UNIVERSITI PUTRA MALAYSIA

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Abnormalities of Platelet

Morphology Workshop for Medical Laboratory Technologist

22 February 2018

BERILMU BERBAKTI
WITH KNOWLEDGE WE SERVE

About platelet…& your personal experience

Learnt so far..

Wish to learn..

PLATELET ALERTS..

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Learning outcomes

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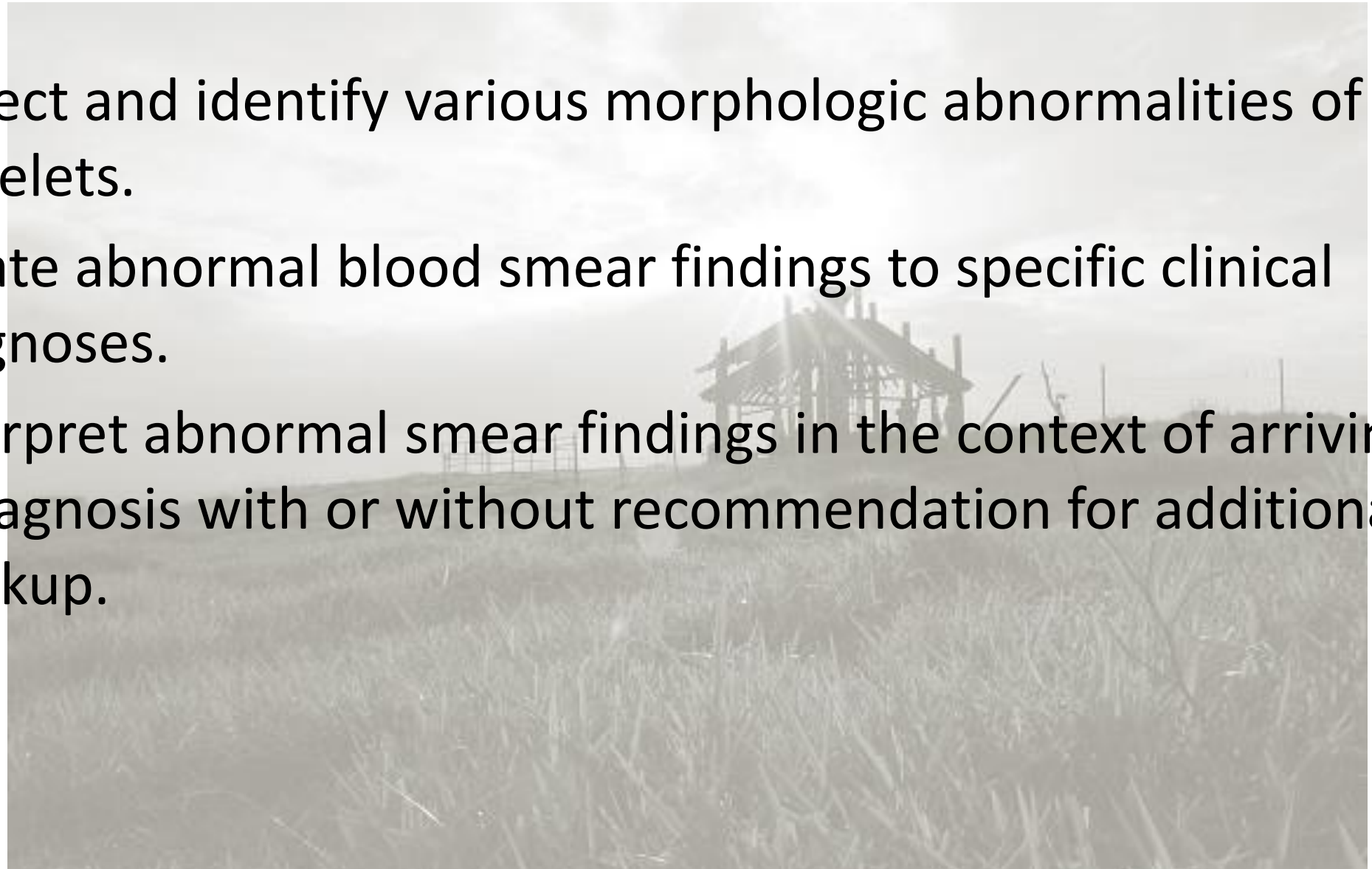
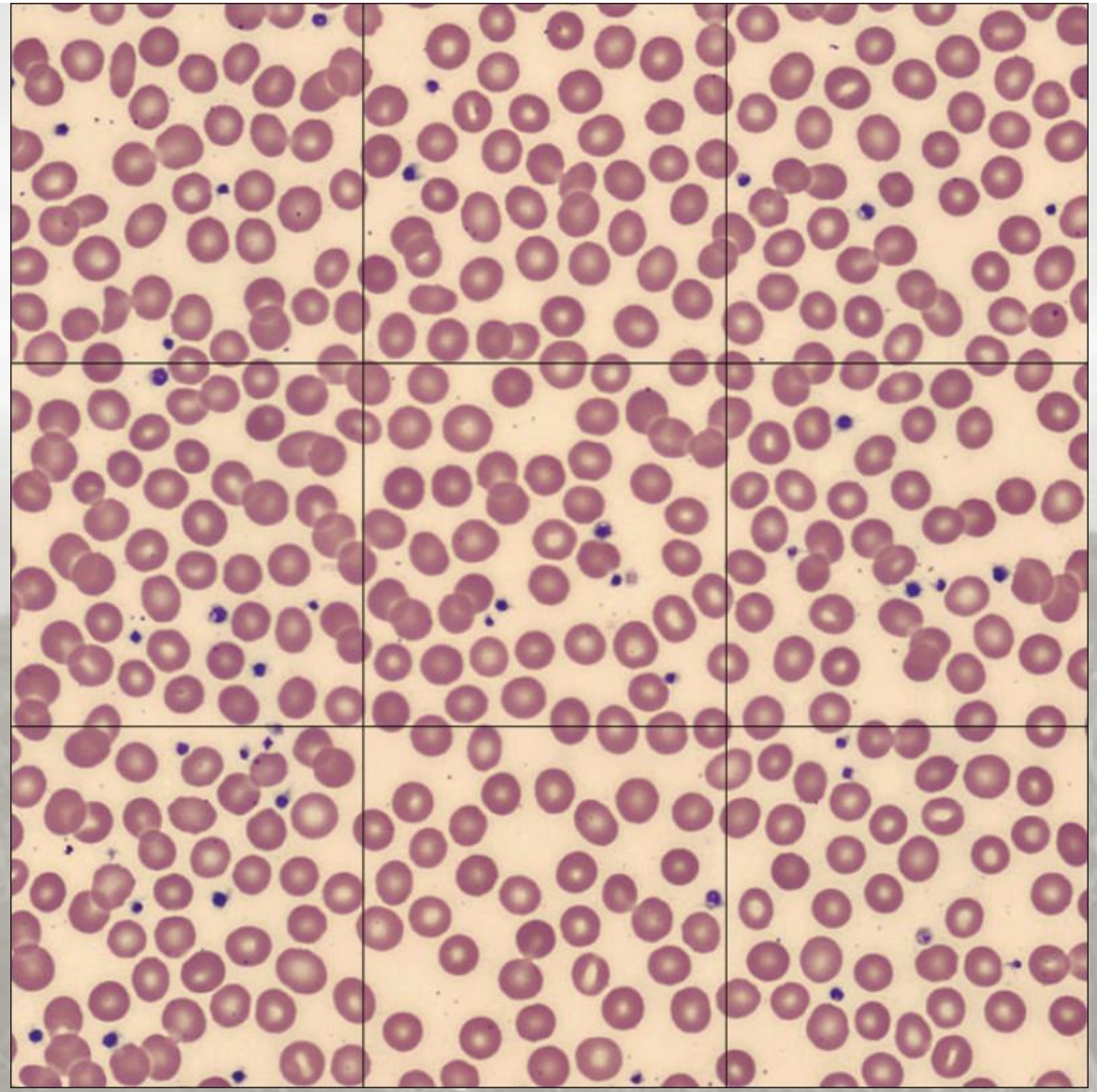
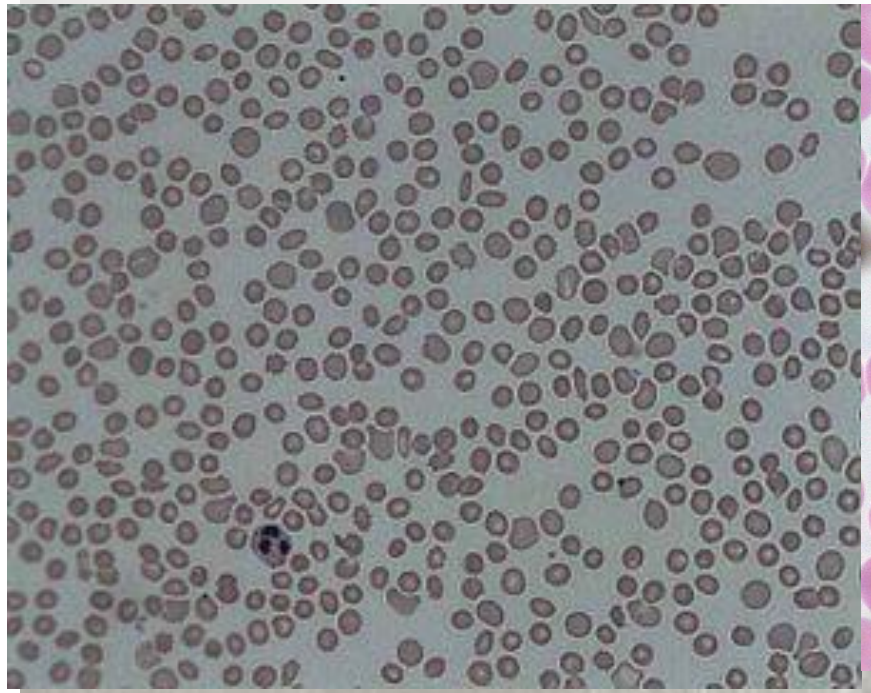
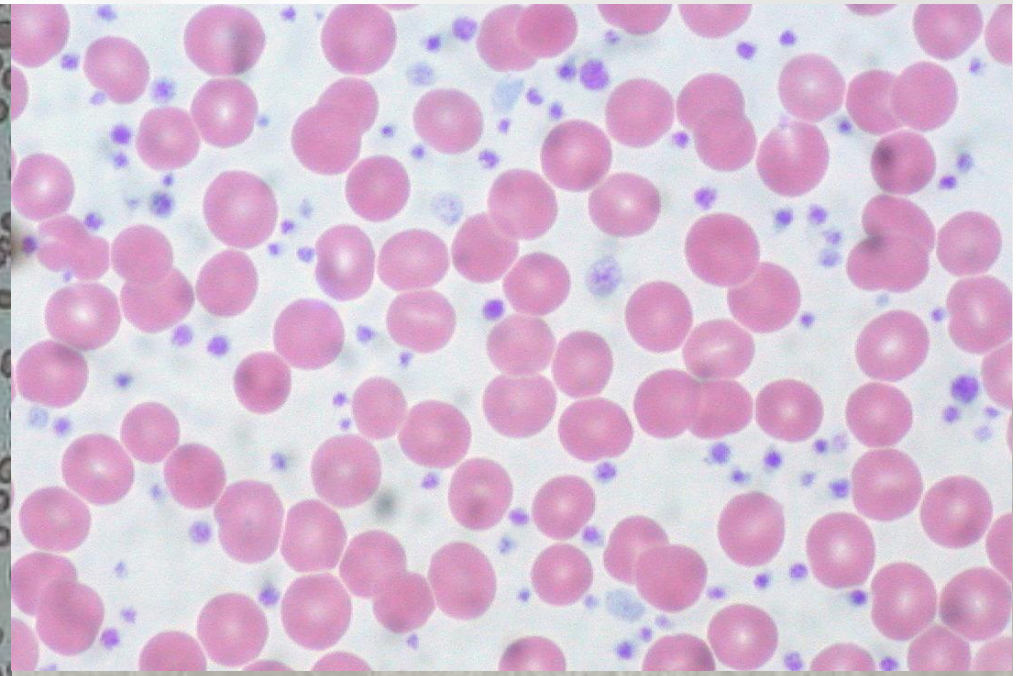


