

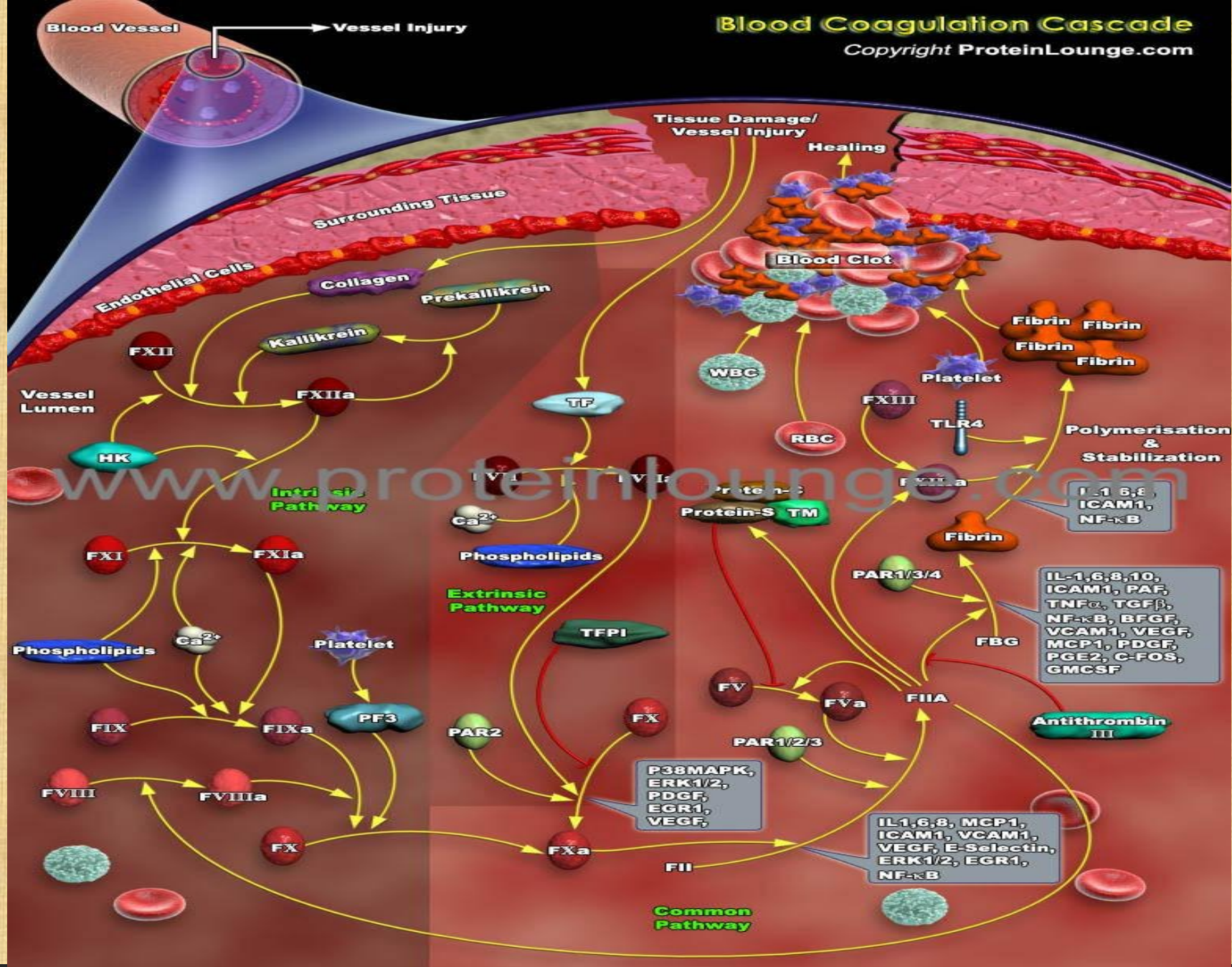
HEMOSTASI S

Limitless creativity

Oday Hamad, md

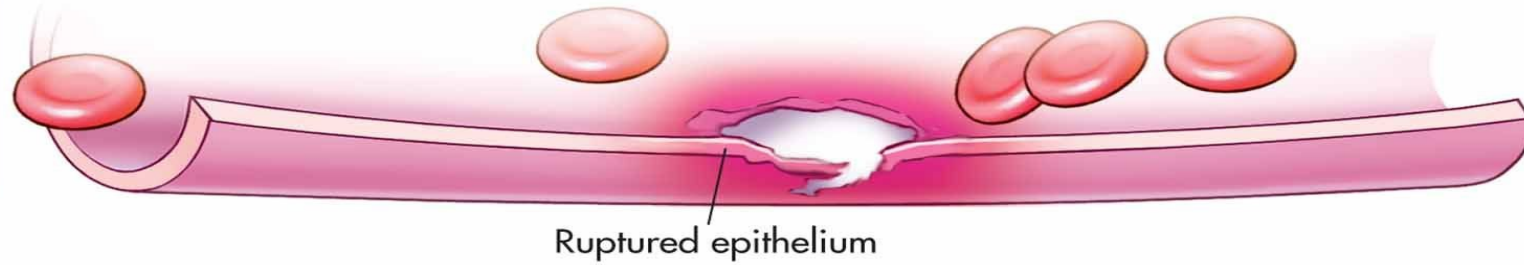


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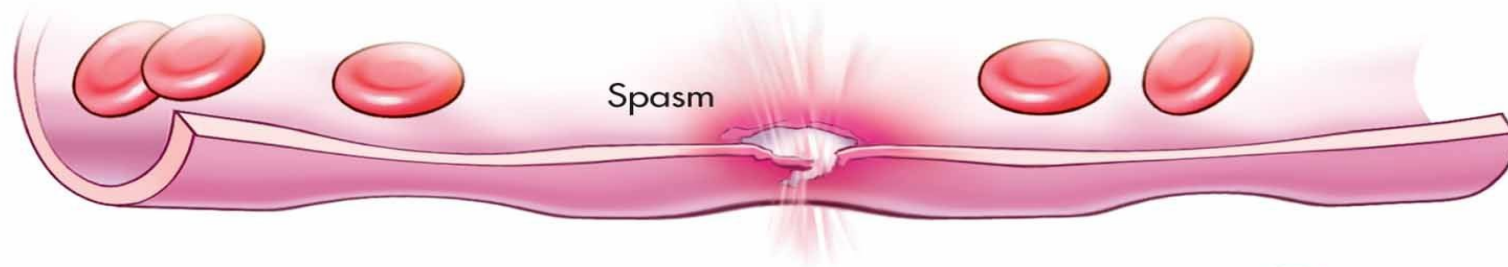


2026/10/11

Vessel injury



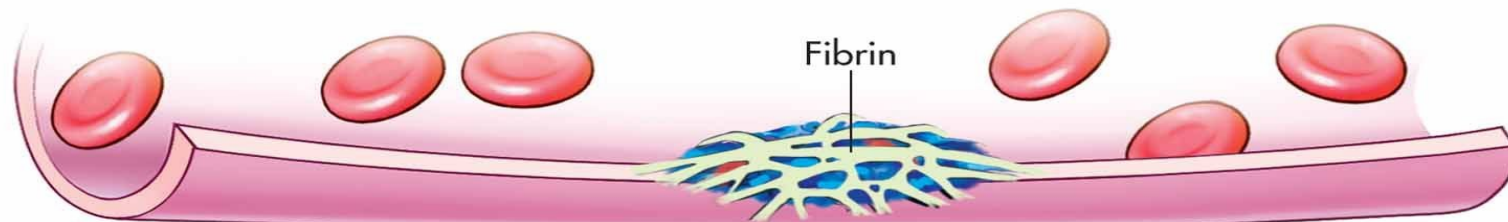
Vessel spasm



Platelets adhere to injury site and aggregate to form plug



Formation of insoluble fibrin strands and coagulation



OVERVIEW

Coagulation after a vascular injury consists of 2 stages: primary hemostasis and secondary hemostasis. Primary hemostasis is the function of the platelets, whereas secondary hemostasis is dependent upon the coagulation factors.

PRIMARY HEMOSTASIS

Primary hemostasis consists of platelet plug formation, vascular spasm, and capillary endothelial adhesion, with capillaries collapsing and sticking closed when empty.

This fix is temporary and lasts for only 12-24 hours. (This is why hemophiliacs often do not have a deep bleed until 12-24 hours after trauma.)

Platelet plug formation = platelet attachment --> platelet activation --> platelet aggregation.

After endothelial injury, platelets rapidly attach to the newly exposed subendothelial collagen. The von Willebrand factor, released from the endothelium, reacts with the platelet surface glycoprotein Ib/IX to increase "stickiness" of platelets to each other and to exposed collagen.

Platelets are then activated, releasing cytokines, including ADP and arachidonic acid, which further stimulate platelet release and aggregation. Arachidonic acid is converted by cyclooxygenase into precursors of thromboxane A2

Thromboxane A2 recruits more platelets and exposes platelet surface glycoprotein IIb/IIIa. Thromboxane A2 is also a potent vasoconstrictor.

Fibrinogen then cross-connects the IIb/IIIa protein on platelets to form platelet plugs.

There are several FDA-approved IIb/IIIa receptor inhibitors available. Approved indications include unstable angina and adjunctive therapy during coronary angioplasty.

