UNIVERSITATEA DE STAT DE MEDICINĂ ȘI FARMACIE
„NICOLAE TESTEMIȚANU” DIN REPUBLICA MOLDOVA

CHILDHOOD BLEEDING DISORDERS

CLINICAL AND LABORATORY DIAGNOSIS
PRINCIPES OF TREATMENT

Cîrstea Olga, MD, PhD
Associate Professor

Department of Pediatrics

DIANOSTIC APPROACH TO

Pediatric Coagulation Disorders

Objectives

- To describe the physiology of hemostasis in the pediatric patient.
- To list clinical signs and symptoms suggestive of a congenital or acquired bleeding disorder.
- To understand laboratory testing and indications in the diagnosis of a bleeding disorder.

PATHOPHYSIOLOGY OF HEMOSTASIS

- Hemostasis is a complex process that requires a balance between maintaining blood in a fluid state and addressing areas of tissue injury in which a local response is generated at the site of vascular endothelial injury to promote healing and prevent hemorrhage.

- This process requires the interaction of the vascular endothelium, platelets, and coagulation factors.

PATHOPHYSIOLOGY OF HEMOSTASIS

- Diminished or dysfunctional activity of any of the components of the hemostatic system leads to coagulopathy, and different bleeding or thrombotic manifestations depend on the severity or lack of function of a particular hemostatic component.

HEMOSTASIS

- The hemostatic process is initiated at the site of tissue or vascular injury.

- The disrupted vascular endothelial cells, exposed subendothelial connective tissue, and smooth muscle activate their procoagulant properties with the release of von Willebrand factor (vWF), which allows platelet binding (primary hemostasis).

HEMOSTASIS

- Platelets are anucleate discoid cells (normal size 0.5–3.0 mm) that contain granules with procoagulant factors and surface receptors that enable their attachment to the damaged endothelium.

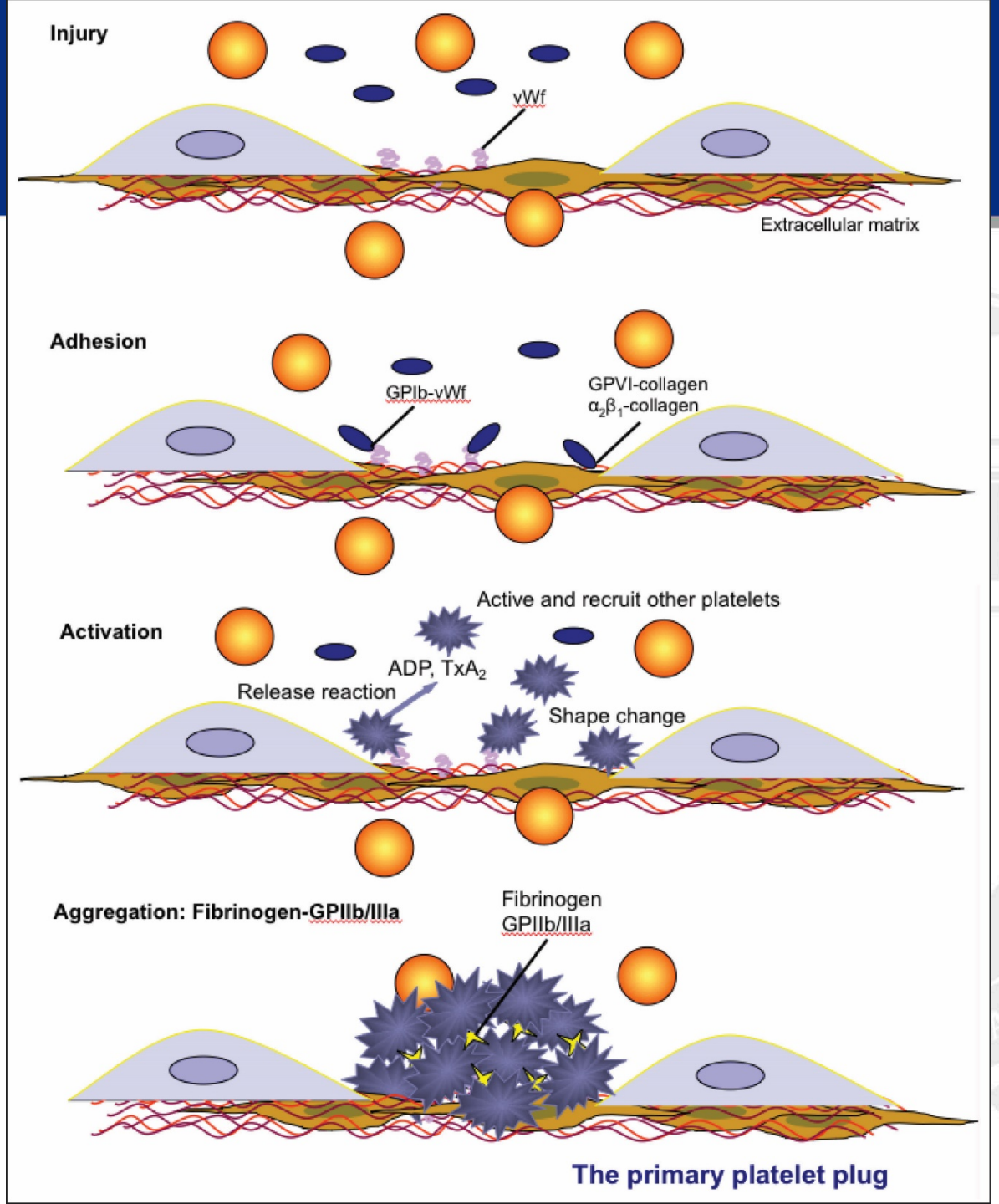
- Three phases traditionally describe platelet activation: **adhesion**, **activation**, and **aggregation**.

- Through adhesion, platelets attach to the damaged endothelium with the help of cell surface receptors (mediated through glycoprotein [GP]Ib-IX-V receptor).

HEMOSTASIS

- Once attached to the endothelium, platelets are activated via intracellular signaling mechanisms, resulting in granule release.

- The released substances constitute chemotactic factors (adenosine diphosphate [ADP] and thromboxane A2) and cofactors for the intrinsic pathway of coagulation cascade and fibrin formation, leading to platelet aggregation (platelet interaction with vWF and platelet-to-platelet binding mediated by GPIIb-IIIa receptor, secondary hemostasis).


Injury
vWf
Extracellular matrix
Adhesion
GPIb-vWf
GPVI-collagen
$\alpha_2\beta_1$-collagen
Activation
Active and recruit other platelets
ADP, TxA_2
Release reaction
Shape change
Aggregation: Fibrinogen-GPIIb/IIIa
Fibrinogen
GPIIb/IIIa
The primary platelet plug

HEMOSTASIS

- Tissue factor binds to factor VII (FVII) (**extrinsic pathway**) and with the help of platelet-derived phospholipids, calcium, further activates factor X (FX).

- FX interacts with factor V (FV), prothrombin, calcium, and phospholipids, ultimately generating thrombin.

- Thrombin can generate further thrombin through activation of the contact factor pathway (**intrinsic pathway**) via positive feedback.

HEMOSTASIS

- Both pathways interact and provide several feedback loops to augment the activity or cause enzymatic activation of several of the coagulation components.

- Both pathways converge in the common pathway, with activation of FX resulting in the conversion of fibrinogen into fibrin, along with factor XIII (FXIII) activation that crosslinks fibrin for better clot stabilization.

NORMAL COAGULATION PATHWAYS

Intrinsic pathway clotting factors

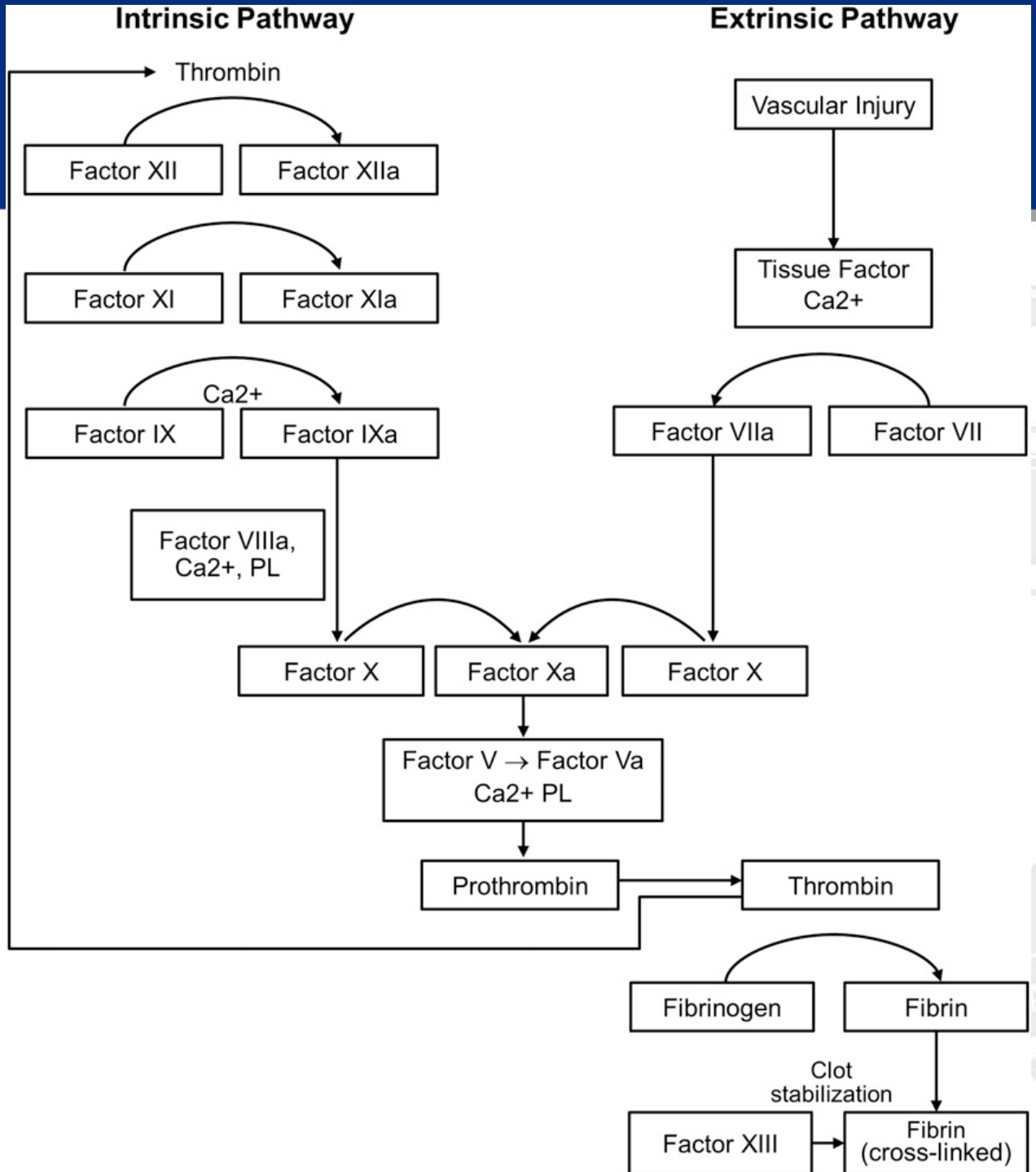
Factor XII
Factor IX
Factor VIII
Factor XI

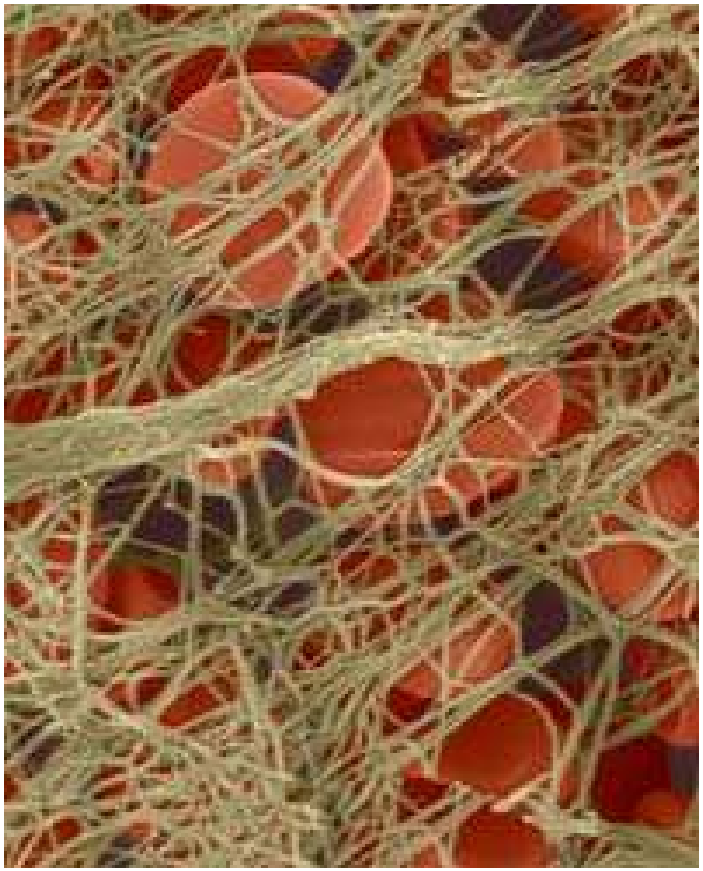
Extrinsic pathway clotting factors

Tissue factor (blood vessel injury exposes TF, normally it is not present in plasma)
Factor VII

Common pathway clotting factors

Factor X
Factor V
Factor II Prothrombin
Factor I Fibrinogen


Intrinsic Pathway
Extrinsic Pathway
Thrombin
Factor XII
Factor XIIa
Factor XI
Factor XIa
Ca2+
Factor IX
Factor IXa
Factor VIIIa, Ca2+, PL
Vascular Injury
Tissue Factor Ca2+
Factor VIIa
Factor VII
Factor X
Factor Xa
Factor X
Factor V → Factor Va Ca2+ PL
Prothrombin
Thrombin
Fibrinogen
Fibrin
Clot stabilization
Factor XIII
Fibrin (cross-linked)



Fibrin

XIIIa

Cross-linked fibrin

HEMOSTASIS

- Several anticoagulant proteins help maintain the blood in a fluid state by neutralizing the activity of thrombin, including antithrombin (AT), heparin cofactor II, and a-2 macroglobulin.
- Protein C, protein S, and thrombomodulin inactivate FV and factor VIII (FVIII) and by their function, inhibit thrombin generation.
- Eventually, fibrinolytic factor plasminogen, when activated to plasmin by plasminogen activators (tissue plasminogen activator, urokinase), acts on the fibrin clot to dissolve it and naturally regulate the coagulation process.

Clotting factor production

Liver: source of plasma clotting factors except VWF

Factor VIII: produced by liver & endothelium

VWF: endothelial cells & megakaryocytes

Vitamin K dependent clotting factors are:

- II
- VII
- IX
- X

IMPORTANT!

- Quantitative or qualitative abnormalities in the activity of procoagulant factors lead to bleeding disorders, while abnormalities in the function and activity of anticoagulant proteins result in an increased risk of thrombosis.

EVALUATION OF A BLEEDING DISORDER

History and Physical Examination

History and Physical Examination

- The best screening test for a bleeding disorder is a comprehensive history and physical examination.

- The primary hindrance to finding such disorders is a lack of surgical challenges or trauma in the pediatric age group that can provide additional clues toward the diagnosis.

History and Physical Examination

- Mild bleeding symptoms, such as epistaxis and easy bruising, are relatively common in children.

- The patient's age, gender, and developmental stage are important to consider when evaluating a possible bleeding disorder.

History and Physical Examination

- The different components of the coagulation system are constantly evolving, and concentrations of coagulation proteins in the pediatric patient might not reach adult reference values until adolescence or adulthood.

- Easy bruising is a common finding in children between ages 1 and 10 years, more frequently over bony prominences such as the forehead, knees, and shins.

History and Physical Examination

- Nonaccidental trauma is always a concern and should be considered in children with unexplained or excessive bleeding symptoms.

- Any type of bleeding in a non-mobile child should be considered to be a bleeding disorder or a result of nonaccidental trauma.

History and Physical Examination

- Factors to consider when evaluating a bleeding disorder are:
  - the age of the patient at the time of the first episode;
  - the site, frequency, and extent of the bleeding;
  - personal history of recurrent unprovoked or spontaneous bleeding;
  - bleeding after surgical or procedural interventions;
  - family history of bleeding;
  - heavy menstrual bleeding in girls.

History and Physical Examination

- Information on the duration must also be sought. This would indicate whether symptoms have been lifelong (since childhood) or of recent onset.

- There should be questions on any childhood history of epistaxis, umbilical stump bleeding, bleeding after circumcision, the answers to any of which would suggest inherited bleeding disorders.

History and Physical Examination

- Any history of blood transfusion or other blood components, as well as a comprehensive review of past medical and surgical history is very important.

- Information on all operations including tooth extractions are to be listed together with any abnormal bleeding during or after surgery or poor wound healing.

History and Physical Examination

- Drug history is of extreme importance since a wide variety of drugs affect hemostasis. The discovery of isolated thrombocytopenia in a patient who is taking several medications is a challenging clinical problem.

- It is very important to distinguish between drug induced thrombocytopenia and idiopathic thrombocytopenic purpura (ITP). In ITP, all other causes of thrombocytopenia must be excluded.

History and Physical Examination

- 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 proper history is vital because the information gathered will ultimately guide the direction and extent of the laboratory evaluation and also help in determining how complications can be managed and prevented.

History and Physical Examination

- A very careful family history is critical. Questions with the four “W's”, **who**, **when**, **where** and **what** are crucial.

1. **Who**: who is the patient, sex, age, race and family history?
2. **When**: when did the bleeding occur, i.e. onset of bleeding? Is it related to drug ingestion or any underlying disorder? Did it develop after surgery or trauma?
3. **Where** : sites of bleeding, skin, muscle etc.
4. **What**: description of the type of bleeding.

History and Physical Examination

- Bleeding symptoms from primary hemostatic defects such as abnormalities of platelets are characterized by easy bruising or petechiae, mucosal bleeding, and bleeding after trauma.

- Defects of secondary hemostasis such as coagulation factor deficiencies cause delayed bleeding after surgery, trauma, deep lacerations, and depending on the degree of coagulation factor deficiency, bleeding into joints, muscles, and soft tissues.

History and Physical Examination

- During the neonatal period, oozing from the umbilical stump, prolonged oozing from heel stick or venipuncture sites, prolonged bleeding from circumcision, large cephalohematoma, and caput succedaneum without a traumatic birth history suggest a congenital bleeding disorder.

- Intracranial hemorrhage in a near-term or term neonate should raise concern about a potential congenital bleeding disorder.

History and Physical Examination

- Other medical disorders that can cause easy bruising or bleeding should be considered.

- Ehlers-Danlos syndrome is a disorder of collagen, and patients typically present with hyperextensible joints and easy/prominent ecchymosis.

- Hemangiomas and hereditary hemorrhagic telangiectasias are vascular disorders that can present with bleeding symptoms, particularly in the airway and gastrointestinal tract.

History and Physical Examination

- A detailed history of medications, nonprescription supplements, and complementary medications should be documented in the history.

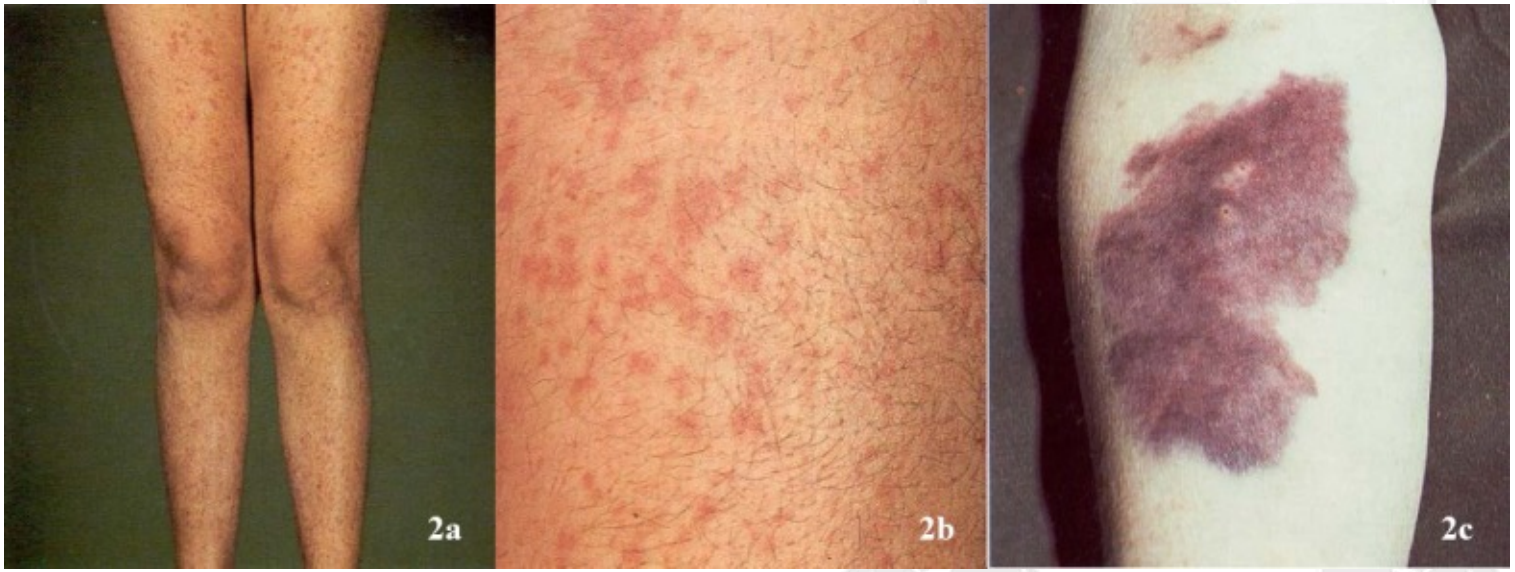
- Some of these can cause acquired coagulation abnormalities, including aspirin, nonsteroidal anti-inflammatory drugs, and Ginkgo biloba extract.

