Hematology

Dr. Hayder Hadi Al-Musawi

- Anemia
- Bleeding tendency
- Malignancies

Learning Objectives:

1) Introduction of blood disorders.
2) Management of:

a. Anemia.
b. Bleeding tendency.

Learning Objectives:

1. Introduction of blood diseases.
2. Management of:

a. Anemia.

b. Bleeding disorders.

Anemia

Introduction

- **Anemia** can be defined as a reduction in hemoglobin concentration, hematocrit, or number of red blood cells per cubic millimeter.
- The **lower limit** of the normal range is set at two standard deviations below the mean for age and sex for the normal population.

Classification

I. ***Impaired red cell formation***

1. Deficiency

A. Iron deficiency
B. Folate deficiency
C. Vitamin B_{12} deficiency
D. Vitamin C deficiency
E. Protein deficiency
F. Vitamin B_6 deficiency
G. Thyroxine deficiency

2. The Bone marrow failure

A. Failure of a single cell line

B. Failure of all cell lines (like aplastic anemia)

C. Infiltration

II. Blood loss

III. Hemolytic anemia

A. Corpuscular

a. membrane defect: spherocytosis, elliptocytosis

b. enzymatic defects : G6PD, pyruvate kinase deficiency

c. hemoglobin defect:

1. Qualitative: sickle cell anemia
2. Quantitative: thalassemia

B. Extra corpuscular

i. Iso-immune: Rh incompatibility

ii. Autoimmune

1. idiopathic: autoimmune hemolytic anemia
2. secondary : immunological disorder e.g. lupus

Aplastic Anemia

Introduction

Definition: Pancytopenia with bone marrow hypocellularity with no malignancy and fibrosis.

A child with aplastic anemia is usually has a serious condition with The following criteria:
Hypoxia to the organs, tissues, and cells (from too few RBCs).
Increased risk of infection (from too few WBCs).
Increased risk of bleeding problems (from too few platelets).

It is a less common cause of anemia in children with an incidence rate of 1-5 per one million population a year.
It has an equal male to female ratio.

Etiology

Congenital: 20%

- Fanconi anemia: autosomal recessive disorder.

Clinical presentation:

- Absent, hypoplastic, or bifid thumb.
- Delayed development and short stature.
- Dark skin color.
- Anemia and purpura of skin is a presenting symptom.
- Bone marrow failure usually develops 5-10 years age.

Fanconi anemia

Laboratory diagnosis:

- Pancytopenia.
- Low reticulocyte count.
- Hypoplastic bone marrow on (BM) biopsy.
- Chromosomal breaks on chromosomal study.

Management:

- Supportive: RBC, and platelet transfusion.
- Drugs: androgens- oxymethalone.
- BM transplant.

Etiology

Acquired: 80%

1) Idiopathic:

- Autoimmune cytotoxicity.
- T-lymphocyte cytokines suppress hematopoiesis.

2) Viral infections:

- Hepatitis (B & C), Epstein-Barr virus (EBV), Parvo B19 virus, and Human immunodeficiency virus (HIV).

3) Medications:

- Chloramphenicol, sulfonamides, cytotoxic drugs, and chemicals.

Clinical features

RBC deficiency:

Pallor, irritability, fatigue, poor appetite, dyspnea, and nausea.

WBC deficiency:

- Fever frequently.
- Pneumonia.
- Sepsis.

Platelet (pl) deficiency:

- Purpura and epistaxis.
- Gum bleeding.
- Malena.

Laboratory investigations

- Pancytopenia.
- Low hemoglobin (Hb).
- Low total red blood cell (RBC) count.
- MCV, MCH, MCHC are normal.
- Blood film: normochromic normocytic anemia.
- Low reticulocyte count.
- Low white blood cell (WBC) count < 4000 mm^3.
- Low absolute neutrophil count (ANC) < 1500.
- Low pl count: < 100 000 mm^3.
- Bone marrow biopsy: hypocellular with excess fat.

Differential diagnosis

- Acute leukemia:

Lymphadenopathy, and hepatosplenomegaly.

- Megaloblastic anemia (folate and vit B_{12} def.):

Macrocytes (high MCV).

- Hypersplenism:

Large spleen due to various causes.

- Systemic lupus erythromatosis (SLE):

Autoimmune disease.

- Myelodysplastic syndrome: BM dysplasia.

Treatment: supportive

- Anemia:

Packed RBC.

- Hemorrhage:

Pl transfusion.

- Infections:

➢ Antibiotics

➢ Antivirals

➢ Granulocyte colony stimulating factor (G-CSF) cytokines.

Specific treatment

1) Immunosuppressive treatment:

- Cyclosporin (immunomodulator).
- Steroids (methylprednisolone).
- Specific anti-bodies:

➢ ATG: anti-thymocyte globulin.

➢ ALG: anti-lymphocyte globulin.

2) BM transplantation: 80% cure rate.

Medical treatment has only 50% cure rate.

IRON DEFICIENCY ANEMIA

Introduction

- Is the most common hematological problem of infancy and childhood.
- Iron is required for hemoglobin (Hb) synthesis, enzyme system and newly regenerated tissue

Iron metabolism-1

- The body of a ***newborn*** infant contains about 0.5g of iron, whereas the ***adult*** content is estimated at 5g.
- Accordingly, to maintain positive iron balance in childhood, about ***1mg of iron must be absorbed each day***.
- ***Factors affect absorption*** and requirement of iron include:

***1) Amount*:**

because absorption of dietary iron is assumed to be about ***10%,*** a diet containing ***8–10mg*** of iron daily is necessary for optimal nutrition.

Iron metabolism-2

***2) Type*:**

Iron is absorbed two to three times more efficiently from *human milk* than from cow's milk.

***3) Age*:**

Infants breast-fed exclusively should receive iron supplementation from 4 months of age.

Adolescents are also susceptible to iron deficiency .

Iron metabolism-3

4) ***Dietary factors*:**

enhance iron absorption

I. *ascorbic acid*

II. *meat*

Etiology

1. ***Deficient intake*:**

2. ***Low birth weight and unusual perinatal***
3. ***hemorrhage*:**

1. ***Increased demand*: as in** LBW, premature babies.

Etiology

4. ***blood loss*** **:**

- ***Chronic diarrhea*** may be associated with unrecognized blood loss.

4. ***Exchange transfusion*****:**
5. ***Intense exercise conditioning*****:**
6. ***Impaired absorption***: malabsorption syndromes or celiac disease.

Clinical manifestations-1

- **Pallor** is the most important clue to IDA.
- **Blue sclera** are also common, although also found in normal infants.
- **Irritability.**
- **Pagophagia**, the desire to ingest unusual substances such as ice or dirt, may be present.
- **Anorexia**
- **Splenomegaly and stroke,** rarely.

Clinical manifestations-2

- Neurologic and intellectual function, such as changes in attention span, alertness, and learning difficulties in both infants and adolescents.

Laboratory findings-1

In progressive iron deficiency, a sequence of biochemical and hematologic events may occur :

1. First, the tissue iron stores represented by bone marrow *hemosiderin* disappear. The level of *serum ferritin*, decreased. Next,

1. *Serum iron* level decreases, the *iron-binding capacity* of the serum increases, and the percent saturation decreases.

$$\textit{Transferrin saturation} = \frac{\text{S. iron}}{\text{TIBC}}$$

<15% in IDA

Laboratory findings-2

3. *Hematological changes*: blood film:

- As the deficiency progresses, the RBCs become smaller than normal (microcytosis) and their hemoglobin content decreases (hypochromia).
- The morphologic characteristics of RBCs are best quantified by the determination of mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV).
- With increasing deficiency, the RBCs become deformed and misshaped and present characteristic *poikilocytosis*, and *increased RBC distribution width* (RDW).

Laboratory findings-3

5. The ***bone marrow*** is:

- *Hypercellular*, with erythroid hyperplasia.

6. ***Occult blood*** can be detected in the stools of about one third of cases.

Differential diagnosis

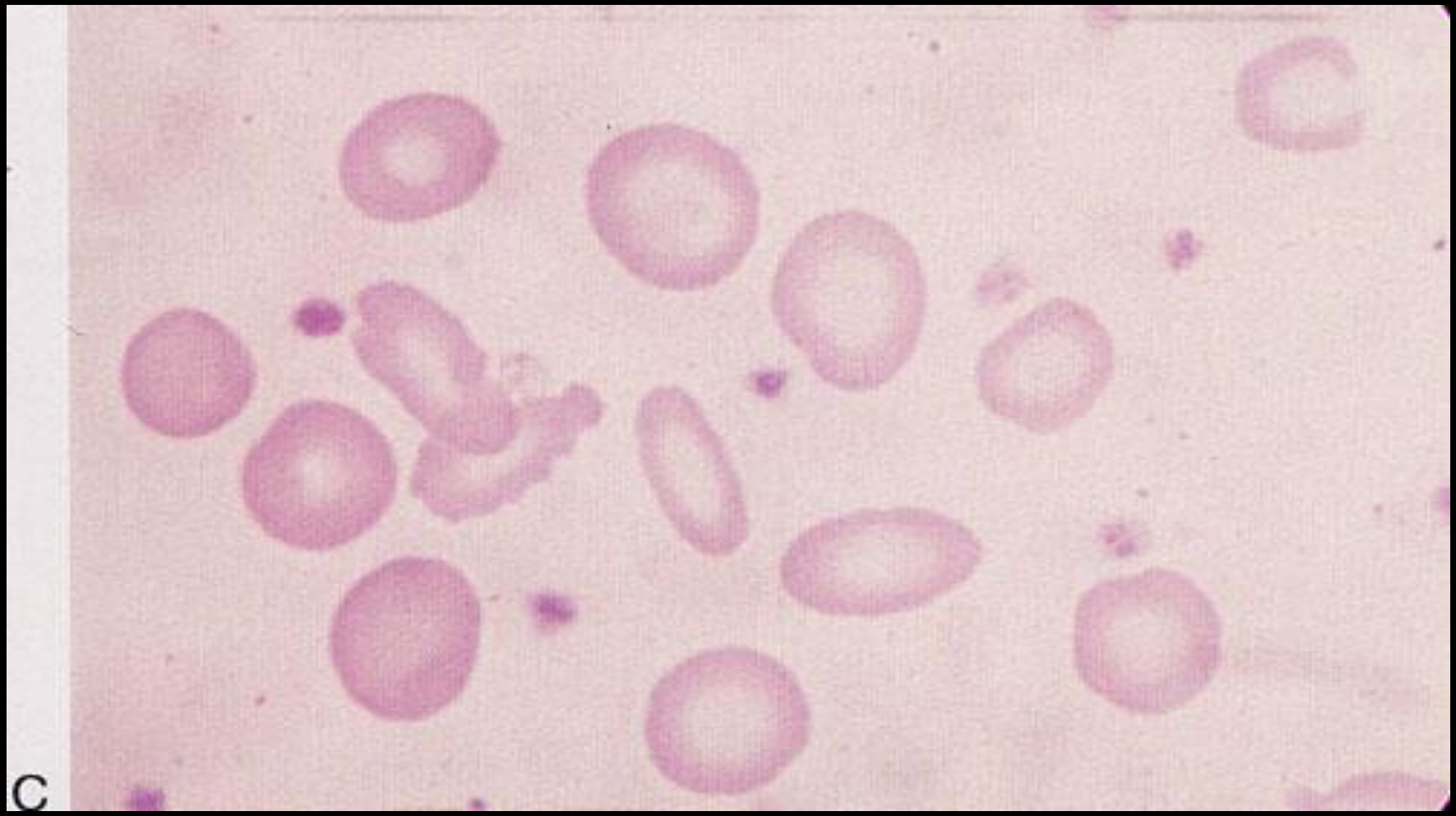
1) *Lead poisoning*
2) *Thalassemia syndrome*
3) *Anemia of chronic inflammation and infection*