Aspirin irreversibly acetylates cyclooxygenase and thus decreases platelet function. Chronic ASA use of as little as 40 mg/day causes suppression of 95% of the thromboxane A₂. NSAIDs bind reversibly with cyclooxygenase; they may block the desired effect of ASA if they are administered at the same time. Clopidogrel irreversibly inhibits ADP binding to the platelet receptor, resulting in decreased platelet aggregation

SECONDARY HEMOSTASIS

The Coagulation Cascade

All coagulation is initiated by tissue factor (released at the site of injury) interacting with Factor VII. The intrinsic pathway factors (VIII, IX, and XI) serve solely to amplify this formation of thrombin-and can do so only after a small amount of thrombin is formed by the extrinsic pathway. Tissue factor is in short supply and short-lived-so the extrinsic pathway can produce only a small amount of thrombin.

Thrombin is the key. As you can see in the next slide, this little bit of thrombin immediately starts building more thrombin while it builds the thrombus.

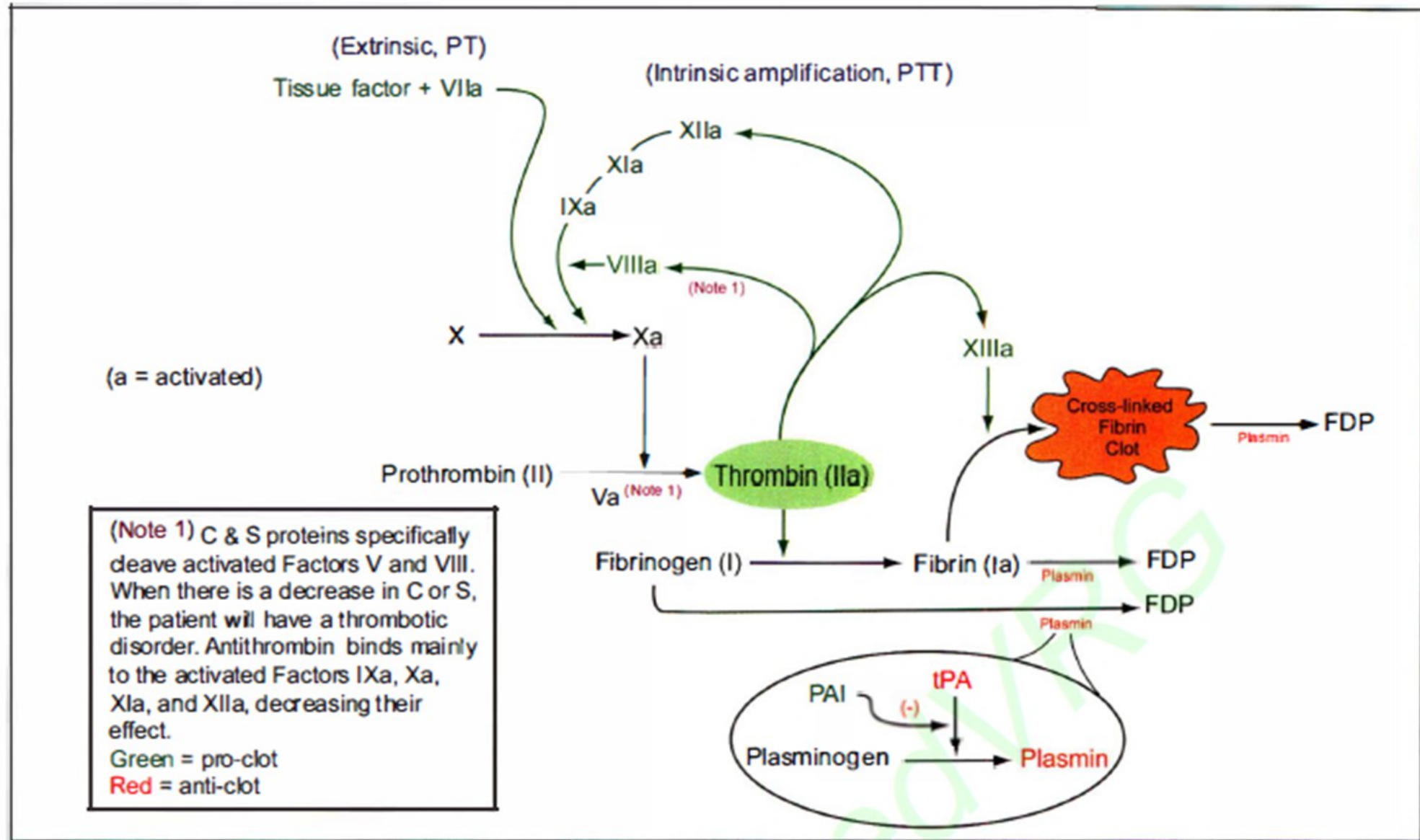


Figure 8-3: Clotting Cascade

Thrombin does the following:

- Converts fibrinogen to fibrin
- Activates Factor XIII, which causes this fibrin to cross-link and form the thrombus
- Activates Factor XII, which, in turn, activates Factor XI, which, in turn, activates Factor IX
- Activates VIII; Factors VIIIa and IXa together

So, the first 2 processes help make the thrombus while the second 2 are part of a powerful "intrinsic" amplification system that makes more thrombin.

