Common Consultations in Outpatient Hematology in 30 mins

Lala Cornelius, MD

Disclosures:

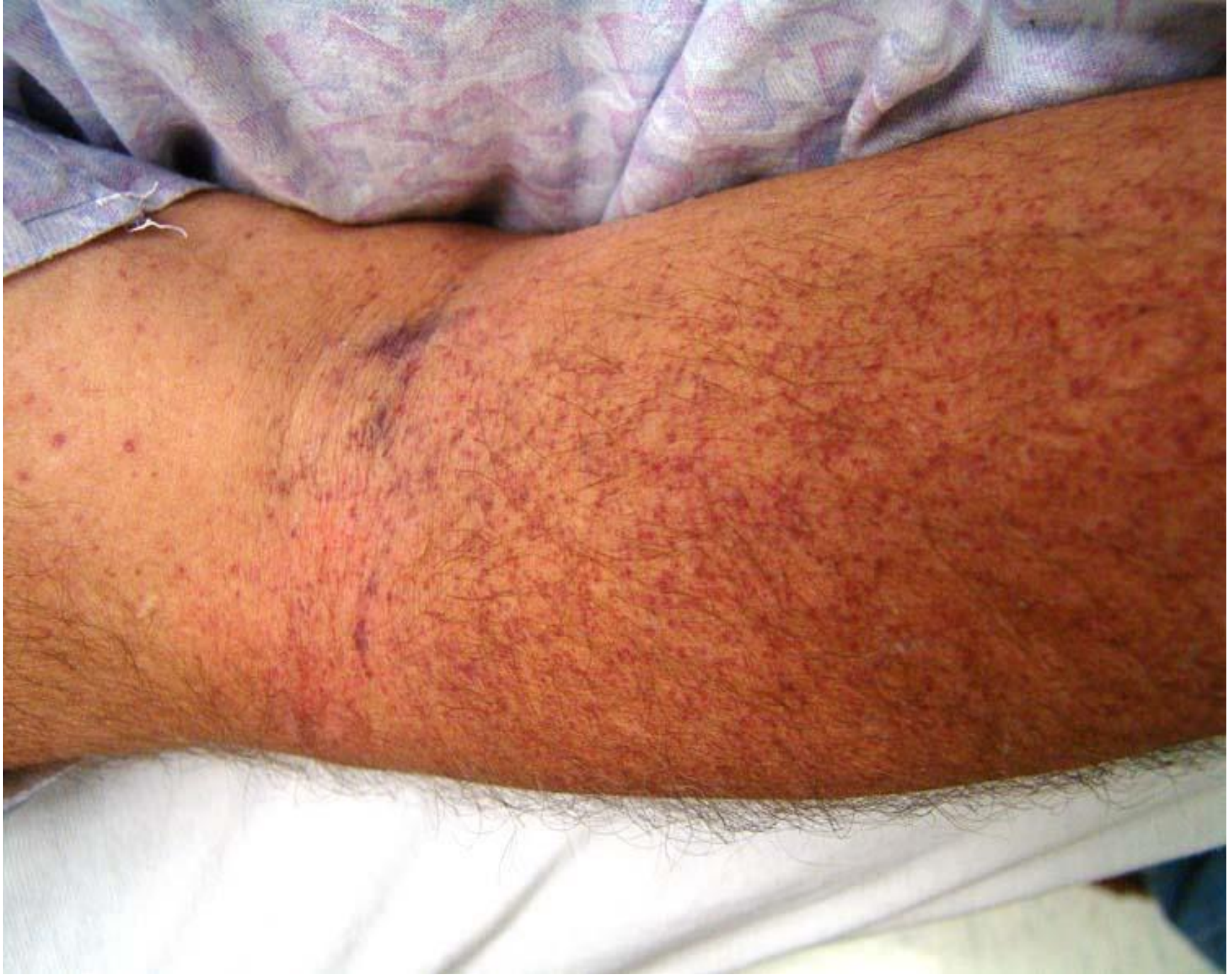
None

Objectives:

1- Decrease referrals to heme/onc for mild heme abnormalities (leukocytosis, thrombocytopenia)
2- Appropriate evaluation and manaegment of thrombocytosis;
3- Identify areas of concern re: low platelet counts, when to worry about bleeding and when to worry about thrombosis
4-Identify normal variation in leukocytosis and common reversible etiologies