Treatment

- ***Oral iron***: 6 mg/Kg/ day of elemental iron in divided doses until normal Hb is achieved, then continue for 2-3 months to replace the iron store.
- ***Parenteral iron***: intramuscular & not intravenous, but it has no advantages over the oral route.
- ***Blood transfusion***:

  It is indicated only when the *anemia is very severe.*

Hypochromic microcytic (iron deficiency)



MEGALOBALSTIC ANEMIAS

- Megaloblastic morphology may be seen in several conditions; almost all cases in children result from a deficiency of folic acid, vitamin B_{12}, or both.
- Both substances are cofactors required in the synthesis of nucleoproteins.

FOLIC ACID DEFICIENCY

Causes

Primary : is rare

- *Inadequate dietary intake.*
- *Goat milk.*

Secondary: is more common, account for most cases:

1) GIT: surgical removal or GIT disorders.
2) Increased requirement:
   rapid growth
   infections

Clinical features

- *Peak incidence* at the age of 4-7 months (slightly earlier than IDA).
- Mild *anemia* has been reported in very low birth weight infant and routine folic acid supplementation is required.
- The usual clinical features of anemia.

Laboratory findings

- Blood smear (film) :
  - Macrocytic anemia (high MCV).
  - The neutrophils are large, some with hypersegmented nuclei.
  - Decreased serum folic acid .
  - Levels of RBC folate are a better indicator of chronic deficiency.
- Serum activity of lactic acid dehydrogenase (LDH) is markedly elevated.
- The bone marrow is hypercellular because of erythroid hyperplasia. Megaloblastic changes are prominent.

Treatment

- folic acid may be administered orally or parenterally for one month.
- Because a hematologic response can be expected within 72 hours, blood transfusions are indicated only when the anemia is severe, or the child is very ill.

VITAMIN B12 DEFICIENCY

Source: vitamin B_{12} is derived from cobalamin in food from animal sources.

Metabolism:

- The cobalamins are released in the acidity of the stomach and combine there with R proteins and intrinsic factor (IF) and are absorbed in the distal ileum via specific receptors.

Causes

- ***dietary deficiency*** is rare. It may occur in cases of extreme dietary restriction (strict vegetarians: "vegans")
- *Surgery or any disease* involving the stomach or terminal ileum,
- *Juvenile Pernicious anemia*:
  - Rare autosomal recessive disorder results from an inability to secrete gastric IF or secretion of a functionally abnormal IF.
  - The symptoms of juvenile pernicious anemia become prominent at 9mo–11yr of age. This interval is consistent with exhaustion of the stores of vitamin B12 acquired in utero.
- *Lack of secretion of IF* by the stomach.

Clinical features

- Signs and symptoms of anemia.

- Sub acute dorsolateral degeneration of spinal cord (rare in children).

  Neurologic manifestations include ataxia, paresthesias, hyporeflexia, Babinski responses, clonus, and coma.

- Glossitis (common in children).

Laboratory findings-1

- *Peripheral smear (CBC)* shows
  - ✓ Macrocytic RBCs.
  - ✓ Neutrophil is large and hypersegmented
- *Serum B12* levels are decreased.
- *Serum LDH* activity is markedly increased.
- Excessive excretion of *methylmalonic acid in the urine* is a reliable and sensitive index of vitamin B12 deficiency.

Laboratory findings-2

- Absorption of vitamin B_{12} is usually assessed by :

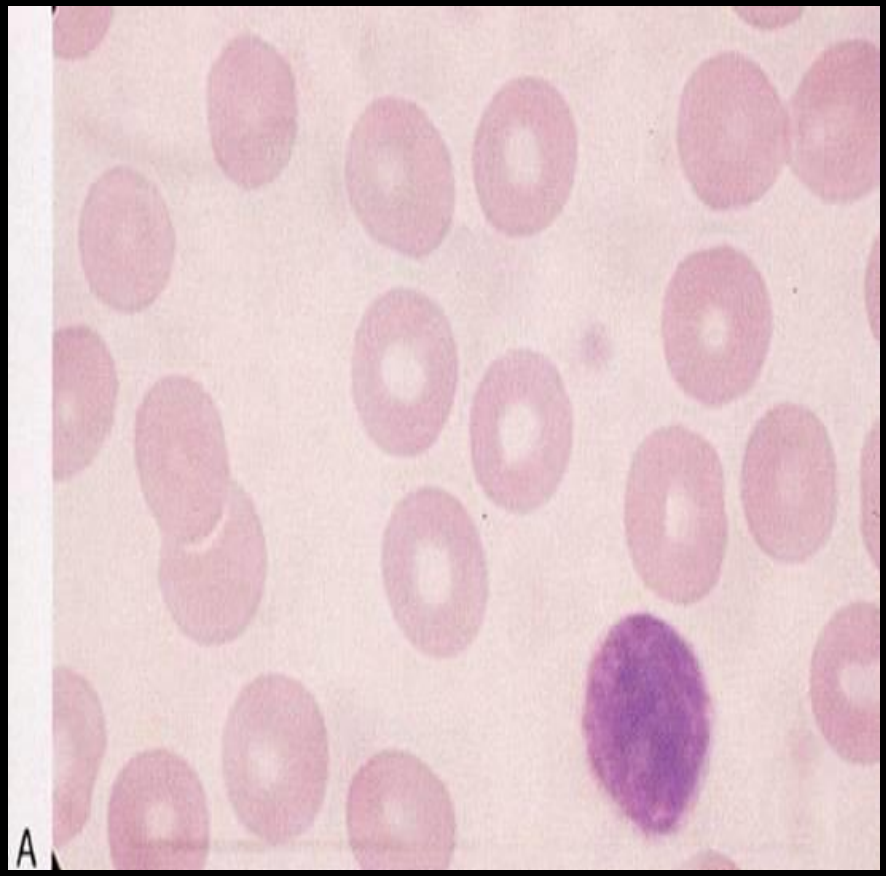
Schilling test

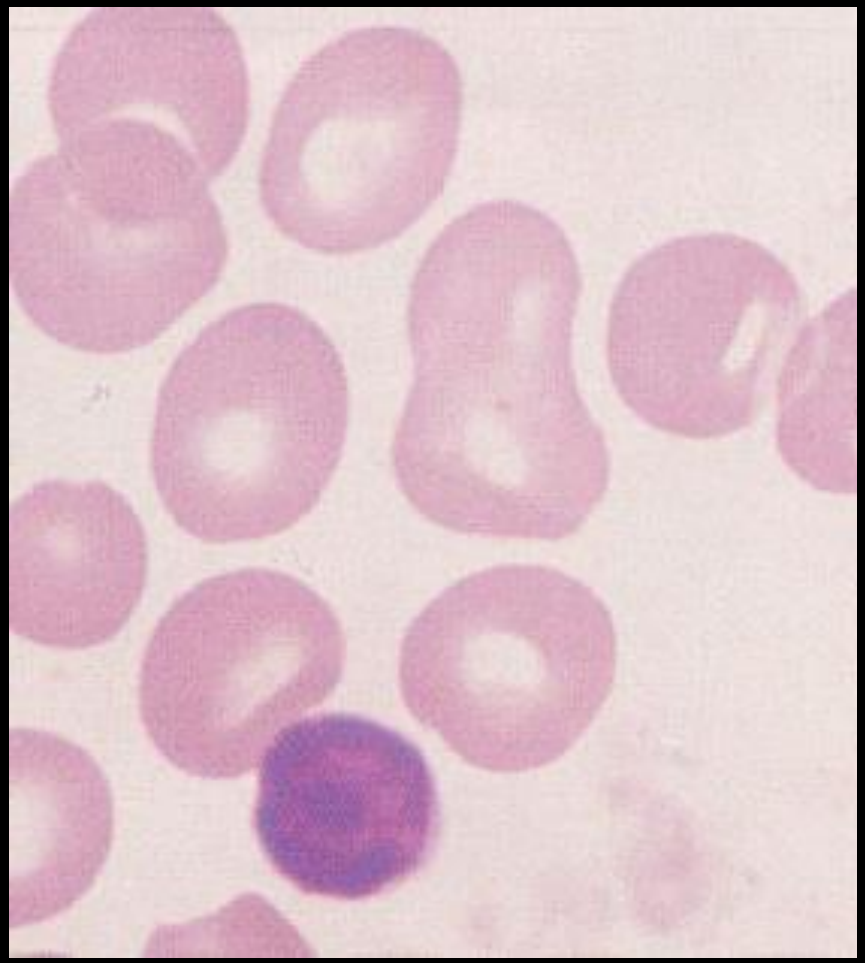
Vitamin B_{12} and / or IF are given to confirm the diagnosis.

Treatment

- A prompt hematologic response follows parenteral administration of vitamin B_{12} (1mg).
- Oral therapy is not generally advisable owing to uncertainty of absorption.

Morphologic abnormalities of the red blood cell. *A,* Normal. *B,* Macrocytes (folic acid or vitamin B_{12} deficiency).