Okay, so how does the body stop this process?

Thrombus dissolution, or fibrinolysis, is initiated by tissue plasminogen activator (tPA) and released from the endothelial cells. tPA converts plasminogen to plasmin, which then breaks down fibrin and fibrinogen and limits the size of the thrombus. Proteins C and S are natural anticoagulants; they inactivate Factors Va and VIIIa.

Protein C also blocks the inhibitor of tPA (plasminogen activator inhibitor-!).

In healthy people, this results in fibrinolysis. In the absence of proteins C and S, thrombosis goes unchecked.

AN APPROACH TO THE PATIENT

It is often possible to differentiate between a primary and a secondary hemostatic problem at the bedside:

- **Primary hemostatic problems** (90% involve either platelet dysfunction or low platelets) result in multiple, tiny, superficial hemorrhages, causing petechiae, purpura (large petechiae), ecchymoses, and mucocutaneous bleeding.
- **Secondary hemostatic disorders**, on the other hand, such as hemophilia, develop deep tissue bleeding, including hematomas or hemarthroses.

Typically, 4 tests can quickly assess coagulation and platelet status:

- 1) **Prothrombin time (PT)** measures the function of extrinsic and common pathways.
- 2) **Activated partial thromboplastin time (PTT or aPTT)** measures the function of the intrinsic amplification.
- 3) **Platelet count.**
- 4) **Platelet function tests** evaluate platelet aggregation when stimulated by epinephrine, ADP, and collagen.

DISORDERS OF PRIMARY HEMOSTASIS

Disorders of primary hemostasis involve the skin and vascular endothelium as well as platelets. This review focuses on the latter, which includes both quantitative and qualitative defects.

Thrombocytopenia has multiple etiologies, which can be categorized into defects of production, sequestration, and destruction.

Pseudo thrombocytopenia (i.e., artifact) occurs fairly often--- so the 1st test to do after observing a low platelet count result is a repeat platelet count. A peripheral blood smear to look for **platelet clumping**, which is perceived by automated counters as a low platelet count, is also helpful.

You can see abnormal platelet function after aspirin ingestion and in von Willebrand disease, Bernard-Soulier (giant platelet) syndrome, Glanzmann thrombasthenia, paraproteinemia (multiple myeloma), chronic kidney disease, and connective tissue disease.

Thrombocytopenia

Thrombocytopenia has 3 causes: impaired bone marrow production, splenic sequestration, or decreased platelet survival (destruction).

1) **Impaired production:** due to bone marrow failure from toxins (including alcohol), infiltration, aplasia, sepsis, and HIV infection. Often there is concomitant anemia and/or leukopenia.

2) **Hypersplenism:** Thrombocytopenia is usually modest and accompanied by a reduction in the other cell lines (leukopenia and anemia).

3) **Survival defects:**

- Consumptive process such as DIC, HIT (heparin-induced thrombocytopenia), TTP/HUS, and HELLP.
- Immune thrombocytopenia (ITP), either idiopathic or drug-induced. Common drug offenders include quinidine, rifampin, sulfonamide combinations, and digoxin.

If the platelet count is $> 20 \times 10^9/L$, there is usually no serious spontaneous bleeding.

When the count is $< 10,000$, the risk of serious bleeding increases and platelet transfusions are often considered. Do not transfuse platelets if you suspect HIT or TTP unless the patient has active life-threatening bleeding.

Immune Thrombocytopenic Purpura

Immune thrombocytopenic purpura (ITP) is an autoimmune syndrome that occurs in children and adults.

In children, it often has an acute presentation, occurs after a viral illness, and is commonly self-limited with a good prognosis. Chronic ITP generally occurs in adults and has a relapsing course. Both acute and chronic ITP are associated with IgG antibodies directed against the GPIIb/ GPIIIa glycoproteins on platelets. When associated with an underlying disease in which antiplatelet antibodies are formed, patients are said to have "secondary ITP."

Underlying diseases that may be associated with secondary ITP include: viruses (e .g., HIV, hepatitis C), SLE, antiphospholipid syndrome, and CLL. Recall that many of these same diseases also are associated with autoimmune hemolytic anemias.

The adult patient with ITP usually presents with easy bruising, petechiae, and **nonpalpable purpura**-which differentiates this from **Henoch-Schonlein purpura (HSP)** in which the purpura is **palpable**. Patients with ITP have mucosal bleeding (gingival, menorrhagia, epistaxis).

When ITP occurs in an elderly patient, the patient may present with a GI or nervous system bleed.

Platelets in patients with ITP are often hyperfunctional, and, even with severe thrombocytopenia, significant spontaneous bleeding is rare.

Primary ITP is a diagnosis of exclusion, so rule out other causes. Do not order an antiplatelet antibody test. The result is too nonspecific to be helpful!

Do the following:

- As with all cases of thrombocytopenia, repeat the platelet count.
- Examine the peripheral smear to make sure platelets aren't clumping, and that schistocytes are absent (if present, suggests TTP is underlying diagnosis, not ITP). Around 1/1,000 automated platelet counts are falsely low. Clumping is caused by platelet activation by EDTA. Collecting the sample in a citrate tube corrects this problem.

The peripheral smear in ITP typically reveals few (but giant) platelets, and normal RBCs and WBCs.

- Patients > 60 years of age may need a bone marrow biopsy to exclude myelodysplasia before diagnosing them with ITP. In ITP, marrow cellularity is normal with evidence of megakaryocyte hyperplasia.

Treat chronic ITP only if symptomatic or if the platelet count is very low:

- Corticosteroids (prednisone 1 mg/kg or equivalent daily) are 1st line treatment.
- Give IV immunoglobulin (IVI G) as a 2nd line treatment to satiate voracious macrophages, which then become less hungry for antibody-coated platelets, leading to an increase in platelet count. IVIG is useful if a rapid improvement in platelet count is desired, as in a pre-op or bleeding patient. Response, however, is regularly transient-lasting only several weeks.
- Before sending a patient for surgery, many hematologists try anti-D immunoglobulin if patients are Rh-positive and have a functional spleen. This induces a mild hemolytic state, with resultant RBC stromal release and uptake by reticuloendothelial cells. The uptake of RBC stroma (as with IVIG) interferes with the ingestion of antibody-coated platelets and results in the elevation of platelet counts.

Response to IVIG predicts a good response to splenectomy.

Splenectomy induces a complete response in 2/3 of patients, but there may be relapses

Splenectomy is indicated in any of the following:

1. No response to steroids
2. Frequent relapses
3. Unable to taper off steroids within 3-6 months

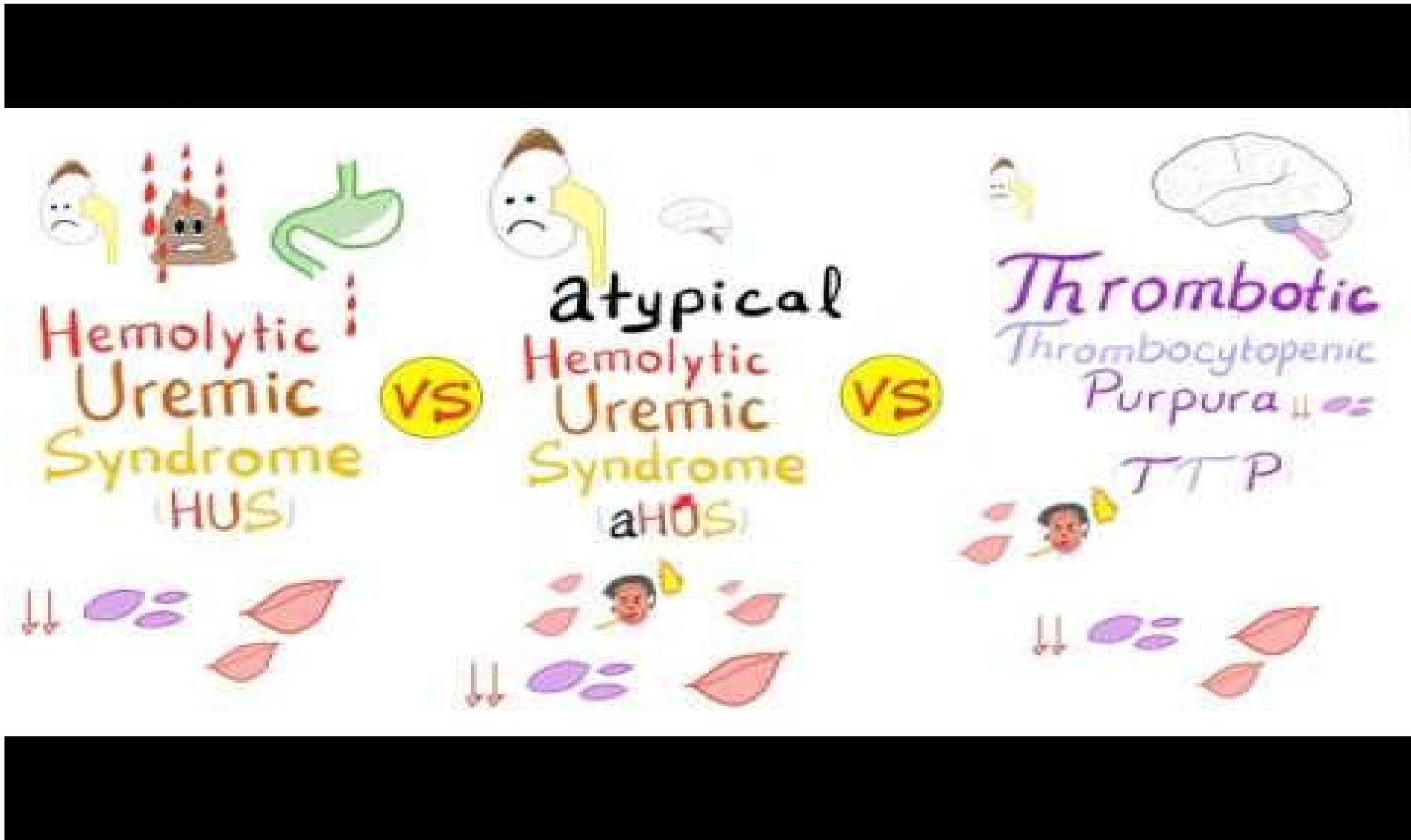
Remember: All patients should receive vaccinations for pneumococcus, H. influenzae, and Neisseria meningitidis at least 2 weeks prior to elective splenectomy because splenectomized patients are at an increased risk of infections from these organisms.

A few drugs are available for ITP refractory to steroids, IVIG, and splenectomy:

- Rituximab is an alternative to splenectomy, particularly if there is no response to IVIG.

Rituximab is a monoclonal antibody directed against CD20 present on B lymphocytes.

- Give platelet transfusions if there are signs of severe bleeding and prior to invasive procedures. While platelet counts may not rise, transfusions may be hemostatically effective. Even so, they are not effective for long-term management.



Thrombotic Thrombocytopenic Purpura

Acquired thrombotic thrombocytopenic purpura (TTP) and the atypical hemolytic uremic syndrome (aHUS) in adults were once considered variants on a spectrum of disease, although it is now understood they have different pathophysiology.

In general, there are 2 types of TTP (inherited and acquired) and 2 types of HUS (atypical HUS and typical/childhood/diarrhea-associated HUS).

Inherited TTP is a defect in the ADAMTS gene causing a deficiency in the **ADAMTS13 enzyme**; it affects only newborns and children. Acquired TTP affects adults and is due to an inhibitor causing decreased activity of ADAMTS 13 enzyme. This enzyme is responsible for cleaving ultra-large multimers of von Willebrand factor.

TTP is a fulminant disorder of increased platelet consumption, with high mortality, that is marked by thrombocytopenia and microangiopathic hemolytic anemia.

TTP generally affects younger adults, with a peak in the 3'd decade of life. Most commonly, TTP is idiopathic, but also is associated with:

- drug exposures (quinine, cancer chemotherapy, clopidogrel, ticlopidine),
- post-hematopoietic stem cell transplant,
- pregnancy,
- oral contraceptives,
- disseminated occult mucin-producing adenocarcinomas,
- HIV infection,
- SLE, and
- antiphospholipid syndrome (APS).

Clinical manifestations of TTP:

- 1) Anemia (microangiopathic hemolytic anemia with schistocytes on peripheral blood smear)
- 2) Thrombocytopenia
- 3) Neurological changes (e.g., confusion, severe headache, seizure)
- 4) Fever
- 5) Renal failure (unusual in TTP)

The dyad of thrombocytopenia and microangiopathic hemolytic anemia is sufficient to narrow the differential to TTP vs. aHUS (vs. HELLP if pregnant). TTP typically presents with neurologic involvement and minimal or no renal dysfunction. Patients infrequently present with all 5 findings.

Peripheral blood smear shows thrombocytopenia and anemia with schistocytes. Labs commonly indicate a Coombs-negative hemolysis with an elevated LDH and indirect bilirubin, +/- increased creatinine. Unlike in DIC, the PT, PIT, fibrinogen, Factor V, and Factor VIII usually are normal because the coagulation cascade is not activated in TTP.

Low functional ADAMTS 13 enzyme levels can be used to support a TTP diagnosis, but results are generally not available in a timely manner.

Treat TTP with plasma exchange using fresh frozen plasma or cryosupernatant (plasma from which cryoprecipitate has been removed-because the cryoprecipitate contains vWF multimers that might contribute to increased clotting).

Know that there are 2 situations where plasmapheresis has not been shown to have any effect:

- 1) Cancer chemotherapy drugs
- 2) Post -hematopoietic stem cell transplant

Unless life-threatening bleeding is present, **do not give platelet transfusions**, because extra platelets will simply be consumed and cause more thrombosis. If the patient does not respond to plasmapheresis, corticosteroids and/ or rituximab are additional options .