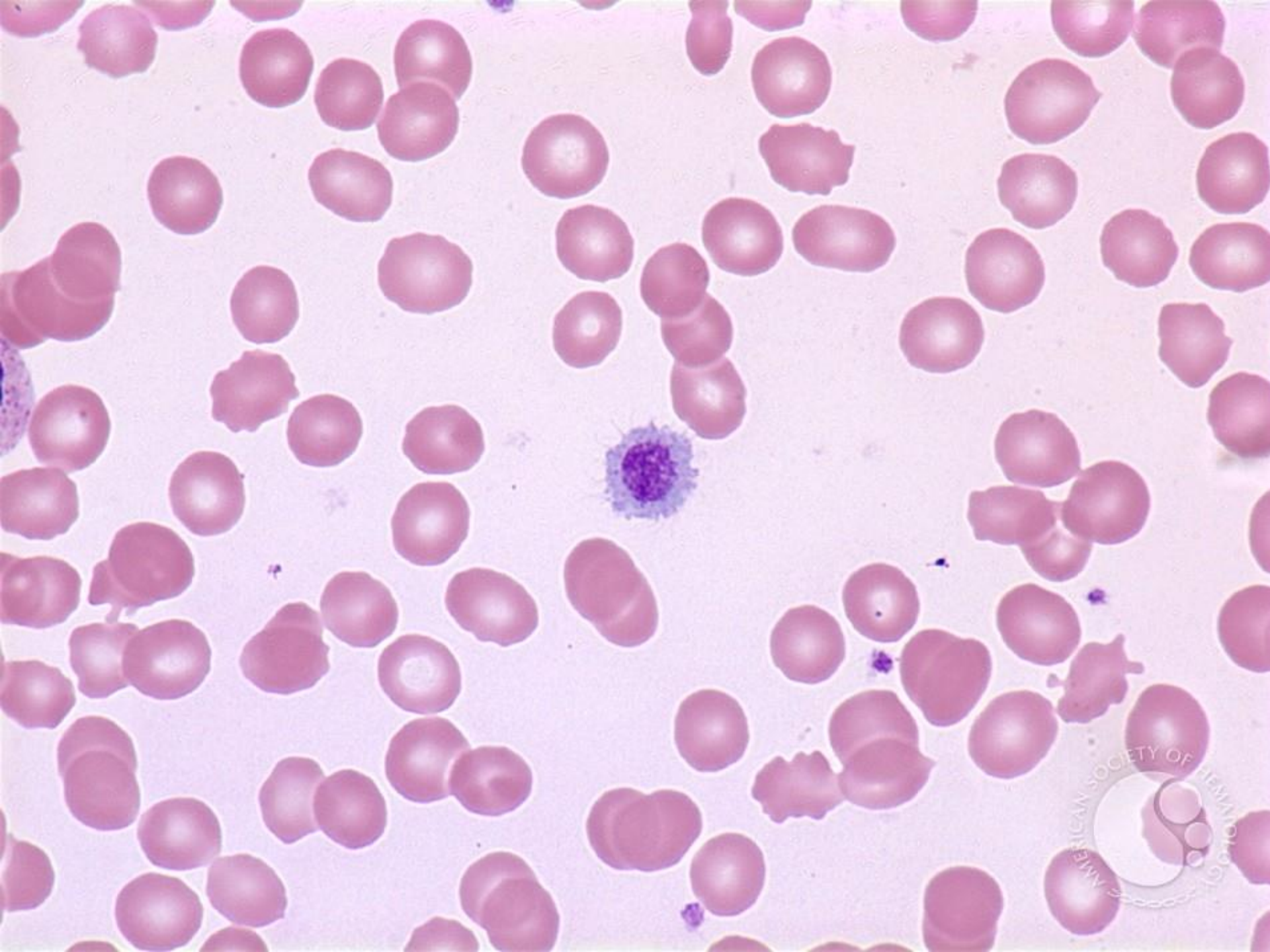
Case I

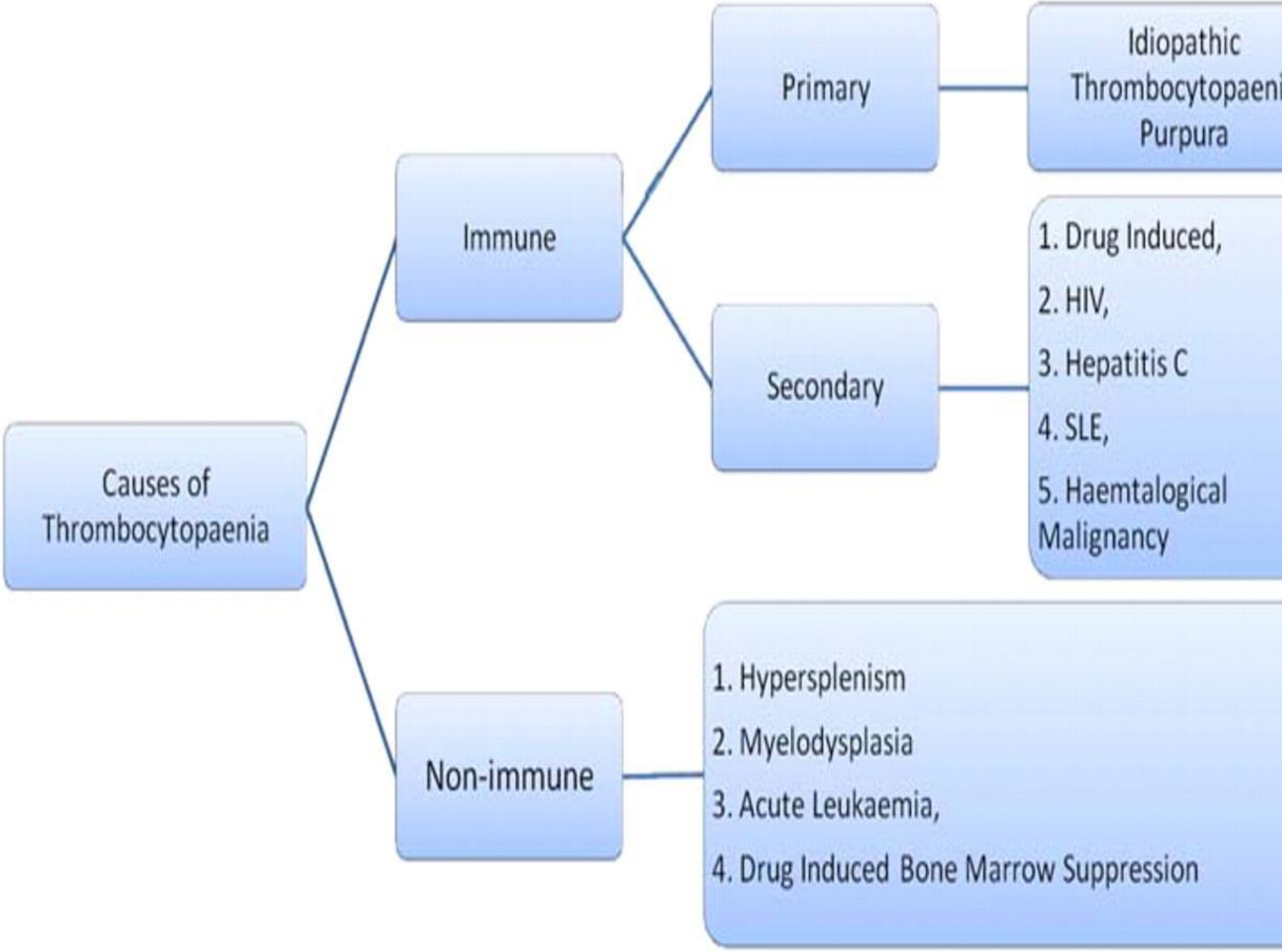
- A 22 y old woman is seen by her PCP because of her plt count of 5K. She felt healthy until 1 week ago, when she noticed that she was bruising easily and had gingival bleeding with flossing. She has no significant medical history and is not taking any medications. Her plt count 1 year ago was normal.
- On PE: scattered ecchymosis over arms and petechia over the shins . There is no lymphadenopathy or splenomegaly .
- CBC : Hgb , 12 (normal) WBC 7.9 with normal Diff ; plt 3K



ITP

- Diagnosis of exclusion
- Hx and PE – normal (apart from symptoms and HX of bleeding)
- Specifically no splenomegaly, no drugs, no viral infections (incl HIV), no SLE or other autoimmune disease
- CBC -isolated thrombocytopenia


AMERICAN SOCIETY OF HEMATOLOGY


Causes of Thrombocytopaenia
Immune
Primary
Idiopathic Thrombocytopaeni Purpura
Secondary
1. Drug Induced,
2. HIV,
3. Hepatitis C
4. SLE,
5. Haemtalogical Malignancy
Non-immune
1. Hypersplenism
2. Myelodysplasia
3. Acute Leukaemia,
4. Drug Induced Bone Marrow Suppression

ITP

Acute

- 2-6 years old
- No sex predilection
- Prior infection
- Abrupt onset
- Plst <20 K
- 6-8 weeks duration
- Usually spontaneous remissions

Chronic

- 20-40 yrs
- Women 3:1
- No infection
- Insidious
- Plts 20-80K
- Chronic
- Unusual remission

Recommendations for surgery

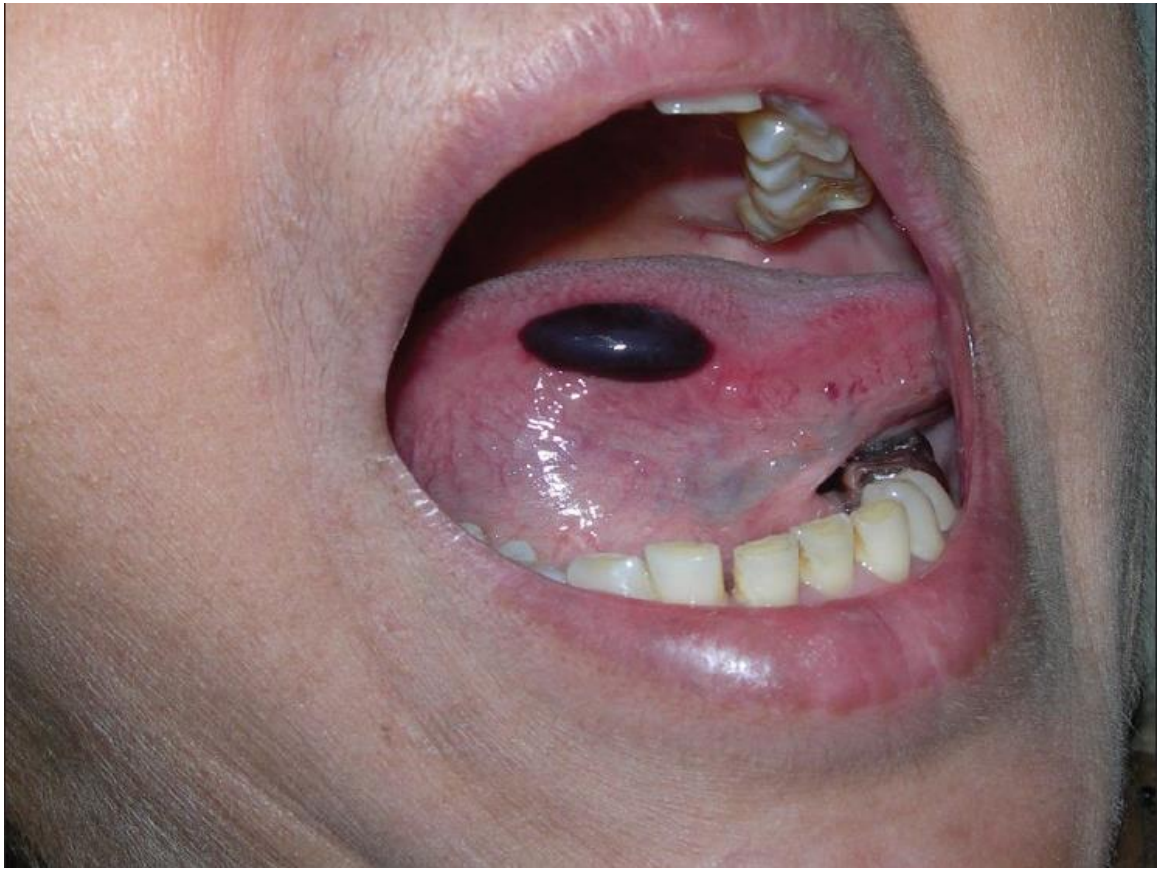
Surgery	Recommended plts counts
Dental prophylaxis(cleaning/scaling)	>20-30,000
Simple dental extraction	> 30,000
Complex Dental Extraction	>50,000
Minor Surgery	>50,000
Major Surgery	>50,000
Major Neurosurgery	>100,000

