V.N. Karazin National University
Medical School
Internal Medicine Department

HEMOPHILIA AND THROMBOCYTOPENIC PURPURA

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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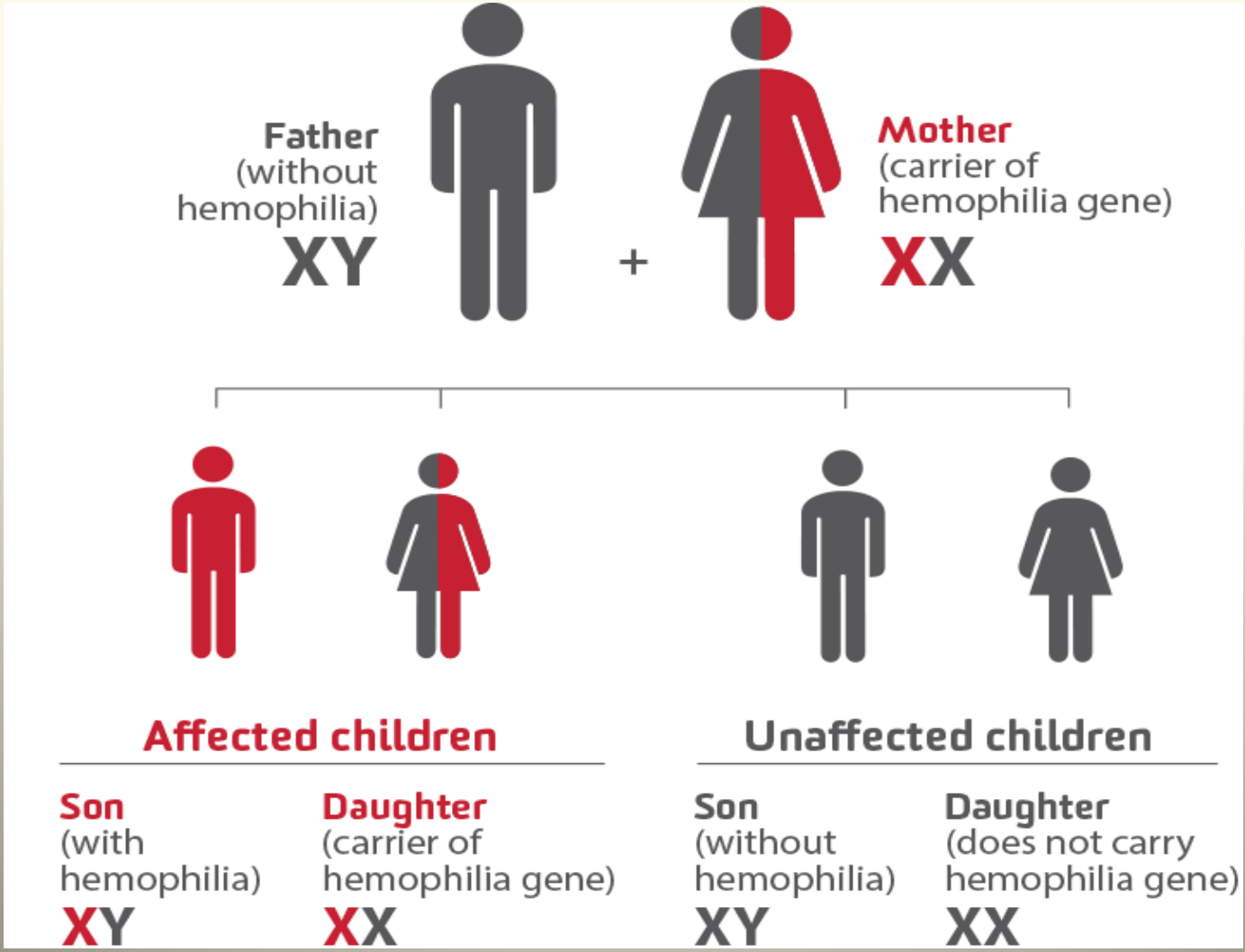
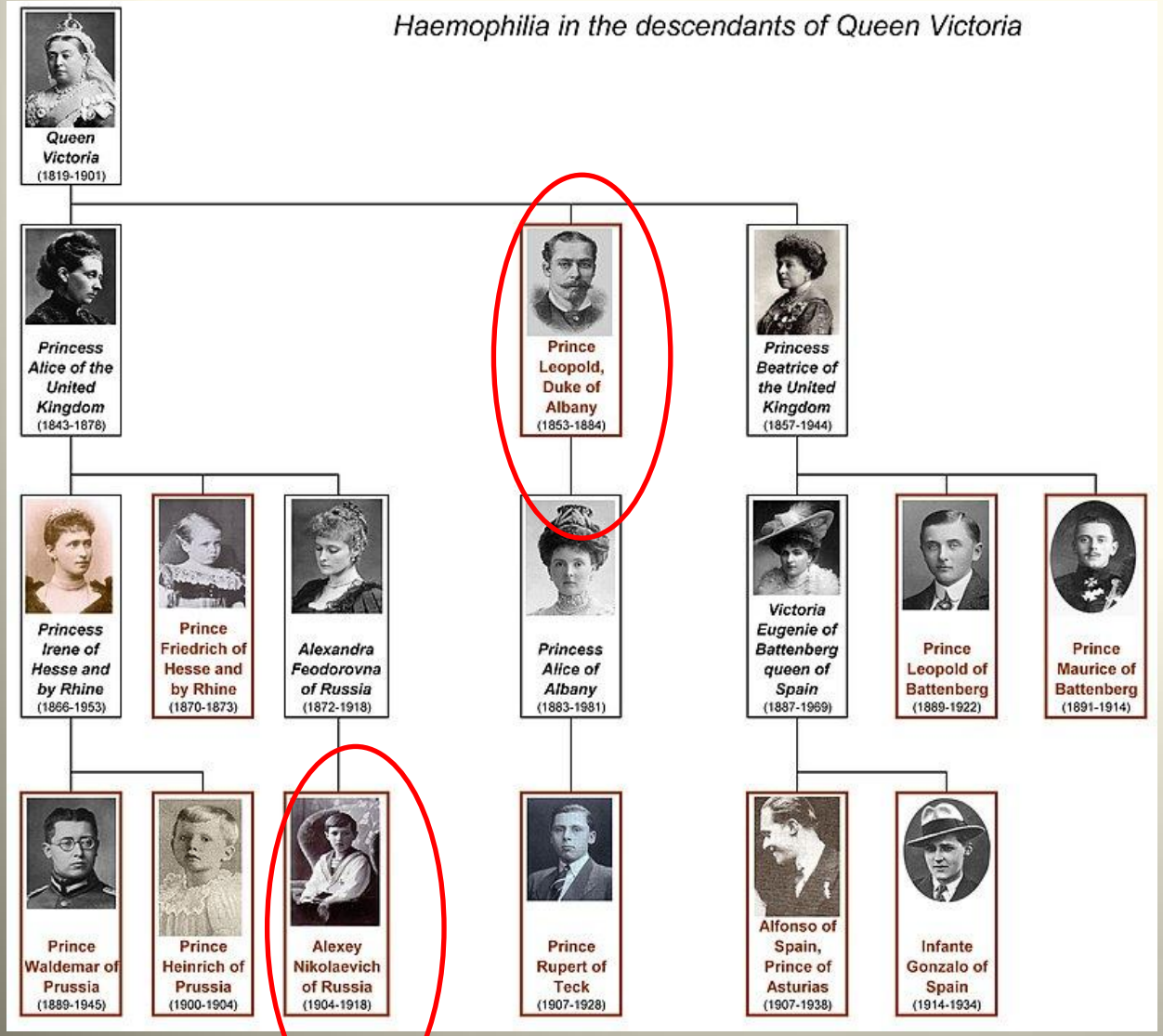
Hemophilia: Definition

