Haemostasis

   2. Secondary : Fibrin deposition .

**Stage 1** : Pre-injury :
   . Vascular endoth. Produce subs. Prevent adhesion of plat. & WBC to vessel wall (NO2 , prostocyclin)

**Stage 2** : Early Haemostasis :
   . Plat. Adher. & coagulation activation → Thrombin

**Stage 3** : Fibrin clot formation .

**Stage 4** : Limiting clot formation by natural anticoagulants (antithrombin , TFPI , protein C & S ).

**Stage 5** : Fibrinolysis . Plasmin degrades fibrin → vessel recanalisation & tissue repair .
# Clotting Factors:

<table>
<thead>
<tr>
<th></th>
<th>Factor</th>
<th>Half life</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fibrinogen</td>
<td>4-5 days</td>
</tr>
<tr>
<td>2</td>
<td>Thrombin</td>
<td>3 days</td>
</tr>
<tr>
<td>3</td>
<td>Tissue F.</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ca++</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Labile F.</td>
<td>12-13 h</td>
</tr>
<tr>
<td>6</td>
<td>No longer used</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Proconvertin</td>
<td>4-7 h</td>
</tr>
<tr>
<td>8</td>
<td>AHF</td>
<td>8-10 h</td>
</tr>
<tr>
<td>9</td>
<td>Christmas F</td>
<td>1 day</td>
</tr>
<tr>
<td>10</td>
<td>Stuart power F</td>
<td>2 days</td>
</tr>
<tr>
<td>11</td>
<td>Plasma Thromboplastin antecedent</td>
<td>2-3 days</td>
</tr>
<tr>
<td>12</td>
<td>Hagman F</td>
<td>1 day</td>
</tr>
<tr>
<td>13</td>
<td>Fibrin stabilisig F.</td>
<td>8 days</td>
</tr>
</tbody>
</table>

All produce by the liver, FV also by plat. & endoth. Cells.

VIT. K dependent factors  II VII IX X (inhibited by WARFARIN)
Blood Coagulation:
1. Extrinsic pathway: initiated by F VII interacting with Tissue Factor.
2. Intrinsic pathway: initiated after exposure of subendoth. Collagen after vessel damage. XII XI IX VIII
Platelets:
- Formed in Bone marrow from Megakaryocytes.
- Thrombopoiten (liver) stimulate formation & Maturation of plat.
- Circulate in Bl. For 8-10 days before destroyed in RES.
- 30% pooled in spleen.
- Discoid 2-4 Mm diameter.
- Invaginated surface Memb. to form Canaliculi.

Screening tests for bleeding disorders
1. Plat. Count (normal = 150-400 X 10^9 /L)
5. Prolonged PT & PTT = common pathway (X, V, II & I) , or > one factor def.
6. Fibrinogen conc. (normal 1.5-4 g/L) hypofibr. e.g. liver dis. DIC.
7. Mixing tests with normal plasma differentiate between coag. Factor def. & presence of inhibitors (the prolonged time does not correct).
8. plat. Functions tests.
Bleeding Disorders: suspect if

1. Multiple sites
2. Spontaneous
3. Prolonged

1. Vascular purpura

2. Platelets defects: Quantity, Quality

3. Coagulation defects:
   Reduced synthesis of Fs
   Abnormal Fs
   Destruction (DIC)
   Inhibitors

4. Fibrinolytic defects:
   e.g. Excessive fibrinolysis following therapeutic thrombolysis
Clinical assessment

1. Site of bleeding
   - Ms, Joints, Retrop, indicate coagulation defect.
   - Purpura, Epistaxis, G.I.T., Menorrhagia, indicate low plat, plat. F. defect, WWD.
   - Recurrent in single site – local abn.

2. Duration: Acq. Or Cong.

3. Precipitating Fs: Spont., or traumatic.

   - Immediate: Pri. Haemostasis
   - Delayed: Coag. def.

5. F.H.: Absence does not exclude hereditary dis.

6. Drugs.
## Differentiation bet. Plat. dis & Coagul. dis

<table>
<thead>
<tr>
<th></th>
<th>Plat dis.</th>
<th>Coagul. dis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td>F &gt; M</td>
<td>M &gt; F</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>20-40 y</td>
<td>childhood</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Type</strong></td>
<td>Mucocut</td>
<td>Deep Ts.</td>
</tr>
<tr>
<td><strong>Local pr.</strong></td>
<td>Effective</td>
<td>Not</td>
</tr>
<tr>
<td><strong>Ex.</strong></td>
<td>ITP</td>
<td>Haemophilia</td>
</tr>
</tbody>
</table>
Platelets Disorders

1. Thrombocytopenia $< 150 \times 10^9 / L$
2. Thrombocytosis $> 400 \times 10^9 / L$
3. Functional.

Thrombocytopenia:

Spont. Bleeding – plat $< 20 \times 10^9 / L$
$< 10 \times 10^9 / L$ – Risk of intracranial bleeding

Plat. Transfusion: indicated in

1. Bone marrow failure $< 10 \times 10^9 / L$
2. Serious Haemorrhage.
Causes of thrombocytopenia:

1. Reduced production: Bone marrow dis.
   - Aplastic Anaemia, Leukemia, Cytotexics
   - $B_{12}$ Folic ac. def.

2. Increased Consumption:
   - ITP, DIC, TTP.

Non Thrombocytopenic purpura

1. Senile
2. Factitious
3. H. S. P.
4. Vasculitis
5. Paraproteinaemia
Idiopathic Thrombocytopenic Purpura (ITP)

Aetiology: Auto Abs against plat. Membr. Glucoprotein IIb/IIIa leads to premature removal by RES. May be assoc. with CTD, HIV, Pregnancy, Drugs.

Clinical: Depends on degree of thrombocytopenia.

- Spont. Bl. < 20 X 10⁹ / L
- < 10 X 10⁹ / L – Risk of I.C. Bleeding
- Higher count: Easy Bruising, Epistaxis, Menorrhagia
- > 50 X 10⁹ / L – accidental.
- F > M
- Preceeding Viral inf. – unusual.
- CTD at presentation or later
- Splenomegally – Unusual.

Lab.: Bl. Film – reduced plat.

- B. M. – Incr. or normal Megakaryocytes.
- Plat. Abs - positive

D.D.: Acute leulcemia, Apl. An., DIC, SLE.
Management of ITP:

- Stable, plat $>30 \times 10^9$ / L – No treatment, except with Surgery or Biopsy
- Spont. Bleeding – Prednisolone 1 mg / kg / day (suppress Ab. Prod. and inhibit phago.) count will increase to normal or less in 2-4 weeks, then reduce does gradually.
- Relapse – Reintroduce Steroids
- Immunoglobulin i.v. (Block Ab receptor on RES) + steroids in severe haemostatic Failure
- Anti-D i.v. (Bind RBC and saturate Ab. Receptors in Rh + ve (+ spleen)
- Persistent or life threatening Bleeding needs plat. Transfusion
- 2 Relapses or Pri. Refractory needs splenectomy.
  - 70% complete remission.
  - 20-25% - improvement
  - 5-10% require further treat. e.g. low dose steroids, Immunosup. (Rituximab, Ciclosporin)
Thrombotic Thrombocytopenic Purpura (TTP) (HUS)  

Aetiology: Autoimmune disorder, mediated by Abs. against ADAMTS – 13 enzymes.

(This enz. normally clears VWF multimers to produce normal functional units and its deficiency results in large VWF multimers which cross – link platelets and leads to microvascular occlusion by plat. Thrombi e.g. brain, kidney).

Idiopathic, associated with drugs (Ticlopidine, Ciclosporine), HIV, Malignancy.

