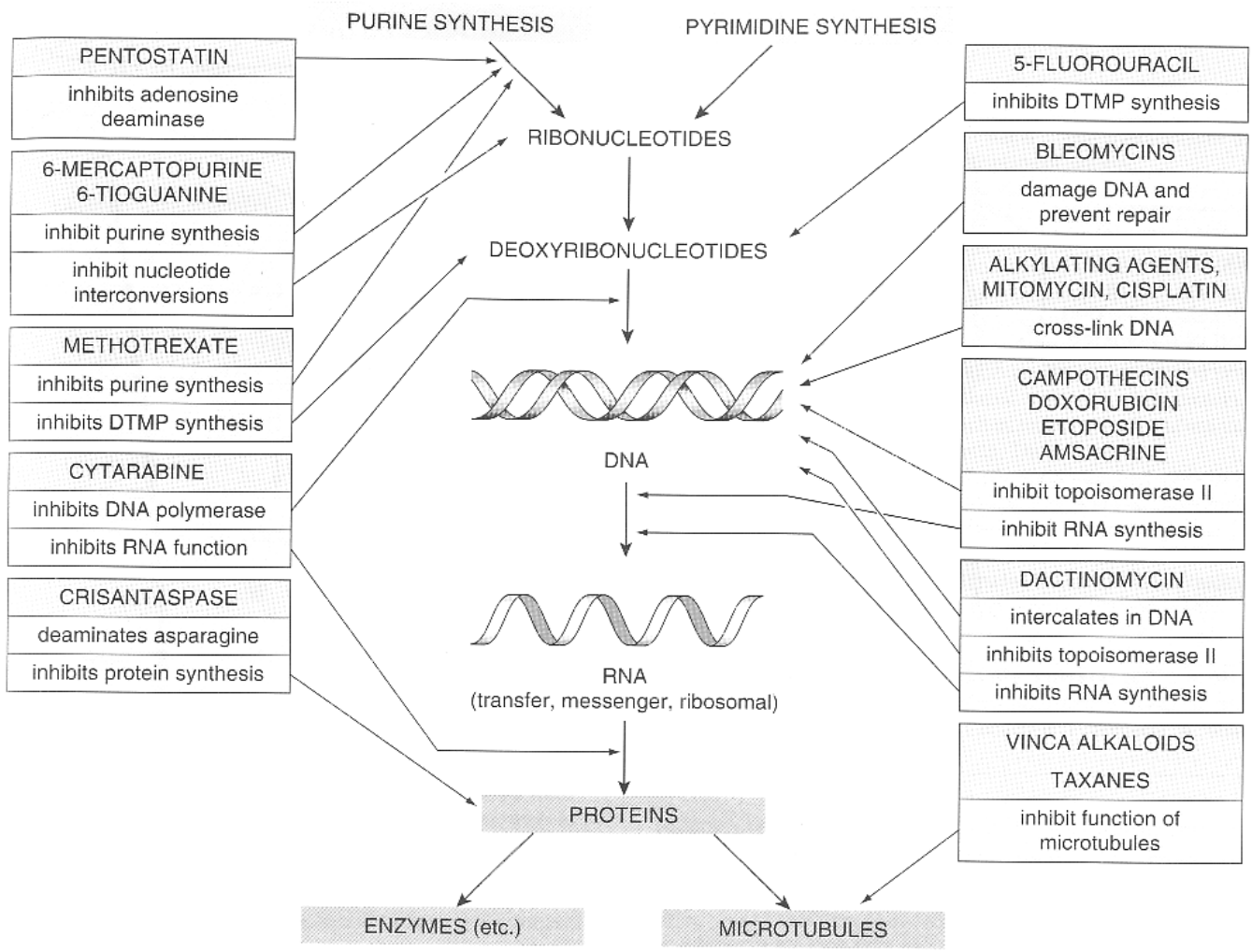
  Disrupt DNA synthesis by covalently bonding to **nucleophilic sites**
  eg guanine therefore → cross-linking
  THUS apoptosis occurs

  - **EXAMPLES:**
    - NITROGEN MUSTARDS
      - Cyclophosphamide
      - Chlorambucil
      - Melphalan
      - Cisplatin
      - Carboplatin

Avoid QOL-bolloxing side effects- its already shit enough.

