APPROACH TO BLEEDING DISORDERS

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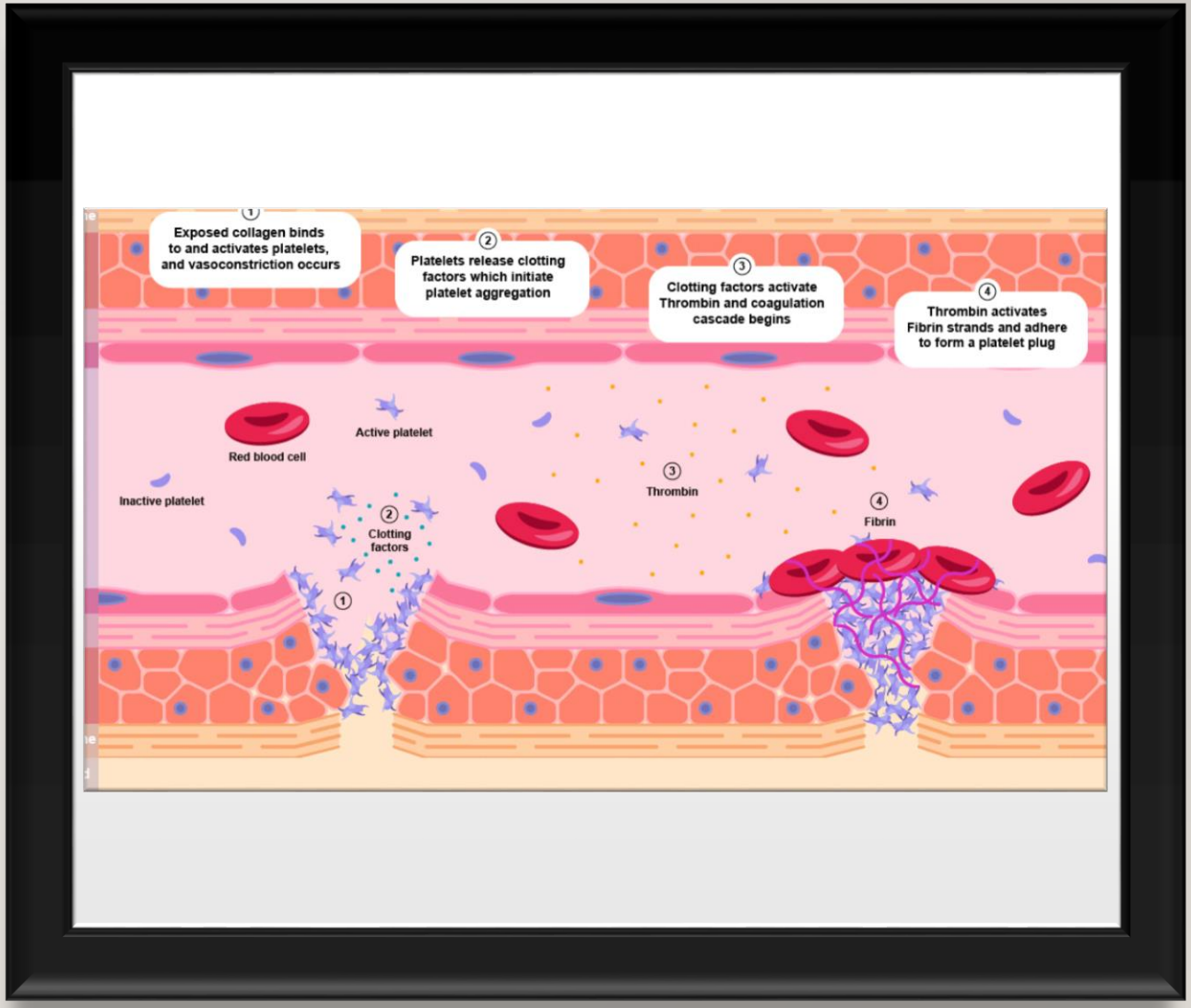
INTRODUCTION

