HEMOPHILIA AND THROMBOCYTOPENIC PURPURA

LECTURE IN INTERNAL MEDICINE FOR IV COURSE STUDENTS

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Plan of the lecture
1. hemophilia

Hemophilia' modern understanding

- Definition
- Epidemiology
- Classification
- Risk Factors and etiology
- Mechanisms
- Classification
- Clinical presentation
- Complications
- Diagnosis
- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders
.supportourribbons.com/custom-magnet-image/21023-custom-ribbon-magnet-sticker-Hemophilia+Awareness.png

Hemophilia (HL): definition

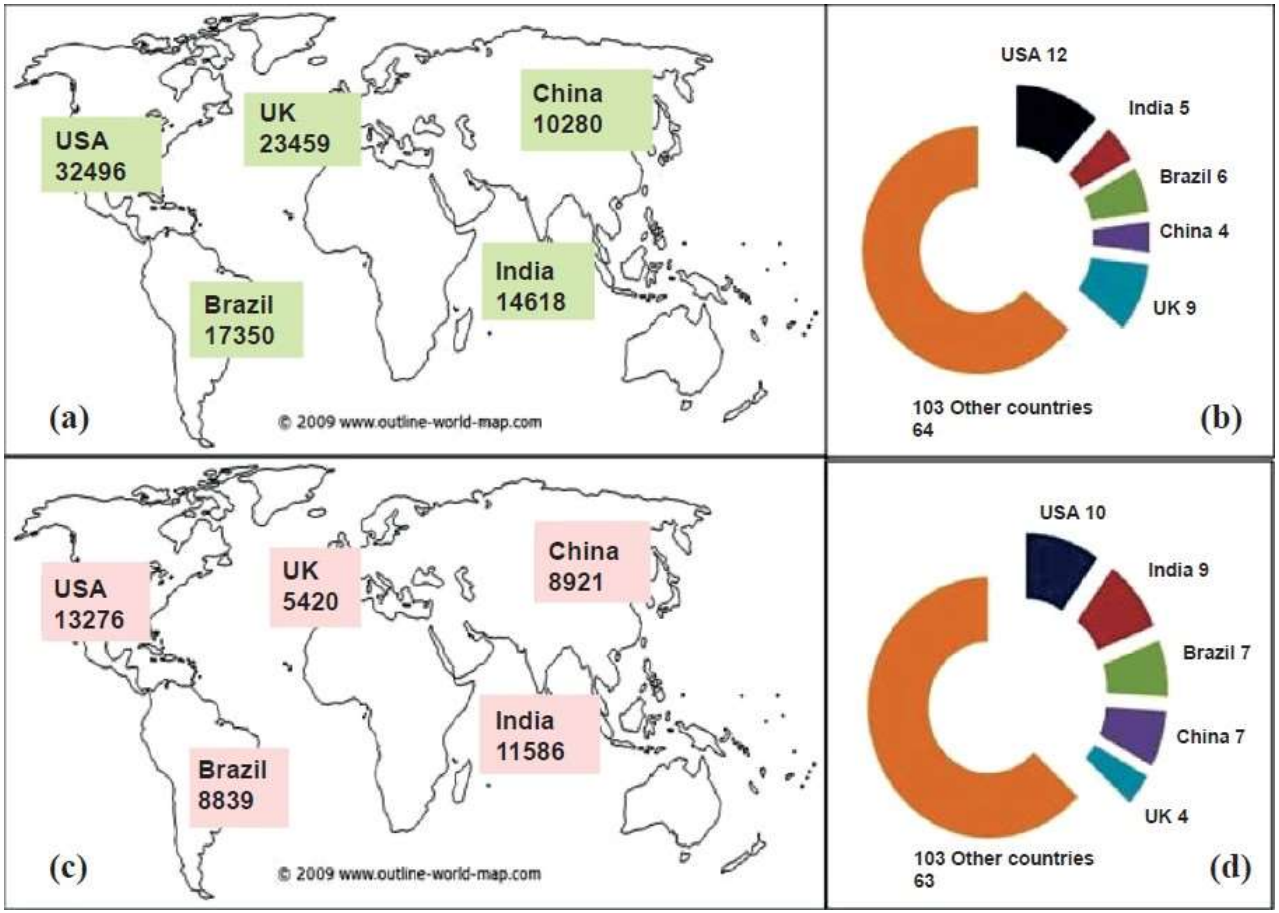
HL is a group of a sex-linked hereditary genetic disorders that occurs almost exclusively in males and impairs the body's ability to control blood clotting, which is used to stop bleeding when a blood vessel is broken even after minor injuries

Types:

- HL A (clotting factor VIII deficiency) is a recessive X-linked most common form of the disorder which occurs in 1 in 5,000–10,000 male births
- HL B (factor IX deficiency) is a recessive X-linked form of the disorder which occurs in 1 in 20,000–34,000 male births
- HL C or plasma thromboplastin antecedent (PTA) deficiency or Rosenthal syndrome (factor XI deficiency) is an autosomal (i.e. not X-linked) genetic disorder which occurs in both sexes

http://www.merriam-webster.com/dictionary/hemophilia https://en.wikipedia.org/wiki/Haemophilia
http://emedicine.medscape.com/article/955690-overview

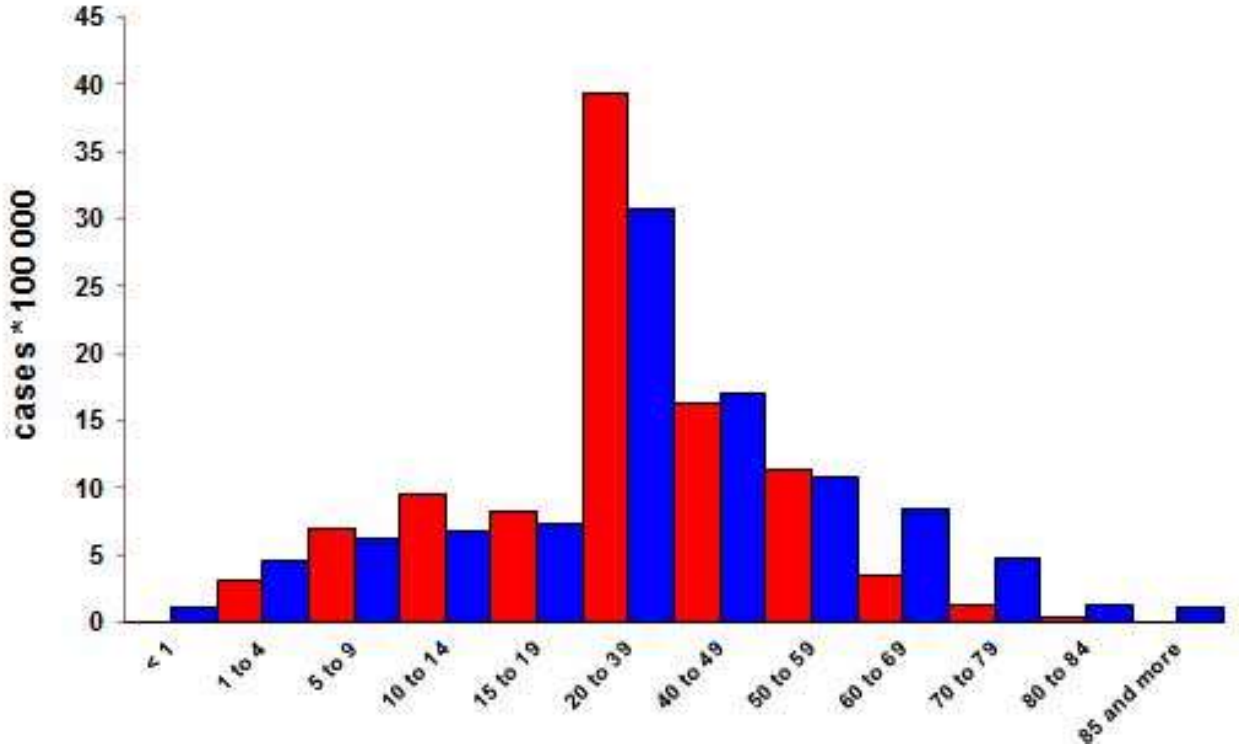
Hemophilia (HL): epidemiology



Global distribution of total reported cases of bleeding disorders (a) and HL A (c) in five countries reporting the highest number of patients (b) and (d) show s that nearly 5 and 9% of global patients with bleeding disorders and HL A are from India

http://www.ijmr.org.in/article.asp?issn=0971-5916;year=2014;volume=140;issue=1;spage=19;epage=31;aulast=Kar

Hemophilia (HL): epidemiology



Distribution by age for patients with HL A&B: median age for patients diagnosed with mild HL was 3 years for HA and 5 for HB