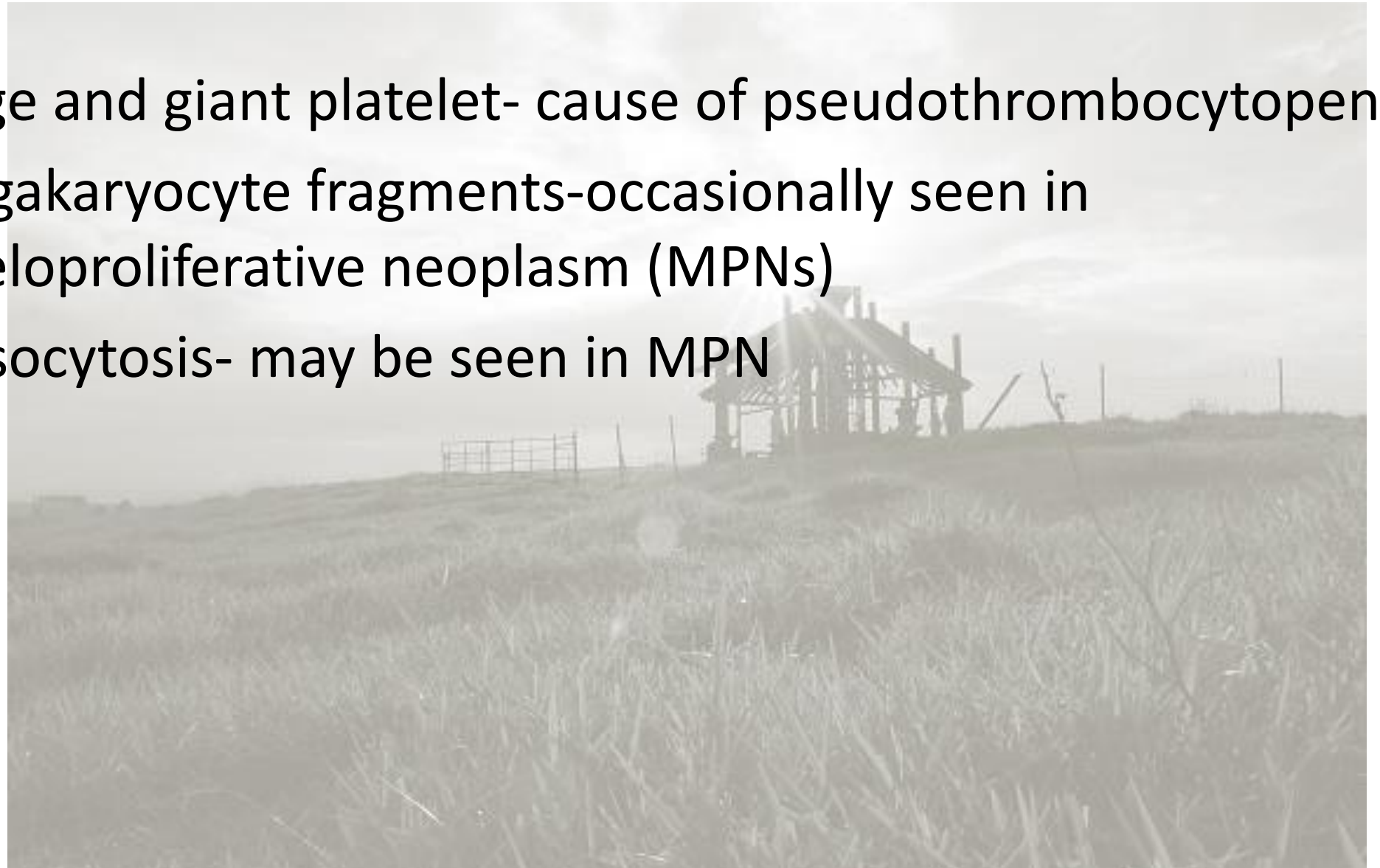
- Detect and identify various morphologic abnormalities of platelets.
- Relate abnormal blood smear findings to specific clinical diagnoses.
- Interpret abnormal smear findings in the context of arriving at a diagnosis with or without recommendation for additional workup.