Atypical Hemolytic Uremic Syndrome

Atypical HUS (aHUS) is confused with TTP because aHUS has the same 5 manifestations and same labs as TTP **except that renal involvement occurs and neurologic involvement either does not occur or is minimal.**

There are many causes of aHUS- all related to disorders in complement regulation. ADAMTS 13 enzyme levels are >10% and generally stay within normal reference intervals.

Treatment is eculizumab, a monoclonal antibody that selectively inhibits the terminal complement cascade.

Note that eculizumab predisposes the patient to fulminant meningococcal infections. For some types of aHUS, eculizumab is not effective and plasma exchange transfusion is done.

Diarrhea-Associated HUS

A childhood form of HUS exists that is often precipitated by infection with enterohemorrhagic *E. coli* (0157:H7) and is associated with a prodrome of bloody diarrhea.

This presentation has been termed "diarrhea –associated HUS" or "childhood HUS" to differentiate the disease from aHUS. Treatment is supportive. Cases typically self-resolve.

Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Table 24. TTP and HUS

adult

Small

	TTP	HUS (See Pediatrics , P78)
Epidemiology	Predominantly adult	Predominantly children
Etiology	Deficiency of metalloproteinase that breaks down ultra-large vWF multimers • Congenital (genetic absence of ADAMTS-13) • Acquired (drugs, malignancy, transplant, HIV-associated, idiopathic)	Shiga toxin (<i>E. coli</i> serotype O157:H7) Other bacteria, viruses, genetic causes, drugs
Clinical Features	1. Thrombocytopenia 2. MAHA 3. Renal failure 4. Neurological symptoms: headache, confusion, focal defects, seizures 5. Fever	1. Severe thrombocytopenia 2. MAHA 3. Renal failure 4. Diarrhea
Investigations (both TTP, HUS)	CBC and blood film: <u>decreased platelets</u> and <u>schistocytes</u> PT, aPTT, fibrinogen: <u>normal</u> Markers of hemolysis: <u>increased unconjugated bilirubin</u>, <u>increased LDH</u>, <u>decreased haptoglobin</u> Negative Coombs test • NOT ALWAYS NEGATIVE <u>Creatinine</u>, <u>urea</u>, to follow renal function <u>Stool C&S</u> (HUS)	
Management (both TTP, HUS)	Medical emergency <u>Plasmapheresis ± steroids</u> <u>Platelet transfusion is contraindicated</u> (increased microvascular thrombosis) <u>Plasma infusion</u> if plasmapheresis is not immediately available <u>TTP mortality</u> —90% if untreated	

do you

HELLP Syndrome

The HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) occurs in 20% of patients with preeclampsia and in 10% of patients with eclampsia. The anemia is microangiopathic, with schistocytes on the peripheral blood smear (as with TTP and aHUS). Hepatic rupture is an uncommon, but potentially devastating, complication. Treatment is delivery of the fetus, with no role for plasma exchange.

Both HELLP syndrome and TTP/HUS can occur in the peripartum period, so it is important to consider each in the evaluation. TTP/HUS additionally has fever, renal involvement, and/or neurologic symptoms.

Heparin-Induced Thrombocytopenia (HIT)

HIT Type I is a clinically insignificant, nonimmune drop in platelets after starting heparin; platelets return to normal within 2 days.

HIT Type II occurs when an antibody is formed that recognizes heparin/**platelet factor 4** (heparin -PF4) complexes. The antibody activates platelets, causing clumping and thrombocytopenia **within 5-10 days** of heparin initiation. Previous exposure to heparin and an anamnestic response may shorten the onset to **< 12 hours**. **Venous and/or arterial thrombosis, not bleeding**, is the major complication of HIT-II. Always suspect HIT-II in a patient presenting with clot 1-2 weeks after a hospitalization, even if the platelet count is normal. (The highest risk of thrombosis occurs when platelet count has returned to normal.)

Table 1. 4T Scoring System for Evaluating the Pretest Probability of Heparin-Induced Thrombocytopenia.*			
Variable	Score		
	2	1	0
Acute thrombocytopenia	Platelet count decrease of >50% and nadir $\geq 20,000/\text{mm}^3$	Platelet count decrease of 30–50% or nadir 10,000–19,000/ mm^3	Platelet count decrease of <30% or nadir $\leq 10,000/\text{mm}^3$
Timing of onset	Day 5–10, or day 1 if recent heparin exposure	>Day 10 or unclear exposure	$\leq$ Day 4 with no recent heparin exposure
Thrombosis	New thrombosis or anaphylactoid reaction after heparin bolus	Progressive or recurrent thrombosis	None
Other cause of thrombocytopenia	None	Possible	Definite
Total score	6–8, indicating high score	4 or 5, indicating intermediate score	0–3, indicating low score