- Hemophilia is an X-linked recessive hemorrhagic disease due to mutations in the F8 gene (factor VIII- FVIII) (hemophilia A or classic hemophilia) or F9 gene (factor IX –FIX) (hemophilia B)
- The disease affects 1 in 1 0000 males worldwide, in all ethnic groups; hemophilia A represents 80% of all cases
- Male subjects are clinically affected; women, who carry a single mutated gene, are generally asymptomatic

Hemophilia: Etiology



Hemophilia - Royal disease



You may have heard hemophilia being referred to as a “royal disease”. This is because **Queen Victoria**, who was the monarch of the UK in the 1800s, was a carrier of the disorder. She passed the condition on her son Leopold. Several of her daughters were also carriers and they passed on the faulty gene to other royal families in Spain, Germany and Russia

http://www.cuckari.cz/view.php?cisloclanku=2008090004

Classification

Hemophilia A is an X-linked, recessive disorder caused by deficiency of functional plasma clotting **factor VIII (FVIII)**, which may be inherited or arise from spontaneous mutation. Depending on the level of FVIII activity, patients with hemophilia may present with easy bruising; inadequate clotting of traumatic or even mild injury; or, in the case of severe hemophilia, spontaneous hemorrhage.

Hemophilia B, or **Christmas disease**, is an inherited, X-linked, recessive disorder that results in deficiency of functional plasma coagulation **factor IX**. Hemophilia B constitutes about 20% of hemophilia cases, and about 50% of these cases have factor IX levels greater than 1%. The hallmark of hemophilia is hemorrhage into the joints, resulting in permanent deformities, misalignment, loss of mobility, and extremities of unequal lengths.

Hemophilia C (deficiency of factor XI) was described first in two sisters and a maternal uncle of an American Jewish family. Unlike the bleeding tendency in **hemophilia A** or **hemophilia B**, even in severe deficiency of factor XI, the bleeding tendency is mild. Some patients with severe deficiency do not have a bleeding tendency, whereas some patients with mild deficiency bleed excessively. Complications of factor XI deficiency commonly involve the unpredictable nature of bleeding.

Acquired hemophilia is a rare but potentially life-threatening bleeding disorder caused by the development of autoantibodies (inhibitors) directed against plasma coagulation factors, most frequently **factor VIII (FVIII)**.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3629762/

Hemophilia: Pathophysiology 1.2.

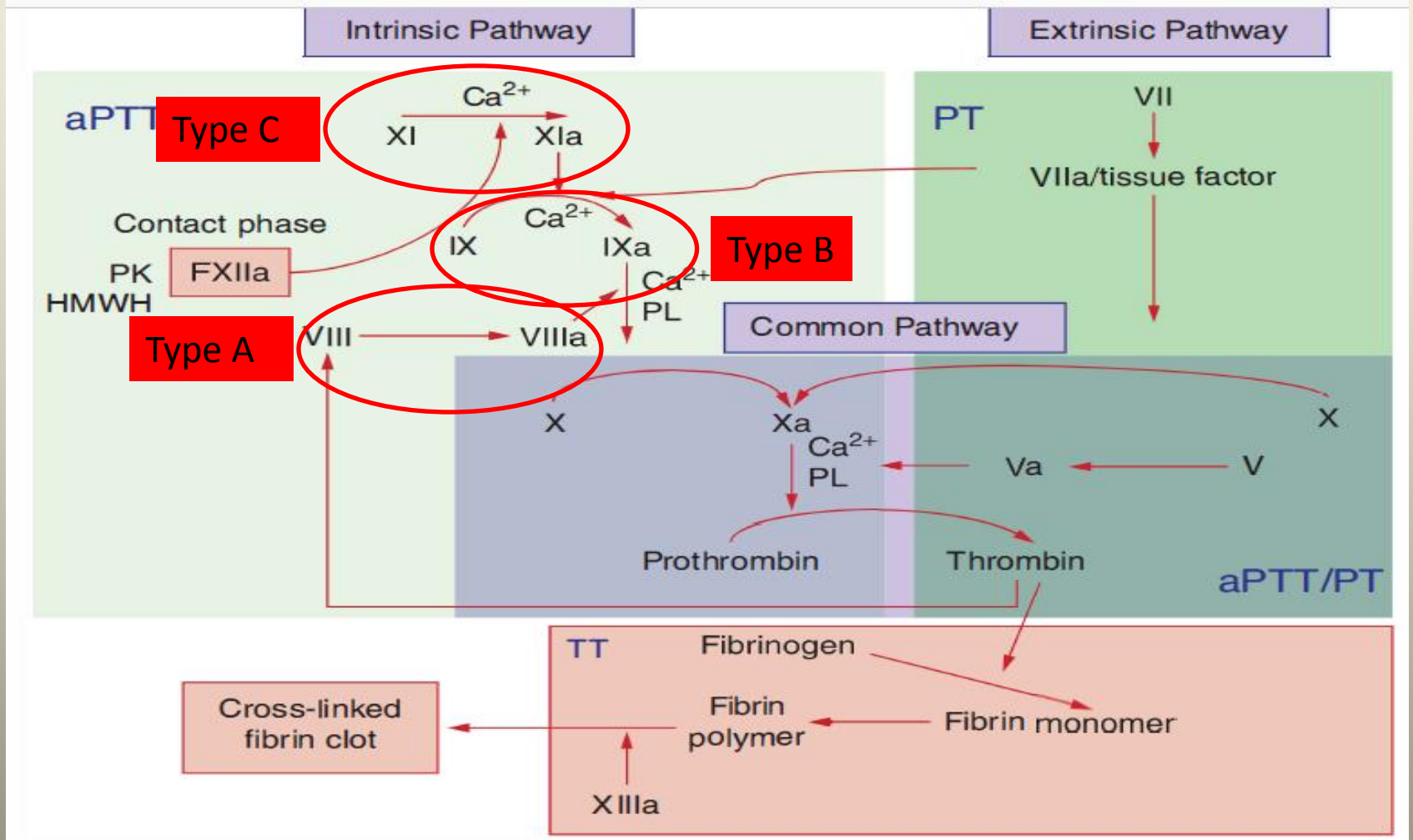


FIGURE 141-1 Coagulation cascade and laboratory assessment of clotting factor deficiency by activated partial prothrombin time (aPTT), prothrombin time (PT), thrombin time (TT), and phospholipid (PL).

Hemophilia: Pathophysiology 2.2.

https://www.youtube.com/watch?v=nkC1vZaUpxs

Hemophilia: Sings and Symptoms 1.2.