History and Physical Examination

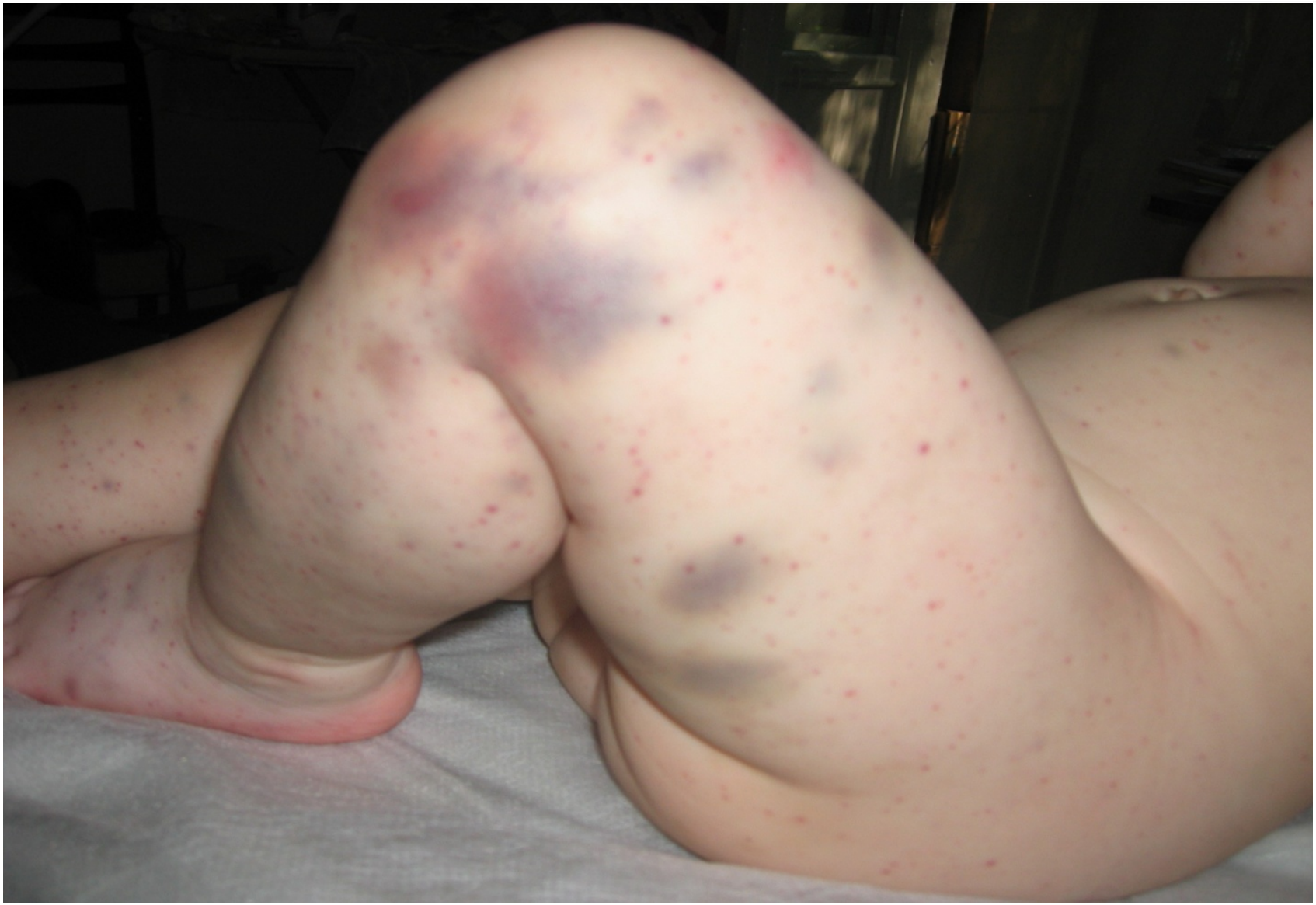
- The history is followed by a careful thorough physical examination to assess the sites and severity of the bleeding and evaluate whether the bleeding is part of a systemic illness, a local anatomical defect or a haemostatic disorder.

- From the clinical assessment, one is able to assess whether:
  - (1) the bleeding is the result of a local anatomic defect or part of a systemic defect in hemostasis,
  - (2) the bleeding is due to a vascular defect, platelet abnormality or coagulation disorder, or
  - (3) the haemostatic defect is inherited or acquired.

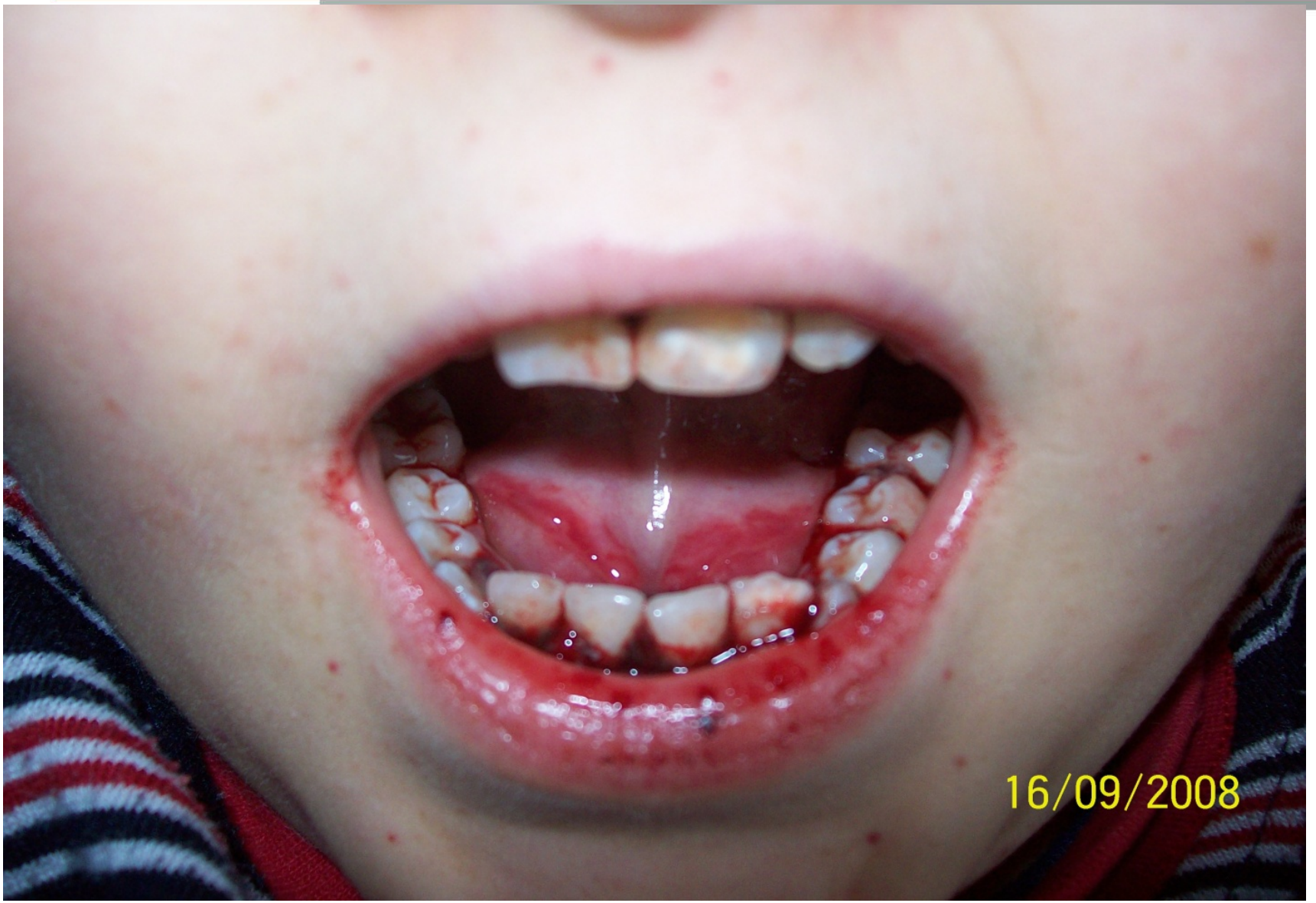
scattered petechiae and purpura and large ecchymosis