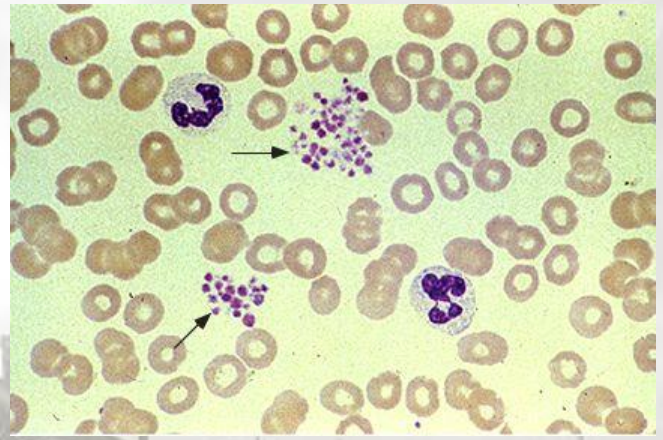
Morphologic abnormalities

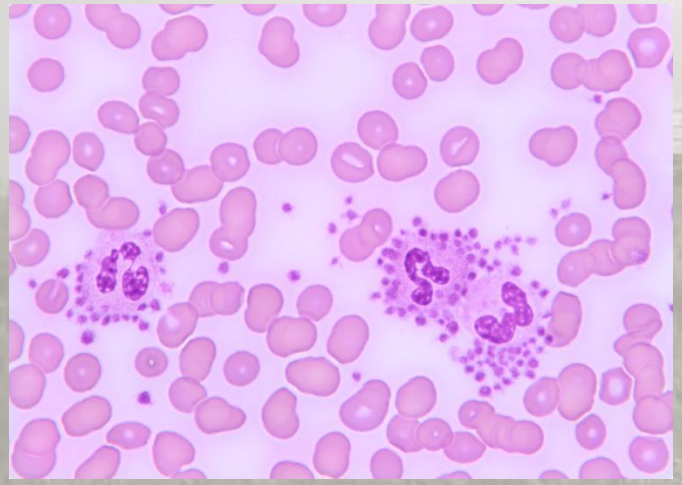


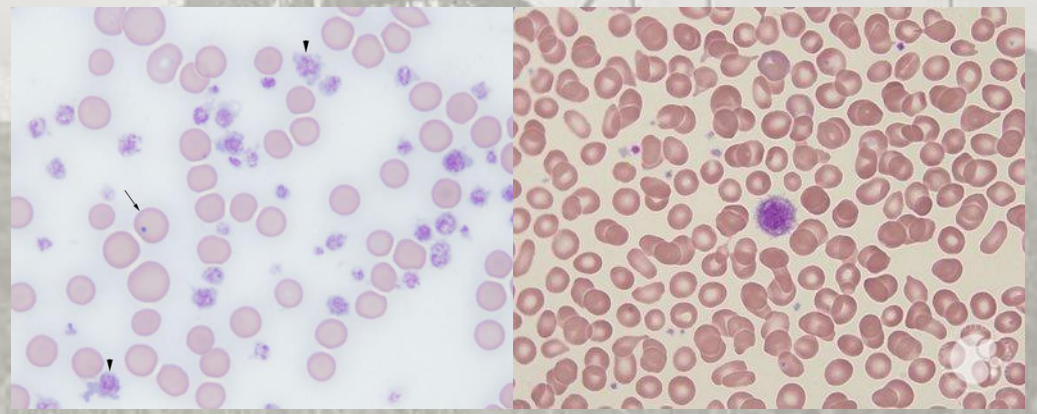
- Large and giant platelet- cause of pseudothrombocytopenia
- Megakaryocyte fragments-occasionally seen in myeloproliferative neoplasm (MPNs)
- Anisocytosis- may be seen in MPN

