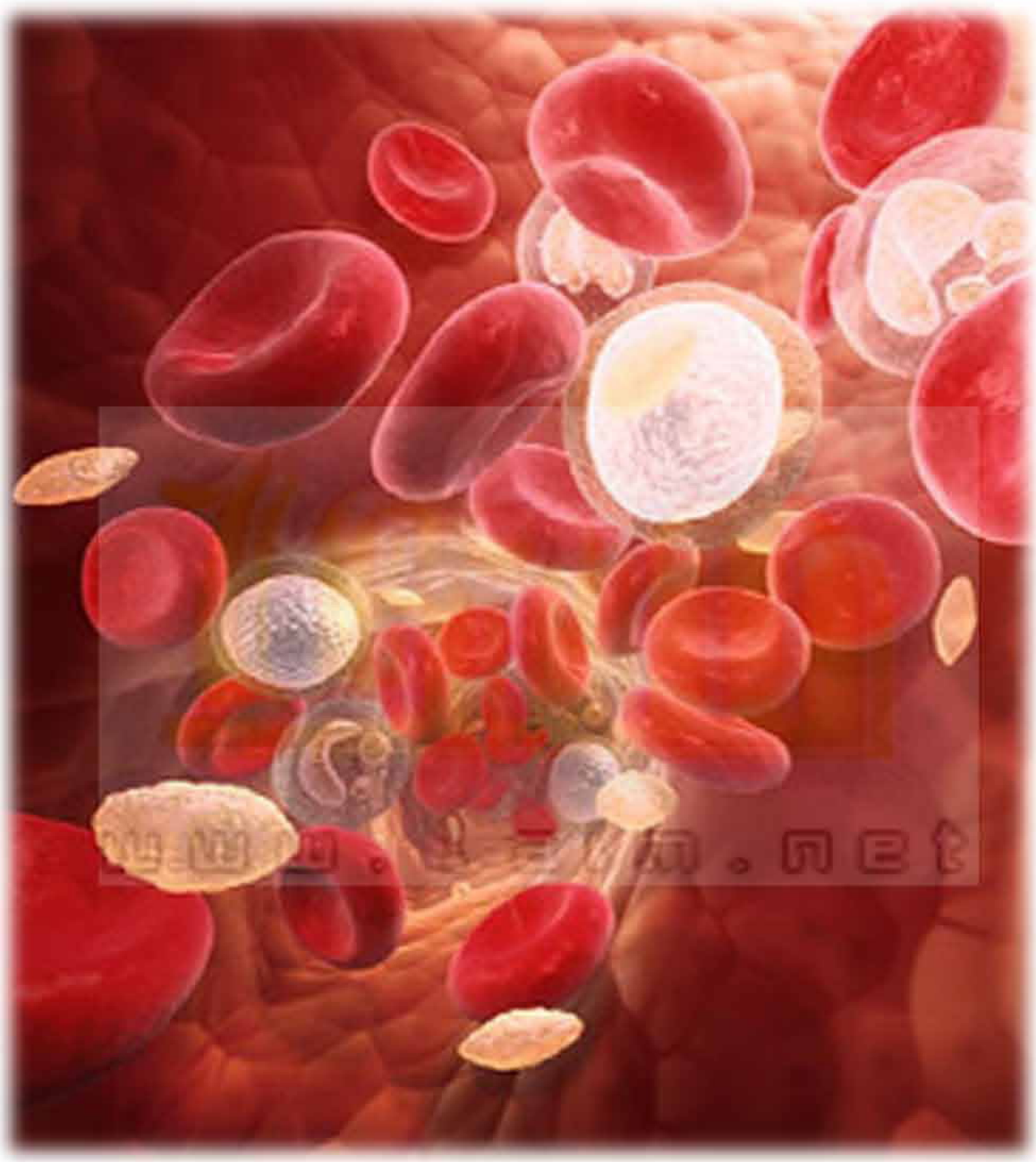
Blood



2009-2010

Index:

LEUKEMIA

ACUTE

LYMPHO-BLASTIC

لوكيميا الأطفال .. تستجيب للعلاج

MYELOID

لوكيميا الشباب ... عنيفة جدا

CHRONIC

MYELOID (M)

لوكيميا ..... منتصف العمر

LYMPHO-CYTIC

لوكيميا العواجيز .... طيبة .. شبيهة الـLymphoma

Malignant proliferation of

B/M Blast Cells ⇒ B/M & Tissue infiltration.

(ALL = 75 % B CELL / 25 % T CELL WHICH IS RESISTANT TO TTT. ⇒ WORSE PROGNOSIS)

↓ neutrophils

Malignant proliferation of

Myelo-Promyelocytes & Mature Neutrophils.

(SMALL CELLS..... ESCAPE B/M.... TISSUE INFILT. + LATE B/M FAILURE)

↑ neutrophils

Accumulation of

Mature B lymphocytes in Blood, BM, Lymphoid T.

"CELL OF ORIGIN B-LYMPHOCYTE.....ABNORMAL Ig"

➢ Cl./P

1) BM INFILTRATION ⇒ BM FAILURE

- ↓RBCs → ANEMIA → PALLOR.
- ↓WBCs → INFECTIONS → FEVER. (SOME TIMES WEAK T RESPONDING TO TTT. / PEG-ASNASE ADMIN.)
- ↓PLATELETS → BLEEDING. (EPSITAXIS / PURPURA)

2) TISSUE INFILTRATION:

a) BONE ⇒ fractures / sternal tenderness.

b) LIVER - SPLEEN – LN++ ...(ALL > AML)

c) CNS ⇒ MENNGEAL INFILT.

d) RETINA ⇒ ↓ VISION.

e) HEART ⇒ CARDIOMYOPATHY.

f) LUNG ⇒ HEMOPTYSIS.

g) PORTA HEPATIS ⇒ OBST. JAUNDICE.

h) KIDNEY ⇒ TUBULAR DAMAGE ⇒ ↓ K ↓ NA.

i) SKIN ⇒ ITCHING. "LEUKEMIA CUTIS"

j) LEUCO-STASIS.

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1) ASYMPTOMATIC. (30%) ACCIDENTLY DISCOVERED.

2) MASSIVE SPLEEN ⇒ PAIN

- DRAGGING PAIN / IN LT. HYPO-CH.
- STITCHING PAIN DT SPLENIC INFARCTION. DT LEUCOSTASIS.

3) BONY ACHES + BLOOD CELLS

- ↓RBCs ⇒ ANEMIA.
- N. NEUTROPHIL → NO INFECTION.
- N. PLATELETS → NO BLEEDING.

4) FEVER & SWEATING. (NOT DUE TO INFECTION) (↑WBCs turnover → ↑BMR → low grade fever)

5) LEUCO-STASIS ⇒ brain, lung, penis.

6) BLAST CRISIS: "هيقلب فتك هي المشكلة ... هيموت"

(CML TRANSFORMS TO AML ⇒ BM failure ⇒ DEATH)

---

1) Asymptomatic. (mainly)

2) LIVER - SPLEEN – LN++

3) IMMUNE DISORDERS

- ↓RBCs → AIHA (+ve COOMB'S TEST)
- ↓PLATELETS → BLEEDING.
- ↓ IG → INFECTIONS E MRSA

أهم حاجة ... هيموت

HUGE SPLEEN (CROSSING UMBILICUS)

1) CML.
2) Myelo-fibrosis.
3) Amyloidosis.
4) CHRONIC MALARIA. "tropical spleen"

Acute leukemia

Chronic leumkemia

Invest.

	Lympho-blastic	Myeloid	Myeloid (M)	Lympho-cytic
• WBCs .. TLC	Variable so Don't depend on ↑TLC But excessive Blasts in blood if NOT, see BM dt		خرافي > 25,000 ⇒ Up to million / mm³ ○ Myelo & Pro-myelocytes. ○ Mature Neutrophils. (marked shift to the Lt.) ○ Basophilia. ○ Eosinophilia. **In Blast crisis** ↑↑ Myelo- Blasts > 20-30%	Sustained Absolute Lymphocytosis > 5,000 upto Million / mm³ ○ dt infections ○ Mature Lymphocytes.
• RBCs	Normo / Normo		✓	✓ (dt BM failure / AIHA)
• Platelets	↓		Normal or ↑ (Myelo-Prolif.) or ↓.	↓ (dt BM failure / Immune D.)
BM exam. "Confirmatory"	1) > 20% Blasts in BM to exclude ITP in Aleukemic leukemia 2) AML → Auer Rods in cytoplasm of blasts. 3) AML → +ve Myeloperoxidase/ (-ve) in ALL		• Myelo & Pro-myelocytes.	• Immature Lymphocytes > 30%
Others	1) ↑↑↑ ESR (Leukemia / Lymphoma / MM) 2) ↑ Uric acid & LDH dt Tumor lysis $. 3) ↓ALP. (Variable) 4) Others: ✓ Kidney & Liver profile ✓ CT brain ✓ Pelvi – abdominal Sonar.		1) ↓ALP (dt Immature Malignant WBCs ↑ in leukemoid reaction) 2) ↑↑↑ Uric acid dt ↑↑ TLC – LDH. 3) ↑ Vit. B_{12} (Tumor Marker) dt ↑ WBCs production of Trans-cobalmin I 4) Philadelphia Chromosome by PCR. (fusion of Ch. 9 - 22 → Fusion Oncogene → Stem cells turn-off apoptosis → ↑ no. in BM & bl.)	• +ve Coomb's test ⇒ AIHA "Warm Ab" • ↓ Ig or normal.
prognosis	ALL better than AML 1) Age: 2 - 10 ys. TLC > 1000,000 2) Platelets < 25,000 L_3.		Blast crisis.	Reichter's transf (High grade Lymphoma.

When to Suspect Aleukemic leukemia?!

- Infections ... sore throat.
- ↓ Neutrophils / RBCs. / platelets.
- BM exam ... Blasts in BM.

	Sub-leukemic Leukemia	Aleukemic Leukemia
TLC	Normal	Normal
Blasts in Bl.	↑↑	------ but Blasts in BM.

Not Viral

Treatment of Leukemia

Acute Lymphoblastic / Acute Myeloid

General measures: ⇒ تعنش العيان

1) **BM failure:**
   a) ↓RBCs ⇒ BL. transfusion.
   b) ↓WBCs ⇒ Isolation & Abs / Anti-viral / Fungal
      Sumin for pneumocystis Carnii.
   c) ↓Platelet ⇒ Platelet transfusion. (TO > 20,000)
2) **Leuko-stasis** ⇒ Leukopharesis.
3) **Tumor lysis $:** ⇒ S. Creatinine
   a) hyper-Uricemia → ARF (↑ s. Creatine) ⇒ Allo-purinol + Alkaline Diuresis.
   b) hyper-Phosphatemia ⇒ phosphate binders (Ca_2CO_3)

Specific ttt. of B/M

A) Induction ⇒ (VAP-L) 4 wks الضربة القاضية

1) V incristine
2) A drriamicin.
3) P redniSolone. "Lympholtic"
4) L-Asparginase

Aim: Destroy Tumor Bulk in BM
Orient in normal BM

B) Consolidation ⇒ (CC) 4 wks عشان يسلم و ميقمش تاني

1) C yclo-phosphamide
2) C ytosine arabinoside. (Ara-C)

CNS prophylaxis ⇒ Intra-thecal Methotrexate.

Signs of Remission:
- improv. CLP.
- BM blasts < 5%
- No blasts in bl.

D) Maintenance ⇒ (MM) 2ys.

1) 6-M ercaptopurine
2) M ethotrexate

A) Induction: CTA هذا هو لطم

1) C ytosine arabinoside
2) 6-T hioguanine
3) A drriamicin.

Delay All BM (Blasts & Normal)

C) Consolidation:
(As above + CNS prophylaxis)
for M4, M5

E) Maintenance (MM)
صعب جدا اذن الهدف
Induction then BM Transplant.

Chronic Myeloid

Aim of CML ttt.:

1) ↓ TLC ↓ leuco-stasis.
2) Delay BM failure.
3) Control Blas crisis.

General measures.

Specific ttt.

1) **hydroxy-urea:**
   ⇒ Myelo-suppressive
   ⇒ to keep TLC with in Normal
   ⇒ to avoid leuc-stasis
2) **Interferon:** (Anti-prolif.)
   ↓ PH (+VE) cells → ↓ PH Chromosome
3) **Imatinab to CML & Blast crisis.**
   ⇒ (-) Throsin kinase
   ⇒ ↓ Activity of fusion proteins
4) **Blast crisis as ALL / AML.**
5) **Spleen** ⇒ Radio-th. / splenectomy.
6) **Leuco-pharesis.** (DT million TLC)
7) **BM Transplant. "of choice"**

Chronic Lymphocytic

Indications of ttt. in CLL:

- Anemia. (AIHA)
- Spleen & LN ++++++
- Reichter's transformation.

Stage A: (no B/M failure)

- No specific ttt.
- Re-assure & follow up.

Stage B: CLL

- Chlorambuci + Cyclophosphamide.
- Radio-therapy to LN.

Stage C: SC

1) Chlorambucil + Cyclophosph.
2) Cortico-Steroids (if AIH failure + AIHA)
3) ↓RBCs ⇒ packed RBCs trans.
4) ↓Platelet ⇒ platelet trans.
5) **Rituximab** (MCA against tumor cells & CD-20 Ag)

➢ **Splenectomy if:**
- AIHA.
- Huge spleen.
- Hyper-splenism.

FAB classif. Of ALL

- L_1 Small cells.
- L_2 Large cells.
- L_3 Burkit like large cells.