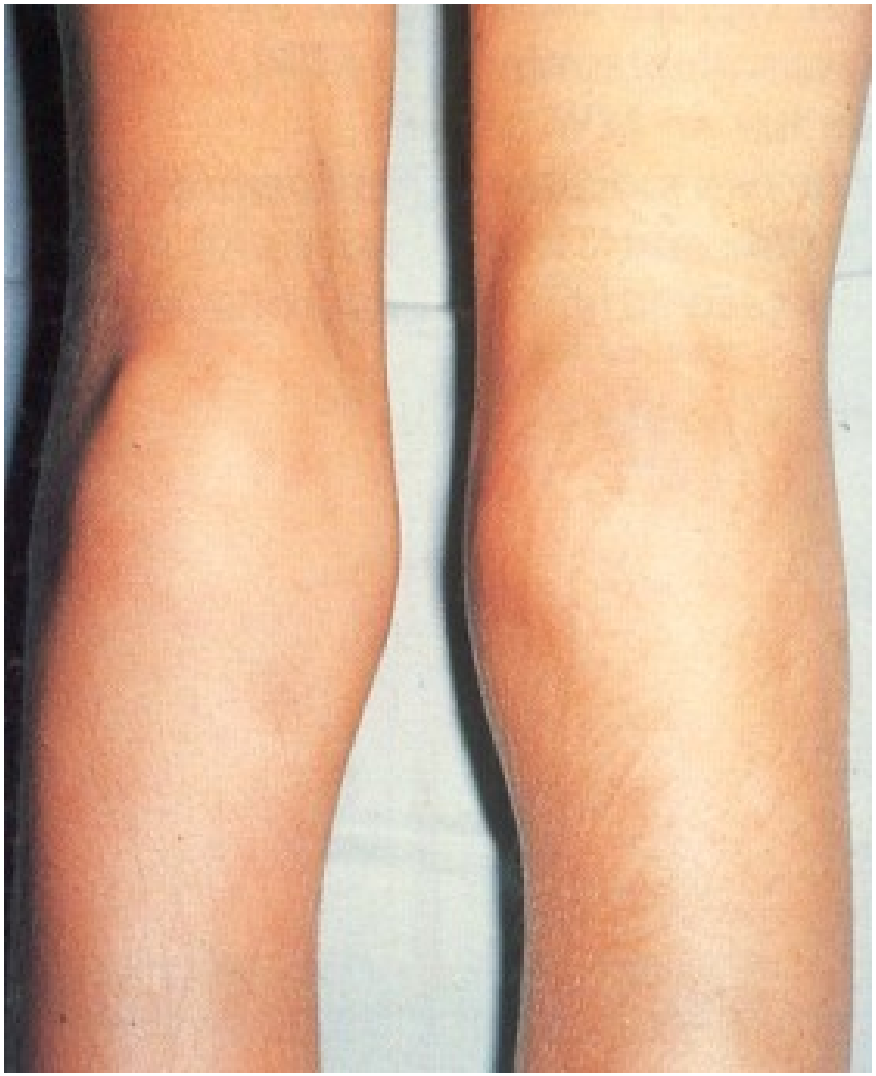
Skin manifestations

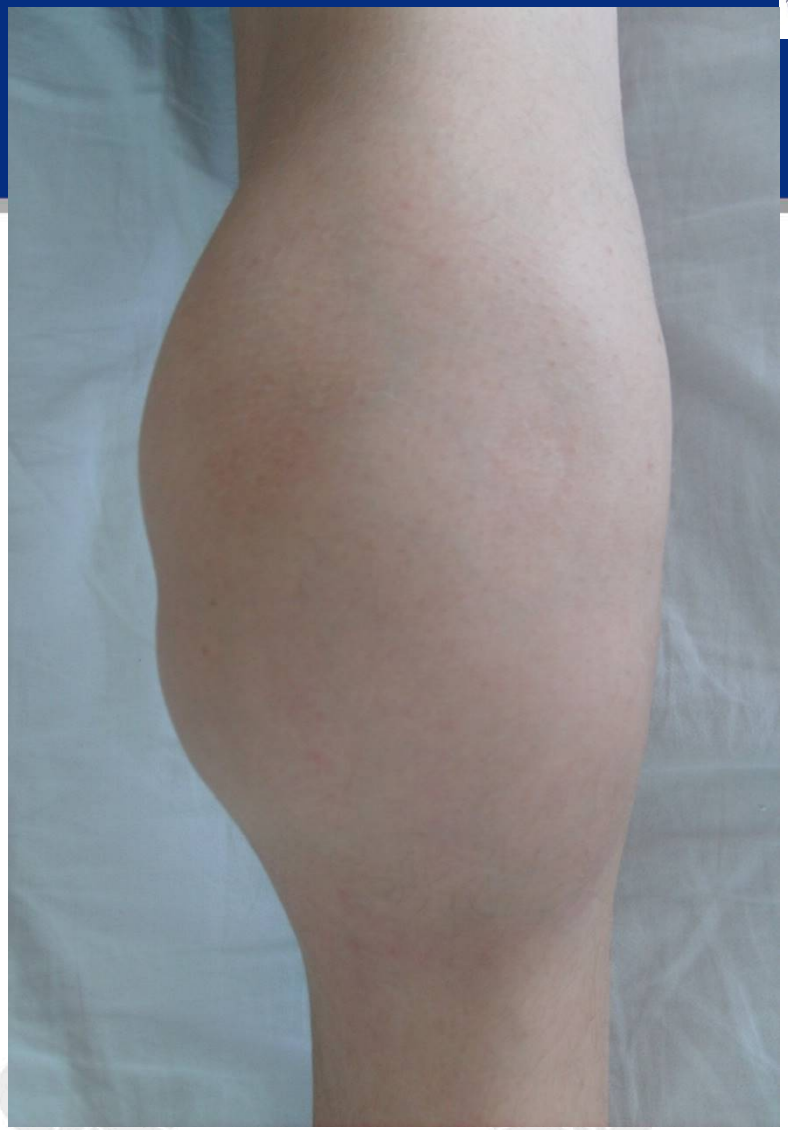


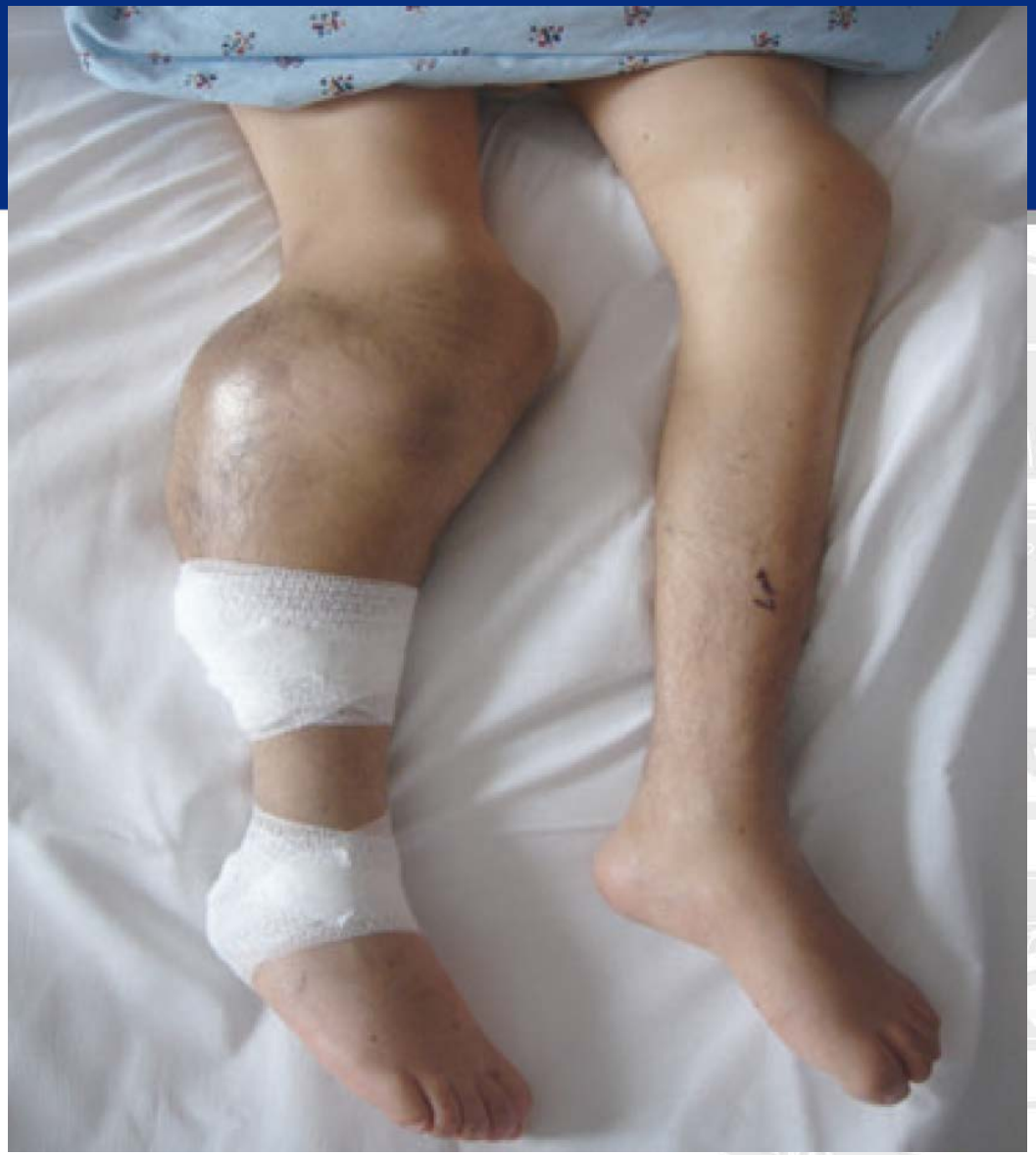
Mucosal bleeding



Hemarthrosis in hemophilia

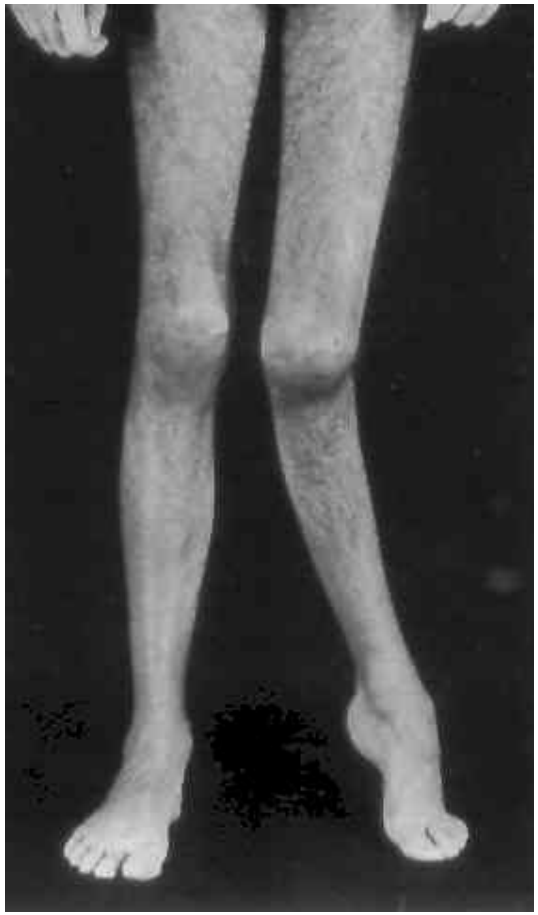


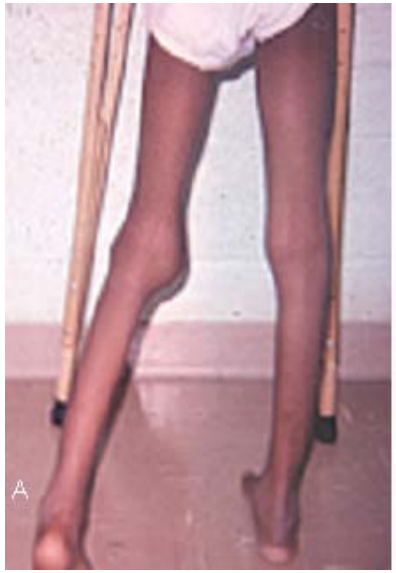


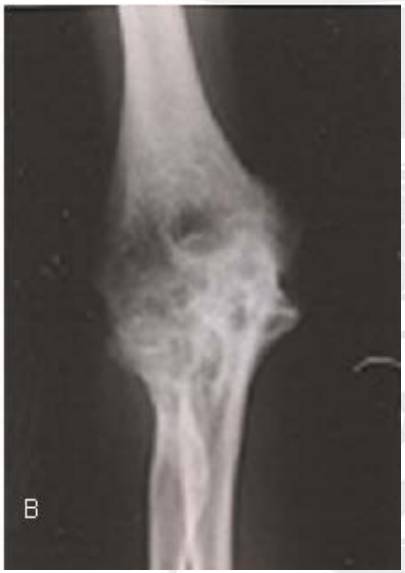


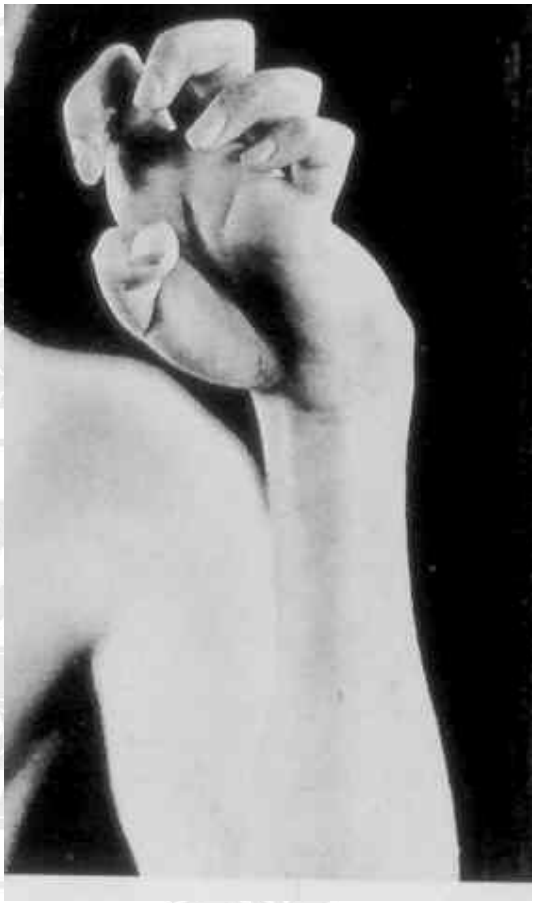
Muscle hematoma (pseudotumor)

LONG-TERM COMPLICATIONS OF HEMOPHILIA





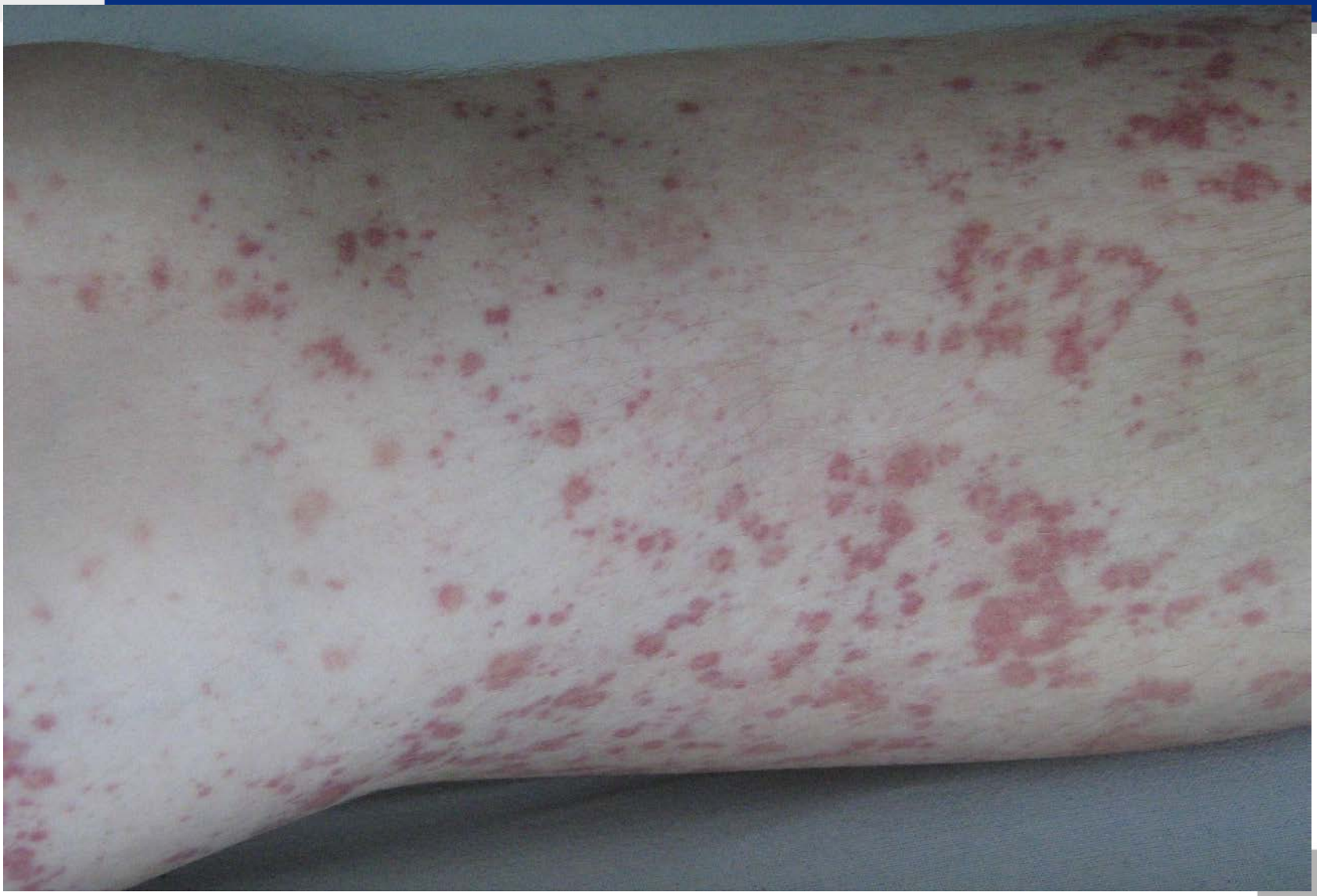




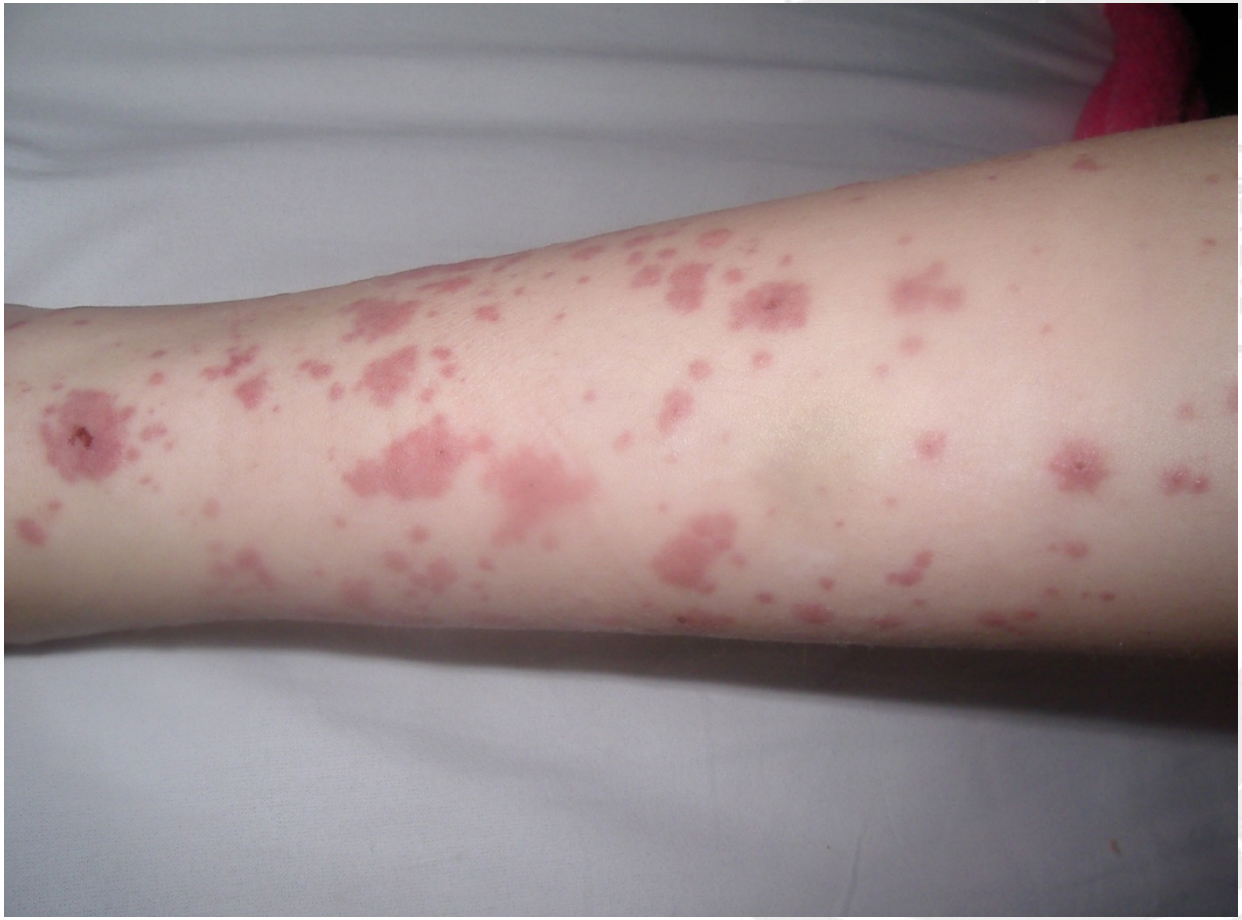
Joint destruction

Nerve damage

Henoch-Schönlein Purpura



Henoch-Schönlein Purpura



EVALUATION OF A BLEEDING DISORDER

Initial Laboratory Evaluation

Initial Laboratory Evaluation

- The initial laboratory evaluation of a child with a suspected bleeding disorder should include:
  - a complete blood cell (CBC) count,
  - peripheral blood smear,
  - prothrombin time (PT),
  - activated partial thromboplastin time (aPTT),
  - fibrinogen,
  - thrombin time,
  - von Willebrand antigen and activity (vWF activity or ristocetin cofactor activity),
  - FVIII and factor IX (FIX).

Initial Laboratory Evaluation

- The CBC count and peripheral blood smear complement each other.

- They not only provide diagnostic evidence of quantitative platelet disorders but can also assist in the evaluation of white cell and platelet morphology that can offer clues toward the diagnosis of congenital platelet disorders (eg, Döhle bodies in white cells and large platelets in May-Hegglin anomaly) or confirm the diagnosis of a malignant disorder such as leukemia.

Initial Laboratory Evaluation

- Morphologic evaluation of red cells can exclude disorders such as a microangiopathic process that can lead to fragmented red blood cells and thrombocytopenia (eg, hemolytic-uremic syndrome/thrombotic thrombocytopenia purpura).

Initial Laboratory Evaluation

- Prolongation of PT and aPTT in an asymptomatic child may be due to several factors.

- A common cause of prolonged clotting times is error in obtaining an adequate amount of blood or delay in processing the blood samples.

Initial Laboratory Evaluation

- Lupus anticoagulants (LA) are often present in children after viral infections and can prolong phospholipid-dependent assays such as PT and aPTT without any bleeding consequences.

- LA cause thrombosis most commonly in patients with autoimmune disorder. In rare instances, LA can cause acquired prothrombin deficiency.

Platelet tests

- Test platelet phase: evaluation of platelet function
- Normal (140,000 to 400,000/mm3)
- Thrombocytopenia : <140,000/mm3
- Clinical bleeding problem : <50,000/mm3
- Spontaneous bleeding with life threatening : <20,000/mm3

Platelet tests

Test	Comment
Mean platelet volume (MPV)	Some analyzers provide MPV measurement; in healthy individuals, MPV varies inversely with platelet count
Platelet aggregation and secretion tests	Not routine tests, used only in special circumstances

Activated PTT (aPTT)

- The APTT is a test of the integrity of the intrinsic and common pathways of coagulation.
- The *in vitro* clotting time is measured after addition to plasma of calcium and the APTT reagent, which contains phospholipid (a platelet substitute, also called 'partial thromboplastin' as it lacks tissue factor), and an intrinsic pathway activator e.g. kaolin.
- The APTT should be designed to detect bleeding disorders due to deficiencies of factors VIII, IX, and XI and inhibitors of the intrinsic and common pathway factors (including lupus anticoagulant and therapeutic anticoagulants).
- Inevitably, it also detects deficiency of factor XII.

Activated PTT (aPTT)

- Activated by contact activator (kaolin)
- Tests intrinsic and common pathway
- Normal (25-35 sec)
- Heparin therapy- PTT in 50-65 sec range by promote AT III

PT (Prothrombin Time)

- The PT assesses the integrity of the extrinsic and common pathways.
- The *in vitro* clotting time is measured after addition of the PT reagent, which contains thromboplastin (phospholipids with tissue factor) and calcium to citrated plasma.
- PT prolongation should detect important deficiencies (or rarely inhibitors) of factors II, V, VII and X.
- Its main use is for anticoagulant monitoring and detection of acquired bleeding disorders (especially disseminated intravascular coagulation, liver disease and vitamin K deficiency).

PT (Prothrombin Time)

- Activated by tissue thromboplastin
- Tests extrinsic (factor VII) and common (I,II,V,X) pathways
- Normal (11-15 sec)
- Coumarin therapy- PT at 1.5 to 2.5 time

PT (Prothrombin Time)

- International normalized ratio (INR): the ratio of a patient's prothrombin time to a normal (control) sample, raised to the power of the ISI value for the analytical system used.

(1) surgery can be done under INR< 3.0

(2) when INR=3.0-3.5, consultation is needed

(3) delay surgery when INR>3.5

TT (Thrombin Time)

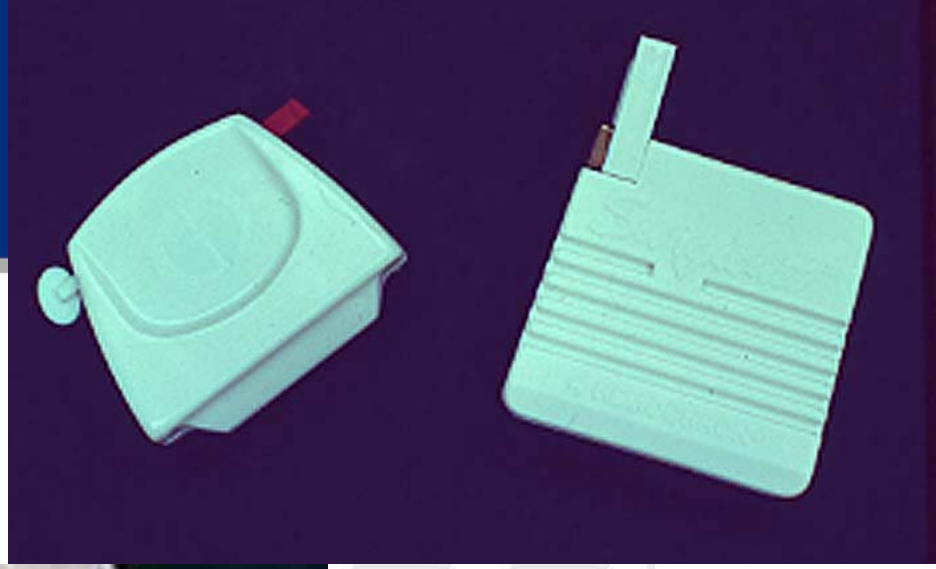
- Activated by thrombin
- Tests ability to form initial clot from fibrinogen
- Normal (9 to 13 seconds)

Skin bleeding time

- This is the only *in vivo* haemostasis test available.

- It is used to test for defects of platelet-vessel wall interaction and should detect inherited or acquired disorders of platelet function, von Willebrand disease (VWD) and abnormalities of vessel wall integrity.

Bleeding Time



Skin bleeding time

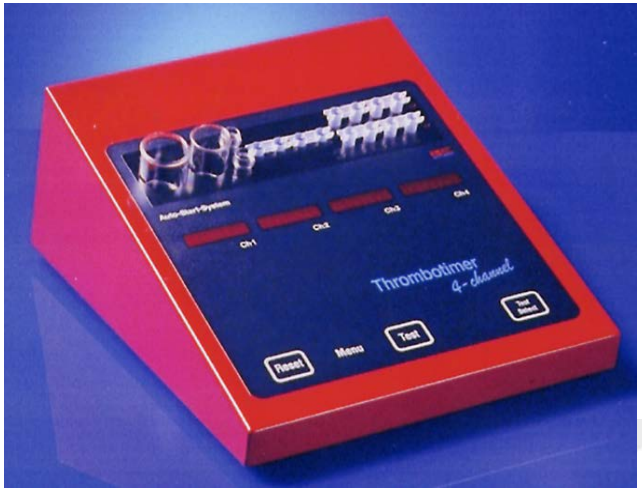
- Duke (1910) on earlobes
- Ivy (1941) on arm with 1mm x 3mm incision
- Mielke (1969) with 1mm x 10mm template
- 1980's: disposable devices (e.g., Simplate, Surgicutt)

BT (Ivy method)

- Test platelet & vascular phase
- Normal if adequate number of platelets of good quality present intact vascular walls
- Normal (1 to 6 minutes)

Other tests

- A number of tests designed to better reflect primary haemostasis and global haemostatic mechanisms have been developed.
- These include the platelet function analyser-100 (PFA-100), the thrombelastogram and measures of endogenous thrombin potential.