Cuker A and Cines DB Hematology 2010 ; p 377-384

ITP practice guideline- adult

- Rx with steroids is indicated
  - When plts<20-30,000
  - When plts <50,000 and there is significant mucous membrane bleeding
- Hospitalization is indicated:
  - In patients with plts<20,000 & significant mucous membrane bleeding (wet purpura)or in non-compliant pt

George JN et al, Blood 1996; 88:3-4

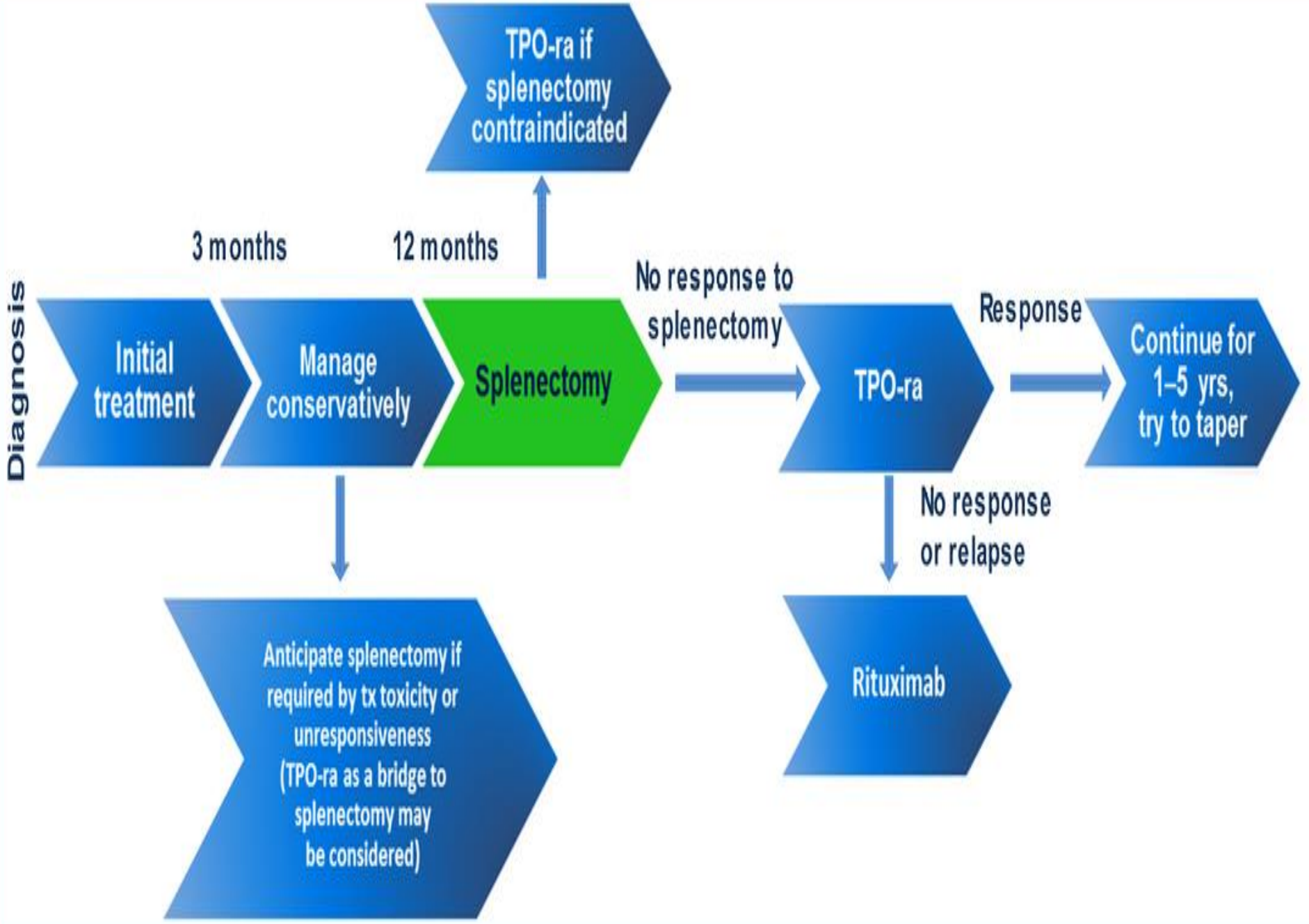


Wet purpura

ITP steroid Rx

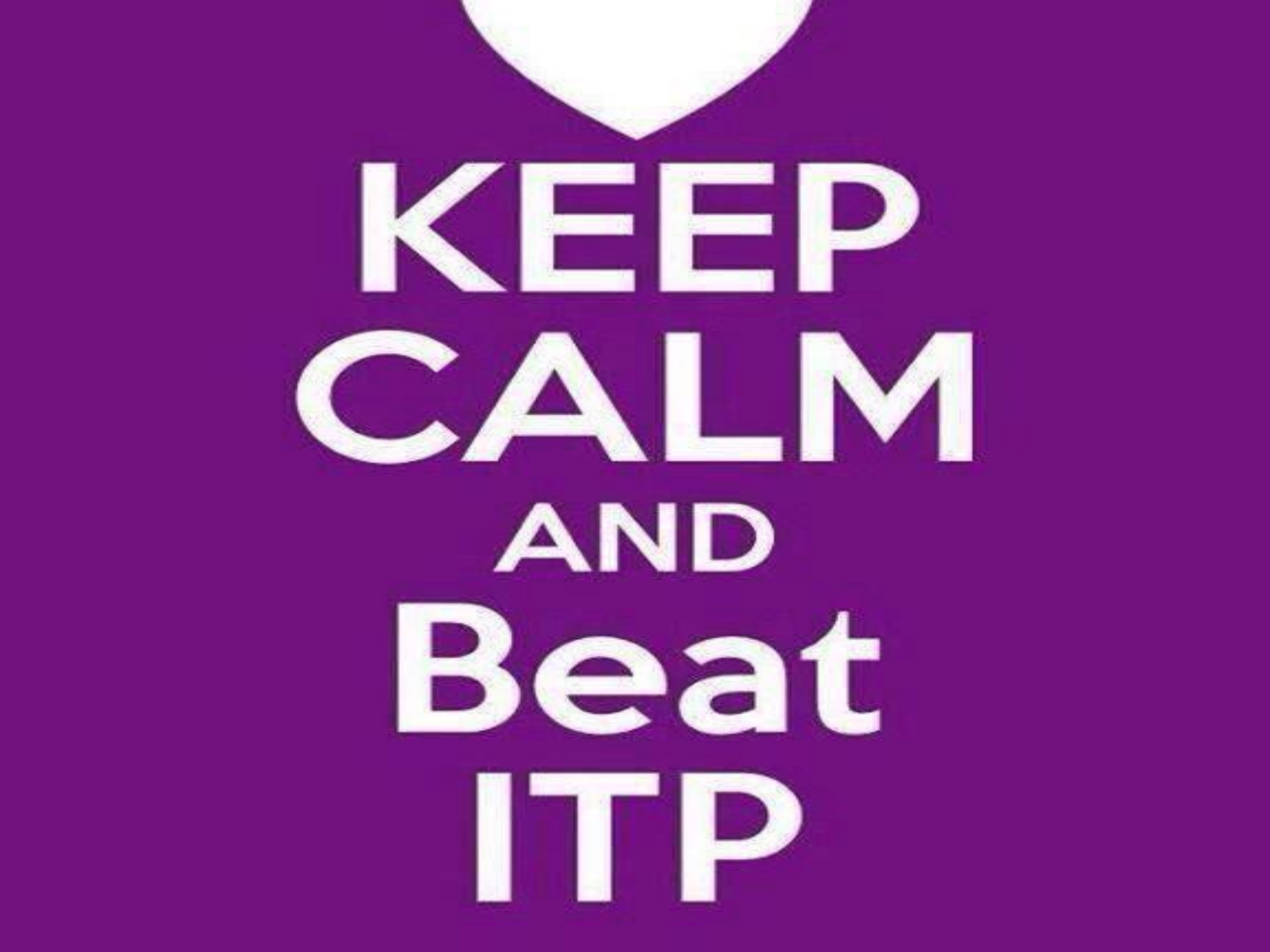
- Prednisone orally 1 mg/kg
  - Improvement usually within 3 days
  - Max improvement in 14 days
- Dexamethasone orally 40 mg x4
  - Max response at 7 days, 50% sustained response
  - Plts counts < 90,000 – high relapse risk, most within 3 months

Cheng Y et et al, NEJM 2003;349:831-6


Diagnosis
Initial treatment
3 months
Manage conservatively
12 months
Splenectomy
TPO-ra if splenectomy contraindicated
No response to splenectomy
TPO-ra
Response
Continue for 1–5 yrs, try to taper
No response or relapse
Rituximab