CHEMO IS MYELOSUPPRESSIVE therefore ➔ pancytopenia; therefore ➔ infection

Consider antiviral and antibacterial drugs- **infection is often FATAL.**



Chemo: QOL is main aim;
Pre-Chemo: counselling, dentist, fertility (sperm/ova donation)
During Chemo: Antiemetics, Benzos
Post Chemo: Antiemetics, laxative, Benzos, sometimes subcutaneous GM-CSF (for immune suppression)

RULES OF THUMB: ALL CHEMO CAUSES ANOREXIA, NAUSEA and VOMITING
AND myelosuppression, EXCEPT bleomycin, vincristin, 5FU
AND hair loss, EXCEPT carboplatin, mitoxantrone, 5FU

5FU is a radiosensitizer!

Prognosis

Childhood ALL; greater than 98% remission, 75-80% cure.
Adult ALL; 75% remission rate, cure 30%.
Adult AML; 65% remission rate, 30-40% cure.

Follicular lymphoma has the best prognosis even without treatment

CML – new treatments targeting the product of the Philadelphia chromosome mean that cure rates are now unknown.
CLL – the only way to cure it is with a bone marrow transplant and full-body irradiation

Epidemiology

ALL

- Almost always a disease of **CHILDREN**

AML

- Most common Acute Leukemia of adults

CLL

- Most common Leukemia in the United States
- **Elderly patients** (usually over age 50 years)
- More common in men
- Rare in Asian patients

CML

- Common in Atomic bomb survivors
- Peak Incidence at ages 30 to 50 years old

Basic Sciences and Comparitive Diseases

BONE MARROW FAILURE + STEM CELL TRANSPLANT

Consequences of bone marrow failure:

Damage to
- **erythropoiesis,**
- **granulopoiesis,**
- **megakaryopoiesis, and**
- **lymphopoiesis**

has the following consequences:

Cell Lineage	Mature Cell	Deficiency State	Physiological Consequences	Clinical Symptoms & Signs
Erythroid	Red blood cell	Anaemia	Reduced oxygen carrying capacity	Pallor, fatigue, dyspnoea
Myeloid	Neutrophil	Neutropenia	Impaired phagocytosis	Fever, infections, mouth ulcers
Megakary-ocytic	Platelet	Thrombo-cytopenia	Bleeding	Bruising, petechiae, bleeding
Lymphoid	Lympho-cyte	Lymphopeni a	Immuno-deficiency	Infections

Causes of bone marrow failure

A wide variety of disease processes can result in damage to bone marrow function. Infiltration of bone marrow can be caused by:

- Haematological malignancy: leukaemia, lymphoma, myeloma, myeloproliferative disorders, myelodysplasia
- Solid tumours: especially breast and prostate cancer
- Fibrosis, for example from radiation damage or infections, especially tuberculosis
- Storage disorders eg Gaucher's disease
- Nutritional, particularly megaloblastic anaemia due to vitamin B_{12} (pernicious anaemia) or folic acid deficiency
- Virus, eg parvovirus, hepatitis viruses
- Drugs, including anti-cancer drugs, propothiouracil, chloramphenicol
- Stem cell defects/damage as in aplastic anaemia

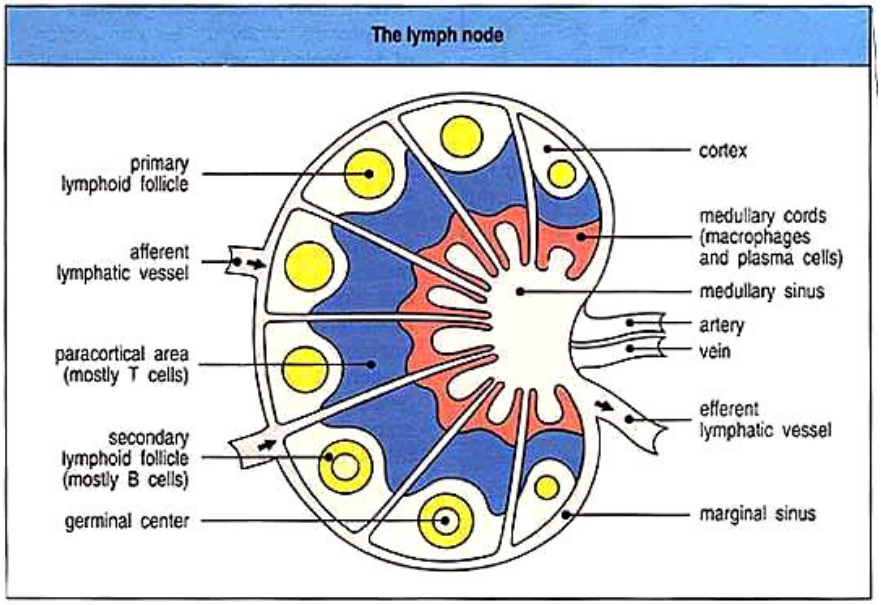
Other consequences of bone marrow infiltration
Pathological processes involving the bone marrow can also extend to effect cortical bone, resulting in
- bone pain,
- skeletal demineralization,
- osteopenia,
- pathological fractures,
- hypercalcaemia.