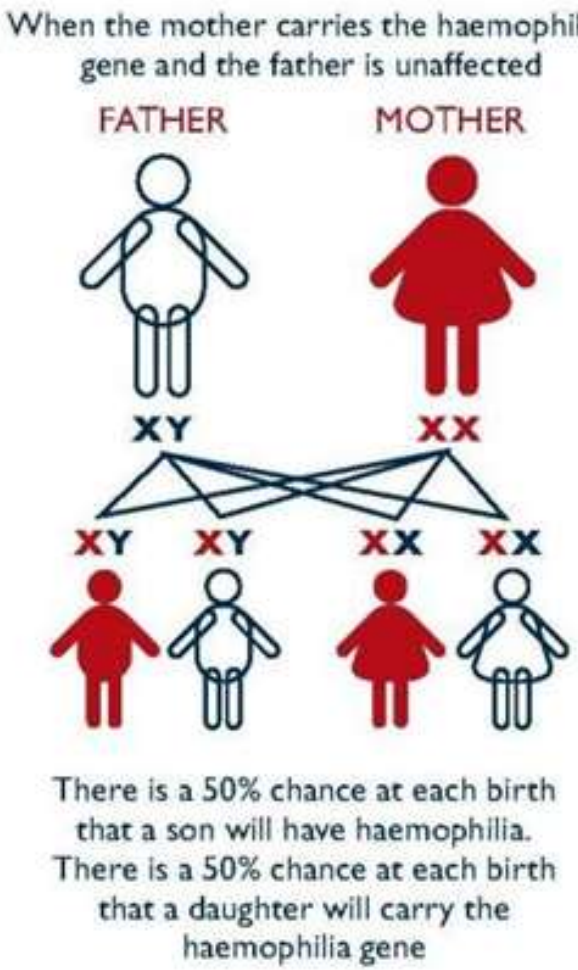
http://www.revhematologia.sld.cu/index.php/hih/article/view/145/118

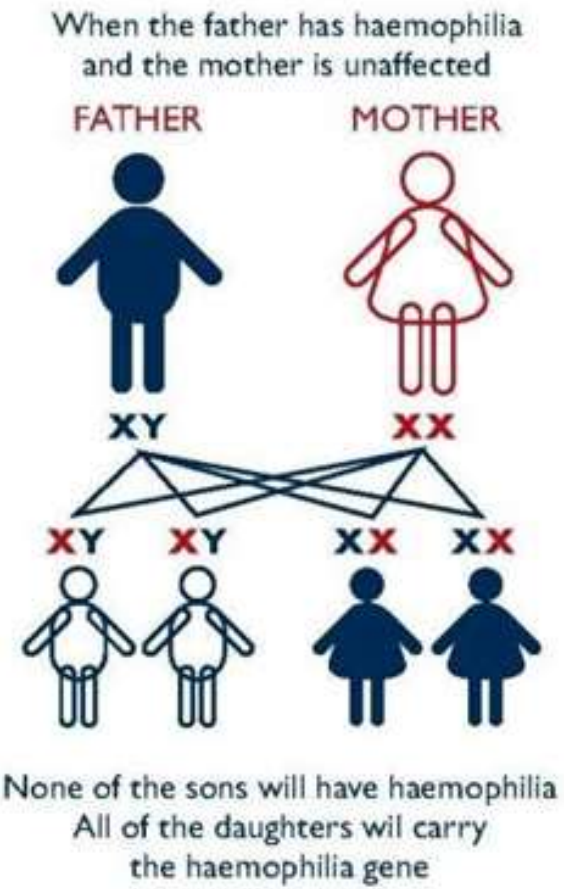
Hemophilia (HL): risk factors and etiology

- Risk factors for HL include family history of bleeding and almost always being male
- HL is caused by an inherited X-linked recessive trait, with the defective gene located on the X chromosome
- Males have only one X chromosome, and if the factor VIII gene or if the factor IX gene is missing on a boy's X chromosome, he will have HL A or HL B
- If a woman has a defective factor VIII gene or a defective factor IX gene, she is considered a carrier: boys born to such women have a 50% chance of having hemophilia A or hemophilia B, and their daughters have a 50% chance of being a carrier
- HL C with deficiency of factor XI was described first in 2 sisters and a maternal uncle of an American Jewish family after bled from dental extractions; unlike the bleeding tendency in HL A or HL B, which is clearly related to the factor level, the bleeding risk in HL C is not always influenced by the severity of the deficiency, especially in individuals with partial deficiency
- All female children of men with HL carry the defective gene

http://emedicine.medscape.com/article/955690-overview
https://www.nlm.nih.gov/medlineplus/ency/article/000538.htm

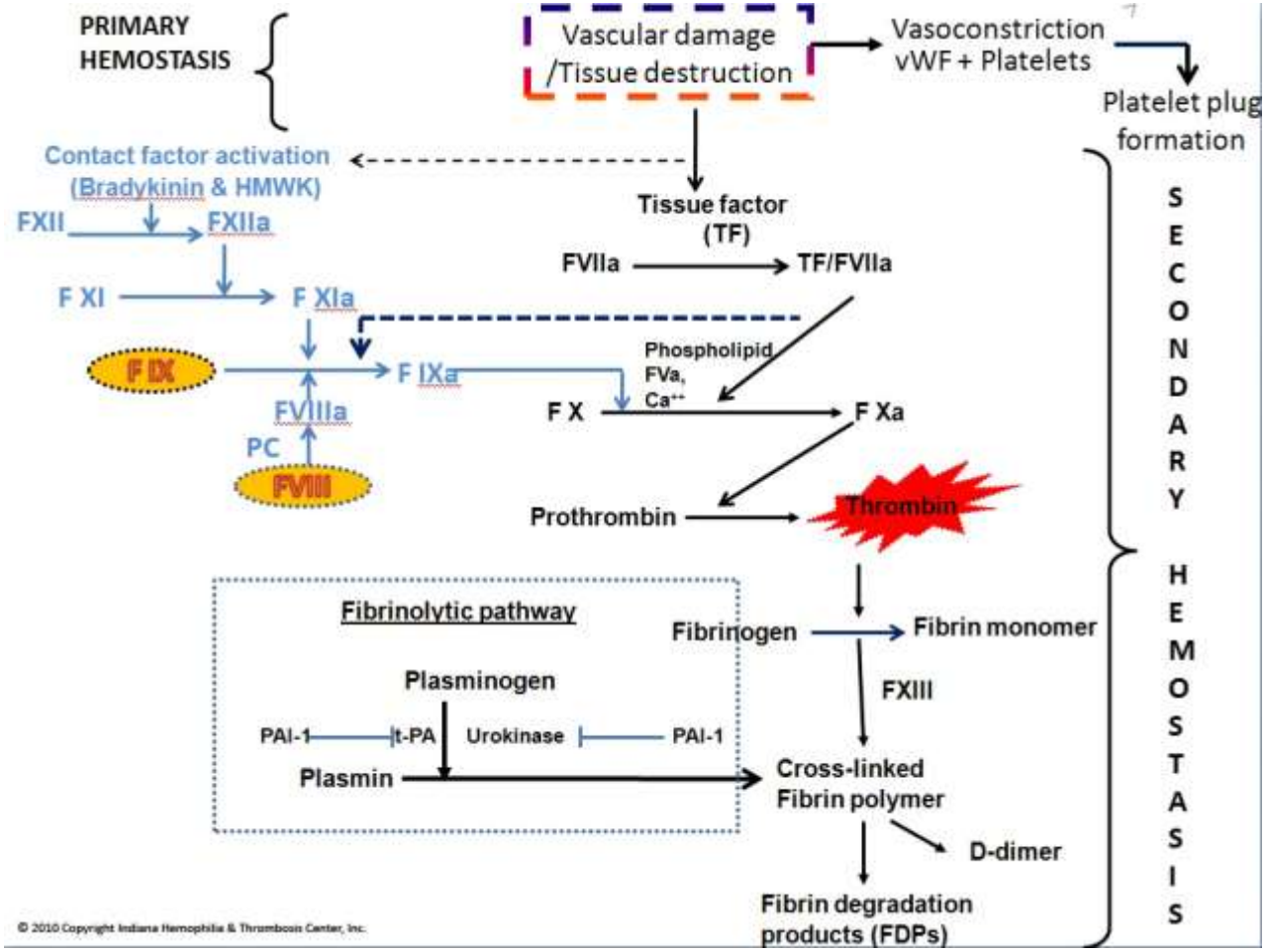
Hemophilia (HL): risk factors and etiology





http://www.moh.gov.sa/en/HealthAwareness/EducationalContent/Diseases/Hematology/Pages/006.aspx

Hemophilia (HL): mechanisms 1



Normal blood clotting is a complex process requiring as many as 20 blood proteins, or clotting factors. The deficiency or absence of one of these factors may disrupt the clotting process

http://www.ihtc.org/medical-professionals/blood-disorders/bleeding-disorders/hemophilia-a-and-b/