Causes of pseudothrombocytopenia

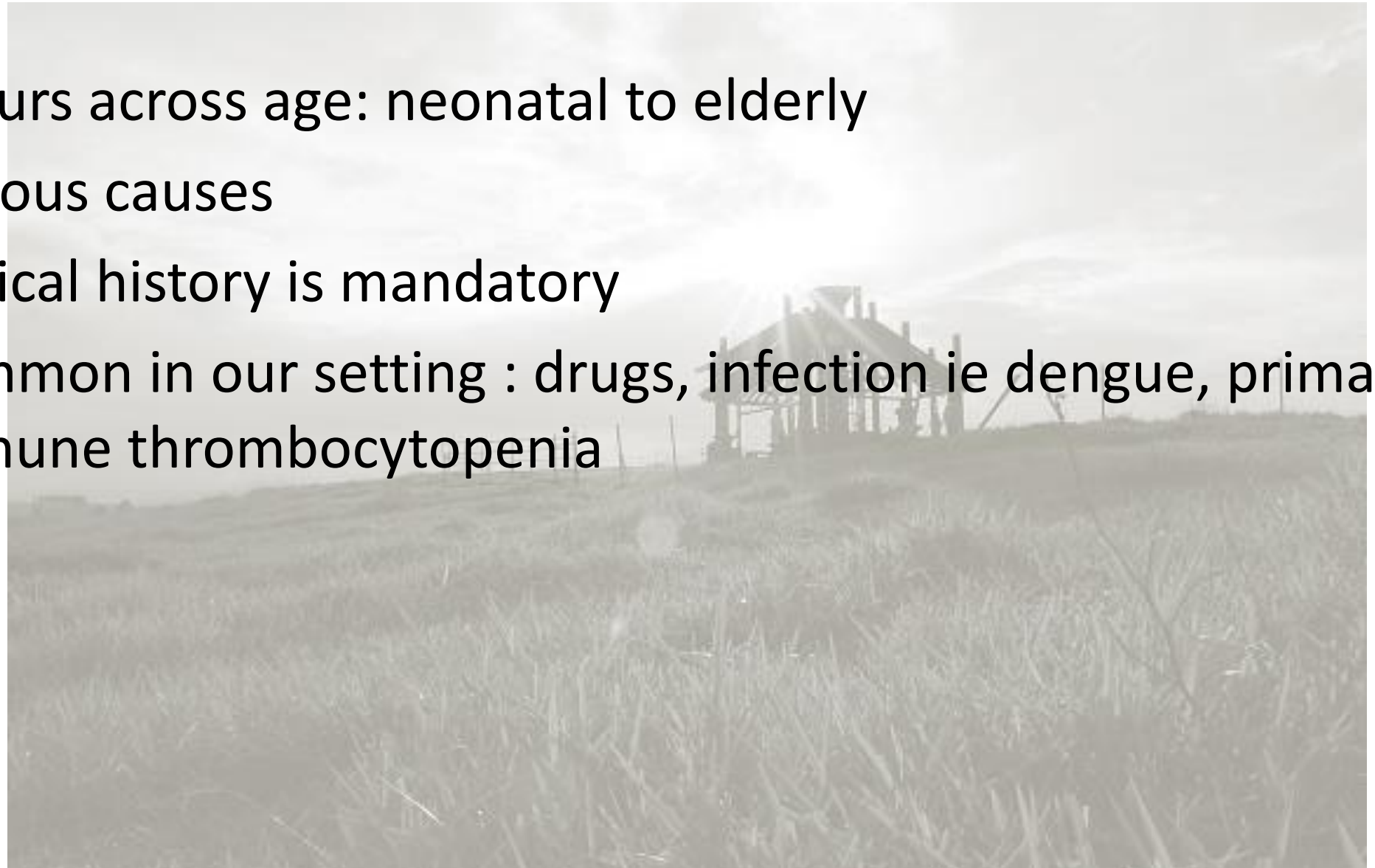
- Platelet clumping
- Large and giant platelets
- Platelet satellitism



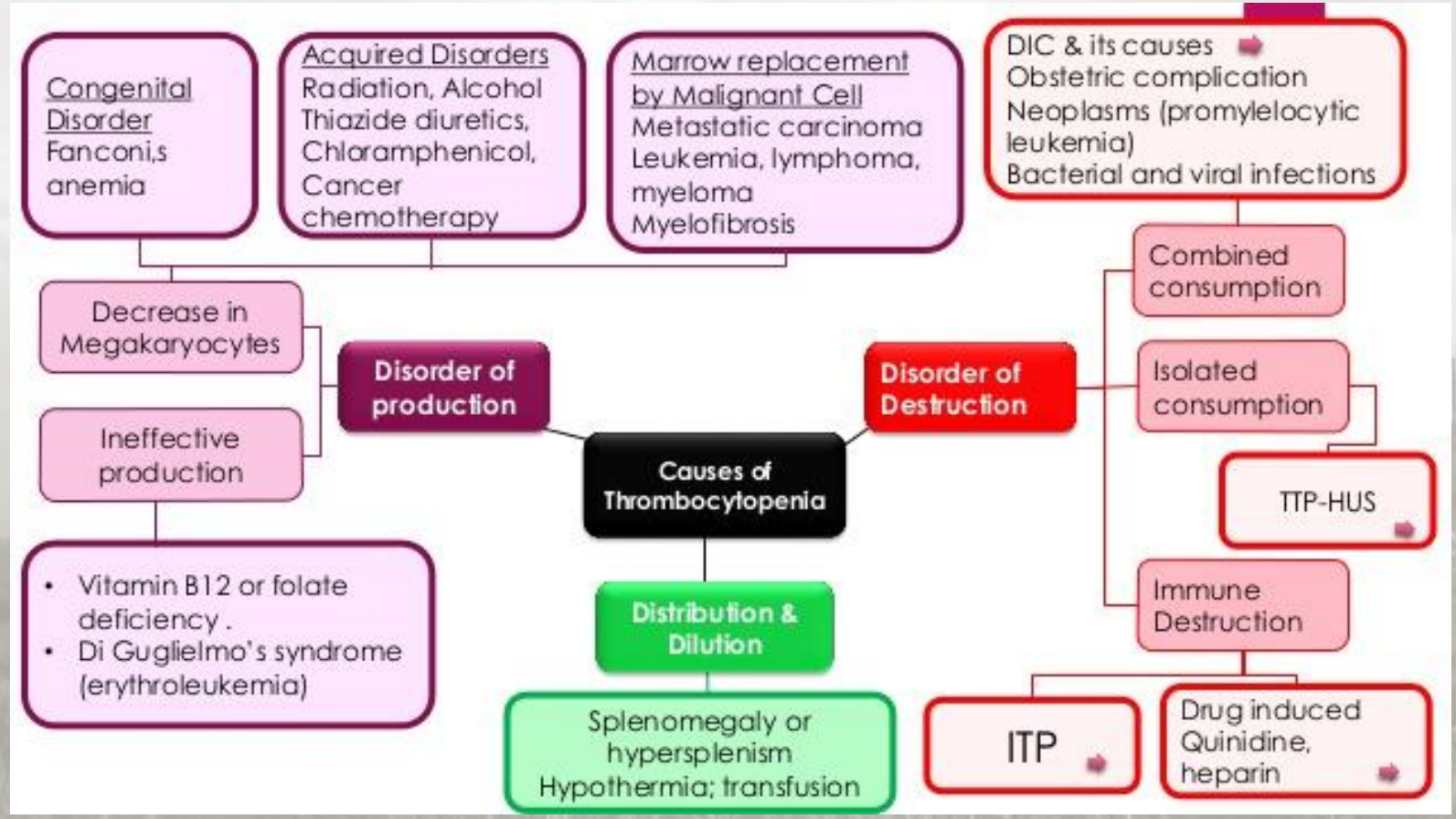




Thrombocytopenia



- Occurs across age: neonatal to elderly
- Various causes
- Clinical history is mandatory
- Common in our setting : drugs, infection ie dengue, primary immune thrombocytopenia


Congenital Disorder
Fanconi,s anemia
Acquired Disorders
Radiation, Alcohol
Thiazide diuretics,
Chloramphenicol,
Cancer chemotherapy
Marrow replacement by Malignant Cell
Metastatic carcinoma
Leukemia, lymphoma, myeloma
Myelofibrosis
DIC & its causes
Obstetric complication
Neoplasms (promylelocytic leukemia)
Bacterial and viral infections
Decrease in Megakaryocytes
Ineffective production
Disorder of production
Causes of Thrombocytopenia
Disorder of Destruction
Combined consumption
Isolated consumption
TTP-HUS
Immune Destruction
ITP
Drug induced
Quinidine, heparin
• Vitamin B12 or folate deficiency .
• Di Guglielmo's syndrome (erythroleukemia)
Distribution & Dilution
Splenomegaly or hypersplenism
Hypothermia; transfusion