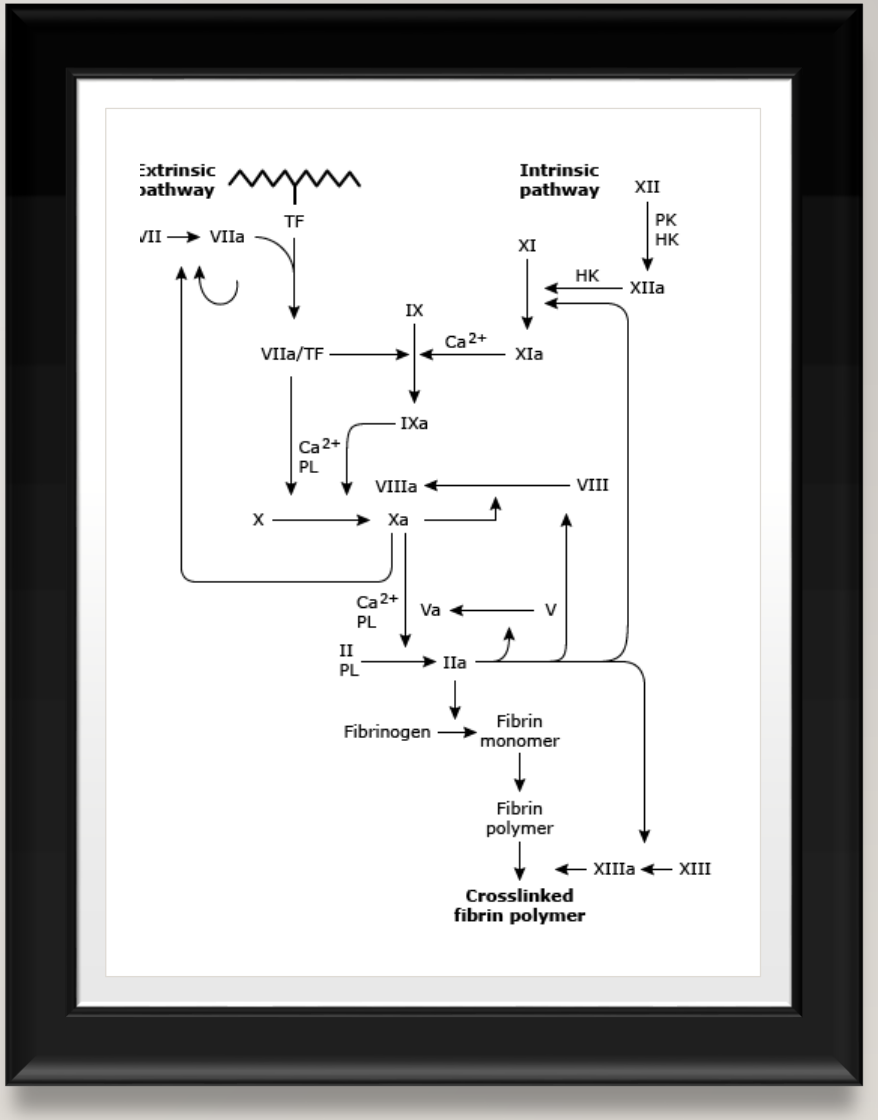
- **Primary homeostasis :**

Platelet plug – Platelets are activated at the site of vascular injury to form a platelet plug that provides the initial hemostatic response, including exposure of procoagulant phospholipids on the platelet surface and the assembly of components of the clotting cascade.



INTRODUCTION

- **Secondary Homeostasis**
- Fibrin deposition – Generation or exposure of tissue factor at the wound site, its interaction with factor VIIa and the subsequent generation of activated factor X, are the primary physiologic events in initiating clotting, while components of the intrinsic pathway (ie, factors VIII, IX, XI) are responsible for amplification of this process.



FOCUSED HISTORY EXAMINATION

- Given the **variability in patients' perceptions** of bleeding, as well as the lack of a uniform clinical measure of bleeding severity, a dialogue between the patient and physician is essential for the consideration of a bleeding diathesis.
- A careful assessment of the presenting complaint can provide important clues as to where a defect might reside in the hemostatic process and whether the defect is inherited or acquired, providing a rational approach to laboratory investigation
- **Clinical manifestations of disordered hemostasis can be divided into two major categories:**
- 1) those associated with disorders of blood vessels or qualitative or quantitative platelet abnormalities. (disorders of primary hemostasis)
- 2) those associated with disorders of coagulation cascade (disorders of secondary hemostasis)

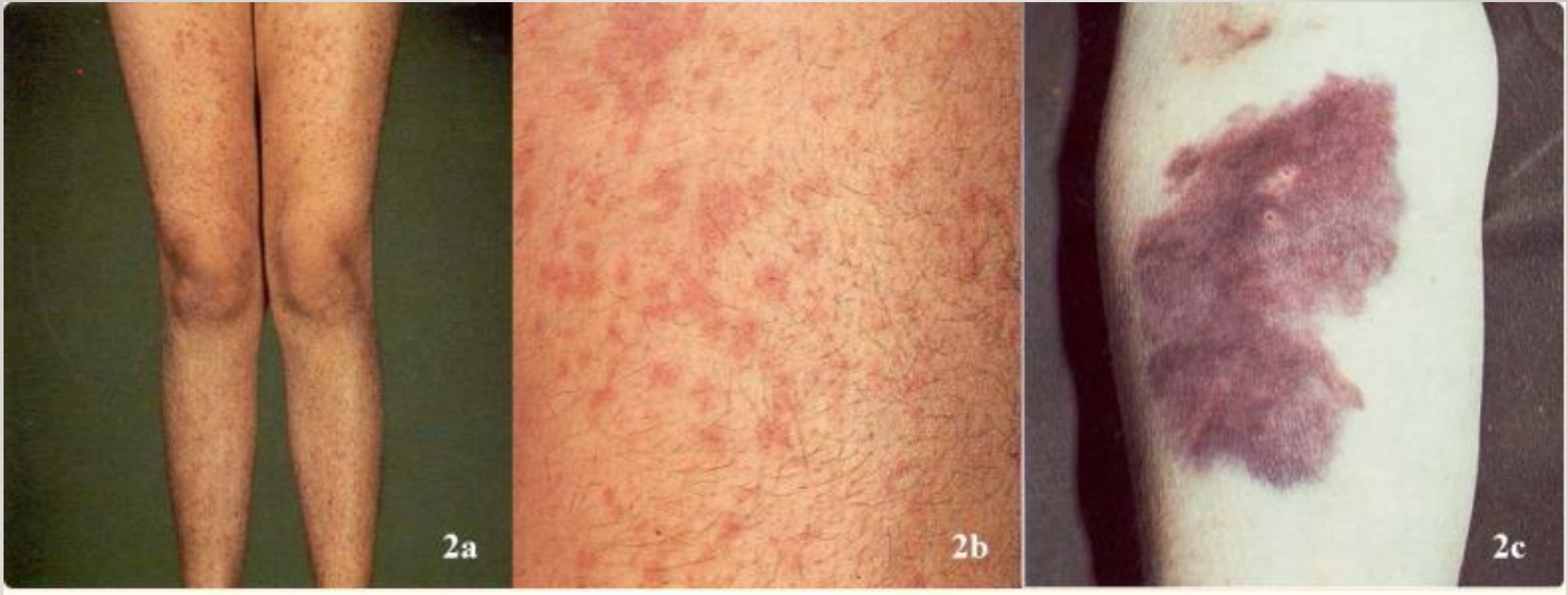
FOCUSED HISTORY EXAMINATION

- **Onset** (when did you first notice)/ **Duration** (how long have you had bleeding ?) (acute or chronic / acquired or inherited) **Site and Type of bleeding (see next slides)**
- Was it **spontaneous**? Or **after trauma**? If after trauma, was it **immediate or delayed**?
- **Response to previous coagulation stress? See next slides)**
- **Viral illness or sore throat? (ITP?)**
- **Associated symptoms** (bleeding from any other site) (tiredness weight loss fever or sweats>. Leukemia?) Skin rash (SLE causing autoimmune thrombocytopenia?) Widespread itchiness (myeloproliferative cancer causing acquired bleeding disorder?)
- Any aches and pains in **joints or muscles**
- **Past medical history** (acquired bleeding disorder occurring with hypothyroidism, liver disease, renal failure, SLE, and some cancers like Multiple Myeloma)
- **Drug History** (acquired bleeding disorder may be due to certain medications like aspirin, NSAIDs, anticoagulant therapy, thiazide diuretics
- **Family History** of bleeding disorders or bleeding symptoms
- **Social History**: Alcohol (alcoholic cirrhosis can cause acquired bleeding disorder)