Tests, Associated Abnormalities, and Differential Diagnosis

LABORATORY FINDING	DIFFERENTIAL DIAGNOSIS
PT abnormal, aPTT normal	• FVII deficiency
aPTT abnormal, PT normal	• FVIII, FIX, FXI, FXII deficiency; • high-molecular weight kininogen, prekallikrein, or kallikrein deficiency; • severe vWD; • heparin effect
PT and aPTT abnormal	• FI, FII, FV, combined FV/FVIII, or FX deficiency • vitamin K coagulation factor deficiency
No abnormalities in PT and aPTT	• FXIII, FVIII, or FIX (mild deficiencies); • fibrinolytic disorders (α-2 antiplasmin deficiency, • plasminogen activator inhibitor deficiency); • platelet function disorders

Tests, Associated Abnormalities, and Differential Diagnosis

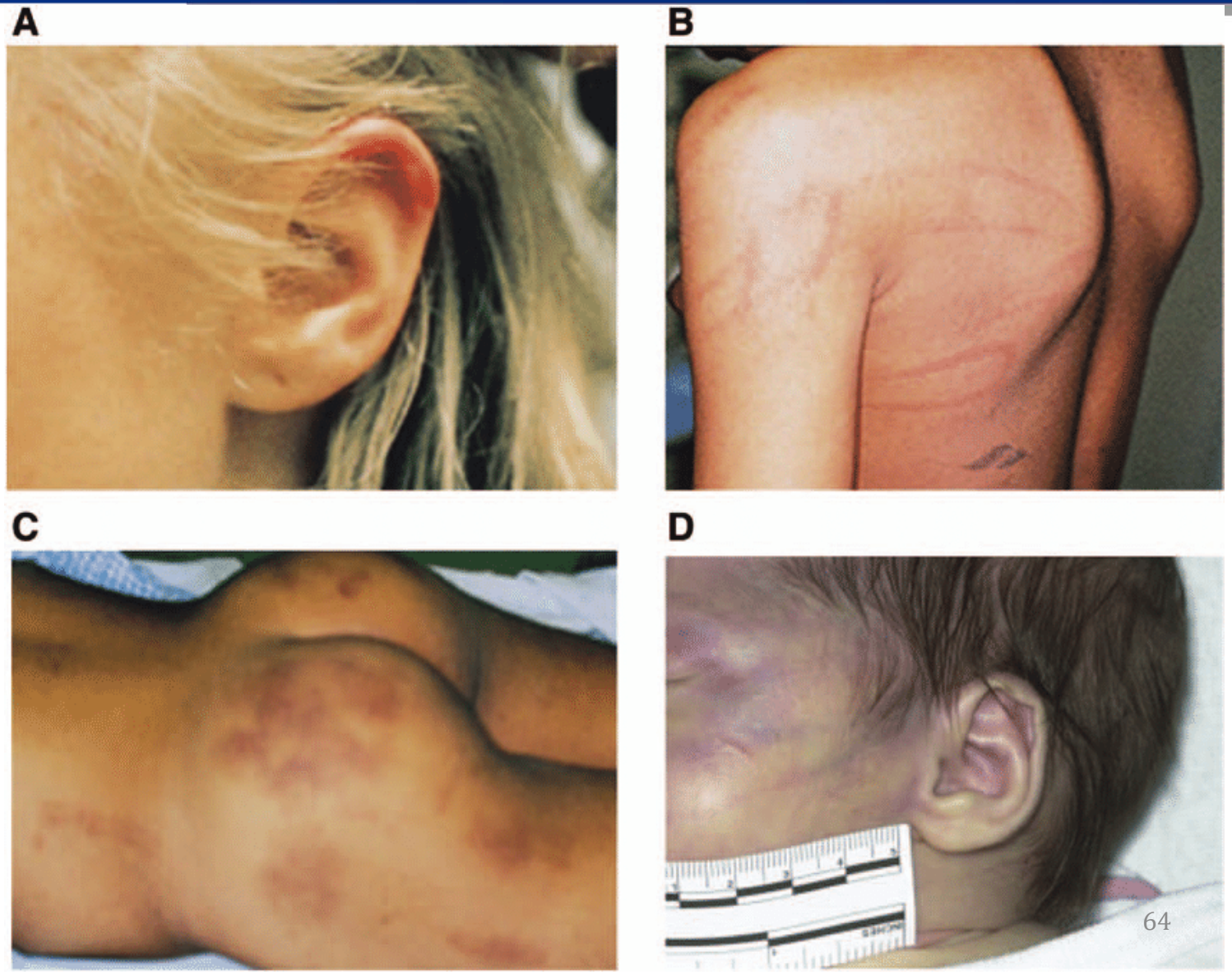
LABORATORY FINDING	DIFFERENTIAL DIAGNOSIS
PT and aPTT prolonged with prolonged TT	• afibrinogenemia, • dysfibrinogenemia, • DIC, • heparin effect
PT and aPTT prolonged with normal TT	• liver disease; • vitamin K deficiency; • FII, FV, FX deficiency; • DIC; • lupus anticoagulant; • warfarin effect
Platelet count low	• idiopathic thrombocytopenic purpura, • hereditary platelet disorder, • bone marrow failure syndrome
Platelet function analysis (abnormal platelet function analysis)	• vWD, • platelet disorder (hereditary or acquired)

Nonaccidental Trauma

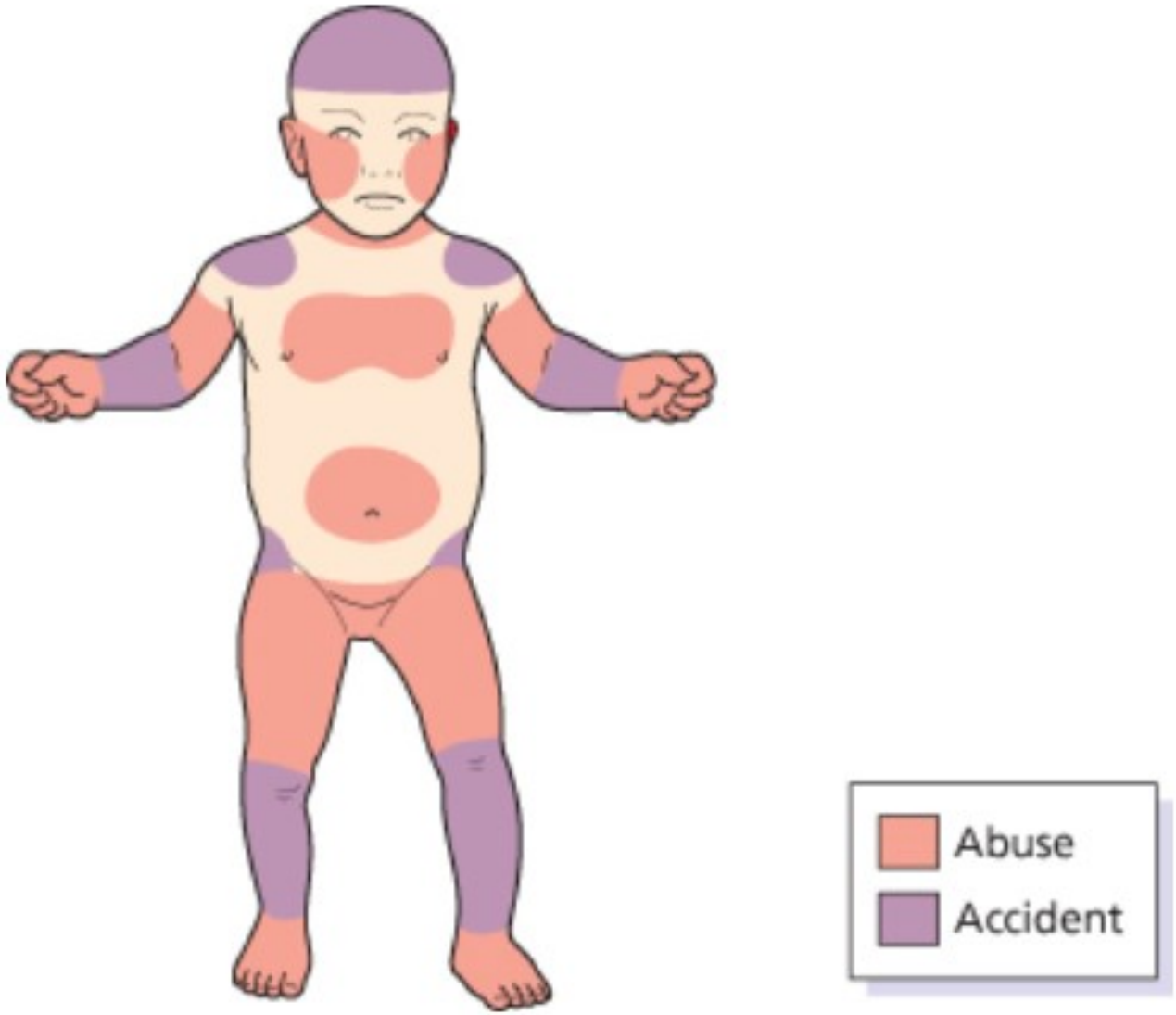
- If bleeding or bruising raises concern for nonaccidental trauma, careful history, physical examination, and detailed description of physical findings are warranted.

- Bruises in areas less prone to trauma, such as the face, ears, neck, upper arms, trunk, hands, genitalia, buttocks, and anterior and medial thighs, as well as the pattern of bruises (eg, hand marks, bite marks, object marks, bruises in clusters, or large cumulative bruises) should raise concern for **child abuse**.

Nonaccidental Trauma



Nonaccidental Trauma



Nonaccidental Trauma

- Laboratory evaluations need to be undertaken but with the understanding that the presence of a bleeding disorder or coagulation abnormality does not rule out abuse or nonaccidental trauma as an explanation for recurrent bruising or bleeding.

- If the history and physical findings disclose or provide a clear explanation for the easy bruising or bleeding, a bleeding disorder evaluation might not be needed.

Nonaccidental Trauma

- However, in the absence of a clear explanation or findings on physical examination such as petechiae or bruising in areas of pressure to the skin (eg, bruising on the chest in areas where infant's seat fasteners-belts are applied or areas of clothing pressure), evaluation for a bleeding disorder should be considered.

- If the child presents with intracranial hemorrhage, a disseminated intravascular coagulation (DIC) panel (d-dimer and fibrinogen) in addition to the previously mentioned coagulation laboratory tests should be obtained.

PRIMARY HEMOSTASIS DISORDERS

IDIOPATHIC THROMBOCYTOPENIC PURPURA - General considerations

- most patients recover spontaneously within a few months.

- in 10–20% - chronic ITP (> 6 months' duration)

ITP - General considerations

- The thrombocytopenia results from clearance of circulating IgM- or IgG-coated platelets by the reticuloendothelial system.

- The spleen plays a predominant role in the disease by forming the platelet cross-reactive antibodies and sequestering the antibody-bound platelets.

Symptoms and Signs

- Onset of ITP is usually acute, with the appearance of multiple petechiae and ecchymoses.

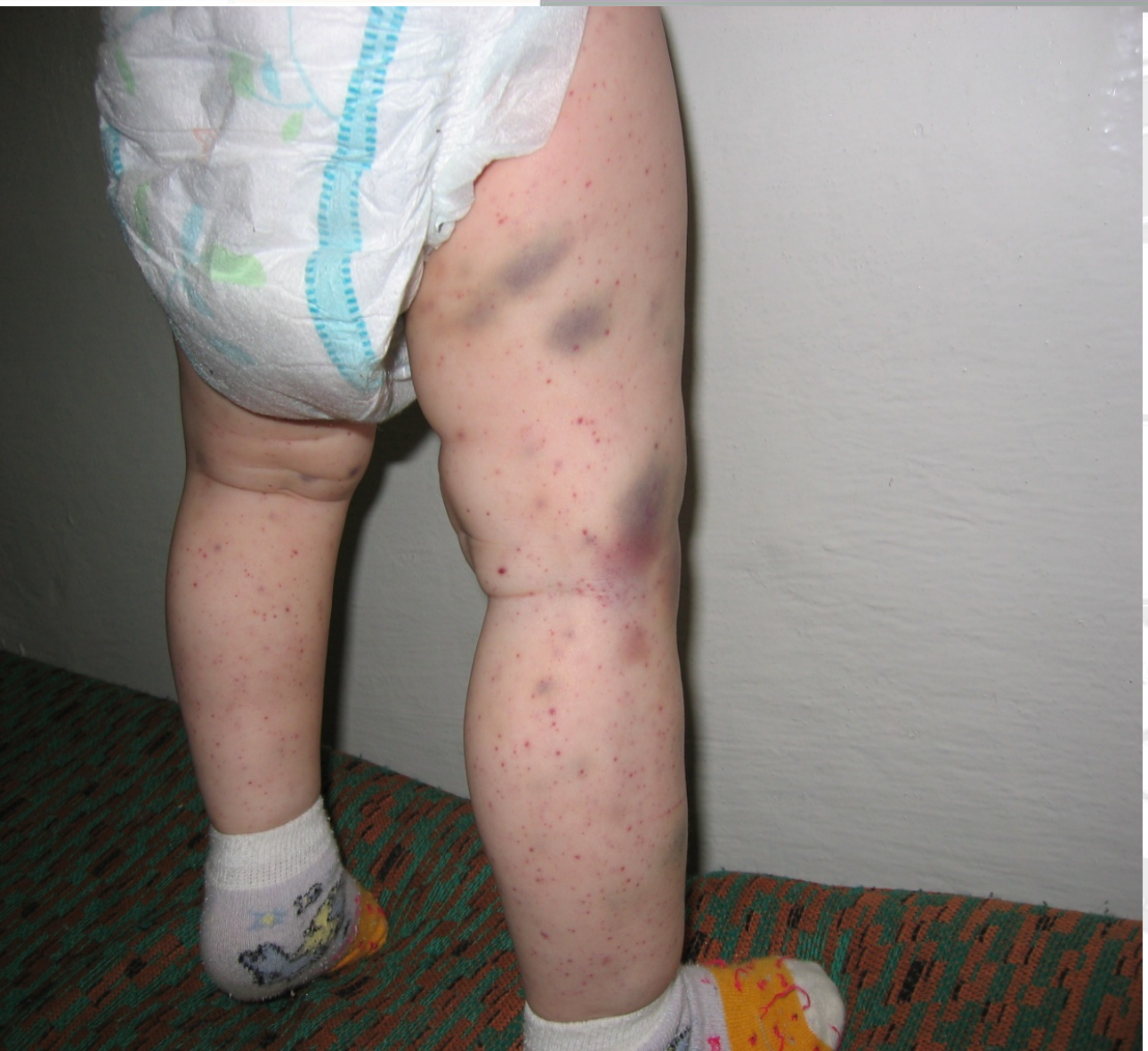
- Epistaxis is also common at presentation.

Symptoms and Signs

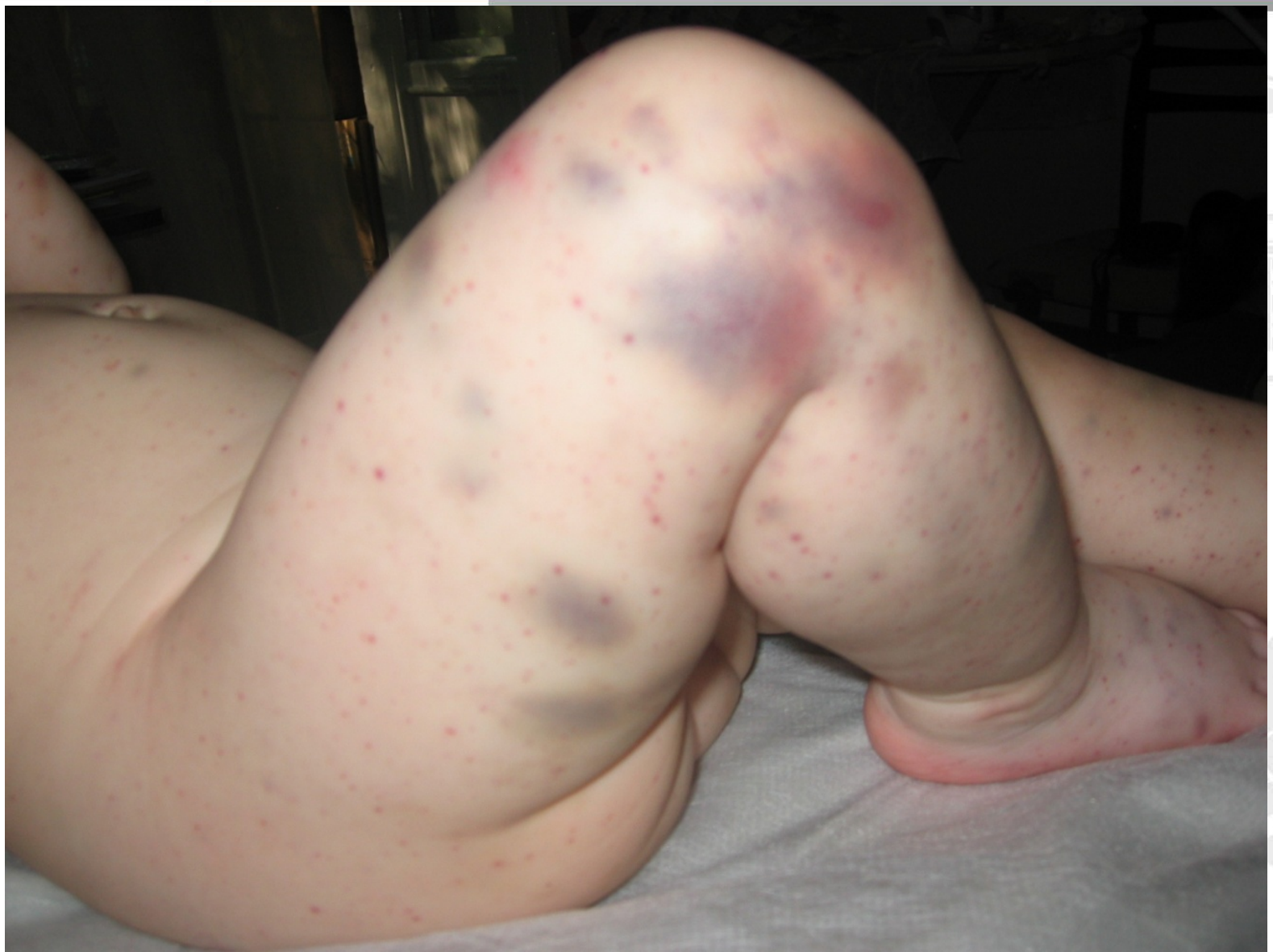
- No other physical findings are usually present.

- Rarely, concurrent infection with EBV or CMV may cause hepatosplenomegaly or lymphadenopathy, simulating acute leukemia.

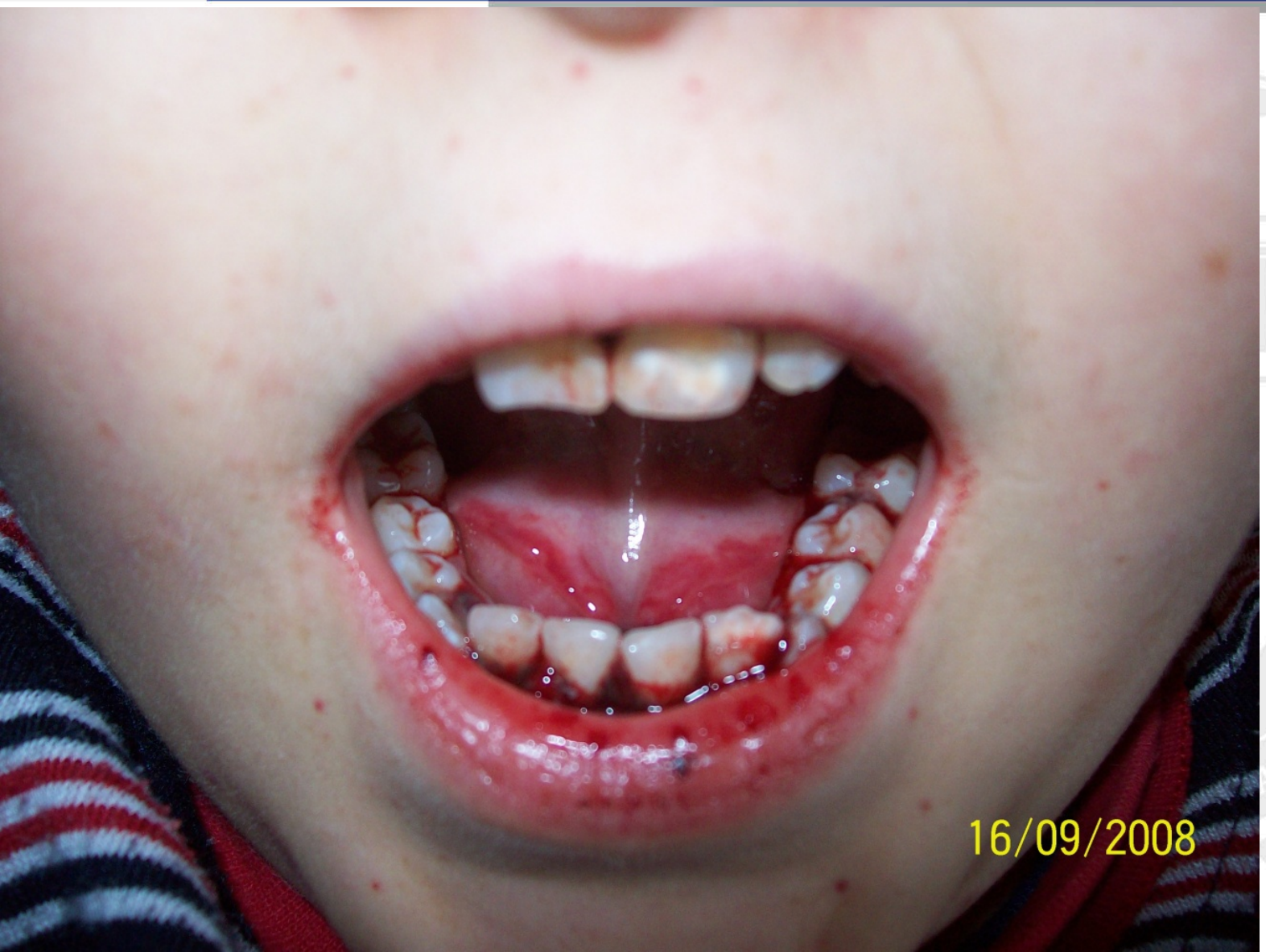
Idiopathic Thrombocytopenic Purpura



Idiopathic Thrombocytopenic Purpura



Idiopathic Thrombocytopenic Purpura



Laboratory Findings

- the platelet count is markedly reduced (usually <50,000/μL and often <10,000/μL)

- platelets frequently are of larger size on peripheral blood smear, suggesting accelerated production of new platelets

Laboratory Findings

- the white blood count and differential are normal
- the hemoglobin concentration is preserved unless hemorrhage has been significant
- Bone Marrow - the number of megakaryocytes is increased; erythroid and myeloid cellularity is normal

Laboratory Findings

- Other Laboratory Tests:

- platelet-associated IgG or IgM, or both, may be demonstrated on the patient's platelets or in the serum.