Pseudothrombocytopenia
Disorders of decreased platelet production • Certain viral infections • Myelosuppressive therapy (e.g. chemotherapy, radiation) • Congenital thrombocytopenias • Ethanol toxicity • Folate or vitamin B12 deficiency • Bone marrow disorders (e.g. MDS, myelofibrosis, leukemia, other malignancies involving the marrow)
Disorders of decreased platelet survival • Certain drugs (e.g. heparin, quinine) • Alloimmune thrombocytopenias (e.g. post-transfusion purpura) • Disseminated intravascular coagulation • Thrombotic thrombocytopenic purpura-Hemolytic uremic syndrome • Cardiopulmonary bypass
Dilutional thrombocytopenia
Splenic sequestration • Portal hypertension • Infiltrative diseases of the spleen

Immune thrombocytopenia

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	Immune Thrombocytopenia	Neonatal Alloimmune Thrombocytopenia	Posttransfusion Purpura
Immune reaction	Autoimmune	Alloimmune	Features of both allo- and autoimmunity
Incidence	Five per 100,000 population	40 per 100,000 births (or one per 2,500)	One per 100,000 blood transfusions
Principal antigenic target	GPIIb/IIIa	HPA-1a	HPA-1a plus autoantigens
Nature of the antibody	Intermittent	Persistent (past 1 year)	Persistent often at high titers
Mode of sensitization	Autoantibody	Alloantibody	Features of allo- and autoantibodies
Sensitizing event	Mostly unknown; some viral illnesses, chronic infection	Exposure to fetal platelet antigens early in first pregnancy	Blood transfusion (RBCs or platelets) 5-10 days earlier
Bleeding frequency	Uncommon	Common	Very common
Epidemiology	Higher incidence in children and elderly adults; female predominance in early adulthood	Majority affects fetus or newborn carrying the HPA-1a antigen	Almost all are HPA-1bb women sensitized by previous transfusion or pregnancy

Drug induced thrombocytopenia

Type	Mechanisms	Examples
Hapten-induced antibody	Drug forms covalent linkage to membrane glycoprotein and acts as a hapten to induce a drug-dependent antibody response.	Penicillin and penicillin derivatives
Drug-dependent antibody	Drug binds to membrane glycoprotein and forms a compound epitope or induces a conformational change elsewhere in the molecule for which the antibody is specific. The immunogen can be a drug metabolite.	Quinidine, quinine, NSAIDs, various antibiotics, sedatives, anticonvulsants, many others
GP IIb/IIIa inhibitors (ligand mimetic)	Drug reacts with the RGD recognition sequence on GP IIb/IIIa and induces a conformational change elsewhere in the integrin complex that is recognized by antibody.	Tirofiban, eptifibatide, roxifiban, others
Drug-specific antibody	Drug (chimeric Fab fragment) induces antibodies specific for murine sequences that control specificity for GP IIb/IIIa.	Abciximab
Drug-induced autoantibody	Drug perturbs the immune response so that drug-independent antibodies specific for a cell membrane glycoprotein are produced.	Gold salts, procainamide
Immune complex	Drug forms an immunogenic complex with PF4; antibody binds and forms an immune complex; the immune complex activates platelets by way of Fc receptors.	Heparin

Drug induced antibody

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Classification	Mechanism	Specific Drugs
Autoantibody	Drug induces antibody that reacts with autologous platelets in the absence of the drug	Gold, procainamide
Drug specific antibody	Antibody recognizes murine component of chimeric Fab fragment specific for platelet membrane glycoprotein IIIa	Abciximab
Fiban-type drug	Drug reacts with glycoprotein IIb/IIIa to induce a conformational change recognized by antibody	Eptifibatide, tirofiban
Hapten-dependant	Hapten links covalently to membrane protein and induces drug-specific immune response	Cephalosporins, piperacillin
Immune complex	Drug binds to platelet factor 4 to produce an antigenic complex against which antibodies react; resulting immune complexes bind to platelet Fc receptors resulting in platelet activation	Heparin and low molecular weight heparin
Quinine-type	Drug induces antibody that binds to membrane protein in presence of soluble drug	Quinine, quinidine, NSAIDs, sulfonamides

Inherited thrombocytopenia

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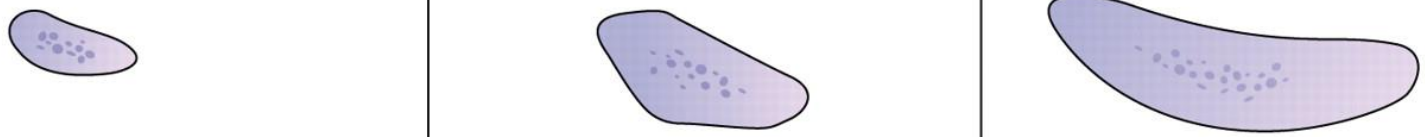
Algorithm for Diagnosis of Familial Thrombocytopenia

PLATELET SIZE



SMALL	NORMAL	LARGE
Eczema, X-linked WAS	**AR, High TPO** CAMT	**Flow for GPIb/IX** BSS
No eczema, X-linked XLT	**Radial defects** TAR, ATRUS	**AD, WBC inclusions** MYH9
	AD, FHx AML Runx1	**VWF multimers, RIPA** Type IIB VWD, TTP GPIb mutation
	11q deletion Paris Trousseau	**Red cells abnl** GATA1 ABCG5/8
	AD, minimal bleeding Cytochrome C ANKRD26	**EM** Granule disorder

Approach to thrombocytopenia

THROMBOCYTOPENIA

↓

rule out pseudothrombocytopenia

SEQUESTRATION	**↓ PRODUCTION**	**↑ DESTRUCTION**
look for splenomegaly	bone marrow investigation review meds	look for underlying disorders review meds
Causes of splenomegaly • infection • inflammation • congestion • maligancy • red cell disorders • storage diseases	• aplasia • infiltration • ineffective megakaryopoiesis eg. MDS • selective impairment of platelet production	• immune auto-immune (ITP, SLE drugs infections allo-immune • non-immune sepsis DIC, TTP, HUS hypertensive disorders of pregnancy