Relevant anatomy : LYMPHADENOPATHY

= NODES BIGGER THAN 1cm
0.5 for Epitrochlear
1.5 for Inguinal

HISTORY:

- duration of enlargement
- previous episodes
- associated symptoms:
  - fever
  - night sweats
  - weight loss
  - pruritus(itching)
  - myalgia
  - arthralgia
  - bone pain
  - limp
  - overseas travel
  - recently arrived migrants (within one to two years)
  - pet exposure
  - medications



!! LISTEN CAREFULLY TO THE MOTHER !!
In kids MAJOR CAUSE IS INFECTION –80%
In adults, think NEOPLASM

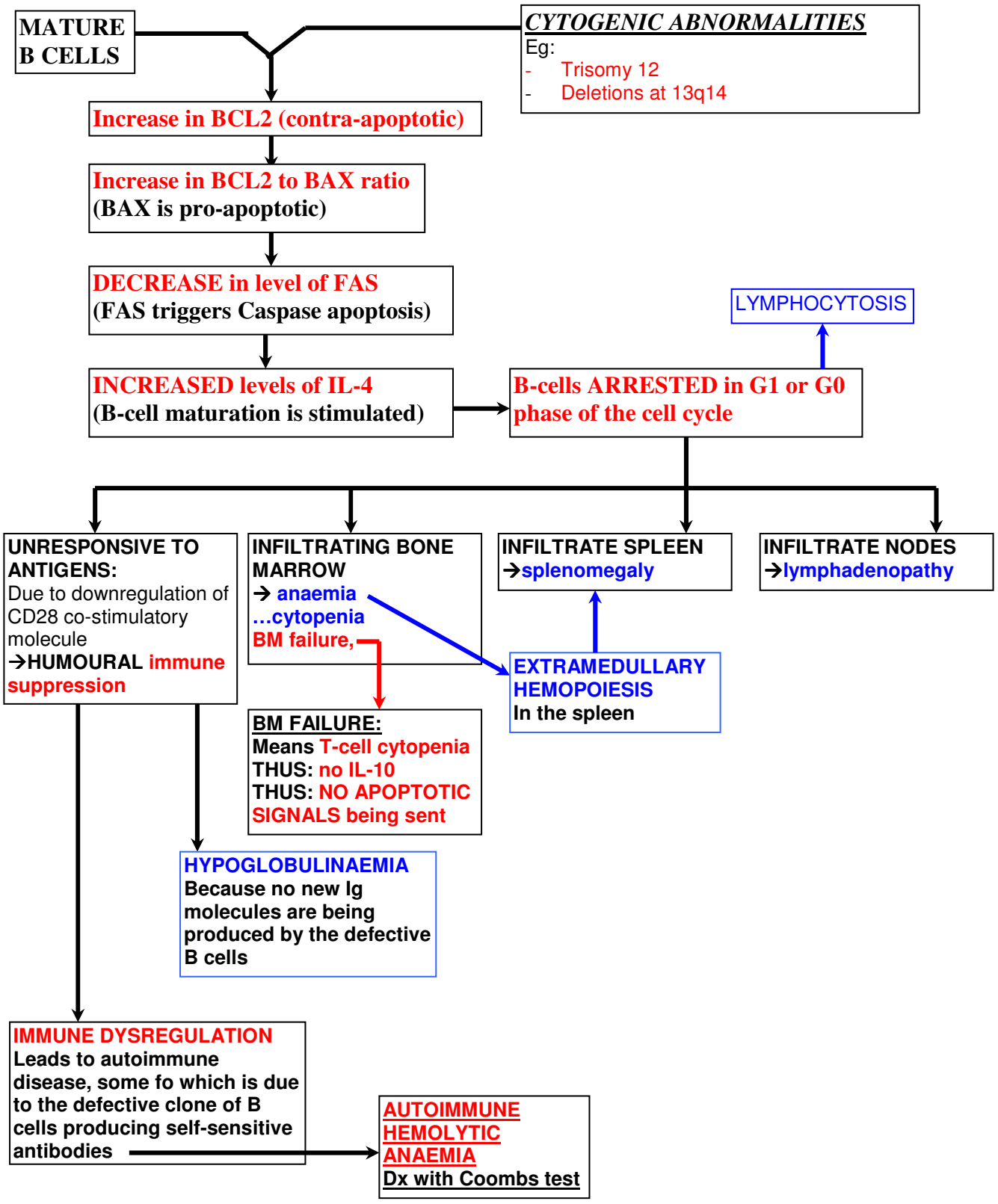
PHYSICAL:
Determine:
- regional versus general lymphadenopathy
- mediastinal or abdominal masses
- hepatomegaly and/or splenomegaly
- anaemia and bleeding.