- Ecchymoses
- Joint pain
- Joint swelling and redness
- Decreased range of motion
- Muscle hemorrage
- Sings of nerve compression
- Oral bleeding
- Haematuria
- Intracranial hemorrhage
- Excessive postsurgical bleeding

SITES OF BLEEDING IN HEMOPHILIA

Serious	Joints (hemarthrosis)
	Muscles, especially deep compartments (iliopsoas, calf, and forearm)
	Mucous membranes in the mouth, gums, nose, and genitourinary tract
Life-threatening	Intracranial
	Neck/throat
	Gastrointestinal

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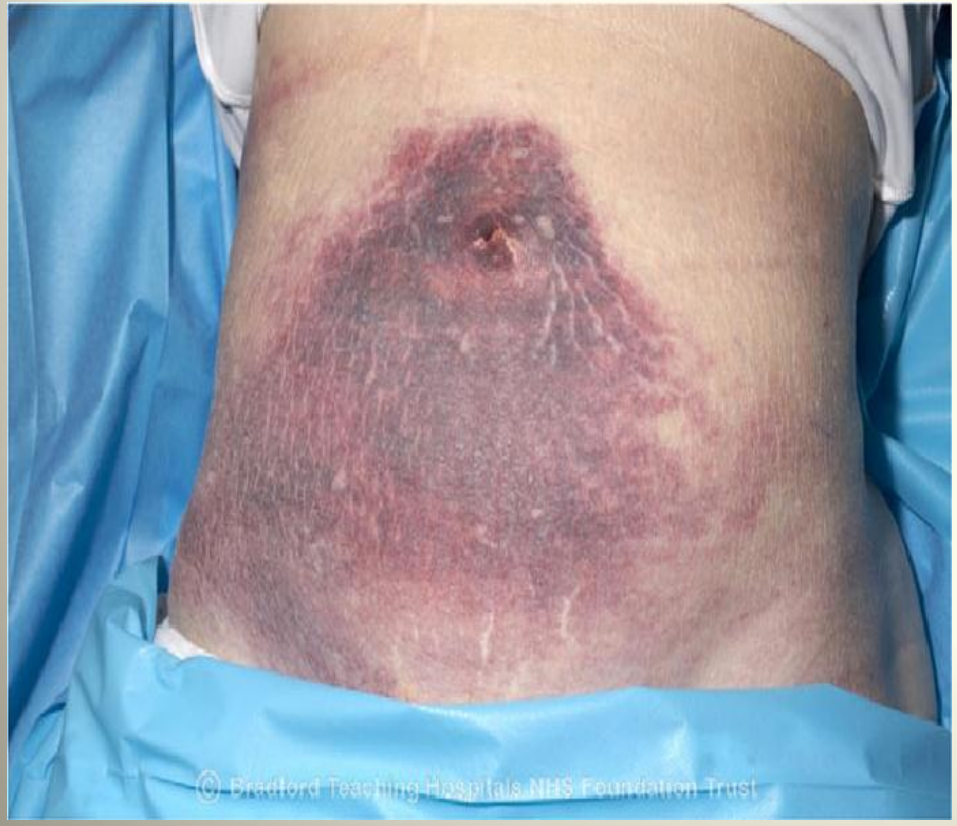
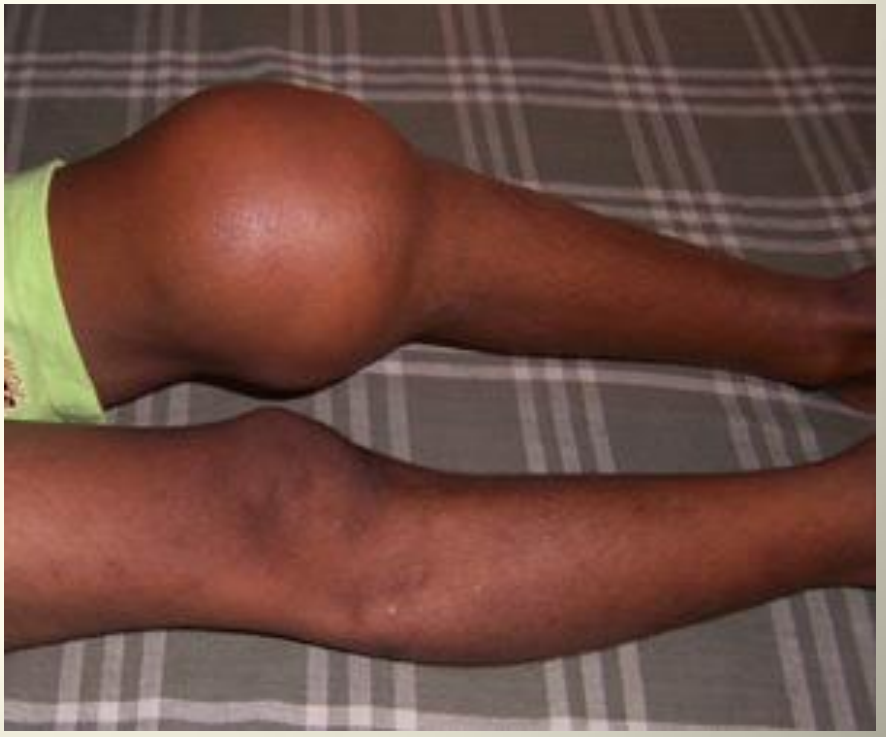
Hemophilia: Sings and Symptoms 2.2.





Ecchymosis

Joint bleeds

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Hemophilia: Diagnosis 1.2.

Accurate diagnosis is important and essential for effective management. Hemophilia should be suspected in patients presenting with a history of:

- Easy bruising in early childhood
- Spontaneous bleeding (particularly into the joints and soft tissue)
- Excessive bleeding following trauma or surgery

http://illinoisaap.org/wp-content/uploads/guidelines-Hemophilia-WHF-2005.pdf

Hemophilia: Diagnosis 2.2.

- While the history of bleeding is usually lifelong, some severe hemophilic children may not have bleeding symptoms until after the age of one or later when they begin walking and exploring their world. Patients with mild hemophilia may not have excessive bleeding unless they experience trauma or surgery

- A family history of bleeding is commonly obtained

- However, both FVIII and FIX genes are prone to new mutations, and as many as 1/3 of all patients may not have a family history of these disorders

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Hemophilia: Laboratory diagnosis 1.3.

- Using screening tests to identify the potential cause of bleeding: platelet count, bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (APTT)
- These screening tests may not detect abnormalities in patients with mild bleeding disorders and in those with factor XIII (FXIII) deficiency or those with low fibrinolytic inhibitor activity (alpha 2 antiplasmin, PAI-1)

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Hemophilia: Laboratory diagnosis 2.3.

Possible condition	PT	APTT	BT	Platelet count
Normal	Normal	Normal	Normal	Normal
Hemophilia A or B	Normal	Prolonged	Normal	Normal
vWD (Von Willebrand disease)	Normal	Normal or prolonged	Normal or prolonged	Normal or reduced
Platelet defect	Normal	Normal	Normal or prolonged	Normal or reduced

bleeding time (BT), prothrombin time (PT), activated partial thromboplastin time (APTT)

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Hemophilia: Laboratory diagnosis 3.3.

Factor assay is required in the following situations:

- To determine diagnosis
- To monitor treatment

- The laboratory monitoring of clotting factor concentrates is possible by performing pre- and post-infusion clotting factor levels

- The actual amount of infused clotting factor given to the patient should predict the rise in blood levels. This approach is especially important when surgical procedures are to be performed

- Lower than expected recovery may be an early indicator of the presence of inhibitors

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Hemophilia: The severity of bleeding manifestations

The severity of bleeding manifestations in hemophilia is generally correlated with the clotting factor level as shown in the following table.

Severity	Clotting factor level % activity (IU/ml)	Bleeding episodes
Severe	1% (< 0.01)	Spontaneous bleeding, predominantly in joints and muscles
Moderate	1%-5% (0.01-0.05)	Occasional spontaneous bleeding. Severe bleeding with trauma, surgery
Mild	5%-40% (0.05-0.40)	Severe bleeding with major trauma or surgery

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Hemophilia: Chronic complications

- **Musculoskeletal complications:**
  - Chronic hemophilic arthropathy;
    - ❍ Chronic synovitis;
    - ❍ Deforming arthropathy;
  - Contractures
  - Pseudotumour formation (soft tissue and bone);
  - Fracture;
  - Inhibitors against FVIII/FIX;
- **Transfusion-related infections of concern in people with hemophilia:**
  - Human immunodeficiency virus (HIV);
  - Hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV);
  - Parvovirus B19;
  - Others

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Hemophilia: Treatment

History

The treatment of hemophiliacs has evolved significantly over the past 50 years. Initially, the mainstay treatment modalities available for hemophilia were whole blood and fresh-frozen plasma. As a result of low factor VIII and IX levels in those products, most patients with severe hemophilia did not survive past early adulthood.

The modern era of hemophilia management came into existence in the 1970s with the availability of plasma concentrates

Desmopressin, a synthetic medication that increases factor VIII and von Willebrand factor levels, provided a new, inexpensive method of safely treating patients with mild hemophilia A while minimizing risks of blood-borne infections. In the early 1980s, new challenges in the treatment of hemophilia arose as a vast number of patients with severe hemophilia became infected with HIV and hepatitis C transmitted by contaminated factor concentrates pooled from thousands of donors

As a result of this epidemic, the need for safer treatment of hemophilia developed

This lead to the cloning of factor VIII and IX genes, when the industrial production of recombinant factor VIII and factor IX became readily available. Additional measures have since been implemented to improve safety during the manufacturing process

https://www.uspharmacist.com/article/hemophilia-review

Hemophilia: Treatment

The general principles of care for hemophilia management include the following:

- Prevention of bleeding should be the goal
- Acute bleeds should be treated early (within two hours, if possible)
- Home therapy should be used to manage only uncomplicated mild/moderate bleeding episodes

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Hemophilia: Treatment

The general principles of care for hemophilia management include the following:

- Clotting factor concentrate replacement or DDAVP should be given to achieve appropriate factor levels prior to any invasive procedures
- As much as possible, patients should avoid trauma by adjusting their lifestyle
- Patients should be advised to avoid use of drugs that affect platelet function, particularly acetylsalicyclic acid (ASA) and non-steroidal anti-inflammatory drugs (NSAIDs), except certain COX-2 inhibitor
- The use of paracetamol/acetaminophen is a safe alternative for analgesia

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Hemophilia: Treatment

The general principles of care for hemophilia management include the following:

- Intramuscular injections, difficult phlebotomy, and arterial punctures must be avoided
- Regular exercise should be encouraged to promote strong muscles, protect joints, and improve fitness
- Contact sports should be avoided, but swimming and cycling with appropriate gear should be encouraged

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Hemophilia: Treatment

Adjunctive management

- **RICE** (rest, ice, compression, and elevation) is an important adjunctive management for bleeding in muscles and joints in addition to increasing factor level with clotting factor concentrates or desmopressin in mild hemophilia A
- Application of cold/ice packs is useful to decrease inflammation, but ice should be wrapped in a towel and not be applied directly to the skin
- It is recommended that ice be applied for 20 minutes, every four to six hours, until swelling and pain decrease

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Hemophilia: Treatment

Management of bleeding

One unit is defined as amount of FVIII (100 ng/m L) or FIX (5 µg/mL) in 1 mL of normal plasma.

One unit of FVIII per kilogram of body weight increases the plasma FVIII level by 2%. One can calculate the dose needed to increase of FVIII levels to 100% in a 70-kg severe hemophilia patient (< 1 %) using the simple formula below. Thus, 3500 units of FVIII will raise the circulating level to 100%.

FVIII dose (IU)=Target FVIII levels- FVIII baseline levels*body weight (kg)*0.5 unit/kg

The doses for FIX replacement are different from those for of FVIII, because FIX recovery after infusion is usually only 50% of the predicted value. Therefore, the formula for FIX replacement is as follows:

FIX dose (IU)=Target FIX levels- FIX baseline levels*body weight (kg)*1 unit/kg

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Hemophilia: Treatment

Management of bleeding

- The FVIII half-life of 8-12 h requires injections twice a day to maintain therapeutic levels, whereas the FIX half-life is longer-24 h, so that once-a-day injection is sufficient
- Cryoprecipitate is still in use in some developing countries, but because of the risk of bloodborne diseases, this product should be avoided in hemophilia patients when factor concentrates are available

Hemophilia (PTG)

TABLE 1-222 Treatment of Hemophilia

Type of Hemorrhage	Hemophilia A	Hemophilia B
Hemarthrosis*	50 IU/kg factor VIII concentrate† on day 1; then 20 IU/kg on days 2, 3, 5 until joint function is normal or back to baseline. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.	80-100 IU/kg on day 1; then 40 IU/kg on days 2, 4. Consider additional treatment every other day for 7-10 days. Consider prophylaxis.
Muscle or significant subcutaneous hematoma	50 IU/kg factor VIII concentrate; 20 IU/kg every-other-day treatment may be needed until resolved.	80 IU/kg factor IX concentrate‡; treatment every 2-3 days may be needed until resolved.
Mouth, deciduous tooth, or tooth extraction	20 IU/kg factor VIII concentrate; antifibrinolytic therapy; remove loose deciduous tooth.	40 IU/kg factor IX concentrate‡; antifibrinolytic therapy§; remove loose deciduous tooth.
Epistaxis	Apply pressure for 15-20 min; pack with petrolatum gauze; give antifibrinolytic therapy; 20 IU/kg factor VIII concentrate if this treatment fails.‖	Apply pressure for 15-20 min; pack with petrolatum gauze; antifibrinolytic therapy; 30 IU/kg factor IX concentrate‡ if this treatment fails.
Major surgery, life-threatening hemorrhage	50-75 IU/kg factor VIII concentrate, then initiate continuous infusion of 2-4 IU/kg/hr to maintain factor VIII >100 IU/dl for 24 hr‖ then give 2-3 IU/kg/hr continuously for 5-7 days to maintain the level at >50 IU/dl and an additional 5-7 days to maintain the level at >30 IU/dl.¶	120 IU/kg factor IX concentrate‡, then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dl for 5-7 days, and then at >30 IU/dl for 7 days.
Iliopsoas hemorrhage	50 IU/kg factor VIII concentrate, then 25 IU/kg every 12 hr until asymptomatic, then 20 IU/kg every other day for a total of 10-14 days.**	120 IU/kg factor IX concentrate‡; then 50-60 IU/kg every 12-24 hr to maintain factor IX at >40 IU/dl until patient is asymptomatic; then 40-50 IU every other day for a total of 10-14 days.**††
Hematuria	Bed rest; 1½ × maintenance fluids; if not controlled in 1-2 days, 20 IU/kg factor VIII concentrate; if not controlled, give prednisone (unless patient is HIV-infected).	Bed rest; 1½ × maintenance fluids; if not controlled in 1-2 days, 40 IU/kg factor IX concentrate‡; if not controlled, give prednisone (unless patient is HIV-infected).
Prophylaxis	20-40 IU/kg factor VIII concentrate every other day to achieve a trough level ≥1%.	30-50 IU/kg factor IX concentrate‡ every 2-3 days to achieve a trough level ≥1%.

*For hip hemarthrosis, orthopedic evaluation tor possible aspiration is advisable to prevent avascular necrosis of the femoral head.

†For mild or moderate hemophilia, desmopressin, 0.3 μg/kg, should be used instead of factor VIII concentrate, if the patient is known to respond with a hemostatic level of factor VIII; if repeated doses are given, monitor factor VIII levels for tachyphylaxis.

‡Stated doses apply for recombinant factor IX concentrate; for plasma-derived factor IX concentrate, use 70% of the stated dose.

§Do not give antifibrinolytic therapy until 4-6 hr after a dose of prothrombin complex concentrate.

‖Over-the-counter coagulation-promoting products may be helpful.

¶Alternatively, give 25 IU/kg every 12 hr to maintain a trough level >50% for 5-7 days followed by 25-30 IU/kg for an additional 5-7 days to maintain trough >25%.

**Repeat radiologic assessment should be performed before discontinuation of therapy.

††If repeated doses of factor IX concentrate are required, use highly purified, specific factor IX concentrate.

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Pain management

Acute and chronic pain are common in patients with hemophilia. Pain can be treated with local measures (eg, cold packs, immobilization, splinting), acetaminophen, or codeine

STRATEGIES FOR PAIN MANAGEMENT IN PATIENTS WITH HEMOPHILIA

1	Paracetamol/acetaminophen *If not effective* ↓
2	COX-2 inhibitor (e.g. celecoxib, meloxicam, nimesulide, and others) OR Paracetamol/acetaminophen plus codeine (3-4 times/day) OR Paracetamol/acetaminophen plus tramadol (3-4 times/day)
3	Morphine: use a slow release product with an escape of a rapid release. Increase the slow release product if the rapid release product is used more than 4 times/day

Notes:

- If for any reason medications have been stopped for a period of time, patients who have been taking and tolerating high-dose narcotic drugs should re-start the drug at a lower dose, or use a less powerful painkiller, under the supervision of a physician.
- COX-2 inhibitors should be used with caution in patients with hypertension and renal dysfunction.

Chronic hemophilic arthropathy develops in patients who have not been adequately treated with clotting factor concentrates for joint bleeding. COX-2 inhibitors have a greater role in this situation. Other NSAIDs should be avoided. When pain is disabling, orthopedic surgery may be indicated.

Pain caused by joint or muscle bleeding While clotting factor concentrates should be administered as quickly as possible to stop bleeding, additional drugs are often needed for pain control. Other measures include cold packs, immobilization, splints, and crutches

Hemophilia: Treatment

Agents used to treat hemophilia

Brand/Product	Prescribing Information
Factor VIII concentrates (plasma-derived)	
Monoclate P Hemophil M	• Treatment of choice for hemophilia A • Available in dosages from 250-3,000 units each • Each unit/kg of body weight is expected to raise plasma levels approximately 2 IU/dL • $T_{1/2}$ approximately 8-12 h • Dose: pt wt (kg) × desired rise in factor levels × 0.5
Factor IX concentrates (plasma-derived)	
AlphaNine SD Mononine	• Treatment of choice for hemophilia B • Available in dosages: 250-2,000 units/vial • Each unit/kg of body weight is expected to raise plasma levels approximately 1 IU/dL • $T_{1/2}$ approximately 18-24 h • Dose: pt wt (kg) × desired rise in factor level
Recombinants	
Factor VIII First generation (human albumin): • Recombinate Second generation (sucrose): • Helixate FS • Kogenate FS Third generation (plasma free): • Advate • Xyntha **Factor IX** • BeneFIX • Rixubis	• Recombinants have a lower rate of factor recovery compared with plasma-derived products • Adults: Each unit raises factor IX levels 0.8 IU/dL • Children <15 y: Each unit raises factor IX levels 0.7 IU/dL

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Prophylaxis

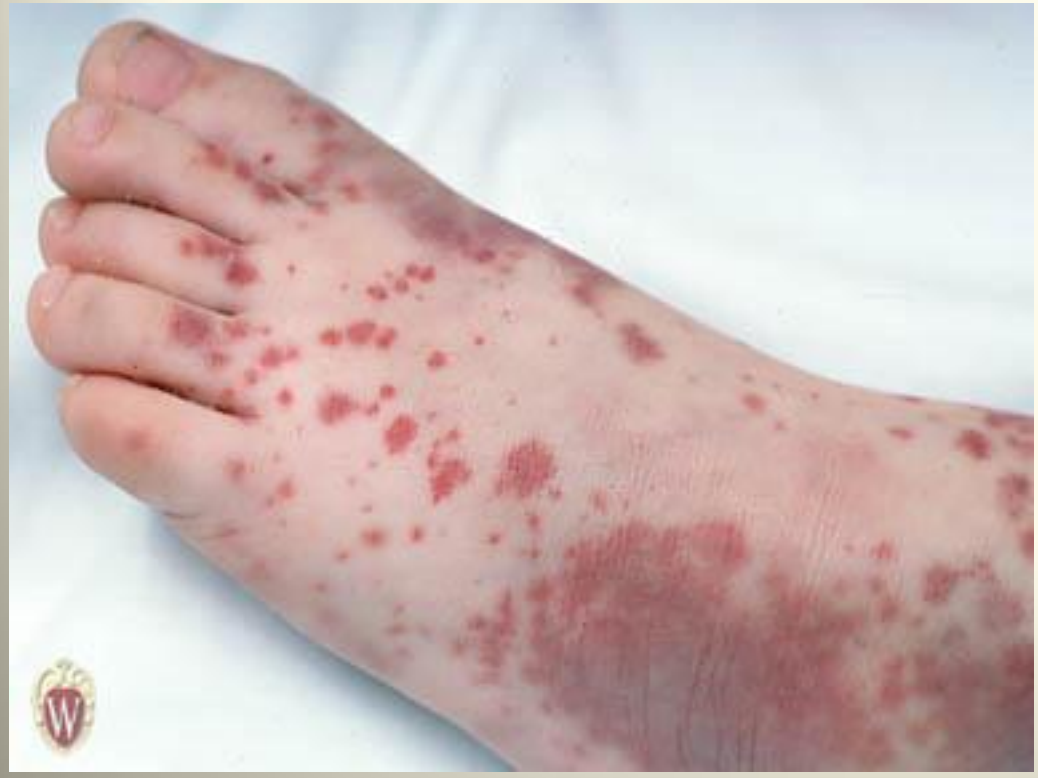
Continuous prophylaxis Primary prophylaxis	Regular continuous* treatment initiated in the absence of documented osteochondral joint disease, determined by physical examination and/or imaging studies, and started before the second clinically evident large joint bleed and age 3 years**
Secondary prophylaxis	Regular continuous* treatment started after 2 or more bleeds into large joints** and before the onset of joint disease documented by physical examination and imaging studies
Tertiary prophylaxis	Regular continuous* treatment started after the onset of joint disease documented by physical examination and plain radiographs of the affected joints
Intermittent ("periodic") prophylaxis	Treatment given to prevent bleeding for periods not exceeding 45 weeks in a year

* continuous is defined as the intent of treating for 52 weeks/year and receiving a minimum of an *a priori* defined frequency of infusions for at least 45 weeks (85%) of the year under consideration.

**large joints = ankles, knees, hips, elbows and shoulders

Prophylaxis prevents bleeding and joint destruction and **should be the goal of therapy** to preserve normal musculoskeletal function

Thrombocytopenic purpura (TP): definition



TP is the general term for purpura that accompanies a decrease in platelet density. When that density is less than 100,000 per microliter, subcutaneous bleeding is easily produced by bruising

When it is less than 50,000 per microliter, bleeding becomes marked and causes **purpura**

https://www.derm-hokudai.jp/shimizu-dermatology/pdf/11-04.pdf

Platelets

Platelets are released from the megakaryocyte, likely under the influence of flow in the capillary sinuses. The normal blood platelet count is 150,000 - 450,000/µL

The **major regulator** of platelet productionis the **hormone thrombopoietin (TPO)**, which is synthesized in the liver.

Platelets circulate with an average **life span of 7 - 10 days**

Approximately one - third of the platelets reside in the spleen, and this number increases in proportion to splenic size, although the platelet count rarely decreases to <40,000/µL as the spleen enlarges

Platelets are physiologically very active, but are anucleate, and thus have limited capacity to synthesize new proteins

Thrombocytopenic purpura (TP): classification

TPis classified by pathogenesis into:

- **Immune thrombocytopenic purpura** (also termed *idiopathic thrombocytopenic purpura* **(ITP)**, which is caused by auto-antiplatelet antibodies
- **symptomatic thrombocytopenic purpura (STP)**, which accompanies drug-induced purpura, leukemia, bone-marrow cancer, SLE, infectious diseases
- **hereditary thrombocytopenic purpura (HTP)**, which accompanies Wiskott-Aldrich syndrome and Fanconi syndrome

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ITP: Epidemiology

- The incidence of primary ITP in adults is 3.3/100 000 adults per year with a prevalence of 9.5 per 100 000 adults
- There is a predilection for female patients in younger adults, but the prevalence of ITP in men and women is fairly even in the elderly (>65 years)

https://www.derm-hokudai.jp/shimizu-dermatology/pdf/11-04.pdf

ITP: Pathogenesis

- Thrombocytopenia results from pathologic antiplatelet antibodies, impaired megakaryocytopoiesis and T-cell–mediated destruction of platelets with each pathologic mechanism playing varying roles in each patient
- Decreased platelet density (100,000 per microliter or less) and an extended duration of bleeding (3 minutes or longer) are observed. **Platelet associated IgG (PAIgG)** is found in the blood in more than 90% of cases
- In a bone-marrow biopsy, the megakaryocyte count is found to be elevated from consumption of platelets

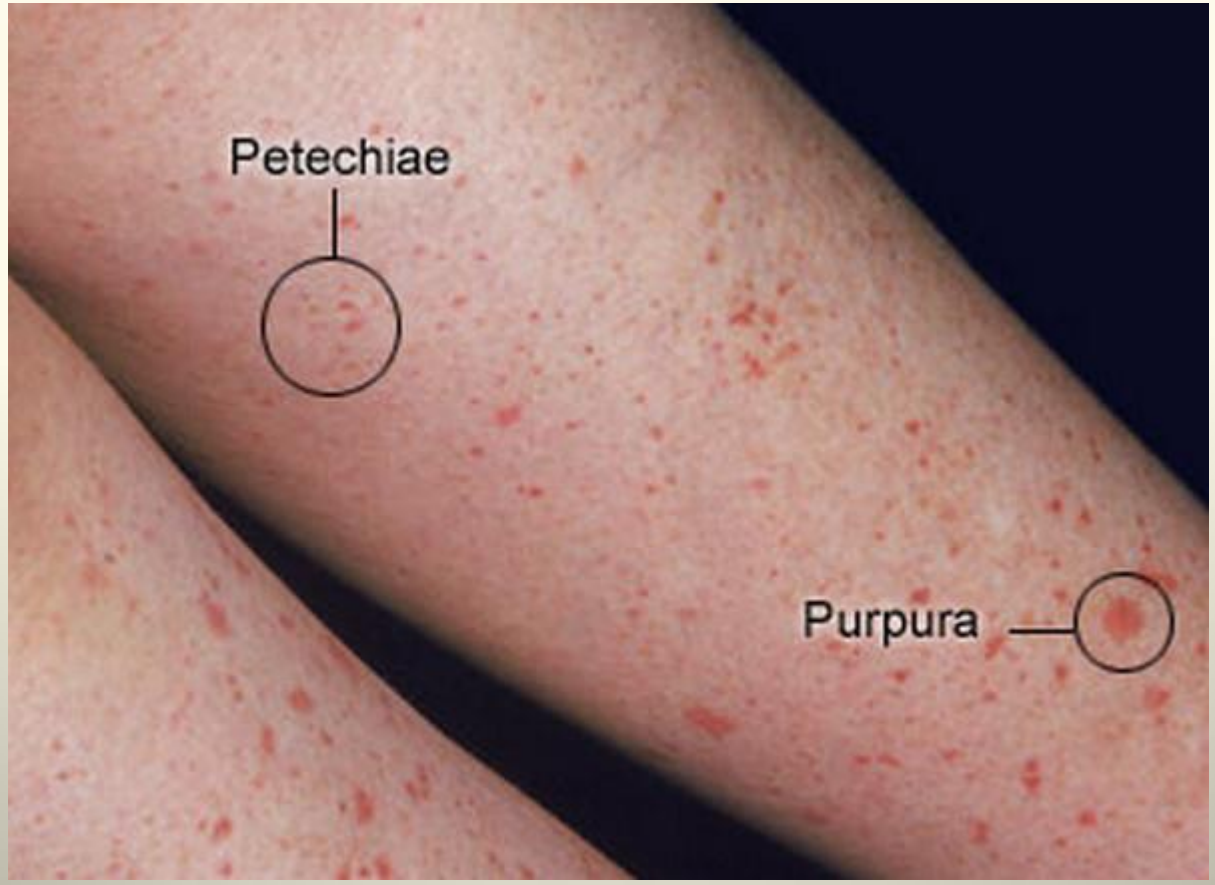
https://www.derm-hokudai.jp/shimizu-dermatology/pdf/11-04.pdf
http://www.bloodjournal.org/content/bloodjournal/129/21/2829.full.pdf?sso-checked=true

ITP: Clinical picture 1.2.

- ITP occurs in children during recovery from infectious disease
- In adults it develops without any particular pathogenesis
- Its main symptoms are cutaneous **petechiae and ecchymosis**, which are followed by bleeding in the oral mucosa, nasal mucosa and gingiva; hematuria; melena and menorrhagia
- Splenomegaly is not found

https://www.derm-hokudai.jp/shimizu-dermatology/pdf/11-04.pdf

ITP: Clinical picture 2.2.



Petechiae vs Purpura

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ITP: Descriptive terminology

Term	ITP description
Newly diagnosed	<3-mo duration
Persistent	3-12-mo duration
Chronic	>12-mo duration
Severe	Clinically relevant bleeding of sufficient magnitude to mandate treatment or requiring additional interventions or increase in drug dose
Refractory	Presence of severe ITP after splenectomy
Response	Platelet count $\geq 100 \times 10^9$/L measured on 2 occasions >7 d apart
Response	Platelet count $\geq 30 \times 10^9$/L and a greater than twofold increase in platelet count from baseline measured on 2 occasions >7 d apart

http://www.bloodjournal.org/content/bloodjournal/129/21/2829.full.pdf?sso-checked=true

ITP: Laboratory testing

- **Serologic testing is usually not helpful** due to the low sensitivity and specificity of the current tests. Bone marrow examination can be reserved for those who have other signs or laboratory abnormalities not explained by ITP or in patients who do not respond to initial therapy
- The peripheral blood smear may show large platelets, with otherwise normal morphology
- Depending on the bleeding history, iron-deficiency anemia may be present
- Laboratory testing is performed to **evaluate for secondary causes** of ITP :
  - HIV infection and hepatitis C (and other infections if indicated)
  - serologic testing for SLE
  - serum protein electrophoresis
  - immunoglobulin levels to potentially detect hypogammaglobulinemia
  - selective testing for IgA deficiency or monoclonal gammopathies
  - testing for H. pylori infection should be considered
- If anemia is present, direct antiglobulin testing (Coombs' test) should be performed to rule out combined autoimmune hemolytic anemia with ITP (Evans‘ syndrome)

ITP: Treatment 1.2.

First-line management

- Initial treatment in patients without significant bleeding symptoms, severe thrombocytopenia (<5 000/µL), or signs of impending bleeding (such as retinal hemorrhage or large oral mucosal hemorrhages)can be instituted as an outpatient using single agents
- **Prednisone 1 mg/kg/d for 2 to 4 weeks has been the standard first-line treatment for many years**
- However, recent work has investigated whether intensification of treatment, in adults with ITP, by using high dose dexamethasone (HDD), rituximab, or the TPO-RA may result in increased remission rates

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ITP: Treatment 2.2.

Second-line therapy

- Splenectomy has been used for treatment of patients who relapse after glucocorticoids are tapered
- Splenectomy remains an important treatment option
- However, the long-term complications of splenectomy in ITP patients are hemorrhage, infection, and venous thromboembolism (VTE)
- The **most recent clinical development** that has changed the landscape of second-line ITP therapy is the **TPO – receptor agonists (TPO-RA)** (romiplostim and eltrombopag are both US Food and Drug Administration approved for adults with chronic ITP, and eltrombopag is approved for use in children as well)

http://www.bloodjournal.org/content/bloodjournal/129/21/2829.full.pdf?sso-checked=true

STP: Thrombotic thrombocytopenic purpura

- Thrombotic thrombocytopenic purpura (TTP) is rare, with a reported incidence of six cases per million per year
- It is an important diagnosis to make because the untreated mortality is 90%, which can be reduced with the prompt delivery of plasma exchange
- Early death still occurs: approximately half of the deaths occurred within 24 h of presentation, primarily in women

STP: Causes

Decreased productivity of platelets	
Disease	Aplastic anemia
	Paroxysmal nocturnal hemoglobinuria
	Leukemia, lymphoma, cancer invasion
	Hereditary thrombocytopenia
Causative therapy	Drugs, radiotherapy
Enhanced consumption and destruction of platelets	
Disease	Diseases associated with collagen diseases
	Disseminated intravascular coagulation (DIC)
	Thrombotic thrombocytopenic purpura (TTP)
	Hemolytic-uremic syndrome (HUS)
	Viral infection
Causative therapy	Drugs, blood transfusion

https://www.derm-hokudai.jp/shimizu-dermatology/pdf/11-04.pdf

STP: Thrombotic thrombocytopenic purpura

- **Defined** by thrombocytopenia, microangiopathic haemolytic anaemia (MAHA) and small vessel thrombosis
- Thrombotic thrombocytopenic purpura (TTP) and hemolytic-uremic syndrome (HUS), were previously considered overlap syndromes. However, in the past few years, the pathophysiology of inherited and idiopathic TTP has become better understood and c1early differs from HUS.
- The pathogenesis of inherited (Upshaw-Schulman syndrome) and idiopathic TTP is related to a deficiency of, or antibodies to, the metalloprotease ADAMTS 13

STP: Thrombotic thrombocytopenic purpura

Presenting clinical features and signs in acute thrombotic thrombocytopenic purpura

Thrombocytopenia	Epistaxis, bruising, petechiae, gingival bleeding, haematuria, menorrhagia, gastrointestinal bleeding, retinal haemorrhage and haemoptysis
Central neurological – often flitting and variable 70–80%	Confusion, headache, paresis, aphasia, dysarthria, visual problems, encephalopathy, coma (10%)
Fever (>37·5°C)	
Non-specific symptoms	Pallor, jaundice, fatigue, arthralgia or myalgia
Jaundice	Resulting from microangiopathic haemolytic anaemia
Renal Impairment	Proteinuria, microhaematuria
Cardiac	Chest pain, heart failure, hypotension
Gastro-intestinal tract	Abdominal pain

https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2141.2012.09167.x

STP: Thrombotic thrombocytopenic purpura

Laboratory tests for diagnosis

Full blood count and blood film	Anaemia, thrombocytopenia, fragments on film
Reticulocyte count	Raised
Haptoglobin	Reduced
Clotting screen including fibrinogen	Normal
Urea and electrolytes	Renal impairment
Troponin T/Troponin I	For cardiac involvement
Liver function tests	Usually normal
Calcium	May reduce with PEX
Lactate dehydrogenase	Raised due to haemolysis
Urinalysis	For protein
Direct antiglobulin test	Negative
Blood group and antibody screen	To allow provision of blood products
Hepatitis A/B/C and human immunodeficiency virus testing	Pre-blood products and to exclude an underlying viral precipitant

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STP: Thrombotic thrombocytopenic purpura
Laboratory tests for diagnosis

Pregnancy test (in women of child-bearing age)	
ADAMTS 13 assay (activity/antigen and inhibitor/antibody in specialized laboratory)	Do not wait for result before starting treatment in suspected TTP
Electrocardiogram/Echocardiogram	To document/monitor cardiac damage
CT/MRI brain	To determine neurological involvement[a]
For possible underlying cause	
Thyroid function tests	To exclude Graves Disease
Auto-antibody screen (ANA/RF/LA/ACLA), including lupus anticoagulant	Exclude associated autoimmune disease
Stool culture	For pathogenic *Escherichia coli* (if diarrhoea)
CT Chest/abdomen/pelvis (if indicated) ± tumour markers	To look for underlying malignancy

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STP: Thrombotic thrombocytopenic purpura

Treatment

- Plasma exchange remains the mainstay of treatment of TTP
- ADAMTS 13 anti body-mediated TTP (idiopathic TTP) appears to respond best to plasma exchange
- Plasma exchange is continued until the platelet count is normal and signs of hemolysis are resolved for at least 2 days
- Although never evaluated in clinical trials, the use of glucocorticoids seems a reasonable approach, but should only be used as an adjunct to plasma exchange
- Additionally, other immunomodulatory therapies have been reported to be successful in refractory or relapsing TIP, including rituximab, vincristine, cyclophosphamide, and splenectomy

https://onlinelibrary.wiley.com/doi/full/10.1111/j.1365-2141.2012.09167.x

HTP: Wiskott-Aldrich syndrome

- **Wiskott–Aldrich syndrome (WAS)** is an X-linked primary immunodeficiency disorder that is characterized by the classic triad of severe immunodeficiency, microthrombocytopenia and eczema
- The incidence of this rare X-linked primary immunodeficiency disorder is approximately one to four cases per 1,000,000 live male births, with an average age at diagnosis of 24 months in families without a previously affected family member
- The estimated prevalence of WAS in the US is 1.2% of patients with identified primary immune defects

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4012343/

HTP: Wiskott-Aldrich syndrome Symptoms

- Thrombocytopenia and very small platelets usually present at birth which can result in:
  - Bleeding inside the brain, which can be very fatal
  - Mucosal bleeding
  - Bloody diarrhea
  - Purpura and petechiae
  - Life-threatening bleeding (occurs in 30% of males prior to diagnosis)
- Red patches of red and irritated skin (eczema), occurs in about 80% of the cases and can be mild to severe
- Other skin diseases such as impetigo, cellulitis, and abscesses
- Increased risk of infections, especially to recurrent bacterial and viral infections
- Increased risk of developing autoimmune disorders
- Increased risk of developing some types of cancer, such as lymphoma

https://rarediseases.info.nih.gov/diseases/7895/wiskott-aldrich-syndrome

HTP: Wiskott-Aldrich syndrome Treatment

- The prevention of infectious complications is required. Intravenous Ig (IVIG) is an important adjunct in the treatment of WAS patients
- For severe manifestations of autoimmunity, immunomodulatory therapy including IVIG may improve symptoms. Corticosteroids are widely utilized; however, the toxicity associated with the use of these agents is often large
- Transplantation is the current accepted curative approach for patients with WAS

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4012343/

Case report 1.4.

- An 85-year-old man presented with bruising of his hands, which he first noticed after shovelling snow 3 days earlier
- His past medical history included benign prostatic hypertrophy and glaucoma
- He was not taking anticoagulants or nonsteroidal anti-inflammatory drugs
- Over the last 3 days the bruising had become extensive, encompassing the palmar and dorsal aspect of both hands and spreading to the lower forearms (Figure 1)
- The patient had no other bruising, nosebleeds, hematuria, bloody stools or hemoptysis, and he reported having no joint or muscle pains
- He did not have a history of liver disease, nor did he have any personal or family history of bleeding or clotting disorders.

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1942092/

Case report 2.4.

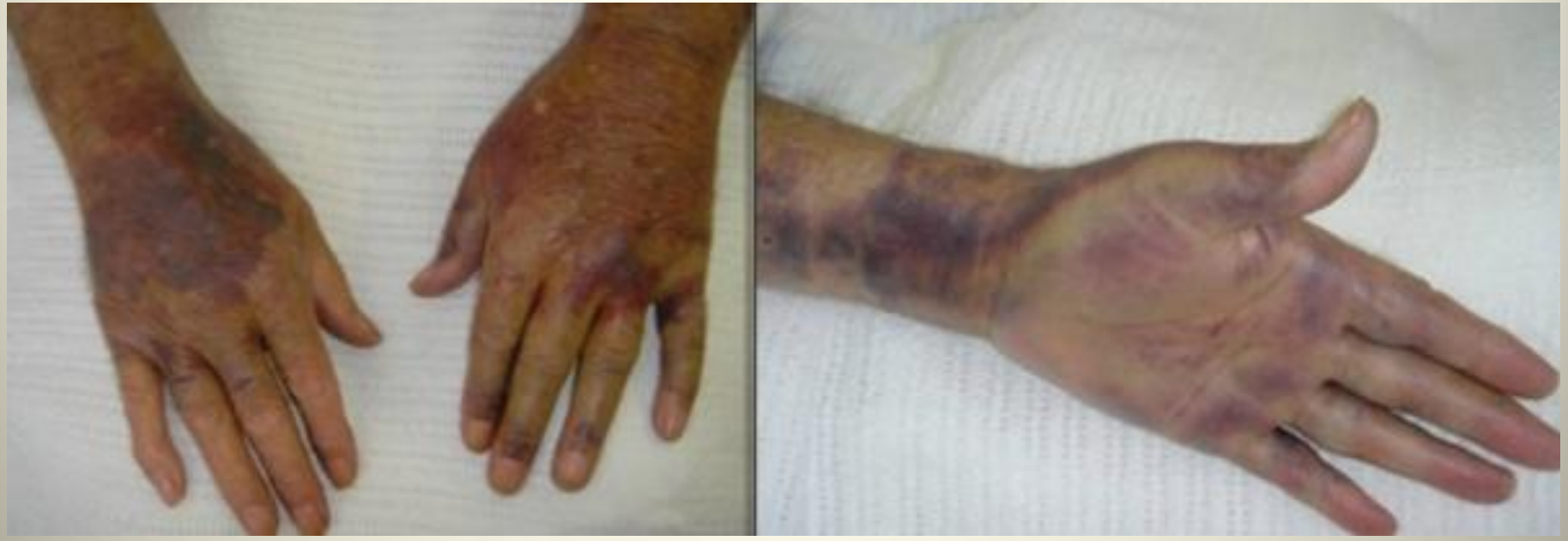

Figure 1: Hands of elderly man showing bruising on palmar and dorsal aspects of both hands that extended to forearms

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1942092/

Case report 3.4.

- On examination, the patient looked well and was afebrile, and his vital signs were stable. Aside from the extensive bruising of both hands, no other bruising, petechiae or sites of active bleeding were discovered, and there was no evidence of hemarthrosis.
- Initial laboratory investigations revealed a normal complete blood count, with a Hb of 130 g/L, a platelet count of 199 × 10^9/L and normal electrolyte levels. Kidney and liver function were normal, as was the blood glucose level. The D-dimer level was slightly elevated, at 250–500 (normal < 250) ng/mL.
- The prothrombin time and international normalized ratio were normal; the activated partial thromboplastin time was elevated, at 117 (normal < 35) seconds. A 1:1 mixing assay initially showed a corrected activated partial thromboplastin time of 41 seconds; however, a time-delayed 1:1 mix could not correct the thromboplastin time, which suggested that clotting factor inhibitors were present in the patient's blood
- Because only the activated partial thromboplastin time was affected, we assayed for clotting factors specific to the intrinsic pathway and determined that the patient had a factor VIII deficiency (titre < 0.01 [normal 0.5–1.5] U/mL)
- Further assays revealed factor VIII inhibitors in the patient's serum, at a level of 12.0 (normal 0) Bethesda units
- Acquired hemophilia was diagnosed

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1942092/

Case report 4.4.

- The patient was admitted to hospital and given **oral prednisone therapy (60 mg/d).** Because no sites of active bleeding were identified, no additional treatment was initiated. His activated partial thromboplastin time gradually improved, and no further bleeding or bruising occurred. He was discharged home 4 days later and given a tapered course of prednisone.
- One month after the patient completed the course of prednisone, his activated partial thromboplastin time was again prolonged. He required a combined course of cyclophosphamide and prednisone. His condition is currently maintained on 50 mg of cyclophosphamide daily, with a normal activated partial thromboplastin time and no further bleeding.
- Investigations into the cause of this patient's acquired hemophilia included chest radiograph, computed tomography of the chest and abdomen, and blood work to rule out malignant or autoimmune diseases
- **Findings were normal, and the acquired hemophilia was assumed to be idiopathic in nature**

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1942092/