Anticipate splenectomy if required by tx toxicity or unresponsiveness (TPO-ra as a bridge to splenectomy may be considered)

Clinical Pearl 1- ITP

- Most pts with stable mild thrombocytopenia (plts counts 100-150K) do not develop worsening thrombocytopenia or other autoimmune disease


KEEP
CALM
AND
Beat
ITP

Case 2

- A 22 y old woman found to have gradually decreasing plt counts from 180K to 38 K over the past 4 months
- Her only medication is valproic acid started 12 months ago and which has led to good seizure control
- She reports no episodes of bleeding and there is no obvious bruising or petechia on PE

Drug-induced thrombocytopenia

- Frequency is uncertain
- Frequency of medication use increases with age
- Frequency of alternative medicine use is increasing at all ages
- Usually first diagnosed as ITP
- Correct diagnosis is essential to :

  -Avoid inappropriate treatment

  -Prevent recurrences

Clinical Pearl 2- Drug Induced Thrombocytopenia

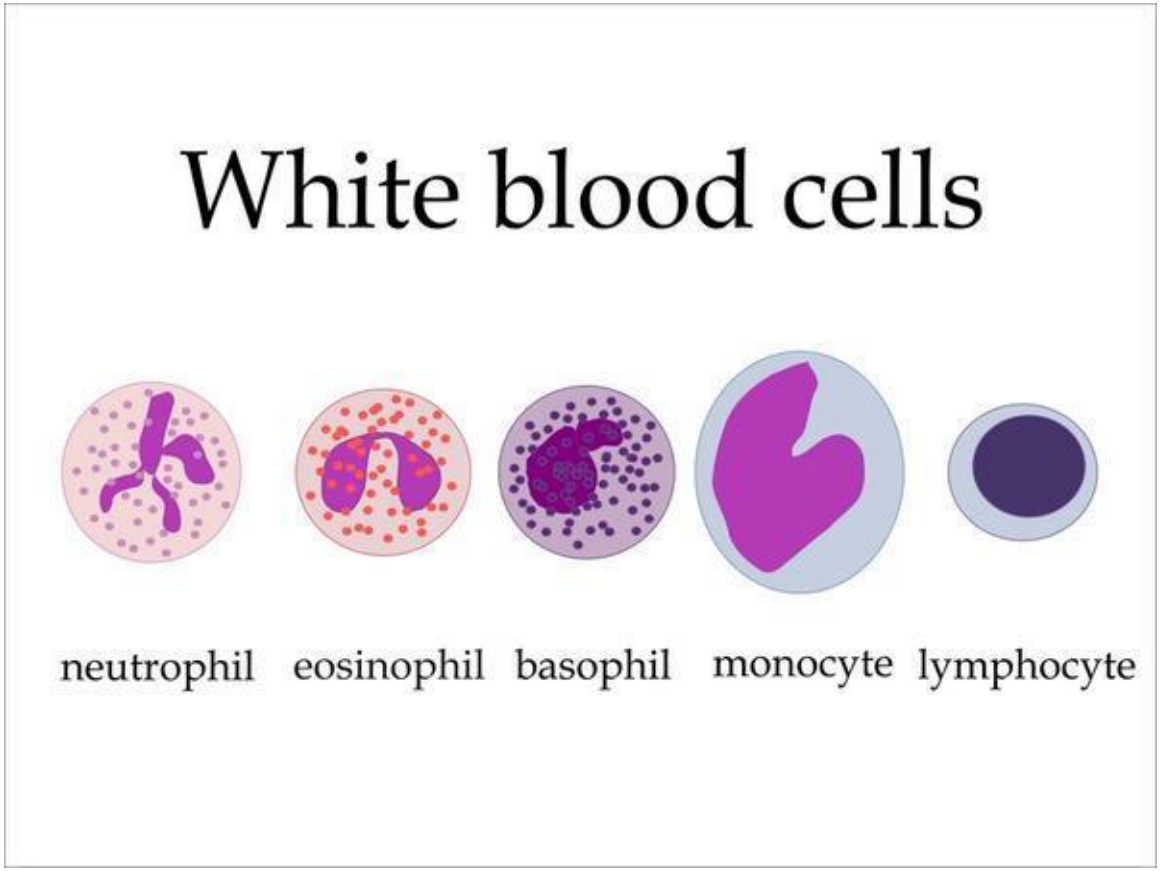
- Thrombocytopenia caused by medication may be immune mediated or dose dependent