(Vacuolated Cytoplasm v. aggressive)

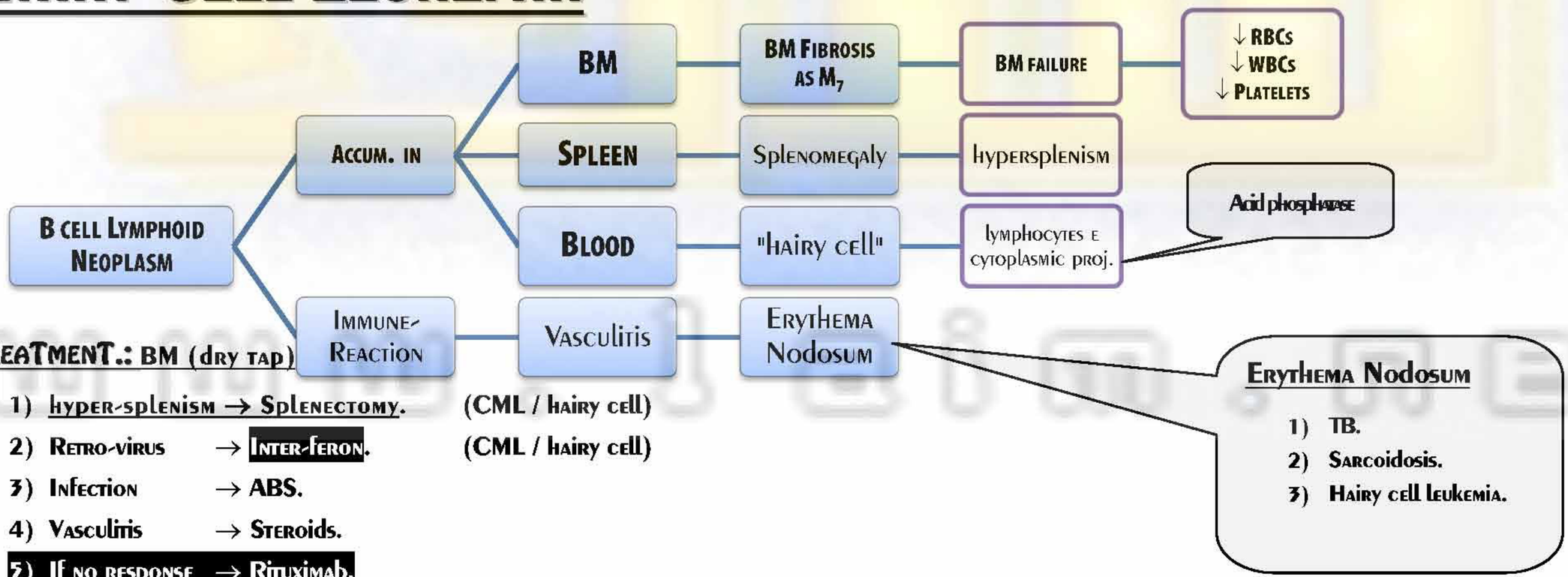
FAB classif. Of AML

M_0	un-diff.	
M_1	Myelo-blast	+ No maturation
M_2	Myelo-blasts	+ Maturation.
M_3	pro-myelocyte	⇒ DIC
M_4	Myelo-monocytic.	
M_5	Mono-cytic	⇒ Gum hypertrophy.
M_6	Erythro-leukemia ⇒ Multi-N. RBC blasts in BM.	
M_7	Megakaryo-blastic ⇒ v. aggressive. "Myelo-fibrosis"	

Staging of CLL

	A	B	C
lympho-cytosis	✓	✓	✓
LN++	< 3 LN++	> 3 LN++	Regardless No.
BM failure	×	×	✓

Hairy Cell Leukemia



Treatment.: BM (dry tap)

1) hyper-splenism → Splenectomy. (CML / hairy cell)
2) Retro-virus → Inter-feron. (CML / hairy cell)
3) Infection → ABS.
4) Vasculitis → Steroids.
5) If no response → Rituximab.

	Hodgkin's	Non-Hodgkin's
Def.	malignant prolif. of Unknown cell (Reed Sternberg Cell)	malignant prolif. of lymphoid cells. (B-cell > T-cell)
Age	1st peek: (20-30) 2nd peak: (50-70)	60-75 ys.
etiology	Unknown, no Relation to EBV	1) EBV ⇒ Burkitt's lymphoma. 2) h. pylori ⇒ MALT lymphoma. 3) Immuno-comp. ⇒ HIV + post-Transplant.

➢ Cl./P (pallor - purpura - HSM)

General

- Fever.
- Nt. sweat.
- loss of wt.
- Itching.

Hodgkin's & NHL
"NHL more Systemic & T. Infiltration"

- **LN++**
  - Superficial LN → "Scalene & Supra-clav. LN" → painless. Rubbery.
  - Deep LN → **Mediastinal $**
    - **Despine's sign?!** Bronchial br. below Tracheal bifurcation over spine
- **T. infilt.**
  - Liver – Spleen
    - Bone → fractures.
    - Brain
    - Skin → itching.
    - Lung → pl. eff.
- **Immune Disorders**
  - ↓ RBCs → AIHA.
  - ↓ platelets → purpura.
  - GN → Nephrotic $. "minimal lesion"

Mediastinal LN:
1) TB - Sarcoidosis.
2) NHL.
3) Bronchogenic Carc.

➢ Classification

- *Stage I ⇒ single LN region.*
- *Stage II ⇒ 2 or more LN on one side.*
- *Stage III ⇒ LNs on both sides.*
- *Stage IV ⇒ Diffuse extra-lymph. (Liver & BM)*

1) *Low grade.*
2) *Intermediate.*
3) *High grade. "Burkitt & non-Butkit"*

Invest.

1) CBC: Anemia – Eosinophilia - Neutrophilia.	1) Ig profile.
2) ↑↑ESR Lymphopenia	2) ↑↑ESR
3) ↑Uric acid & Ca++.	3) ↑Uric acid & Ca++.
4) LN biopsy - CXR – CT scan. "Diagnostic"	4) LN biopsy & BM exam. "Diagnostic"

➢ Treatment

1) **Radio-th.** → *Stage 1 & 2 + Serious pr. manifest.*
2) **Chemo-th.** → *Stage 3 & 4.*

Old	Recent	Most recent	
MOPP	**ABVD**	**BEA COPP**	
*M*ustin.	*A*driamycin.	*B*leomycin.	*V*incristine.
*V*incristine.	*B*leomycin.	*E*toposide.	*P*rednisolone.
*P*rednisolone.	*V*inblastine.	*A*driamycin.	*P*rocarbazine.
*P*rocarazine.	*D*acarbazine.		

1) **Low grade NHL:**
   a) Radio-th.
   b) Chemo-th. → Chlorambucil – Cycloph.
   c) **Rituximab. "CLL "Reichter's transf."**
2) **High grade NHL: R-CHOP regime:**
   - *R*ituximab. *C*yclophosphamide. *D*xorubicin.. *V*incitracin. *P*rednisolone.

Myelo-proliferative D.

pan-hyper-cellularity of BM

- PV → ↑ RBCs mainly.
- CML → ↑ WBCs.
- ET → ↑ Platelets
- MF → ↑ Fibroblasts.

Criteria:

- Splenomegaly.
- Basophilia.
- ↑ B_{12}
- Tr. by hydroxyurea

Plasma Cell = Gammopathies

poly-cythemia Rubra-Vera

pan hyper-cellularity of BM
mainly RBCs + ↑ WBCs / Platelets

⇓

hyper-viscosity $

Myelo-fibrosis

pan hyper-cellularity of BM
mainly Fibro-blasts

↑↑ Mega-karyocytes as in M_7
→ *F-GF*
→ ⊕ *Fibroblasts in BM.*
→ BM fibrosis.

EMH dt BM fibrosis
⇓
HSM (Th. Major)

Multiple Myeloma

Malignant prolif. of Plasma cells

secreting Monoclonal Ig. (GADE)

"old male – bony aches - ↑↑↑ ESR >100"

Walden-strom's

Mono-Clonal D. of Plasma cells

⇒ ***↑↑ IgM secretion (HMW)***
⇒ ***Remains IV.***
⇒ ***Hyper-viscosity $.***

Cl./P

1) **↑ RBCs ⇒ hyper-viscosity $:**
   a) *Plethora.* *CHF, ↓ CBF "dizziness"*
   b) *Engorged retinal v. → Thrombosis.*
   c) *Vertigo – Tinnitus – Visual dist.*
   d) *Intermittent Claudication.*
2) **↑ WBCs ⇒ Basophilia** ⇒ *histamine .. Itching esp. after hot bath.*
3) **↑ Platelets** ⇒ *Thrombosis or Hge.*
4) **1 + 2 + 3 ⇒ Spleen ++**

شبه ال ***CML so ...BM exam.***

- ↓ RBCs → **Anemia "early".**
- ↑ WBCs → **Leucocytosis remains persistent for long time.**
- ↓ platelets → **Bl. Tendency.**
- **Huge Spleen.**

Malignant prolif. of BM Plasma cells

- Secrete cytokines that ⊕ Osteo-clasts → **Bone Resorption**
  - Hyper-calcemia
  - Hyper-uricemia *"Tumor lysis S"*
  - Ig light chain *"Toxic to Tubules"*
  - Amyloidosis *"try AL Type"*
  - Dehydration → Renal F.
  - **Bony Aches** "DT Osteolytic lesions & Osteoporosis"
    - Vertebral Collapse → SC compr. tingling & paraplegia
- BM infilt.
  - 1) ↓ RBCs Anemia
  - 2) ↓ Platlets → Bl. tendency.
  - as ALL but No HSM & LN++
- ↑↑ Ig
  - Immune-disorders → Infections dt defective opsonization of capsulated org. "pneumococci"
  - ↑↑ M protein → hyper-viscosity $

1) Nose bleeds, retinal Hge.
2) **Liver – Spleen – LN ++**
3) **Hyper-viscosity $:**
   - Cong. HF
   - Vascular occ. c gangrene.
   - Raynaud's ph. PN.
   - Cyanosis in fingers.
4) No Renal Disease.

➢ Investigations

1) CBC ⇒ ↑↑ all cells mainly RBCs. (↓ESR)
2) BM exam.
3) **Criteria for Diagnosis of PC Vera.**

A_1	↑ Red cell mass.	B_1	↑ Platelet > 400.000
A_2	Normal O_2 (↓EP) to exclude hypoxia in 2° polycyth..	B_2	↑ TLC > 12.000
A_3	Splenomegally	B_3	↑ AlP. (WBCs are mature)
		B_4	↑ Vit. B_{12} (CML & PV)

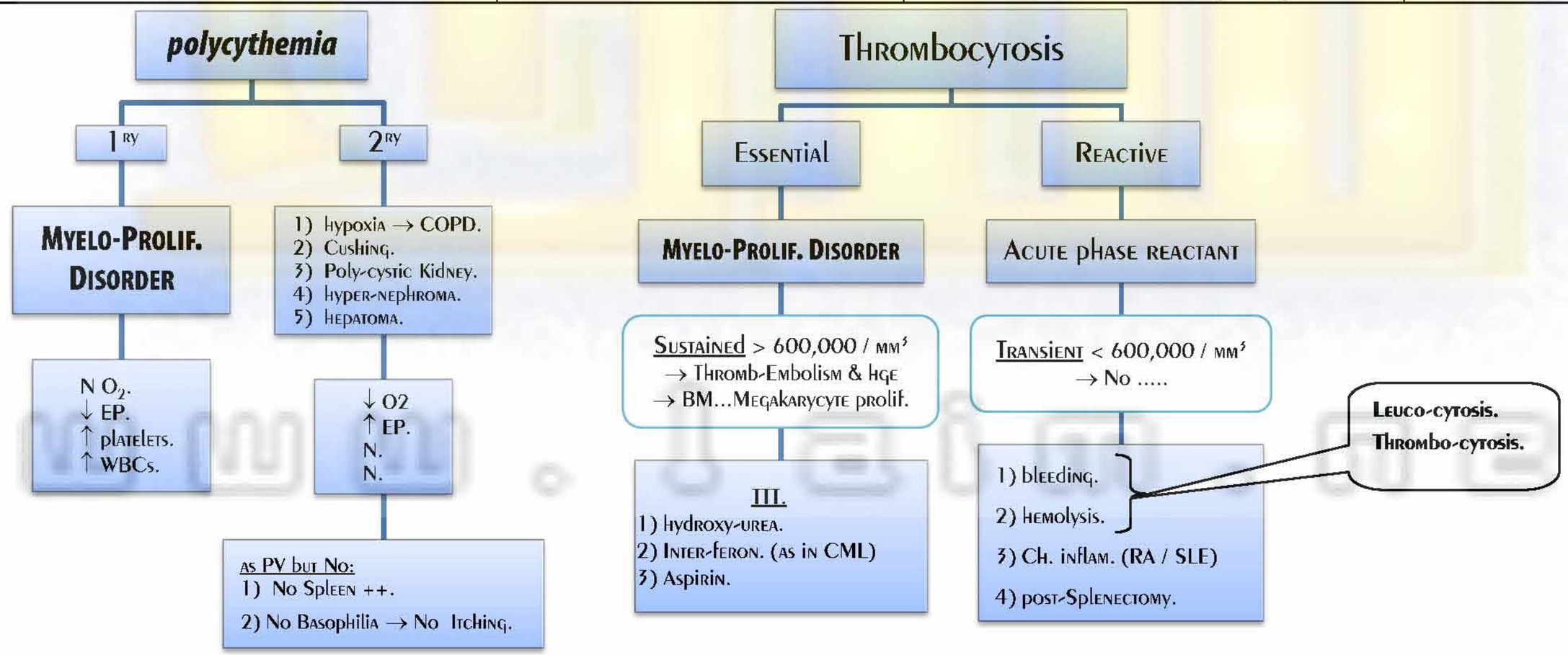
1) **CBC:**
   a) ↓ RBCs → *Normo Normo.* → Tear drop cells.
   b) ↑ WBCs → *Immature Leucocytosis.*
2) **BM biopsy ⇒ *dry tap from ASIS***
   (hairy cell leukemia / Myelo-fibrosis)