Hemophilia (HL): mechanisms 2

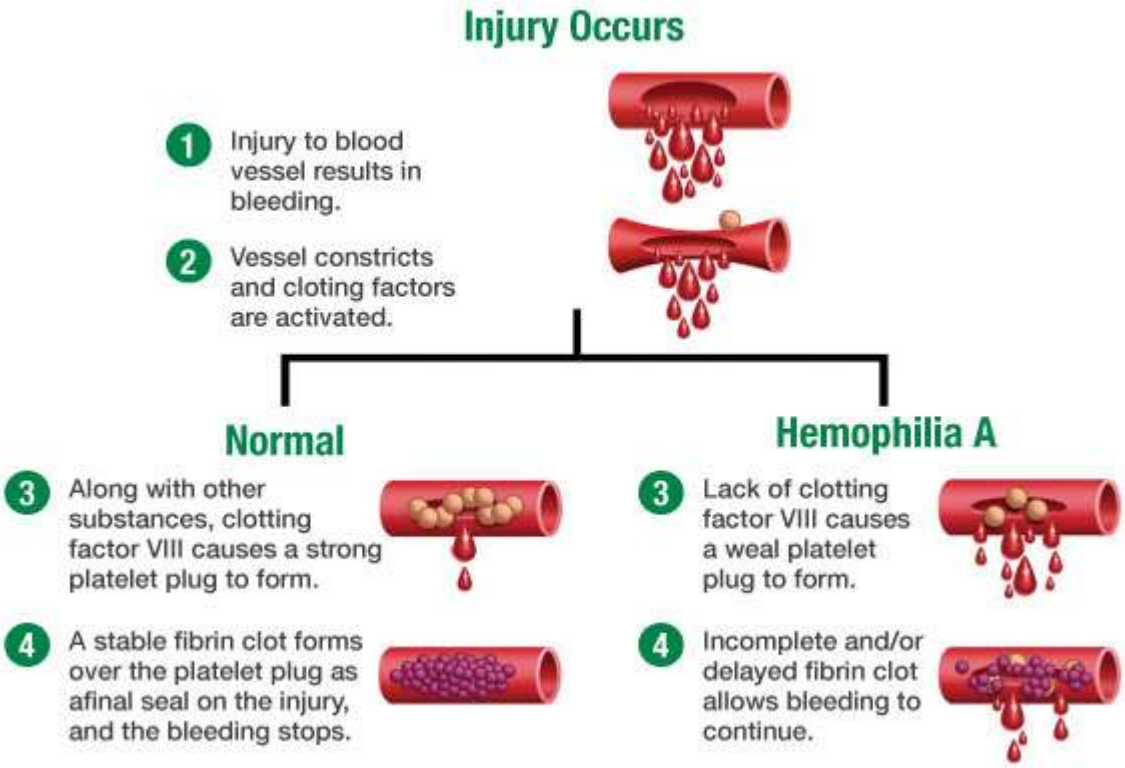


Diagram showing how in hemophilia patients, blood cannot clot properly because of poor platelet plug

http://www.koate-dviusa.com/about-hemophilia-a-pages-13.php

Hemophilia (HL): severity classification

- HL is classified as mild, moderate, or severe depending on the amount of the clotting factor present in a person's blood
- The normal range of FVIII and FIX is between 50% and 150%

Severity	Blood clotting factor level
Normal	50%-150%
Mild hemophilia	6%-49%
Moderate hemophilia	1%-5%
Severe hemophilia	<1%

•In mild HL , bleeding problems occur after injury, trauma, or surgery; the condition may have very few symptoms otherwise - 25% of the HL population
•In moderate HL bleeding episodes tend to occur after minor injuries, though in some cases spontaneous bleeding episodes may occur - 15% of the HL population
•In addition to bleeding after injury, trauma, or surgery, severe hemophilia characterized by spontaneous bleeding into joints and muscles - 60% of the HL population

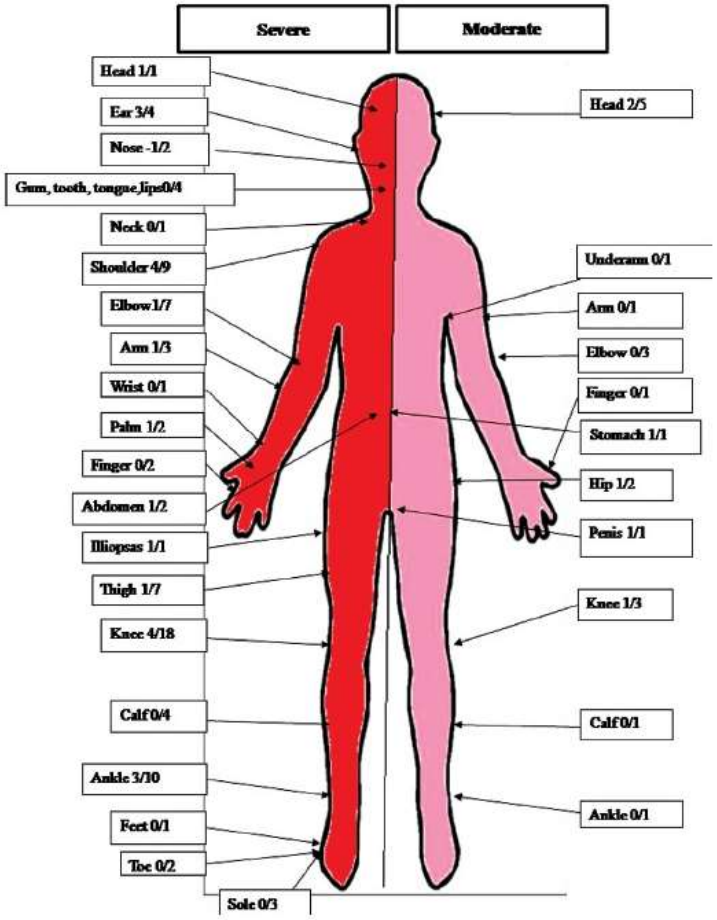
http://www.ihtc.org/medical-professionals/blood-disorders/bleeding-disorders/hemophilia-a-and-b/

Hemophilia (HL): clinical presentation 1

- All symptom of HL are related to uncontrolled or unexpected bleeding, either externally (e.g. skin cut, nosebleed) or internally (e.g. knee, muscle, brain)
- The extent of bleeding depends on the amount of functional clotting factors present in the body; when the amount of clotting factor is low, bleeding symptoms become more severe
- Internal bleeding into the joints, muscle and brain is serious and requires immediate medical attention
- The following bleeding symptoms are associated with HL:
- Excessive bleeding following minor injuries (e.g. skin cut)
- Large skin bruises from bleeding within the skin
- Uncontrolled bleeding after receiving a shot or pulling a tooth
- Frequent nosebleeds that are hard to stop
- Blood in the urine or stool
- Pain and swelling in the joints due to internal bleeding
- Infantile bleeding after birth or circumcision
- Headaches and difficulties with vision

http://www.innerbody.com/diseases-conditions/hemophilia

Hemophilia (HL): clinical presentation 2



Frequency and sites of bleeding in patients with severe and moderate HL A

http://www.ijmr.org.in/article.asp?issn=0971-5916;year=2014;volume=140;issue=1;spage=19;epage=31;aulast=Kar

Hemophilia (HL): clinical presentation 3

- Bleeding may occur anywhere in the body
- The most serious sites of bleeding are joints, muscles, digestive tract and brain
- Muscle and joint haemorrhages (hemarthrosis) are indicative of hemophilia, while digestive tract and cerebral haemorrhages are also germane to other coagulation disorders
- Though typically not life-threatening, joint bleeds are one of the most serious symptoms of HL
- Repeated bleeds into a joint capsule can cause permanent joint damage and disfigurement resulting in chronic arthritis and disability
- Joint damage is not a result of blood in the capsule but rather the healing process
- When blood in the joint is broken down by enzymes in the body, the bone in that area is also degraded

https://en.wikipedia.org/wiki/Haemophilia

Hemophilia (HL): clinical presentation 4

Topic	Severity of HL		
	Severe	Moderate	Mild
Cause of bleeding	Spontaneous	Minor trauma, not commonly spontaneous	Major trauma, surgery
Frequency of bleeding	2 – 4/month	4 – 6/year	Uncommon
Pattern of bleeding	Joint, soft tissue, bleeding after circumcision, neonatal intracranial hemorrhage, bleeding with surgical procedures	Joint, soft tissue +/- bleeding after circumcision, +/- neonatal intracranial hemorrhage, bleeding with surgical procedures	Joint, soft tissue, +/- bleeding after circumcision, bleeding with surgical procedures

Relationship Between Symptoms, Topic and Severity of HL

http://www.ihtc.org/medical-professionals/blood-disorders/bleeding-disorders/hemophilia-a-and-b/

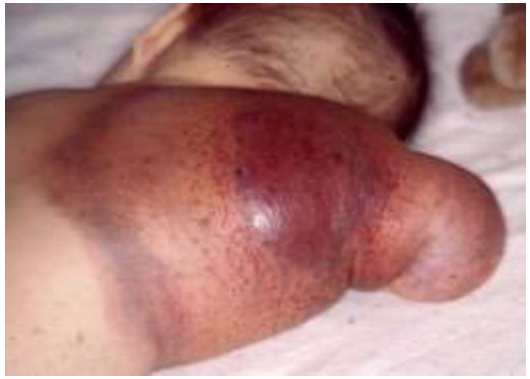
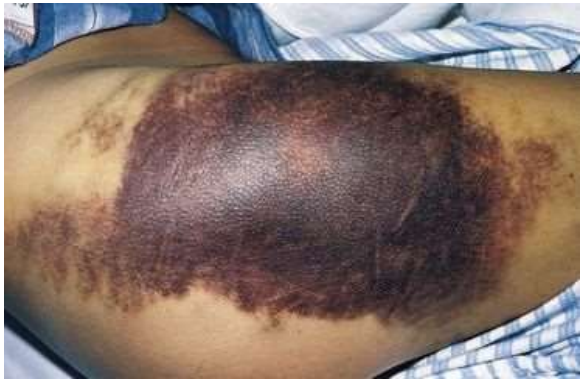
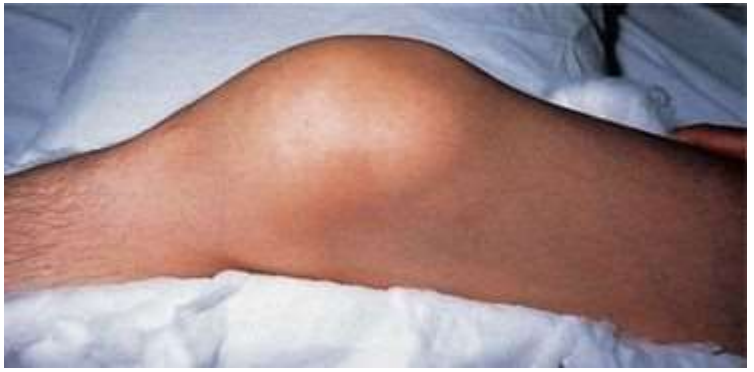
Hemophilia (HL): complications 1