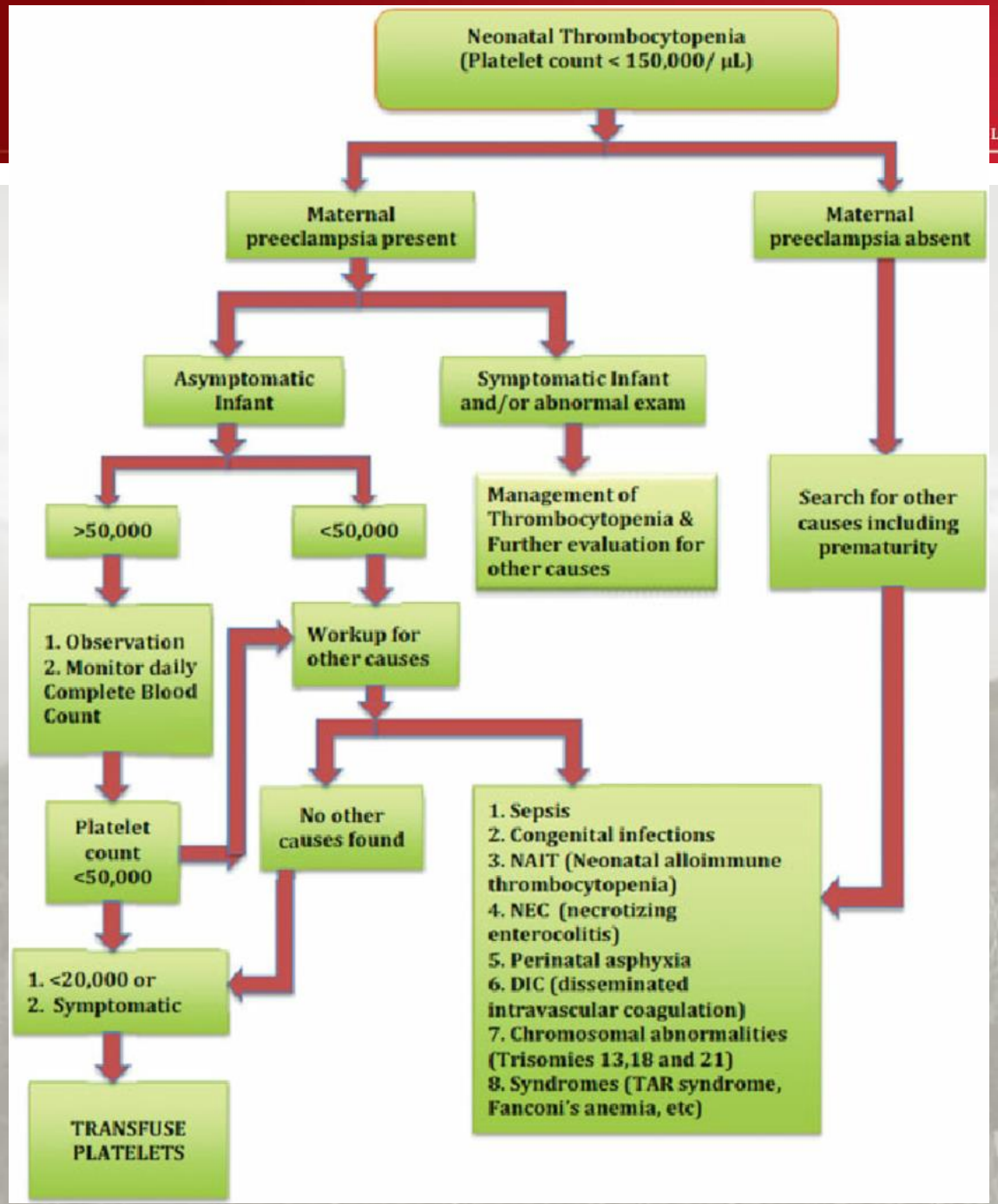
Also

Artefactual (false) or pseudothrombocytopenia

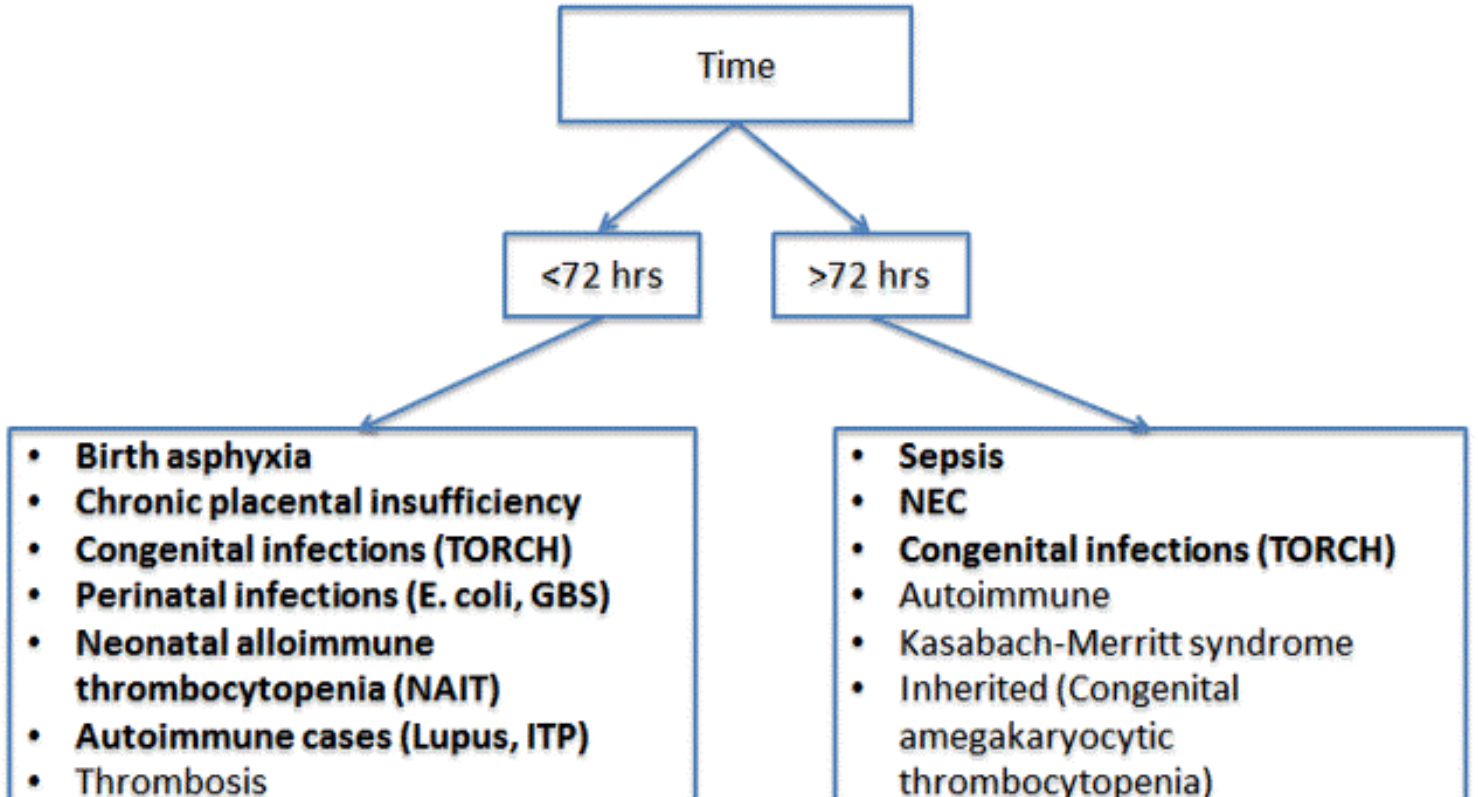
–**Clot in the sample.- Platelets clumped.**

Congenital thrombocytopenia

–Rare inherited disorders (eg May Hegglin Anomaly).