1) **Blood:**
   - ↑↑↑ ESR > 100.
   - Electroph. ⇒ monoclonal Ig. (if Normal..)
   - **ALP ⇒ normal (No ⊕ of Osteo-blasts)**
   - β_2 Microglobulin → for follow up.
2) Urine ⇒ **+ve Bence Jones proteins (Light Chain Ig).**
3) **BM (diagnostic) ⇒ plasma cells >20%**

Electrophoresis ⇒ IgM

Treatment

poly-cythemia Rubra-Vera	Myelo-fibrosis	Multiple Myeloma	Walden-strom's
1) **hydroxy urea** (Chlorambucil & Radio-Avtive P → acute leukemia) 2) **Symptomatic:** • hyper-uricemia ⇒ Allopurinol. • hyper-viscosity ⇒ Thrombolytic th. • ↑ platelets ⇒ Aspirin • Itching ⇒ Anti-hist. + avoid hot baths. 3) **Venesection** ⇒ keep PCV < 45%.	1) **hydroxy urea** 2) **Symptomatic** • Folic A., iron. • **Splenectomy in hyper-splenism.** • AIHA →Steroids with. • Bl. Transfusion + BM. 3) BM Transplant.	**Supportive ttt.** 1) hyper-calcemia ⇒ Bisphosphanate. 2) Infections ⇒ Pneumococcal v. + ABs. 3) hyper-viscosity $ ⇒ plasmapharesis. 4) IV γ globulin. **Specific** 5) Melphalan. 6) V A D. Thalidomide?! Teratogenic…phaco-malia.	1) *Plasmapharesis* 2) *Cytotoxic drugs*



Iron ↓ Anemia

"M/C CAUSE OF ANEMIA IN THE WORLD"

1) ↓ Intake: infancy > 6m/ anorexia /old age.
2) ↓ Absorption: ↓ HCl – Antacids – phytate (cereals)
3) ↑ Demand: pregnancy – Adol. growth spurt.
4) ↑ Loss ⇒ Chronic blood loss in Adults + انظر الاطفال
   a) GIT bleeding:
      - PU. Ankylostoma.
      - EV
   b) Uterine bleeding.

Megalo-Blastic Anemia

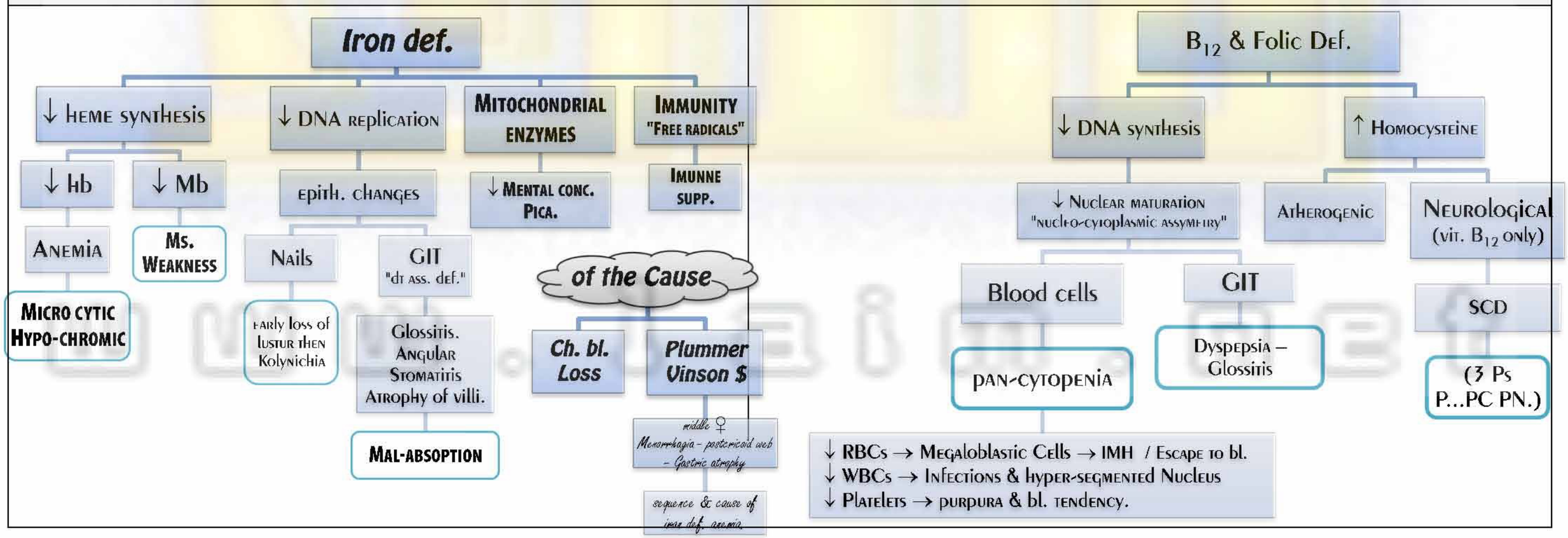
Vit. B_{12}

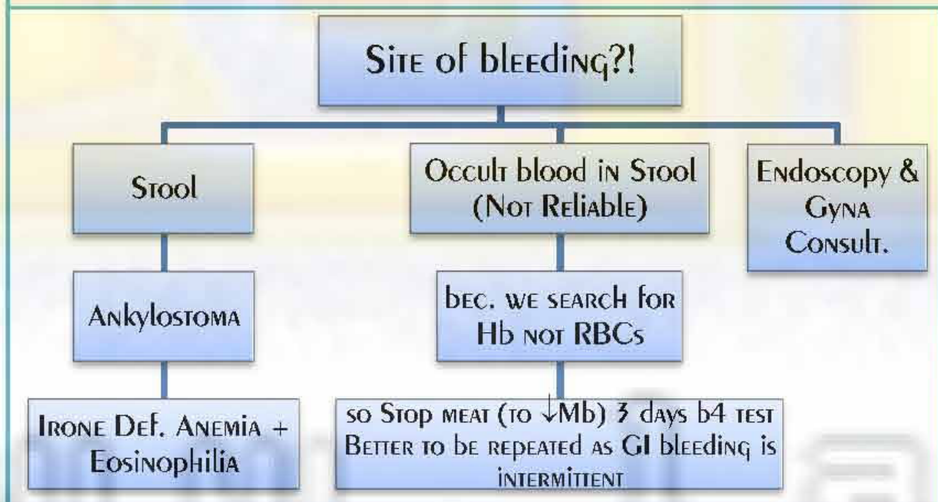
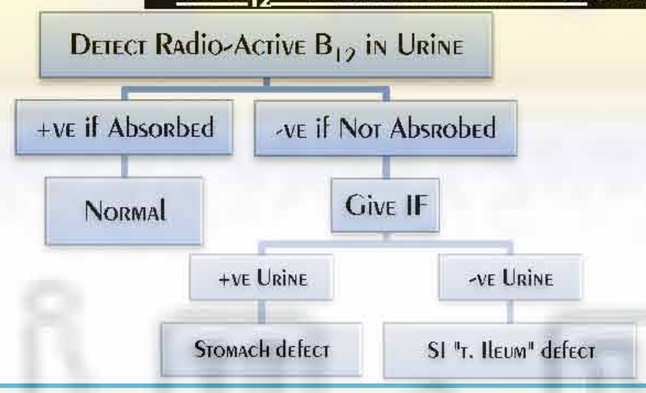
1) ↓ Intake strict vegetarians "v. rare dt ↑ stores".
2) ↓ Absorption from: الاسباب خطيرة لأن المخزون كبير
   a) Stomach → dt ↓ Intrinsic f.
      - pernicious An.
      - G. Atrophy. (A = Auto-immune type)
      - Gastrectomy. (B = Helico-bacter)
   b) T. ileum:
      - Mal-ab. $ tropical sprue / Crohn's D.
      - B_{12} Utilization by bacteria + D. latum.
3) Drugs Colchicine, neomycin ⇒ ↓ BM uptake of B_{12}.

Folic Acid

1) ↓ intake (IN ALCOHOLICS)
2) ↓ absorption Malab. $.
3) ↑ Demand preg. hemolytic crisis
4) Drugs: phenytoin – cytotoxic drugs, 6 mercaptopurine.

➢ Cl./P = G. features of anemia + ...



	Iron ↓ Anemia	Megalo-Blastic Anemia
Invest.	• **Anemia?!** ↓Hb + ↓Retics.	• **Anemia?!** ↓Hb
	• **Micro-cytic Hypo-chromic Anemia?!**	• **Megalo-Blastic Anemia?!**
	a) **Blood indices** ↓MCV - MCH - MCHC b) **Bl. film** ↑**RDW** (*An-iso + Poikilo-cytosis in any Def. anemia*)	a) **Blood indices** ↑MCV - MCHC: N. b) **Bl. film** **Macro-cytosis** + ***Howell Jolly bodies.*** *"Nuclear remenants"*
	• ***Iron def. ?!***	• **Vit B_{12} def. ?!**
	1) ***↓retics + ↑platelets*** *(if active bl. Loss)* 2) ***Iron profile:*** ○ ↓**Iron.** ○ ↑**IBC.** ↑**FEP** ○ **↓Transferrin sat.** ○ ↓ **s. Ferretin.** *"not accurate bec it is a phase reactant*	➢ **Pan-cytopenuia:** a) ↓**RBCs dt→ IMH →** ↑**S. bilirubin +**↑**LDH.** b) ↓**WBCs** ⇒ **hyper-segmented neutrophil.** c) ↓**platelets.** ➢ ↓**s. B_{12} < 100**
	Of the Cause?!	
		**Anti-parietal & IF Abs** **+ve Schilling test** to determine site of lesion • **IM B_{12} → saturate stores → Oral Radioactive B_{12}.** 

Treatment

Prophylactic	Curative		
1) *Adequate Fe for pregnant.* 2) *Fe supplements after the 4TH month (earlier in pre-mature*	1) **Iron therapy.** *(see later)* 2) **Bl. transf.** *(Packed RBCs if sever)* 3) **of the Cause** *EV – PU – ankylostoma*	**Vit B_{12}** Hydroxy-cobolamine IM. parentral not Oral dt ↓ Abs.	**Folic A. Oral** → 5 mg/d till improvement then low MD. (1 mg/d)

Sidero-blastic Anemia

Heme synthesis disorder = Ineffective BM Erythropoiesis

→ Failure of Fe incorporation into proto-porphyrin in Normo-blasts.

→ dep. Of Fe granules in mitochondria of Normoblasts in BM.

→ Ringed shaped Sidero-blasts in BM. **"Diagnostic"**

Causes:

1) Hereditary → X-LR. "dt Abnormal B_6 metabolism"
2) Acquired → Alcohol – **INH** – lead → (-) proto-porph. Synthesis.

Investigations:

1) **Anemia?!** ↓Hb + ↓retics.
2) **Micro-cytic hypo-chromic An.?!**
   - Blood indices → ↓MCV - MCH - MCHC
   - Bl. film → **Papenheimer bodies in RBCs.** (Iron granules in RBCs)
   - → **Dimorphic RBCs.** (hypochromic & Normochromic)
3) **Sidero-blastic ?!**
   a) Iron profiles → No Iron def.
   b) Hb electroph. → No Th. Minor.
   c) **BM exam. "Diagnostic"** → Sidero-blasts + ↑Iron stores.

1) PN.
2) Hepato-toxicity.
3) Sidero-blastic An.

Treatment: *Stop the drug + Vit. B_6 "high dose"*

Pernicious Anemia

- B_{12} def. → Megalo-blastic anemia.
- Dt Auto-Immune Abs. *against IF, parietal cells.*
- **Associations:** *other autoimmune e.g. myxedema, thyroiditis, vitiligo – DM type 1.*

Micro-cytic Hypo-chromic An.
But Not Responding to TTT.

	Iron def.	Anemia of Chronic D.	β Thalasemia Minor	β Thalasemia Major	Sideroblastic
RDW	↑	Normo / Normo	↑	↑	N
Retics	N or ↓		↑	↑	
Iron profile:					
• s. Iron	↓	↓	↑	↑	↑
• IBC	**↑**	**↓**	**↓**	**N**	**N**
• s. Ferritin	↓	↑ or N.	↑	↑	↑
• Iron stores	↓	↑	↑	↑	↑ + Ring Sidero-blasts
Hb electroph.	N	N	**↑ Hb A_2** ($\alpha + \delta$)	**↑ Hb F** **↑ N ↓ Hb A_2**	N **Bl. film** (Papenheimer bodies in RBCs)

3 parasites & Anemia

1) Ankylostoma → Iron def. Anemia + Eosinophilia.
2) D. latum → Vit. B_{12} → Megalo-blastic an.
3) Malaria → Hemolytic An.