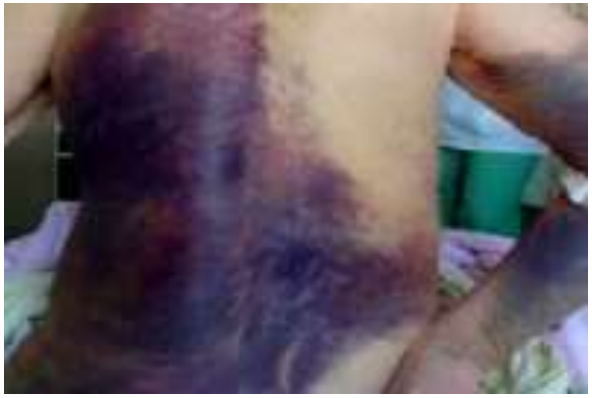
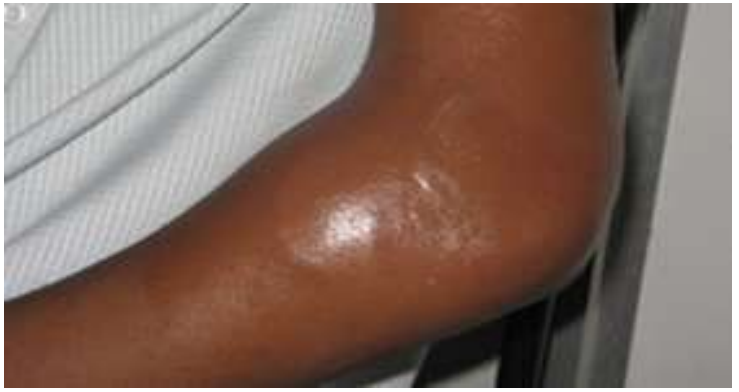
Complications may be both directly from the disease or from its treatment:

- Deep internal bleeding, e.g. deep-muscle bleeding, leading to swelling, numbness or pain of a limb
- Joint damage from hemarthrosis (hemophilic arthropathy), potentially with severe pain, disfigurement, and even destruction of the joint and development of debilitating arthritis
- Transfusion transmitted infection from blood transfusions that are given as treatment
- Adverse reactions to clotting factor treatment, including the development of an immune inhibitor which renders factor replacement less effective
- Intracranial hemorrhage is a serious medical emergency caused by the buildup of pressure inside the skull, that can cause disorientation, nausea, loss of consciousness, brain damage, and death

https://en.wikipedia.org/wiki/Haemophilia

Hemophilia (HL): complications 2

HL bleedings

http://www.obizur.com/images/hemo-bleed.png http://hubpages.com/health/Bleeding-Disorders-Due-To-Deficiency-Of-Coagulation-Factors-Hemophilia-A-Factor-VIII-deficiency# http://www.hemophiliabangalore.org/images/gall-2.jpg https://i.ytimg.com/vi/hzb_RHk0-fl/hqdefault.jpg http://pocketdentistry.com/25-congenital-bleeding-and-hypercoagulable-disorders/

Hemophilia (HL): diagnosis 1

- Personal history of bleeding
- Family history of bleeding and its inheritance pattern
- Laboratory evaluation
- Genetic testing to determine an individual's risk of attaining or passing on HL

https://en.wikipedia.org/wiki/Hodgkin%27s_lymphoma

Hemophilia (HL): diagnosis 2

Laboratory Evaluation

- In a patient with suspected HL, screening coagulation tests along with mixing studies are performed
- The activated partial thromboplastin time (aPTT) assay evaluates the intrinsic pathway of coagulation and is quite often prolonged in patients with HL
- If the aPTT is prolonged, a mixing study is performed to evaluate the correction of a patient's aPTT with a pooled plasma from healthy donors
- In patients with coagulation factor deficiencies, the aPTT is corrected in a 1:1 mixing study
- If a factor deficiency is suspected, then specific factor assays such as FVIII and FIX levels are performed to diagnose the type and severity of the deficiency
- In patients with mild hemophilia, the aPTT assay may be normal
- Once the diagnosis of HL is established, the screening of other at-risk family members, including females, should be performed to diagnose other affected individuals and determine the clotting factor level of carriers

http://www.ihtc.org/medical-professionals/blood-disorders/bleeding-disorders/hemophilia-a-and-b/

Hemophilia (HL): treatment 1

- Treatment is comprehensive and focused on preserving both physical health and quality of life of individuals with the disorder
- The primary goal of treatment is the prevention or cessation of bleeding episodes
- Prompt treatment of acute bleeding episodes is essential to minimize long-term complications
- Both nonpharmacologic and pharmacologic strategies are used in the treatment

http://formularyjournal.modernmedicine.com/formulary-journal/news/clinical/clinical-pharmacology/hemophilia-etiology-complications-and-current-

Hemophilia (HL): treatment 2

Nonpharmacologic therapy consists of supportive care

- Rest, ice, compression, and elevation (RICE) are important measures for treatment of joint or muscle bleeding episodes
- Splints, crutches, or casts can be used to allow the affected joint or muscle to rest after a bleeding episode
- Cold or ice compresses can help reduce associated inflammation and should be applied for 20 minutes every 4 to 6 hours
- Once pain and swelling begin to resolve, physiotherapy can be initiated to maintain joint and muscle function
- It is recommended that people affected with HL do specific exercises to strengthen the joints, particularly the elbows, knees, and ankles which increase flexibility, tone, and strength of muscles, increasing their ability to protect joints from damaging bleed

Hemophilia (HL): treatment 3

Pharmacologic strategies

- Though there is no cure for HL, it can be controlled with regular infusions of the deficient clotting factor, i.e. factor VIII in HL A or factor IX in HL B
- Factor replacement can be either isolated from human blood serum, recombinant, or a combination of the two
- Some patients develop antibodies (inhibitors) against the replacement factors given to them, so the amount of the factor has to be increased or non-human replacement products must be given, such as porcine factor VIII
- If a patient becomes refractory to replacement coagulation factor as a result of circulating inhibitors, this may be partially overcome with recombinant human factor VII

en.wikipedia.org/wiki/Haemophilia formularyjournal.modernmedicine.com/formulary-journal/news/clinical/clinical-pharmacology/hemophilia-etiology-complications-and-current-

Hemophilia (HL): treatment 4

Treatment regimens

- Prophylactic Infusion (Prophylaxis) as optimal therapy for patients with severe HL A or B involves regular administration of clotting factor concentrates, often 2 to 3 times per week, to increase the factor level to a moderate range (> 1%) to prevent spontaneous bleeding or bleeding after minor injury
- Episodic Infusion ("On-Demand") treatment is defined as utilization of clotting factor concentrates in response to an acute bleeding episode to stop bleeding after it has started
- In general, individuals with mild and moderate HL, who tend to bleed less frequently, use episodic infusion of factor concentrates

http://www.ihtc.org/medical-professionals/blood-disorders/bleeding-disorders/hemophilia-a-and-b/

Hemophilia (HL): treatment 5

New approaches (gene therapy)

- On 10 December 2011, a team of British and American investigators reported the successful treatment of HL B using gene therapy
- The investigators inserted the *F9* gene into an adeno-associated virus-8 vector, which has a propensity for the liver, where factor 9 is produced, and remains outside the chromosomes so as not to disrupt other genes
- The transduced virus was infused intravenously
- To prevent rejection, the people were primed with steroids to suppress their immune response
- In October 2013, the Royal Free London National Health Society Foundation Trust in London reported that after treating six people with HL in early 2011 with the genetically modified adeno-associated virus, over two years later all were still producing blood plasma clotting factor

https://en.wikipedia.org/wiki/Haemophilia

Hemophilia (HL): treatment 6

Contraindication

- Anticoagulants such as heparin and warfarin are contraindicated for people with HL as these can aggravate clotting difficulties
- Contraindicated are also those drugs which have "blood thinning" side effect (medicines which contain aspirin, ibuprofen, or naproxen sodium)
- Contraindicated are activities with a high likelihood of trauma, such as motorcycling and skateboarding, American football, hockey, boxing, wrestling, rugby, soccer, baseball, and basketball

https://en.wikipedia.org/wiki/Haemophilia

Hemophilia (HL): prognosis

- People with severe HL who don't receive adequate, modern treatment have greatly shortened lifespans and often do not reach maturity
- Prior to the 1960s when effective treatment became available, average life expectancy was only 11 years
- By the 1980s the life span of the average haemophiliac receiving appropriate treatment was 50–60 years
- Today with appropriate treatment, males with HL typically have a near normal quality of life with an average lifespan approximately 10 years shorter than an unaffected male

https://en.wikipedia.org/wiki/Haemophilia

Hemophilia (HL): clinical case 1a

Successful management of factor IX inhibitor-associated nephrotic syndrome (NS) in a hemophilia B patient