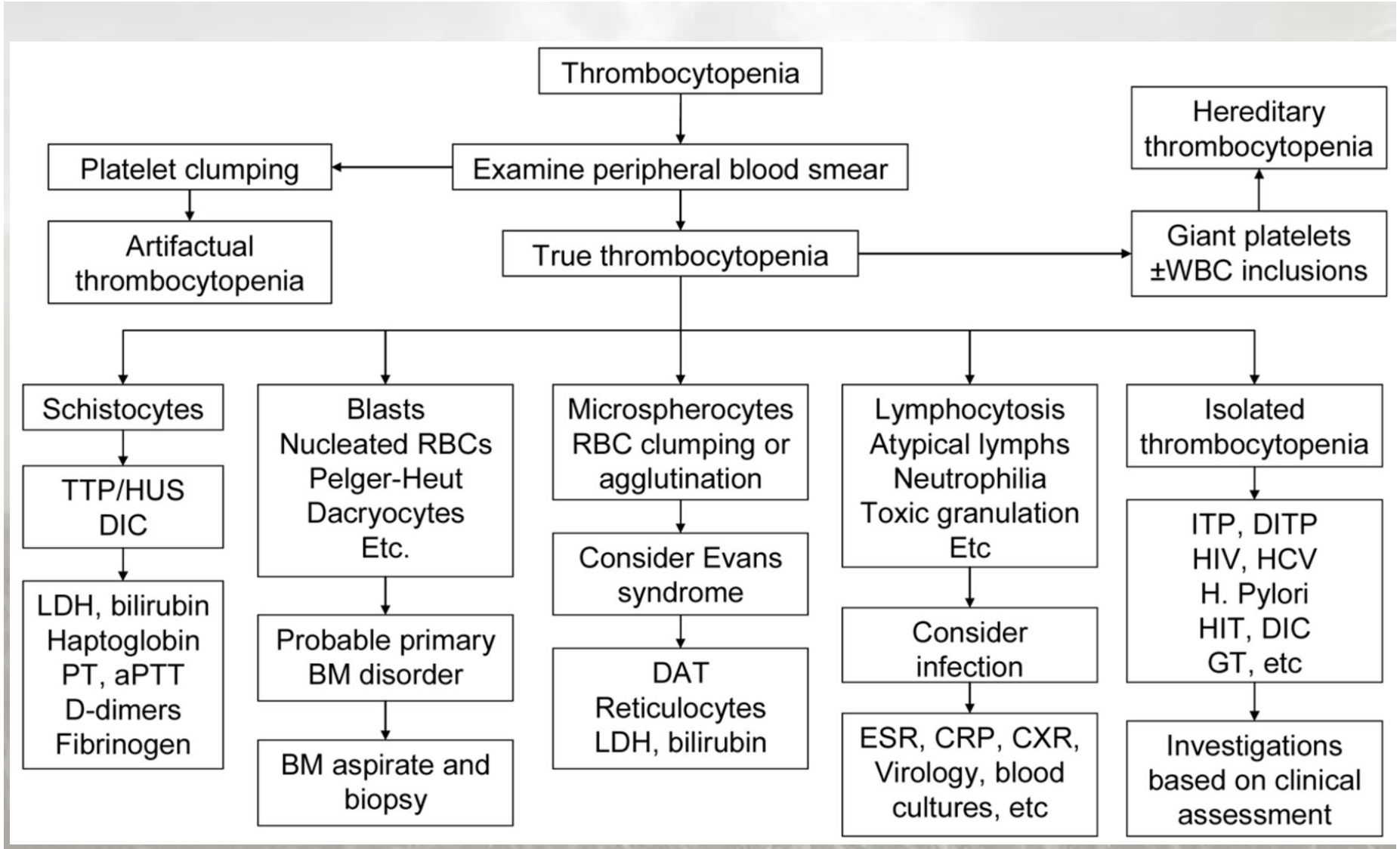

Neonatal Thrombocytopenia
(Platelet count < 150,000/ µL)
Maternal preeclampsia present
Maternal preeclampsia absent
Asymptomatic Infant
Symptomatic Infant and/or abnormal exam
>50,000
<50,000
Management of Thrombocytopenia & Further evaluation for other causes
Search for other causes including prematurity
1. Observation
2. Monitor daily Complete Blood Count
Workup for other causes
Platelet count <50,000
No other causes found
1. Sepsis
2. Congenital infections
3. NAIT (Neonatal alloimmune thrombocytopenia)
4. NEC (necrotizing enterocolitis)
5. Perinatal asphyxia
6. DIC (disseminated intravascular coagulation)
7. Chromosomal abnormalities (Trisomies 13,18 and 21)
8. Syndromes (TAR syndrome, Fanconi's anemia, etc)
1. <20,000 or
2. Symptomatic
TRANSFUSE PLATELETS

Neonatal thrombocytopenia



Williams hematology, 8e. Chapter 119
Chakravorty et al, Brit Jour of Hematology, 2011

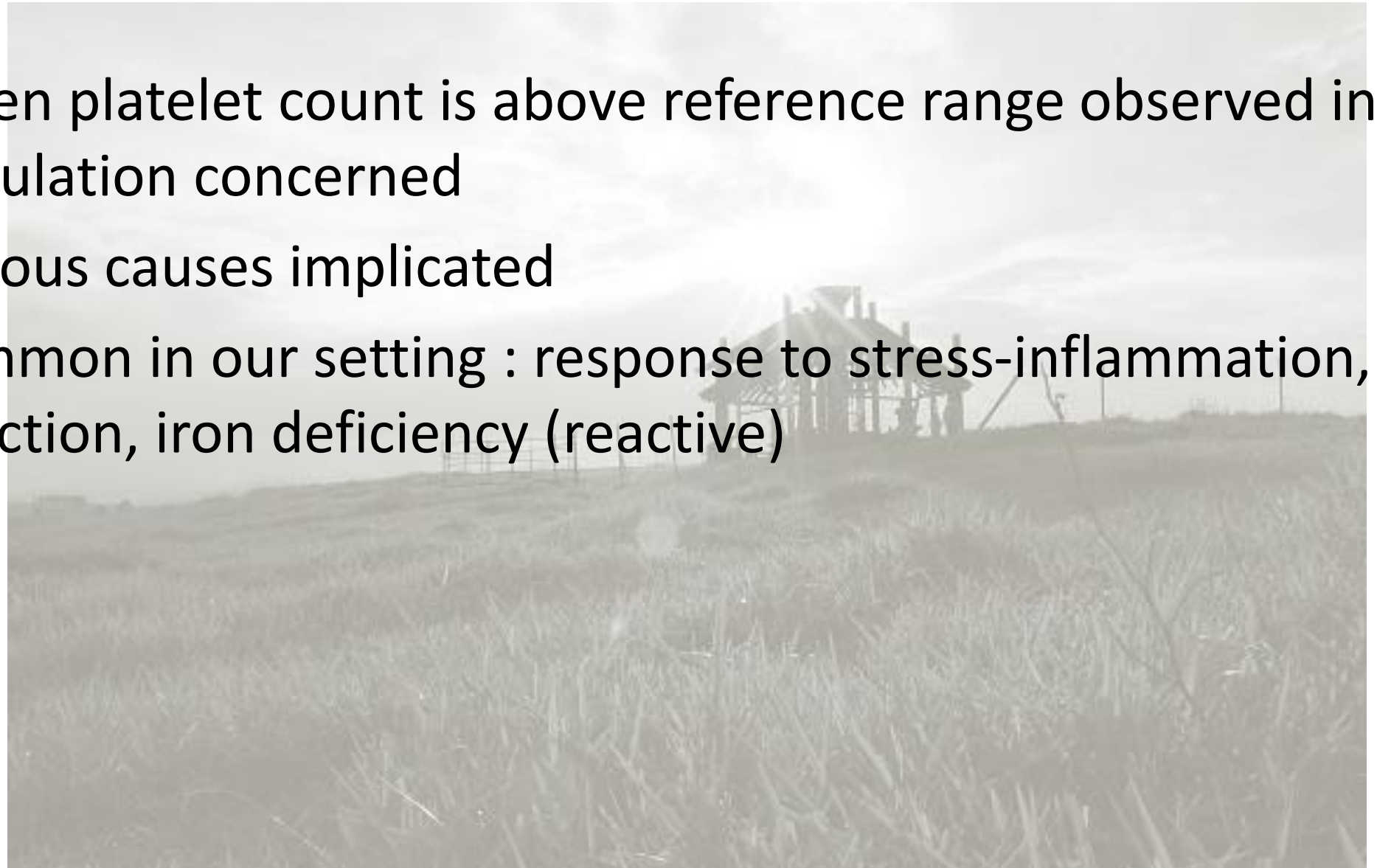
Thrombocytopenia-approach



URGENT ATTENTION NEEDED…

MAHA + Low Plts	Pathophysiology	Abdominal pain	AKI	ALI	High PT/PTT	Treatment	Unique feature(s)
TTP	Deficiency in ADAMSTS 13 (<10%) (antibodies) vs. hereditary form (Upshaw-Shulman Syndrome)	++	+	+/-	-	Plasma exchange (PEX) Glucocorticoids Rituximab	Recombinant ADAMTS13 and anti-vWF on the horizon Plt transfusions reserved for those with active bleeding
HUS	Shiga toxin (*Shigella dysenteriae* and *EColi* O157:H7) with direct epithelial and endovascular damage vs. hereditary form (atypical HUS)	++	++	+/-	-	Supportive care Eculizumab (anti-complement therapy) for hereditary forms for aHUS	Plt transfusions reserved for those with active bleeding
HELLP	? severe pre-eclampsia; no clear understanding of pathophysiology but felt to be systemic inflammatory response	++ (40-90% per UpToDate)	+	+++ (Criteria: TBili >1.2 and AST >2x ULN)	+	Delivery of fetus Supportive care Steroids?	Plt transfusions reserved for those with active bleeding (if c-section, consider Plt 40-50k)
DIC	Abnormal regulation of coagulation and fibrinolysis because of a variety of etiologies	+/-	+ (25-40%)	+ (19%)	+++ (Bleeding 64%) *From 1978 case series of 118 pts with acute DIC	Treat the underlying etiology Supportive care Prevention/Treatment of bleeding and thrombosis: ? heparin infusion, fibrinogen (100-150)	Etiologies include but are not limited to: Sepsis, malignancy, trauma, ob complications (preeclampsia, fetal demise, AFLP), intravascular hemolysis, drugs and toxins

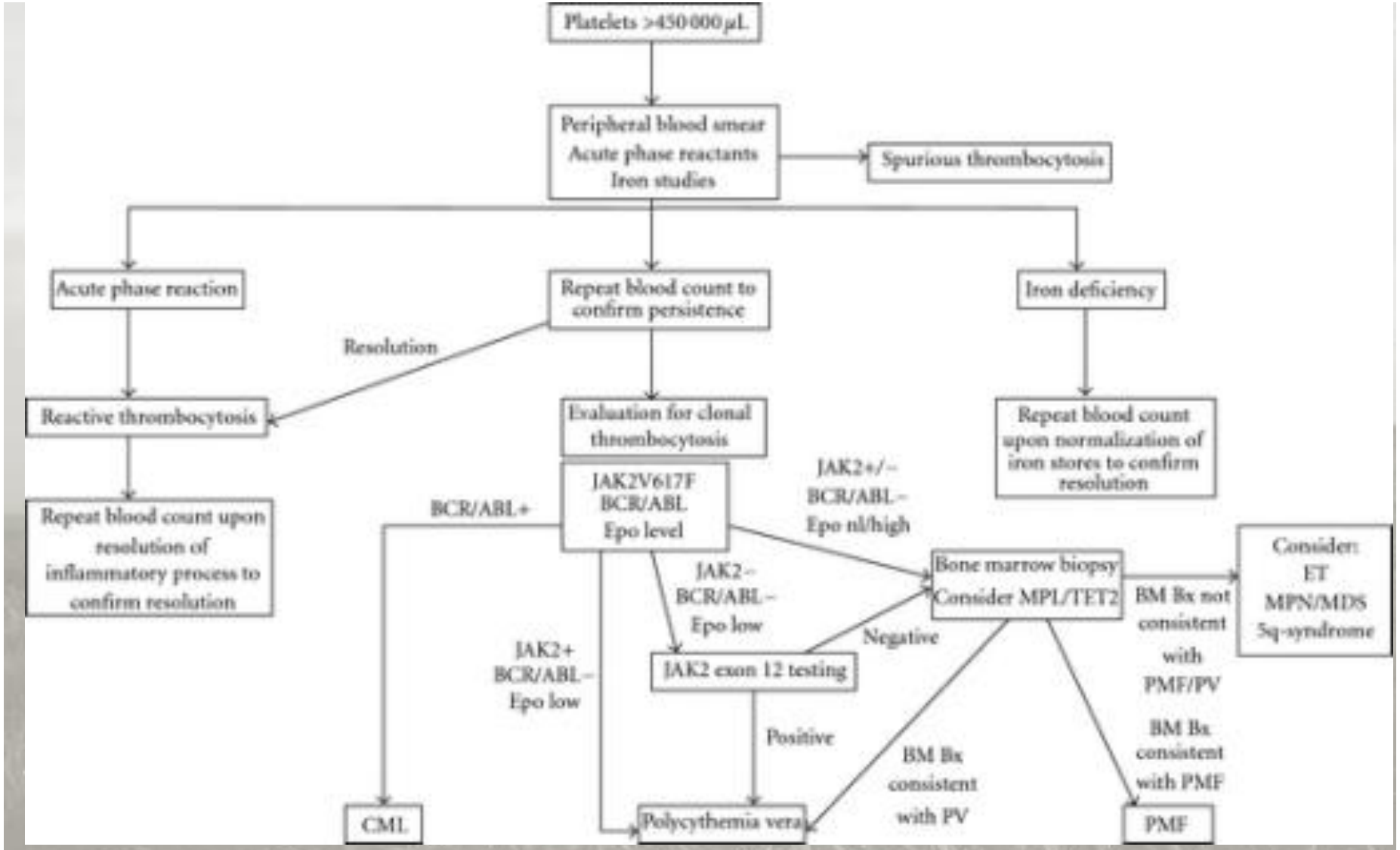
Thrombocytosis



- When platelet count is above reference range observed in population concerned
- Various causes implicated
- Common in our setting : response to stress-inflammation, infection, iron deficiency (reactive)

Causes of Thrombocytosis[3]
SPURIOUS THROMBOCYTOSIS
Cryoglobulinemia Cytoplasmic fragmentation in acute leukemia Red cell fragmentation Bacteremia
REACTIVE (SECONDARY) THROMBOCYTOSIS
Transient thrombocytosis Acute blood loss Recovery from thrombocytopenia (rebound thrombocytosis) Acute infection or inflammation Response to exercise Response to drugs (vincristine, epinephrine, all-trans-retinoic acid) Sustained thrombocytosis Iron deficiency Splenectomy or congenital absence of spleen Malignancy Chronic infection or inflammation Hemolytic anemia
FAMILIAL THROMBOCYTOSIS
CLONAL THROMBOCYTOSIS
Essential thrombocythemia Polycythemia Vera Primary myelofibrosis Chronic myeloid leukemia Refractory anemia with ringed sideroblasts and thrombocytosis 5q minus syndrome

Approach to thrombocytosis in MPN



Take home message

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- Be aware of various causes of platelet abnormalities
- Always check with clinical history and previous results (if available)
- When in doubt/unsure, ask for help.

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TERIMA KASIH/*THANK YOU*

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