HEMOLYTIC ANEMIAS

- Hemolysis is defined as the premature destruction of red blood cells (RBCs).
- During hemolysis, RBC survival is shortened, and increased marrow activity results in an increased reticulocyte (new RBC) count.
- the reticulocyte index is 1% normally.
- Indirect bilirubin is increased leading to jaundice.
- CBC : destructed, fragmented & misshaped RBCs (poikilocytosis). Hb levels are decreased.
- Decreased serum haptoglobin levels.
- Urine examination shows Hb in urine (hemoglobinuria) and appearance of urobilinogen.

ENZYMETIC DEFECTS

Glucose 6 Phosphate Dehydrogenase Deficiencies

- Is the most important disease of the hexose monophosphate pathway.
- This is an example of X-linked recessive disease.
- It is responsible for two clinical syndromes:
  1. An acute episodic hemolytic anemia.
  2. Chronic hemolytic anemia.

Clinical manifestations 1

- In the usual pattern of G6PD deficiency, symptoms develop 24–48hr after a patient has ingested a substance that has oxidant properties.
  - *Drugs* that have these properties include aspirin, Sulfonamides, and antimalarials such as primaquine.
  - In some patients, ingestion of *fava beans*, may also produce an acute and severe hemolytic syndrome called *favism*.
  - Infection and fever are trigger factors.

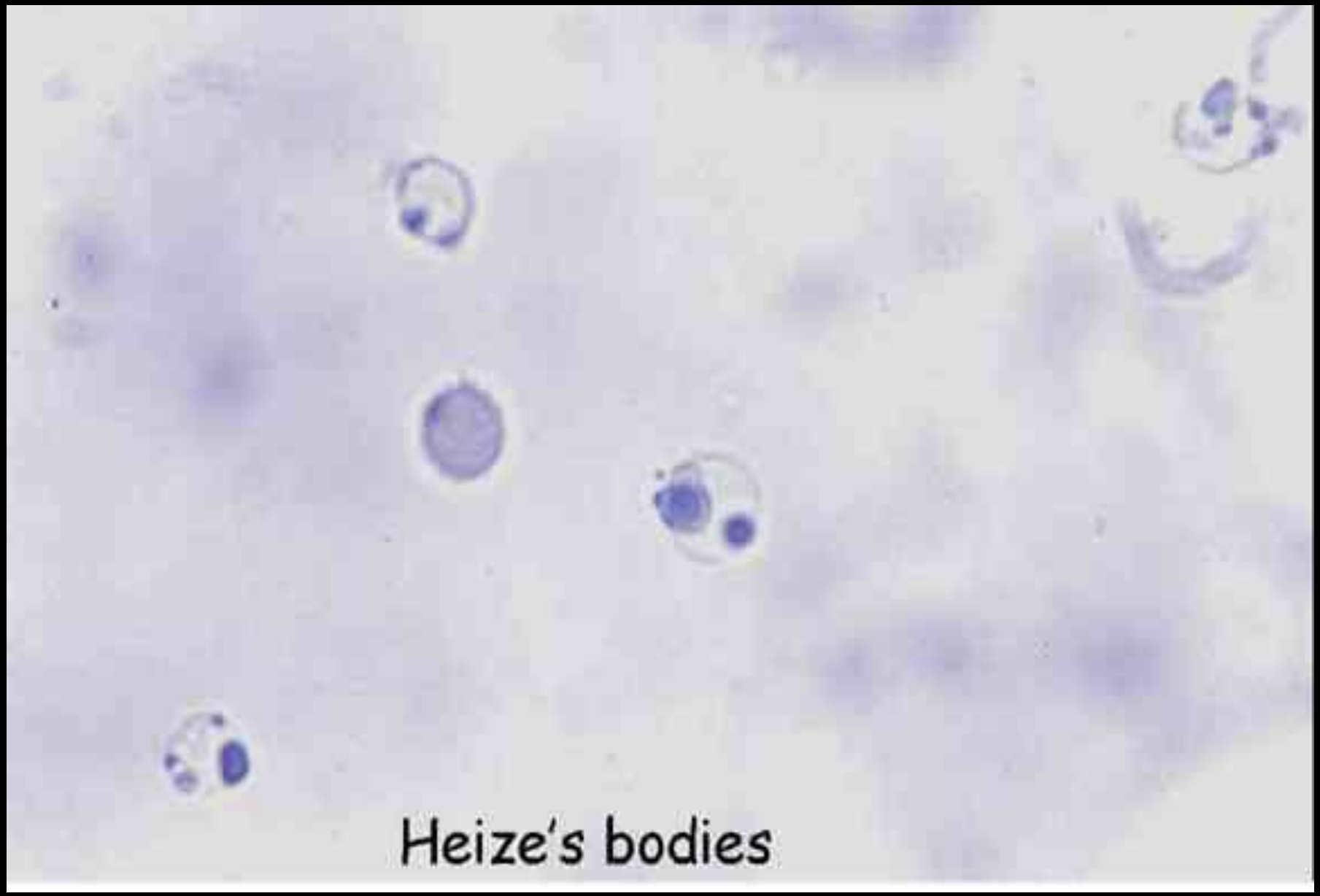
Clinical manifestations 2

- hemoglobinuria and jaundice may occur, and the hemoglobin concentration may fall precipitously with the resultant of life-threatening condition.

- Neonatal hyperbilirubinemia and potential kernicterus.

Laboratory findings

- The onset of acute hemolysis results in a progressive fall in hemoglobin (Hb).
- Blood film: unstained RBCs reveal Heinz bodies (precipitated hemoglobin). They are not seen after the first 3–4 days of illness. The blood film reveals a few fragmented RBCs.


Heize's bodies

Diagnosis

- Demonstration of a reduced G6PD activity in RBCs. By direct measurement.
- The young RBCs (reticulocytes) have significantly higher enzyme activity than do older cells. Testing may therefore have to be deferred for 8-12 weeks before a diagnostically low level of enzyme can be shown.
- G6PD variants also can be detected by electrophoretic analysis.

Prevention and treatment

- Prevention of hemolysis constitutes the most important therapeutic measure.
- Avoidance of oxidants in known patients.
- When hemolysis occurs, supportive therapy may require I/V fluids and blood transfusions, although recovery is the rule when the oxidant agent is removed.

STRUCTURAL DEFECTS

HEREDITARY SPHEROCYTOSIS

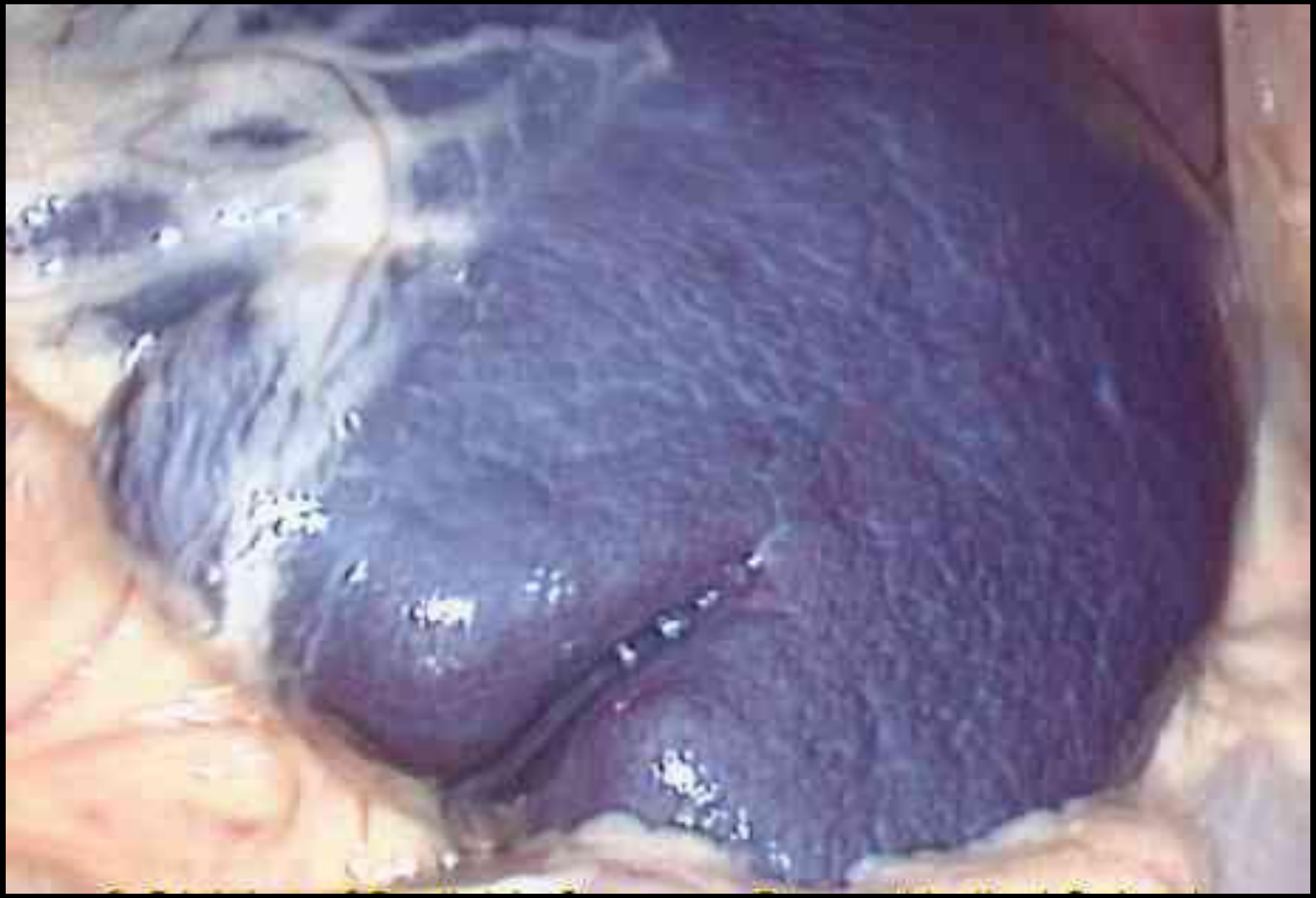
- Usually is transmitted as an autosomal dominant and, less frequently, as an autosomal recessive disorder, but it may occur because of mutations.

Clinical manifestations 1

- ***Neonates***: Hereditary spherocytosis may be a cause of hemolytic disease in the newborn and may present with anemia and hyperbilirubinemia sufficiently severe to require phototherapy or exchange transfusions.
- ***Infant and older children***: The severity is variable, but may have severe anemia with pallor, jaundice, fatigue, and exercise intolerance.

Clinical manifestations 2

- ***Examination***: splenomegaly & gallstones.
- ***Aplastic crises***: which is caused by a viral infection, called parvovirus B_{19} virus, and hypoplastic crises are associated with various other infections.



Laboratory findings

- ***CBC*: (complete blood count)**

Spherocytes usually account for more than 15–20% of the cells when hemolytic anemia is present.

- Erythroid hyperplasia is evident in the **bone marrow aspirate or biopsy**.
- ***osmotic fragility test.***
- ***Auto hemolysis test.***
- ***gel electrophoresis:*** *to demonstrate RBC membrane defect.*

Treatment

- ***splenectomy*** eliminates most of the hemolysis associated with this disorder.

  splenectomy is not preferred before 5 years of age,

  otherwise, patients should receive hepatitis B vaccination

  and regular benzathine penicillin injections on monthly basis,

  or penicillin V orally on daily basis.

  this is due to loss of splenic immunologic function against

  some viruses & encapsulated bacteria, such as pneumococci, meningococci, and *Hemophilus influenzae* type b.

- ***Folic acid***, should be administered to prevent secondary folic acid deficiency.

THALASSEMIA SYNDROMES

Introduction

- The thalassemias are a *heterogeneous group of heritable hypochromic anemias* of various degrees of severity.
- Underlying genetic defects include *total or partial deletions* of globin chain genes.

Introduction 2

- Important types of thalassemia are :
  - α- thalassemia; which may lead to hydrops fetalis in sever cases.
  - β- thalassemia :

a) thalassemia minor (trait).

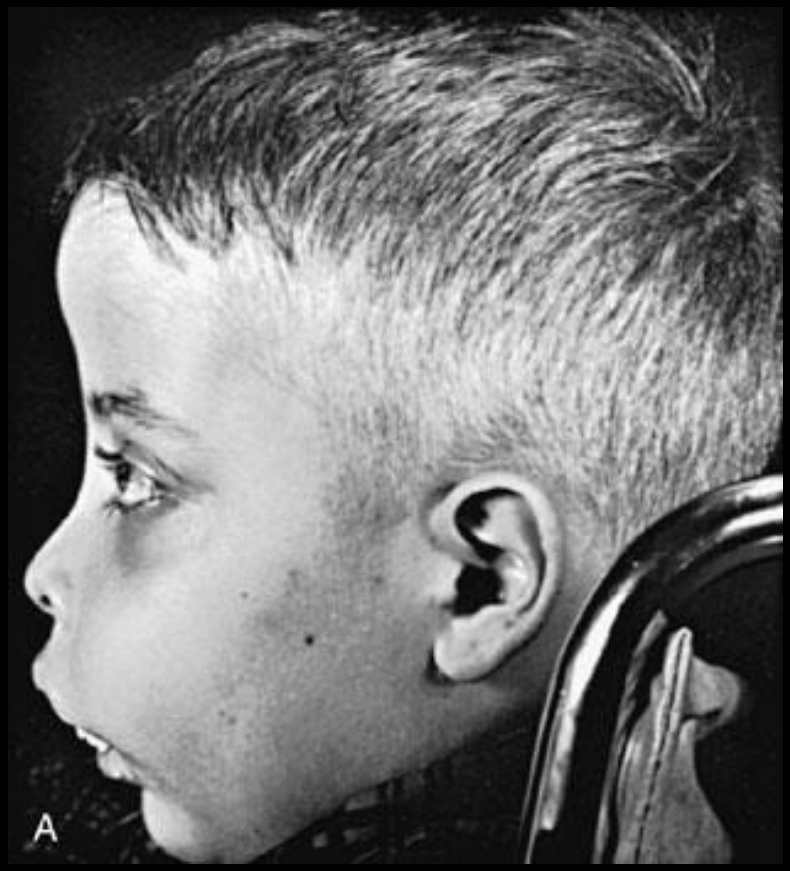
b) b) thalassemia major.

c) thalassemia intermedia; which is in between the above.

HOMOZYGOUS β – THALASSEMIA
THALASSEMIA MAJOR: COOLY`s ANEMIA

Clinical manifestations

- Pallor, hemosiderosis, and jaundice combine to produce a greenish-brown appearance color.
- hypertrophy of erythropoietic tissue occurs in medullary and extramedullary locations. The bones become thin, and pathologic fractures may occur. Massive expansion of the marrow of the face and skull produces characteristic facies.
- Hepatosplenomegaly.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Laboratory findings

- ***CBC***: The RBC morphologic abnormalities are extreme. Such as severe hypochromic and microcytic RBCs, with many bizarre, fragmented poikilocytes are present. The hemoglobin level falls progressively to lower than 5g/dL unless transfusions are given. .
- Increased serum ferritin levels.
- The diagnosis can be made by Hb – electrophoresis (Hb-f is increased).

Management

A. Regular blood transfusion.

B. ***Iron Chelation therapy:***

Like :

- Desferal, which is given subcutaneously for 12 hours 5 nights / week.
- Exjade, which is an oral therapy.

D. Splenectomy.

E. Folic acid.

F. Bone marrow transplantation.

E. Gene therapy.

SICKLE CELL HEMOGLOBINOPATHIES

Introduction

- Sickle hemoglobin (Hb S) differs from normal adult hemoglobin by a substitution of ***glutamic acid*** at the ***6th position*** of its ***β chains*** by ***valine***.

SICKLE CELL ANEMIA

Clinical manifestations

- Hemolytic anemia gradually develops over the 1st 2 – 4 months of life.
- Acute sickle dactylitis (hand-foot syndrome),may occur during 1st year of life.

Crises

1. ***Vaso-occlusive crises***

- ❑ Acute painful episodes represent the most frequent and prominent manifestation of sickle cell disease.
- ❑ Intercurrent illnesses, fever, hypoxia, and acidosis, are trigger factors for these crises.

- ***Splenic*** infarcts causing pain and "auto-splenectomy."
- ***Pulmonary*** infarctions leading to chest pain and *acute chest syndrome*.
- ***Strokes***.
- Ischemic damage may also affect any organ.

Crises

2. Sequestration crises

acute splenic sequestration

3. A plastic crisis

with parvovirus B19 infection.

***4. Hyper hemolytic crises*:**

sickle cell anemia and G6PD deficiency.

Laboratory findings

- CBC: hemoglobin concentrations usually range from 5–9 g/dL. The peripheral blood smear typically contains poikilocytes, and irreversibly sickled cells.
- Diagnosis is made by Hb-electrophoresis (Hb-S is increased).

Treatment

1) *Preventive measures :* to prevent serious illnesses by immunizations, prophylactic antibiotics, and prompt treatment of any infection.
2) Painful crises : treated by analgesics and blood transfusions.
3) Splenectomy for repeated splenic sequestration crises.
4) *Stimulation of Hb-f synthesis : using drugs like hydroxyurea.*
5) *Bone marrow transplantation : curative measure.*