- NS is a recognized complication of immune tolerance induction (ITI) therapy, a treatment strategy used to treat inhibitors in patients with HL B receiving factor IX concentrate
- There was presentation of a 4-year-old boy with HL B and an inhibitor who underwent ITI, and developed NS 19 months into this therapy
- A percutaneous renal biopsy was safely performed with factor IX (FIX) concentrate administration both preceding and following the procedure
- The patient's inhibitor level had increased to 1.4-1.6 Bethesda Units just prior to the onset of proteinuria
- Histology confirmed segmental membranous nephropathy (MGN)

http://dgcases.docguide.com/successful-management-factor-ix-inhibitor-associated-nephrotic-syndrome-hemophilia-b-patient

Hemophilia (HL): clinical case 1b

Successful management of factor IX inhibitor-associated nephrotic syndrome (NS) in a hemophilia B patient

- The patient was continued on FIX concentrate as ITI and also received 4 weekly doses of rituximab and ongoing immunosuppression with mycophenolate mofetil
- This resulted in the complete resolution of his inhibitor and his NS
- He continues with a modified ITI regimen and remains inhibitor-free without proteinuria >12 months post-biopsy
- HL B patients undergoing ITI should be regularly screened for NS
- At first detection of proteinuria, with proper precautions, a percutaneous kidney biopsy can be performed safely in patients with low levels of inhibitor

http://dgcases.docguide.com/successful-management-factor-ix-inhibitor-associated-nephrotic-syndrome-hemophilia-b-patient

Hemophilia (HL): clinical case 2

Treatment of refractory hemorrhage with Factor XIII in a patient with HL A with inhibitor

- An 11-year-old male with HL A and a known high-titer Factor VIII inhibitor was admitted with retroperitoneal hemorrhage
- The patient was receiving infusions of recombinant activated Factor VII (rFVIIa) for a recent elbow hemorrhage when retroperitoneal bleeding commenced
- Despite increased dosing of rFVIIa and a dose of activated prothrombin complex concentrate (aPCC), he continued to hemorrhage and required several blood transfusions
- Factor XIII was administered 1 hour after rFVIIa and the patient demonstrated cessation of bleeding and normalization of clot strength
- Factor XIII may act as an adjuvant in effective clot stabilization in patients with HL and inhibitory antibodies

http://dgcases.docguide.com/treatment-refractory-hemorrhage-factor-xiii-patient-hemophilia-inhibitor

Hemophilia (HL): clinical case 3a

Successful percutaneous coronary intervention (PCI) for acute coronary syndrome (ACS) in a patient with HL B

- HL is a congenital coagulation defect brought about by the deficiency or lack of coagulation factor IX
- The prevalence of coronary artery disease and ACS is lower among hemophiliacs than in the normal population
- Data regarding a treatment protocol for ACS and PCI in patients with HL limited
- There was a report of a 41-year-old male patient with HL B who presented with a non-ST elevation myocardial infarction, and in whom PCI was performed following monitoring of factor IX levels
- The patient had no cardiovascular risk factor except smoking

http://dgcases.docguide.com/successful-percutaneous-coronary-intervention-acute-coronary-syndrome-patient-haemophilia-b

Hemophilia (HL): prophylaxis

Patients are advised to

- Stay up-to-date on vaccinations
- Attend annual comprehensive clinic evaluations
- Avoid situations and high-risk activities that may cause bleeding
- Maintain good oral hygiene (to prevent extensive dental procedures)
- Exercise regularly and maintain a healthy body weight
- Identify and treat bleeding events promptly, as directed by the hematologist

http://www.ihtc.org/medical-professionals/blood-disorders/bleeding-disorders/hemophilia-a-and-b/

Hemophilia (HL): abbreviations

- ACS - acute coronary syndrome
- aPCC - activated prothrombin complex
- aPTT - activated partial thromboplastin time
- ITI - immune tolerance induction
- HL - Hemophilia
- NS - nephrotic syndrome
- PCI - percutaneous coronary intervention
- pPTA - plasma thromboplastin antecedent
- rFVIIa - recombinant activated Factor VII

Hemophilia (HL): diagnostic and treatment guidelines

- Guidelines for the Management of Hemophilia
- WFH Treatment Guidelines - World Federation of Hemophilia
- Consensus recommendations for the diagnosis and treatment of acquired hemophilia A
- Diagnosis & Treatment Guidelines for Bleeding Management
- Haemophilia - Diagnosis - Guidelines - Best Practice

Plan of the lecture
2. thrombocytopenic purpura (TP)

Thrombocytopenic purpura' modern understanding

- Definition
- Epidemiology
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- Complications
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- Treatment
- Prognosis
- Prophylaxis
- Abbreviations
- Diagnostic guidelines

https://www.hemophilia.org/Bleeding-Disorders/Types-of-Bleeding-Disorders
.supportourribbons.com/custom-magnet-image/21023-custom-ribbon-magnet-sticker-Hemophilia+Awareness.png

Thrombocytopenic purpura (TP): definition

Thrombocytopenic purpura is purpura associated with a reduction in circulating blood platelets which can result from a variety of causes

Types

- Immune TP (primary immune thrombocytopenia, primary immune TP or autoimmune TP), in most cases is immune-mediated and is defined as isolated low platelet count with normal bone marrow
- Thrombotic TP (acquired - Moschcowitz syndrome, genetically inherited - Upshaw–Schulman syndrome), is a rare disorder of the blood-coagulation system, arising from inhibition or dysfunction of the enzyme ADAMTS13, and causing extensive microscopic clots (thrombi) to form in the small blood vessels throughout the body

en.wikipedia.org/wiki/Thrombotic_thrombocytopenic_purpura en.wikipedia.org/wiki/Idiopathic_thrombocytopenic_purpura en.wikipedia.org/wiki/Thrombocytopenic_purpura

Thrombocytopenic purpura (TP): epidemiology 1

- The incidence of Immune TP is estimated at 50–100 new cases per million people per year, with children accounting for half of that amount
- At least 70% of childhood cases will end up in remission within six months, even without treatment
- A third of the remaining chronic cases will usually remit during follow-up observation, and another third will end up with only mild thrombocytopenia (defined as a platelet count above 50,000)
- Immune TP is usually chronic in adults and the probability of durable remission is 20–40%
- The male to female ratio in the adult group varies from 1:1.2 to 1.7
- The mortality rate due to chronic Immune TP varies but tends to be higher relative to the general population for any age range
- No significant difference was noted in the rate of survival between males and females

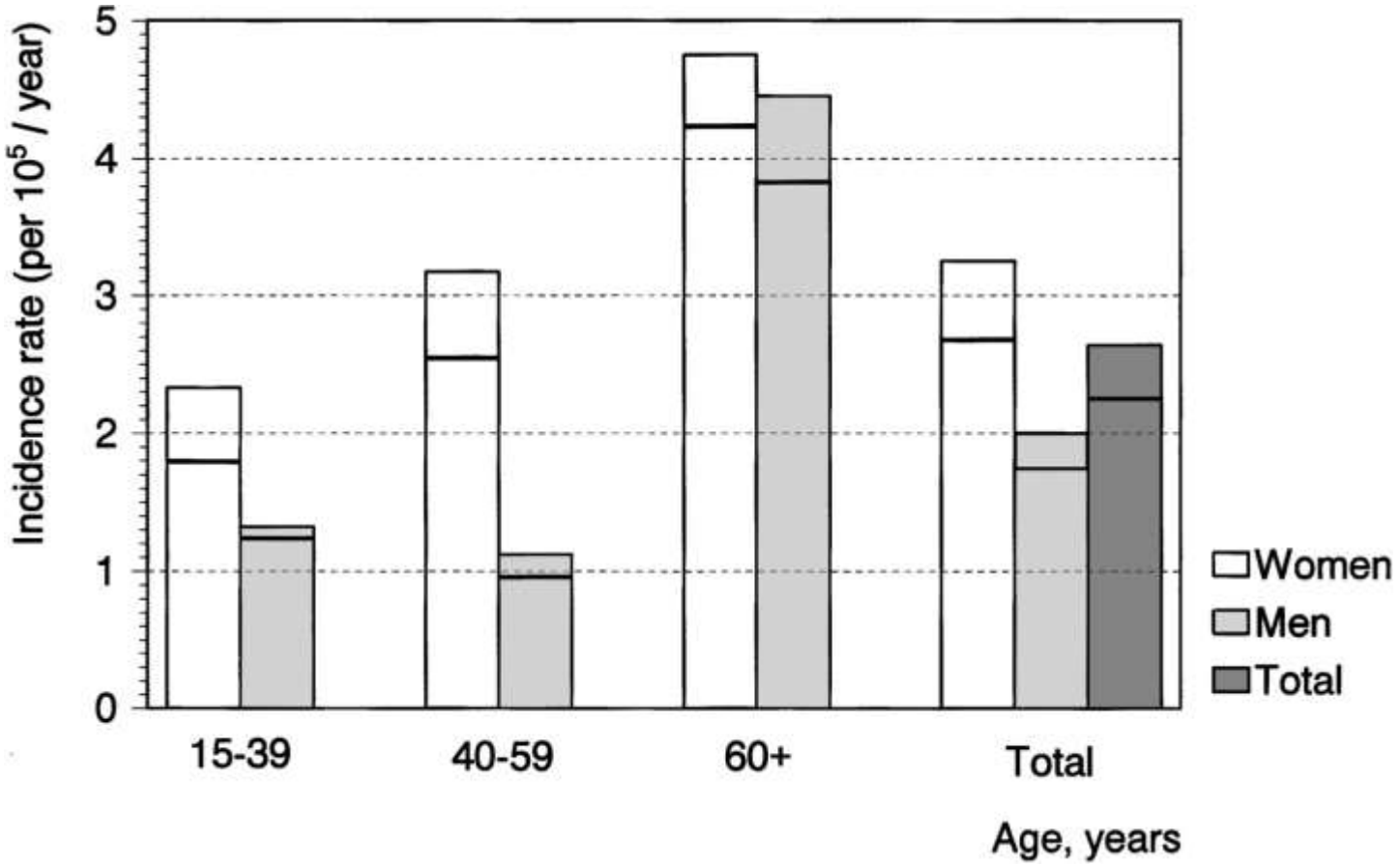
https://en.wikipedia.org/wiki/Idiopathic_thrombocytopenic_purpura#Pathogenesis