Iron Therapy

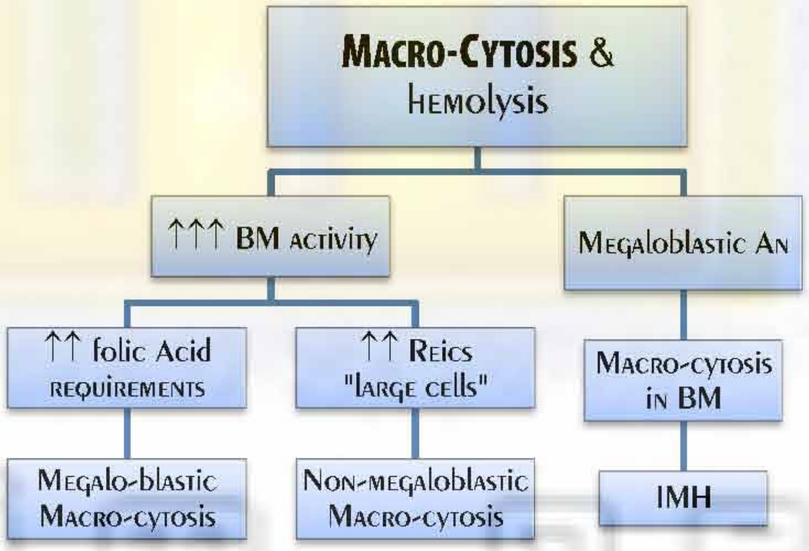
- **Dose:** 3 – 6 mg / kg /d. **for 3 mns to fill the stores.**
- **Rout:**

	Oral	Parenteral
Type of Iron	• Ferrous SO_4 • Ferrous Gluconate. 3 divided doses bet. Meals & + Vit. C.	• IM → Dextran. • IV → Saccarated Iron (Frosac)
	• ↑ Abs. → Vit. C. • ↓ Abs. → phytates – tanic A. & cereals.	**Indications = failure of Oral:** 1) Wrong diag. "Th. Minor diagnosed as Iron def." 2) Iron Intol. 3) Mal-Absorption $. 4) Ch. He. 5) Ch. Infection (IL1 → ↓ BM utilization of Fe)
S/E	• GIT upset. (NV) • Constipation. "non-compliance" • Black stools. "pt. should be informed"	1) V. painful. 2) No control → toxicity.

- **Response to tit.:** ↑↑ Normoblasts → Fe^{++} → ↑↑ Retics.
  - 1st day → improvement of GC & Appetite.
  - 2nd day → ↑↑ BM Retics.
  - 3rd day → ↑↑ periph. Retics upto 5%.
  - 4th day → gradual steady ↑ of Hb % (1 gm / wk)
  - Regaining of s. Ferritin.

Macro-Cytosis

	Megalo-blastic	Non-Megaloblastic
• Causes.	↓ Vit. B_{12} or Folic A.	1) Chronic LD. 2) Alcohol excess. 3) hypo-Thyroidism. 4) Retics. "in hemolytic crisis"
• Path.	↓ Nuclear Maturation.	→ ↑ Free Cholsterol → ↑ fat deposits on periphery of RBCs → ↑ size of RBCs.
• BM.	Megalo-Blasts in BM.	Normal BM.



Hemolytic Anemias

Anemia dt ↑ Rate of RBCs destruction → ↓ Their LS.

General features of CHA:

1) pallor. (Anemia)
2) Jaundice. (hemolytic)
3) Th. facies. (Chronic)
4) HSM. Esp. in Th. Major.

Hemolysis

IVH "AHC"

- Hb emia
  - ↓ Hapto-globin
  - ↓ Hemopexin
  - "if sever" Hb uria
    - Hemosidrinuria
    - s. pallor
  - AHC
    - dark urine
    - s. Jaundice
    - ± loin pain.
    - ± ARF.
    - ± Anemic HF.
    - ± fever & rigors

EVH "CHA"

- ↑ Fe
  - ↑ s. ferritn
  - ↓ IBC
  - ↑ t. ferritn
  - repeated bl. transfusion
  - **Hemo-sidrosis "Thalasemia Major"**
- spleen++ dt RES hyperplasia
- ↑ Indirect Billirubin
  - ↑ D. Bilirubin in bile secretion
    - ↑ Stericobillin in stools → Dark Stool
    - ↑ Urobilinogen in urine → No change in urine colour. → Alcholuric Jaundice

Jaundice "lemon yellow"

Gall Stones "more e spherocytosis dt ↑ Hb compensated from hyper-active BM" → CBD → Obst. Jaundice
olive green - dark urine, - clay stool

J

1) Liver → cirrhosis.
2) Spleen → splenomegaly. Hyper-splenism.
3) Heart → cardio M. → Arrhythmia.
4) Lung → infiltrates.
5) Skin → Muddy complexion (J. + pallor + ↑ melanin dep.)
6) SC → skin ulcers.
7) WBCs → recurrent inf.
8) PN
9) Endocrine
   - Pituitary → DI
   - PTH → hypo-calcemia
   - Pancreas → DM.

Anemia = Pallor

- Tissue hypoxia
  1) CNS → dizziness.
  2) Ms. → Fatigue.
  3) FTT.
  4) CVS → Anginal pain.
- comp. mechanism

comp. mechanisms

"doesn't occur in hemolytic crisis"

- **CVS**
  - Acute "hypoxia...VD"
    - ↑ HR → Tachycardia & palpitations
  - Chronic
    - ↑ SV → F. AS/PS, Hemic murmur
- **BM ⊕**
  - Acute
    - ↑ Retics, Normoblasrs
  - Chronic
    - BM exp. → Th. Facies
    - EMH → HSM → Marked in Th. Major dt Abnormal BM hematopoeisis.
- **RBCs**
  - ↑2,3 BPG
  - ↓ Hb affinity to O_2
  - shift of O_2 to tissues.

Investigations for all cases of CHA

1) Anemia?! (↓Hb)

2) Hemolytic?!

a) **RBC destruction** → ↑ **Indirect billirubin.**

b) **BM⁺⁺** → ↑ **Retics / platelets / TLC** (diff. from infection by ↓ hb)

c) **Bl. Indices:** → **Normo / Normo .....except**

1) **Micro / Hypo.** → **Th. Major.**

2) **Macro-cytosis dt:**

a) ↑ **Retics.** (hemolysis – IGE – Response to Iron th.)

b) ↓ **Folic A.** in hemolytic crisis → **Megalo-blastic crisis.**

3) **Sphero-cytosis** → **Relative ↓ MCV → ↑ MCHC**

(so BM exam isn't essential in H. anemia)

d) **IVH = (G6PD + AIHA "cold")** → ↓ **hapto-globin & hemopexin + ↑ LDH.**

3) Specific?! (Bl. film + Specific tests)

4) X-Ray of CHA:

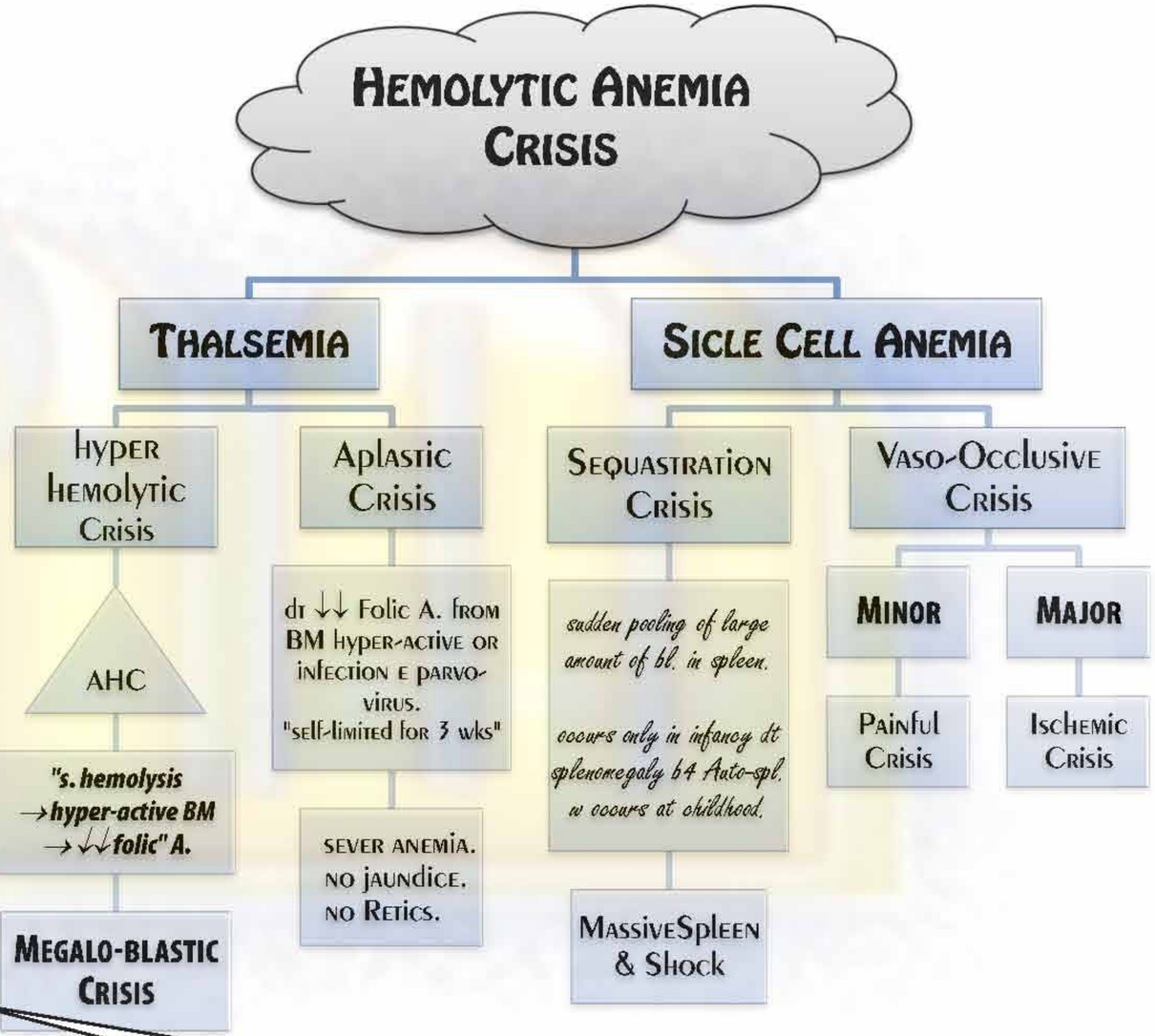
a) **Skull** → *hair on end app. / wide diploid space.*

b) **Long bones** → *Thin cortex / Wide medullay cavity / Mosaic app.*

c) **Bone destruction in SCA.**

➢ **NB:**

- **RBCs e labeled Chromium → Sphero-cytosis & hyper-splensim.**
- ↑ **ESR in Anemias except (Spherocytosis & SCA dt ↓ roloeux)**



Hemolytic an. with No Splenomegaly:

1) **SCA** *(splenomegaly in SCA = Sickle β-Thalasemia = (hbF + hbS))*
2) **G6PD.**
3) **PNH.** *(C3 comp.)*
4) **AIHA.** *(cold IgM Ab → IVH)*
5) **Mech. hemolysis.**

Thalasemia

- ↓↓ α Chains
  - α Thalasemia
    - 4 genes on α Chains on Chromosome 6

	Degree of Anemia	Hb electroph.
↓ 1 gene	→ silent carrier. (Trait)	Normal
↓ 2 genes	→ mild anemia.	Normal
↓ 3 genes	→ mod. to sever. (Major)	Hb H (β4)
↓ 4 genes	→ "hydrops fetalis "incompatible ε life"	Hb Bart's (γ4)

- ↓↓ β Chains
  - Homo-zygous
    - $\beta^0\beta^0$
      - β-Th. Major
        - Discussed in detailes
    - $\beta^+\beta^+$
      - β-Th. Intermedia
        - Moderate Jaundice & Splenomegaly. (bet Th. Major & Minor)
  - Hetero-zygous
    - $\beta\beta^+$ / $\beta\beta^0$
      - β-Th. Minor "Trait"
        - DD (see below)

Cl./P of β –Th. Minor:

- *Mild anemia (micro / hypo)*
- *Splenomegally.*
- **Hb F & Hb A2 mildly ↑**
  → mild symptoms.
- **TTT.: Family councilling.**

Cl./P

1) Mild hemolysis → mild anemia.
2) **Just palpable Spleen++** for DD. (Osis)

TTT. No need for ttt. but Family Counseling.

Invest. Micro-cytic Hypo-chromic Anemia (see before)

Causes of Pan-cytopenia in β-Thalasemia

	hyper-splenism	Aplastic An.	Folic A.
• Onset • Course	➢ Gradual. ➢ Progressive.	➢ Acute onset. ➢ Self-limited.	Gradual dt ↑ *Folic A. require by hyper-active BM. (6-8x)*
• Diagnosis	1) Pancytopenia + ↑ Retics. 2) ↑ Bl. Transf. 3) Radio-labeled RBCs Trapped in Spleen.	Pancytopenia. + ↓ Retics.	**Megalo-blastic Crisis.**

H. Spherocytosis

AD (no FH in 10-20%)

Hereditary CM defect

↓ spectrin
"↓ membrane phospho-lipid"

- Integrity of CM
  - Spherocyte
  - Osmotic fragility test
- Deformed RBC
  - Rigid CM… Trapped in Spleen
  - EVH
- ↑ Na & H_2O permeability
  - ⊕ Na/K Atpase .. "↓ Energy stores"
  - ↓ LS of RBCs
  - Auto-hemolysis at 24 - 48 hrs "corrected b adding G."

β-Thalasemia Major

AR ⇒ ↑Hb F (70 - 80%)

inability to form β-chain

↑↑↑ α chains
- IMH of RBC precursors ⇓ ineffective BM erythropoiesis ⇓ ⊕ EMH
- Membrane defect ⇓ RBCs can't pass RES ⇓ EVH

→ RES ++ → HSM
+ Repeated bl. Trans. → ↑Fe load → Hemosidrosis

↓↓ β chains ⇓ μ cytic hypo-chromic an.

↑ γ chains (dt incomplete switch off) ⇓ ↑ Hb F "high O_2 affinity"

→ T. hypoxia → ↑ EP
- BM ++ → Th. Facies
- ⊕EMH → HSM

Sickle Cell Anemia (SCA)

AR (Intermediate Inherit. / Co-dominant / Incomplete AD)

HbS de-oxygenation dt…

(hypoxia – Dehydration – Infection)

→ Insoluble Hb → polymerization → filaments (hb)

→ Sickeling of RBCs
- Trapped in Spleen ⇓ EVH (Chronic)
- ↑ Bl. viscosity ⇓ Vaso-occlusion (Intermittent attacks)

G6PD def.