GUISHER

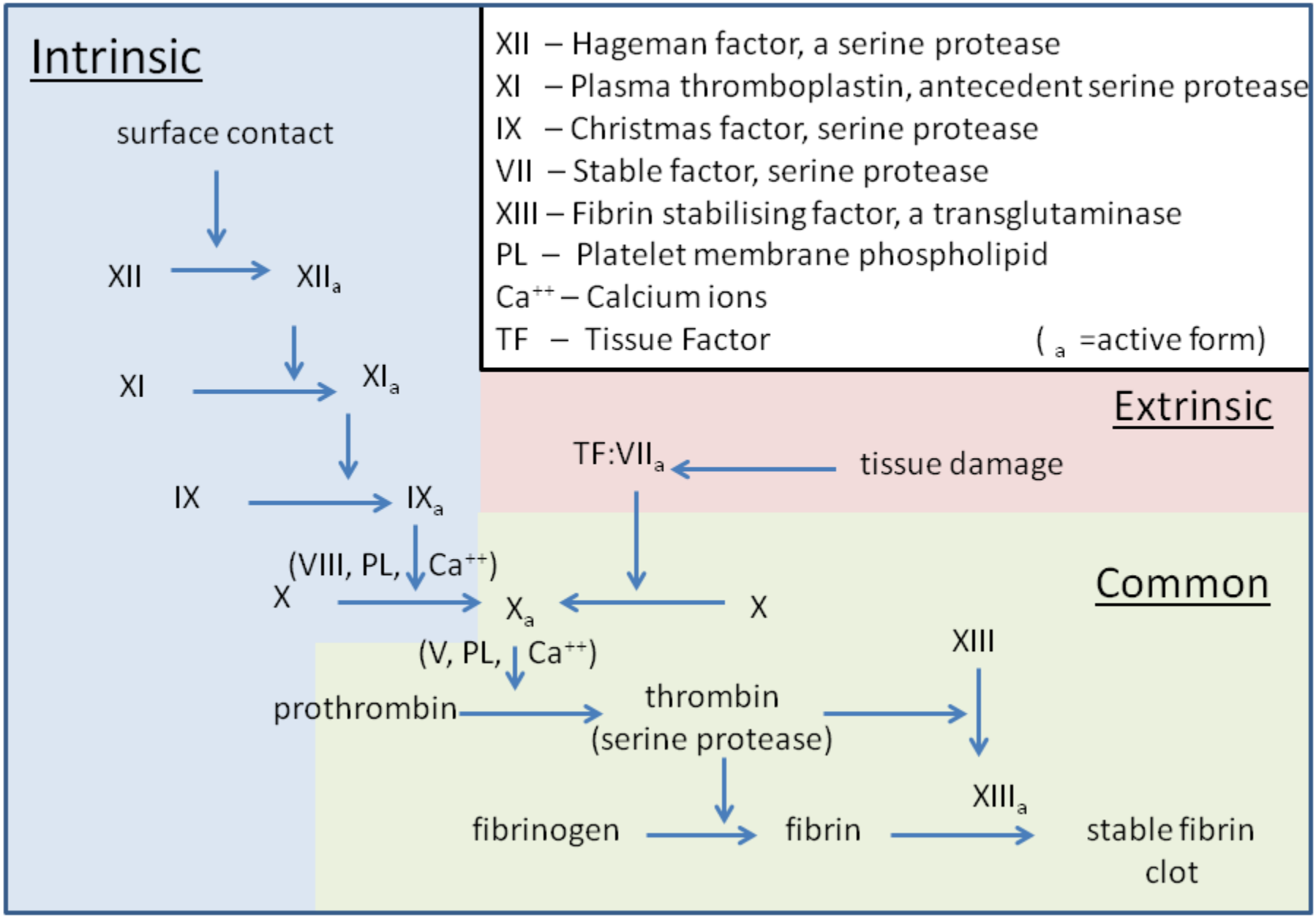
BLEEDING TENDENCY

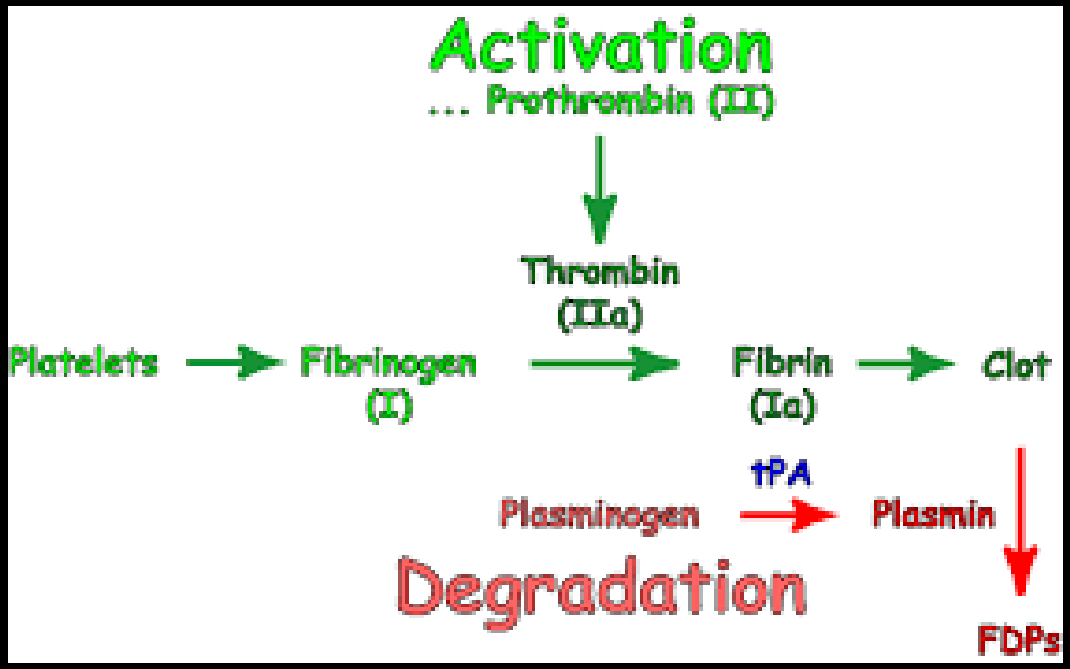
Dr. Hayder Hadi Al-Musawi

HEMOSTASIS

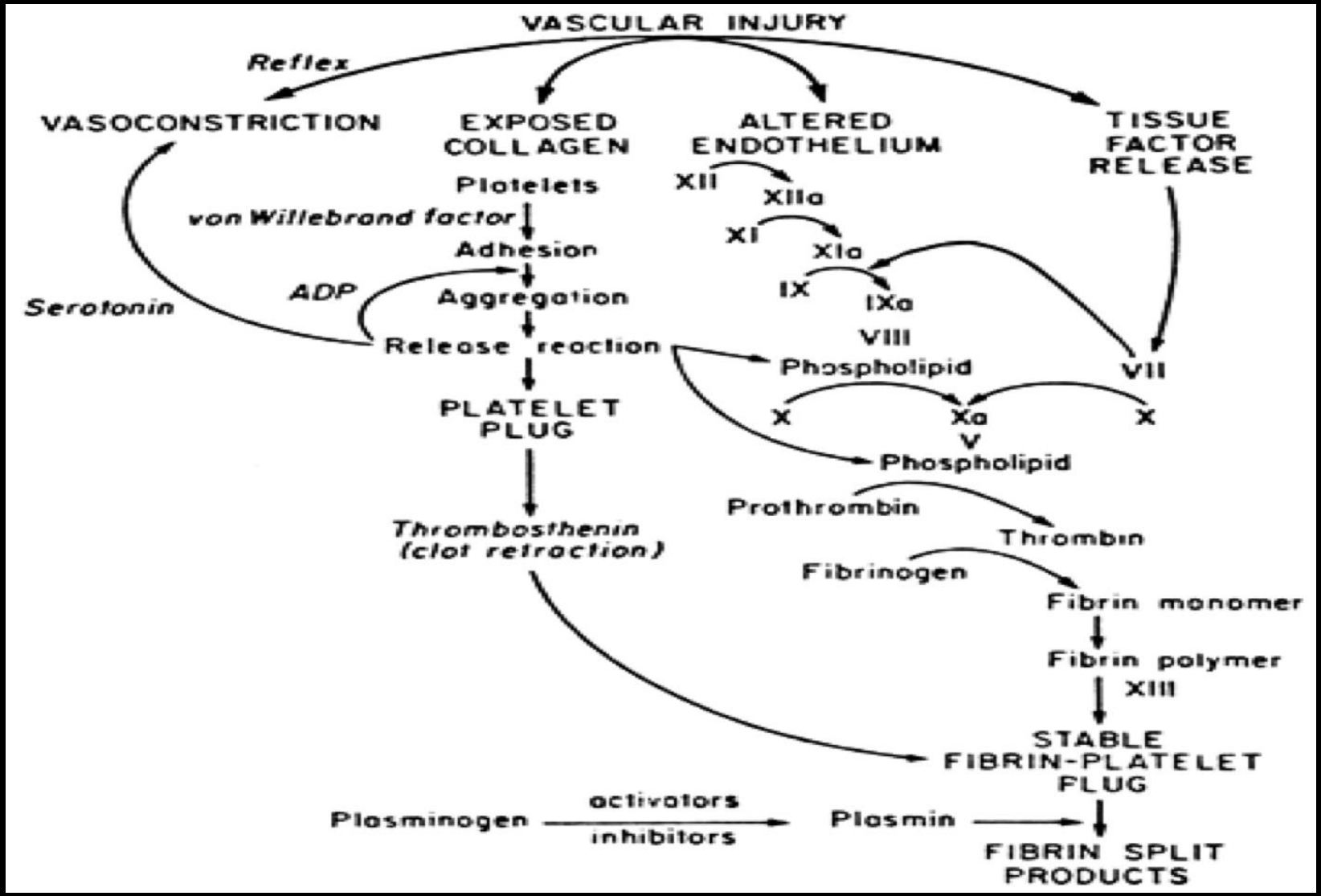
- When blood vessels are injured, the clotting process causes blood flow to cease through the injured vessel.
  - If clotting is ***impaired***, hemorrhage occurs.
  - If clotting is ***excessive***, thrombosis and its complications occur.
  - ***Small blood vessels*** : vasoconstriction + platelet
  - ***Large blood vessels***: full hemostatic process to provide a firm stable fibrin clot.
- The extent of clotting is localized by the anticoagulant system. The removal of the clot requires appropriate fibrinolysis.

The three pathways that makeup the classical blood coagulation pathway





tPA: tissue plasminogen activator.
FDPs: fibrin degradation products.


VASCULAR INJURY
Reflex
VASOCONSTRICTION
EXPOSED COLLAGEN
ALTERED ENDOTHELIUM
TISSUE FACTOR RELEASE
Platelets
von Willebrand factor
Adhesion
ADP
Aggregation
Serotonin
Release reaction
PLATELET PLUG
Thrombosthenin (clot retraction)
XII
XIIa
XI
XIa
IX
IXa
VIII
Phospholipid
VII
X
Xa
V
X
Phospholipid
Prothrombin
Thrombin
Fibrinogen
Fibrin monomer
Fibrin polymer
XIII
STABLE FIBRIN-PLATELET PLUG
Plasminogen
activators
inhibitors
Plasmin
FIBRIN SPLIT PRODUCTS

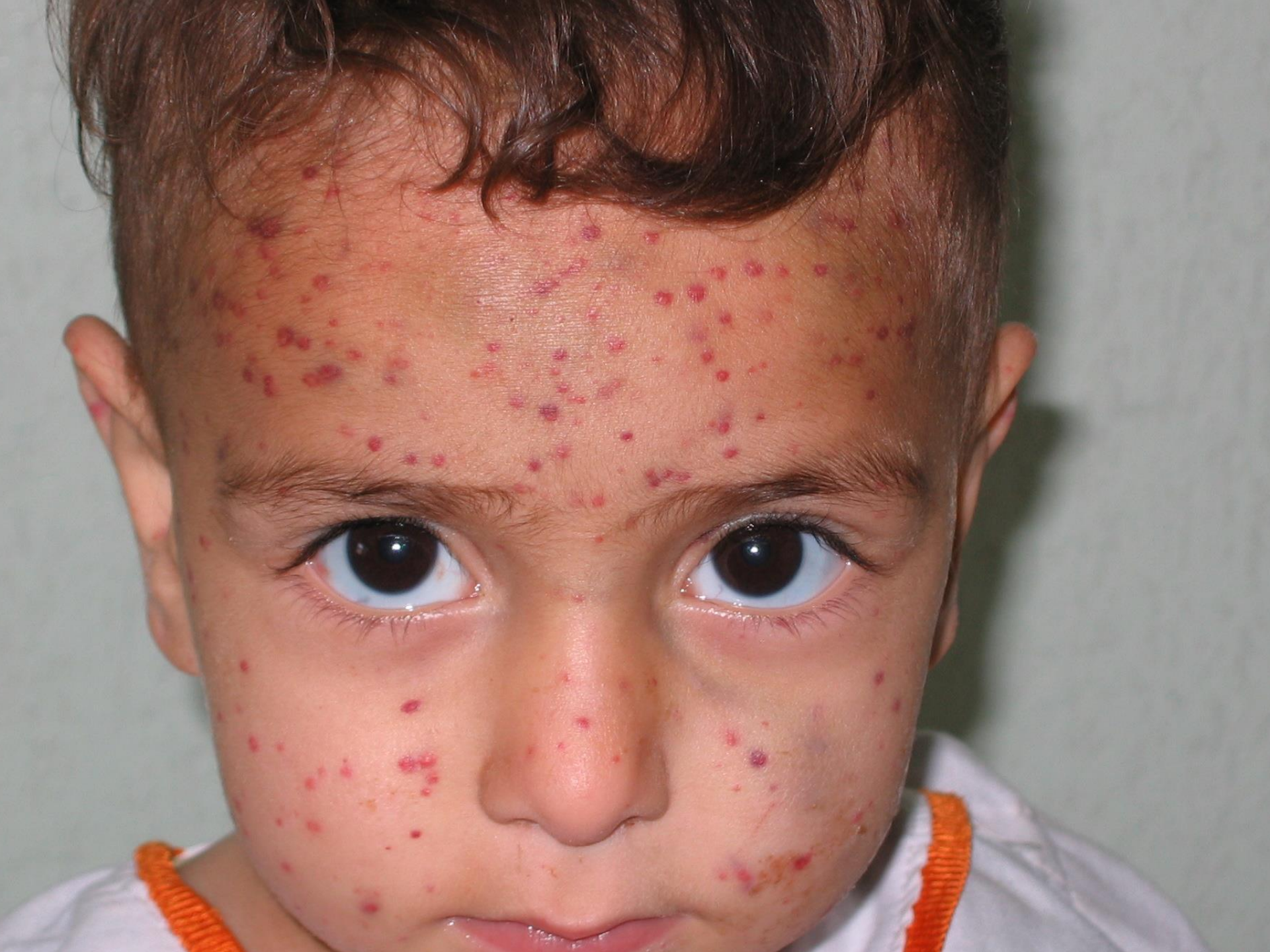
IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)

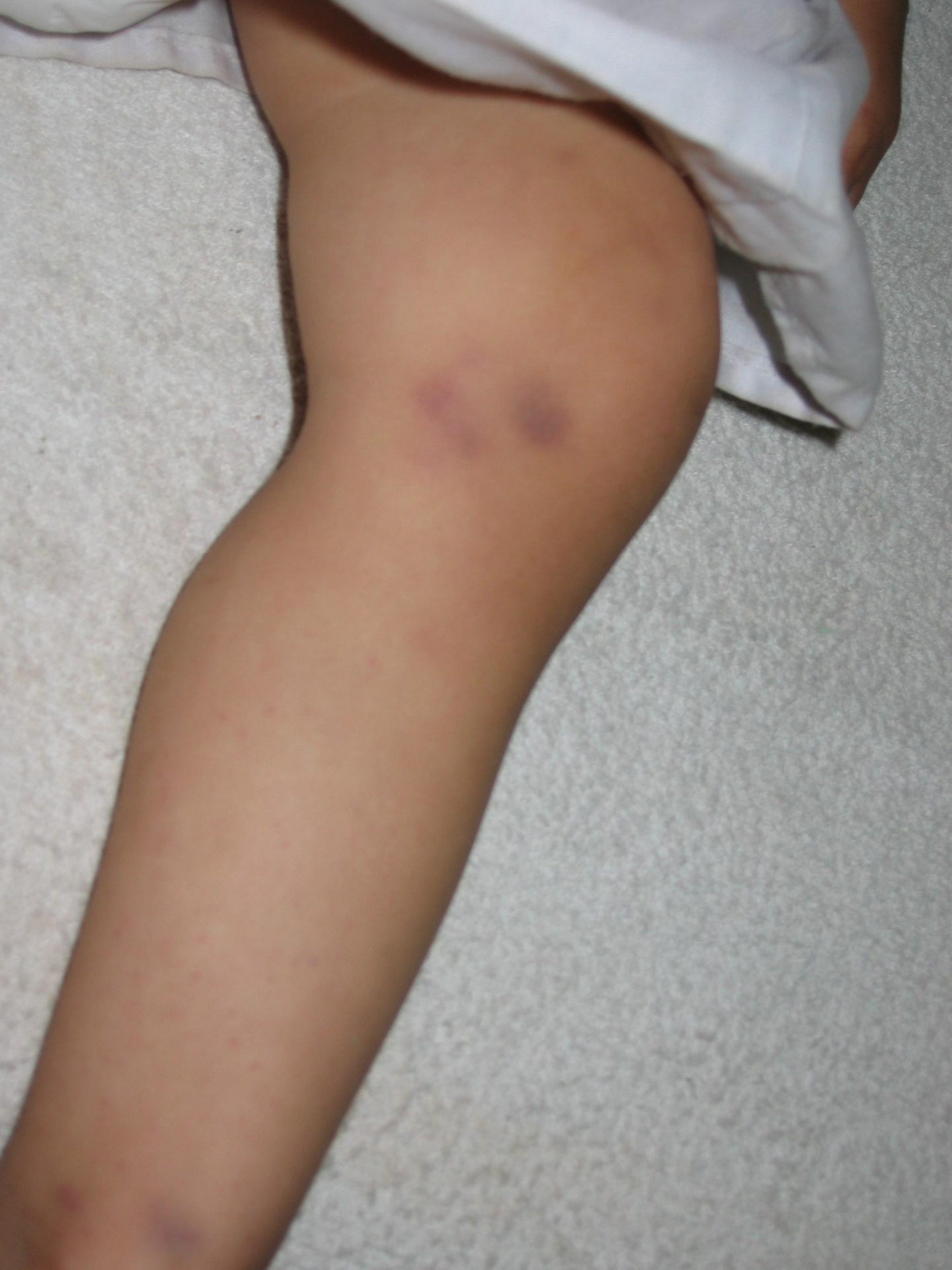
Etiology

- ITP is the most common cause for acute onset thrombocytopenia in an otherwise well healthy child.
- One to four weeks following exposure to a common viral infection, a small number of children develop an autoantibody directed against the platelet surface.

Clinical manifestations

- The classic presentation of ITP is that of a perfectly healthy 1- to 4-yr-old child who has the sudden onset of generalized petechiae and purpura. The parents often state that the child was fine yesterday and now is covered with bruises and purple dots. Often there is bleeding from the gums and mucous membrane.
- Less than 1% of cases develop intracranial hemorrhage.
- Minority of children who present with acute ITP go on to develop chronic ITP.

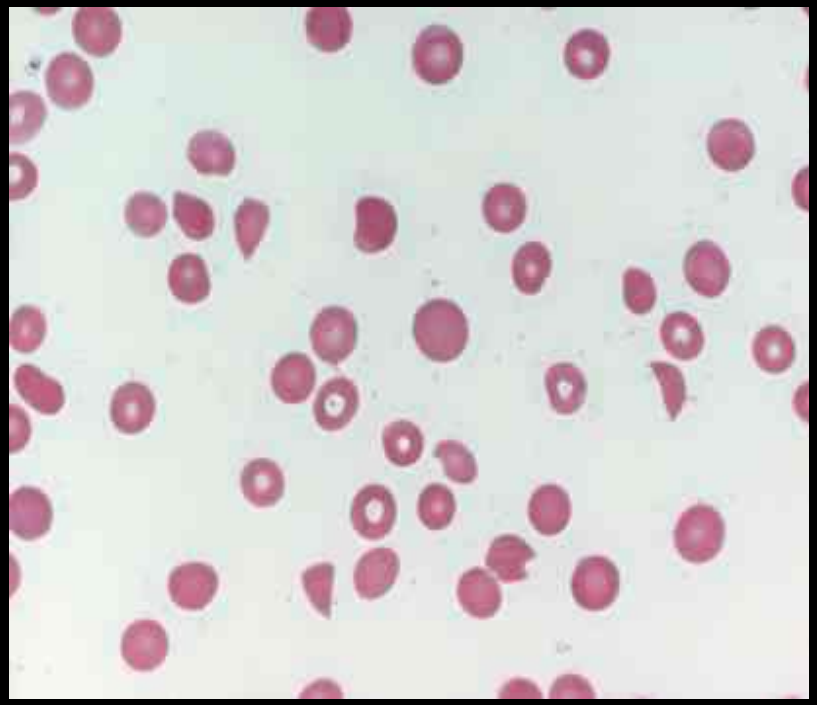


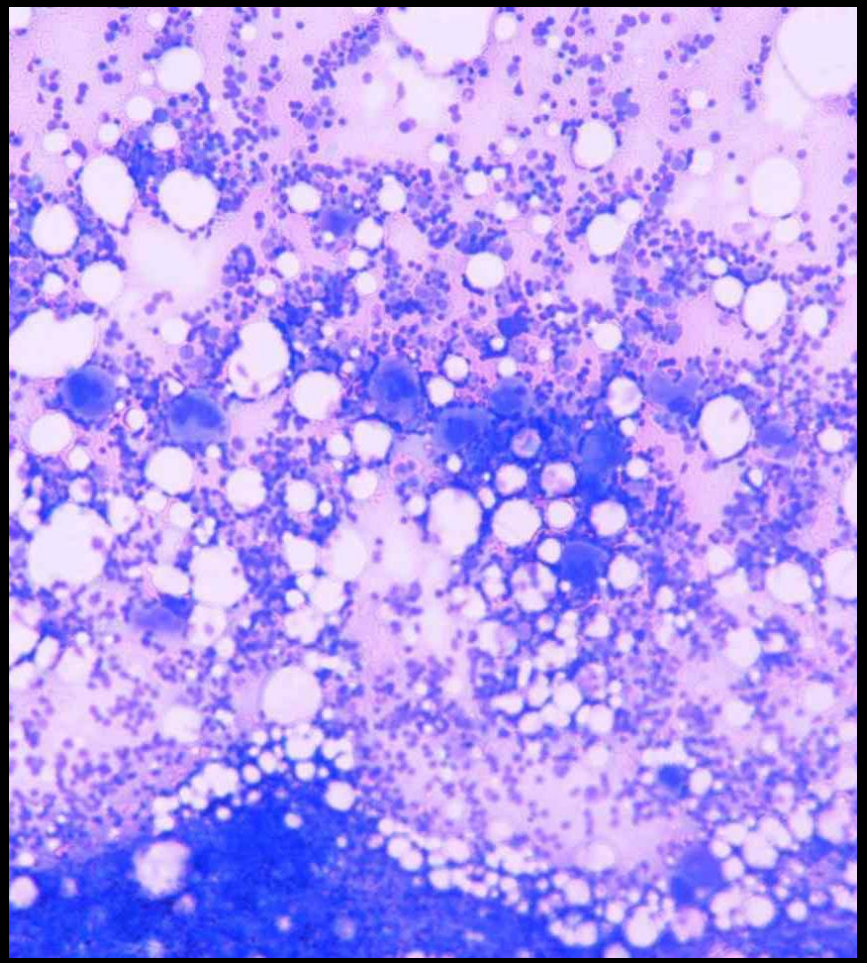


Laboratory findings

1) Severe thrombocytopenia (platelet count <20 000/ mm^3) is common.
2) The hemoglobin may be decreased if there have been profuse nosebleeds or menorrhagia.
3) Coombs test should be done if there is unexplained anemia to rule out Evans syndrome (autoimmune hemolytic anemia and thrombocytopenia).
4) The bone marrow examination, reveals normal or increased numbers of megakaryocytes.

Low peripheral platelet count with increased bone morrow megakaryocytes





Treatment 1

- Treatment appears to be capable of inducing a more rapid rise in platelet count to the theoretically safe level of 20,000/mm3.
- Most of children will have spontaneous resolution of their ITP within 6 months.
- Initial treatment options include the following:

A. Intravenous immunoglobulin

a. IVIG for 1–2 days induces a rapid rise in platelet count (usually >20 000/mm^3) within 2days.

Treatment 2

B. Prednisone:

a. Doses of 1–4 mg/kg/24 hr of prednisone.

b. Corticosteroid therapy is usually continued for 2 to 3 wk or until a rise in platelet count above 20,000 has been achieved with a rapid taper to avoid the long-term side effects.

C. IV Anti-D Therapy :

The role of IV anti-D in initial therapy of acute ITP is under investigation.

Treatment 3

D. Splenectomy

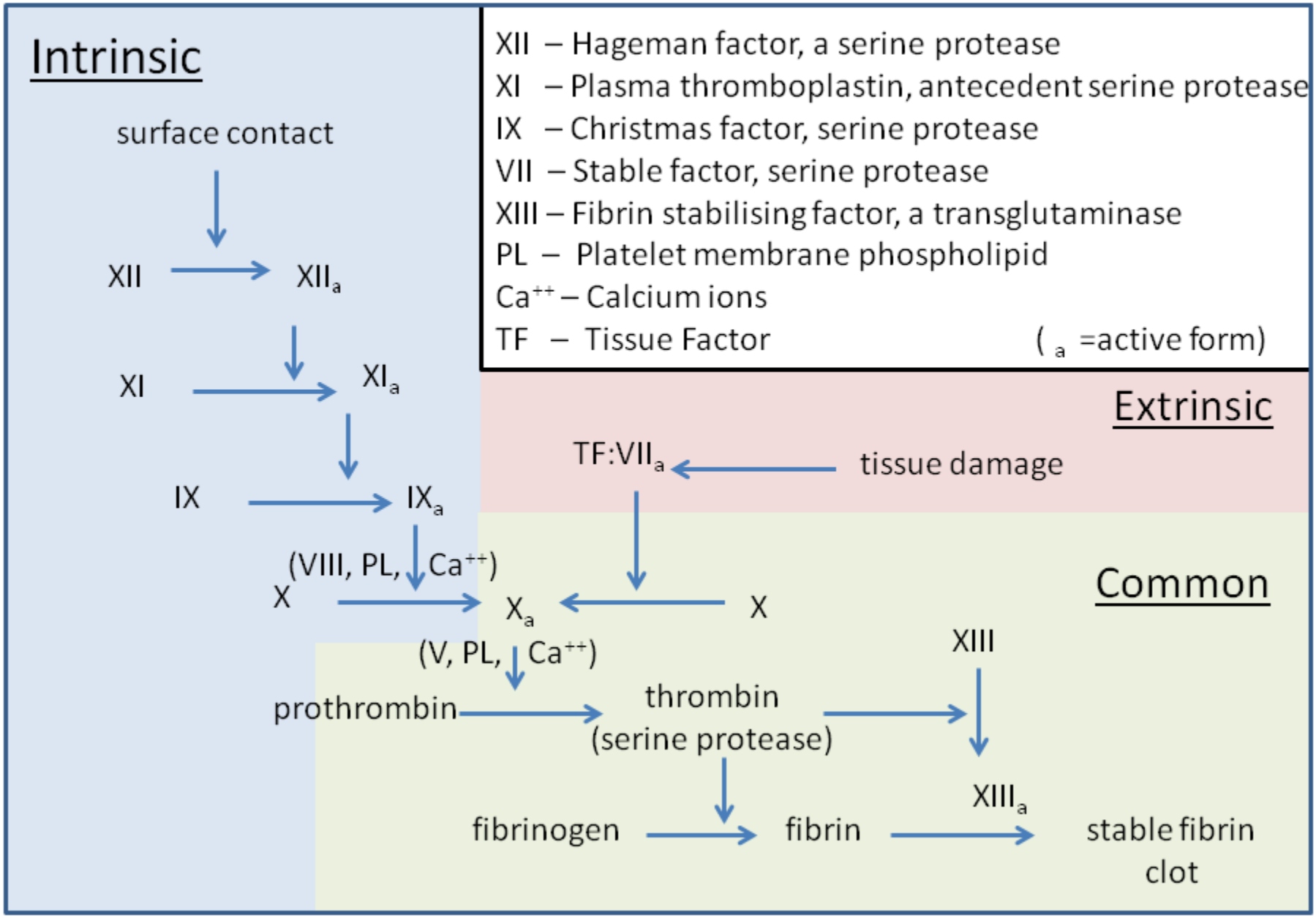
The role of splenectomy in ITP should be reserved for one of the following circumstances:

- The older child ($\geq$ 4 yr) with severe ITP that has lasted longer than 6 months (chronic ITP).
- Splenectomy must also be considered when life-threatening hemorrhage (intracranial hemorrhage).
- Failure of other treatment options.

HEMOPHILIA A & B

Factor VIII and factor IX deficiencies are the most common severe inherited bleeding disorders

The three pathways that makeup the classical blood coagulation pathway



Pathophysiology 1

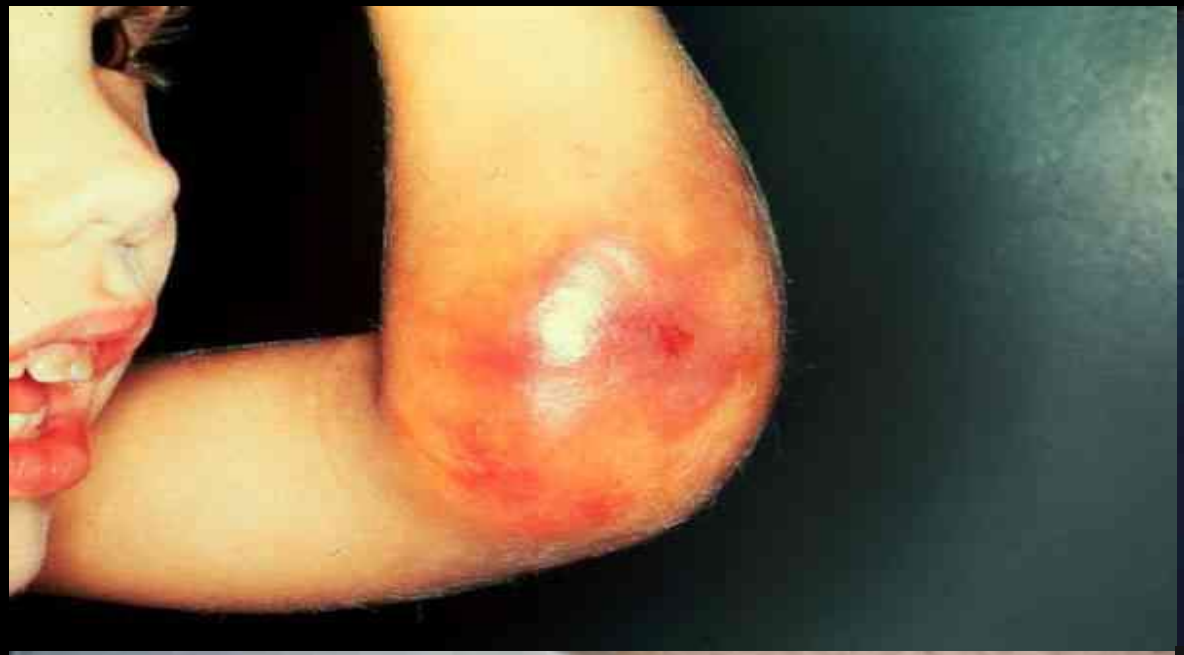
- PT (Prothrombin Time): is prolonged if any deficiency is found in the extrinsic pathway.
- PTT (Partial Thromboplastin Time): is prolonged if any deficiency is found in the intrinsic pathway.
- TT (Thrombin Time): is prolonged if any deficiency is found in the common pathway.

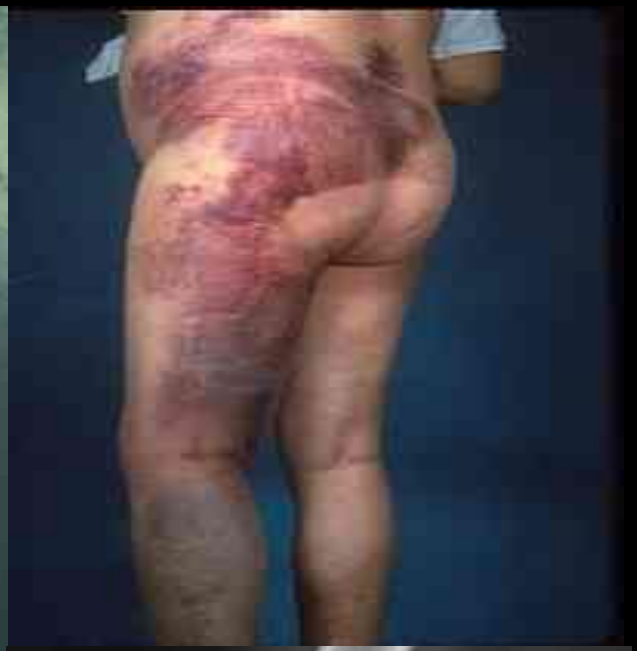
Pathophysiology 2

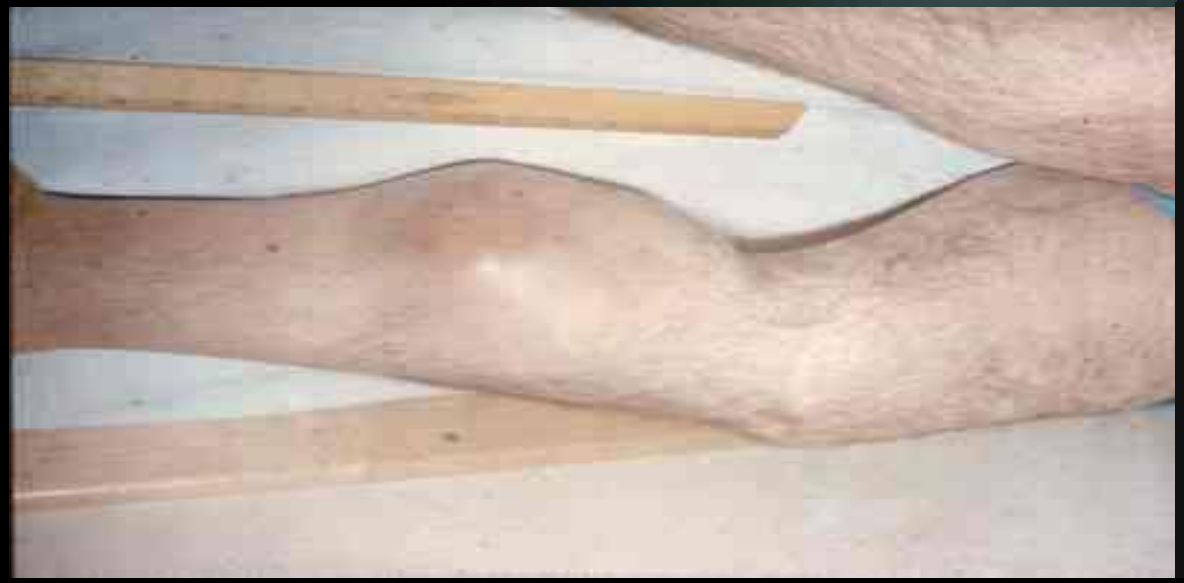
- In hemophilia A (factor VIII deficiency) or hemophilia B (factor IX deficiency) , the clot formation is delayed and is not robust.
- The clot that is formed may be friable, and re-bleeding occurs during the physiologic lysis of clots or with minimal trauma.

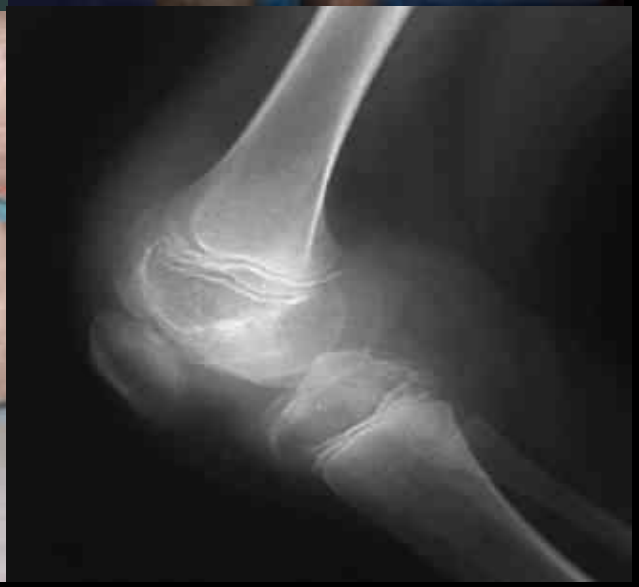
Clinical manifestation

- Neither factor VIII nor factor IX crosses the placenta; thus, bleeding symptoms may be present from birth or occur in the fetus.
- Evidences of increased bleeding such as easy bruising.
- Although bleeding may occur in any area of the body, the hallmark of hemophilia is the hemarthrosis. Bleeding into joints may be induced by minor trauma; nonetheless, many hemarthrosis are spontaneous.
- Life-threatening bleeding in the hemophilic patient is caused by:
  - Bleeding into vital structures (CNS, upper airway).
  - Exsanguination (external, gastrointestinal, or iliopsoas hemorrhage).









Laboratory findings

- PTT is prolonged.
- PT, TT, PL , BT (bleeding time), are normal.
- The confirmatory test is the specific assay for factor VIII and factor IX
- Mixing of normal plasma with patient plasma results in correction of the PTT. If correction does not occur on mixing, an inhibitor may be present In such patients the quantitative assay for inhibitor should be performed.

Genetics

- Hemophilia is an X – linked recessive disorder, so it occurs mainly in males.
- Some female carriers of hemophilia A or hemophilia B will have sufficient reduction of their factor VIII or factor IX through lionization of the X chromosome (bar body), or even gene mutation, to produce mild bleeding disorders in carriers.

Treatment

1. ***General measures:***
    a. Avoidance of trauma; a course between over protection and permissiveness should be followed.
    b. Avoid deep I.V and I.M injections.
    c. Avoidance of aspirin and other NSAID because it produce platelet dysfunction.
    d. Immunization against hepatitis B early in the neonatal period.
    e. Regular screening for hepatitis and abnormalities in LFT (Liver Function Test).

2. Calculation of the dose of factors VIII & IX:

Dose of FVIII (unit, U)=

(u/dl(%) desired raised in plasma FVIII) x body weight (Kg) x 0.5

Dose of FIX (unit, U)=

(u/dl(%) desired raised in plasma FIX) x body weight (Kg) x 1.0

3. Replacement therapy

Type of bleeding	Desired % rise of FVIII	Desired % rise of FIX
Hemarthrosis Other bleedings	50%	30%
Major surgery or life - threatening hemorrhage Iliopsoas muscle	100%	80%

Hemophilia A :

- Half life of factor VIII in the plasma is about 12 hours.
- Repeated infusions can be given as necessary to maintain the desire level of activity.
- *3 ways to give factor* VIII *:*

➢ ***Cryoprecipitate:*** one bag prepared from 250 ml of plasma. It is the most inexpensive; it contains 100 U of F VIII.

One bag / 5 kg will raise the recipient's level to about 50%.

➢ ***F VIII concentrate***: more expensive than cryoprecipitate.

c) Desmopressin: With mild factor VIII hemophilia, the patient's endogenously produced factor VIII can be released by the administration of desmopressin acetate **(**DDAVP**)**.

it is given either by an intranasal spray or parenterally.

Hemophilia B :

We have 2 ways to give factor IX :

- FFP (fresh frozen plasma).
- Factor IX concentrate.

3) Gene Therapy : *is a hope and may be available soon.*

Complications

A. Chronic joint destruction:
B. Transfusion-transmitted infectious diseases:
C. Development of an inhibitor to either factor VIII or factor IX:
   - may need to go through desensitization programs, in which high doses of factor VIII or factor IX are infused to saturate the antibody.
   - If desensitization fails, these patients are treated with either activated prothrombin complex concentrates or factor VIIa. The use of these products bypasses the inhibitor in many instances but increases the risk for thrombosis.

VON WILLEBRAND DISEASE

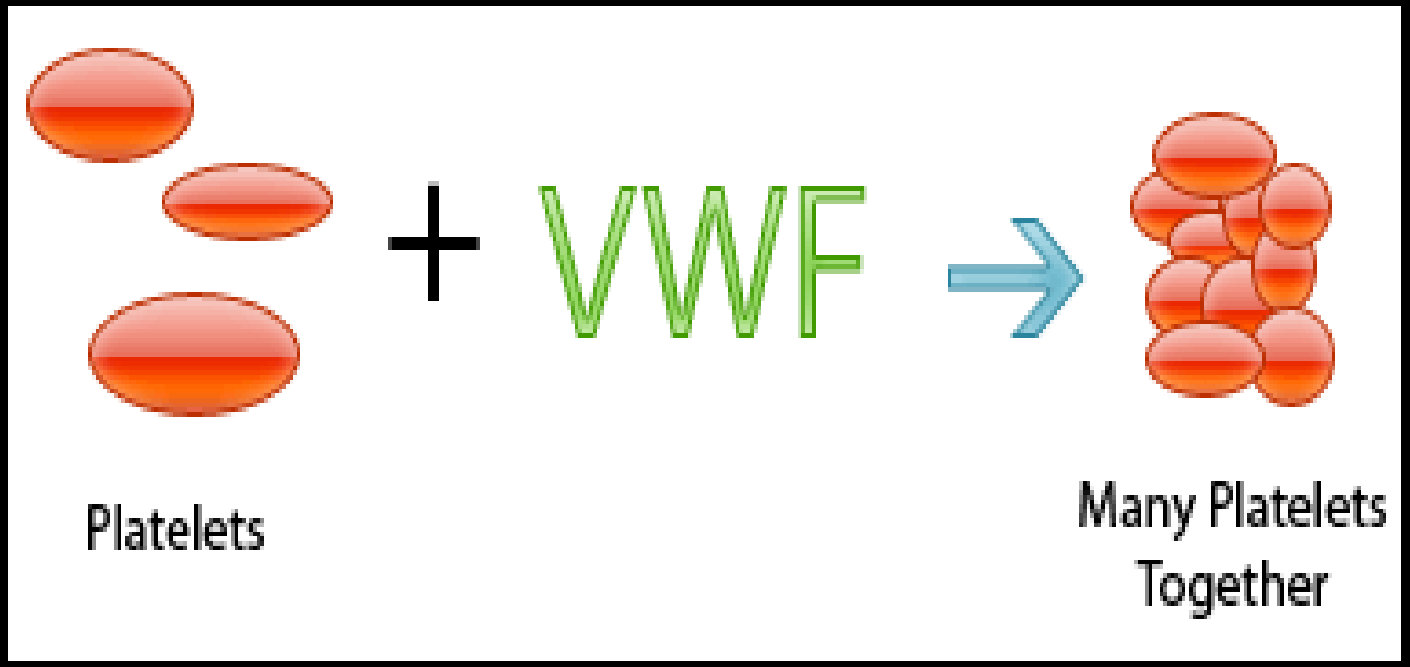
- Von Willebrand disease is the most common hereditary bleeding disorder.
- Is inherited autosomally, but most centers report more women than men, as menorrhagia is a major symptom.
- In boys, abnormal bleeding after circumcision is a major finding.

Classification

- Type 1 (most common): VWF (protein) is quantitatively reduced but not absent
- Type 2: the protein is qualitatively abnormal
- Type 3 (most sever): the protein is absent

Pathophysiology

- Von Willebrand factor (VWf) is important for platelet adhesion & aggregation.
- VWF also serves as the carrier protein for plasma factor VIII. Deficiency of vWf may cause a secondary deficiency in factor VIII.


+
VWF
Platelets
Many Platelets
Together

Clinical manifestation

- Patients with von Willebrand disease usually have symptoms of muco-cutaneous hemorrhage, including excessive bruising, epistaxis, menorrhagia, and postoperative hemorrhage, particularly after mucosal surgery such as tonsillectomy or wisdom tooth extraction.
- In homozygous von Willebrand disease (type 3), bleeding symptoms are much more profound &may have joint or spontaneous CNS hemorrhages.

Laboratory findings

- PTT : prolonged.
- BT : prolonged.
- PL (Platelet count) & TT : normal.

These tests are not universally prolonged except in patients with type 3.

So, to confirm the diagnosis :

1) Quantitative assay for VWf antigen.
2) VWf activity.

Treatment

- the synthetic drug DDAVP (desmopressin) induces the release of vWf from the endothelial cells.
- replacement therapy of vWf, if no response to DDAVP.


Thank
you!