Thrombocytopenic purpura (TP): epidemiology 2

- The incidence of Thrombotic TP is about 4-5 cases per million people per year
- Idiopathic Thrombotic TP occurs more often in women and people of African descent
- Thrombotic TP secondary to autoimmune disorders such as systemic lupus erythematosus occurs more frequently in people of African descent
- Untreated, Thrombotic TP has a mortality rate of as high as 90%
- With plasma exchange, the mortality rate is reduced to 10-20%
- Acute morbidities include ischemic events such as stroke, transient ischemic attacks, myocardial infarction and arrhythmia, bleeding, and azotemia
- TTP during pregnancy may precipitate fetal loss
- In general, survivors have no long-term sequelae, with the exception of residual neurologic deficits in a minority of patients
- Relapses are not uncommon, occurring in 13-36% of patients

https://en.wikipedia.org/wiki/Thrombotic_thrombocytopenic_purpura#Unknown_cause http://emedicine.medscape.com/article/206598-overview#a6

Thrombocytopenic purpura (TP): epidemiology 3



Immune TP incidence rates according to age and sex. The horizontal bars correspond to incidence rates using a platelet count cut-off point of 50 × 10^9/L.

www.bloodjournal.org/content/94/3/909?sso-checked=true

Thrombocytopenic purpura (TP): risk factors and etiology

Immune TP

- The acute form often follows an infection and has a spontaneous resolution within 2 months
- The chronic form persists longer than 6 months with a specific cause being unknown
- Immune TP can be triggered by drugs, or associated with infection, pregnancy, or immune disorders such as systemic lupus erythematosus, but about half of all cases are classified as "idiopathic," meaning the cause is unknown

Thrombotic TP

- Acquired forms arise from inhibition of the enzyme ADAMTS13, a metalloprotease responsible for cleaving large multimers of von Willebrand factor (vWF) into smaller units with increased platelet adhesion to areas of endothelial injury, particularly at arteriole-capillary junctions
- Genetically inherited form arising from dysfunction of ADAMTS13 with tendency for increased coagulation exists

en.wikipedia.org/wiki/Idiopathic_thrombocytopenic_purpura medicinenet.com/script/main/art.asp?articlekey=24151

Thrombocytopenic purpura (TP): mechanisms 1

Immune TP

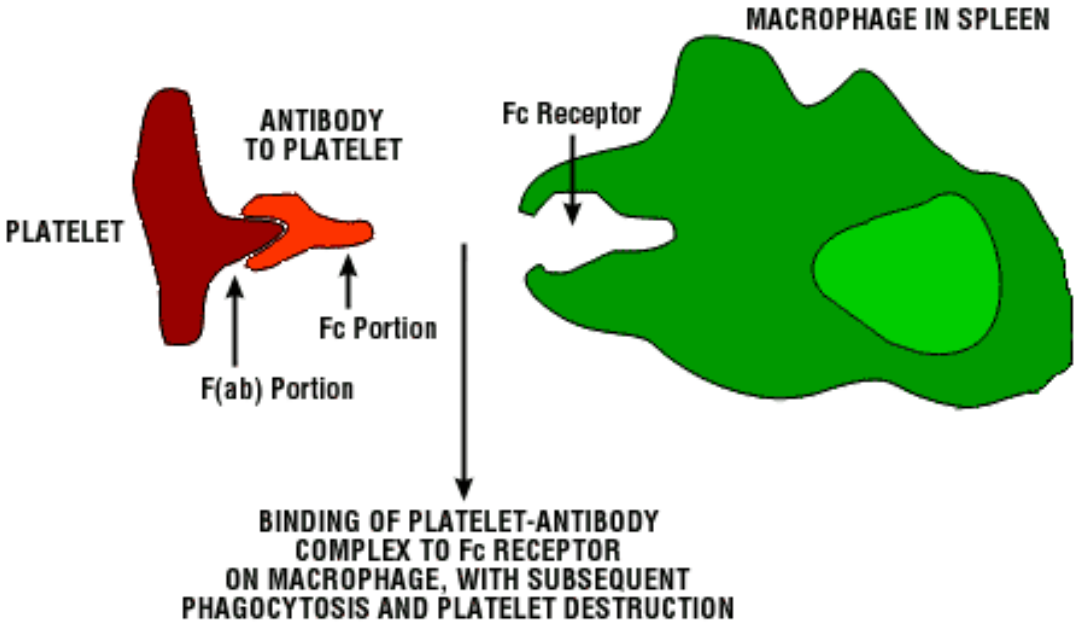
- In 60% of cases, antibodies against platelet membrane glycoproteins IIb-IIIa or Ib-IX can be detected, and are of the immunoglobulin G (IgG) type
- The coating of platelets with IgG renders them susceptible to opsonization and phagocytosis by splenic macrophages, as well by Kupffer cells in the liver
- The IgG autoantibodies are also thought to damage megakaryocytes

Thrombotic TP

- Thrombotic TP is characterized by clotting in small blood vessels of the body (thromboses), resulting in a low platelet count
- In its full-blown form, the disease consists of the pentad of microangiopathic hemolytic anemia, thrombocytopenic purpura, neurologic abnormalities, fever, and renal disease
- Reduced blood flow due to thrombosis and cellular injury results in end organ damage

en.wikipedia.org/wiki/Thrombotic_thrombocytopenic_purpura#Unknown_cause en.wikipedia.org/wiki/Idiopathic_thrombocytopenic_purpura#Pathogenesis
emedicine.medscape.com/article/206598-overview

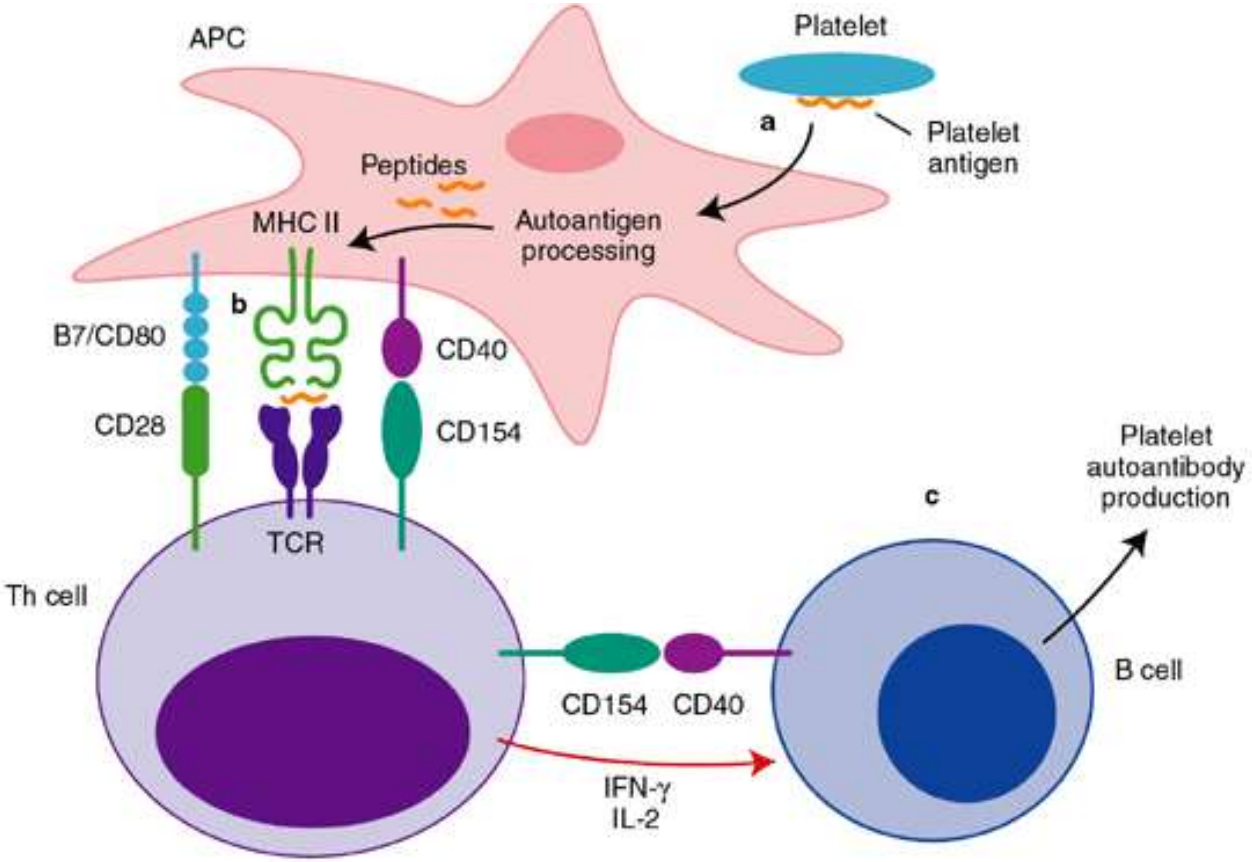
Thrombocytopenic purpura (TP): mechanisms 2