- PT and aPTT are normal.

Differential Diagnosis

Increased Turnover			Decreased Production	
Antibody-Mediated	**Coagulopathy**	**Other**	**Congenital**	**Acquired**
Idiopathic thrombocytopenic purpura	Disseminated intravascular coagulopathy	Hemolytic-uremic syndrome	Fanconi anemia	Aplastic anemia
Infection	Sepsis	Thrombotic thrombocytopenic purpura	Wiskott-Aldrich syndrome	Leukemia and other malignancies
Immunologic diseases	Necrotizing enterocolitis	Hypersplenism	Thrombocytopenia with absent radii	Vitamin B12 and folate deficiencies
	Thrombosis	Respiratory distress syndrome	Metabolic disorders	
	Cavernous hemangioma	Wiskott-Aldrich syndrome	Osteopetrosis	

- ITP is a diagnosis of exclusion

- Family history or the finding of predominantly giant platelets on the peripheral blood smear is helpful in determining whether thrombocytopenia is hereditary

- Bone marrow examination should be performed if

  ✓ the history is atypical (ie, the child is not otherwise healthy, or if there is a family history of bleeding)

  ✓ abnormalities other than purpura and petechiae are present on physical examination, or

  ✓ other cell lines are affected on the CBC

Complications

- Severe hemorrhage and bleeding into vital organs are the feared complications of ITP.
- Intracranial hemorrhage is the most serious (but rarely seen) complication, occurring in less than 1% of affected children.
- The most important risk factors for hemorrhage are a platelet count less than 10,000/μL and mean platelet volume less than 8 fL.

Treatment

- Treatment is optional in most children in the absence of bleeding.
- Aspirin and other medications that compromise platelet function should be avoided.
- Bleeding precautions (eg, restriction from physical contact activities and use of helmets) should be observed.

Treatment

- Platelet transfusion should be avoided except in circumstances of life-threatening bleeding, in which case emergent splenectomy is to be pursued.

- In this setting, administration of corticosteroids and IVIG is also advisable.

Corticosteroids

- Patients with clinically significant but non–life-threatening bleeding (ie, epistaxis, hematuria, and hematochezia) and those with a platelet count of less than 10,000/µL may benefit from prednisone at 2–4 mg/kg orally per day for 3–5 days, decreasing to 1–2 mg/kg/d for a total of 14 days.

- The dosage is then tapered and stopped.

Corticosteroids

- No further prednisone is given regardless of the platelet count unless significant bleeding recurs, at which time prednisone is administered in the smallest dose that achieves resolution of bleeding episodes (usually 2.5–5 mg twice daily).

- Follow-up continues until the steroid can again be discontinued, spontaneous remission occurs, or other therapeutic measures are instituted.

Intravenous Immunoglobulin (IVIG)

- IVIG is the treatment of choice for severe, acute bleeding, and may also be used as an alternative or adjunct to corticosteroid treatment in both acute and chronic ITP of childhood.

- IVIG may be effective even when the patient is resistant to corticosteroids; responses are prompt and may last for several weeks.

Intravenous Immunoglobulin (IVIG)

- Most patients receive 1 g/kg/d for 1–3 days. Infusion time is typically 4–6 hours.

- Platelets may be given simultaneously during life-threatening hemorrhage but are rapidly destroyed.

Intravenous Immunoglobulin (IVIG)

- Adverse effects of IVIG are common, including transient neurologic complications (eg, headache, nausea, and aseptic meningitis) in one-third of patients.
- These symptoms may mimic those of intracranial hemorrhage and necessitate radiologic evaluation of the brain.
- A transient decrease in neutrophil number may also be seen.

Splenectomy

- Many children with chronic ITP have platelet counts greater than 30,000/μL.
- Up to 70% of such children spontaneously recover with a platelet count greater than 100,000/μL within 1 year.

Splenectomy

- Splenectomy produces a response in 70–90%, but it should be considered only after persistence of significant thrombocytopenia for at least 1 year.

- Preoperative treatment with corticosteroids, IVIG, or anti-D immunoglobulin is usually indicated.

Splenectomy

- Postoperatively, the platelet count may rise to 1 million per microliter, but is not often associated with thrombotic complications in the pediatric age group.

- The risk of overwhelming infection (predominantly with encapsulated organisms) is increased after splenectomy, particularly in the young child. Therefore, the procedure should be postponed, if possible, until age 5 years.

Splenectomy

- Administration of pneumococcal and *H. influenzae type b* vaccines at least 2 weeks prior to splenectomy is recommended. Meningococcal vaccine, although controversial, may be considered.

- Penicillin prophylaxis should be started postoperatively and continued for 1–3 years.

Prognosis

- Ninety percent of children with ITP will have a spontaneous remission.

- Features associated with the development of chronic ITP include female gender, age greater than 10 years at presentation, insidious onset of bruising, and the presence of other autoantibodies.

Prognosis

- Older child- and adolescent-onset ITP is associated with an increased risk of chronic autoimmune diseases or immunodeficiency states.

- Appropriate screening by history and laboratory studies (eg, antinuclear antibody) is warranted.

Thrombotic Thrombocytopenic Purpura (TTP)

- Disorder of systemic platelet aggregation in microvasculature
- Stimulus: unusually large vWf
- Deficiency in vWf metalloproteinase to break down vWf
- Low PLT count, intravascular hemolysis, RBC fragmentation, high LDH

Qualitative Platelet Disorders

- Berhard-Soulier: GP-Ib deficiency, adhesion problem
- Von Willebrand's: vWF deficiency, adhesion problem
- Glanzmann's thrombasthenia: GP-IIb/IIIa deficiency, aggregation problem -- cannot bind vWF and Fib
- Storage pool disease: dense body defect, secretion problem

Qualitative Platelet Disorders

- Individuals with platelet function defects typically develop skin and mucosal bleeding similar to that occurring in persons with thrombocytopenia.

- Historically, platelet function has been screened by measuring the bleeding time.

- If this is prolonged, in-vitro platelet aggregation is studied using agonists, such as adenosine diphosphate, collagen, arachidonic acid, and ristocetin, and simultaneous comparison with a normal control subject.

Qualitative Platelet Disorders

- While labor-intensive, platelet aggregometry remains important in selected clinical situations.

- The PFA-100 has become available to evaluate platelet dysfunction and vWD, and has replaced the template bleeding time in many clinical laboratories.

Qualitative Platelet Disorders

- Platelet dysfunction may be inherited or acquired, with the latter being more common.

- Acquired disorders of platelet function may occur secondary to uremia, cirrhosis, sepsis, myeloproliferative disorders, congenital heart disease, and viral infections.

Qualitative Platelet Disorders

- Many pharmacologic agents decrease platelet function.
- The most common offending agents in the pediatric population are aspirin and other NSAIDs, synthetic penicillins, and valproic acid.
- In acquired platelet dysfunction, the PFA-100 closure time is typically prolonged with collagen-epinephrine, but normal with collagen-ADP.

Qualitative Platelet Disorders

- The inherited disorders are due to defects in platelet-vessel interaction, platelet-platelet interaction, platelet granule content or release (including defects of signal transduction), thromboxane and arachidonic acid pathway, and platelet-procoagulant protein interaction.

Qualitative Platelet Disorders

- Individuals with hereditary platelet dysfunction generally have a prolonged bleeding time with normal platelet number and morphology by light microscopy.

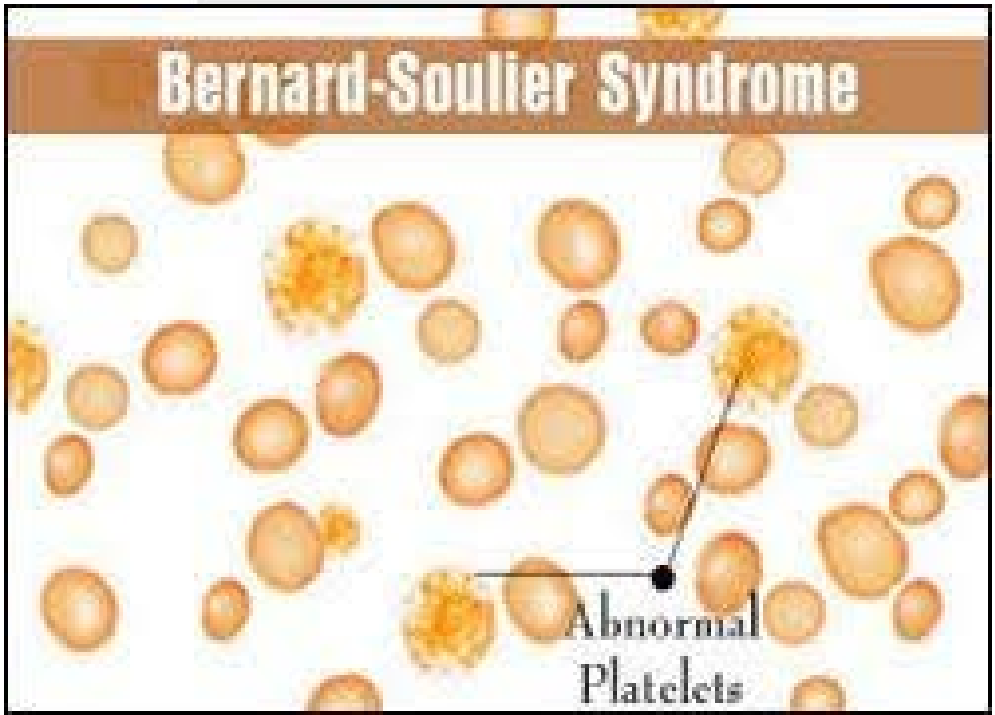
- PFA-100 closure time, in contrast to that in acquired dysfunction, is typically prolonged with both collagen-ADP and collagen-epinephrine.

Qualitative Platelet Disorders – Bernard-Soulier syndrome

- Congenital causes of defective platelet–vessel wall interaction include **Bernard-Soulier syndrome**.
- This condition is characterized by increased platelet size and decreased platelet number.

Bernard-Soulier Syndrome

- The molecular defect in this autosomal recessive disorder is a deficiency or dysfunction of glycoprotein Ib-V-IX complex on the platelet surface resulting in impaired von Willebrand factor (vWF) binding, and hence, impaired platelet adhesion to the vascular endothelium.

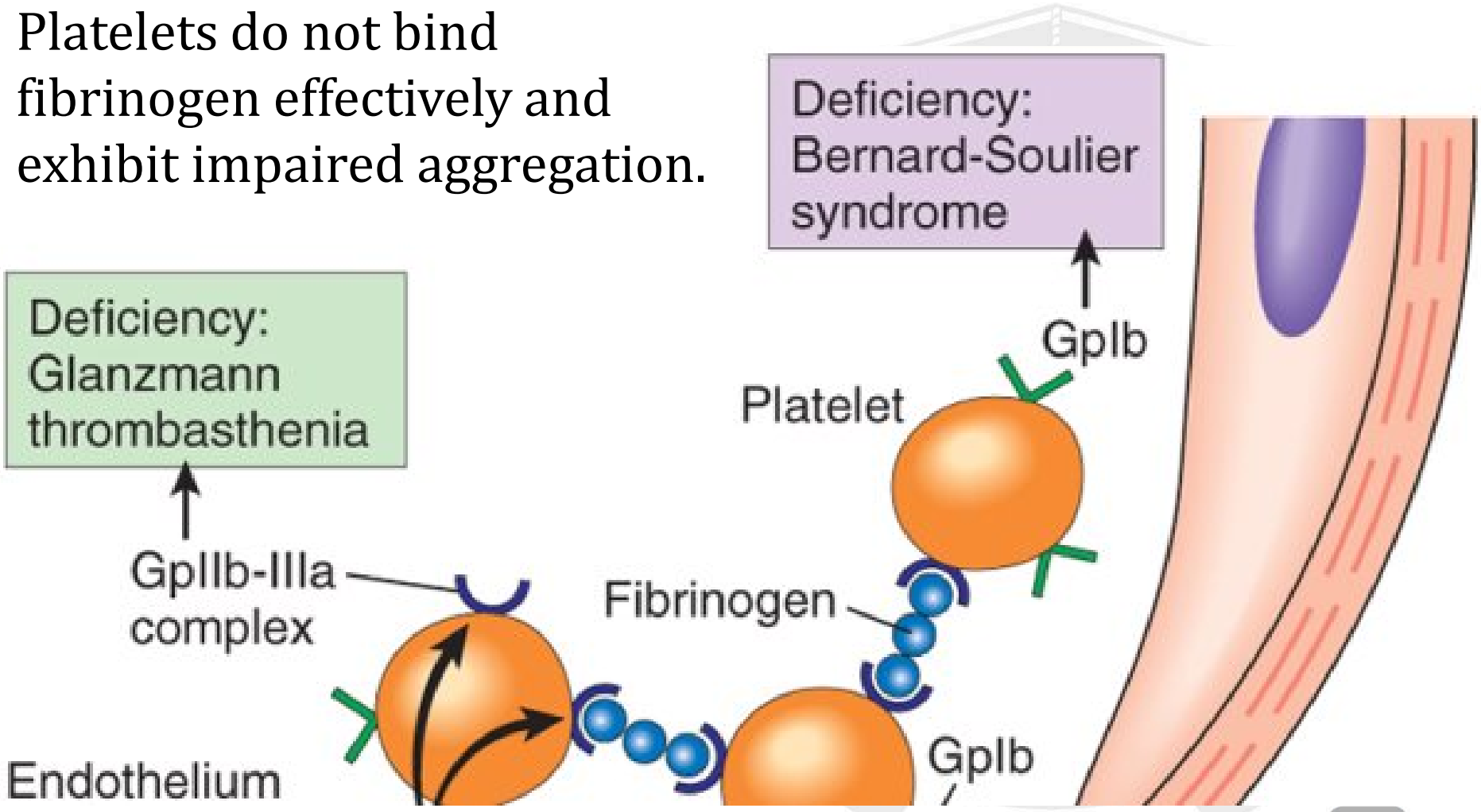


Glanzmann thrombasthenia

- **Glanzmann thrombasthenia** is an example of platelet-platelet dysfunction.
- In this autosomal recessive disorder, glycoprotein IIb-IIIa is deficient or dysfunctional.
- As in Bernard-Soulier syndrome, acute bleeding is treated by platelet transfusion.

Glanzmann thrombasthenia

Platelets do not bind fibrinogen effectively and exhibit impaired aggregation.



Qualitative Platelet Disorders

- Disorders involving platelet granule content include storage pool disease and Quebec platelet disorder.

- In individuals with storage pool disease, platelet-dense granules lack adenosine dinucleotide phosphate and adenosine trinucleotide phosphate and are often found to be low in number by electron microscopy.

- These granules are also deficient in Hermansky-Pudlak, Chédiak-Higashi, and Wiskott-Aldrich syndromes.

Treatment in Qualitative Platelet Disorders

- Acute bleeding in many individuals with acquired or selected congenital platelet function defects responds to therapy with desmopressin acetate, likely due to an induced release of vWF from endothelial stores.

- If this therapy is ineffective, or if the patient has Bernard-Soulier syndrome or Glanzmann syndrome, the mainstay of treatment for bleeding episodes is platelet transfusion, possibly with HLA type-specific platelets.

- Recombinant VIIa has variable efficacy and may be helpful in platelet transfusion-refractory patients.

VASCULAR DISORDERS

Henoch-Schönlein Purpura

- Henoch-Schönlein purpura (HSP), the most common type of small vessel vasculitis in children, primarily affects boys 2–7 years of age.

- Occurrence is highest in the spring and fall, and upper respiratory infection precedes the diagnosis in two-thirds of children.

- Antigens from group A β-hemolytic streptococci and other bacteria, viruses, drugs, foods, and insect bites have been proposed as inciting agents.

Henoch-Schönlein Purpura

- Leukocytoclastic vasculitis in HSP principally involves the small vessels of the skin, gastrointestinal tract, and kidneys, with deposition of IgA immune complexes.

- The most common and earliest symptom is palpable purpura, which results from extravasation of erythrocytes into the tissue surrounding the involved venules.

Symptoms and Signs

- Skin involvement may be urticarial initially, progresses to a maculopapules, and coalesces to a symmetrical, palpable purpuric rash distributed on the legs, buttocks, and elbows.

- New lesions may continue to appear for 2–4 weeks, and may extend to involve the entire body.

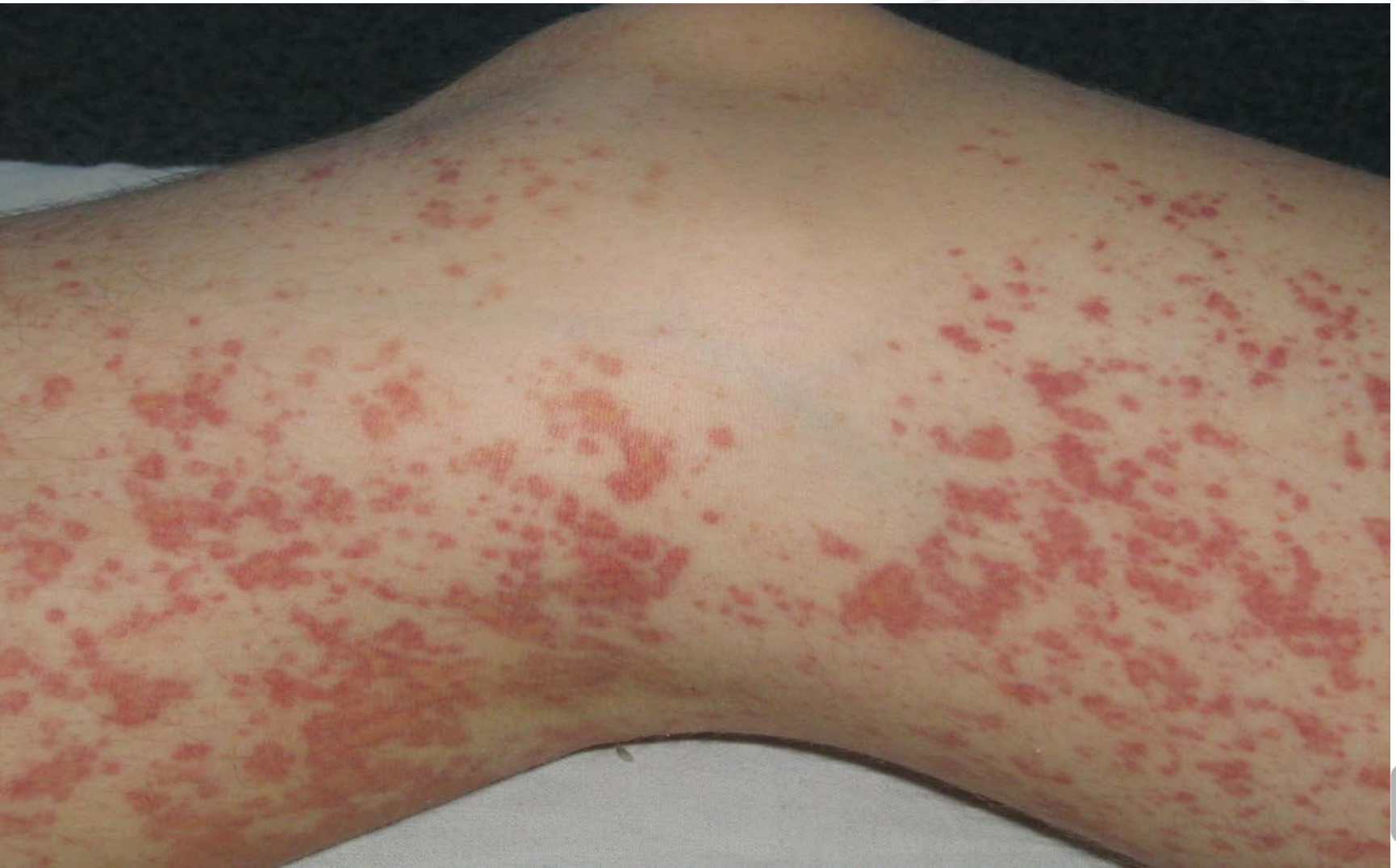
Symptoms and Signs

- Two-thirds of patients develop migratory polyarthralgias or polyarthritis, primarily of the ankles and knees.
- Intermittent, sharp abdominal pain occurs in approximately 50% of patients, and hemorrhage and edema of the small intestine can often be demonstrated.
- Intussusception may develop.