* Adapted from Lo et al.³¹ A low 4T score (0 to 3 points) has a high negative predictive value. The day that heparin was started is considered as day 0. The onset of heparin-induced thrombocytopenia (HIT) is defined as the day that the platelet count begins to decrease. Patients in whom the score is difficult to apply, owing to missing platelet count values or co-existing conditions causing thrombocytopenia, and those with an intermediate or high score require further evaluation. This score can be included on ordering forms for HIT laboratory testing (e.g., www2.medizin.uni-greifswald.de/transfus/fileadmin/user_upload/doku_thrombo_gerinnung/platelet_lab_request_form.pdf).

Treatment of HIT-II

Stop all heparin exposure (including low-molecular-weight heparin [LMWH]), even though this does not fully resolve the problem. This is because once the antibodies to heparin- PF4 complex are formed, the antibodies continue to bind to PF4 alone and, thus, continue to activate platelets, causing clots. LMWH should not be substituted because of antibody cross-reactivity.

Treat this hypercoagulable state with direct thrombin inhibitors (lepirudin or argatroban) at the time of diagnosis, even in the face of thrombocytopenia, whether or not a clot is present. Continue to administer the anticoagulant until the platelet count recovers. Remember that argatroban artificially elevates the INR; goal INR during argatroban/warfarin overlap is > 4 . Use lepirudin with caution in patients with renal insufficiency (requires dose reduction).

Warfarin should not be started until the platelet count returns to normal. Do not start warfarin alone, since it transiently lowers levels of proteins C and S and can contribute to clot formation. Warfarin should be continued for at least 3 months. There is no role for platelet transfusions.

Once again: Remember that TTP and HIT are thrombotic thrombocytopenic disorders. So you never give these patients platelet transfusions for the thrombocytopenia unless there is life-threatening bleeding present.

Platelet Function Disorders

Von Willebrand Disease

Von Willebrand disease (vWD) is the most common inherited bleeding disorder. Patients typically have mucocutaneous bleeding, including epistaxis, menorrhagia, postpartum and surgical bleeding, bleeding after dental extractions, and excessive bruising.

The von Willebrand factor (vWF) binds platelets to exposed subendothelial collagen and to other platelets with the platelet receptors Ib/IX and IIb/IIIa, respectively.

VWF is also the carrier protein for Factor VIII, which is degraded in its absence.

Inheritance pattern of von Willebrand disease is usually autosomal dominant. Penetrance is variable, with some patients experiencing bleeding only after surgery or major trauma and others suffering from frequent spontaneous bleeds of the mucosal surfaces of the gastrointestinal and genitourinary tracts.

Individuals with type O blood have lower baseline levels of vWF. Levels of vWF increase during pregnancy and with estrogen use.

The PTT is often increased because of decreased levels of Factor VIII. The bleeding time is prolonged.

Classification of vWD:

1) Type 1: a quantitative defect and the most common type (~75%).

2) Type 2: 4 subtypes (A, B, M, N)-all qualitative defects.

- Type 2A: the 2nd most common type of Vwd (10-15%) and the result of too little of the large vWF multimer (the same one that causes TTP).
- Type 2B: Mutant vWF has increased affinity for platelets, causing spontaneous binding of large vWF multimers to platelets and subsequent clearing of the complex. Causes mild thrombocytopenia. Do not use desmopressin (DDAVP®) to treat because it causes increased release of mutant vWF and increased clearance of platelet-vWF complex, exacerbating thrombocytopenia.
- Type 2M: decreased affinity for platelets.
- Type 2N: an abnormal vWF protein with impaired ability to bind Factor VIII. This leads to loss of protection for Factor VIII while in circulation and therefore increased Factor VIII clearance and decreased Factor VIII levels. Presentation is similar to classic hemophilia.

3) Type 3: rare and severe. Autosomal recessive.

Minimal-to-undetectable levels of vWF lead to spontaneous bleeding. The presentation also resembles that of classic hemophilia.

Patients with mild defects may have varying laboratory test results over time, often requiring repeated testing to confirm the diagnosis.

Treat mild-to-moderate cases of vWD with desmopressin (except Type 2B), which causes a release of vWF and Factor VIII from endothelial cells. For active bleeding, use Factor VIII concentrates, which typically have some vWF as well. Cryoprecipitate is almost never required.

Note: Desmopressin (DDAVP®) is a synthetic analog of antidiuretic hormone (ADH, vasopressin), which boosts plasma levels of Factor VHI and vWF. It does not have vasopressor activity and it is not effective in severe vWD or severe Factor VIII deficiency.

Desmopressin can worsen Type 2B vWD. Watch for hyponatremia when treating with desmopressin.