Mechanism of platelet destruction in Immune TP

http://www.medscape.org/viewarticle/420904_6

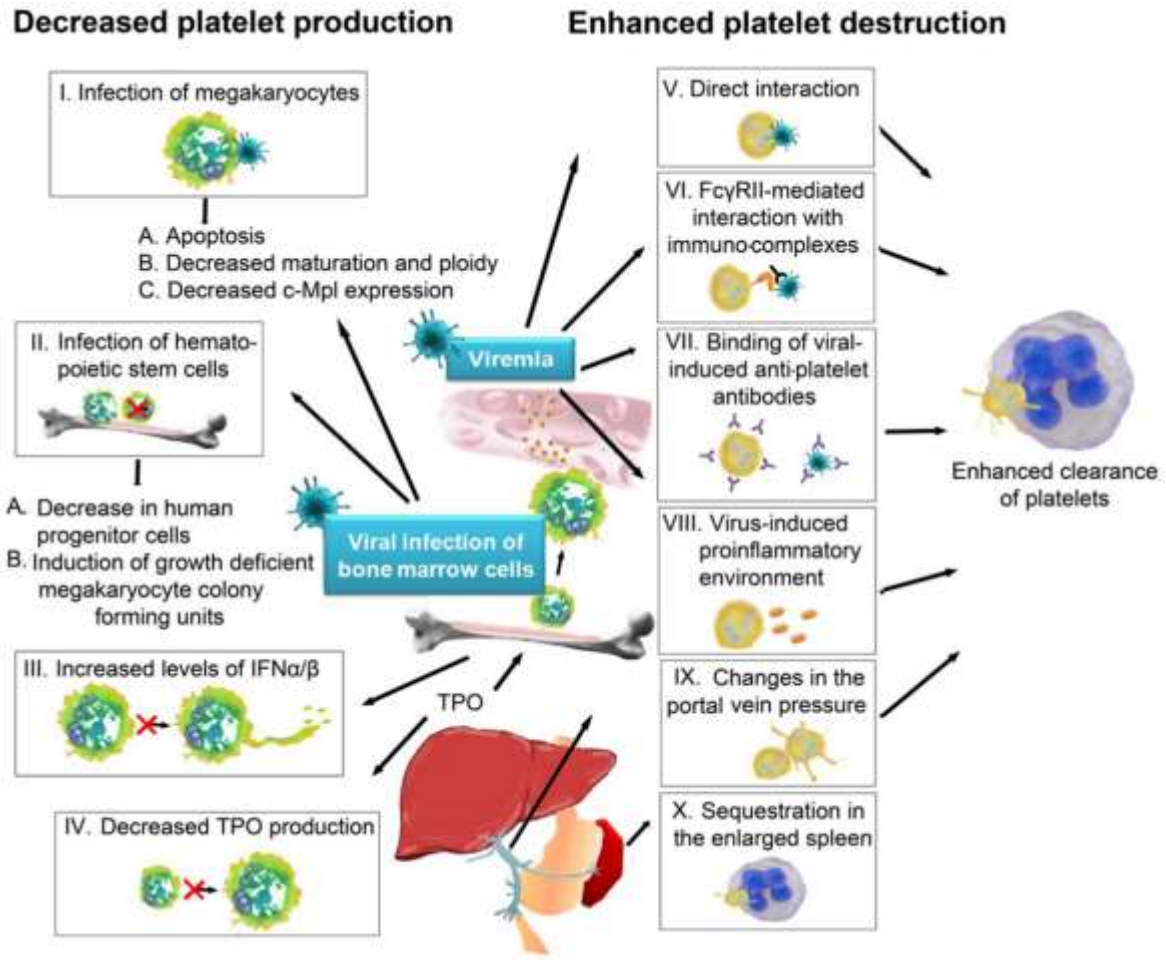
Thrombocytopenic purpura (TP): mechanisms 3



Model of platelet autoantibody production in Immune TP

http://4.bp.blogspot.com/_uiyskjNZYt8/TAevdJAWUSI/AAAAAAAABrU/cPJSHNFjl_g/s1600/Immune+thrombocytopenic+purpura.gif

Thrombocytopenic purpura (TP): mechanisms 4



Mechanisms of virus-induced thrombocytopenia

http://www.frontiersin.org/files/Articles/124104/fimmu-05-00649-HTML/image_m/fimmu-05-00649-g001.jpg

Thrombocytopenic purpura (TP): classification 1

Immune TP

- Primary (hereditary, idiopathic acquired)
- Secondary (human immunodeficiency virus (HIV), hepatitis C, *Helicobacter pylori*, immunodeficiencies, Evans' syndrome, autoimmune (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA)), lymphoproliferative disorders, adenocarcinoma, drug-induced)

Thrombotic TP

- Primary (hereditary, idiopathic acquired)
- Secondary (HIV, pregnancy, bacterial endocarditis, autoimmune (SLE, RA), lymphoproliferative disorders, adenocarcinoma, drug induced (ticlopidine, oral contraceptives, iodine, sulfonamides)

http://shp.missouri.edu/vhct/case2300/types_ttp.htm bestpractice.bmj.com/best-practice/monograph/138/basics/classification.html

Thrombocytopenic purpura (TP): clinical presentation 1

Immune TP

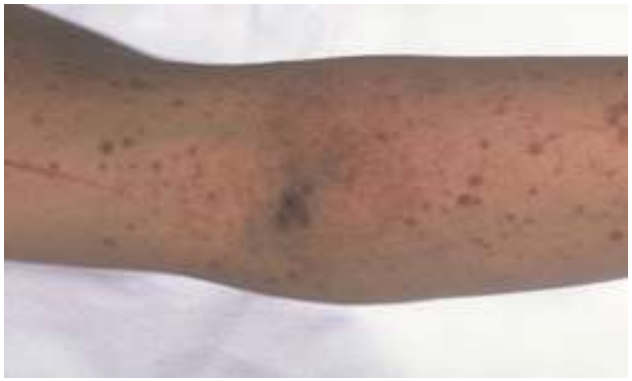
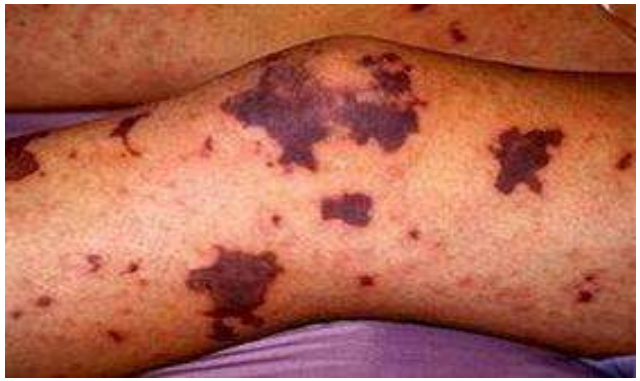
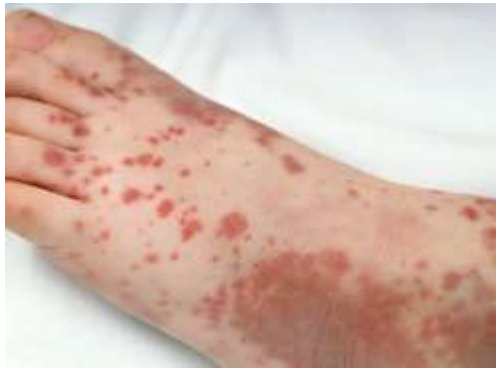
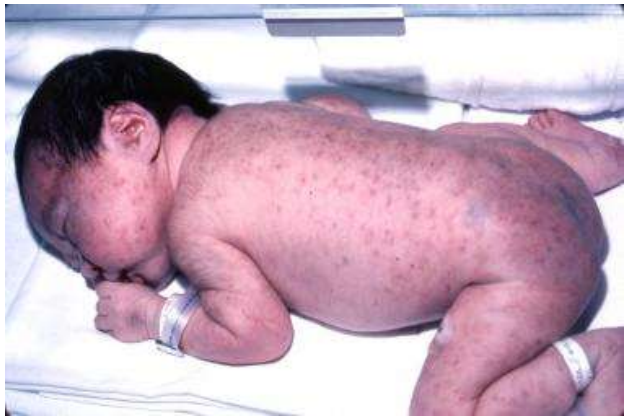
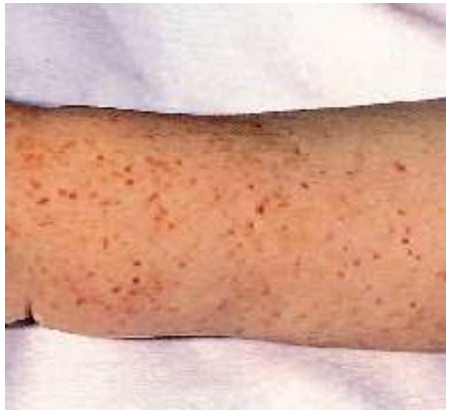
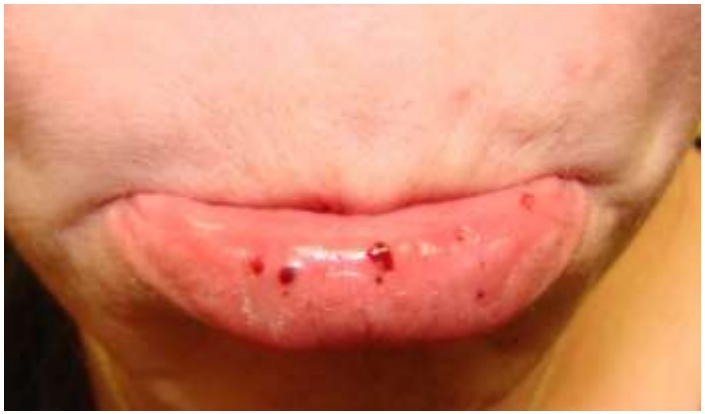
- Bruising
- Petechiae
- Purpura
- Prolonged bleeding from cuts
- Spontaneous bleeding from nose
- Bleeding gums, especially after dental work
- Blood in urine or stools
- Unusually heavy menstrual flow
- Fatigue