X-LR

↓ G6PD

(source of NADPH in HMP shunt)

⇓ ↓↓ Reduced Glutathione ⇓ ↓ Resist to Oxidative stress (Drugs – Infection – Favism)
- protein → ↓ Hb denat. → ↓ ppt. in RBCs as Heinz bodies
- lipid peri-ox. → ↓ Dest. of CM → IVH

➢ Cl./P

Onset: Neo-natal Jaundice

General as CHA but e 3 diff.

1) Neonatal onset of hemolysis.
2) Huge Spleen since infancy.
3) ↑ Gallstones dt ↑ D. Bilirubin

"Although Thalasemic hemolysis > Spherocytosis but No Gall stones in Th. bec. RBCs are hypo-chromic → small Hb released during hemolysis"

Onset: After 6 ms. (start of ↑ β activity)

General as CHA + Complications… 3 HIB

1) Hemo-sidrosis. (dt repeated bl. Transf.)
2) hyper-splenism. (pan-cytopenia + ↑ Retics)
3) Infections. (due to 1& 2)
4) HF dt (1 + s. Anemia + Toxic myo)
5) of Bl. Transfusion.

Onset: After 6 m

General as CHA +
- Ch. Leg ulcers dt → hemosidrosis & Vasc. occ.
- Auto-splectomy "dt repeated splenic infarcts" → Functional hypo-splenism → ↑ Infections "Staph. & Salmonella" & Thrombosis

Acute Crisis (All 4)
- Vasc. Occ.
  - Minor → Pain Crisis "H & F $"
  - Major → Ischemic infarcts
- Sequestration → sudden pooling of large amount of bl. in spleen, occurs only in infancy dt splenomegaly b4 Auto-spl. ω occurs at childhood, → Massive Spleen & Shock.

Onset: ….. ms.

1) AHC.
2) history of PDF.

NB: No Splenomegaly Except in Chronic Cases.

(v. rare)

➢ Investigations "Specific"

1) Blood film ⇒ Spherocytes (also appears in AIHA dt WARM Ab)
2) Osmotic fragility test. (Start at 0.7 % Normal at 0.4 %)
3) Auto-hemolysis after 24-48 hrs. (corrected by adding G.)

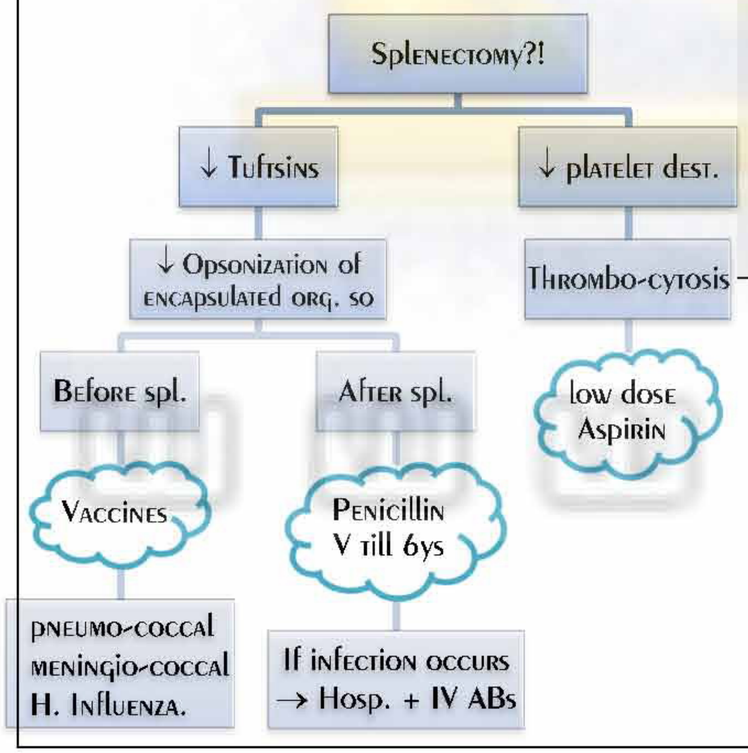
1) Blood film ⇒ Target cells
2) Alk. Denat. test. (Hb F is resistant)
3) Hb Electrophoresis ⇒ ↑ Hb F.
4) Antenatal diag. by DNA analysis of CVB.

1) Blood film ⇒ Sickle cells. (If bl. is Oxyg. in air ..no sickling)
2) Sickling test ⇒ blood + Na bisulphate → hypoxia → sickling. (or squeeze finger → ischemia)
3) Hb Electrophoresis ⇒ ↑Hb S.
4) Antenatal diag……..

1) Blood film ⇒ Heinz bodies
2) G6PD assay test.
   - Immediately after h. → Retics & young RBCs are rich in G6PD → ↓ Inaccurate
   - After 6-9 wks → steady sate → ↓ Accurate

➢ Treatment of Hemolytic Anemias

	H. Spherocytosis	β-Thalasemia Major	Sickle Cell Anemia	G6PD def.
1) Bl. Transfusion 2) Iron Chelation 3) Folic A. 4) Splenectomy?!	Clinical improv. only but RBCs remain Spherocytes. **Indications:** 1) Cass e Bl. Transfusion. 2) S. hemolysis. 3) One of the FM died.	Not curative but good "bec. the main site of Hemolysis in Th. is BM (IMH) not Spleen → so Indications of Spl.?! a) hyper-splenism (↑ Bl. Transf > 300 ml packed RBCs / kg / yr.) b) huge spleen e mech. Discomfort. c) Trauma & rupture spleen even if b4 5 ys.	• Auto-splenectomy. • Sequest. crisis. (if Recurrent or resistant)	of no value.
5) Specific TTT.?!	Cholecystectomy after Splecentomy(if gall stones)	1) BM Transplant. "of choice" 2) Drugs ⊕ hb F to → ↑γ activity. → ↓ unopposed α-chains. → ↓ hemolysis. 3) Genetic Counsiling.	1) Sequest. Crisis: → whole bl. Transf. 2) Vaso-occ. Crises: a) Minor → Analgesic - O_2 - $NaHCO_3$ - fluids. b) Major → Exchange transf. in life threatening conditions to replace HbS e HbA, (Acute Chest S) 3) Drugs ⊕ hb F ⇒ ↓ sickling of HbS (hydroxy urea or Butyrates)	1) Avoid (Drugs – Infections – Favism) 2) Alk. Diuresis to avoid acid hematin deposition. 3) Bl. Transfusion during the attack avoid Anemic HF.



Pyruvate Kinase Def.:

- AR Trait.
- CBC: Normo / Normo. Normal RBC morphology.

Sickle Cell Trait

- heterozygous. (SA)
- Black Races resist p. falciparum.
- Asymptomatic.
- Sickling only in s. hypoxia. (GA or high altitudes)

G6PD Types

	Type A	Type B
Race	blacks	Cucasuians
Deficiency	Mild	Marked
hemolysis	No except in PDF.	moderate & ↑↑ e PDF.

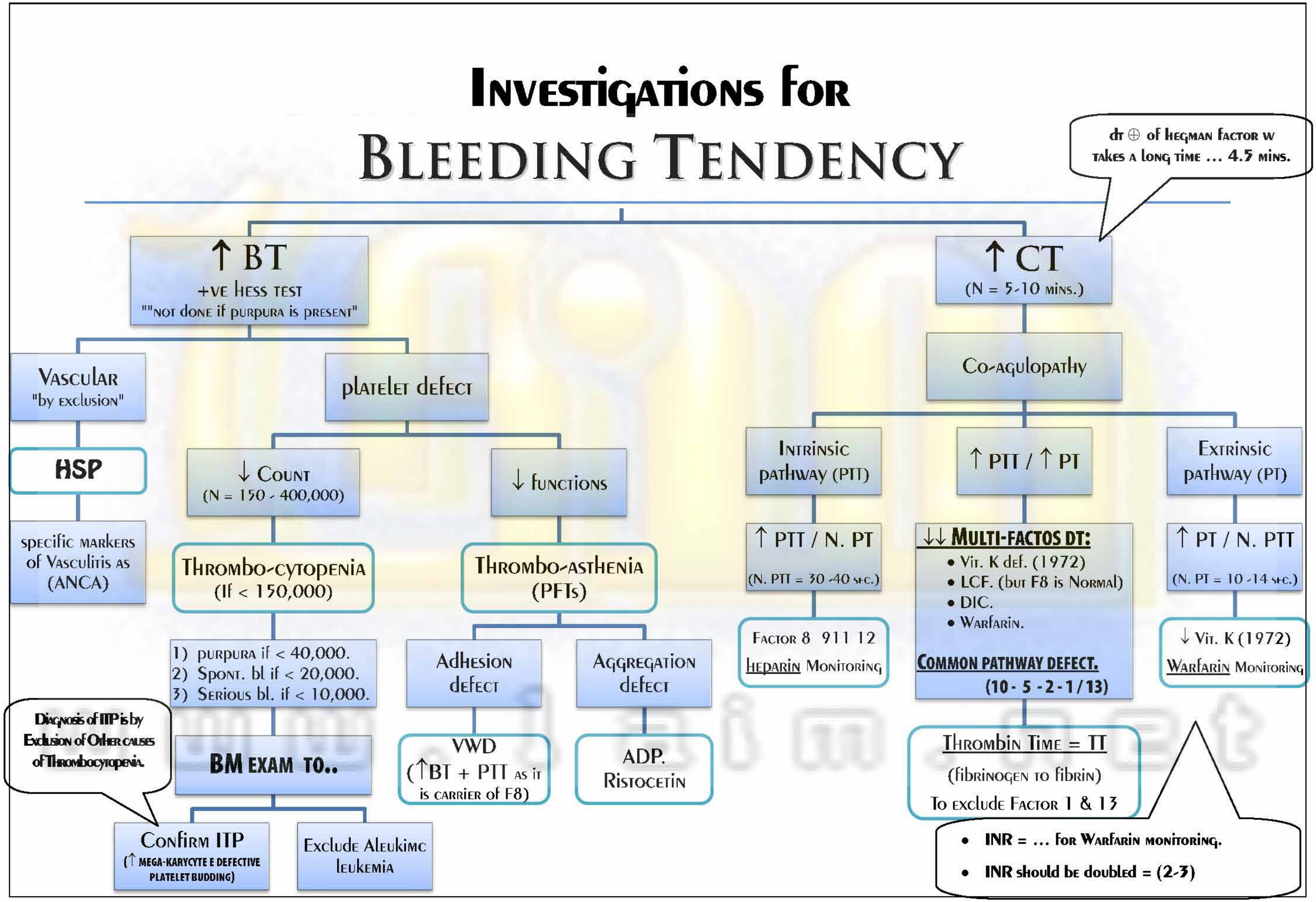
	AIHA dt Warm Ab	AIHA dt Cold Ab	Paroxysmal Nocturnal Hb-uria
Def.	Ab attacks RBCs at 37 C in vitro. (M/C of hemolytic An. In Adult)	Ab attacks RBCs at < 37C in vitro.	Acquired defect in BM stem cell ⇒ Aplastic anemia.
etiology	IgG attack RBCs ⇒ RBCs become Spherocytes. ⇒ ⊕ Splenic phagocyte Activity. ⇒ EVH in Spleen.	IgM Ab attack RBCs ⇒ IVH (Paroxysmal Cold Hb-uria *IgG Donath – landsteiner Ab dt S or Viral)*	As Sickle Cell Anemia (hemolysis – infections – Vasc. Occ.) RBCs: absence of GPI protein in CM → ⊕ C_3 against RBCs during sleep (↓PH) → IVH (hemolysis) so no Spleen++ WBCs: PNL dysfunction → Infections Platelets: aggregation… thrombus. → Vascular occ. → Budd – chiari $
Causes	أسباب ساخنة 1) 3L (lupus – leukemia (CLL) – lymphoma) 2) Viral - α methyl Dopa.	أسباب باردة • Viral. (IMN / EBV) … NHL • Mycoplasma pneumonia. (problem)	
Cl./P	• hemolytic Anemia. • Of the Cause. • Just palpable spleen. (dt EVH)	• hemolytic Anemia. • Of the Cause.	
Invest.	1) of hemolytic an. (↓Hb / ↑I. bilirubin / ↑Retics) 2) Of the Cause = 3L • lupus → ANA. • leukemia → BM exam. • lymphoma → LN biopsy. 3) of AIHA • +ve Coomb's test. (IgG on RBCs) • Acquired Spherocytes. (dt attack of RBCs by IgG)	1) of hemolytic an. 2) of the cause. (viral markers of EBV) 3) of AIHA → Direct Coomb's Test. (IgM on RBCs مسقعة) Spherocytosis → Heridetary / Aquired → AIHA (Warm = 3L)	1) ↓ RBCs ⇒ *recent flow cytometry.* 2) ↓ WBCs ⇒ *Leucopenia.* 3) ↓ Platelets ⇒ *Thrombocytopenia.* 4) –ve Coomb's Test. (C_3 only with no Ab) 5) +ve Ham's Test ⇒ Blood + Acid hematin. (↓pH) ⇒ hemolysis.
Ttt.	1) Of the Cause. 2) Steroid. 3) Splenectomy. (Acquired Spherocytosis) 4) Immuno-supp. (if no response to Splenectomy)	1) Of the Cause. 2) Steroids. 3) Splenectomy is of no value. (as it is IVH)	1) Steroids. 2) BM Transplant dt BM Aplasia. هذا المريض يتحول من hemolytic An. To Aplastic An.