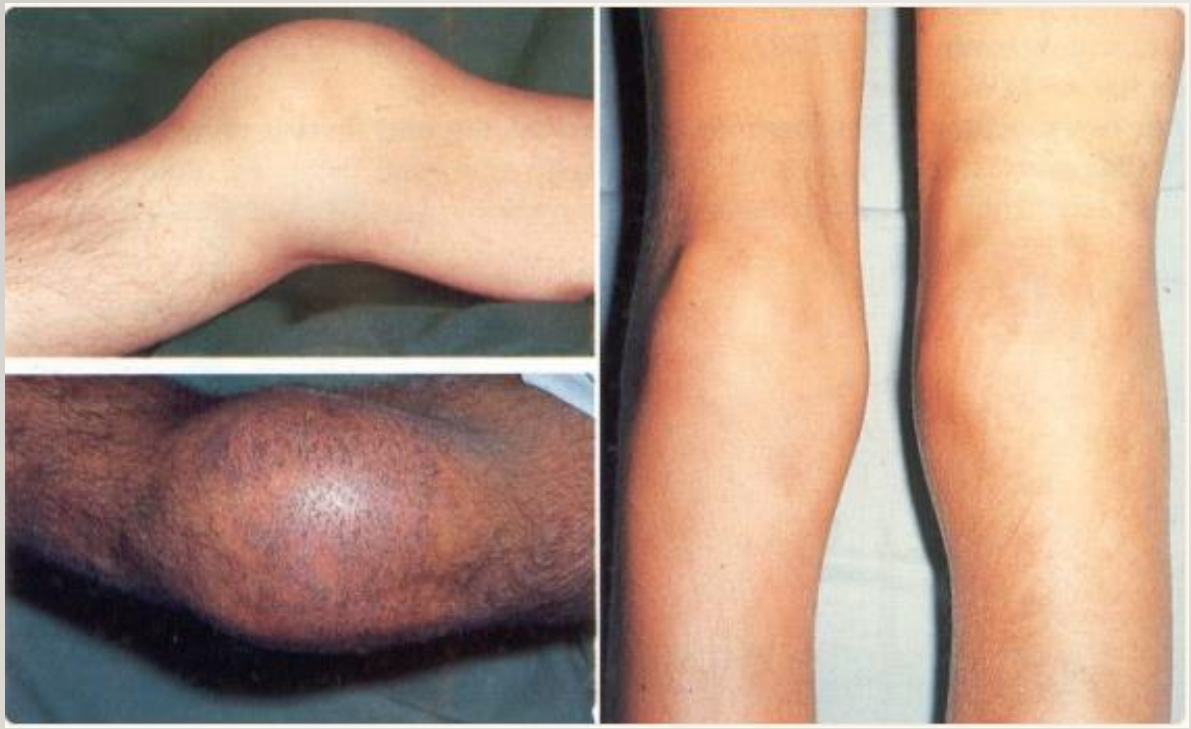
FOCUSED HISTORY EXAMINATION

- The type and sites of bleeding, (give a clue if it is a ***primary or secondary*** disorder of hemostasis)
- whether it involves the skin (cutaneous) (manifested as petechiae or superficial ecchymoses) and mucous membranes (Mucosal bleeding may be manifest as epistaxis and/or gingival bleeding, menorrhagia) which are often seen in **disorders of platelets and blood vessels**
- large palpable ecchymoses and large, spreading, deep soft tissue hematomas (Bleeding into deep tissue, joints and muscles) which are often seen **in disorders of coagulation cascade**.
- Hemorrhage into synovial joints (hemarthrosis) most often indicates a severe inherited coagulation disorder, such as hemophilia)
- Patients with platelet abnormalities tend to bleed immediately after vascular trauma and rarely experience delayed bleeding, which is more common in the coagulation disorders

FIGURES 2A AND 2B SHOWS SCATTERED PETECHIAE AND PURPURA AND FIGURE 2C SHOWS A LARGE ECCHYMOSIS PETECHIAE (1-3MM) (PURPURA ARE LARGER) ARE SMALL CAPILLARY HEMORRHAGES. THEY CHARACTERISTICALLY DEVELOP IN CROPS IN AREAS OF INCREASED VENOUS PRESSURE, SUCH AS THE DEPENDENT PARTS OF THE BODY. AS A RESULT, THEY ARE MOST DENSE ON THE FEET AND ANKLES, FEWER ARE PRESENT ON THE LEGS. PETECHIAE ARE NOT FOUND ON THE SOLE OF THE FOOT WHERE THE VESSELS ARE PROTECTED BY THE STRONG SUBCUTANEOUS TISSUE. THEY ARE ASYMPTOMATIC AND NOT PALPABLE. ECCHYMOTIC LESIONS CHARACTERISTICALLY ARE PURPLE IN COLOR AND ARE SMALL, MULTIPLE, AND SUPERFICIAL IN LOCATION. THEY USUALLY DEVELOP WITHOUT NOTICEABLE TRAUMA AND DO NOT SPREAD INTO DEEPER TISSUES.



HEMARTHROSIS SEEN IN HEMOPHILIA



FOCUSED HISTORY EXAMINATION

- It can be informative to learn if there was the presence or absence of excessive bleeding with past hemostatic challenges such as :

1. character of menses
2. bleeding outcome following invasive surgical procedures
3. dental extractions

- History of blood transfusion or other blood components
- Childhood history of epistaxis and relevant specific hemostatic challenges include postdelivery cephalohematoma, umbilical stump bleeding, excessive bleeding with heel prick or venipuncture and/or bleeding at the time of circumcision. **which might suggest an inherited bleeding disorder.**