Thrombotic TP

- Bruising
- Petechiae
- Purpura
- Mucosal bleeding
- Microangiopathic hemolytic anemia
- Neurologic symptoms (hallucinations, bizarre behavior, delirium, stroke, hemiplegia, paresthesias, visual disturbance, aphasia, headaches)
- Kidney failure
- Fever

https://www.merckmanuals.com/professional/hematology-and-oncology/thrombocytopenia-and-platelet-dysfunction/immune-thrombocytopenia-(itp)
http://www.mayoclinic.org/diseases-conditions/idiopathic-thrombocytopenic-purpura/basics/symptoms/con-20034239 http://emedicine.medscape.com/article/206598-overview

Thrombocytopenic purpura (TP): clinical presentation 2

Petechiae (red/purple dots) and purpura (bruises) in the skin

http://www.skinerrors.com/wp-content/uploads/Idiopathic-thrombocytopenic-purpura.jpg https://my.clevelandclinic.org/health/diseases_conditions/hic-immune-thrombocytopenia
https://upload.wikimedia.org/wikipedia/commons/0/02/Oral_petechiae.JPG http://www.primehealthchannel.com/idiopathic-thrombocytopenic-purpura.html http://healthool.com/purpura/

Thrombocytopenic purpura (TP): diagnosis

Immune TP

- The diagnosis is a process of exclusion
- It has to be determined that there are no blood abnormalities other than a low platelet count, and no physical signs other than bleeding
- Secondary causes should be excluded
- Bone marrow examination is not required to make the diagnosis but is done if blood counts or blood smear reveals abnormalities in addition to thrombocytopenia, when clinical features are not typical, or if patients fail to respond to standard therapies

Thrombotic TP

- Measuring ADAMTS13 activity level
- Laboratory studies
  - Complete blood count (CBC)
  - Total white blood cell count is normal or slightly elevated
  - Hemoglobin concentration is moderately depressed at 8-9 g/dL
  - Platelet count generally ranges from 20,000-50,000/µL
  - coagulation studies
  - Blood urea nitrogen (BUN) creatinine,
  - serum bilirubin and lactate dehydrogenase as indirect measures of the degree of hemolysis
- Imaging studies and biopsies are not required for diagnosis

emedicine.medscape.com/article/206598-overview en.wikipedia.org/wiki/Idiopathic_thrombocytopenic_purpura#Diagnosis
merckmanuals.com/professional/hematology-and-oncology/thrombocytopenia-and-platelet-dysfunction/immune-thrombocytopenia-(itp)

Thrombocytopenic purpura (TP): treatment

Immune TP

- There is usually no need to treat based on platelet counts
- Current guidelines recommend treatment only in cases of significant bleeding
- Initial treatment usually consists of corticosteroids, the dose and mode of administration is determined by platelet count and whether there is active bleeding
- In chronic refractory cases, immunosuppresants (mycophenolate mofetil and azathioprine) and chemotherapy (vincristine) agent may be attempted
- Anti-RhD therapy for patients with certain blood types
- Infusions of high-dose gamma globulin
- Thrombopoietin receptor agonists (romiplostim, eltrombopag) that stimulate the bone marrow to make more platelets
- Platelet transfusion is recommended in an emergency

Thrombotic TP

- The therapy of choice is plasma exchange with fresh frozen plasma
- Another option, is intravenous administration of octaplas, a sterile, frozen solution of pooled human plasma from several donors as alternative to single-donor plasma
- Corticosteroids may also be used in refractory patients

https://en.wikipedia.org/wiki/Idiopathic_thrombocytopenic_purpura#Treatment https://en.wikipedia.org/wiki/Thrombotic_thrombocytopenic_purpura#Unknown_cause
http://emedicine.medscape.com/article/206598-overview

Thrombocytopenic purpura (TP): prognosis

Immune TP

- With treatment, the chance of remission (a symptom-free period) is good
- In rare cases, disease may become a long-term condition in adults and reappear, even after a symptom-free period

Thrombotic TP

- The mortality rate is around 95% for untreated cases, but the prognosis is reasonably favorable (80–90% survival) for patients diagnosed and treated early with plasmapheresis

https://www.nlm.nih.gov/medlineplus/ency/article/000535.htm https://en.wikipedia.org/wiki/Thrombotic_thrombocytopenic_purpura#Unknown_cause

Thrombocytopenic purpura (TP): prophylaxis

- There is no known way to prevent Immune TP and Thrombotic TP

http://www.ncbi.nlm.nih.gov/pubmedhealth/PMHT0023094/ https://www.nlm.nih.gov/medlineplus/ency/article/000535.htm

Thrombocytopenic purpura (TP): clinical case 1a

Use of a thrombopoietin mimetic for chronic immune thrombocytopenic purpura (TP) in pregnancy

- Romiplostim, a thrombopoietin mimetic, is a novel therapeutic option for patients with chronic immune TP
- A 28-year-old primigravid woman with chronic immune TP initiated a planned pregnancy on romiplostim
- The second and third trimesters were marked by a cyclic pattern of thrombocytopenia requiring supplemental corticosteroids or intravenous immunoglobulin and resultant thrombocytosis
- Increased romiplostim doses and daily corticosteroids stabilized the platelet count before induction of labor at 33 weeks of gestation

http://dgcases.docguide.com/use-thrombopoietin-mimetic-chronic-immune-thrombocytopenic-purpura-pregnancy

Thrombocytopenic purpura (TP): clinical case 1b

Use of a thrombopoietin mimetic for chronic immune thrombocytopenic purpura (TP) in pregnancy

- The newborn manifested intraventricular hemorrhage at birth, although no developmental delay was present on follow-up at 10 months of age
- The decreased efficacy of romiplostim monotherapy is attributed to increased target-mediated drug disposition and the physiologic changes of pregnancy
- Safety concerns still exist for the developmental effects of romiplostim on the fetus

http://dgcases.docguide.com/use-thrombopoietin-mimetic-chronic-immune-thrombocytopenic-purpura-pregnancy

Thrombocytopenic purpura (TP): clinical case 2

Multivessel coronary thrombosis in a patient with idiopathic TP

- A 49-year-old woman who had idiopathic TP was admitted to our hospital with severe chest pain
- Electrocardiography revealed inferolateral myocardial infarction
- The patient underwent immediate coronary angiography, which revealed thrombi in the left coronary system
- Percutaneous intervention was not indicated, because the thrombi had occluded the distal segments of multiple coronary arteries
- Administration of tirofiban satisfactorily dissolved the thrombi

http://dgcases.docguide.com/use-thrombopoietin-mimetic-chronic-immune-thrombocytopenic-purpura-pregnancy

Thrombocytopenic purpura (TP): clinical case 3

Thrombotic TP with unusual 33 recurrences: a case report

- The hereditary or acquired deficiency of ADAMTS-13 activity leads to an excess of high molecular weight von Willebrand factor multimers in plasma, leading to platelet aggregation and diffuse intravascular thrombus formation, resulting in Thrombotic TP
- There was a report of a 36 year old male with a long history of Thrombotic TP associated with 33 relapses
- As a result of early transfusions, the patient acquired Hepatitis C
- This time, the patient presented with a Thrombotic TP relapse after a 10 year remission, following PEG-interferon-Alpha (IFA) therapy for Hepatitis C
- Since IFA has been reported to activate autoimmune reactions, it may have augmented production of ADAMTS-13 antibody

http://dgcases.docguide.com/thrombotic-thrombocytopenic-purpura-unusual-33-recurrences-case-report

Thrombocytopenic purpura (TP): abbreviations

- CBC - complete blood count
- IFA - interferon-alpha
- HIV - human immunodeficiency virus
- RA - rheumatoid arthritis
- SLE - systemic lupus erythematosus
- TP - thrombocytopenic purpura
- vWF - von Willebrand factor

Thrombocytopenic purpura (TP): diagnostic and treatment guidelines

- Diagnosis and treatment of idiopathic thrombocytopenic purpura: recommendations of the American Society of Hematology. The American Society of Hematology ITP Practice Guideline Panel.
- Management of Immune Thrombocytopenic Purpura: An Update
- Immune Thrombocytopenic Purpura
- Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies