ESSENTIAL THROMBOCYTOSIS

INTRODUCTION

- Non reactive chronic myeloproliferative disorder
- Clonal disorder involving pluripotent hematopoietic progenitor cells
- Manifest clinically by OVERPRODUCTION of platelets
- Isolated thrombocytosis can be the initial clinical manifestation of PV, PMF, or chronic myelogenous leukemia

- First described by Epstein and Goedel in 1934

Platelets

*Disc shape cells 2-4 mm in diameter.

*They have blue grey cytoplasm with red lysosomal granules, but devoid of nuclei.

*They are formed in BM from their progenitors the megakaryocytes.

*Megakaryocytes are giant cells with multilobed nuclei (4-6) that produce platelets from their cytoplasm by the process of budding.

*A hematopoietic growth factor for megakaryocytes is thrombopoietin

*IL-11 also stimulates platelet production.

*Each megakaryocyte produces 1000-3000 platelets.

*Their normal count in peripheral blood is 150000-300000/µL.

*One third resides in splenic pool & two thirds in circulation.

*Their life span is 9-10 days.

Platelet structure

- **plasma (surface) membrane protein:**

  GPIIb-IIIa – fibrinogen receptor

  GP Ib-IX-V: vWF receptor

  GPIa-IIa: collagen receptor

- **secretory granules:**

  A-Granules

  Dense granules

  Lysosomes

Platelet function

They contain 3 types of secretory granules:
*lysosomes,
*α-granules,
*dense bodies.

α- granules

contain
*platelet-specific proteins (PF4, β-thromboglobulin) &
*several growth factors including PDGF & TGF-β.

*They also contain several hemostatic proteins including fibrinogen, FV, vWF synthesized by megakaryocytes.

Dense bodies (δ-granules)

contain
*ATP,
*ADP,
*Ca^{+2},
*Serotonin

*Adhesion to blood vessel wall,

*Aggregation to form the primary hemostatic plug at site of blood vessel injury, &

* Release of vasoconstrictor substances from intracellular granules in response to variety of substances are the main functions of platelets. Platelets also provide surface for activation of coagulation factors. Activated platelets expose specific receptors that bind to F Xa & F Va increasing their local concentration thus accelerating prothrombin activation. F X is activated by F IXa & F VIII on platelet surface.

They contain a membrane - phospholipase C that can be stimulated by activating agents to hydrolyze endogenous phosphatidyl inositol to form a diglyceride.

This is converted to arachidonic acid by diglyceride lipase enzyme.

Arachidonic acid will be converted to prostaglandins (PG G2 & thromboxane A2) under the influence of cyclo-oxygenase .

Platelet function tests

1. Bleeding time --- It is prolonged in thrombocytopenia, functional platelet abnormalities & vW disease.
2. Platelet aggregometry --- Response of platelets to variety of aggregating agents (ADP, fibrinogen, Collagen, ristocetin & adrenaline) is quantitated. It is useful in diagnosing hereditary platelet disorders.

Platelet receptors in clinical practice

- Cyclooxygenase inhibitors (TXA2 –e.g. Aspirin)
- Adenosine diphosphate inhibitors

-ticlopidine hydrochloride (Ticlid), clopidogrel bisulfate (Plavix)

- GPIIb-IIIa receptor antagonists

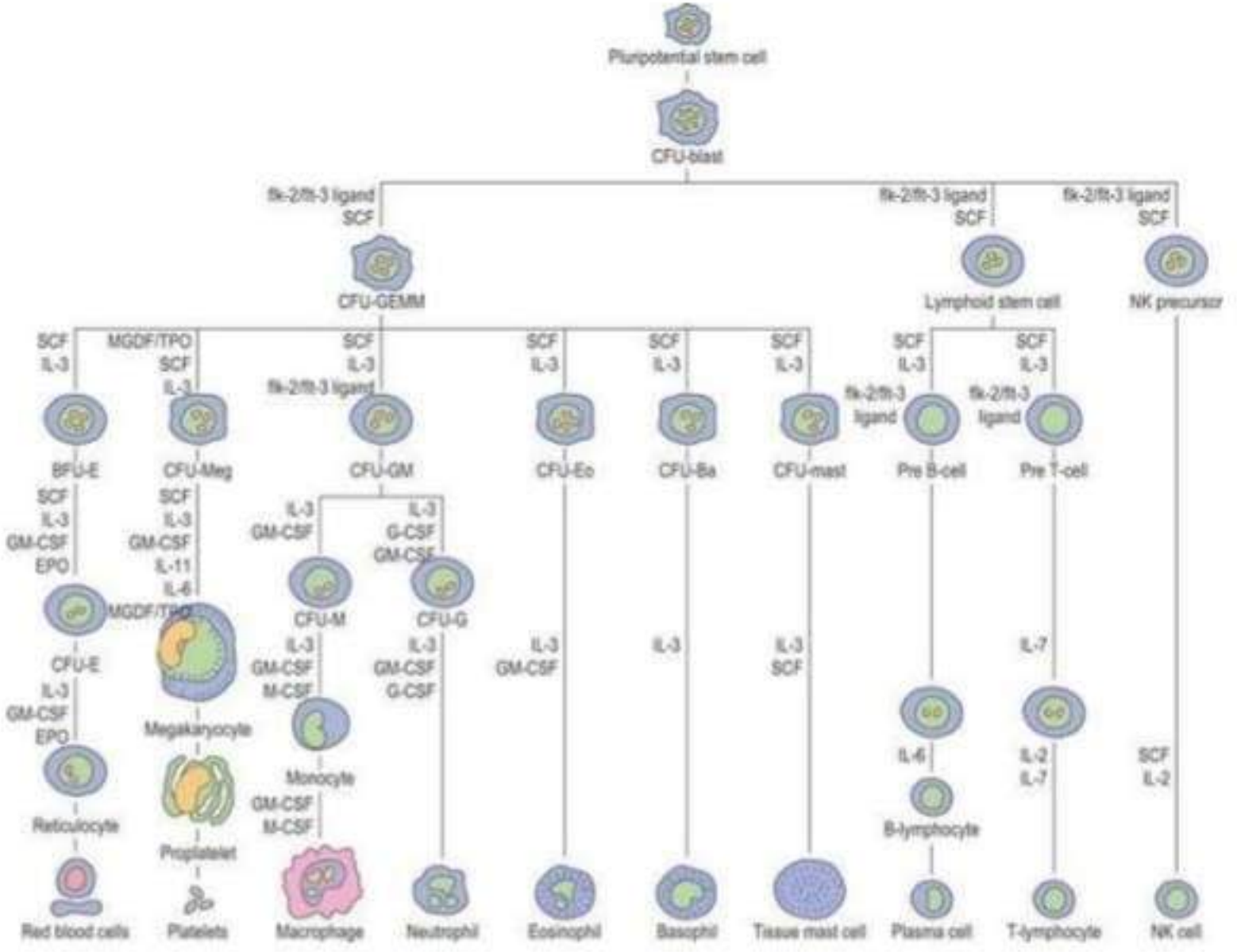
- Abciximab, Epifibatide, Tirofiban

NORMAL PLATELET COUNT

- 1.5 – 4.5 Lac/mm3

THROMBOCYTOSIS

- >4.5 Lac/mm3


Pluripotential stem cell
CFU-blast
flk-2/flt-3 ligand
SCF
CFU-GEMM
Lymphoid stem cell
NK precursor
BFU-E
CFU-Meg
CFU-GM
CFU-Eo
CFU-Ba
CFU-mast
Pre B-cell
Pre T-cell
CFU-E
CFU-M
CFU-G
Megakaryocyte
Monocyte
Reticulocyte
Proplatelet
B-lymphocyte
Red blood cells
Platelets
Macrophage
Neutrophil
Eosinophil
Basophil
Tissue mast cell
Plasma cell
T-lymphocyte
NK cell

EPIDEMIOLOGY

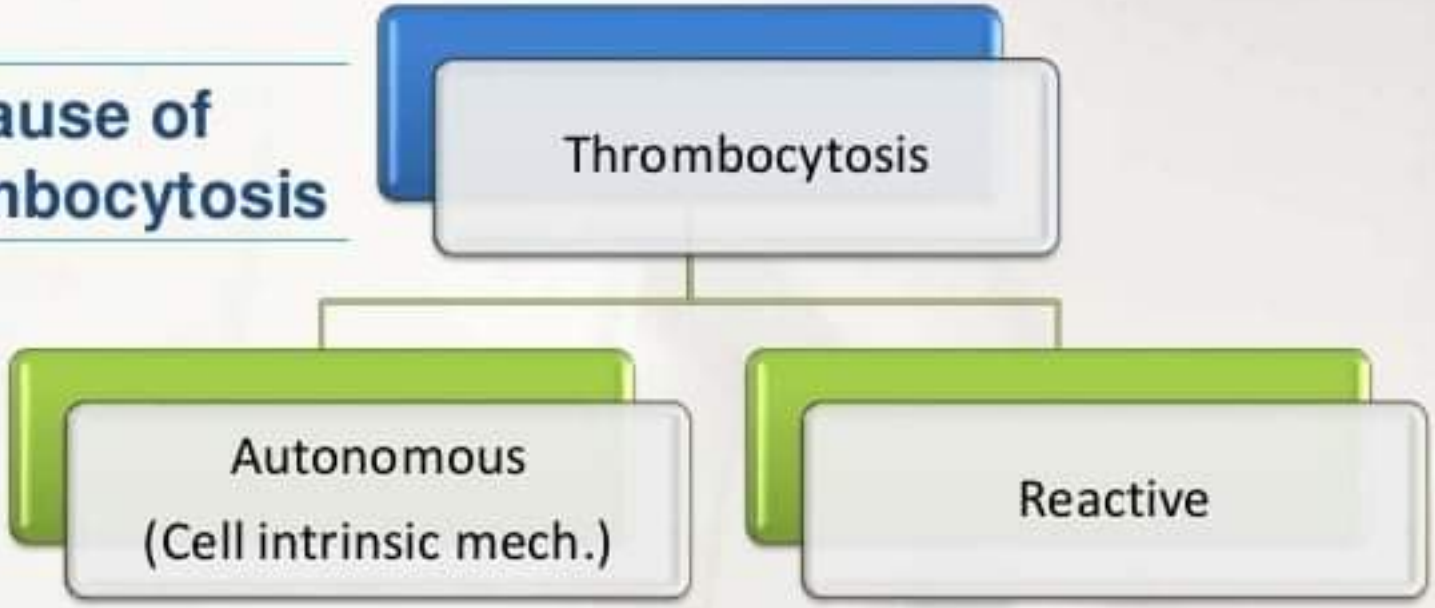
- Incidence: 1-2 / 100 000
- Female predominance (younger patients)

- Median age at diagnosis is 60 years
- Rare in children
- Can occur at any age

Thrombocytosis

- **Thrombocytosis resulting from myeloproliferation**
  - essential thrombocythemia
  - polycythemia vera
  - chronic myelogenous leukemia
  - myeloid metaplasia
- **Secondary (reactive) thrombocytosis**
  - systemic inflammation
  - malignancy
  - iron deficiency
  - hemorrhage
  - postsplenectomy

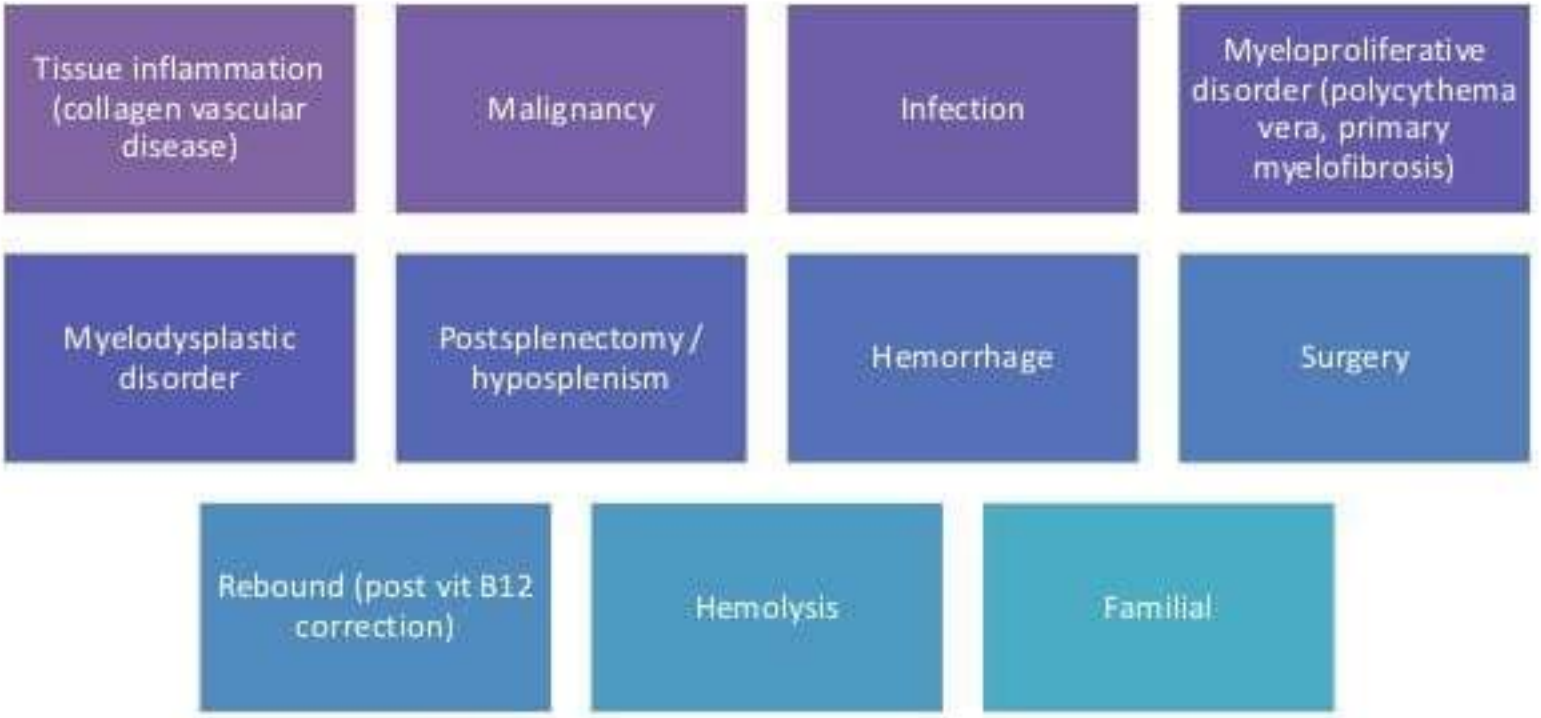
Cause of Thrombocytosis



- ✓ Its clonal, caused by acquired mutations of genes & are associated with MPNs.
- ✓ Rarely familial.

- ✓ Anemia/Blood loss
- ✓ Infections
- ✓ Inlfamatory conditions
- ✓ Post-splenectomy

Non clonal reactive cause of thrombocytosis



ETIOLOGY

Autonomous production

- CFU-Meg form colonies in the absence of exogenous thrombopoietin (Tpo)

Increased sensitivities to cytokines (interleukin-3 [IL-3])

Decreased effect of platelet-inhibiting factors (transforming growth factor [TGF] beta)

mutation

Janus kinase 2 (JAK2) V617F

- 50% in ET patient
- Turn thrombopoietin receptor on permanently, leading to overproduction of megakaryocytes

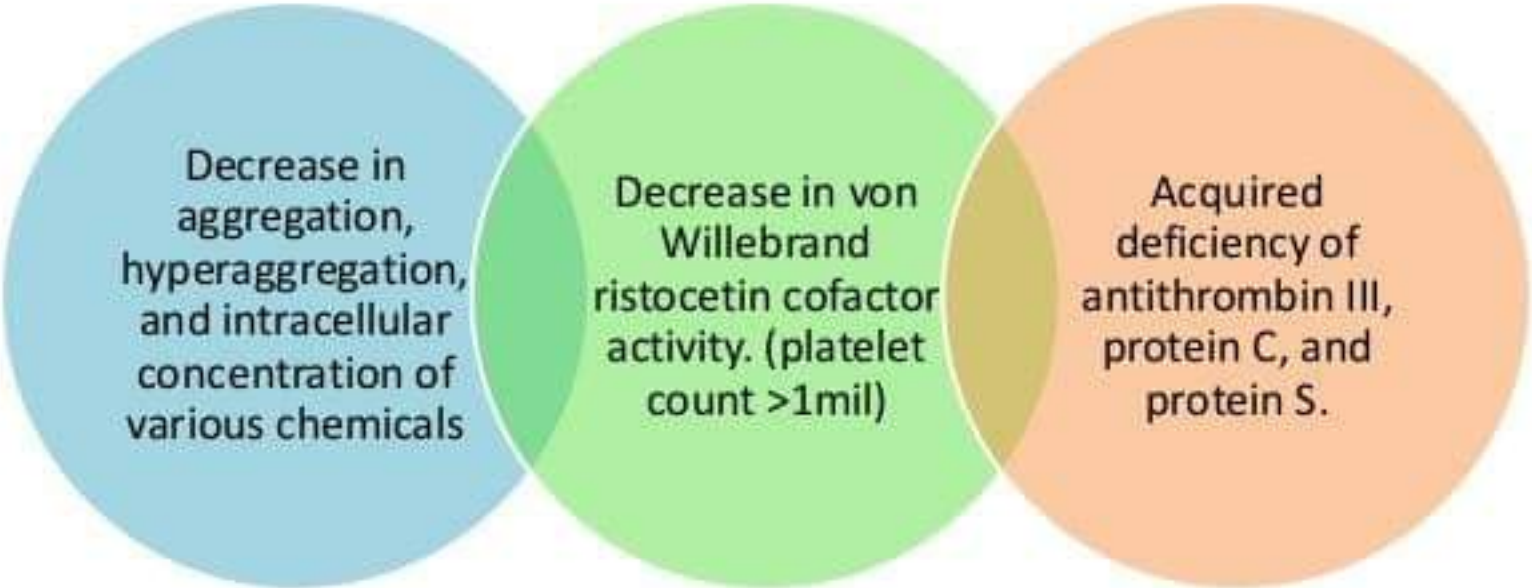
Calreticulin (CALR)

- 25% of ET patient
- Exclusive of JAK 2 and MPL mutation

Myeloproliferative leukemia virus oncogene (MPL)

- 3-5% of ET patient
- constitutive activation of the thrombopoietin receptor protein

hemorrhage and thrombosis



CLINICAL FEATURES	
Asymptomatic at diagnosis	45-50%
Vasomotor symtoms	13-40%
Thrombosis	9-22%
Haemorrhage	3-37%
History of fetal loss	43%
Palpable splenomegaly	35%

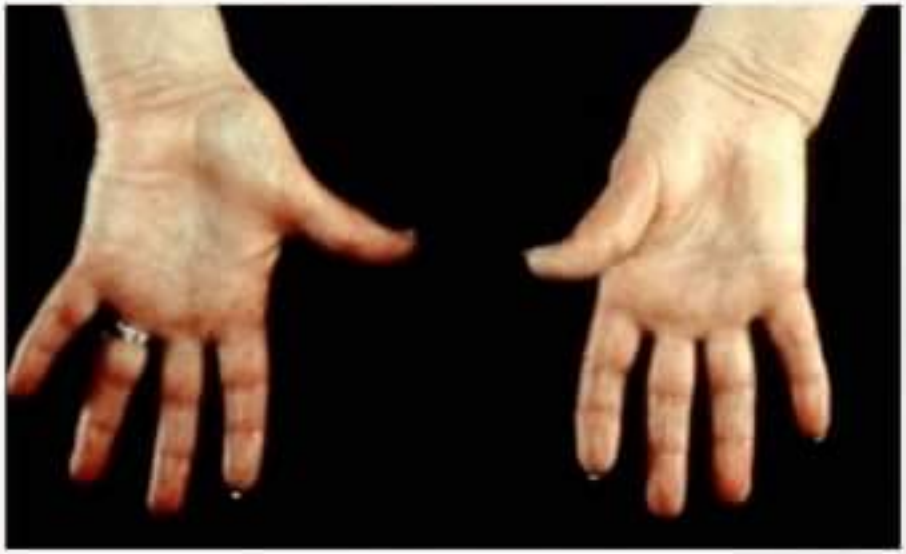
CLINICAL FEATURE

- 25-33% of patients asymptomatic at diagnosis

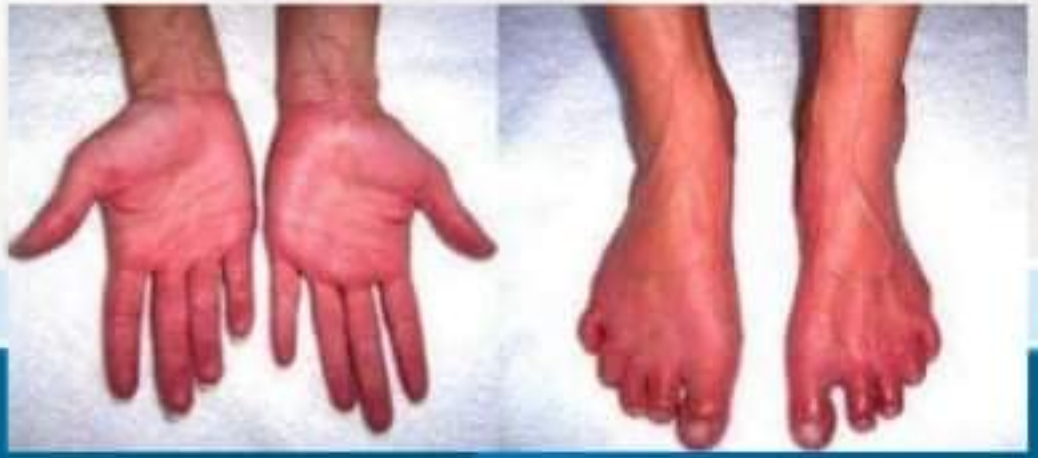
Hemorrhagic tendency	Thrombotic tendency
• Easy bruising • The gastrointestinal tract is the primary site of bleeding complications • Other sites of bleeding include the skin, eyes, gums, urinary tract, joints, and brain • Bleeding is usually not severe and only rarely requires transfusion • The bleeding is generally associated with a platelet count greater than 1 million/μL	• Erythromelalgia • Ocular migraine • TIA • Occlusion of the leg, coronary, and renal arteries • Venous thrombosis of the splenic, hepatic, or leg and pelvic veins may develop • Pulmonary hypertension may result from pulmonary vasculature occlusion

Vasomotor symptoms

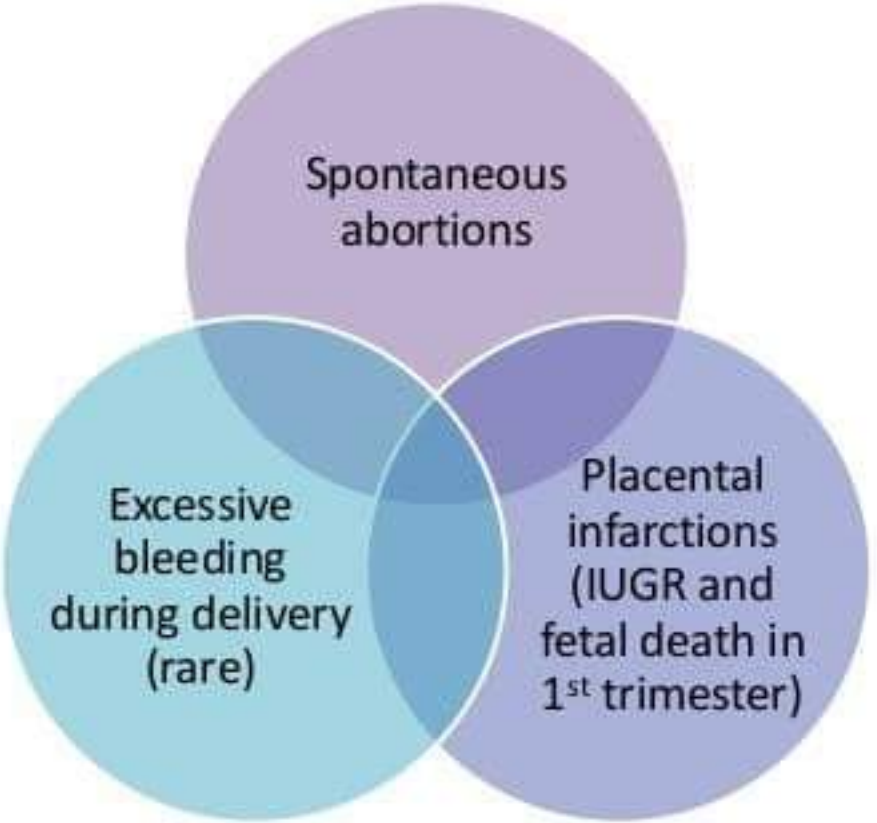
- *symptoms related to microvascular disturbances*
✓Headache
✓Lightheadedness
✓Syncope
✓Atypical chest pain
✓Acral paresthesia
✓Livedo reticularis
✓Erythromelalgia (burning pain of the hands or feet associated with erythema and warmth)
✓Transient visual disturbances (eg, amaurosis fugax, scintillating scotomata, ophthalmic migraine)



Erythromelalgia



Pregnancy complication



Hemorrhage and Thrombosis

Hemorrhagic tendency

- Easy bruising
- The gastrointestinal tract is the primary site of bleeding complications
- Other sites of bleeding include the skin, eyes, gums, urinary tract, joints, and brain
- Bleeding is usually not severe and only rarely requires transfusion
- The bleeding is generally associated with a platelet count greater than 1 million/μL

Thrombotic tendency

- Erythromelalgia
- Ocular migraine
- TIA
- Occlusion of the leg, coronary, and renal arteries
- Venous thrombosis of the splenic, hepatic, or leg and pelvic veins may develop
- Pulmonary hypertension may result from pulmonary vasculature occlusion

THROMBO-HEMORRHAGIC EVENT : HIGH RISK FACTOR

Increased Thromobsis risk
JAK2 V617F mutation
History of thrombosis
WBC >11000/µl
Male gender
Obesity
Cardiovascular RF (smoking, hypertension, and hypercholesterolemia, HTN, T2DM, tobacco use)
Age >60 years

Increased Hemorrhagic risk
Platelet count >10 lac/µl
Patient on Aspirin / NSAIDs with high platelet count (>10 lac/µl)
Post Surgery.
Patient receiving thromboprophylaxis.

PHYSICAL EXAMINATION

May be Unremarkable

Erythromelalgia

35-40% present with splenomegaly

20% present with hepatomegaly

INVESTIGATION

Complete blood count

- sustained, unexplained elevation in the platelet count
- Mild neutrophilic leukocytosis

Peripheral smear

- Increased platelet number
- Large and hypogranular and clumps platelets

Coagulation profile

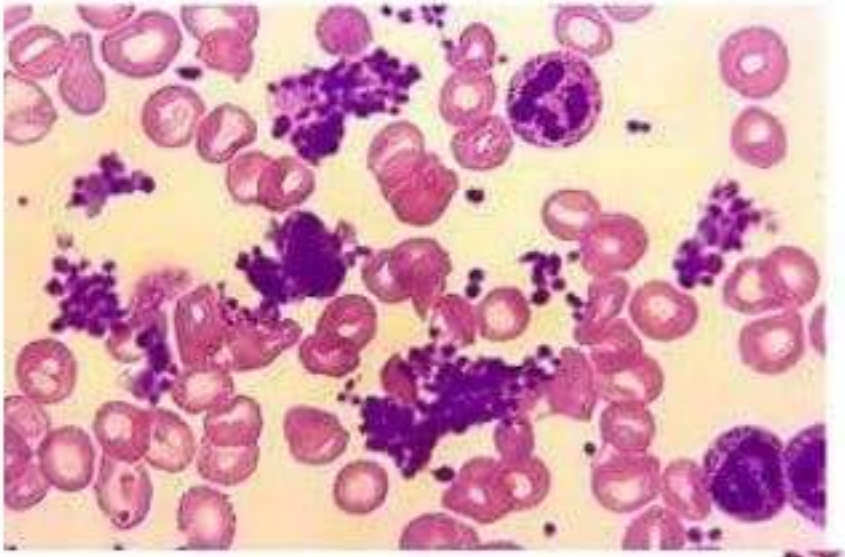
- PT and aPTT normal

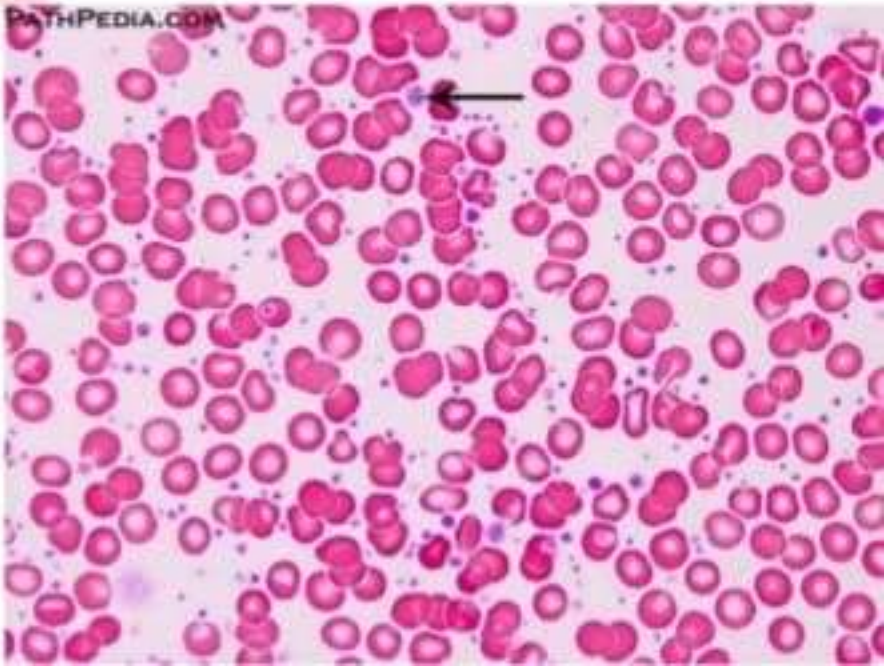
Bleeding time

- Maybe prolonged

Serum potassium

- Hyperkalemia (lab artifact not demonstrated by ECG)

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Platelets aggregation studies

- impaired platelet aggregation
- Spontaneous platelets aggregation

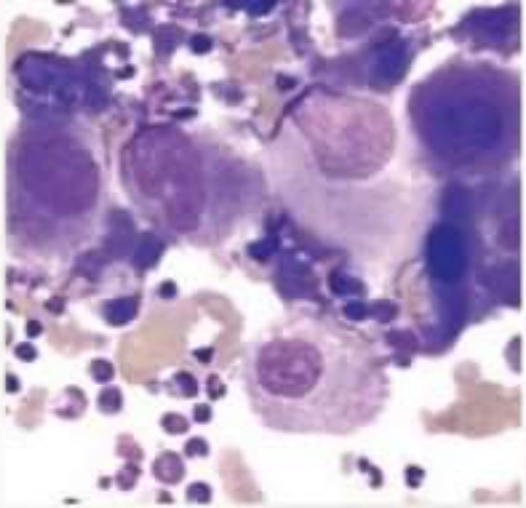
Bone marrow biopsy

- Hypercellular marrow (90%)
- Megakaryocytic hyperplasia
- Giant megakaryocyte with staghorn and hyperlobulated nuclei
- bone marrow iron stain results may be negative even when other studies do not support the presence of iron deficiency (bleeding)

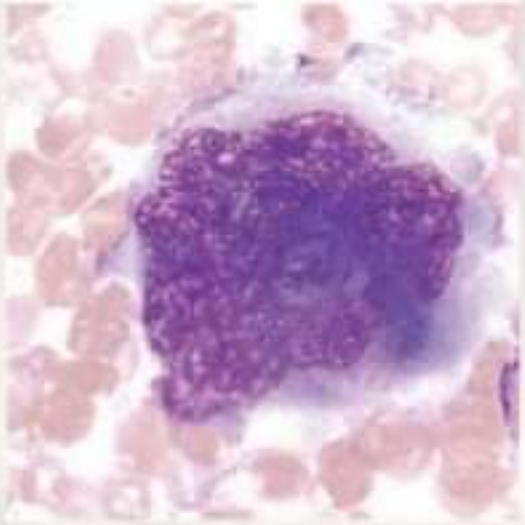
Genetic studies

- JAK2 V617F, CALR, and MPL mutations

Peripheral blood (original magnification 1000)

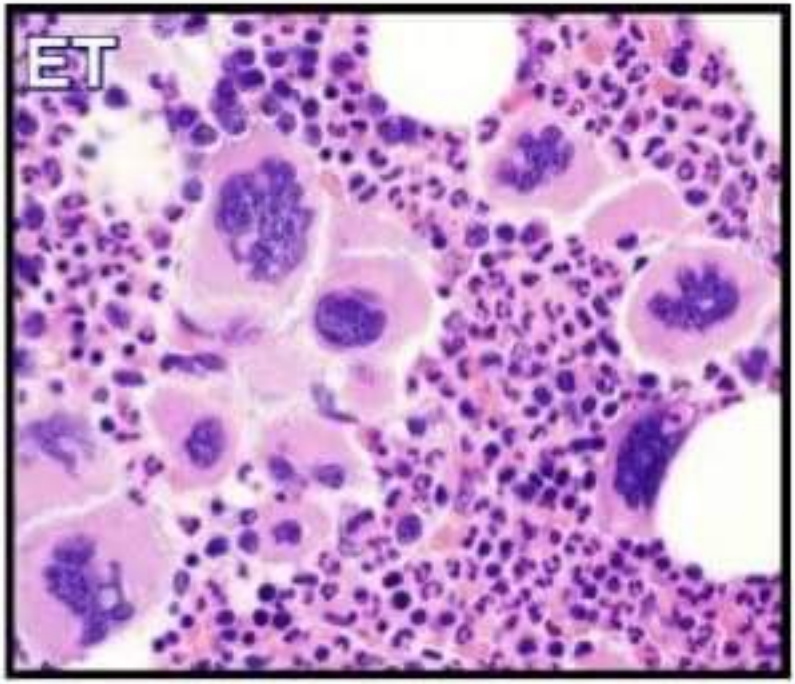


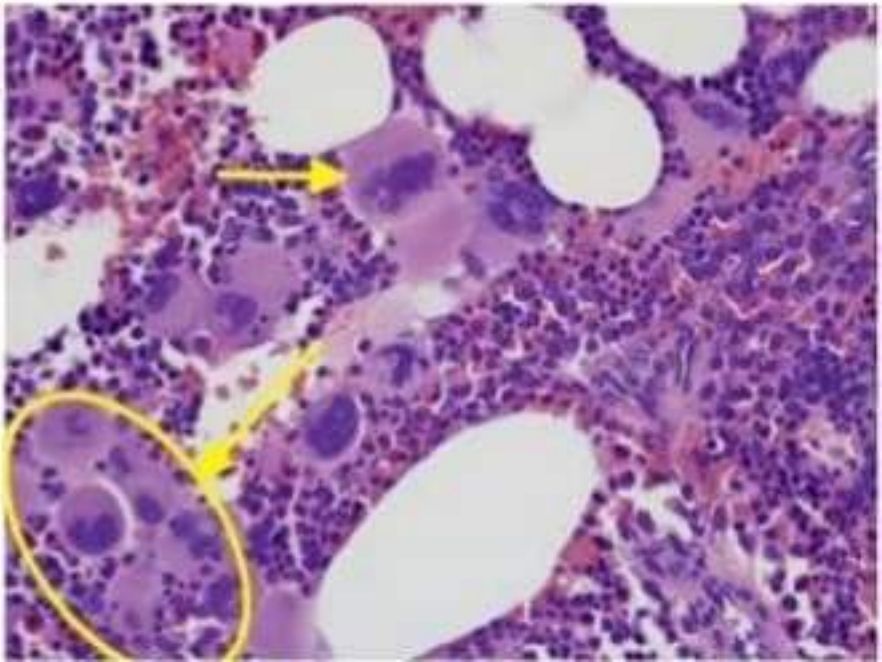
Bone marrow (original magnification x500)



Bone marrow showing abnormal hyperlobulated megakaryocyte (original magnification x1000)

ESSENTIAL THROMBOCYTHEMIA


ET



Bone marrow biopsy findings s/o alternative diagnosis

- Megakaryocytes with highly atypical morphology.
- Increased myeloblasts.
- MDS features.
- Significant (>grade 1) reticulin fibrosis or collagen fibrosis.

CLINICAL PRESENTATION – depending on the mutations present

1

JAK2 V617F

- **High thrombosis risk.**
- PV transformation risk
- High TLC, Hb.
- Relatively lower platelet count.

2

CALR

- Presents usually in young age.
- Frequently in male
- **Lower thrombosis risk**
- High platelet count
- Low Hb./TLC count.

3

MPL

- No prognostic significance.

WHO diagnostic criteria Essential thrombocythemia

MAJOR CRITERIA

- Platelet count ≥ 4.5 lac/microl
- Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei.
- Not meeting WHO criteria for *BCR-ABL1*+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms
- Presence of *JAK2*, *CALR*, or *MPL* mutation

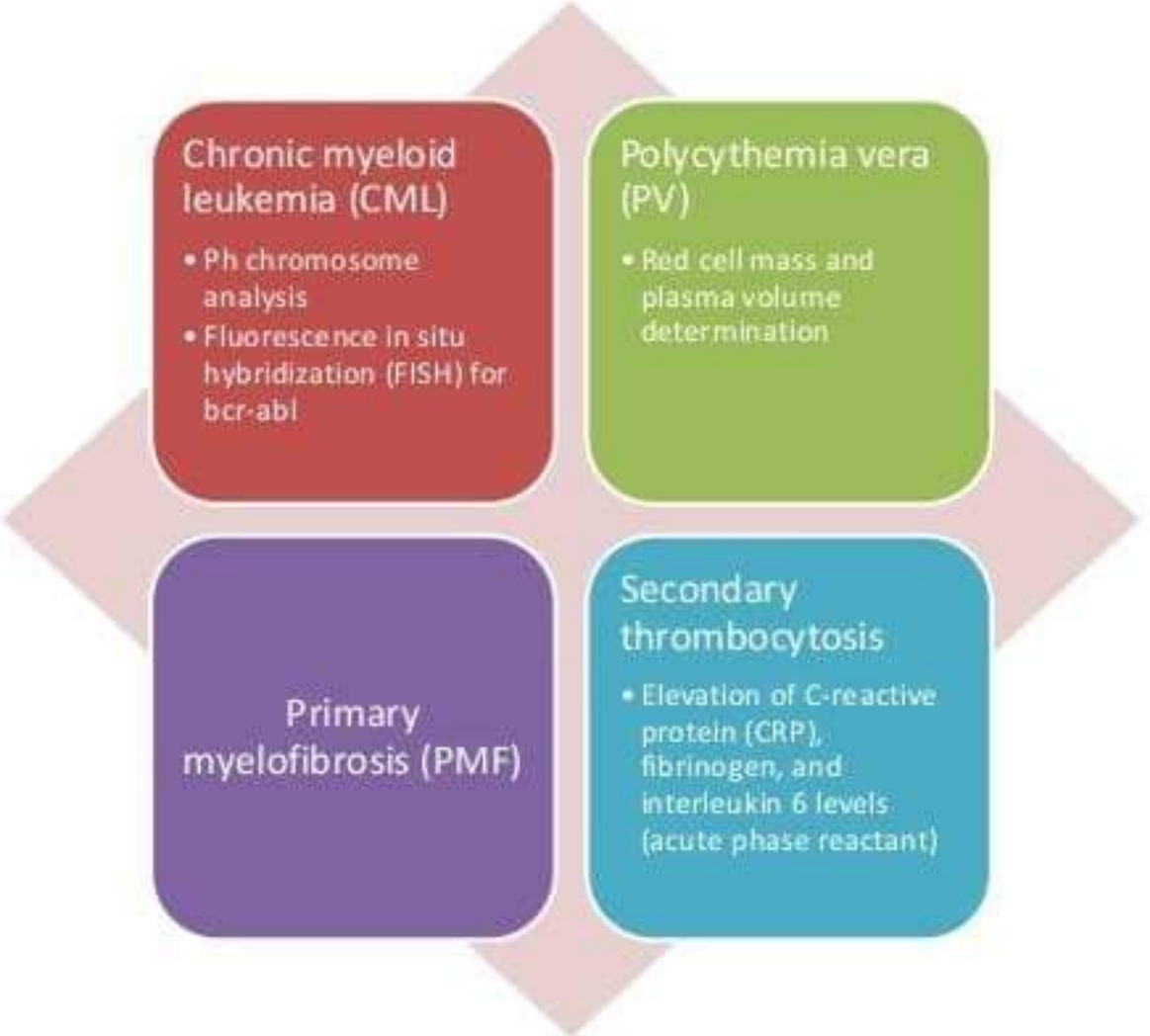
MINOR CRITERIA

- Presence of a clonal marker or absence of evidence for reactive thrombocytosis

DIAGNOSIS (WHO 2008)

ESSENTIAL THROMBOCYTHEMIA (ET)	Major criteria	Minor criteria
Platelet count ≥450 x 10^9/L	○	○
Bone marrow biopsy showing proliferation mainly of the megakaryocyte lineage with increased numbers of enlarged, mature megakaryocytes with hyperlobulated nuclei; no significant increase or left-shift in neutrophil granulopoiesis or erythropoiesis and very rarely minor (grade 1) increase in reticulin fibers	○	○
Not meeting WHO criteria for *BCR-ABL1*+ CML, PV, PMF, myelodysplastic syndromes, or other myeloid neoplasms	○	○
Presence of *JAK2*, *CALR*, or *MPL* mutation	○	○
Presence of a clonal marker or absence of evidence for reactive thrombocytosis	○	○
TOTAL		
Diagnosis requires meeting all 4 major criteria or the first 3 major criteria and the minor criterion		

DIFFERENTIAL DIAGNOSIS



HIGH RISK FACTOR FOR THROMBOHEMORRHAGIC EVENT

- Age >60 years
- History of thrombosis
- Platelet count >1500 x 10 9/L (1.5 million/µL),
- Obesity
- Cardiovascular RF(smoking, hypertension, and hypercholesterolemia)
- Markers of hypercoagulability (factor V Leiden, antiphospholipid antibodies)
- JAK2 mutation

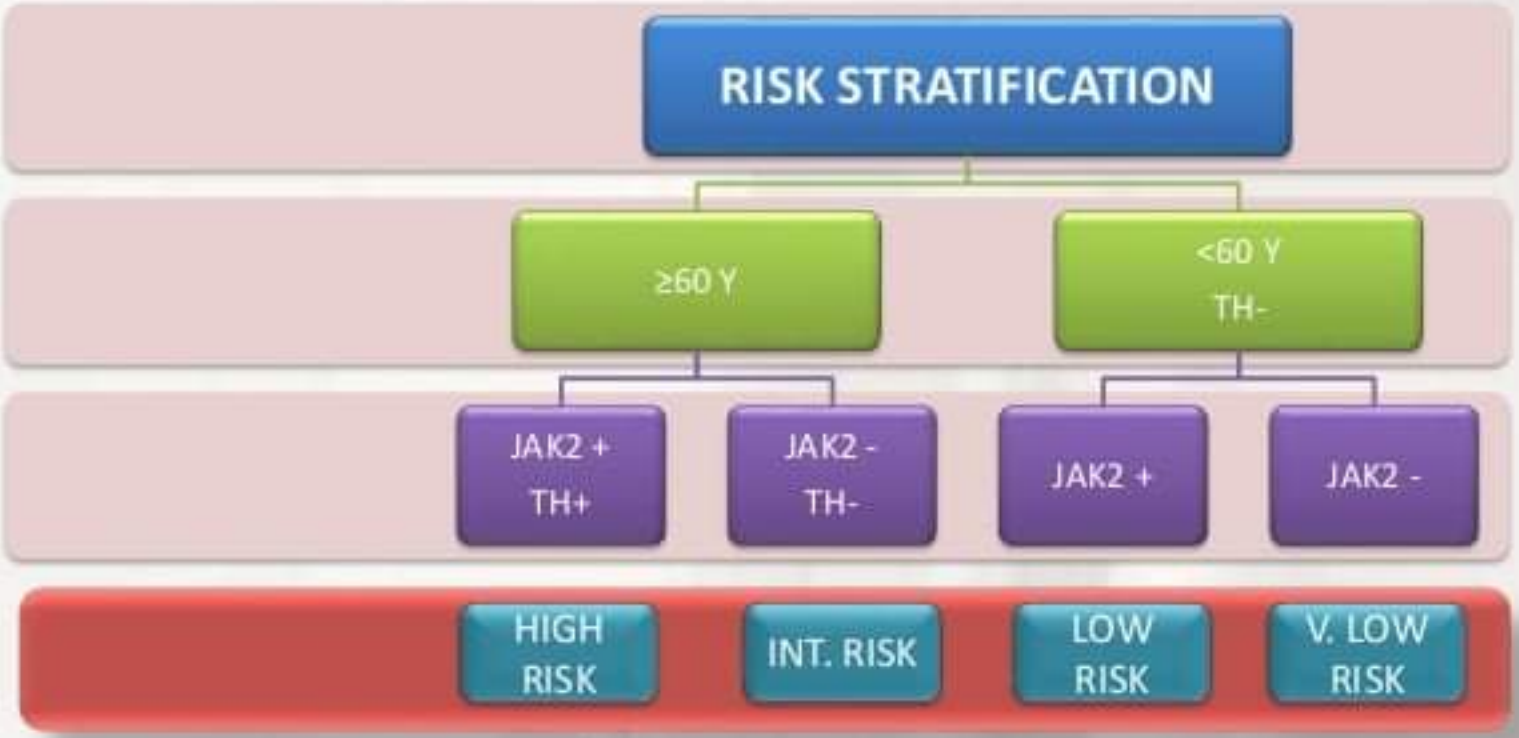
- Lifestyle modifications should be recommended
- Cytoreductive therapy to decrease the platelet count
  - Hydroxyurea
  - Low dose aspirin
  - Busulfan
  - Anagrelide
  - Interferon alfa
  - Phosphorus-32 (32 P)

MANAGEMENT GOALS

1. To alleviate symptoms
2. To prevent thrombotic / Hemorrhagic complications
3. No curative treatment
4. No survival benefit
5. Treatment doesnot prevent disease transformation (AML/Post ET Myelofibrosis)

International Prognostic Score for Thrombosis in Essential Thrombocythemia (ET)

Score	Risk cat.	Annual thrombosis risk
0 - 1	Low	1.03%
2	Interm ediate	2.35%
3 - 6	High	3.56%



 # History of thrombosis at any age : HIGH RISK DISEASE

**CVS Risk factors are considered during devising treatment strategy*

TH: History of Thrombosis

+/- : Present/Absent

LOW RISK PATIENT	• Observation may be appropriate • Low-dose aspirin may be useful in treating patients with symptoms of microvascular occlusion (erythromelalgia).
PLATELETPHERESIS	• In emergency temporary inefficient remedy • acute thrombosis and/or marked thrombocytosis
SURGERY	• increased risk for bleeding and thrombosis • Cytoreductive therapy

TREATMENT MODALITIES

SPECIFIC THERAPIES
1. LOW DOSE ASPIRIN
2. CYTOREDUCTIVE THERAPY - Hydroxyurea -Anagrelide -Interferon
3. PLATELETPHERESIS
4. OTHER -Pipobroman -32P -Busulphan

LOW- DOSE ASPIRIN

- Prevent thrombotic events
- Control vasomotor symptoms

- Act by inhibiting plt. TXA2 synthesis through COX-1 Inhibition irrev.
- Dose : 40-100mg (once or twice daily)

- Twice daily regimen: Pts with JAK2 mutation/CVS risk factors/microvascular vasomotor symptoms not controlled on OD dosing.

- Avoided in Acquired vWD, platelet count > 10 lac/mm3.
- Higher dose – Increased incidence of GI hemorrhage.

HYDROXYUREA in ET

- Preferred cytoreductive agent.
- Reduce platelet count.
- Decrease thrombosis risk in ET

- Dose : 15mg/kg day PO
- Target platelet count is 1 – 4 lac/mm3.

- Can cause Anemia with megaloblastic features, neutropenia.
- Potential teratogen

- Since there is inherent tendency for ET to evolve into AML (2-5% RISK), impact of HU on the risk of leukemic transformation cannot be ascertained.

Clinical properties of HYDROXYUREA

Drug class	Antimetabolite
Mechanism of action	Not genotoxic, impairs DNA repair by inhibiting ribonucleotide reductase, increases HbF production
Specificity	Affects all cell lines
Pharmacology	Half-life 4 hours; 40% renally excreted, 60% metabolized
Starting dose	15 to 20 mg/kg per day orally for routine treatment of MPNs or sickle cell disease; 50 to 100 mg/kg per day orally for treatment of hyperleukocytosis
Onset of action	3 to 5 days for routine treatment of MPNs; weeks, up to 6 months, for treatment of sickle cell disease; 1 to 2 days for hyperleukocytosis
Side effects observed in >10% of patients	Neutropenia, anemia, oral ulcers, mild gastrointestinal upset, hyperpigmentation, rash, nail changes
Side effects observed in<10% of patients	Ankle ulcers, lichen planus-like lesions of the mouth and skin, nausea, diarrhea, Fever, liver function test abnormalities
Contraindications	Severe bone marrow suppression; pregnancy, breast feeding

Resistance or intolerance to HU

(requires one or more of the following)

Platelet count >6lac/microL after three months of ≥2 g/day of HU (≥2.5 g/day in patients with a body weight >80 kg)	Platelet count >400,000/microL combined with white blood cell (WBC) count <2500/microL or hemoglobin <10 g/dL at any dose of HU	Leg ulcers or other unacceptable mucocutaneous manifestations at any dose of HU	HU-related fever

ANAGRELIDE

- Cytoreductive agent
- Oral imidazoqinazoline derivative

- Lowers platelet count.
- At high doses inhibit plt aggregation via plt *anti-cAMP phosphodiesterase activity.*

- Dose: 0.5mg PO two to four times daily (1-4mg/d)
- Use limited by cardiac toxicity (iCMP/HF)& post ET myelofibrosis.

- Similar efficay to HU, but unfavourable toxicity profile.
- Non-leukomogenic.

Peg-INTERFERON

- Can control platelet count
- Reduce thrombotic complications
- Reduce abnormal clone in some patients.

- Peg-IFN 2a dose: 45mcg/wk SC (slowly increased upto 180mcg/wk).
- Has anti-angiogenic, anti-proliferative, pro-apoptotic properties, immunomodulatory, differentiating properties.

- No overall survival benefit
- No reduction in AML transformation or Post ET-myelofibrosis

- Considering increased toxicity profile, parenteral route of adm., higher cost, use is restricted in young patients (<40 yrs), during pregnancy, or who are resistant or intolerant to HU

PLATELETPHERESIS

- Removal of platelets by apheresis technique.
- Employed in extreme degree of thrombocytosis

- Lowers platelets only transiently, should be used along a myelosuppressive agent.

- **Indications:**
- Severe or life threatening organ dysfunction.
- Acute bleeding due to acquired Vwd.

Other pharmacological agents

Pipobroman: oral piperazine derivative, an alkylating agent. Dose is 0.8-1mg/kg/d PO. Monotherapy doesnot increase leukemogenicity, however when used with HU increases AMLrisk.

32P (Alkylating Agent), lowers platelet count but increases rates of AML transformattion, preferred only in patients with serious life shortening comorbidities.

Bulsulphan (Alkylating Agent), lowers platelet count but increases rates of AML transformattion, preferred only in patients with serious life shortening comorbidities.

SPECIAL CONSIDERATIONS

While chosing cytoreductive agent, patients age, other comorbid conditions, childbearing potential,and anticipated life expectancy should be considered.

Patient who recieve more than one cytotoxic agent are at high risk of developing MDS/AML, a non-leukemogenic drug (IFN, anagrelide) should be used in intolerant/resistant cases.

In resistant/intolerance cases, prefer Peg-INF 2a.

Other options are Anagrelide; or a repeat trial of HU with lower dose (in intolerant cases)

Pregnancy: Choice of treatment

Mx of pregnant woman with ET should be informed by IPSET-Thrombosis risk stratification.

Extreme Thrombocytosis

-Plt count >10 lac/mm3.

-Not itself an indication for cytoreductive therapy.

-It may induce hemostatic defect due to excessive adsorption of large von willebrand factor multimers.

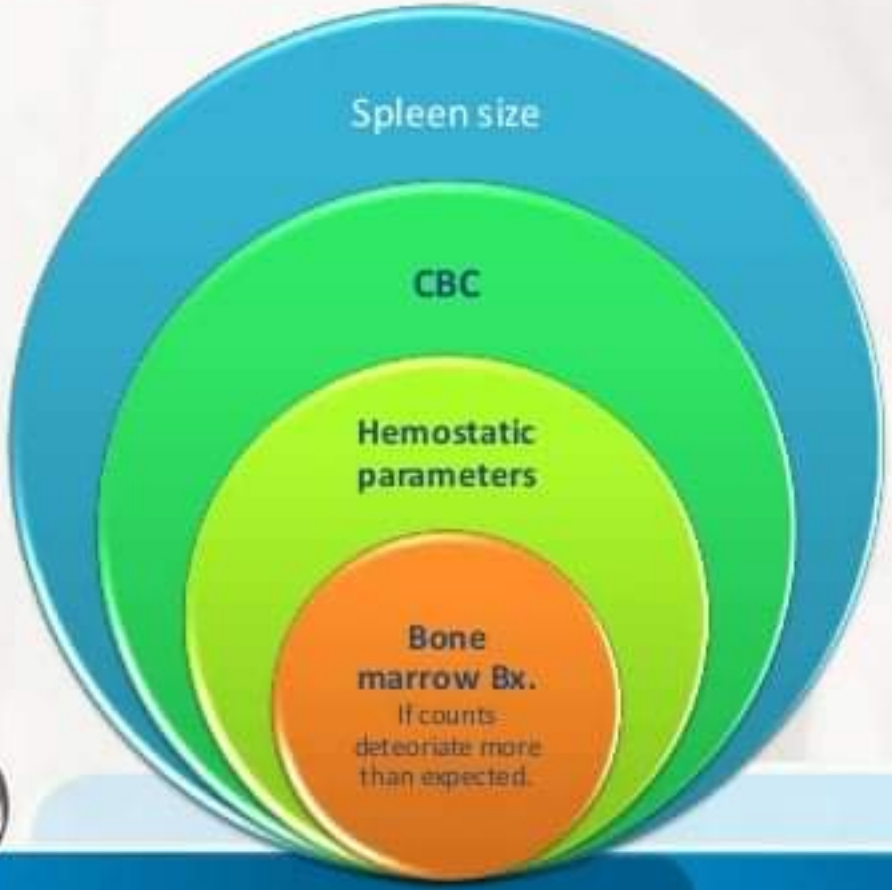
-Screen for Acquired vWD.

-By ristocetin cofactor activity.

-Aspirin should be avoided in patients with Ristocetin cofactor activity <30% (acq vWD) due to the risk of hemorrhage.

-Cytoreductive therapy can be given in such cases to decrease the platelet count to 1-4 lac/mm3 in the setting of acq vWD

Follow up



PROGNOSIS

- **The life expectancy is nearly that of the healthy population.**
- **A retrospective study revealed:**

✓ 5-year survival rate of 81%
✓ 10-year survival rate of 64%
✓ Variable rates of transformation into AML/MDS (carries poor prognosis)
✓ Can undergo delayed disease progression into a fibrotic state called post ET-myelofibrosis (<5%).

PROGNOSIS

- The life expectancy is nearly that of the healthy population.
- A retrospective study revealed:
  - 5-year survival rate of 81%
  - 10-year survival rate of 64%

Platelets Disorder

- Disorder of platelet number
  - thrombocytopenia
  - thrombocytosis
- Disorder of platelet function