Case 3

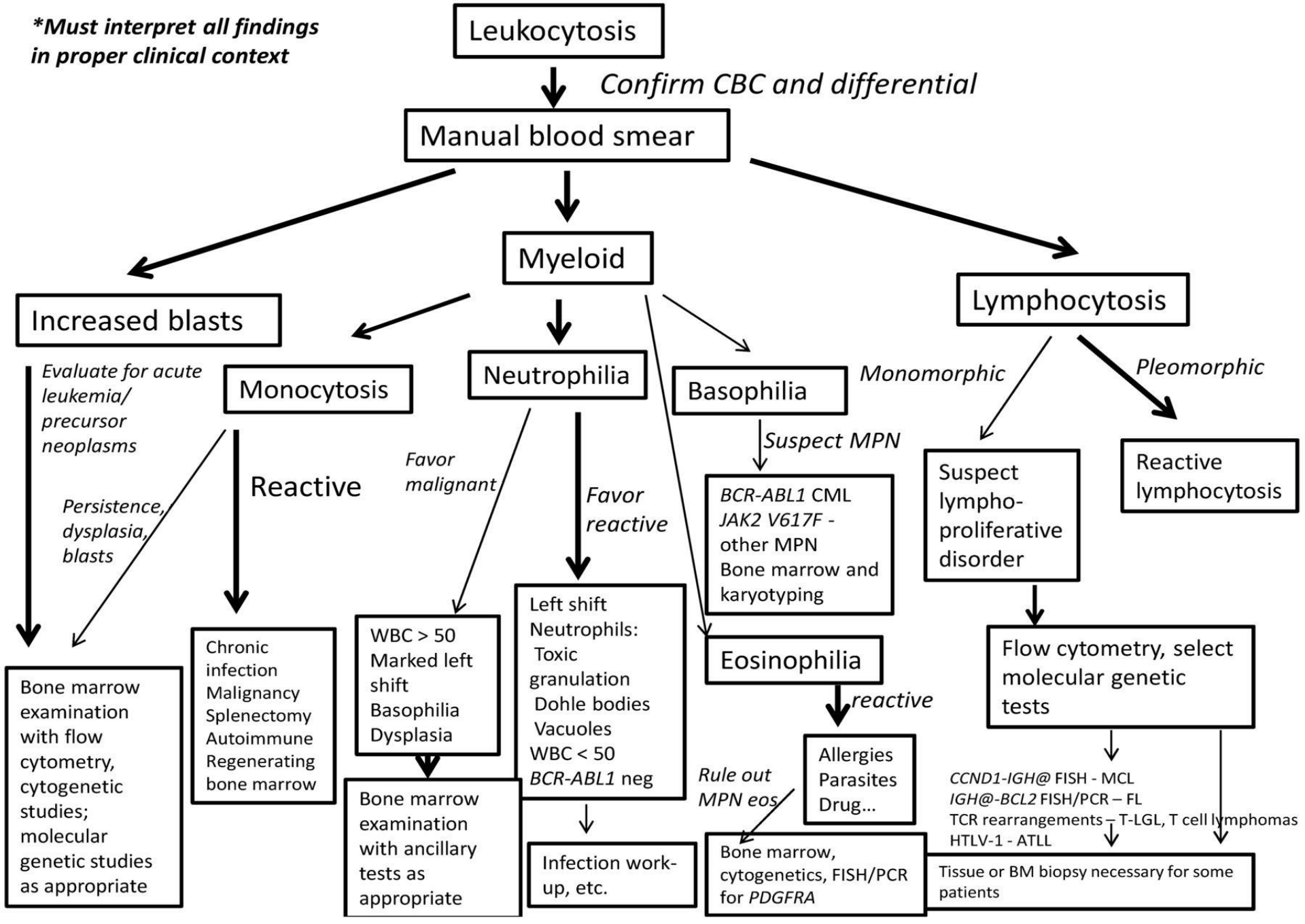
- A 55 y old man was found to have a leukocytosis on routine CBC. The patient has no fatigue, fever, chills, night sweats, or unintentional weight loss.
  His other medical problems include well controlled HTN and allergic rhinitis .
- He has smoked 1 pack of cigarettes per day for the last 30 years.
- Meds: HCTZ
- PE: afebrile and VSS , exam is negative for lymphadenopathy or splenomegaly
- CBC: diff – elevation of absolute number of leukocytes with increase in immature neutrophilic cells
- His Hgb and plts are normal and WBC is stable in comparison with 4 weeks ago

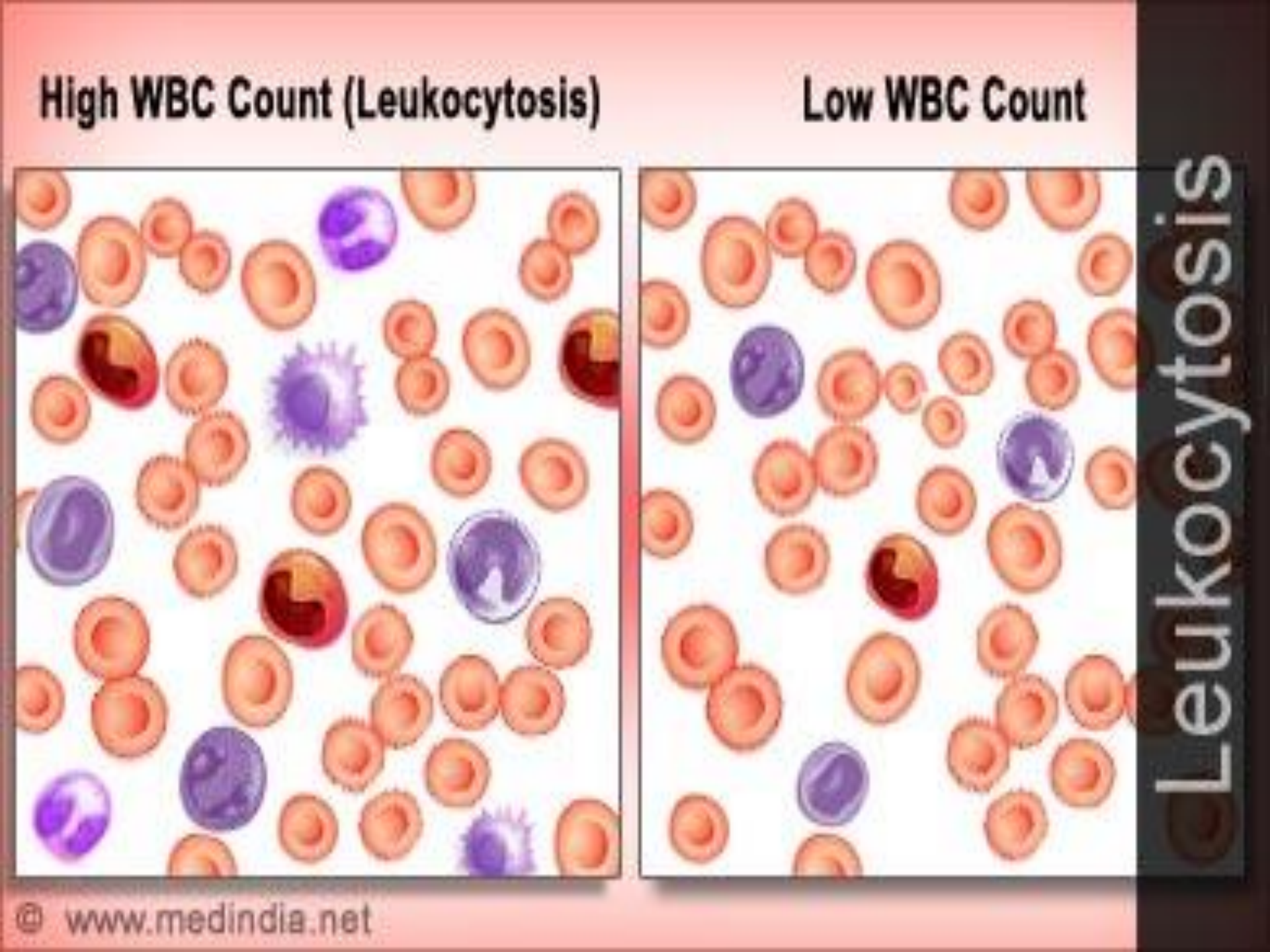
Elevation of WBC count

- Acute rapid: changes in distribution (demargination)
- Chronic elevation: chances in production and release from storage



If myeloid cells are present, the leukocytosis should be stratified into neutrophilia, monocytosis, basophilia, or eosinophilia; more than one type of leukocytosis may be present


*Must interpret all findings in proper clinical context
Leukocytosis
Confirm CBC and differential
Manual blood smear
Myeloid
Increased blasts
Lymphocytosis
Evaluate for acute leukemia/ precursor neoplasms
Monocytosis
Neutrophilia
Basophilia
Monomorphic
Pleomorphic
Persistence, dysplasia, blasts
Reactive
Favor malignant
Favor reactive
Suspect MPN
Suspect lympho-proliferative disorder
Reactive lymphocytosis
BCR-ABL1 CML
JAK2 V617F - other MPN
Bone marrow and karyotyping
Bone marrow examination with flow cytometry, cytogenetic studies; molecular genetic studies as appropriate
Chronic infection
Malignancy
Splenectomy
Autoimmune
Regenerating bone marrow
WBC > 50
Marked left shift
Basophilia
Dysplasia
Left shift
Neutrophils:
Toxic granulation
Dohle bodies
Vacuoles
WBC < 50
BCR-ABL1 neg
Eosinophilia
reactive
Flow cytometry, select molecular genetic tests
Allergies
Parasites
Drug…
Rule out MPN eos
CCND1-IGH@ FISH - MCL
IGH@-BCL2 FISH/PCR – FL
TCR rearrangements – T-LGL, T cell lymphomas
HTLV-1 - ATLL
Bone marrow examination with ancillary tests as appropriate
Infection work-up, etc.
Bone marrow, cytogenetics, FISH/PCR for PDGFRA
Tissue or BM biopsy necessary for some patients


High WBC Count (Leukocytosis)
Low WBC Count
Leukocytosis
@ www.medindia.net

Clinical Pearl 3A-Leukocytosis

- Smoking one of the most common causes in asymptomatic patient
- The leukocyte count in smoker can be 25% higher than value within normal range
- After smoking cessation WBC can normalize

Differential Diagnosis of Neutrophilia Secondary to other illnesses

- Infection
- Acute: demargination/release storage pool
- Chronic: granulomatous dx (leukoerythroblastic)
- Stress
- Drug induced (steroids, B-agonist, lithium)
- Chronic inflammation (including smoking-one of the most common causes)
- Post-splenectomy
- Non-hematologic malignancy
- Marrow stimulation (ITP, hemolysis, CMT)
- Sterile inflammation (MI, burn)

Clinical Pearl 3B-Neutrophilia

- Neutrophilia should prompt examination for left shift, signs of activated neutrophils, basophilia, dysplasia, and degree of leukocytosis.
- Most neutrophilias are reactive in nature.
- WBC count < 50×10^9/L, but usually < 30×10^9/L, is typical.
- Signs of activated neutrophils, mild left shift, and an absence of basophilia all suggest a reactive process.

Differential Diagnosis of Neutrophila Primary Hematologic Disease

- CML (BCR-ABLE)
- Other myeloproliferative neoplasm- usually will have elevated Hg or plt counts or splenomegaly (JAK2)

Clinical Pearl 3C- Leukocytosis

- Marked leukocytosis of >50 × 10^9/L, marked left shift, dysplasia, or basophilia should prompt a BM examination to evaluate for a myeloid malignancy.
- Basophilia, although rare, is most suggestive of a MPN, especially CML.
- PCR for *BCR-ABL1* and *JAK2* mutational studies can be performed in blood, but a BM examination with cytogenetic studies should also be performed

Case 4

- 23 y old college student who plays football presents to his PCP with 2 week Hx of extreme fatigue and sore throat and new–onset fever of 101F. He has no significant PMHx.
- On PE: T 101.2F and he has posterior cervical lymphadenopathy, splenomegaly, an erythematous posterior pharynx with whitish-gray exudate and generalized macularpapular rash on his trunk and neck. He takes proton pump inhibitor fro GERD.
- His Lab work :
  - Hgb, plt- normal; WBC 12.9; differential Neutr- 22%(low); Lymp-75%(high); Mono -3% (normal); Baso- 1%(normal)

Clinical Pearl 4A

- 50% have splenomegaly and at risk of rare complication as spontaneous or trauma-induced splenic rupture – should avoid sports

Differential diagnosis of lymphocytosis Secondary to Illness

- Viral illnesses
  - Mononucleosis s-m
  - CMV
  - EBV
  - HIV
- Pertussis
- Cat scratch disease
- Toxoplasmosis
- Babesiosis
- Drug reaction
- Reactive granular lymphocytosis
- Post splenectomy lymphocytosis

Differential diagnosis of lymphocytosis Primary hematologic disease

- CLL
- Monoclonal B cell lymphocytosis

Clinical Pearl 4B

- Age of the patient (CLL is more common in middle-aged to elderly adults)
- Correlation with clinical findings is necessary; a monospot test for EBV or viral serologies can also be performed, Hx of prior diagnosis of lymphoma
- A pleomorphic lymphocytosis favors a reactive lymphocytosis.
- If monomorphic lymphocytosis is present, a lymphoproliferative disorder should be searched for using flow cytometric immunophenotyping.
- Depending on these results, select molecular genetic tests will be helpful. (Refer to Hematology)
- A BM biopsy or extramedullary tissue biopsy may be necessary for a final diagnosis of lymphoma.

Differential diagnosis of Eosinophilia Secondary to Illness

- Allergic rhinitis
- Asthma
- Tissue invasive parasite
- Bronchopulmonary aspergillosis
- HIV
- Vasculitis
- Adrenal insufficiency
- GI symptoms (infection, IBD)
- Occult malignancy

Differential diagnosis of Eosinophilia Primary hematologic disease

- Hypereosinophilic syndrome

Clinical Pearl 4C

- Most eosinophilias are reactive in nature and should be evaluated
- Once reactive eosinophilias are excluded, myeloid and lymphoid neoplasms with eosinophilia and *PDGFRA*, *PDGFRB*, and *FGFR1* should be searched for by performing a BM examination, cytogenetic studies, and FISH or PCR for the *PDGFRA* mutation (Refer to Hematology)

Differential diagnosis of Monocytosis Secondary to Other illnesses

- Pregnancy
- TB
- Syphilis
- Sarcoidosis
- SLE
- Aslenia
- Corticosterids

Clinical Pearl 4D

- Most monocytoses are reactive in nature.
- If reactive causes have been excluded, a persistent monocytosis of more than 3 months or the findings of dysplasia, blast cells, or significant left shift should trigger a BM examination to evaluate for malignancy. (Refer to Hematology)