Clinically: Sporadic, Fluctuating, Familial: reported, F > M , young – adolescent

1. Fever
2. Anemia: Microangiopathic haemolytic (Fragmented RBCs), ↑ Reticulocyte count, Jaundice, ↑ LDH, -ve coomb’s test.
3. Thrombocytopenia – Purpura, count usually < 20 X 10^9 /L
4. Neurological: Convulsion, Coma, Paralysis (Transient or prolonged), Psychological.
5. Renal: intermittent proteinuria, Renal Failure (more in HUS)
Lab. ↑ WBC, ↓ plat.
PT, PTT ------ Normal
B.M. ------ Normal or increase cellularity
Gingival Biosy – Helpful

DD : ITP

Prognosis : 10% Recurrent.
Untreated – 90% Mortality in 10 days
Treated – Mortality 20-30% at 6 months
Sudden death due to cardiac Microthrombi

Treatment : Plasmapharesis with FFP 12 bags/day for weeks – Months
Corticosteroids, Rituximab have a role.
Pregnant – May needs termination if no response
Thrombocytosis

1. Reactive (most Common)
   a. Chr. Infl. Dis. E.g. ulc. Collitis
   b. CTD e.g. Rh. Arthritis.
   c. Malignancy e.g. Hodgkin’s dis.
   d. Acute Haemolysis
   e. Fe. Def. An.
   f. GI bleeding
   g. Post – splenectomy

2. Clonal
   a. Pri. Thrombocythaemia (ET)
   b. PRV
   c. Myelofibrosis.
   d. CML.
   e. MDS.

Clinically :
Those of the underlying dis.
Haemostasis rarely affected
PRV, ET, Myelofibrosis, may present with thrombosis and rarely bleeding
Reactive : small plat. No splenomegally.
Plat. Function disorders

1. Acquired
   a. Iatrogenic
      Aspirin – Cyclo – Oxygenase inhibitor
      Clopidogrel – ADP receptor inhibitor
      Abciximab – Gp 11 b / 111 a inhibitor
      Tirofiban – Gp 11 b / 111 a inhibitor
      Dipyridamol – phosphodi esterase inhibitor
   b. Antibiotics: Penicillin, Cephalosporines
   c. Heparin
   d. CRF
   e. Myelofibrosis
   f. Paraproteinaemia
   g. CTD
2. Congenital

a. Glanzmann’s thromboasthenia - Def. of GP 11b / 111a AR, bleeding variable, often severe.

b. Bernard – Soulier dis. def. of GP 1b. AR

c. Defective plat. Granules – deficiency of dense granules
   (b & c cause mild bleeding e.g. after trauma or surgery, rarely spont.)

Management:

Local mechanical pressure .

Antifibrinolytic e.g. Tranexamic acid may be useful .

Plat. Transf. in severe bleeding.

Recombinent FVIIa in resistant bleeding in Glanzmann.
VESSEL WALL ABNORMALITIES

1. Hereditary: HHT, EDD, Osteogenesis imperfecta
2. Inflammatory: Bacterial, Viral, Vasculitis.
5. Others: Factitious, Paraproteinaemia, Drugs.

Hereditary Haemorrhagic Telangiectasia (HHT)
(Osler – Rendu – Weber synd.)


Signif. No. have Pul. A.V. malformation (PAVMS) → Arterial Hypoxaemia due to Rt. To It. Shunt → paradoxical embolism → stroke or cerebral abscess.

Recurrent Bleeding e.g. Epistaxis or Malaena → Fe def. An.

Treatment: Difficult bec. Of multiple Bleeding sites.

Regular Fe therapy
Local Cuatary or Laser, Oestrogens?
Ehlers – Donalos Dis:
AD. Collagen defect
Fragile Bl. Ves. And organ memb. → Bleeding and organ rupture
Joint Hypermobility

Scurvy
- Vit C def. → affect normal synthesis of collagen
- Perifollicular and patechial haemorrhage, sub- periosteal bleeding
- Diagnosis: Dietary History
Henoch – Schonlein Purpura (HSP)

- Children and young adults.
- Immune complex deposition in small ves. With vasculitis.
  Often preceded by upper resp. inf.

Clinically:

1. Purpura: (raised) Buttocks and legs
2. Abdominal colicky pain and bleeding
3. Arthritis: Knees, Ankles.
4. Nephritis: 40% (May be later – 4 wks.)

Diagnosis: Clinical, Tissue biopsy (IgA deposition in bl. Ves.)

Prognosis: good, Adverse if HTN, RF, Proteinuria > 1.5 g / day

Treatment: Nonspecific

Steroids for joint or GI involvement
Nephritis – pulse iv steroids ± immunosup.
COAGULATION DISORDERS

Congential:
X-linked: Haemoph. A and B
Autosomal: VWD, F II V VII X XI XII def.
  Combined II VII IX X def.
  Combined V and VIII
  Hypofibrogenaemia
  Dysfibrinogenenaemia

Acquired
  Under prod.: Liver failure.
  Incr. Consumption: DIC
  Immune – mediated: Acq. Haemophelia & VWD.
  Others: Acq. F X def. (in amyloid)

Drug – induced
  Inh. Of function: Heparin
  Inh. Of synthesis: Warfarin
Haemophilia A:

- X-linked Rec.

Haemophilic Male $\rightarrow$ 100% carrier daughters, boys all normal
Carrier Female $\rightarrow$ 50% carrier female, 50% Haemophilic male

- Antenatal diagnosis: chorionic villous sampling
- Similar severity in same family
- Female carrier: 50% have low F VIII, Mild bleeding?

Clinically:

<table>
<thead>
<tr>
<th>Severe</th>
<th>Moderate</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>F VIII &lt; 1%</td>
<td>2-10%</td>
<td>10-15%</td>
</tr>
<tr>
<td>Spont. Bl.</td>
<td>Mild Trauma</td>
<td>Major Trauma</td>
</tr>
<tr>
<td></td>
<td>or surgery</td>
<td>or surgery</td>
</tr>
</tbody>
</table>

- Recurrent bleeding into large joints (Knee, Elbow, Ankle, Hip)
  Muscles (Calf, Psoas)
If no early treatment: Hot, swollen, very painful joint.
Rec. bleeding into joints $\rightarrow$ synov. Hypertrophy, Cartilage destruction With OA.
Muscles Haematoma: depend on site

Psoas → compress fem. N
Calf → compartement synd. → Isch., necrosis, fibrosis, contracture and shortening of Achilles tendon.


Manag. : Avoid Trauma.
. Severe : 1- ↑ F VIII: (Donar Plasma or Recombinent) iv infusion F VIII concentrate.
   2- Rest of bleeding site
   3- If bleeding settled → Mobilisation & physio.
   4- Hepatitis A,B immunisation
   5- Prophylactic: F VIII 2-3 X /wk – (at home) - expensive
   ↑ F VIII X 4, it covers minor surgery e.g. Exo

Complications :
1- HIV , HBV , HCV (< 1986)
2- Anti F VIII Abs. ( inhibitors ) 20%
3- OA & deformities.
Haemophilia B (Christmas dis)

↓ F IX

X – linked

Clinically similar to A

Treatment: F IX concentrate

Inhibitors < 1%
**Von Willebrand Dis. (VWD)**

AD, M > F / most common bleeding disorder, usually mild.

Function of VWF: 1- Carrier for F VIII (↓ VWF → ↓ F VIII).

   2- Forms bridges bet. plat. & sub endoth. → plat. Function.

**Classification**: Type 1: most common, ↓ quantity.

   Type 2: abn. Function (quality), 2A, 2B, 2M, 2N – Auto. Rec..

   Type 3: severe quantitative (AD).

**Clinically**: different severity in same family, bleeding similar to plat. Dysf.

   Brusing, Epistaxis, Menorrhagia, G.I. bleeding.

   severe bleeding: ± after trauma or surgery.

**Lab.**: ↑ BT, ↑ PTT, normal PT, ↓ VWF, secondary ↓ F VIII.

**Manag.**: Mild bleeding: local means or DDAVP, Tranexamic ac. may be useful in mucosal bleeding.

   Severe or persistent bl. : selected F VIII concentrate (contain F VIII + VWF).
Aquired Bleeding Disorders:

Disseminated Intravascular Coagulation (DIC)

**Definition**: Acq. Thrombohemorrhagic disorder, characterise by systemic activation of coagulation (Thrombosis), with simultaneous coagulation Fs. (Notably F V & VIII), plat. & fibrinogin consumption causing bleeding.

Lysis of fibrin → fibrin degredation products (FDP) including D – dimers.

**Causes**:
1- Infection (sepsis).
2- Trauma.
3- Obstetric (Amniotic fluid embolism, placental abruption, pre-eclampsia).
4- Severe liver failure.
5- Malignancy.
6- Tissue destruction (Pancreatitis, burn).
7- Toxic / immulog. (ABO incompatab. , snake bite).
Clinically:

1- Signs of Thrombosis: Jaundice, blue toes, fingers gangrene, delerium, coma, respiratory failure, oliguria.


Lab.

Anaemia (Microangiopathic Haemolytic).

↑PT & PTT

↓Fibrinogen

↑Bilirubin, ↓plat., FDP +ve

Manag.: Treat. Of underlying cause.

Deal with acidosis, dehyd., RF, Hypoxia.

FFP, cryoppt., plat. – if bleeding, or cover intervention (not roteinly)

Heparin – prophylactic doses (unless contraindicated) to treat established thrombosis.
Liver diseases: ↓ synthesis of coagulation Fs.
   ↓ clearance of plasminogin activators.
   ↓ plat. (Hypersplenism)
   ↓ vit K absorp. (cholestatic jaundice) → ↓ F II VII IX X
   Lab. ↑ PT, ↑ PTT (in severe cases).
   Treatment FFP, Plat. Vit. K

Renal Failure: Bleeding proportional to Urea concentration.
   Similar to Plat. Dysf. Type (GIT is common).
   Causes: An. ↓ plat. waste products.
   Treatment Dialysis, plat. transf., Bl. cryo. DDAVP.

Vit K deficiency:
   Sources: Green vegetables, intestinal flora.
   Causes: ↓ intake, malabsorp., biliary obst., antibiotics.
   Clinical: plat. dysf. type of bleeding.
   Lab: ↑ PT, ↑ PTT (in severe cases).
   Treatment: Vit. K, im or iv for 3 days + treat. Of underlying cause.
Deep Vein Thrombosis: (DVT)

Mortality: 1-3%

Predisposing Factors:

1. Patients Factors: ↑Age, Obesity, Varicose veins, Previous DVT, F.H. Pregnancy, CCP, Puerperium.
2. Surgical: Major surgery, ( > 30 min ), abdom., pelvic or lower limb ortho..
5. Antiphospholipid synd.

Clinically:

Lower limb DVT: Typically Unilat. (may be bilat.).
Pain, swelling, high temp., tender, dilated superficial Vs.
Examine thigh for DVT (proximal Involv.) → ↑ risk of PE.
**Dif. Diagnosis:**

1. Spontaneous or traumatic calf M. tear (sudden).
2. Ruptured Baker cyst (Rh. Arthritis).
3. Infective cellulitis (well demarkated swelling).

**Investigations:**

1. D-diamer.
2. Compression ultrasound (doppler), sensitivity 99.5% in prox. (poplit. & above), ↓ sensitivity & specificity for calf Vs.
3. Contrast venography – rarely used.

**Management:**

1. Elevation & Analgesia.
2. Thrombolysis for limb threatening DVT.
3. Main treat. : Anticoagulation : Heparin for at least 5 days, start warfarin while on heparin which should be continued until INR in target range for 2 successive days (2-3, average 2.5).

If strong contraindication to anticoag. Or continue to have PE → IVC filter. Warfarin – 6 wks to 6 Ms (or longer).

Recurrence : 2-3% /y in temporary risk, 10% in unprovoked DVT.
Post – thrombotic synd.: Damage to ven. valves by thrombous → persistant leg swelling, heaviness & discolouration, sometimes ulceration.

Patient PT
INR = \[\text{normal control} \times \text{international sensitivity index}\]

Indications for Anticoagulation

**Heparin**
1. Prev. & treat. of VTE.
3. Post thrombolysis MI.
4. Unstable Angina pectoris.
5. Non Q wave MI.

**Warfarin**
1. Prev. & treat. of VTE.
3. AF with stroke risk.
4. Mobile mural thrombus.
5. Extensive Ant. MI.
6. Dilated cardiomyopathy.
8. MR & MS + AF, Rec. ven. Throm. mechanical prosth. H. valves

APS
Heparin: potentiate antithrombin anticoagulant activity.

1. Unfractioned (UFH).
2. Low molecular wt. (LMWH).

Advantage of LMWH:
1. 100% bioavailability = reliable dose dependent anticoagulation, no need for monitoring, except in very thin pt. & R.F.
3. ↓ Osteoporosis & Thrombocytopenia.

Dose:
1. UFH:
   Therapeutic: 5000 u iv followed by 20u/Kg/h by contin. Iv inf.
   Assess by PTT (Target 1.5-2.5 the control).
   Prophylactic: 5000 u X 2 / S.C.

2. LMWH:
   a. Enoxaparin:
      Therapeutic: 150 u / Kg / S.C. daily.
   b. Tinzaparin:
      Therapeutic: 175 u / Kg / S.C. daily.
      Prophylactic 3500 - 4500 u / S.C. daily.
Complications:

1. Bleeding: Treatment: Stop Heparin is usually enough (short half life) If necessary protamine sulphate (Anti-dote).

2. Thrombocytopenia:
   a. Early: First 24 hours (benign, due to plat. Clumping).

3. Osteoporosis (Herarin > 6 Ms).
**Warfarin**: inhibit vit K depend. Fs (II VII IX X).

Take 3 days for anticoagulation.

**Drug interaction**


2. Inhibition: Barbiturates, Rifampicin, CCP, Pregnancy.

**Dose**: 10 mg on 1st & 2nd day, 5 mg 3rd day, & then according to INR.

**Complications**:

Bleeding: 1% fatal (intracranial)

Manag.: Look for the cause, e.g. drug interaction or ↑dose, stop warfarin temporarily.

- Major: 5-10 mg vit. K iv. Slowly + FFP (15-30 ml / kg)

Prolonged INR with no bleeding: Stop or reduce the next Dose, small Dose vit. K orally or iv. 1-2.5 mg.

especially if INR > 8
# Prophylaxis of ven. Thrombosis

## Moderate risk
1. Major surgery (> 40 y + risk F)
2. Major medical illness e.g. HF, MI, Sepsis, Active malign., Neph. Synd., Stroke + Paralysis

## High risk
1. Major abd. Or pelvic surgery for malign. or with history of DVT or known thrombophilia.
2. Major Hip or Knee surgery.
3. Neurosurgery

## Methods
1. Mechanical: intermit. Pneumatic compr., /feet pump, compression stoking
2. Pharm.: LMWH, UFH, Warfarin, Aspirin.

## Contraindications
1. Recent surgery
2. Pre-Existing Haemorrhagic state (liver dis., Haemophilia)
3. Peptic ulcer.
4. Recent cerebral Hemorrhage.
5. Uncontrolled HTN
6. Frequent falls in old age.
Antiphospholipid Syndrome (AS)

Acquired prethrombotic tendency, in which arterial & or venous thrombosis associated with finding in the plasma of lupus anticoagulant (LA) & or seropositivity for antiphospholipid Ab., most commonly Anticardiolipin Ab. (ACA).

Clinically

1. Primary APS

2. Secondary APS is associated with: SLE, Rh. arthritis, Systemic sclerosis, Behcets dis, Temporal arteritis.

Criteria A: Clinical:

1. Vacular thrombosis, one or more episode of arterial or venous or small vessel thrombosis in any tissue/organ.

2. Pregnancy morbidity:
   a. One or more unexplained death >10 wk gest.
   b. 3 or more unexplained spont. Abortion, <10 wk gest.
   c. One or more premature birth <34 wk gest.

B: Lab:

1. Anticardiolipin Ab. On 2 or more occasions, 6 Wks apart.

2. Lupus anticoagulant Ab. On 2 or more occasions, 6 Wks apart.

3. Prolonged PTT.

Diagnosis: At least ONE clinical & ONE lab. Criteria
Treatment:

- Arterial thrombosis (stroke): Warfarin.
- Recurrent VTE: Long term anticoagulation
- Pregnancy: Heparin + Aspirin (Increase chance of successful pregnancy).
Blood Products & transfusion

Donation:
1. Whole Blood.
2. Apheresis e.g. platelets.

Blood components:
1. Red cell concentrate: (most of plasma removed), ABO & Rh compat. required.
   Indication: Acute blood loss replac. & severe An.
2. Platelet Concentrate: ABO compat. preferable.
   Indication: Thrombocytopenia, Plat. Dysfunction.
3. FFP (150-300 ml): ABO compat. recommended. Dose: 15 ml / Kg.
   Indic.: Replac. Of coagul. Fs def., TTP.
4. Cryoprecipitate: (10-12 ml pack): Contain fibrinogen (150-300 mg) & coagulation
   (80-120u FvIII & VWF)
   Indication: hypo- Fibrinopenaemia, VWD, Haemophilia.
Plasma Derivatives:

2. Immunoglobulins: IV IgG (Ab.def., ITP, Gullian Bar. Synd.)
   - Prophylaxis of Varicella zooster.
   - Anti Rhesus D Ig
3. Human albumin:
   - 5%: colloid fluid (Crystalloid sol. Cheaper)
   - 20%: Hypoprot. Odema (Nephrotic synd.), Ascitis in chr. liver dis.
<table>
<thead>
<tr>
<th>Group</th>
<th>Red cell A or B Ag</th>
<th>Abs. in plasma</th>
<th>% UK</th>
</tr>
</thead>
<tbody>
<tr>
<td>O</td>
<td>None</td>
<td>Anti A &amp; B</td>
<td>46</td>
</tr>
<tr>
<td>A</td>
<td>A</td>
<td>Anti B</td>
<td>42</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
<td>Anti A</td>
<td>9</td>
</tr>
<tr>
<td>AB</td>
<td>A &amp; B</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Storage</td>
<td>Red cells</td>
<td>FFP</td>
<td>Pooled plat.</td>
</tr>
<tr>
<td>---------</td>
<td>-----------</td>
<td>-----</td>
<td>--------------</td>
</tr>
<tr>
<td></td>
<td>4°C</td>
<td>-30°C</td>
<td>22</td>
</tr>
<tr>
<td>35 d</td>
<td></td>
<td>1 yr</td>
<td>5 d (agitated)</td>
</tr>
</tbody>
</table>
**Adverse effects**

- **Death:** 0.5/100,000
- **1%:** Symptoms e.g. fever, itch, urticaria (repeated transfusions).

Any symptoms or signs _take it seriously_ **WARNING!**

1. **ABO incompatibility:**
   
   Recep. IgM (Anti-A, Anti-B or Anti AB + Transfused red cells)

   Activate complement system

   intravascular haemolysis, hypoten. RF, peribronchial oedema & smooth M.cont

2. Other immunological complic. e.g. Transf. associated lung injury.

3. **Infections:** HBV, HCV, HIV, less than 1/1000,000, (bact. Contam. of plat. packs)

   **Conclusion:** avoid unnecessary transfusion.
Signs & Symptoms of acute transfusion reaction:
(Fever, Chills, Tachycardia, Hyper or Hypotension, Collapse, Rigors, Flushing, Urticaria, bone, M., Chest & abd. Pain, SOB, Nausia, Resp.distress)

Stop Transfusion

Temp, PR, BP, pt.identity, Bl.pack, compatibility form
1. Reaction only Fever or urticaria
   ↓
   FEVER
   *Febrile Non Haemolytic Transf. Reaction
   Treatment: Paracetamol
   Restart Transf. after 15-30min. at slower rate
   under observation if no more complications

URTICARIA
* Mild Allergic Reaction
Chlorpheneramine 10mg iv
Suspect ABO incompatibility

- **Wrong Bl. Transfusion**

  - **YES**
    - ABO incompat.
    - Pack & giving set → Blood Bank
    - i.v. Saline, Urine Output (catheter)
    - U.O. < 100 ml/h: give Frusemide
    - Treat DIC
  - **NO**
    - Severe Allergic Reaction
    - Bronch. Spasm, Angiodema, Abd. pain
    - Hypotension.

**YES**
- Bact. Contam.
- Pack & Giving Set back to Bl. Bank, Bl. Culture,
- Repeat Bl. group & comp.
- FBC, Coagul. screen, Bioch.
- GUE.
- Broad spectrum antibiotics.
- O2, Fluid.
- Stop Transf.
No Bact. Contam.


↓

High CVP

Fluid Overload

O2, Frusemide 40-80 mg

↓

Normal CVP

Transf. related Acute Lung Injury (Typically within 6h)

SOB, cough, CXR: bilat. nodular infiltr.

Stop Transf. 100% O2

Treat as RDS, Ventilation if necessary.
Bone Marrow & peripheral stem cell Transplant (BMT)

**Allogenic** : Stem cell from Donar, given i.v. to patient( previously conditioned by chemo ± radioth. → engraft into pt.BM (function 3-4 wks).

Sources :
1. Related (HLA identical subling ).
2. Unrelated ( closely HLA matched Volunteer ).

Indications :
1. Neoplastic disorders (Leukemia, AML, ALL, CML, MDS, Myelofibrosis )
2. Failure of haemostasis e.g.( Aplastic an.)
3. Inherited Defects e.g.( Thalassemia ).

Complications : Mucositis, infection, bleeding, pneumonitis, infertility, Chr.GVHD.

Complications : Mucositis, infection, bleeding, pneumonitis, infertility, Chr.GVHD.

Complications : Mucositis, infection, bleeding, pneumonitis, infertility, Chr.GVHD.

Secondary malignant dis.

Best results : pt. with minimal residual dis. .Age < 20 yr. +HLA identical subling.

25 % die from procedure ,GVHD,

Long survival :50% for leukemia.
GVHD:

Aetiology: cytotoxic activity of donor T lymphocytes, which become sensitised to their new host, regarding it as foreign. This may cause acute or chr. GVHD.

Acute: lst 100 d, one third of pt. Mild – Lethal, → Skin rash, jaundice, diarrhoea.

Prevention: HLA matching + Immunosupp. drugs

Chronic: May follow acute or independent, later than acute, resemble CTD.

Reduced intensity BMT:

↓ mortality
↓ Intensive conditioning
↓ Toxic, old pt.
↑ relapse?
**Autologous:**

Pt. own stem cell, from Bl. Or BM, harvested & frozen → conditioning → reinfuse.

Indications: Dis. do not primarily involving haematological Tissues, or Pt. who had achieved good Remission.

   e.g. AML CR2, Myeloma, poor-risk Hodgkin, High-grade Non-Hodgkin.

Marrow recovery: 2-3 wks.

No risk of GVHD.

↓ mortality.

↑ Recurrence.

Stem cells treated to remove any residual leukemic cells is still invesigated.
# Polycythaemia

Hb $>$ 180 gr/L in M  PCV $>$ 0.52  
165gr/L in F  PCV $>$ 0.48

<table>
<thead>
<tr>
<th>Classification</th>
<th>RBC Mass</th>
<th>Plasma Vol</th>
</tr>
</thead>
<tbody>
<tr>
<td>True</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Relative</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
</tbody>
</table>

Relative: e.g. Dehydration, Diuretics, Alcohol.

True: Primary Myeloproliferative Disorders (PRV)

- EPO (Hypoxia)
- Altitude
- Lung dis. CHD
- Affinity Hb

Secondar:  
- Inappropriate

- Renal dis.
- Hepatoma
- Bronchogen. Ca.
- Uterine fibroid.
- Phaeochromocyt.
- Cerebellar haemangioblastoma.
**Polycythemia Rubra Vera**

Age: more than 40y.

Clinically:

1. Incidental.
2. Symtomatic: Hyperviscosity: Lassitude, loss of conc., headache, diziness, blackouts, pruritis (worse after hot bath), epistaxis, peripheral art. dis.
   e.g. CVA (thrombosis), venous thromboembolism.
   Peptic ulcer is common (sometimes bleeding).
   Plethoric face, majority: palpable spleen.

Diagnosis: ↑ RC mass, ↑ PCV, ↑ Plat. & Neutrophil (often), JAK -2 Mut. (97%)
   Hypercellular B.M. + Absence of secondary causes.

Treatment: ↓ risk of thrombosis: Venesection 400-500 ml (elderly less) every 5-7 wks → PCV 45%-& MAINTAIN AT THIS LEVEL.
   Hydroxycarbamide (Hydroxyurea), or α interferon → supress marrow prolif.
   & ↓ transform. Into myelofibrosis, control spleen size.

RA P ³² In old pt.

Prognosis: Survival 10-20 y with Treatment. CVA & IHD 60%

Conversion to other myeloprolif. Dis. 15%, Acute leukemia (RA P)
WBC DISORDERS

* Normal Count: \( 4 - 10 \times 10^9 / L \)

* Leucoerythroblastic picture: presence of immature WBC & ERYTHROBLAST in peripheral Bl.

* Peripheral bl. Contain Neutrophils (N), Lymphocytes (L), Eosinophils (E), Basophils (B), Monocytes (M).

* Myelocytes & Metamyelocytes may appear in peripheral Bl. in infection.

* Leucocytosis: ↑ Total WBC or only one type of cell (differential).

* Leucopenia: ↓ Total WBC or only one type of cell.

NEUTROPHILS: \( 2 - 7 \times 10^9 / L \)

Recognise, ingest & destroy foreign particles, spend 6-10 h in circul. → removed by spleen.

* Neutropenia: < \( 1.5 \times 10^9 / L \) (Asymptomatic – Sepsis)
  
  If < \( 0.5 \times 10^9 / L \) – Critical, Fever sore throat, perianal pain, skin inflam. → SHOCK if no antibiotics.
<table>
<thead>
<tr>
<th>Neutrophilia</th>
<th>Neutropenia,</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection:</strong> Bacterial, Fungal</td>
<td>Viral, Bacterial (TF), Protozoal (malaria)</td>
</tr>
<tr>
<td><strong>Trauma:</strong> Surgery, Burn</td>
<td>CTD, Alcohol.</td>
</tr>
<tr>
<td><strong>Infarction:</strong> MI, PE, Sickle C.</td>
<td>BM infilt.: Leukemia, MDS,</td>
</tr>
<tr>
<td><strong>Inflam.:</strong> Gout, R. arth., U.C.</td>
<td>Drugs</td>
</tr>
<tr>
<td><strong>Malignant:</strong> Solid Tumours, Hodgkins.</td>
<td></td>
</tr>
<tr>
<td><strong>Myeloprolif.:</strong> PRV, CML.</td>
<td></td>
</tr>
<tr>
<td><strong>Physiological:</strong> Exercise, Pregnancy.</td>
<td></td>
</tr>
</tbody>
</table>

**Drugs causing Neutropenia**

- Analgesia, Anti-infl.: Gold, Penicillamine.
- Anti-Arrhythmics: Quinidine.
- Anti-Depres.: Amitryptylline.
- Anti-Convulsants: Phenytoin, Carbim.
- Antibiotics: Sulphonamide, Penicillin, Chloramphenicol.
- Miscellaneous: Cimetidine, Ranitidine, Chlorpropamide, Zidovudine.
- Anti-Thyroid: Carbimazole.
- Anti-Hypert.: Captopril, Nifedipine.
- Anti-Malarial: Chloroquine.
**Lymphocytes**: 1.5-4 x 10⁹ / L

- **T Lymphocytes**: Mediate cell immunity.
- **B Lymphocytes**: Mediate humeral immunity.

**Lymphocytosis**
- Infection: Viral, Bacterial (Pertussis)
- Lymphoproliferation: CLL, Lymphoma.
- Post- splenectomy

**Lymphopenia**
- Inflammation: CTD.
- Lymphoma
- R.F., Steroids, Severe comb.im.def.
- Cytotoxics.

**Eosinophils**: 0.04 - 0.4 x 10⁹ / L

1. Intracellular killing of Protozoa & Hellminthes.
2. Allergic reaction.

**Eosinophilia**:
1. Allergy: Hay fever, asthma, eczema.
2. Infection; Parasitic.
3. Drug hypersensitivity: gold, sulphonamide.
4. Skin dis.
5. CTD. Polyarteritis nodosa, Hypersensitivity.
**Basophils**: 0.01 - 0.1 x 10^9/L
Involved in hypersensitivity reaction.

Basophilia: 1. Myeloprolif. dis.: PRV, CML.
2. Inflam.: Acute hypersensitivity, Ulcer. Collitis (UC).

**Monocytes**: 0.2 – 0.8 x 10^9/L
Migrate into tissue → Macrophage.

Monocytosis: 1. Infection (TB).
2. Inflam.: CTD, UC.
Lymphadenopathy

Causes: Infection:
2. Viral: EBV, HIV.
3. Protoz.: Toxoplasmosis.

Neoplastic:
1. Primary: Lymphoma, Leukemia
2. Secondary: Lung, breast, thyroid, stomach.

CTD: Rh. Arthritis, SLE.
Sarcoidosis, Amyloidosis.
Drugs: Phenytoin.

History: Speed of onset, Pain, Associated symptoms, Wt. loss, Night sweat., Itching.

Exam.: Site, Localised or Generalised.
Consistency: Hard, Soft, Rubberly.
Area of drainage, + General exam.

Investigations: CBP (↑ N eutrophils = Inflam., Haematological dis.), ESR, CXR, Biopsy.
**Splenomegally**

**Causes:**

1. **Congestive:**
   - a. Intrahep. Portal. HT. 
     Cirrhosis, Hepatic V. Throm.
   - b. Extrahep. Portal HT.
   - c. Cardiac: CHF, Const. peric.

2. **Infective:**
   - a. Bact.: Endocarditis, Septicemia,
   - b. Viral: Hepatitis, EBV, Cytomegal.
   - c. Protoz.: Malaria, Kala-azar.
   - d. Fungal: Histoplasmosis.

3. **Inflammatory/Granulomatous:**
   - Feltys syndrome, SLE, Sarcoidosis.

+ LN → LymphoProlif.

Abdom. discomfort+ backache, splen. Infarc. → severe abd. Pain., rupture ?

Investig.: FBC (Pancytopenia = Hypersplenism ?), Abd. US & CT, CXR (Mediast. LN)
BM, Splenectomy if all negative.

4. **Haematological:**
   - a. Red cell disorders
     Megalob. An., Haemoglobinopat.
   - b. Autoimmune haemolytic An.
   - c. Myeloprolif. disorders: CML, PRV, Myelofibrosis, ET.

5. **Other Malignancies:**
   - Metast. (rare)

6. **Gauchers dis.**

7. **Miscellan.:**
   - Cysts, Amyl. Thyrotoxico.
Haematological Malignancies

Corruption of the processes controlling proliferation & apoptosis of bl. Cells.
If mature cells involved → Chronic Leukemia or Low grade Lymphoma
Primitive cells involved → Acute Leukemia or High grade Lymphoma

Leukemias: 100/100,000/y. Acute Leukemia < 50% M > F,
Acute: All ages, ALL ↑ in children, AML ↑ in Old.

Risk Factors: 1. Ionising radiation
2. Cytotoxic drugs
3. Retroviruses.
4. Genetics
5. Immunological.
Acute Leukemia: ALL & AML

Failure of cell maturation, accumulation of useless immature cells in B.M. on the expense of normal haemopoietic elements, with spilling of immature cells into Bl. Clinical Feature are: marrow failure (Anemia, Bleeding, or Infection)

Investigations:

CBP: Anaemia, WBC: ↓ 1 X 10^9/L --- ↑ 500 X 10^9/L (Majority < 100 X 10^9/L.
Platelets: usually very low.
BLAST in Peripheral Bl. is DIAGNOSTIC.

BM: Confirm the diagnosis, replacement of normal elements by leukaemic blast cells (> 20% of the cells), presence of Auer rods in the cytoplasm of the blast cells = AML.

Management:
1. Decide whether to give specific treatment or not, (It is aggressive with ↑ S.E.) which may not be appropriate for elderly or pts. with other serious dis. → supportive treatment.
2. Specific treatment:
**Specific Treatment:**

Preparation for specific treat.:

1. Identify & treat infection
3. Thrombocytopenic bleeding → Platelets.
4. Hickman line (if possible)
5. Explain Therapeutic regimen to pt. & obtain consent.

-Aim of Treat. = destroy leukaemic cells without destroying the normal stem cells → Repopulation of haemopoietic Ts.

**Remission induction**: Bulk of tumour is destroyed by combination chemotherapy → Severe bone marrow hypoplasia (require intensive support.)

**Remission consolidation**: If Rem. Achieved → Residual dis. attack by No. of courses of chemo. → marrow hypoplasia (BMT may be included at this stage)

**Remission maintenance**: If still in Rem. (ALL) → Repeated cycles of Chemo. up to 3yr.

+ CNS prophylaxis = Intathecaltal (IT) Methotrexate + cranial radiation.

Failure of Rem. in induction. → Alternative combination of drugs. (poor prognosis)

Relapse during treat. Or after → poor prognosis.
<table>
<thead>
<tr>
<th>phase</th>
<th>ALL</th>
<th>AML</th>
</tr>
</thead>
<tbody>
<tr>
<td>Induction</td>
<td>Vivcristine (iv)</td>
<td>Daunorubicine (iv)</td>
</tr>
<tr>
<td></td>
<td>Prednisolone (po)</td>
<td>Cytarabine (iv)</td>
</tr>
<tr>
<td></td>
<td>L-asparaginase (im)</td>
<td>Etoposide (iv &amp; po)</td>
</tr>
<tr>
<td></td>
<td>Daunorubicine (iv)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Methotrexate (IT)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consolidation</td>
<td>Daunorubicine (iv)</td>
<td>Cytarabine (iv)</td>
</tr>
<tr>
<td></td>
<td>Cytarabine (iv)</td>
<td>Amsacrine (iv)</td>
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<td></td>
<td>Etoposide (iv)</td>
<td>Mitoxantrone (iv)</td>
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<td>Methotrexate (iv)</td>
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<tr>
<td>Maintenance</td>
<td>Prednisolone (po)</td>
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<td></td>
<td>Vincristine (iv)</td>
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<td>Mercaotopurine (po)</td>
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</tr>
<tr>
<td></td>
<td>Methotrexate (po)</td>
<td></td>
</tr>
</tbody>
</table>
Supportivit treatment:  

Anaemia: Red Cell Concentrate Transfusion.

Bleeding: Thrombocytopenic bleeding require platelets. Prphylactic plat. transf. to maintain plat. c. > 10 X 10^9/L. Treat any Coagulation abnormalities.

Infection: Fever > 38oC, > 1h in Neutropenic pt. indicate possible septicemia. Start Broadspectrum antibiotic (Gentomycin + piperacillin± Vancomycin), to continue for at least 3ds after the fever resolved.

Flucanazole for oral & pharangeal moniliasis.

Amphotericin iv for systemic fungal inf. (candida or aspergillosis) for 3wks.

Herpes simplex and zoster: antiviral (aciclovir).

Isolation is debatable (psychological).

Metabolic problems: Monitor fluid, hepatic, renal function, anorexia & deficult drinking → iv fluid & electrolytes. Cellular breakdown during induction (tumour lysis syndrome) → ↑K, ↑Uric acid, ↑phosphate, & ↑Ca. → RF?

Allopurinol + iv Hydration.

Psychological: Keep pt. informed, answer question, allay fear as possible.

Prognosis: Median survival without treat. is 5wks. Few Ms with supportive treatment. 80% < 60y age achieve remission with specific treat. Survival depends on risk factors (chromosomal analysis) 5y survival for AML 21%-76%, ALL 20-37%.
Chronic Myeloid Leukemia (CML)

* Myeloproliferative stem cell disorder resulting in prolif. Of all haematopoietic Lineage but predominantly in the granulocytes series. chiefly 30-80y, 20% of all leukemia.
* 95% philadelphia (ph ch) = shortened ch. 22 resulting from translocation of material with ch 9.
* BCR(breapoint cluster region on chr.22 + Fragment from chr. 9 carries ABL oncogen → BCR ABL Gene codes for protein with Tyrosine Kinase activity → play a role in the dis. As an oncogene.

CML has 3 phases:

1. **Chronic phase**: The dis. is responsive to treat., lasting 3-5y. With the introduction of imatinib → > 5Y.

2. **Accelerated phase**: (not always seen), dis. control more difficult.

3. **Blast crises**: dis transforms into acute leukemia (AML%70, ALL30%), Refractory to treat., It is the major cause of death. Prior to imatinib therapy, 10% CML → AML/y, now only 0.4-2.5% after up to 5y treat.

   ph. Ch. –ve CML: Old pt., ↑Male, ↓Plat. ↑ Monocyte, respond poorly to treat.

   Median survival 1y.
Clinically: 25% - asymptomatic at diagnosis.

- Tiredness: 37%
- Anorexia: 12%
- SOB: 21%
- Abdominal Fullness: 10%
- Abdominal Pain: 21%
- Bruising: 7%
- Lethargy: 13%
- Vague Ill Health: 7%

*Splenomegally: 90% (10% massive) ± friction rub (splenic infarction)
*Hepatomegaly: 50%
*LN: Unusual.

Investigations: 1. FBC: An. (normochromic normocytic). WBC 10-600x10^9/L (full range of granulocytes precursors from myeloblast to mature neutrophils, myeloblast < 10%, ↑Eosinoph. & Basophils.

- Platelets: ↑ in ⅓ (up to 2000x10^9/L). Nucleated RBC are common.
- Accelerated phase: ↑ % of more primitive cells.
- Blast transformation: Dramatic ↑ Blast in circul., ↓ plat.
- Basophils ↑ with dis. Progress.

2. Bone marrow: to confirm diagnosis & phase of the dis. (morphology & chromosome analysis).

3. Bl. LDH & Uricacid ↑ (↑ cell breakdown)
Management:
Chronic phase: 1. **Imatinib** inhibit BCR ABL Tyrosine Kinase (TK) activity & reduce the uncontrolled prolif. of WBC. It is 1st line therapy in chronic phase complete cytogenic response (disappearance of ph chr.) in 76% at 18 Ms of therapy.

Failure of response or progress on imatinib → 2nd generation TK Inh. e.g. **Dasatinib, or Nilotinib**

: 2. Allogenic BMT

3. Hydroxyurea (Hydroxyurea): still used for initial control of the dis. or palliative treat. (no effect on ph chr. & on onset of blast transformation).

4. Interferon-α: was 1st line of treat. ± Ara-C: control CML in 70% of cases.

Accelerated phase: Pt. presented with this phase, imatinib is indicated if not already received. Hydroxyurea is also effective. Low dose cytarabine can be tried.

Blast Transform.: ALL response better than AML. (supportive treat.)

Pts. Progressing to advanced phase on imatinib may respond to 2nd gener. TK inh. or BMT.
**Chronic Lymphocytic Leukemia (CLL)**

* Most common leukemia (30%). M:F is 2:1, median age at presentation 65-70y.
  * B lymphocytes fail to transform & produce Abs → Increasing mass of immuno-incompetent cells → ↓ immune function & normal BM haematopoeisis.

**Clinically:**
  * Insidious onset. 70% incidental diagnosis (routine FBC).
  * Anaemia, Infection, Painless Lymphadenopathy & systemic symptoms e.g. Night sweat, or wt. loss.

**Investigations:**
  1. **FBC:** Mature lymphocytes > 5x 10^9/L. characteristic morphology & markers, CD19 & CD23.
  2. ↑ Reticulocyte count & +ve coombs test. = haemolytic An. (may occur)
  3. **S. Igs:** to assess the degree of immunosuppression (common & progressive).
  4. **B.M. exam.** Is not essential for diagnosis, but helpful for prognosis (diffuse involv. = poor prognosis), & to monitor response to therapy.

  * **Main prognostic factor is stage of the dis.**, CD38, Mutation of IgVH Genes suggest poor prognosis.

**Staging of CLL:**
  * **Stage A:** 60%, no Anaemia, Normal Plat. count, < 3 areas of LN enlargement.
  * **Stage B:** 30%, no Anaemia, N Plat., 3 or more areas of LN enlarg.
  * **Stage C:** 10%, Anaemia & or ↓ Plat., regardless of the No. of areas of LN enlarg.
Management:
* No specific treat for most stage A, unless progression, life expectancy is normal.

*Treatment:
1. BM failure.
2. Massive or progressive LN PATHY or Splenomegally.
3. Systemic symptoms e.g. wt. loss or night sweat.
4. Rapidly ↑ lymphocyte count.
5. Autoimmune haemolytic An., or ↓ Plat.
   Stage B & C: Chlorambucil
   Recently Fludarabine + Cyclophosphamide → ↑ rem. rates & dis. Free survival (↑ risk of infection)
   B.M. Failure or autoimmune cytopenias → corticosteroid.

Supportive care: Symptomatic, Anaemia or thrombocytopenia → Transfusion.
   Treat. Of infec., Ig for hypogammaglobulinaemia.

Radiotherapy: LN causing discomfort or obstruction. & for symptomatic splenomegaly
Splenectomy: may be, to improve low Bl. Count. due to autoimmune destruction
   or due to hypersplenism & can relieve massive splenomegally.

* Prognosis:
Overall survival is 6y., stage C 2-3y, 50% die from infection.
Rarely → Aggressive high grade Lymphoma (Richters syndrome).
**Prolymphocytic Leukemia**

* Variant of CLL, mainly in Male > 60y. 25% T cell variety
* Massive splenomegaly, + Little Lymphadenopathy.
* WBC often > 400 x 10⁹/ L (Characteristic cell is large lymphocyte with prominent nucleolus.
* Treat. : Is generally unsuccessful & prognosis very poor.
  Leukapharesis, Splenectomy, & chemo. May be tried.

**Hairy cell Leukemia** :

* Rare, chronic lymphoproliferative B cell disorder, M 6:F 1, median age 50y.
* General ill health, & recurrent infection.
* Splenomegaly 90%, LN unusual.
* Lab.: Severe Neutropenia, Monocytosis, & characteristic HAIRY CELL in Bl. & B.M..
  → CD25 & CD103.
* Treat.: Cladribine & Deoxycoformycin.
Lymphoma

* Neoplasms arise from lymphoid tissue. Majority are of B cell origin. Diagnosed from pathological changes on biopsy as Hodgkin or Non-Hodgkin lymphoma.

* Non-Hodgkin lymphomas are classified as:
  2. Low-grade: slowly dividing, present for Mns before diagnosis, indolent.

  **Hodgkin lymphoma (HL)**

* Histological hallmark is Reed–Sternberg cells.

* 4/100,000/y, slight M. excess, median age 31y
  Aetiology unknown, ↑ in educated background & small families, X3 ↑ likely with PMH of inf. Mononucleosis, (no association with EBV).

* Pathological classification:
  1. Nodular lymphocyte predominant, (5%), slow growing, localised, rarely fatal.
  2. Classical HL:
     a. Nodular sclerosing (70%), ↑ in young F.
     b. Mixed Cellularity (20%), ↑ elderly.
     c. Lymphocyte-rich: (5%) ↑ M.
     d. Lymphocyte-depleted: (rare)
Clinically:

* **PAINLESS,RUBBERY LN-pathy,** ↑ neck,& supraclavicular. Young with Nod. Sclerosis may have large mediastinal masses (asymptomatic or dry cough & SOB).

Isolated subdiaphragmatic nodes < 10% at diagnosis.

* Hepatosplenomegaly may be present but not always indicate dis. In them.

* Extranodal spread to bone brain or skin --- rare.

Clinical Stages:  (Ann Arbor)

1. **Stage I:** Single LN region(I)or extralymphatic site(IE).

2. **Stage II:** 2 or more LN regions(II),or an extralymph. site & LN regions on the same side of (above or below) the diaphgram(IIE).

3. **Stage III:** LN regions on both sides of the diaph.with(IIE) or without (III) localised extralymph. Involv. Or involv. Of spleen(IIIs) or both (IIISE).

4. **Stage IV:** Diffuse involv. Of one or more extralymph. Tissue e.g. liver or BM.

**Note:** 1. Each ststage is subclassified into:

   A. No systemic symptoms.

   B. Systemic symptoms (Weight loss,drenching sweat)

2. Lymphatic structure = LN, Spleen, Thymus,Waldeyers ring, Appendix & peyers patches.
**Investigations:**
* FBC: may be Normal. Anaemia or Lymphopenia :poor prognostic F.. ± ↑ E , N & ESR.
* Renal f. tests: (to insure normal function before treat.).
* Liver f. tests: Abnormal may reflect hepatic infilt.,LN in porta hapatis → obs.j.
* LDH: ↑ = Poor prognostic F.
* CXR: Medast mass ?
* CT: chest, abd., pelvis → staging. Bulky dis.= > 1o cm single node mass(poor prog.F) * LN biopsy:surgical or percut. Needle biopsy.

**Management:**
* Historically: stage IA & IIA : Local radiotherapy(Radio.T)
  * .Recently: Early-stage dis.has better outcome if chemotherapy(Chemo.T) included.
  
    Majority are now treated with Chemo,T.+ Radio.T.
    ABVD regimen (doxorubicin,vinblastine,bleomycin & dacarbazine).
    Early –stage: 4 courses ABVD,followed by radio.T. to involved LN.
    Response by CT & positron emision tomography(PET).
    S.E.of ABVD: doxorubicin → cardiac,bleomycin → pulmonary.
    ↓ MDS /AML & infertility.
    Advanced stage: Chemo.T. alone. 6-8  cycles ABVD., Therapy resistant → BMT.
Prognosis:
Early-stage: 90% CR, majority cured.
Advanced-stage: 45-70% cured.
Relapse within a year → good salvage rate with autologous BMT.
Relapse after 1y → Chemo.T
Non- Hodgkin lymphoma ( NHL )

* Monoclonal prolif. Of lymphoid cells of B cell (70%) or T cell (30%) origin.
* 12 new cases / 100 000/y. slight ↑ M ,median age 65-70y.

Aetiology:

* Late manifest. Of HIV.
* EBV,HTLV.(Certain lymphoma).
* H pylori –Gastric lymphoma.
* Chrom. Lesion: t(14:18) –Follicular lymphoma.
* Immunosuppressed pts.after organ transplant,congen. immunodef states.

Clinically, the most important factor is grade:

* High grade: Hige prolif. rate, rapidly producing symptoms, fatal if untreated, potentially curable.
* Low grade: Low prolif. Rate, may be asymptomatic for many Ms before presentation.
  indolent course, not curable.
* 85% are either high grade diffuse large Bcell, or low grade follicular lymphoma.

Other forms include: mantle cellL.&MALT lymphoma (less common).
Clinically:
* Often widely spread at presentation, including extranodal sites.
* Extranodal involves BM, gut, thyroid, lung, skin, testis, brain & bone.
  BM involv. is more common in low grade (50-60%) than high grade (10%).
  Compression syndrome: gut obst., ascitis, SVC obst. & SC compression.
* Staging is same as HL, but NHL is more likely to be stage III & IV at presentation.

Investigations: as in HL + the followings:
  1. Routine BM aspirate & trephine biopsy.
  2. Immunophenotyping of surface antigens to distinguish T & B cell tumours.
  3. Igs: some lymphomas are associated with IgG or IgM paraproteins (serve as markers for treatment response).
  4. Uric acid ↑ with treat..
  5. HIV.
Management:

**Low grade lymphoma:**

* Asymptomatic: may not require treat.

  Indications: marked systemic symptoms, LN causing discomfort or disfigurement.

* Options:
  1. Radiotherapy: localised stage I (rare)
  2. Chemotherapy: Chlorambucil (po), well tolerated but not curative.
     - More intensive iv chemo. In young → better quality of life but no survival benefit,
  3. Monoclonal Ab. Therapy: target surface Ag. on tumour cells. → cell apoptosis.
     - Rituximab(R)(anti-CD20) → durable reaponse in 60%, when given alone.
     - 1st line therapy = R-CVP (Cyclophosphamide, Vincristine, Prednisolone)
  4. Relapse: ↑ dose Chemo. + BMT (Study is going on).

**High grade lymphoma:** needs treat. At initial presentation.

  1. Chemotherapy: > 90%: CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Predn)
  2. Radiotherapy: Few stage I, residual bulky dis. After chemo, compression (e.g. SC.)
**Prognosis:**
Low grade: Indolent, remitting & relapsing, median survival - 10y.
High grade: 80% respond initially to treat. But only 35% have dis.-free survival at 5y.
**Paraproteinaemia:**

Gammopathy: Overproduction of 1 or more Ig. (detected by electrophoresis).

- **Polyclonal**: Acute or chr. Inflamm., e.g. Infection, Sarcoidosis, Autoimmune disorder, Malignancy.
- **Monoclonal** (=M Protein) occur with N or ↓ other Igs.
  - Myeloma, Lymphoma, Amyloidosis, CTD e.g. Rh. arthritis, HIV, Solid tumours, or no underlying dis.

**Gammopathy of uncertain origin (MGUS):**
Common condition with increasing age, 1% > 50y, 5% > 80y.
Paraprotein is present in Bl. but with no other features of MM or WM, Lymphoma or related dis.

**Clinical:** Usually asymptomatic, normal FBC & Biochemistry. Ig: small amount with no immune paresis. BM → Plasma cells < 10% of nucleated cells.

**Prognosis:** After 20y → 25% MM or related disorder.
- Annual monitoring.
Waldenstrom macroglobulinaemia

Low-grade lymphoplasmacytoid lymphoma associated with IgM paraprotein, causing clinical features of hyperviscosity syndrome. Rare, ↑ elderly, ↑ M. Clinically: Nose bleed, bruising, confusion & visual disturbance.

May present with An., systemic symptoms, splenomegaly, or LN-pathy.

Lab.: ↑ IgM + ↑ plasma viscosity.

BM: Infiltration with lymphoid cells & prominent mast cells.

Manag.:

Severe hyperviscosity & An. → plasmapheresis.

Chlorambucil: effective but slow.

Fludarabine: more effective.

Rituximab: also effective
Multiple Myeloma (MM)

* Malignant prolif. Of plasma cells.

Normally: Plasma cell produce polyclonal Ig = variety of heavy chains are produced, & each may be of kappa or lambda light chain type.

Myeloma: Plasma cells produce Ig of a single heavy & light chain (monoclonal protein = paraprotein), in some cases only light chain is produced → appear in urine (Bence Jones proteinuria).

Classification:

<table>
<thead>
<tr>
<th>Type of paraprotein</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG</td>
<td>55</td>
</tr>
<tr>
<td>IgA</td>
<td>21</td>
</tr>
<tr>
<td>Light chain only</td>
<td>22</td>
</tr>
<tr>
<td>Others(D,E non-secretory)</td>
<td>2</td>
</tr>
</tbody>
</table>

*Majority of malignant plasma cells are present in BM, small No. in circulation.

*Malignant plasma cells produce cytokines → stimulate osteoclast → bone reab- sorption. → lytic lesions → pain, fracture, & ↑ Ca++.

*BM involv. → An. or pancytopenia.
**Clinically:**

4/100 000/y, M2:Fl, Median age 60-70y,

<table>
<thead>
<tr>
<th>PATHOLOGY</th>
<th>EFFECTS</th>
<th>SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrow involv.</td>
<td>Bone erosion by osteoclast path. Fracture</td>
<td>Pain</td>
</tr>
<tr>
<td></td>
<td>↑Ca++</td>
<td>Severe local pain</td>
</tr>
<tr>
<td></td>
<td>BM failure → An.</td>
<td>Lethargy, thirst.</td>
</tr>
<tr>
<td>↑ paraprot. &amp; L chain</td>
<td>Renal damage</td>
<td>Tiredness</td>
</tr>
<tr>
<td></td>
<td>↑ viscosity</td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td>Amyloidosis</td>
<td>Blurred vision, headach</td>
</tr>
<tr>
<td>↓ Normal plasma cells</td>
<td>↓ immunity</td>
<td>Nephrotic syndrome</td>
</tr>
</tbody>
</table>

**Diagnosis:** Requires 2 of the followings:

1. BM malignant plasma cells. (BM aspiration)
2. S & or urinary paraprotein. (Bl & urine protein electrophoresis)
3. Skeletal lytic lesions. (X-rays/skeletal survey)

**other investigations:**

1. FBC: (Degree of BM failure), ↑ ESR (not specific), urea & electrolytes, creatinine, uric ac., S.Ca++ & albumin.
   coagulation screen?, B2 microglobulin, MRI( SC compr.).
2. Bl. & urine immunoelectrophoresis(type of paraprotein).
3. Quantification of paraprotein, & other Igs(immune paresis).
Management:
Asymptomatic: treat. may not be required.
Immediate support:
1. High fluid intake to treat renal impairment & hyper Ca++.
2. Analgesia for bone pain.
3. Biphosphonates for hyperCa++ (it also reduce bone pain & risk of fracture, may cause apoptosis of malignant plasma cells)
5. Plasmapheresis for hyperviscosity.
Chemotherapy:
1. Old pts.: 1st line chemotherapy: Thalidomide + Melphalan + Prednisolone → median survival to 51 Ms.
2. Young Pts.: 1st line chemo. To max. response (plateau phase), then autologous BMT (prolong survival but no cure).
Radiotherapy:
For localised pain not responding to analgesia, pathological fracture & for emergency treat. Of SC compr. Complicating extradural plasmacytoma.
Prognosis: Poor prognostic features: ↑ B2-microglobulin, ↓ albumin, ↓ Hb or ↑ Ca++ at presentation. 5% survive 5y.
Myeloproliferative disorders:
Group of diseases characterised by clonal prolif. Of marrow erythroid precursors (PRV), Megakaryocytes (Essential thrombocythaemia & Myelofibrosis) or myeloid cell CML, some having overlapping features, & often progression from one to another e.g. PRV to myelofibrosis.

MYELOFIBROSIS:
BM is initially hypercellular, with excess abnormal megakaryocytes which release growth factors e.g. platelet-derived growth factor, to the marrow microenvironment → reactive prolif. Of fibroblasts → marrow fibrosis.

Clinically: Age ↑ > 50y, Lassitude, wt. loss, night sweat. SPLEEN MASSIVELY ENLARGED (extramed-ullary haematopoiesis).

Lab.: 1. FBC: Leukoerythroblastic An. ↑ reticulocyte count, tear drop RBC. WBC: ↓ - ↑.
   Platelets: ↑, N, ↑, Giant form may be seen. 2. ↑ uric ac., folate def. is common.
   4. JAK -2 mutation 50%.
Management & prognosis:
Median survival: 4y. (range 1-20y).
Treat.: Control symptoms:
  RBC transf. for An.
  Folic ac. To prevent def.
  Hydroxycarbamide to control splenic size, WBC count, systemic symptoms.
Splenectomy: grossly enlarged, or pancytopenia (hypersplenism)
BMT: may be considered for young pt.
**Essential thrombocythaemia:**
Malignant prolif. Of megakaryocytes result in raised level of circulating platelets, that are often dysfunctional.
Reactive causes of ↑plat. must be excluded.

**Clinically:** Median age: 60y, may be asymptomatic with ↑ plat. Count.
Vascular occlusion or Bleeding.
Small % → Acute leukemia or Myelofibrosis.

**Lab.:** ↑ plat., JAK-2mutation 50%

**Treat.:**
* ↓ risk pt. ( age < 40y, plat.c. < 1000 x 10^9/L & no bleeding or thrombosis) → may not require treat.
* Plat, c. > 1000 x 10^9/L, with symptoms, or with risk factors for thrombosis (DM, HTN), → Treat. to control plat.c../ e.g. Hydroxycarbamide or Anagrelide (inh. Of megakaryocytes maturation). Radioactive phosphorus (P32) for old age.
* Aspirin for all pts. To reduce risk of thrombosis.
Infectious mononucleosis (IM)

*Acute viral illness, most often caused by EBV (CMV, HIV-1 & Toxoplasmosis may cause similar clinical syndrome). Acquired from asymptomatic excreters via saliva by droplet infection or kissing.


Fever, Headache, & malaise, followed by severe pharyngitis (± tonsillar exudate, Ant. & Post. cervical LN-pathy), palatal petechiae, periorbital oedema, splenomegaly, inguinal & axillary LN. & macular, petechial, or erythema multiforme rashes may occur. Fever resolved in 2 wks & fatigue in another 2 wks.

Death is rare: resp. obst., splenic rupture, thrombocytopenia, or encephalitis.

Investigations:
1. FBC: Atypical Lymphocytes in peripheral Bl.
2. Paul-Bunnel or Monospot test: detect heterophil Ab. present during acute illness & convalescence (to be repeated if initially –ve).
3. Specific EBV serology (immunofluorescence) can be used to confirm the diagnosis
<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe pharyngeal oedema</td>
<td>Neurological</td>
<td>Ruptured spleen</td>
</tr>
<tr>
<td>Antibiotic-induced rash</td>
<td>Cranial nerve palsy</td>
<td>Resp. obstruction</td>
</tr>
<tr>
<td>(80-90% with Ampicillin)</td>
<td>Polyneuritis</td>
<td>Agranulocytosis</td>
</tr>
<tr>
<td>Prolonged post-viral fatigue</td>
<td>Transverse myelitis</td>
<td>Lymphoprolif. Dis.</td>
</tr>
<tr>
<td>Hepatitis (80%)</td>
<td>Meningoencephalitis</td>
<td></td>
</tr>
<tr>
<td>Jaundice (&lt;10%)</td>
<td>Haematological</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Haemolytic An.</td>
<td></td>
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<tr>
<td></td>
<td>Thrombocytopenia</td>
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<tr>
<td></td>
<td>Renal</td>
<td></td>
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<tr>
<td></td>
<td>Abnormal GUE</td>
<td></td>
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<tr>
<td></td>
<td>Interstitial nephritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myocarditis, ECG abn.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pericarditis</td>
<td></td>
</tr>
</tbody>
</table>
Management:
1. Symptomatic:
2. If throat culture revealed B-haemolytic streptococci → penicillin. (avoid ampicillin & amoxicillin → macular rash.
3. Severe pharyng. Oedema → prednisolone 30 mg 5d.
4. Antiviral: not effective.
5. Avoid contact sports (splenic rupture) until splenomegaly has completely resolved.