Bleeding Disorders

- **platelet defect** "non-paplpable purpura"
  - **↓ Count**
    - **Thrombo-cytopenia**
      - **↓ Production**
        - **Hereditary**
          - TAR $
          - Fanconi Anemia
        - **Aquired**
          - as RBCs
          - Myelo-dysplasia
      - **↑ loss in peripheral circulation**
        - **↑ Consumption "Non-immune"**
          - **μ-Angiopathic HA** "dt fibrin deposition in cap. causing RBCs destruction"
            - DIC
            - TTP
            - HU$
        - **↑ Destruction "Immune"**
          - ITP.
          - hypersplenism.
          - Evan's $inSLE.
          - CLL.
          - HIT. (heparin)
          - Infections.
  - **↓ Function**
    - **Thromb-Asthenia**
      - **Hereditary**
        - **Adhesion defect**
          - VWD. (AD)
          - B. Solier $ (AR)
        - **Aggregation defect**
          - Glanz-man. (AR)
      - **Aquired**
        - **Drugs**
          - NSAID - Aspirin
          - heparin high dose.
        - **Diseases**
          - Uremia.
          - Myelo-prolif.
          - Gammopathie
- **Vascular defect** "paplapble purpura"
  - **Hereditary**
    - H. hgic Telengectasia (AD)
  - **Aquired**
    - HSP.
    - SLE.
    - Septicemia.
    - Scurvy.
    - Steroid / Cushing $.
- **Coagulopathy**
  - **Hereditary**
    - hemoptilia A/B.
    - VWD.
    - factor 11&12
  - **Aquired**
    - **Vit. K**
      - LCF.
      - Billiary Obst.
      - Mal-ab. $
      - Warfarin.
    - **Others**
      - DIC

TTP	HU$
Middle aged female	Child –postpartum
↓ RBCs → dt μ-angiopathic HA. ↓ platelets → Thrombo-cytopenia.	
جلاطات في المخ و الكلى.	جلاطات في الكلى فقط.

Investigations for Bleeding Tendency



	purpura		co-agulopathy
	Vascular defect = HSP	**platelet defect = ITP**	**Hemophilia A**
Def:	**HS III vasculitis (small vs.)** • post – strept -Viral or?! Drugs • Age → Children & young Adult.	**Auto-immune Disease Against platelets.** • Acute in Child → (post-viral) vaccines. • Chronic in Adult → Evan's S ⇒ AIHA + TTP	**X-LR** **Deficiency of factor 8.**
Cl./P	1) **Arthritis:** آه يا مفاصلي! • Big joint. • Non-destructive. • Migratory as Rh. fever. • Self-limiting. 2) **Abd. Pain** ⇒ mesenteric occ. آه يا بطني! 3) **painless haematuria.** اده البول أحمر ! • Nephrotic → FSGN. • Mixed → Mesangio-prolif. 4) **palpable purpura on butcks** التوقيع طفل! 5) ±**Allergy: Itching / Wheels / Angio edema.** **NB:** CNS stroke → focal lateralizing sign.. neuro-exam.	**recurrent bleeding** (spont. / Traumatic) • **skin**: petichae. purpura Non-palpable. Echymosis. Hematoma • **Bleeding from orifices**: Epistaxsis. Gingivial. Uterine. Hematuria = ICH → wet purpura (buccal mm) = Dang. Sign **No** No pallor (except in sever bl. + Evan's $ dt AIHA) No HSM (except if chronic) No LN++ No Sternal Tenderness. (to exclude Leukemia) **Diagnosis is of ITP is by Exclusion of Other causes of Thrombocytopenia.**	**recurrent bleeding** (prolonged after circumcision. / Traumatic) • **skin**: Large Echymosis. Hematoma (after IM inj. / begining of mov, in children) → Retro-peritoneal pr. → Femoral Neuropathy; in Brain then Calcified → pseudo-tumor cerebri • **Bleeding from orifices**: Epistaxsis. Gingivial. Uterine → ICH .... → epilepsy & paralysis. (M/D) • **Joints**: Hemo-arthrosis → pain e limited mov. → Ankylosis. (M/C) **Other Complications** • Transfusion.... Hepatitis – AIDS → factor 8 • Formation of F8 Abs.
Invest. (scheme)			
Treatment	a) **Self limited.** b) **Steroids** ⇒ for joint and abd. pains but do not alter the course.	**Acute ITP in Children** Mild: <40,000; Asympt.; Self-limiting Moderate: 20-40,000; Spont. Bl.; Steroids القاعدة Sever: <20,000; Serious bl. (ICH); • IVIg; • Platelet conc. (Total Dilutional Thrombocytopenia) **Chronic ITP in Adults** **Steroids** (↓ cap. Fragility / Ab / phagocytic activity of spleen) ↓ Splenectomy ↓ Cytotoxic D. & Block IgG.	**Avoid trauma & anti-platelet.** 1) **Replacement th.: infusion every 8hrs = ½ life of F8** (FF Plasma (10-15 ml/kg/8hrs.) ↑ IV volum by 30% - Cryo-ppt. - Factor 8) 2) **Hemo-arthrosis** → passive exercise to prevent j. stiffness & fibrosis. 3) **MM hge** → Anti-fibrinolytic. 4) **Desmo-pressin** ⇒ ↑ level of factor 8 "mild cases"

	HSP	ITP	Hemophilia
Invest.	Non-specific ○ ↑ IgA. ○ Complement..normal.	a) ↓ platelet Count. b) B.M ⇒ hyperplasia of megakaryocytes. c) Ig G against plat. (not ess. Exclusion of other causes of thrombo-cytopenia is enough)	1) ↑ CT & N. BT. 2) ↑ PTT - Normal PT & plat. Count 3) ↓ factor 8. **NB:** 1) ↓ Factor 9 = (hemophilia B) Same as factor 8 . 2) ↓ Factor 12 = Hegman factor→ ↑↑ PTT but no bl. tendency.

Von Willebrand's D.

Def.	(AD) Adhesion defect.
Cl./P	Purpura (platelet & Factor 8 dysf.)
Invest.	See
TTT.	1) Factor 8 2) FFP / Cryo-ppt. 3) ADH (DDAVP) → release VWF

Evaluation of a Case with bleeding tendency

	Coag. Defect	Plat. Defect	Vascular defect
Type	Inherited	Acquired	Acquired
Sex.	Male	Female	Female
F.H.	✓	×	×
Cl./P	• Haematoma. • Haemoarthrosis • Echymosis.	• Mucosal (epistaxis) • petichae without raised edge	• Petichae with raised edge
compression	Poor effect	Good effect	Good effect
Bleeding	post- traumatic	Spontaneous	Traumatic

Hyper-coaglubal State "Thrombo-philia"

Heriditary

Deficiency of Anti-Coagulants:

1) ↓ AT III. (dt heparin resistance)
2) ↓ Protein C *(dt warfarin th. without concomitant heparin)*
3) ↓ Protein S.
4) Factor V Leiden *(Resist (-) by protein C)*
   (M/C inherited hypercoagulable state)

Aquired

1) Malignancy (Trousseau's $) Ch. DIC.
2) Behcet's D. (IVC Thrombosis)
3) Nephrotic $ (↓ AT-III – protein C, S)
4) Pregnancy & OCP → ↑ procoagulants & ↓ fibrinolytic & (-) pr.
5) Polycythaemia rubra vera
6) Essential Thrombocytosis.
7) Myelofibrosis
8) PNH.
9) Hyper-lipidemia.

Anti-phospholipid $

Recurrent Thrombosis Although ↑ PTT

Recurrent Thrombosis in placenta → Recurrent Abortions.

"DT Lupus Anti-coagulant & Anti-cardiolipin Ab"

Invest.:

- Ab in vitro (test tube) → ↑ PTT→ bl. tendency
- Ab in vivo → Thrombosis.

TTT.⇒Warfarin.

1) Steroids. → (-) Ab.
2) Anti-Coagulant & Anti-platlet.
3) Aspirin.

Thrombophilia

- Recurrent DVT in young age.
  - Thrombosis in Specific Sites:
    - Budd Chiari $.
    - Cerebral.
  - Abortions. + Superf. Thrombo-phlebitis
- Recurrent Arterial Thrombosis in absence of arterial d.

Investigations for Thrombophilia:

1) ↑↑ PTT.
2) Hereditary → Thrombophilia Gene study → ↑↑ protein C, S and AT-III factor V leiden.
3) Acquired:
   - CBC → Polycythemia + Thrombocytosis.
   - Nephrotic $. → UA.
   - Malignancies → Tumor markers, CT-scan.
4) Anti-phospho-lipid $ → Lupus Anti-coagulants + Anti-cardio-lipin.
5) Duplex → site of thrombosis.

Treatment: قاعدة ذهبية

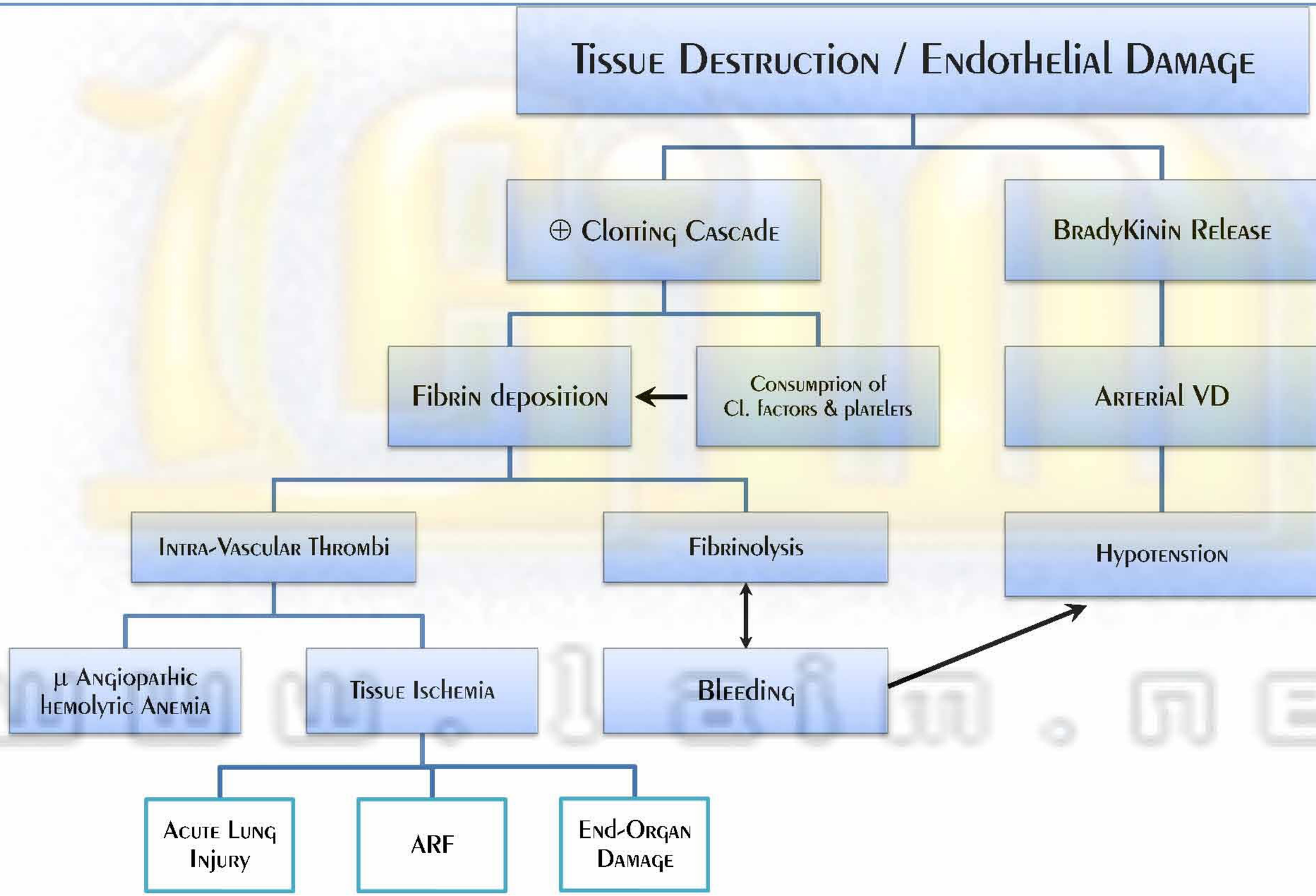
a) Cong. Deficiency → Warfarin.

b) Malignancy → Heparin SC.

Cl./P of Purpura

- Bleeding from.. + of the Cause
  - skin
    - petichae
      - palpable
        - Vascular defect
      - Non-palpable
        - platelet defect
  - MM
    - Bleeding from orifice
      - Epistaxis. Gingivial. Vaginal.
  - Int. Organs
    - ICH in sever conditions

DIC


Tissue Destruction / Endothelial Damage
⊕ Clotting Cascade
BradyKinin Release
Fibrin deposition
Consumption of Cl. factors & platelets
Arterial VD
Intra-Vascular Thrombi
Fibrinolysis
Hypotenstion
μ Angiopathic hemolytic Anemia
Tissue Ischemia
Bleeding
Acute Lung Injury
ARF
End-Organ Damage

D I C

consumption of coagulation factors due to ⊕ of intrinsic or extrinsic pathways ⇒ fibrinolysis ⇒ he or thombosis.

	Acute DIC	Chronic DIC
CAUSES	• Sepsis. • Amniotic Fluid - Abruption placenta • AML = M_3 • ABO in compatibilities.	• Malig i.e. Trousseau's. • Retained dead fetus.
INVEST.	a) **↓ All Elements.** • *↓Platelets.* • *↓F 5 – 8* • *↓fibrinogen.* b) **↑ All Times** • *↑↑ PT - PTT* • *↑↑ FDPs - ↑D-Dimer.* • *↑TT*	• ↓ platelet. (mild) • PT & PTT → Normal. • ↑ FDPs. • Fibrinogen → Normal. • TT → Normal.