HEREDITARY BLEEDING DISORDERS

- Information on the duration must also be sought. This would indicate whether symptoms have been lifelong (since childhood) or of recent onset.
- A very careful **family history** is critical; any family history of abnormal bleeding in both parents, maternal grandparents, aunts, uncles, and siblings, as well as any history of consanguineous marriage (or among relatives), should be taken.
- A congenital bleeding disorder is often suspected when there is a lifelong history of bleeding and a family history of a bleeding disorder and/or consanguinity.
- An inherited disorder is suggested by the onset of bleeding shortly after birth or during childhood and a positive family history with a consistent genetic pattern. Thus, hemophilia A and hemophilia B are characterized by X-linked recessive inheritance.
- However, a negative family history does not exclude an inherited coagulation disorder ,As an example, up to 30 to 40 percent of patients with hemophilia A have a negative family history (new genetic mutation)

ACQUIRED BLEEDING DISORDER

- **Drug history and medications:**

Drug ingestion may be associated with a bleeding diathesis via a variety of mechanisms, such as the induction of thrombocytopenia or platelet dysfunction, aplastic anemia, or vascular purpura. In addition, some drugs can induce or exacerbate a coagulation disorder. Examples include platelet dysfunction induced by aspirin and other commonly used anti-inflammatory drugs, beta-lactam antibiotics, clopidogrel, ticlopidine, and the co-ingestion of drugs that may potentiate the anticoagulant effects of warfarin

- **Dietary habits**

Some dietary supplements, such as the commonly used garlic, ginkgo, and ginseng, have been reported to impair platelet function and increase bleeding symptoms

- **Vitamin K deficiency**

Vitamin k dietary deficiency is rare because the GI bacteria produce sufficient amount / common causes: warfarin(it antagonize vit K activity),antibiotics (deplete bacteria), newborn(sterile GI tract), malabsorption(vit K is fat soluble)

- **Comorbidity**

an acquired bleeding problem may be suspected when there are comorbidities such as renal disease, liver disease, and hypothyroidism.

- **Structural**

Complaints such as hematuria, melena, and menorrhagia are often less helpful since structural causes are more commonly responsible than a bleeding disorder.

- **Other**

The patient should be questioned concerning the presence of thyroid, liver, and kidney disease.

Platelets	Coagulation cascade
think small and early	think big and late
Bleed from skin and mucous membrane(nose/GI/GU)	Deep in soft tissue
Petechia / Tend to bleed after small cuts	No petechia and do not bleed after small cuts
*Small and superficial ecchymosis	*Ecchymosis are common
*Bleeding after surgery is immediate and mild	*Bleeding after surgery is late and severe
	*Positive family history More common in males

FOCUSED PHYSICAL EXAMINATION

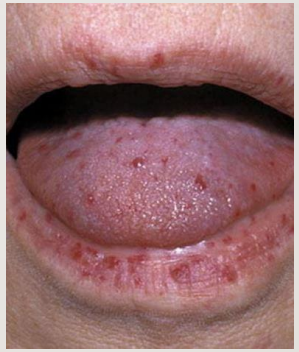
- **In general examination:**

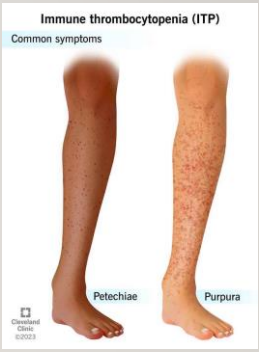
- Examine the skin and mucous membranes.
- Feel the lymph nodes for any enlargement.
- Examine the joints.
- Examine the abdomen and don’t forget the digital rectal exam.
- Look for signs of systemic diseases: thyroid, liver disease or connective tissue/collagen disease.
- Look for current hemorrhage location, amount and nature.

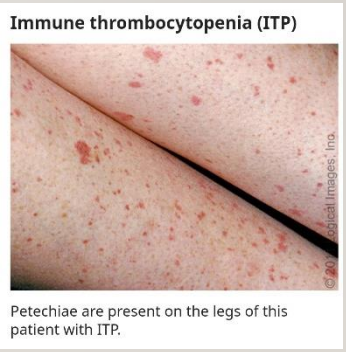
FOCUSED PHYSICAL EXAMINATION

- **The mucocutaneous findings:**

- **Petechiae -** especially if present in dependent areas (legs, sacrum), may indicate thrombocytopenia. look for any sites that has the same sign to determine if it is localized or generalized bleeding disorder.
- **Ecchymosis (Bruises) -** Petechiae, purpura, ecchymosis, and scarring on the arms may indicate solar purpura, which is a common finding related to aging and is generally not considered a bleeding disorder.
- **Telangiectasias** - around the lips or on the fingertips may indicate hereditary hemorrhagic telangiectasia (HHT) (Osler-Weber-Rendu syndrome).







FOCUSED PHYSICAL EXAMINATION

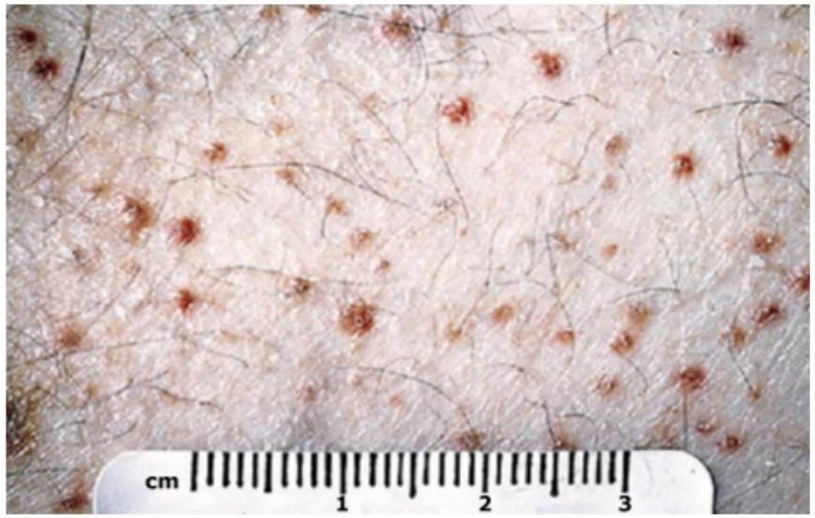
Bruises - Try to differentiate between new bruises and old ones, bruises that are on reachable areas by the patient's hands vs other areas. This differentiation will help you in your diagnosis.

Hair follicle changes - Perifollicular hemorrhages and "corkscrew hairs" are seen in scurvy (vitamin C deficiency).

Albinism - Oculocutaneous albinism is associated with certain platelet disorders (Hermansky-Pudlak and Chediak-Higashi syndromes).