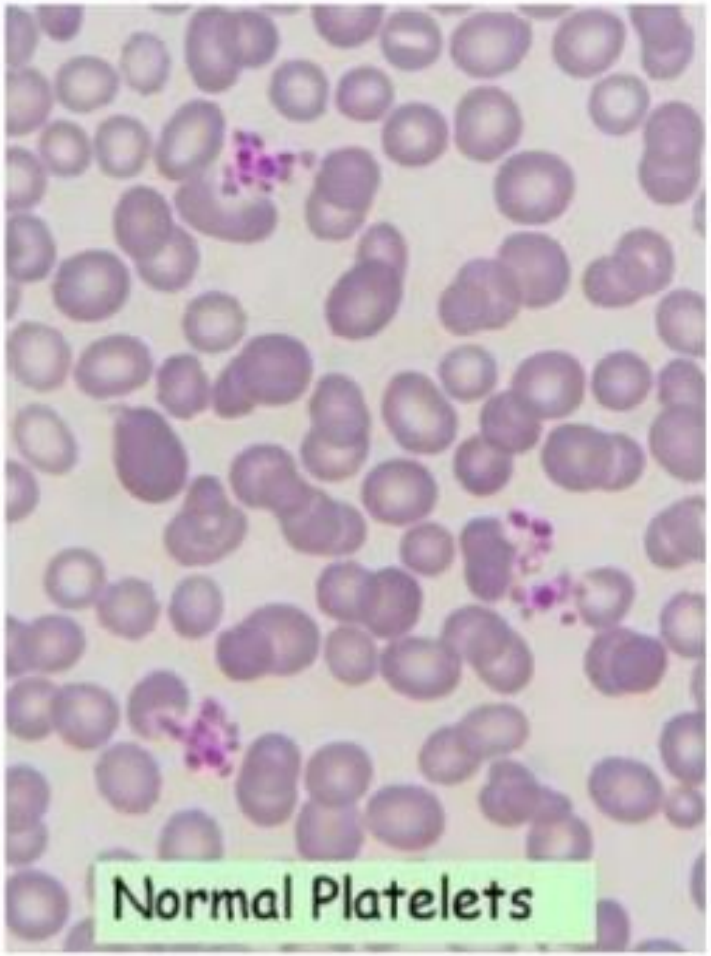
Differential diagnosis of monocytosis Primary hematologic disease

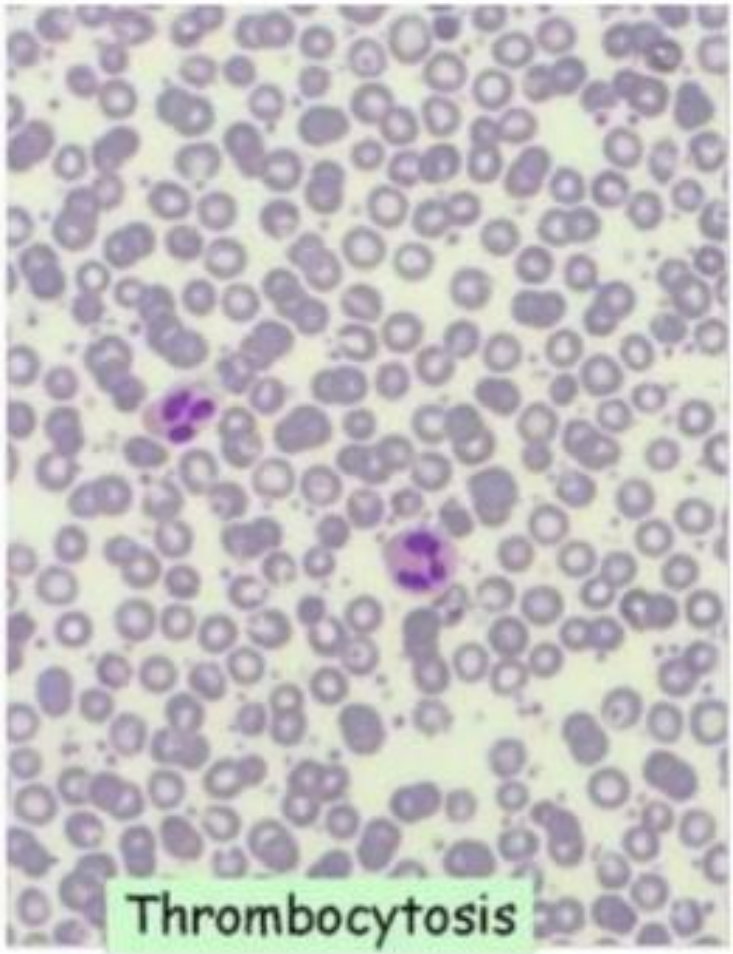
- Juvenile myelomocytic leukemia
- Chronic myelomonocytic leukemia
- Acute monoblastic/monocytic leukemia
- CML
- Atypical (*BCR-ABL* negative) CML
- Myelodysplastic/myeloproliferative neoplasms, unclassifiable

Case 5

- A 45 year old previously healthy female landscaper complains of increasing fatigue and numbness on her face and legs for 3 weeks.
- CBC – plts 1,062K
- Her iron studies and inflammatory markers (Sed rate and C reactive protein)-normal
- FISH BCR-ABL: negative
- Jak-2: mutated

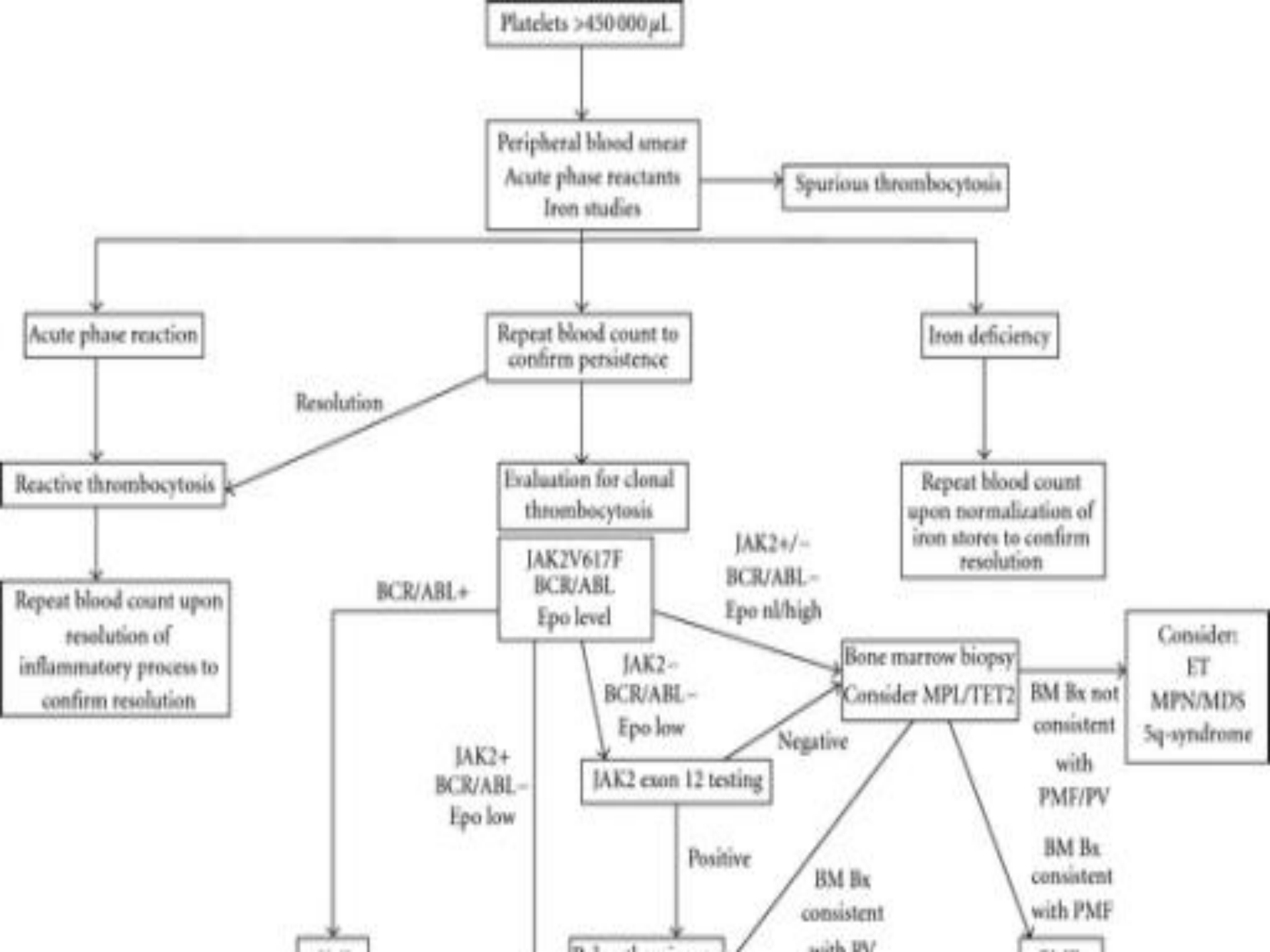
Blood smear of thrmobocytosis





Thrombocytosis

- Primary
  - Essential Thrombocythemia
  - Other forms of myeloproliferative disorders- chronic myelogenous leukemia, polycythemia vera, myelofibrosis