TTT. off DIC

- **HGE → FFP – fresh blood,**
- **↓ platelets → platelet conc.**
- **Thrombosis → heparin.**
- **EA CA → after heparin to avoid thrombosis.**

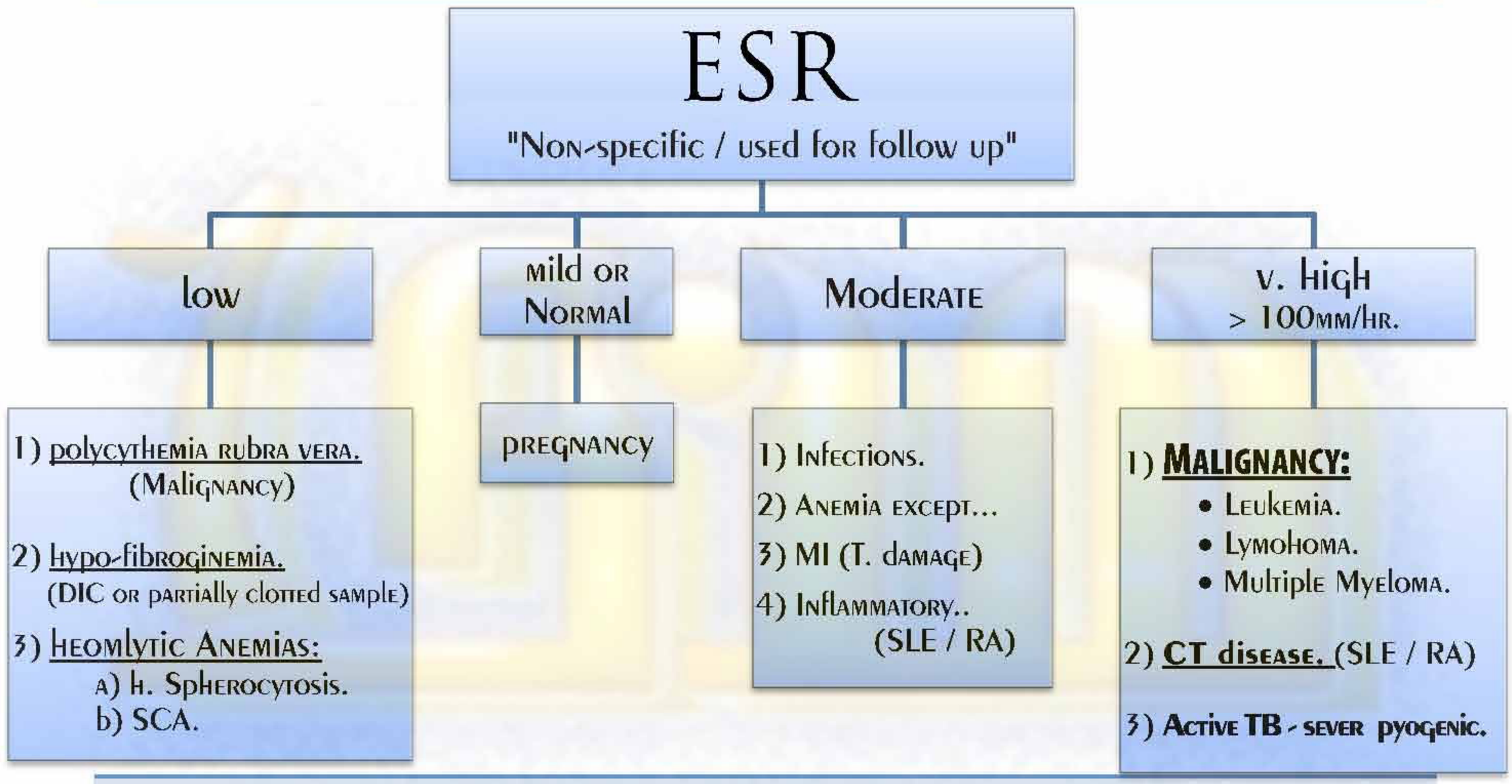
	Acute haemolysis	Febrile Non-hemolytic Transfusion Reactions	Delayed hemolytic Transfusion R.
Def.	• ***occurs within minutes.*** • *Due to ABO incompatibility.*	*Due to anti-WBC or anti HLA Abs reaction with WBCs in the unit.*	***occurs 5-7 days*** *after transfusion ⇒ ⊕ AB w was not detected at the initial cross match.*
C/P	***Acute:*** *→ Rigors and fever* *→ Lumbar pain* *→ Chest tightness* *→ Hypotension*	*Fever – rigors – urticaria*	*Anaemia + J*
ttt	• *Stop transfusion.* • *Re- group & cross match again.* • *Check blood count, bilirubin* • *Monitor pulse, BP.* • *Support pt's circulatory state.*	• *Stop transfusion.* • *Exclude haemolytic reaction* • *Antipyretic* • *Use leucodepleted blood* • *Steroids if further bl. needed.*	• *Ab detection & spherocytes.* • *Compatible blood use.*

Important Notes in Blood

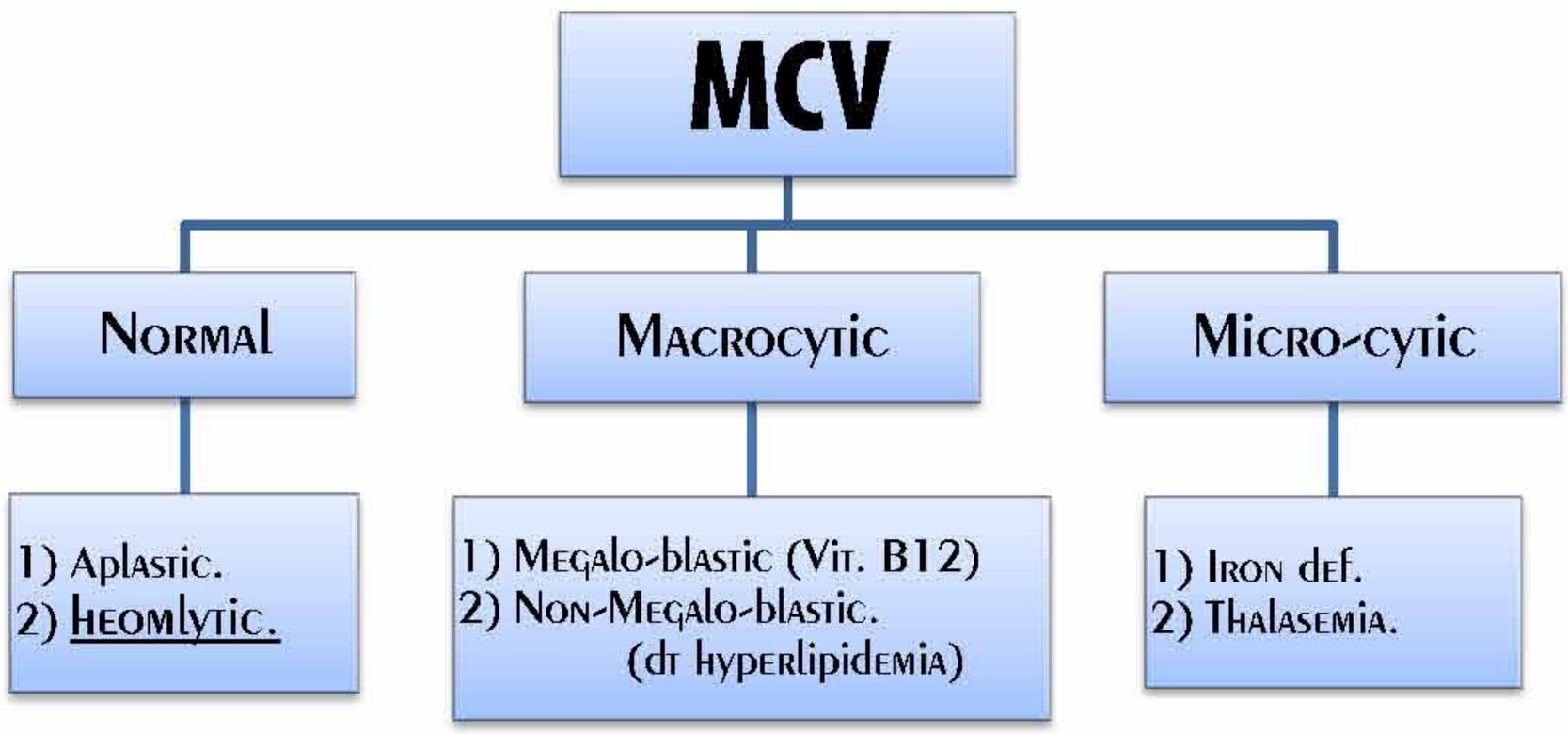
p. 1 **Retics = hyper-active BM**

- ↓ in Aplasia.
- ↑ in (hemolysis – he – Iron th.)

p. 3 **ESR**



p. 4 **pt. e Hb 8 → MCV ... (Anemia مفتاح الـ)**



p. 4

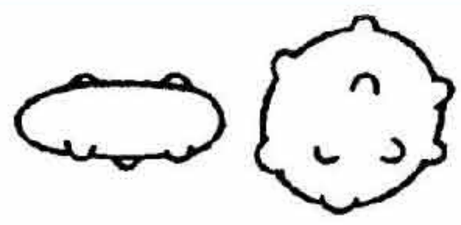
Abnormal Blood film (value of blood film)

• Microcytosis	Iron def. anemia.
• Macrocytosis	megalo or non-megaloblastic an.
• Anisocytosis = RDW (variation in size)	megaloblastic or iron def. an.
• Poikilocytosis (variation in shape)	Non specific.
• Punctuate basophilia	lead poison.
• Howell Jolly bodies (small round nuclear remnants)	Dyshaemopoiesis = (megaloblastic an. & post-splenectomy)
• Pappenheimer bodies in	sideroblastic anaemia.
• Polychromasia = ↑ Retics	haemolysis.
• Shapes of RBCs	(see later)

p. 5

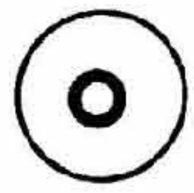
Shape of RBCs in Different Diseases:

• Burr cell	(Echinocyte)	Uremia.
• Stomatocyte	(mouth cell)	hereditary.
• Target cell	(Codocyte)	Thalasemia, Iron deficiency, Liver D.
• Acanthocyte	(Spur cell)	Splenectomy, Advanced LD.
• Sickle cell	(Lancet cell)	SCA.
• Spherocyte		hereditary, Acquired (AIHA "Warm = 3L")
• Elliptocyte	(Oval cell)	hereditary.
• Schistocytes	(Helmet cell)	Mechanical hemolysis.
• Tear drop cell	(Dacrocyte)	Myelofibrosis.



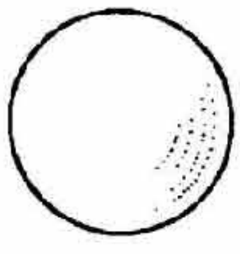
Echinocyte

Stomatocyte

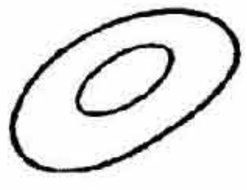


Codocyte

Acanthocyte



Spherocyte



Elliptocyte

Schizocyte

Dacrocyte

Sickle cell

p.17

Jaundice in Hemolytic Anemia:

1) Hemolytic crisis.
2) Hempsiderosis → Iron over-load.
3) Viral Hepatitis → dr bl. transfusion. (↑AST / ALT)
4) Gall Stone → CBD obst. (↑ ALP)

p. 29

Jaundice lymphoma

1) AIHA. (Warm = 3L)
2) LN in porta hepatis.

Jaundice in IMN

1) AIHA. "Cold"
2) Viral hepatitis. "↑Transmainases"

p. 26

Acute Chest $ in SCA:

Def.:	Specific Comlication of SCA.
Cl./P	Fever + hypoxia. (ARDS like)
Invest.	1) ↑↑↑ leuco-cytosis. 2) CXR → lung infiltrates.
TTT.	Exchange Transfusion to ↓ HbS < 50%

p. 30

Drugs causing haemolysis

1) Direct interaction with RBC membrane !? eg **Amphotericin**.
2) Immune mediated
   a) **Methyldopa** → AIHA – Auto-immune hepatitis – Depression..
   b) **Hapten type** → penicillins, cephalosporins.
   c) **Innocent by stander** → Quinidine, Sulfa.
3) Drugs causing haemolysis in G6PD def. e.g. antimalarials, sulfa, nitrofurantoin.

p. 30

Mechanical Hemolysis

1) **March Hb uria → hemolysis in feet capillaries.**
2) **Prosthetic valve.**
3) **Calcific AS.**
4) **μ-angiopathic HA** (fibrin deposition in capillaries → RBCs disruption)
   (DIC - HU$ - TTP - Malignant HTN, Scleroderma)

Diagnosis: Blood film → **shistocytes = helmet (fragmented RBCs).**

p. 30

Toxic causes of haemolysis

- Malaria.
- Clostridium welchii.
- Pneumococci.
- Staph.
- Snake & Spider venom.
- Cu overload (Wilson's D.)

Advanced LD → lipid abnormalities → spur-cell → haemolysis → Anemia.

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DD of pancytopenia.

- **Aplastic Anemia** → pan-cytopenia + No Retics.
- **hyper-splenism** → pan-cytopenia + ↑ Retics.
- **Folic Acid def.** → Megaloblasts in BM.

p. 40

Leukomoid Reaction = Leukemia like

1) **Cause: Infections (Abscess) – hemolysis – hge.**
2) **TLC <50,000/mm3.** → **(Shift to the Lt.)**
3) **↑ALP. Dt functioning WBCs. (in leukemia CML …↓ALP)**
4) **CBC → Normal** → **RBCs – Platelets - BM … No blasts.**
   → **Immature cells never > 5%, but never blasts.**

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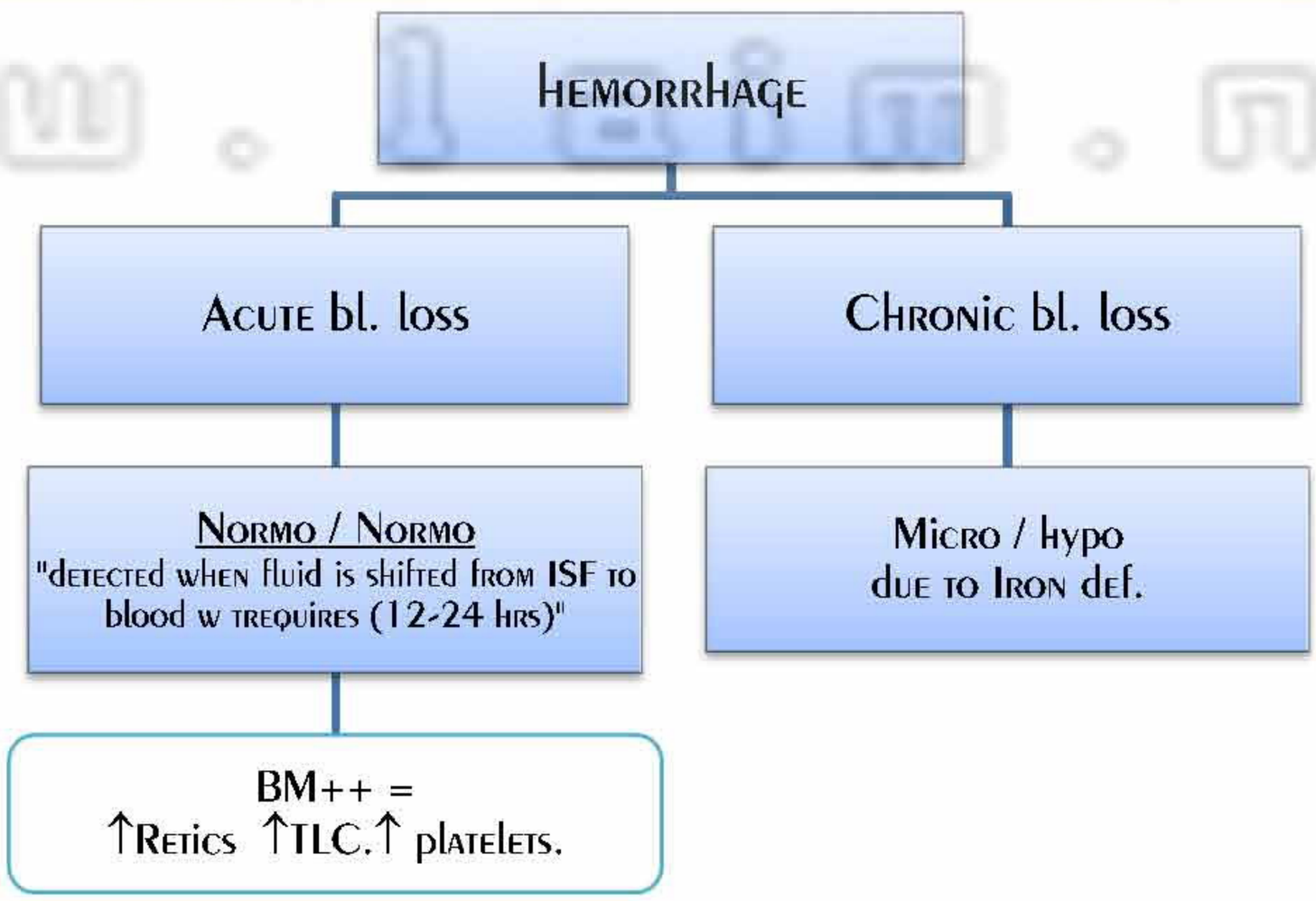
Leuko-Erythroblastic Reaction

Immature Blasts of WBCs / RBCs in peripheral bl.

1) **BM infiltration:**
   - Leukemia.
   - Lymphoma.
   - Multiple Myeloma.
   - Myelo-fibrosis & TB.
2) **Sever hemolysis – hge.**

p. 25

Hemorrhagic Anemia



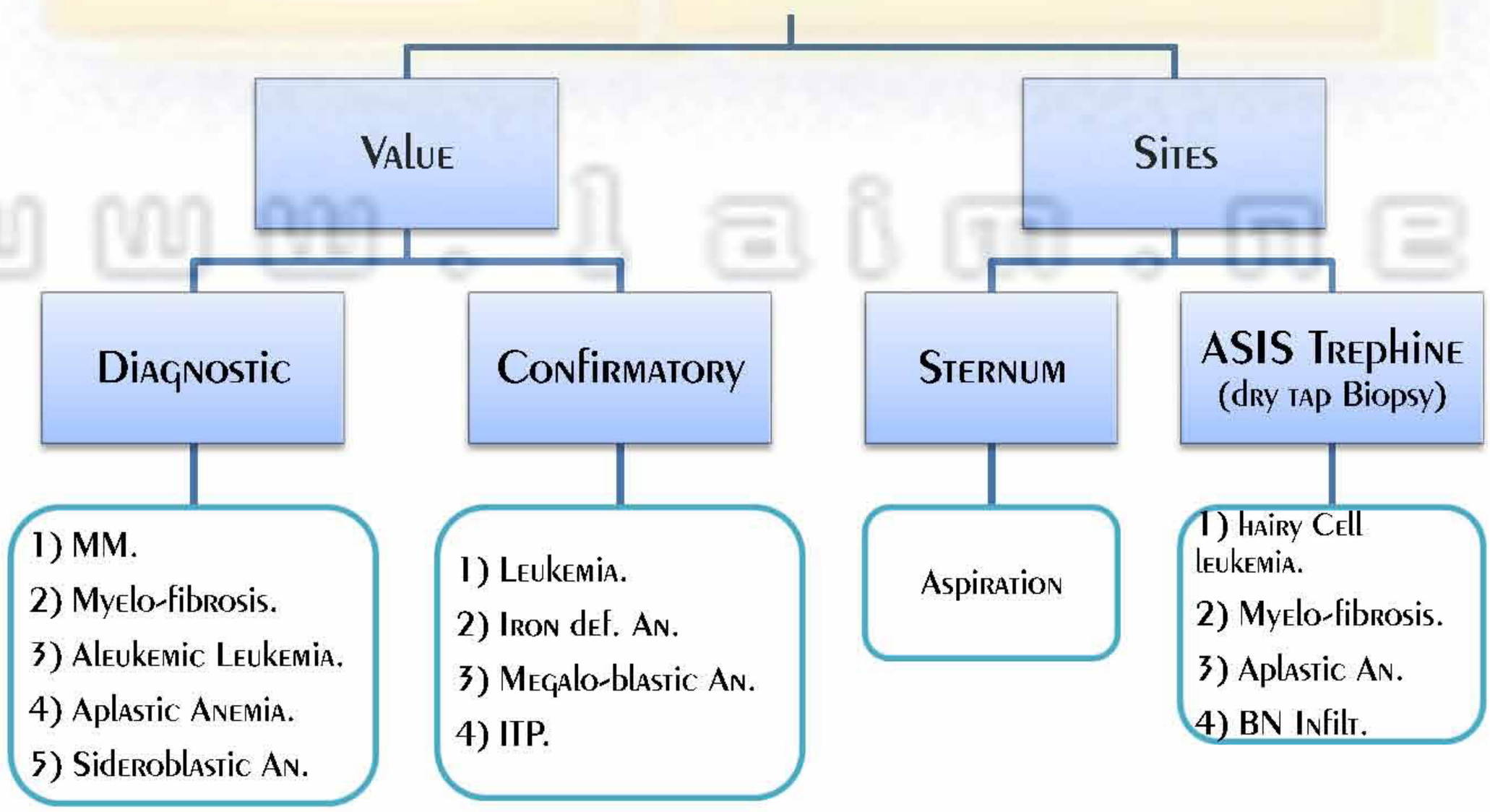
p. 39

Hyper & hypo-splenism.

	Hyper-splenism	Hypo-splenism
Causes	"↑ phagocytic Activity of Spleen → mono upto pan-cytopenia + BM⊕" **Splenomegaly due to any cause** 1) PH dt Cirrhosis. 2) CHA… 3) RA. (felty's $) 4) Lymphoma, leukaemia, 5) Amyloidosis, Myelo-fibrosis.	1) Post-Splenectomy. 2) Auto- Splenectomy → SCA. 3) Congenital Absence.
Invest.	1) **Pan-cytopenia + ↑ Retics.** (N. BM exam.) 2) RBCs e chromium in spleen.	1) Howell jolly bodies in RBCs, 2) **Acanthocytes.** (Chronic LD / post-splenectomy)
Tr.	1) Transfusion 2) Splenectomy 3) ABS for infections.	• Vaccine for encapsulated org. (Pneumococcal & H influenza Meningitis) • Prophylactic penicillin.

p. 40

BM Examination



Aplastic Anemia

- 1ry
  - Idiopathic → Autoimmune dt ⊕ T Cytotoxic … BM failure
  - Congenital → Fanconi Anemia
- 2ry = Aquired
  - Drugs → 1) Anti-biotics → chloramph. sulpha. 2) Anti-RA → penicillamine, gold, indomethacinn. 3) Anti-Thyroid – Anti-convulsants.
  - Infections → HCV - HBV. Parvovirus. EBV. HIV.
  - Chemicals → Benzene - OP
  - PNH → hemolytic an. that ends with Aplastic an.

Cl. /P = pan-cytopenia

- ↓ RBCs → **Anemia** → pallor.
- ↓WBCs → **Recurrent infections** → (Sore throat + scanty pus)
- ↓ Platelets → **purpura.**

Investigations:

- **2ry Causes must be excluded.**
- **History of viral infection.**
- **CBC** → pancytopenia + No Retics.
- **BM exam.** → pancytopenia = hypo-cellular.

pure Red Cell Aplasia
- Thymoma → MG, pure redd cell Aplasia, Mediastinal $. (hoarsness & Dysphagia)
- Diamond Black fan $
- 2ry to Renal D.

Anemia of Chronic Disease

Causes:

Chronic Infection → TB – Bronchiectasis.

Chronic Inflam. → RA - IBD - Malignancy.

Invest.:

- ↓ **RBCs** → **Normo / Normo. due to BM (-) by:**
  - ✓ **IL-1 & TNF** → *Failure of iron utilization* → ↑ *Iron Stores* + ↓ *release from BM to Normoblasts* → *poor response to EP)*
  - ✓ **& Not by …hemolysis – hge – BM infiltration.**
- **Normal WBCS & Platelets.**
- **Iron profile** ⇒ **↓ s. Iron + ↑ Iron stores. (↑ s. Ferritin ..see above)**

TTT.:

1) **Of the Cause.**
2) **BM ⊕ by EP ⇒ poor Response**
3) **No response to Iron th. dt failure of….**

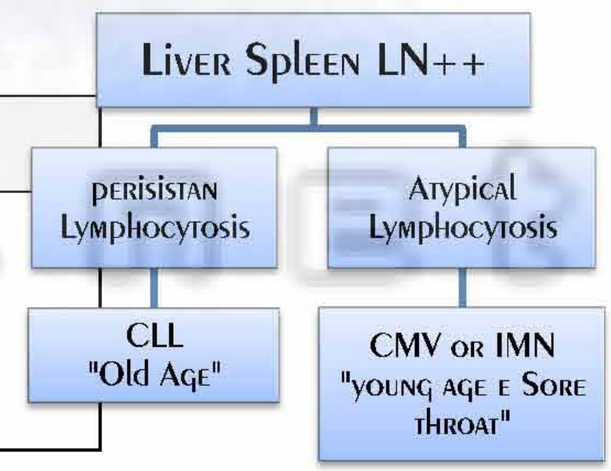
Leucocytes

	Neurtophilia	Eosinophilia	Basophilia	Monocytis
• TLC • Absolute	40-75% (2000 -7000/mm^3)	1 -6% (20 - 500/mm^3)	< 2% (0 -100/mm^3)	2-9 % (200-800/mm^3)
Causes	• Acute pyogenic Infections. • T. damage → burns, MI. • Malignancy. • Myeloprolif. &Leukaemia (CML) • Inflam. D. → RA. • Drugs → CS. • Acute IgE – hemolysis. • Metabolic → Uremia / Eclampsia.	• Allergy / Drug HS. • Parasitic → hydatid - Fasciola - Ankyl. • Addison's D. • Hodgkin's D. / Myelo-prolif. • Vasculitis. (Churg-strauss – Wegner's ± PAN) • 1^{ry} hypereosinophilic $ + Invasive toxic effects to the heart and lung.	• Myelo-prolif. • IBD. • Acute HS. • Reactive. *(Myxedema / Xanthemata)*	1) Bacterial: TB – Brucellosis - SABE. 2) Viral: CMV, IMN. 3) Protozoa: (malaria). 4) AML. (M_4 -M_5) / CML 5) IBD

Lymphocytes

- TLC = 20 - 40%.
- Absolute Count = 1500- 3500/mm^3.

Lymphocytosis	Atypical lymphocytosis	Lymphopenia
- Viral: IMN – CMV. - Bacterial: TB - Brucella, Typhoid - Protozoal: toxoplasmosis. - Malignancy = Lymphoma, CLL.	- Viral : IMN / CMV. - Lymphoma, leukaemia. - hepatitis.	- CS therapy. - Congenital Immunodef. - Chemotherapy. - HIV. – Hodgkin's.



Neutropenia (> 2000) Agranulocytosis (> 500)

1) **Infections:**
   - **Bacterial** → TB – Brucella - Typhoid
     (if Intestinal perf. ...peritonitis → leucocytois).
   - **Viral:** → HIV / hepatitis / Influenza.
2) **Pan-cytopenia:** Aplastic an. + hyper-splenism.
3) **Immunological:** *SLE / Felty's $ in RA*
4) **Drugs:**
   - *Anti-Inflam. / Anti-Bact.*
   - *Anti-Convalsants / Anti-Cancer.*
   - *Anti-thyroid / Anti-Diabetic.*

➢ **Invest.** Neutropenia + Normal RBCs & platelets.

➢ **TTT.:**

4) Of the cause.
5) G-CSF.
6) BM Transplant.