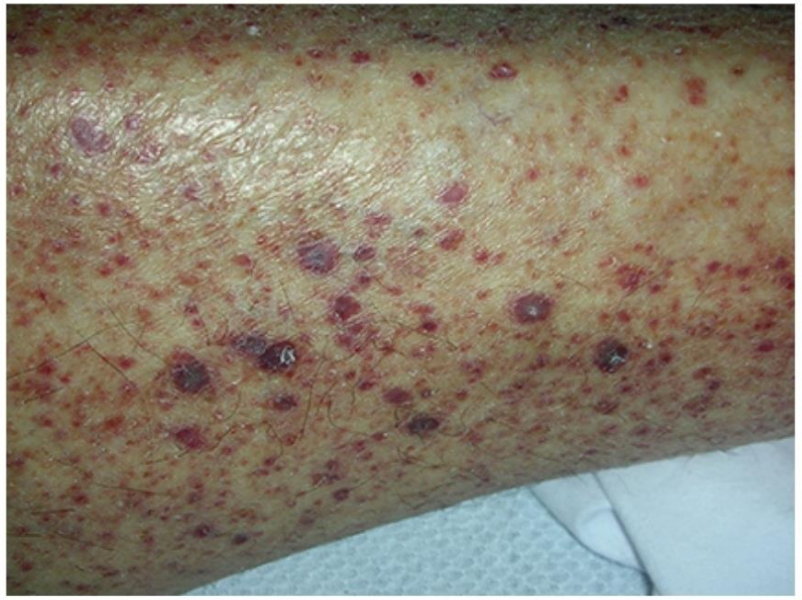
Lymphadeopathy

Perifollicular abnormalities in scurv



In this example, the perifollicular hyperkeratotic papules are quite prominent, with surrounding hemorrhage. These lesions have been misinterpreted as "palpable purpura," leading to the mistaken clinical diagnosis of vasculitis.

Scurvy



Perifollicular, purpuric macules are present in this patient with scurvy.

FOCUSED PHYSICAL EXAMINATION

- • **Hepatosplenomegaly** – Splenomegaly may indicate underlying liver disease, lymphoma, or a myeloproliferative neoplasm. Related findings for liver disease include jaundice, spider angiomata, gynecomastia, and asterixis. Related findings for hematologic malignancies include pallor and lymphadenopathy.
- • **Joint laxity** – Joint hypermobility and skin hyperelasticity may be seen in some Ehlers-Danlos syndromes (EDS). Vascular EDS may lead to bleeding due to arterial rupture (blood vessels are fragile) . EDS can result in spontaneous bruising, which often recur in the same areas causing a characteristic discoloration of the skin from hemosiderin deposition.
- • **Cardiac findings** – A harsh systolic murmur may indicate aortic stenosis, a cause of acquired von Willebrand syndrome (AVWS), which may be associated with bleeding from gastrointestinal arteriovenous malformations (AVMs).
- • **Macroglossia** and **organ infiltration** signs as (carpal tunnel syndrome and periorbital purpura may indicate amyloidosis, which can cause a number of acquired clotting factor deficiencies (factors X and V, VWF).

Symptom	PFD/VWD	Clotting factor deficiencies	Connective tissue disorders
Location of bleeding symptoms	Mucocutaneous bleeding: epistaxis, oral cavity, GI and GU bleeding	Deep tissue bleeding: joints and muscles	Mucocutaneous bleeding
Ecchymoses	Common, superficial, can be associated with small subcutaneous hematomas	Large subcutaneous and soft tissue hematomas	Common and may be associated with subcutaneous hematomas
Petechiae	Common	Uncommon	Common
Bleeding after minor cuts	Common	Uncommon	Common with abnormal healing and scar formation
Deep tissue bleeding (joint and muscle bleeds)	Uncommon	Spontaneous in severe factor deficiencies; provoked in moderate to mild deficiencies	Uncommon
Bleeding with invasive procedures	Immediate	Delayed	Immediate
Manifestations other than bleeding	Rare subtypes of PFD can be associated with hearing loss, mental retardation, albinism	Dysfibrinogenemia has an increased risk of thrombosis; FXIII deficiency is marked by poor wound healing; both are associated with recurrent miscarriages	Skin hyperextensibility; delayed wound healing; atrophic scarring; joint hypermobility

Abbreviations: F, factor; GI, gastrointestinal; GU, genitourinary; PFD, platelet function disorder; VWD, von Willebrand disease.

LABORATORY TESTS

LABORATORY TESTS

Platelet tests :

- Platelets count
- Bleeding time

Coagulation tests :

- Prothrombin time
- Activated partial thromboplastin time
- Thrombin time

PLATELET COUNTS

- Is the most common of all hemostasis tests.
- Should be ordered in every suspected bleeding disorder .
- Tested as a part of the CBC .
- Normal platelet count 150,000 to 450,000 platelet per microliter of blood .

BLEEDING TIME

- Bleeding time assess primary haemostatic defect (blood vessels / platelet) .
- Normal range 4- 8 mins
- Causes of prolonged bleeding time :

1-Thrombocytopenia

2-Primary haemostatic defect in the vessels (like in CT disorder , scurvy)

3-Platelet qualitative disorder

4- vWD

PROTHROMBIN TIME

- Important to assess the extrensic pathway of caogulation
- Sensetive to change in factors (5,7,10) and to lesser extent(1,2).
- Normal range 9.5 – 13.5 seconds
- Causes of prolonged pt:

1- dificiency in factor **VII** ,V , X , II,I

2- Vitamin k deficiency

3- Liver disease

4- Oral anticoagulant (warfarin ; vitamin k inhibitor)

INTERNATIONAL NORMALIZED RATIO (INR)

- Reflects the prothrombin time.
- INR= patient PT/control PT
- Normal = 1
- Therapeutic = 2-3

ACTIVATED PARTIAL THROMBOPLASTIN TIME

- Reflect efficiency of the intrinsic pathway
- Sensitive to change in factor 8,9,11,12
- Also sensitive to heparin and circulating anticoagulant
- Normal range 26 to 40 seconds
- Causes of prolonged aPTT:

1-Deficiency of factor 8 (haemophilia A) : XLr

2- Deficiency of factor 9 (haemophilia B) : XLr

3_ Deficiency of factor 11 (haemophilia C) : AR

4- circulating anticoagulant

5- liver disease

6. heparin therapy or heparin in the blood sent to laboratory (mcc)

7. Deficiency of factor 12 : no clinical bleeding disorder

THROMBIN TIME

- Assess the final step of coagulation (by passing the extrinsic and intrinsic pathway .
- It depend mainly on the concentration of the fibrinogen and presence of inhibitory substances .
- Normal range 13 -19 sec .

THROMBIN TIME

Causes of prolonged TT :

1. Disorder of fibrinogen (qualitative , or quantitve)
2. heparin
3. liver disease

COAGULATION DISORDERS

1. Hemophilia A, B, or C

Intrinsic pathway coagulation defect (increased PTT, normal PT)

A: deficiency of factor VIII; X-linked recessive.

B: deficiency of factor IX; X-linked recessive.

C: deficiency of factor XI; autosomal recessive.

2. Vitamin K deficiency

General coagulation defect (increased PTT,increased PT)

Bleeding time normal.

Decreased activity of factors II, VII, IX, X, protein C, protein S.

PLATELET DISORDERS

1. Bernard-Soulier syndrome

   Autosomal recessive defect in adhesion.low GpIb,decreased platelet-to-vWF adhesion.

   Labs:decreased platelet aggregation

2. Glanzmann thrombasthenia

   Autosomal recessive defect in aggregation.

   Low GpIIb/IIIa , decreased platelet-to-platelet aggregation and defective platelet plug formation.

   Labs: blood smear shows no platelet clumping.

3. Immune thrombocytopenia

Destruction of platelets in spleen.

Anti-GpIIb/IIIa antibodies ,splenic macrophages phagocytose platelets.

May be idiopathic or 2° to autoimmune disorders (eg, SLE), viral illness (eg, HIV, HCV), malignancy (eg, CLL), or drug reactions.

Labs: increased megakaryocytes on bone marrow biopsy, low platelet count.

4. Uremic platelet dysfunction

In patients with renal failure, uremic toxins accumulate and interfere with platelet adhesion.

THROMBOTIC MICROANGIOPATHIES

1. Thrombotic thrombocytopenic purpura

   Typically females

   Inhibition or deficiency of ADAMTS13 (a vWF metalloprotease), decreased degradation of vWF multimers ,large vWF multimers , increased platelet adhesion and aggregation (microthrombi formation).

   Triad of thrombocytopenia, microangiopathic hemolytic anemia (low Hb, schistocytes, high LDH), acute kidney injury (high Cr)+ fever + neurologic symptoms

   Normal PT & PTT

2. Hemolytic-uremic syndrome

Typically in children predominately caused by Shiga toxin–producing Escherichia coli (STEC) infection (serotype O157:H7), which causes profound endothelial dysfunction.

Thrombocytopenia, MAHA, AKI, Bloody diarrhea.

Normal PT &PTT.

MIXED PLATELET AND COAGULATION DISORDERS

1. von Willebrand disease

Intrinsic pathway coagulation defect: low vWF , increased PTT (vWF carries/protects factor VIII).

Defect in platelet plug formation: low vWF , defect in platelet-to-vWF adhesion.

Most are autosomal dominant.

Mild but most common inherited bleeding disorder. Commonly presents with menorrhagia or epistaxis.

2. Disseminatedintravascular coagulation

Widespread clotting factor activation, thromboembolic state with excessive clotting factor consumption ,thromboses, hemorrhages (eg, blood oozing from puncture sites).

May be acute (life-threatening) or chronic (if clotting factor production can compensate for consumption).

Causes: heat Stroke, Snake bites, Sepsis , Trauma, Obstetric complications, acute Pancreatitis, malignancy, nephrotic syndrome, transfusion .

Labs: schistocytes, increased fibrin degradation products (d-dimers),decreased fibrinogen, decreased factors V and VIII.

MANAGEMENT OF BLEEDING DISORDERS

MANAGEMENT OF COAGULATION DISORDERS:

- Hemophilia A, B, or C
- A: deficiency of factor VIII (most common) :

1-**Desmopressin** (moA isnt well understood as for VWF) Route is IV/SC/intranasal - (2- to 6-fold over baseline values) test infusion/injection for every patient

2-**factor VIII concentrate**

3-**Emicizumab**: binds factors IXa and X, resulting in spatial approximation and activation of factor X, thereby mimicking the actions of factor VIII

- B: deficiency of factor IX: factor IX concentrate
- C: deficiency of factor XI: factor XI concentrate

VITAMIN K DEFICIENCY

-Due fat malabsorption syndromes ,diffuse liver disease or absence of Vit-k absorping flora (antibiotics)

1-Acute bleeding disorder due to vit K deficiency should be managed with (Fresh frozen plasma) or (Prothrombin Complex Concentrates,PCC) .

2- Vit K can be given as supplements or IV/IM/SC in high doses depending on the indication.

MANAGEMENT OF MIXED PLATELET AND COAGULATION DISORDERS

- **Von Willebrand disease :**

1-in mild to moderate cases is mainly desmopressin, which releases vWF stored in endothelium., watch for hyponatremia

2-Active bleeding: factor 8 concentrates , recombinant vWF

- **Disseminated intravascular coagulation(DIC):**

1-Stabilize the patient

2-Treatment of the primary cause

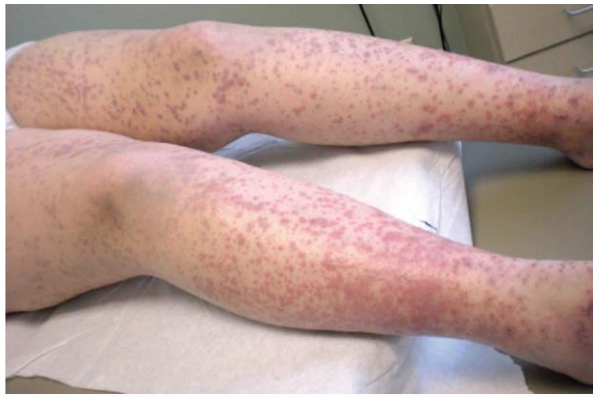
3-Platelets if less than 20.000/mm3

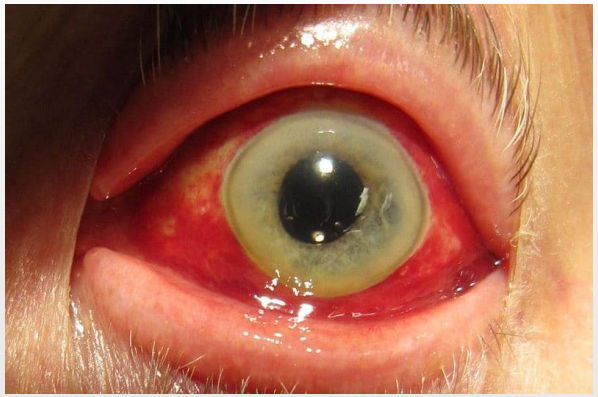
4-Fresh frozen plasma

5-Packed cell transfusion

6-low molecular wt. Heparin ,antithrombin in chronic DIC

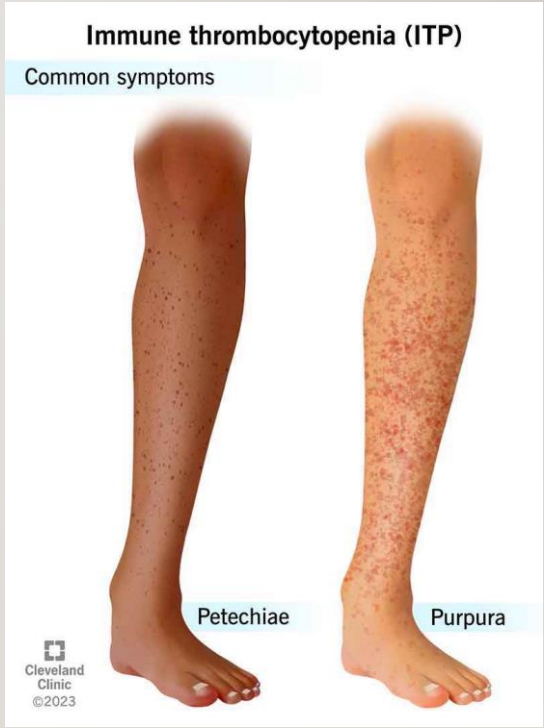
7-Cryoppt in hypofibrinogenemia





MANAGEMENT OF PLATELET DISORDERS

- Immune thrombocytopenia:
- Observation if only cutaneous symptoms AND platelets **≥30,000/mm** (rare in adults)
- Glucocorticoids, IVIG, or anti-D if bleeding or platelets **<30,000/mm^3**



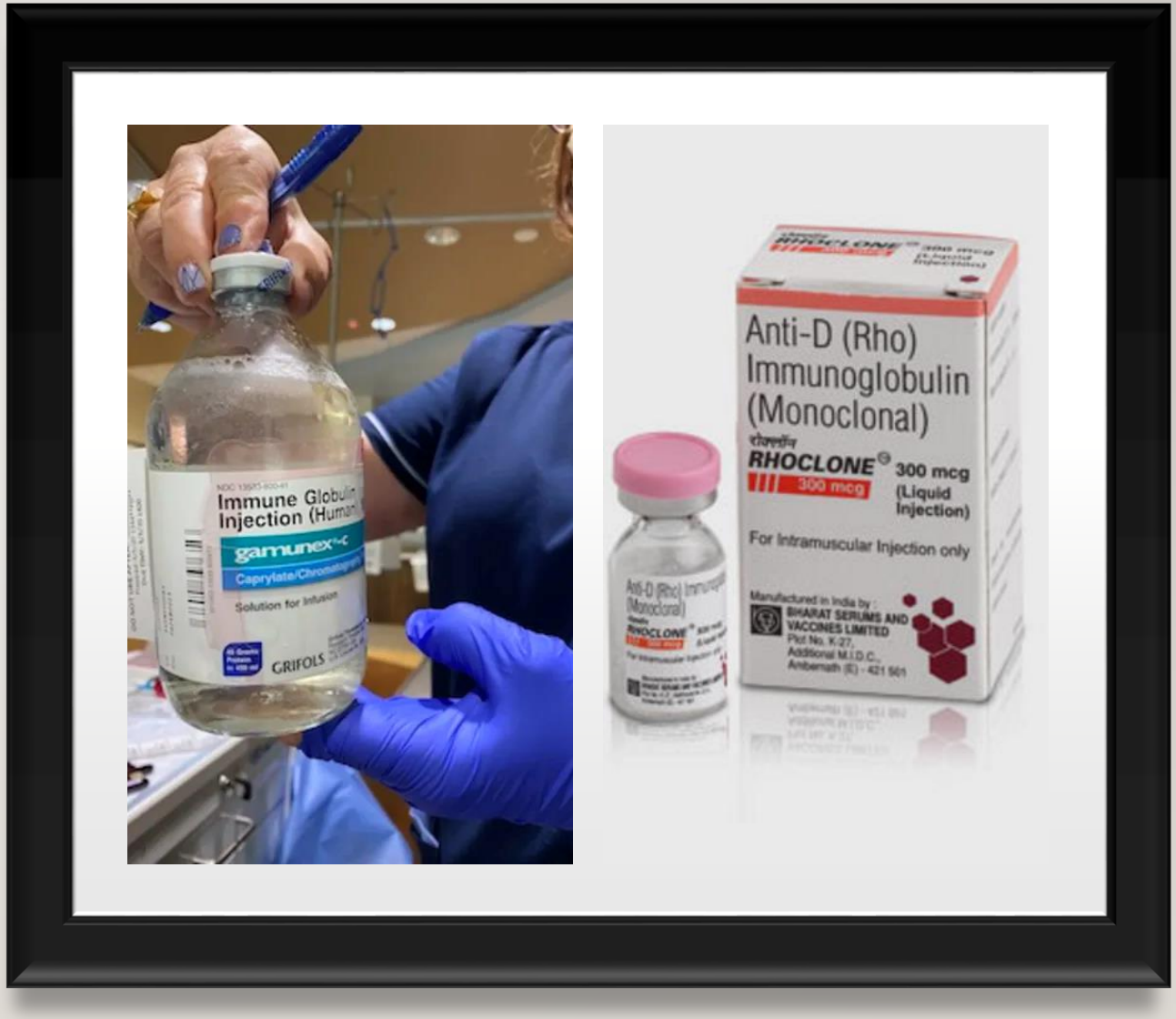
MANAGEMENT OF PLATELET DISORDERS

1- **Glucocorticoids**, either prednisolone (1 mg/kg daily) or dexamethasone (40 mg daily for 4 days), to suppress antibody production and inhibit phagocytosis of sensitised platelets by reticulo-endothelial cells.

2-**IVIG** can raise the platelet count by blocking antibody receptors on reticulo-endothelial cells

3-**Anti-D** therapy appears to inhibit macrophage phagocytosis by a combination of both FcR blockade and inflammatory cytokine inhibition of platelet phagocytosis within the spleen rapidly increasing platelet counts in patients with symptomatic ITP.

- NOTE:Patients aged over 65 years should be considered for a bone marrow examination to look for an accompanying B-cell malignancy and appropriate autoantibody testing performed if a diagnosis of connective tissue disease is suspected



MANAGEMENT OF PLATELET DISORDERS

- Second-line therapies are considered if a patient has two relapses or primary refractory disease;

1-Thrombopoietin receptor agonists (TPO-RA) eltrombopag and romiplostim (which stimulate new platelet formation),

2- the splenic tyrosine kinase inhibitor fostamatinib,

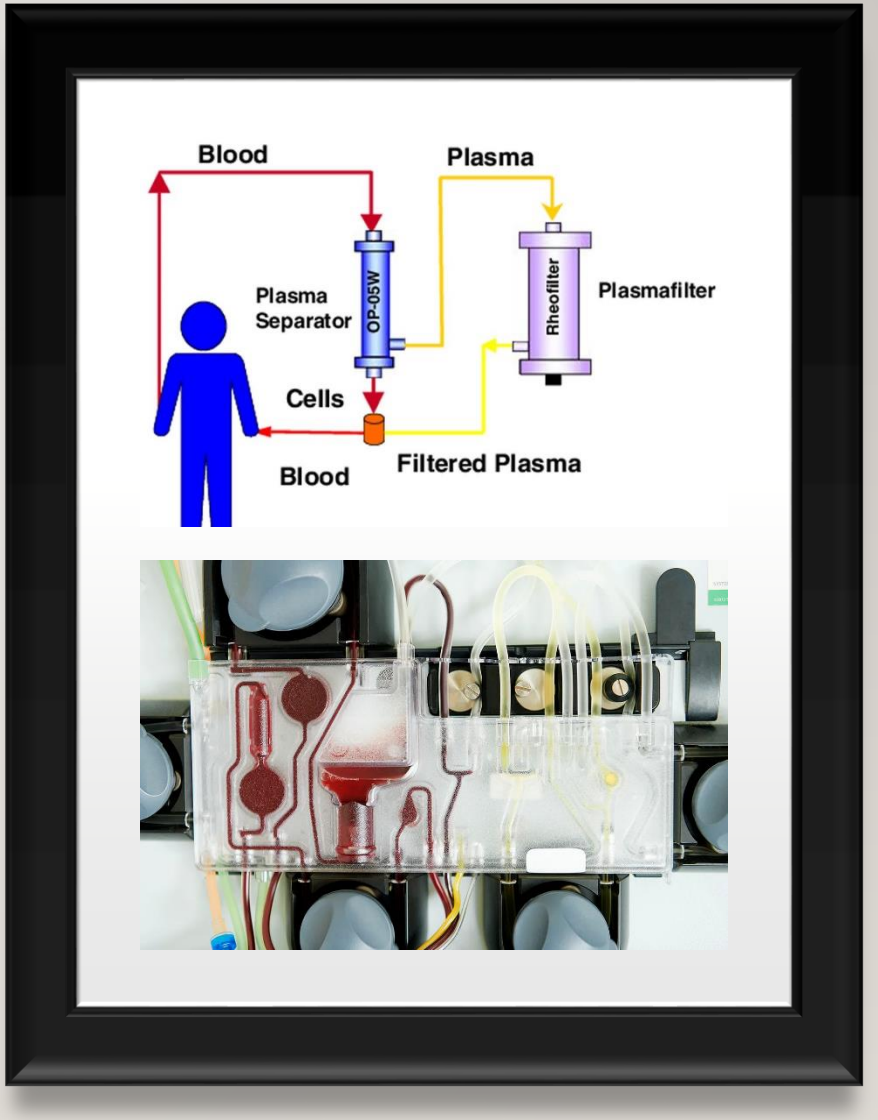
3-splenectomy

4-immunosuppression

- Danazol , Rituximab and vinca alkaloids can also be used

THROMBOTIC THROMBOCYTOPENIC PURPURA:

- Plasma exchange or Fresh frozen plasma (FFP)
- Glucocorticoids
- Rituximab
- Caplacizumab : von Willebrand factor (vWF)-directed antibody fragment



HEMOLYTIC UREMIC SYNDROME:

- TTT is supportive with IVF & possibly blood products.
- Many patients require hemodialysis

Atypical HUS : Disorders in complement regulation

- TTT: eculizumab (terminal complement cascade inhibitor) , plasma exchange transfusion.

Blood transfusion therapy

COMPONENT	DOSAGE EFFECT	CLINICAL USE
Packed RBCs	↑ Hb and O_2 binding (carrying) capacity, ↑ hemoglobin ~1 g/dL per unit, ↑ hematocrit ~3% per unit	Acute blood loss, severe anemia
Platelets	↑ platelet count ~30,000/microL per unit (↑ ~5000/mm^3/unit)	Stop significant bleeding (thrombocytopenia, qualitative platelet defects)
Fresh frozen plasma/ prothrombin complex concentrate	↑ coagulation factor levels; FFP contains all coagulation factors and plasma proteins; PCC generally contains factors II, VII, IX, and X, as well as protein C and S	Cirrhosis, immediate anticoagulation reversal
Cryoprecipitate	Contains fibrinogen, factor VIII, factor XIII, vWF, and fibronectin	Coagulation factor deficiencies involving fibrinogen and factor VIII
Albumin	↑ intravascular volume and oncotic pressure	Post-paracentesis, therapeutic plasmapheresis

Thank you