Platelets >450 000 μL
Peripheral blood smear
Acute phase reactants
Iron studies
Spurious thrombocytosis
Acute phase reaction
Repeat blood count to confirm persistence
Iron deficiency
Resolution
Reactive thrombocytosis
Evaluation for clonal thrombocytosis
Repeat blood count upon normalization of iron stores to confirm resolution
Repeat blood count upon resolution of inflammatory process to confirm resolution
JAK2V617F
BCR/ABL
Epo level
BCR/ABL+
JAK2+/−
BCR/ABL−
Epo nl/high
JAK2−
BCR/ABL−
Epo low
Bone marrow biopsy
Consider MPL/TET2
Consider:
ET
MPN/MDS
5q-syndrome
BM Bx not consistent with PMF/PV
JAK2+
BCR/ABL−
Epo low
Negative
JAK2 exon 12 testing
Positive
BM Bx consistent with PV
BM Bx consistent with PMF

2008 World Health Organization (WHO) Diagnostic Criteria for Essential Thrombocythemia

Diagnosis requires meeting all 4 criteria
1. Sustained platelet count ≥450 × 10^9/L
2. Bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased numbers of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. Not meeting WHO criteria for PV[a], PMF[b], BCR-ABL1+ CML[c], MDS,[d] or other myeloid neoplasms
4. Demonstration of *JAK2*V617F or other clonal marker; or in the absence of *JAK2*V617F, no evidence for reactive thrombocytosis[e]

CML, chronic myelogenous leukemia; ET, essential thrombocythemia; JAK, Janus-associated kinase; MDS, myelodysplastic syndrome; PMF, primary myelofibrosis; PV, polycythemia vera.

[a]Requires the failure of iron replacement therapy to increase hemoglobin level to the PV range in the presence of decreased serum ferritin. Exclusion of PV is based on hemoglobin and hematocrit levels, and red cell mass measurement is not required.

[b]Requires the absence of relevant reticulin fibrosis, collagen fibrosis, peripheral blood leukoerythroblastosis or markedly hypercellular marrow accompanied by megakaryocyte morphology that is typical for PMF (small to large megakaryocytes with an aberrant nuclear/cytoplasmic ratio and hyperchromatic, bulbous, or irregularly folded nuclei and dense clustering).

[c]Requires the absence of *BCR-ABL1*.

[d]Requires the absence of dyserythropoiesis and dysgranulopoiesis.

[e]Causes of reactive thrombocytosis include iron deficiency, splenectomy, surgery, infection, inflammation, connective tissue disease, metastatic cancer, and lymphoproliferative disorders. However, the presence of a condition associated with reactive thrombocytosis does not exclude the possibility of ET if the first 3 criteria are met.

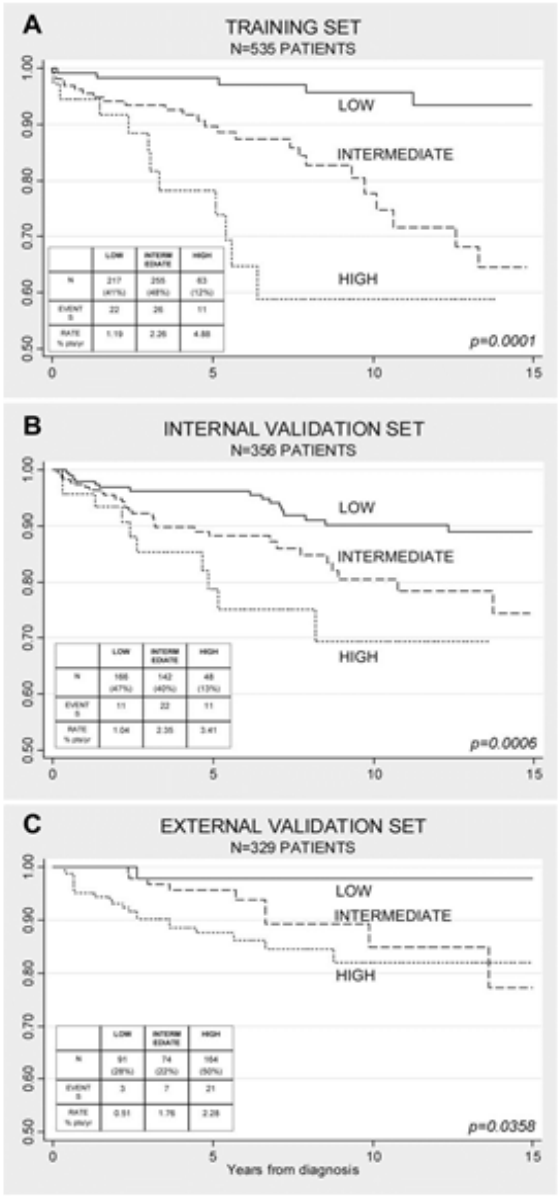
Primary Driver Mutations for Essential Thrombocythemia

- Jak2V617F mutation in 2005 -50% of the pts
- Clarified that mutation is a primary cause of thrombosis
  - MPLW515L &K - 5%
  - CALR – 30% in 2013
  - “Triple negative “ ET - 10%

Prediction of Thrombosis in ET, by IPSET

Risk factors	
Age > 60 years	1 point
Cardiovascular risk factors	1 point
Previous thrombosis	2 points
JAK2V617F	2 points

Risk Categories/score	
Low	0-1
Intermediate	2
High	≥ 3



Barbui T, et al. *Blood* 2012; 120:5128-5133.

Essential thrombocythemia clinical features

- Chronic thrombocytosis (often extreme, >1million)
  - Many pts are asymptomatic
  - Vasomotor symptoms: headache, syncope, visual disturbances, atypical chest pain, erythromelalgia (typically ASA-responsive)
- Thrombocytosis major cause of morbidity and mortality
  - Both arterial and venous; unusual sites
  - No clear association with plts counts
- Paradoxical increase in bleeding complications
  - Risk factors /associations;

    -Extreme thrombocytosis >1 million (controversial)

    -Use of ASA>325 mg /day or other NSAIDS

    -Acquired WVD
- Splenomegaly

Thrombocytosis

- Secondary
- Inflammation
- Surgery (which leads to increase inflammatory state)
- Hyposplenism or asplenia
- Hemorrhage or/ and iron deficiency
- Malignancy
- Trauma
- Infection

Clinical Pearl 5

- Increased level of inflammatory mediators IL-1b,IL-6 , IL-11 have been associated with reactive thrombocytosis
- C-reactive protein is a surrogate marker for increased IL-6; can suggest an occult inflammation
- Absolute value of plt counts can not help distinguish reactive thrombocytosis from ET


CHECK YOUR
STRESS
LEVEL

Appendix

Life span of Myeloid cells

- Maturation in bone marrow: 7-10 days
- Circulation in peripheral blood: 3-6 hours
- Residence in tissues: 2-3 days
- Peripheral neutrophil counts <5 % of total WBC pool, 2% of the total WBC lifespan

White blood cell count

- Myeloid precursors 20%
- Storage pool 75%
- Marginating pool 3%
- Circulating pool 2%