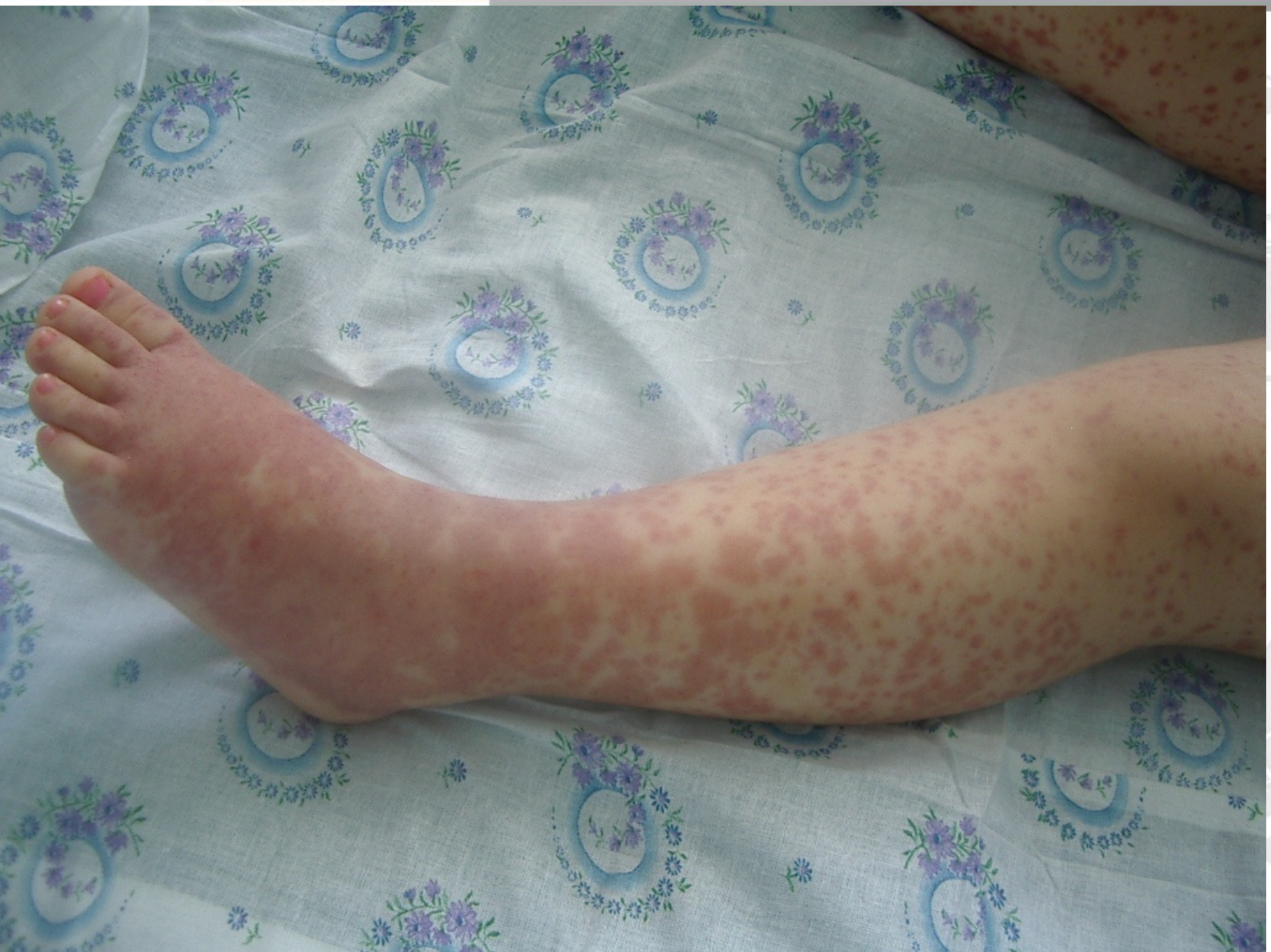
Symptoms and Signs

- From 25% to 50% of those affected develop renal involvement in the second or third week of illness with either a nephritic or, less commonly, nephrotic picture.
- Hypertension may accompany the renal involvement.
- In males, testicular torsion may also occur, and neurologic symptoms are possible due to small vessel vasculitis.

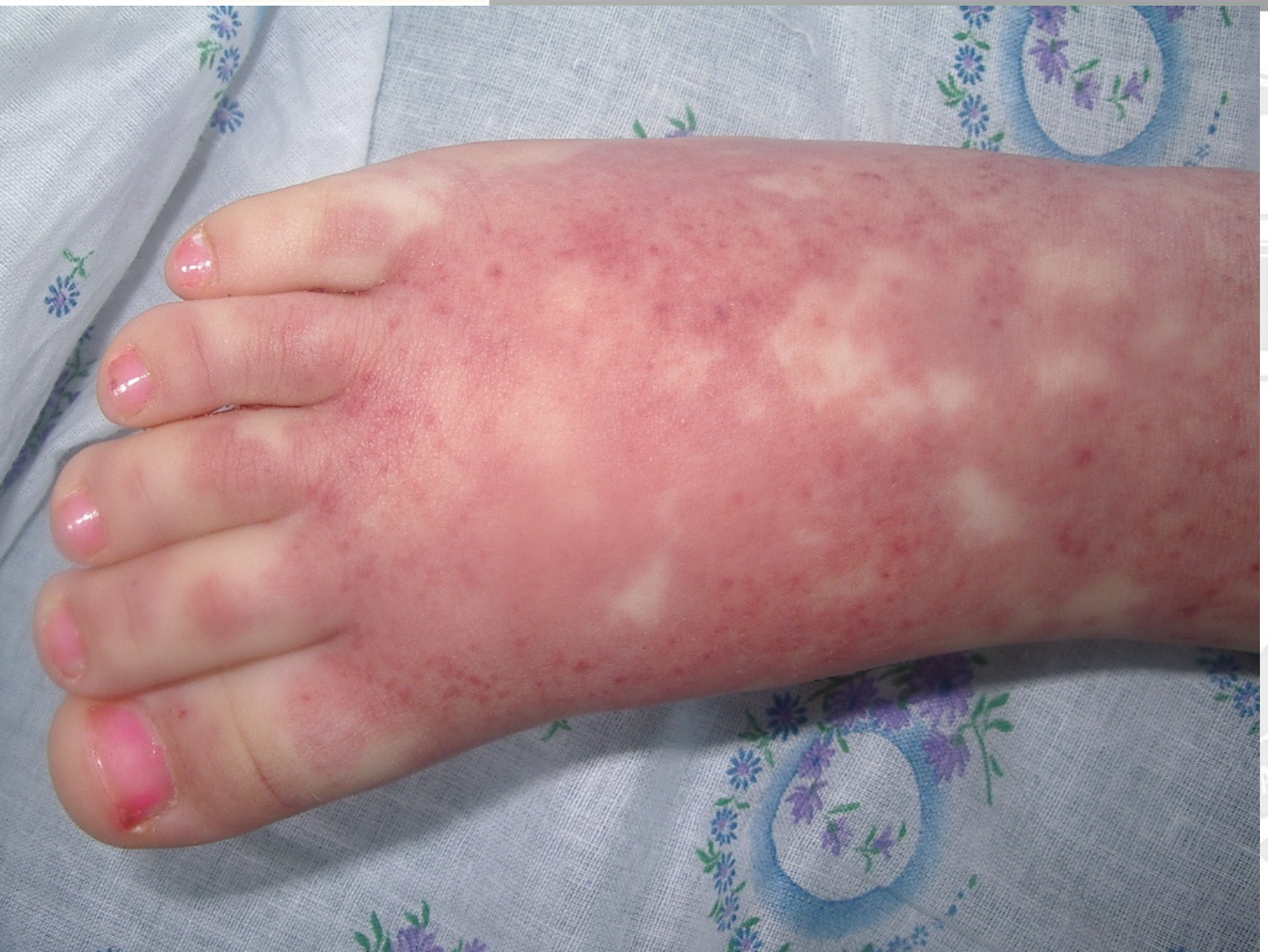
Henoch-Schönlein Purpura



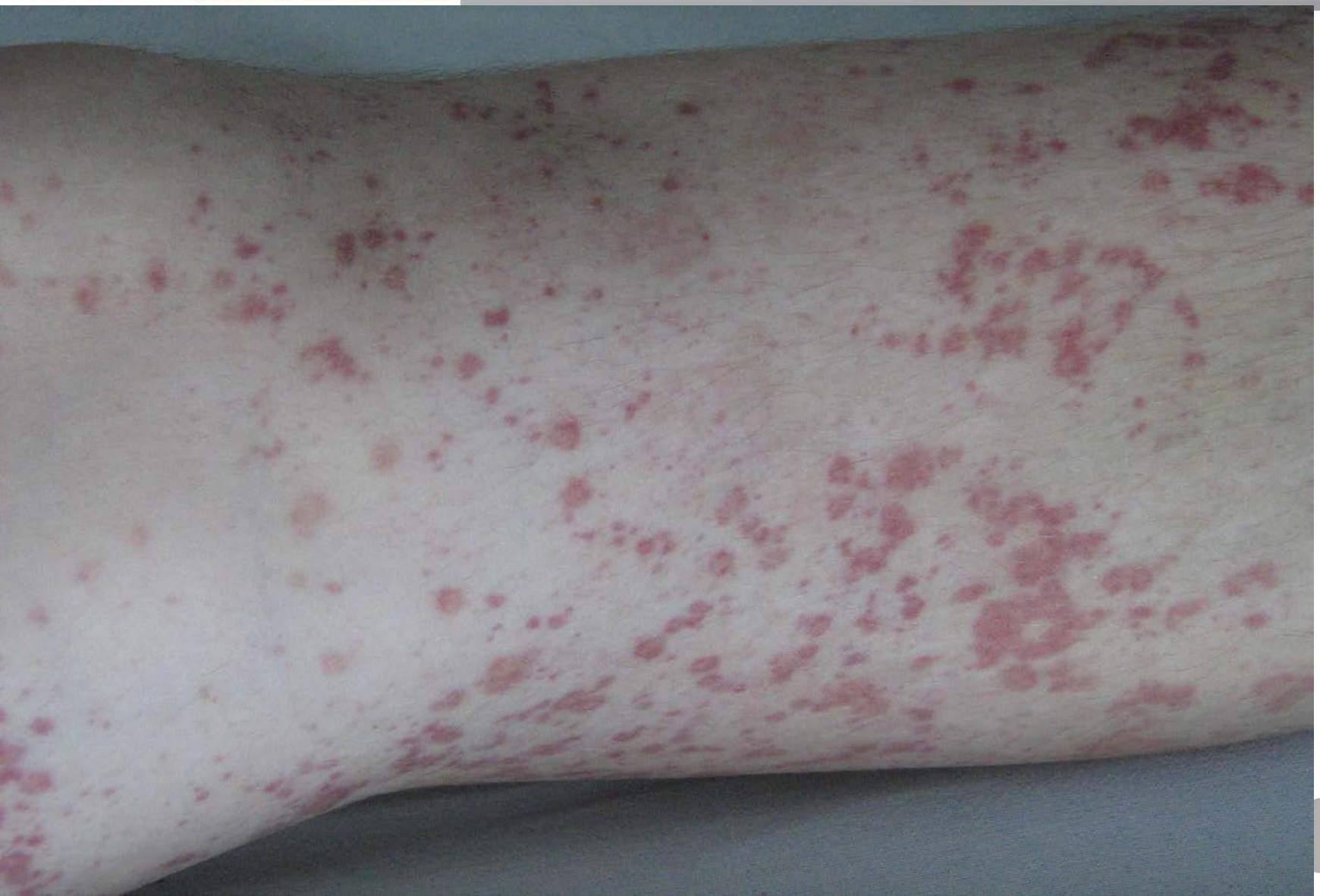
Henoch-Schönlein Purpura



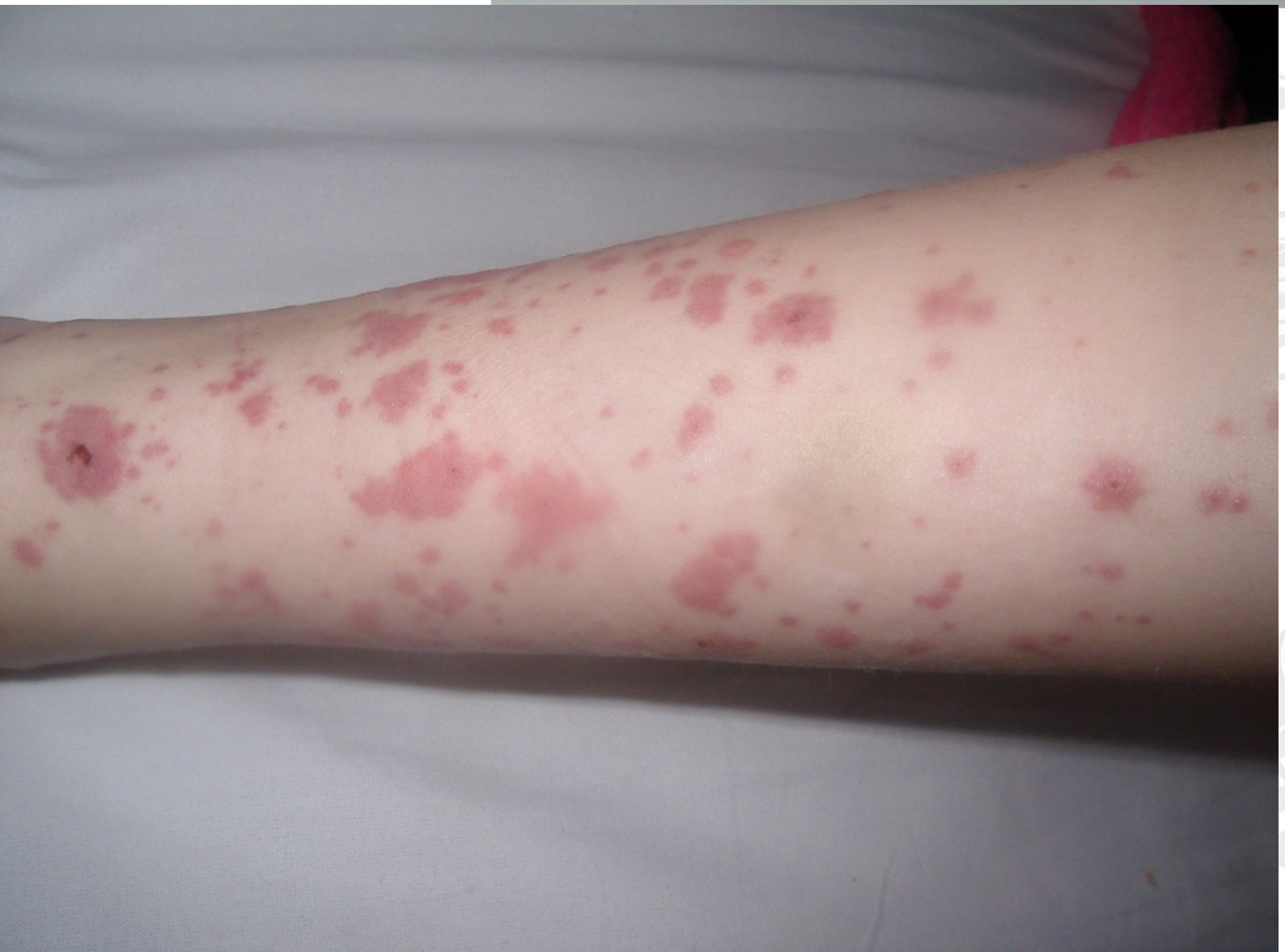
Henoch-Schönlein Purpura



Henoch-Schönlein Purpura



Henoch-Schönlein Purpura



Laboratory Findings

- The platelet count is normal or elevated, and other screening tests of hemostasis and platelet function are typically normal.

- Urinalysis frequently reveals hematuria, and sometimes proteinuria.

Laboratory Findings

- Stool may be positive for occult blood.
- The anti-streptolysin O (ASO) titer is often elevated and the throat culture positive for group A β-hemolytic streptococci.
- Serum IgA may be elevated.

Treatment in Henoch-Schönlein Purpura

- Generally, treatment is supportive.
- NSAIDs may be useful for the arthritis.
- Corticosteroid therapy may provide symptomatic relief for severe gastrointestinal or joint manifestations but does not alter skin or renal manifestations.
- If culture for group A β-hemolytic streptococci is positive or if the ASO titer is elevated, a therapeutic course of penicillin is warranted.

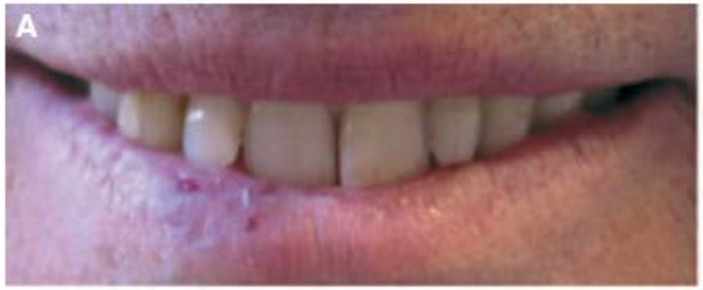
Prognosis

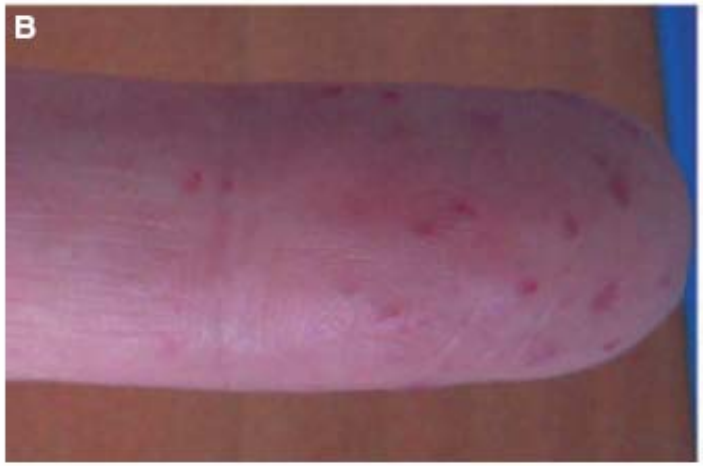
- The prognosis for recovery is generally good, although symptoms frequently (25–50%) recur over a period of several months.
- In patients who develop renal manifestations, microscopic hematuria may persist for years.
- Progressive renal failure occurs in less than 5% of patients with HSP, with an overall fatality rate of 3%.