CAUSE STILL OBSCURE? REVIEW IN 2 WEEKS
OR: give antibiotics and hope its infection (!! STUPID !!)
IF: nodes still large after 6 wks
OR: notes are getting bigger in 2-3 wks
→ THEN INVESTIGATE:

- **FBC + Blood Film**
- Mantoux test
- Chest Xray
- LFTs
- **SEROLOGY** for Epsteen Barr Virus, cytomegalo and HIV

STILL UNCERTAIN? **→ Lymph node biopsy** is suspect **lymphoma**
→bone marrow aspirate if suspect **leucaemia**

Aetiology: MECHANISM of Chronic Lymphocytic Leukaemia



Cell biology

CLL markers on B cells:

CD 5 ***(normally a T cell marker)***
CD 22
CD 19 ***(85% of B cells in CLL have this marker)***
Surface Ig

Smudge Cells:

- Break down and smudge on blood film studies because their phospholipid membrane is weak, as it is used for metabolism. Thus, it breaks and spills cellular contents onto the slide.

Spherocytosis:

- Occurs in CLL because of actin and spectrin malfunction (i.e molecular cytoskeleton is dysfunctional)
- THUS: phospholipid bi-layer degrades slowly, causing the cell to contract into a ball (like a droplet of fat in a soup)

Polychromasia:

- Is a blue colouration of immature RBCs, because they **still have RIBOSOMES which stain blue**

Genetics

Remember Mutation?...

Inversion

- Gene is reversed (most often on X chromosome)

Deletion or Insertion

- Of a whole chunk of DNA or of a whole gene

Translocation

- Chromosomes swap a gene fragment

POINT MUTATION: of one base pair

Frame shift

- Deleted base pair; all amino acids are therefore wrong from that point (each being made of 3 coding base pairs)

Missense

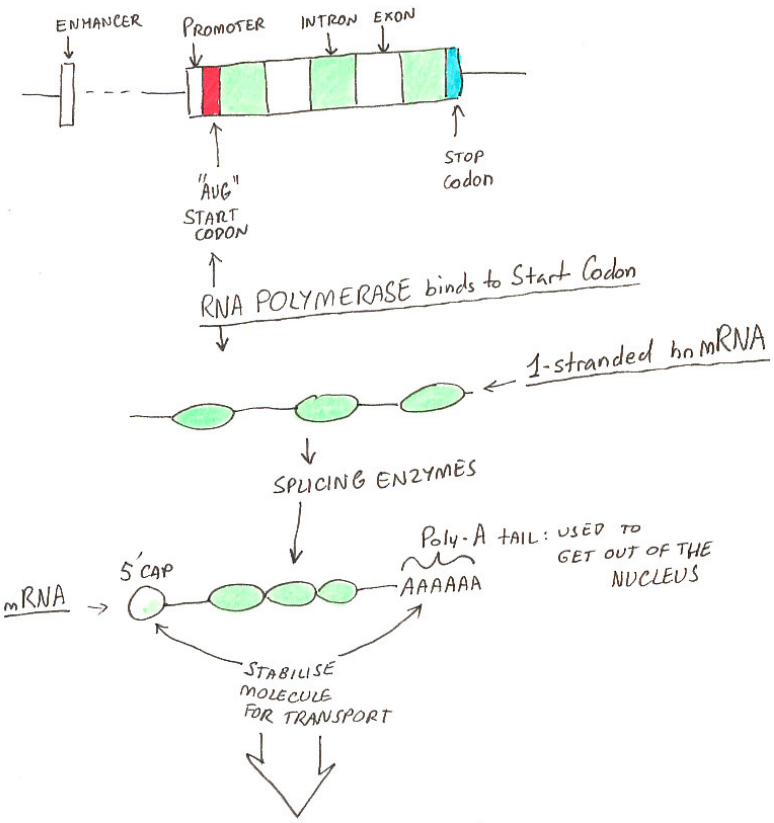
- wrong base pair replacing the right one; one amino acid is wrong (sometimes base pair is synonymous, and no phenotype change occurs- because there are numerous base pair combinations which code for the same amino acid)

Nonsense

- when the wrong base pair is inserted, and the whole 3-bp sequence is read as a stop codon

Splice Site Mutation

- loss or addition of a new, WRONG splice site;
- THUS → wrong mRNA (reads from the wrong point in the code)
- → wrong protein



Immunology: LEUCOCYTES

The NORMALS: in MILLION PER LITRE

Neutrophil	2.00 → 7.5
Eosinophil	0.04 → 0.4
Basophil	0.01 → 0.1
Monocytes	0.2 → 0.8
Lymphocytes	1.5 → 4.0

NEUTROPHILS:
Produced in bone marrow
Serum half-life 6-7hrs
Migrate into tissues through post-capillary venules

MACROPHAGES:
Produced in bone marrow
Serum half-life **3 days**
Migrate into tissues through post-capillary venules
Differentiate into tissue-specific varieties

MEANS OF ATTACK:
Neutrophils and Macrophages attach themselves to their victim and fuse their granules. Then, a **Respiratory burst** follows where they disgorge great volumes of superoxide and H_2O_2
MACROPHAGES ALSO PRESENT ANTIGEN

AUTOIMMUNE HAEMATOLOGICAL DISORDERS

Immune system targetting normal tissue:

- **Red blood cells** (autoimmune haemolytic anaemia)
- **White blood cells** (autoimmune neutropenia)
- **Platelets** (autoimmune thrombocytopenia)
- **Coagulation proteins** (coagulation inhibitors)
- Phospholipids involved in coagulation (lupus anticoagulant, anti-cardiolipin antibodies)
- And other haematological components

non-haematological tissues:
eg. destruction of gastric parietal cells in pernicious anaemia

Autoimmune haematopathology may form part of a wider spectrum of autoimmune disease including such diseases as

- vitiligo,
- diabetes,
- thyroid disease,
- systemic lupus

PATHOLOGY is usually due to a destruction of a normal cell type

- in **autoimmune haemolytic anaemia** the **antibody coats red cells**. The antigen is thought to be a widely expressed protein which is part of the Rh blood group. The disorder is characterised prinicipally by the **anaemia which results**.
- In **autoimmune thrombocytopenia**, the **antibody coats platelets** and the disease is manifested by the resultant reduction in platelet count and the associated increase in bleeding.
- in **lupus anticoagulant, an autoantibody to phospholipid** accelerates clotting and predisposes to thrombosis.

In a small number of patients with B**-lymphocyte lymphoproliferative** disorders, the **malignant clone of cells may produce an antibody** with specificity for an antigen expressed by a component of the haematological system. Autoimmune haemolytic anaemia or autoimmune thrombocytopenia can result. In some such cases, a **paraprotein may be produced** and may be detected in the serum by protein electropheresis and immunoelectropheresis.

Microbiology : Opportunistic Infection in Immune Suppression

Lack of mature leucocytes = immune suppression

PRIMARY: genetic spontaneous
SECONDARY: acquired

OPPORTUNISTIC PATHOGENS: cannot invade unless defences are down

DEFICITS:

B CELLS: humoral immunity impairment **(!! CLL !!)**

- sinusitis,
- otitis media,
- bacterial pneumonia
- infections of the skin.
- Organisms involved are typically **polysaccharide-encapsulated pyogenic organisms,** such as
  - Strep. pneumoniae,
  - H. Influenzae type b,
  - Strep. pyogenes,
  - Moraxella catarrhalis.

Also frequent are

- Staph. aureus,
- Giardia lamblia
- Campylobacter jejuni

T CELLS: intracellular defences

- fungi (mucosal Candida),
- viruses (cytomegalovirus, zoster, Herpes simplex),
- protozoa (Pneumocystis),
- Listeria and others.

These types of infections are common in AIDS, which is the prototype for deficiencies in this arm of the immune system.

PHAGOCYTE DEFECTS: decline in number or function.

- high-grade bacterial infections such as Staph. aureus,
- **gram-negative bacteria**
  - E. coli,
  - P. mirabilis,
  - Serratia marcescens,
  - Pseudomonas aeruginosa
- **Fungi:**
  - invasive Aspergillus
  - systemic candidiasis.

COMPLEMENT DEFECTS:

- Neisseria meningitidis and gonorrhoeae (when any of the components from C5-9 are involved),
- gram-negative bacteria and pyogenic organisms with deficiency in the early components of the complement cascade.

Common Opportunistic Infections

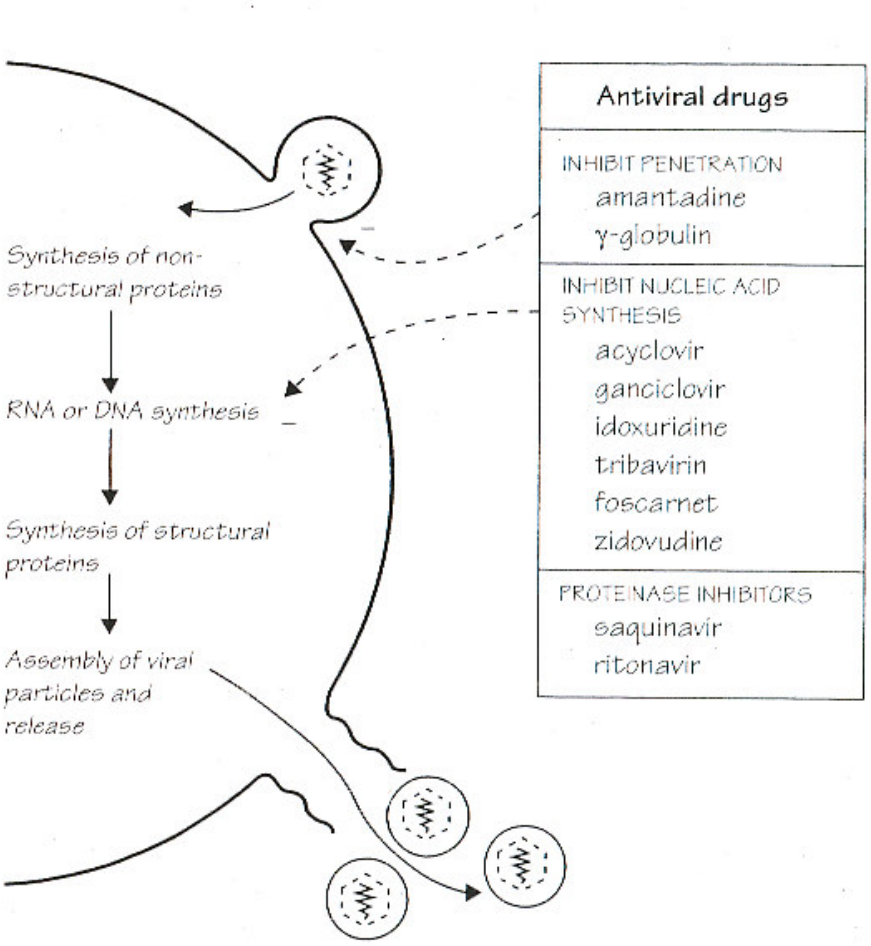
- **Pneumocystis carinii pneumonia (PCP)**
- **Cryptococcal meningitis**
- **Candidiasis.**
- **CMV infection**

Pharmacology of Antiviral Drugs and Corticosteroids for chemo see Management

Why? Viral infections strike the immunocompromised
Autoimmune hemolytic anaemia is treated with corticosteroids

Antiviral Drugs:

Either **prevent entry into host cell** or **inhibit viral nucleic acid synthesis**



Corticosteroids: glucocorticoids:

GLUCOCORTICOID TX: OBSERVE HEMOGLOBIN!!
When back to normal, **taper dose down to 20mg/day**

In CLL: 2 modes of action

1. **INHIBIT ANTIBODY SYNTHESIS** by faulty B cells
2. **INHIBIT PHAGOCYTOSIS** of antibody-coated RBCs by macrophages