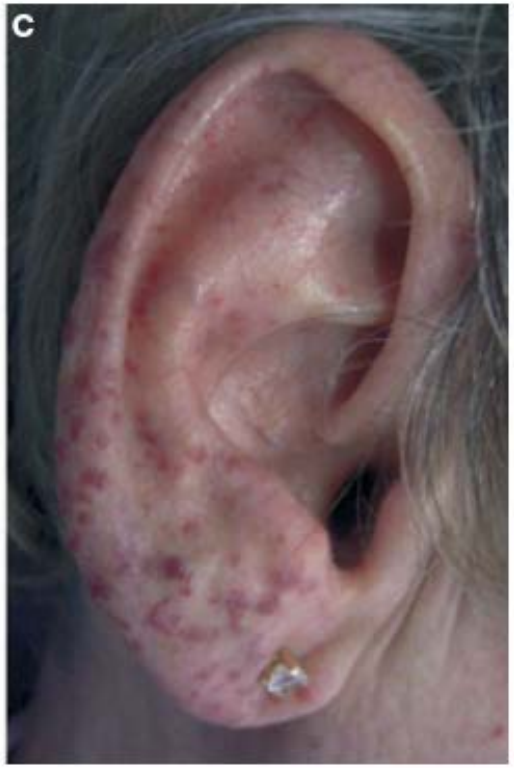
Hereditary Hemorrhagic Telangiectasia

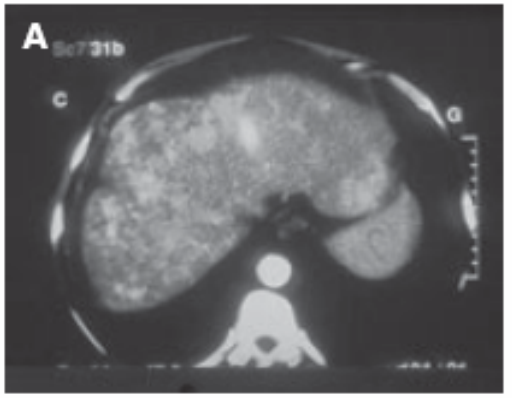
- Autosomal dominant inheritance
- Mutation in endoglin gene that controls vascular remodeling
  - Molecular diagnosis possible
- Multiple small arteriovenous malformations (AVMs) in skin, mouth, GI tract, lungs

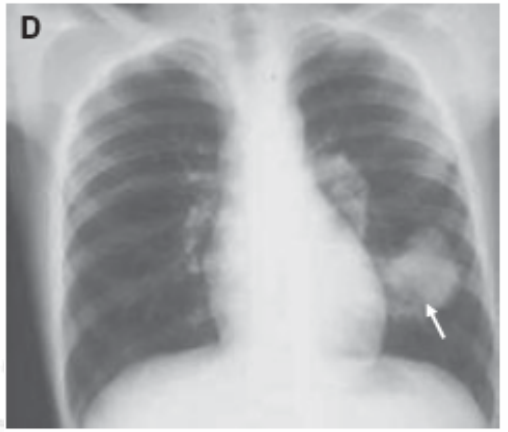
Hereditary Hemorrhagic Telangiectasia











J Thromb Haemost 2010;8:1447

Hereditary Hemorrhagic Telangiectasia

Signs and Symptoms:

- Epistaxis, GI bleeding – may be severe
  - Severe iron deficiency common
- Pulmonary or CNS bleeding often fatal
- Gradual increase in bleeding risk with age
- AVMs enlarge during pregnancy
- Risk of brain abscess
- Hypoxemia from pulmonary HTN and R→L shunting in lung

Hereditary Hemorrhagic Telangiectasia

Treatment:

- No consistently effective method for preventing bleeding
- Aggressive iron replacement
- Antibiotic prophylaxis for dental work etc
- Screen for CNS lesions → consider surgical intervention

Ehlers-Danlos Syndrome

- Defective collagen structure
  - Mutations in genes for various types of collagen
- 9 variants
  - Type IV (mutation in type III collagen gene) most likely to cause bleeding
- Bleeding due to weakening of vessel wall → vessel rupture
- Conventional tests of hemostatic integrity normal

Ehlers-Danlos Syndrome

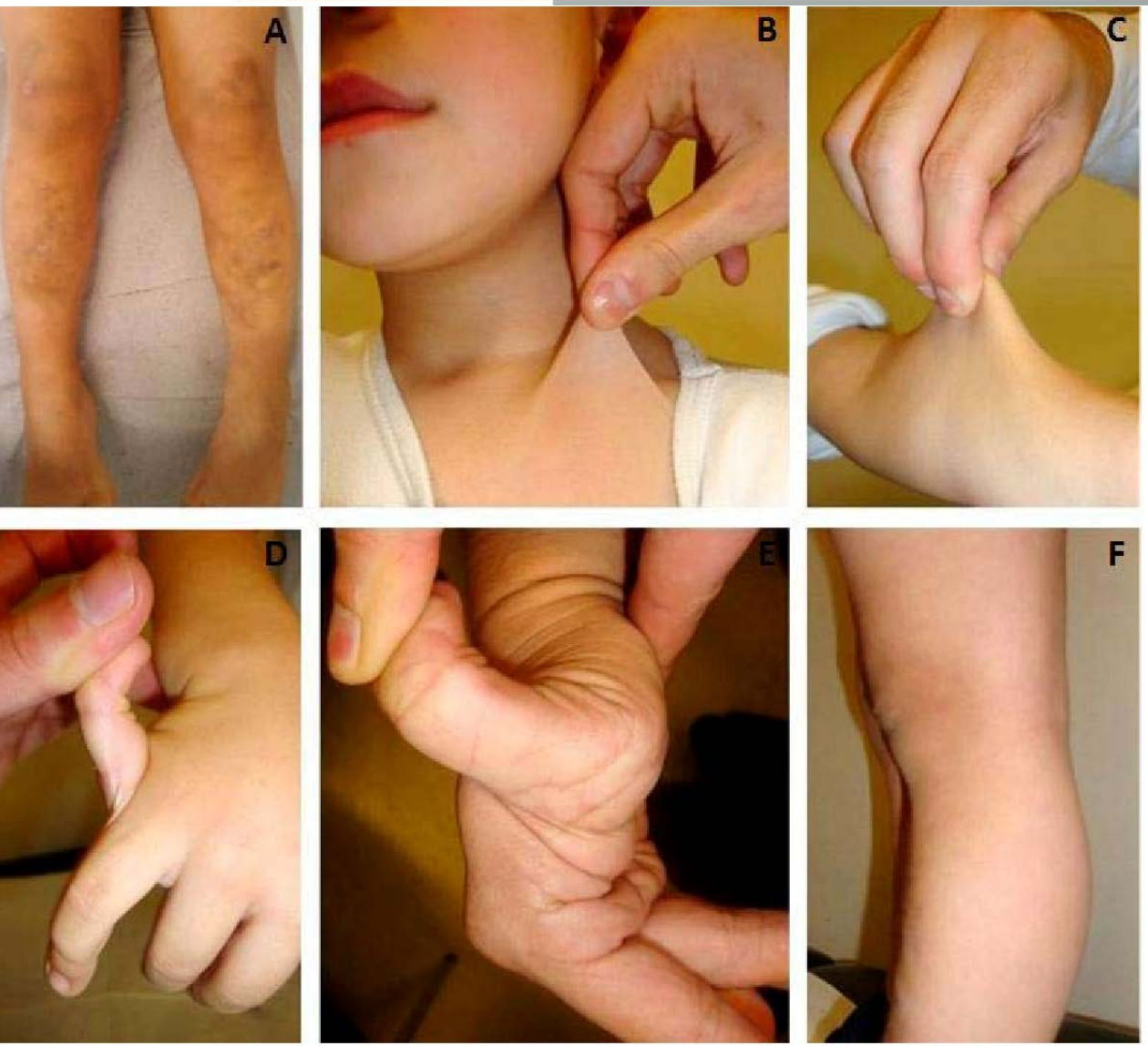


Figure 1. Clinical appearance of the patient: extensive bruising, and atrophic and "cigarette paper"-like

- Thin, weak skin with poor healing ("Cigarette paper" scars)
- Bruising
- Hypermobile joints (spontaneous joint dislocation)

Secondary Hemostasis Disorders

Factor VIII Deficiency (Hemophilia A, Classic Hemophilia)

Typical Features:

- Bruising, soft-tissue bleeding, hemarthrosis.
- Prolonged activated partial thromboplastin time (aPTT).
- Reduced factor VIII activity

Hemophilia A

- Factor VIII activity is reported in units per milliliter, with 1 U/mL equal to 100% of the factor activity found in 1 mL of normal plasma.

- The normal range for factor VIII activity is 0.5–1.5 U/mL (50–150%).

Hemophilia A

- Hemophilia A occurs predominantly in males as an X- linked disorder.
- One-third of cases are due to a new mutation.
- The incidence of factor VIII deficiency is 1:5000 male births

Hemophilia A

Symptoms and Signs:

- Patients with severe hemophilia A (< 1% plasma factor VIII activity) have frequent spontaneous bleeding episodes involving skin, mucous membranes, joints, muscles, and viscera.

- In contrast, patients with mild hemophilia A (5–40% factor VIII activity) bleed only at times of trauma or surgery.

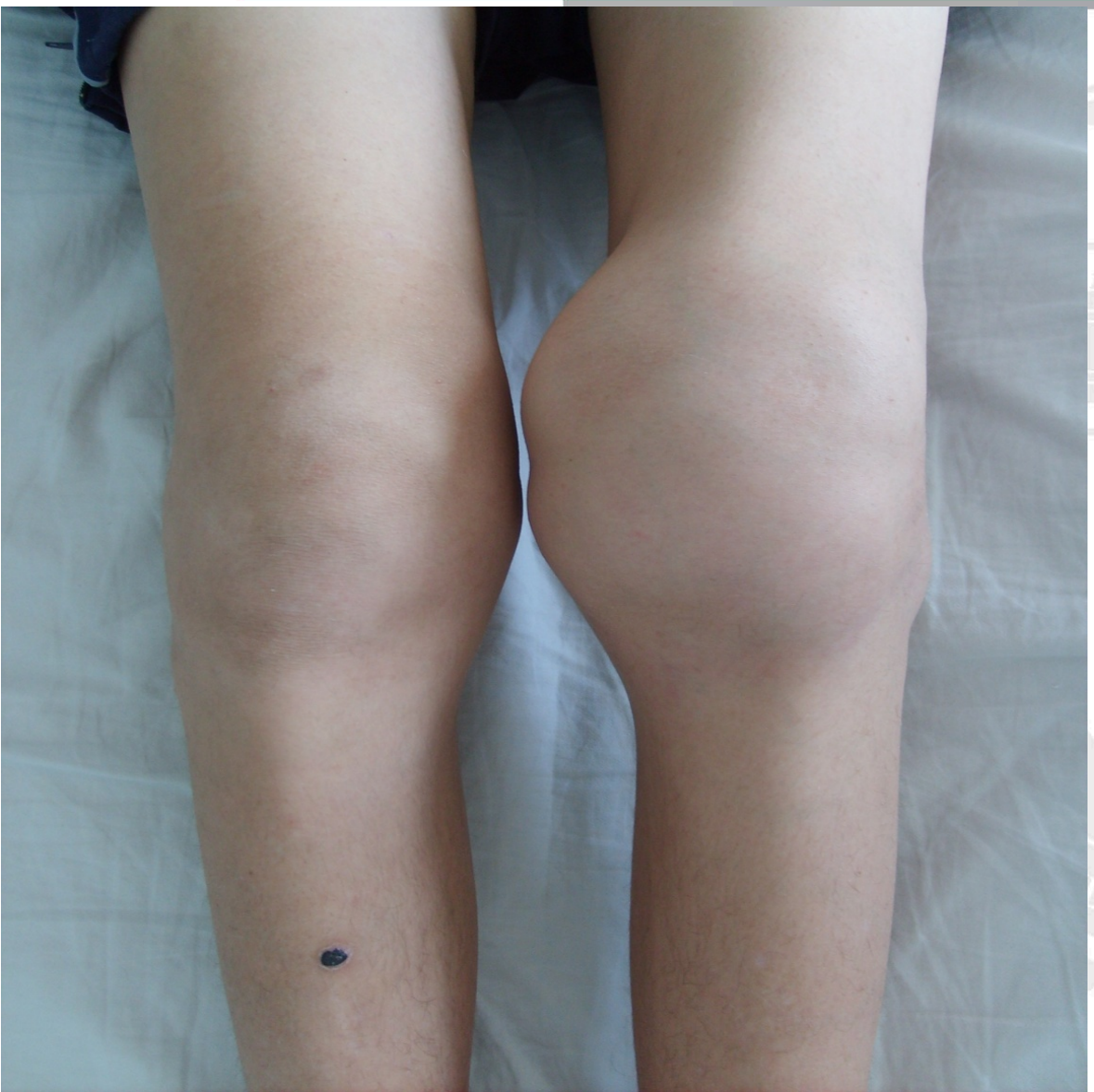
Hemophilia A

Symptoms and Signs:

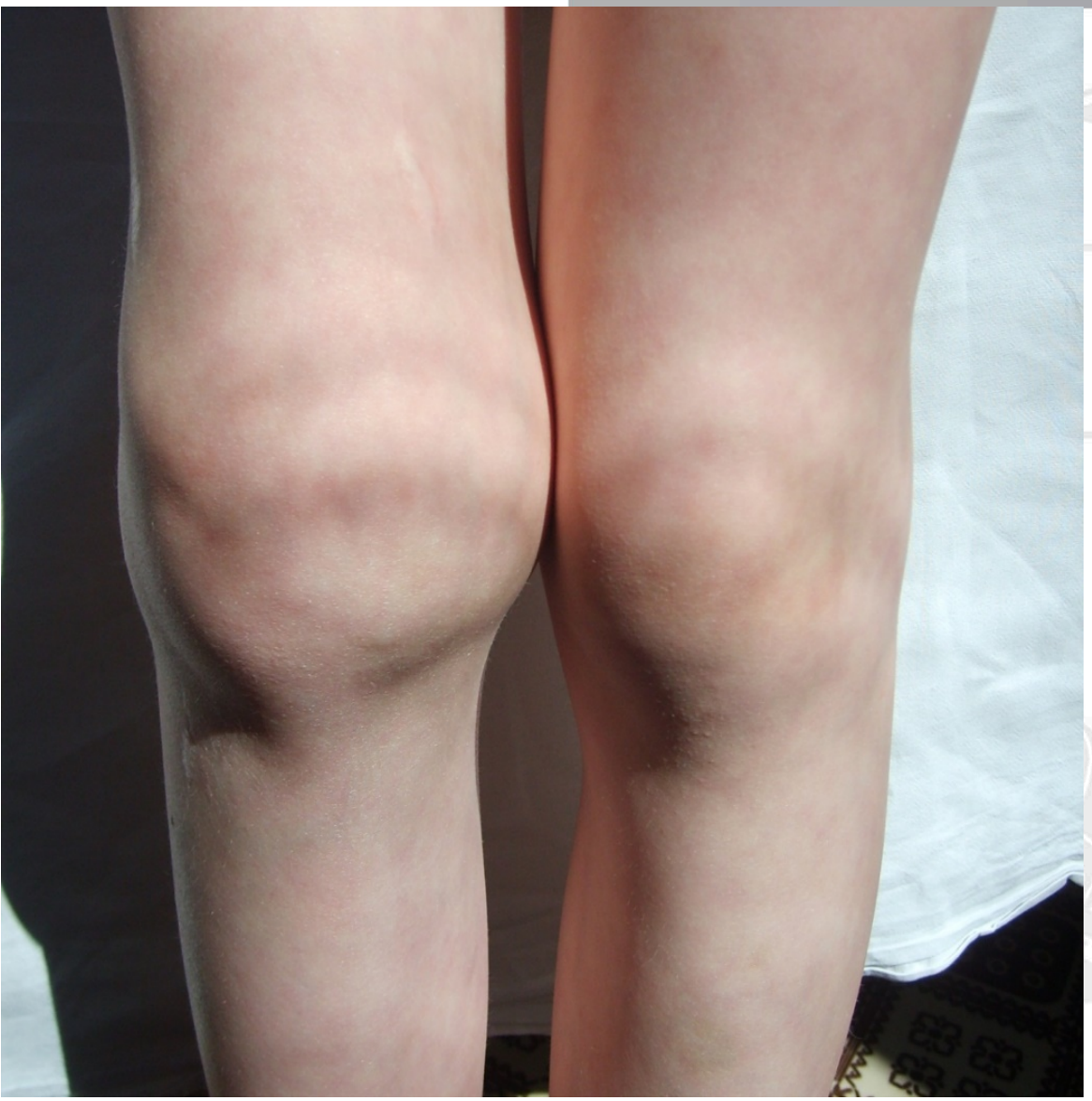
- Those with moderate hemophilia A (1% to < 5% factor VIII activity) typically have intermediate bleeding manifestations.

- The most crippling aspect of factor VIII deficiency is the tendency to develop recurrent hemarthroses that incite joint destruction

Symptoms and Signs - hemarthroses



Symptoms and Signs - hemarthroses



Laboratory Findings in Hemophilia A

- Individuals with hemophilia A have a prolonged aPTT, except in some cases of mild deficiency.
- The PT is normal.
- The diagnosis is confirmed by finding decreased factor VIII activity with normal vWF activity.

Laboratory Findings in Hemophilia A

- In two-thirds of families of hemophilic patients, the females are carriers and some are mildly symptomatic.
- Carriers of hemophilia can be detected by determination of the ratio of factor VIII activity to vWF antigen and by molecular genetic techniques.
- In a male fetus or newborn with a family history of hemophilia A, cord blood sampling for factor VIII activity is accurate and important in subsequent care

Complications in Hemophilia A

- Intracranial hemorrhage is the leading disease-related cause of death among patients with hemophilia.
- Most intracranial hemorrhages in moderate to severe deficiency are spontaneous (ie, not associated with trauma).
- Hemarthroses begin early in childhood and, if recurrent, result in joint destruction (ie, hemophilic arthropathy).

Complications in Hemophilia A

- Large intramuscular hematomas can lead to a compartment syndrome with resultant muscle and nerve death.

- Although these complications are most common in severe hemophilia A, they may be experienced by individuals with moderate or mild disease.

Complications in Hemophilia A

- A serious complication of hemophilia is the development of an acquired circulating antibody to factor VIII after treatment with factor VIII concentrate.

- Such factor VIII inhibitors develop in 15–25% of patients with severe hemophilia A, and whether type of treatment product is associated with risk for inhibitor development is the subject of active study.

Complications in Hemophilia A

- Inhibitors may be amenable to desensitization with regular factor VIII infusion with or without immunosuppressive therapy.

- In recent years, recombinant factor VIIa has become a therapy of choice for treatment of acute hemorrhage in patients with hemophilia A and a high-titer inhibitor.

Complications in Hemophilia A

- In prior decades, therapy-related complications in hemophilia A have included infection with the human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV).

- Through more stringent donor selection, the implementation of sensitive screening assays, the use of heat or chemical methods for viral inactivation, and the development of recombinant products, the risk of these infections is minimal.

Complications in Hemophilia A

- Inactivation methods do not eradicate viruses lacking a lipid envelope, however, so that transmission of parvovirus and hepatitis A remains a concern with the use of plasma-derived products.

- Immunization with hepatitis A and hepatitis B vaccines is recommended for all hemophilia patients.

Treatment in Hemophilia A

- The general aim of management is to raise the factor VIII activity to prevent or stop bleeding.

- Some patients with mild factor VIII deficiency may respond to desmopressin via release of endothelial stores of factor VIII and vWF into plasma; however, most patients require administration of exogenous factor VIII to achieve hemostasis.

Treatment in Hemophilia A

- The in-vivo half-life of factor VIII is generally 8–12 hours but may exhibit considerable variation among individuals depending on comorbid conditions.

- Non–life-threatening, non–limb-threatening hemorrhage is treated initially with 20–30 U/kg of factor VIII, to achieve a rise in plasma factor VIII activity to 40–60%.

Treatment in Hemophilia A

- Large joint hemarthrosis and life- or limb-threatening hemorrhage is treated initially with approximately 50 U/kg of factor VIII, targeting a rise to 100% factor VIII activity.
- Subsequent doses are determined according to the site and extent of bleeding and the clinical response. Doses are rounded to the nearest whole vial size.
- In circumstances of suboptimal clinical response, recent change in bleeding frequency, or comorbid illness, monitoring the plasma factor VIII activity response may be warranted.

Treatment in Hemophilia A

- For most instances of non–life-threatening hemorrhage in experienced patients with moderate or severe hemophilia A, treatment can be administered at home, provided adequate intravenous access exists and close contact is maintained with the hemophilia clinician team.
- Prophylactic factor VIII infusions (eg, two or three times weekly) may prevent the development of arthropathy in severe hemophiliacs, and this approach is becoming more common in pediatric hemophilia care.

Prognosis in Hemophilia A

- The development of safe and effective therapies for hemophilia A has resulted in improved long-term survival in recent decades.

- In addition, more aggressive management and the coordination of comprehensive care through hemophilia centers have greatly improved quality of life and level of function.

Factor IX Deficiency
(Hemophilia B, Christmas Disease)

- The mode of inheritance and clinical manifestations of factor IX deficiency are the same as those of factor VIII deficiency.

- Hemophilia B is 15–20% as prevalent as hemophilia A.

Factor IX Deficiency
(Hemophilia B, Christmas Disease)

- As in factor VIII deficiency, factor IX deficiency is associated with a prolonged aPTT, but the PT and thrombin time are normal.

- The aPTT is slightly less sensitive to factor IX deficiency than factor VIII deficiency.

Factor IX Deficiency
(Hemophilia B, Christmas Disease)

- Diagnosis of hemophilia B is made by assaying factor IX activity, and severity is determined similarly to factor VIII deficiency.

- In general, clinical bleeding severity correlates less well with factor activity in hemophilia B than in hemophilia A.

Treatment in Factor IX Deficiency

- The mainstay of treatment in hemophilia B is exogenous factor IX.
- Unlike factor VIII, about 50% of the administered dose of factor IX diffuses into the extravascular space.
- Therefore, 1 U/kg of plasma-derived factor IX concentrate or recombinant factor IX is expected to increase plasma factor IX activity by approximately 1%.

Treatment in Factor IX Deficiency

- Factor IX typically has a half-life of 20–22 hours in vivo, but due to variability, therapeutic monitoring may be warranted.

- As for factor VIII products, viral-inactivation techniques for plasma-derived factor IX concentrates appear effective in eradicating HIV, HBV, and HCV.

Treatment in Factor IX Deficiency

- Only 1–3% of persons with factor IX deficiency develop an inhibitor to factor IX, but patients may be at risk for anaphylaxis when receiving exogenous factor IX.
- The prognosis for persons with factor IX deficiency is comparable to that of patients with factor VIII deficiency.
- Gene therapy research efforts are ongoing for both hemophilias.

Factor XI Deficiency (Hemophilia C)

- Factor XI deficiency is a genetic, autosomally transmitted coagulopathy, typically of mild to moderate clinical severity.

- Cases of factor XI deficiency account for less than 5% of all hemophilia patients.

Factor XI Deficiency (Hemophilia C)

- Homozygotes generally bleed at surgery or following severe trauma, but do not commonly have spontaneous hemarthroses.

- In contrast to factor VIII and IX deficiencies, factor XI activity is least predictive of bleeding risk.

Factor XI Deficiency (Hemophilia C)

- Although typically mild, pathologic bleeding may be seen in heterozygous individuals with factor XI activity as high as 60%.
- The aPTT is often considerably prolonged.
- In individuals with deficiency of both plasma and platelet-associated factor XI, the PFA-100 may also be prolonged.

Factor XI Deficiency (Hemophilia C)

- Management typically consists of perioperative prophylaxis and episodic therapy for acute hemorrhage.

- Treatment includes infusion of fresh frozen plasma (FFP).

Factor XI Deficiency (Hemophilia C)

- Platelet transfusion may also be useful for acute hemorrhage in patients with deficiency of platelet-associated factor XI.
- Desmopressin has been used in some cases.
- The prognosis for an average life span in patients with factor XI deficiency is excellent.

Inherited factor XIII deficiency

- Autosomal recessive, rare (consanguineous parents)
- Heterozygous woman may have higher incidence of spontaneous abortion
- Most have absent or defective A subunit

Factor XIII

- Transglutaminase: forms amide bonds between lysine and glutamic acid residues on different protein molecules

- Heterotetramer (A_2B_2) in plasma
  - A chains made by megakaryocytes and monocyte/macrophage precursors
  - Platelet XIII (50% of total XIII) has only A chains
  - B chains (non-catalytic) made in liver

Factor XIII

- Proenzyme activated by thrombin
- Crosslinks and stabilizes fibrin clot
- Can crosslink other proteins (e.g., antiplasmin) into clot

Inherited factor XIII deficiency

Clinical features & treatment

- Bleeding begins in infancy (umbilical cord)
- Poor wound healing
- Intracranial hemorrhage
- Diagnosis:
  - Urea solubility test
  - Quantitative measurement of XIII activity
  - Rule out acquired deficiency due to autoantibody
- Treatment: F XIII concentrate or recombinant factor XIII
  - long half life, give every 4-6 weeks as prophylaxis

Von Willebrand Disease

Typical Features:

- Easy bruising and epistaxis from early childhood.
- Menorrhagia.
- Prolonged PFA-100 (or bleeding time); normal platelet count; absence of acquired platelet dysfunction.
- Reduced activity or abnormal structure of vWF.

Von Willebrand Disease

- vWD is the most common inherited bleeding disorder among Caucasians, with a prevalence of 1%.

- vWF is a protein present as a multimeric complex in plasma, which binds factor VIII and is a cofactor for platelet adhesion to the endothelium.

Von Willebrand Disease

- An estimated 70–80% of all patients with vWD have classic vWD (type 1), which is caused by a partial quantitative deficiency of vWF.
- vWD type 2 involves a qualitative deficiency of (ie, dysfunctional) vWF, and
- vWD type 3 is characterized by a nearly complete deficiency of vWF.

Von Willebrand Disease

- The majority (>80%) of individuals with type 1 disease are asymptomatic.

- vWD is most often transmitted as an autosomal dominant trait, but can be autosomal recessive.

Von Willebrand Disease

- The disease can also be acquired, developing in association with hypothyroidism, Wilms tumor, cardiac disease, renal disease, or systemic lupus erythematosus and in individuals receiving valproic acid.

- Acquired vWD is most often caused by the development of an antibody to vWF or increased turnover of vWF.

Von Willebrand Disease

Symptoms and Signs:

- A history of increased bruising and excessive epistaxis is often present.
- Prolonged bleeding also occurs with trauma or at surgery.
- Menorrhagia is often a presenting finding in females.

Laboratory Findings in Von Willebrand Disease

- PT is normal, and aPTT is sometimes prolonged.
- Prolongation of the PFA-100 or bleeding time is usually present since vWF plays a role in platelet adherence to endothelium.
- Platelet number may be decreased in type 2b vWD.

Laboratory Findings in Von Willebrand Disease

- Factor VIII and vWF antigen are decreased in types 1 and 3, but may be normal in type 2 vWD.
- vWF activity (eg, ristocetin cofactor or collagen binding) is decreased in all types.
- Since normal vWF antigen levels vary by blood type (type O normally has lower levels), blood type must be determined.

Laboratory Findings in Von Willebrand Disease

- Complete laboratory classification requires vWF multimer assay.

- The diagnosis requires confirmation of laboratory testing and bleeding history is often helpful when present.

Treatment in Von Willebrand Disease

- The treatment to prevent or halt bleeding for most patients with vWD types 1 and 2 is desmopressin acetate, which causes release of vWF from endothelial stores.

- Desmopressin may be administered intravenously at a dose of 0.3 mcg/kg diluted in at least 20–30 mL of normal saline and given over 20–30 minutes.

Treatment in Von Willebrand Disease

- This dose typically elicits a three- to fivefold rise in plasma vWF.

- A high-concentration desmopressin nasal spray (150 mcg/spray), different than the preparation used for enuresis, may alternatively be used.

Treatment in Von Willebrand Disease

- Because response to vWF is variable among patients, factor VIII and vWF activities are typically measured before and 60 minutes after infusion, if no recent response has been measured.

- Desmopressin may cause fluid shifts, hyponatremia, and seizures in children younger than 2 years of age.

- Because release of stored vWF is limited, tachyphylaxis often occurs with desmopressin.

Treatment in Von Willebrand Disease

- If further therapy is indicated, vWF-replacement therapy (eg, plasma-derived concentrate) is recommended; such therapy is also used in patients with type 1 or 2a vWD who exhibit suboptimal laboratory response to desmopressin, and for all individuals with type 2b or 3 vWD.

- Antifibrinolytic agents (eg, ε-aminocaproic acid) may be useful for control of mucosal bleeding.

Treatment in Von Willebrand Disease

- Topical thrombin and fibrin glue may also be of benefit, although antibodies that inhibit clotting proteins have been described.

- Estrogen-containing contraceptive therapy may be helpful for menorrhagia.

Prognosis in Von Willebrand Disease

- With the availability of effective treatment and prophylaxis for bleeding, life expectancy in vWD is normal.

Rare clotting factor deficiencies

Afibrinogenemia

- Prevalence approx 1:1,000,000
- Recessive inheritance
  - Most reported cases from consanguineous parents
  - Parents typically have asymptomatic hypofibrinogenemia
- Genetically heterogeneous (>30 mutations)
- May be due to failure of synthesis, intracellular transport or secretion of fibrinogen
- Moderate to severe bleeding (typically less than in severe hemophilia)
  - Death from intracranial bleeding in childhood may occur
  - GI and other mucosal hemorrhage
  - Menorrhagia
  - Placental abruption
- Treat with purified fibrinogen concentrate or cryoprecipitate for bleeding, during pregnancy

Inherited dysfibrinogenemia

- Prevalance uncertain (most cases asymptomatic)
- Usually exhibits dominant inheritance
- Most cases due to missense mutations
- Mutations may affect fibrin polymerization, fibrinopeptide cleavage, or fibrin stabilization by FXIIIa
- Variable clinical manifestations (mutation-dependent):
  - Over 50% asymptomatic
  - Approx 25% with bleeding tendency (mild to severe)
  - 20% have a thrombotic tendency (arterial, venous, or both)
    - Decreased thrombin-binding (antithrombin effect) of fibrin?
    - Altered fibrin clot structure?

Diagnosis of dysfibrinogenemia

- Prolonged thrombin & reptilase times
  - PT, aPTT may be prolonged
- Disparity (>30%) between fibrinogen activity and antigen
- Family testing
- Evaluate for liver disease

Recessively inherited clotting factor deficiencies

- Rare
  - Exceptions: XI, XII deficiency
- Homozygotes (often consanguineous parents) or compound heterozygotes
- Heterozygous parents usually asymptomatic
- Quantitative ("type 1") deficiency: parallel reduction in antigen and activity
- Qualitative ("type 2") deficiency: reduced activity with near-normal antigen
- Genetically heterogeneous
- Complete deficiency of II, X not described (lethal?)
- Mutation usually in gene encoding clotting factor

Exceptions:

Combined V, VIII deficiency

Combined deficiency of vitamin K-dependent factors

Combined deficiency of factors V and VIII

- Levels of affected factors 5-20% of normal
- Associated with mutations of LMAN-1 (ERGIC-53) or MCFD2, both of which regulate intracellular trafficking of V and VIII

Deficiency of multiple vitamin-K dependent clotting factors

- Levels of II, VII, IX, X, proteins C and S range from <1% to 30% of normal
- Bleeding symptoms proportional to degree of deficiency
- Usually associated with missense mutations in vitamin K epoxide reductase subunit 1 (VKORC1)

Relative frequencies of recessively inherited factor deficiencies

Table 2. Number of patients and relative frequency of recessively inherited coagulation disorders in Iran and Italy

Deficiency	Iran, n (%)	Italy, n (%)
Fibrinogen	80 (11)	30 (8)
Prothrombin	15 (2)	18 (5)
V	50 (7)	35 (10)
VII	300 (39)	90 (25)
X	75 (10)	28 (8)
XI	50 (7)	80 (24)
XIII	100 (13)	40 (11)
V + VIII	80 (11)	32 (9)
Total	750	353

The general population of Iran is 65 million; Italy, 55 million. Data on RICD are obtained from the most recent adjournments (2004) of the registries kept in Iran (courtesy of Dr. M. Lak, Iman Khomeini Hospital, Tehran) and in Italy (Associazione Italiana Centri Emofilia).

Blood 2004; 104:1243

Clinical features of recessively inherited factor deficiencies

Deficient factor	Main clinical symptoms*	Hemostatic levels	Plasma half-life
Fibrinogen	Umbilical cord, joint, and mucosal tract bleeding; recurrent miscarriages, rarely thrombosis	50 mg/dL	2-4 d
Prothrombin	Umbilical cord, joint, and mucosal tract bleeding	20%-30%	3-4 d
V	Mucosal tract bleeding	15%-20%	36 h
VII	Mucosal tract, joint, and muscle bleeding	15%-20%	4-6 h
X	Umbilical cord, joint, and muscle bleeding	15%-20%	40-60 h
XI	Posttraumatic bleeding	15%-20%	40-70 h
XIII	Umbilical cord, intracranial, and joint bleeding; recurrent miscarriages, impaired wound healing	2%-5%	11-14 d
V + VIII	Mucosal tract bleeding	15%-20%	36 h for factor V and 10-14 h for factor VIII
Vitamin K–dependent, multiple deficiency	Umbilical cord and intracranial bleeding	15%-20%	See corresponding factors

*Excessive bleeding after invasive procedures carried out without replacement therapy is a symptom common to all RICDs.

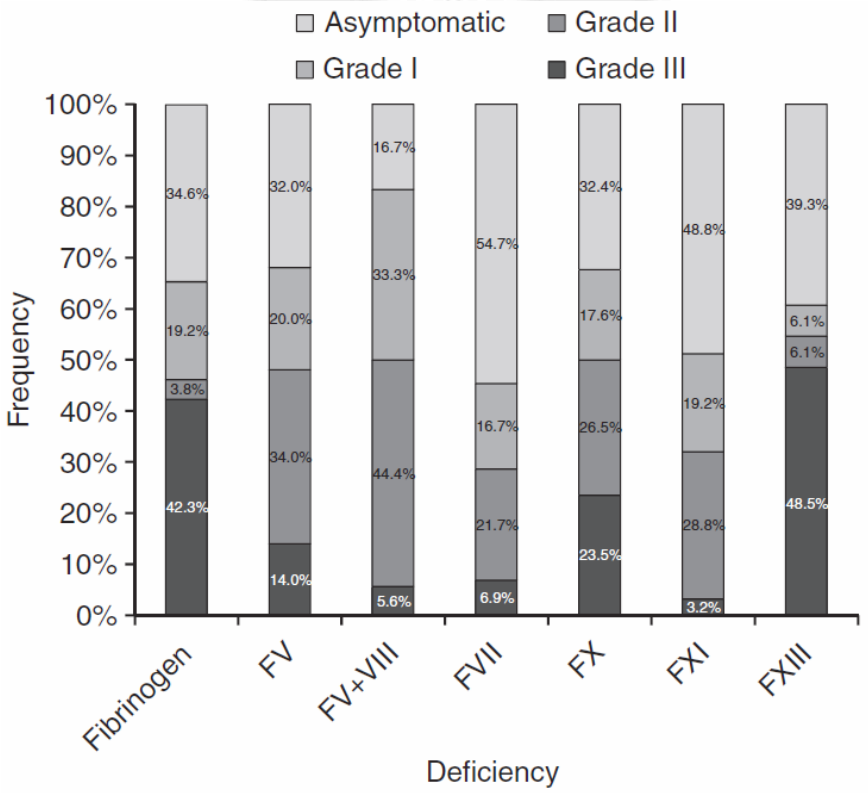
Blood 2004; 104:1243

Severity of bleeding in rare inherited bleeding disorders

Number of patients with each condition

Type of deficiency	*n* (%)
FVII	224 (38)
FXI	133 (22)
FV	60 (10)
Fibrinogen	46 (8)
FX	45 (8)
FXIII	42 (7)
Combined FV + VIII	20 (3)
FII	6 (1)
FXII	6 (1)
Other combined	10 (2)

Frequency of bleeding episodes



J Thromb Haemost 2012;10:615

Factor concentration vs bleeding severity in rare coagulation factor deficiencies

Deficiency	Asymptomatic	Grade I bleeding	Grade II bleeding	Grade III bleeding
Fibrinogen	113 mg/dL	73 mg/dL	33 mg/dL	0 mg/dL
Factor V	12%	6%	0.01%	0%
FV + F VIII	43%	34%	24%	15%
Factor VII	25%	19%	13%	8%
Factor X	56%	40%	25%	10%
Factor XI	26%	26%	25%	25%
Factor XIII	31%	17%	3%	0%

- Grade 1: Bleeding after trauma or anticoagulant/antiplatelet drug ingestion
- Grade 2: Spontaneous minor bleeding
- Grade 3: Spontaneous major bleeding

European Network of Rare Bleeding Disorders: J Thromb Haemost 2012;10:615

Treatment of rare clotting factor deficiencies

- FFP
- Prothrombin complex concentrate (II, VII, IX, X) or specific factor concentrate (XIII – others available in Europe) when appropriate
- Goal is to maintain “minimal hemostatic levels”
- Antifibrinolytic drugs may be helpful in patients with mucosal hemorrhage
- Routine prophylaxis appropriate for F XIII deficiency (long half-life, low levels adequate for hemostasis)
- Otherwise treatment appropriate for active bleeding or pre-procedure

Acquired Bleeding Disorders

Disseminated Intravascular Coagulation

Typical Features:

- Presence of disorder known to trigger DIC and evidence for consumptive coagulopathy -

  ✓(prolonged aPTT, PT, or thrombin time;
  ✓increase in FSP [fibrinfibrinogen split products];
  ✓decreased fibrinogen or platelets.

DIC - General Considerations

- DIC is an acquired pathologic process characterized by tissue factor–mediated diffuse coagulation activation in the host.

- DIC involves dysregulated, excessive thrombin generation, with consequent intravascular fibrin deposition and consumption of platelets and procoagulant factors.

DIC - General Considerations

- Microthrombi, composed of fibrin and platelets, may produce tissue ischemia and end-organ damage.
- The fibrinolytic system is frequently activated in DIC, leading to plasmin-mediated destruction of fibrin and fibrinogen;
- this results in fibrin-fibrinogen degradation products (FDPs) which exhibit anticoagulant and platelet-inhibitory functions.

DIC - General Considerations

- DIC commonly accompanies severe infection and other critical illnesses in infants and children.

- Conditions known to trigger DIC include:
  - ✓ endothelial damage (eg, endotoxin, virus),
  - ✓ tissue necrosis (eg, burns),
  - ✓ diffuse ischemic injury (eg, shock, hypoxia acidosis), and
  - ✓ systemic release of tissue procoagulants (eg, certain cancers, placental disorders).

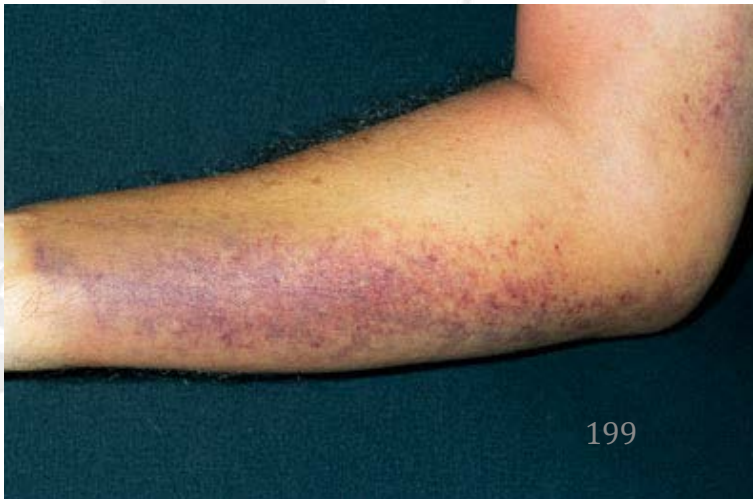
DIC - Symptoms and Signs

Signs of DIC may include:

(1) signs of shock, often including end-organ dysfunction,

(2) diffuse bleeding tendency (eg, hematuria, melena, purpura, petechiae, persistent oozing from needle punctures or other invasive procedures), and

(3) evidence of thrombotic lesions (eg, major vessel thrombosis, purpura fulminans).



DIC - Laboratory Findings

- Tests that are most sensitive, easiest to perform, most useful for monitoring, and best reflect the hemostatic capacity of the patient are the PT, aPTT, platelet count, fibrinogen, and fibrin-fibrinogen split products.

- The PT and aPTT are typically prolonged and the platelet count and fibrinogen concentration may be decreased.

DIC - Laboratory Findings

- However, in children, the fibrinogen level may be normal until late in the course.

- Levels of fibrin-fibrinogen split products are increased, and elevated levels of D-dimer, a cross-linked fibrin degradation byproduct, may be helpful in monitoring the degree of activation of both coagulation and fibrinolysis.

DIC - Laboratory Findings

- However, D-dimer is nonspecific and may be elevated in the context of a triggering event (eg, severe infection) without concomitant DIC.
- Often, physiologic inhibitors of coagulation, especially antithrombin III and protein C, are consumed, predisposing to thrombosis.
- The specific laboratory abnormalities in DIC may vary with the triggering event and the course of illness.

DIC - Differential Diagnosis

- DIC can be difficult to distinguish from coagulopathy of liver disease (ie, hepatic synthetic dysfunction), especially when the latter is associated with thrombocytopenia secondary to portal hypertension and hypersplenism.
- Generally, factor VII activity is decreased markedly in liver disease (due to deficient synthesis of this protein, which has the shortest half-life among the procoagulant factors), but only mildly to moderately decreased in DIC (due to consumption).
- Factor VIII activity is often normal or even increased in liver disease, but decreased in DIC.

DIC - Treatment

Therapy for Underlying Disorder

- The most important aspect of therapy in DIC is the identification and treatment of the triggering event.

- If the pathogenic process underlying DIC is reversed, often no other therapy is needed for the coagulopathy.

DIC - Treatment

Replacement Therapy for Consumptive Coagulopathy

- Replacement of consumed procoagulant factors with FFP and of platelets via platelet transfusion is warranted in the setting of DIC with hemorrhagic complications, or as periprocedural bleeding prophylaxis.
- Infusion of 10–15 mL/kg FFP typically raises procoagulant factor activities by approximately 10–15%.
- Cryoprecipitate can also be given as a rich source of fibrinogen; one bag of cryoprecipitate per 3 kg in infants or one bag of cryoprecipitate per 6 kg in older children typically raises plasma fibrinogen concentration by 75–100 mg/dL.

DIC - Treatment

Anticoagulant Therapy for Coagulation Activation

- Continuous intravenous infusion of unfractionated heparin is sometimes given in order to attenuate coagulation activation and consequent consumptive coagulopathy.

- The rationale for heparin therapy is to maximize the efficacy of, and minimize the need for, replacement of procoagulants and platelets.