Disorder	Etiology	Pathophysiology and Presentation	Lab Findings and Diagnosis	Treatment
INHERITED COAGULOPATHY				
HEMOPHILIA A and B	Hemophilia A: deficiency in XIII (85%) Hemophilia B: deficiency in IX (15%) X-linked inheritance	**Minor (5 – 30%) activity**: bleeding during surgery or major truama **Moderate (1 – 5% activity)**: bleeding with minor trauma **Severe (< 1% activity):** spontaneous deep tissue bleeding into joints and muscular compartments Muscular hematomas Hemarthrosis Hemophilic arthropathy (due to iron deposition in joint spaces) Neuropathy	aPTT : prolonged PT : NML Decreased VIII or IX activity Corrected by mixing EXCEPT with acquired inhibitor	**Factor replacement** (isolated purified protein) leads to generation of isoAbs → circulating inhibitor
von WILLEBRAND DISEASE (vWD)	Deficiency in vWF Typically decreased production AD inheritance	Typically also associated with deficiency in VIII **Mucocutaneous bleeding** If VIII is NML (> 30%) **Deep tissue and joint bleeding** If VIII is severely depressed Presents as menorrhagia, surgical bleeding, and ecchymosis	Delayed PFA-100 Decreased plasma vWF Decreased ristocetin agglutination Decreased VIII aPTT and PT : NML if VIII is intact	**DDAVP** Stimulates vWF secretion from endothelium **Factor Replacement** with vWF-VIII complex **Antifibrinolytics** (aminocaproic acid) **Cryoprecipitate** May contain viable virus
ACQUIRED COAGULOPATHY				
VIT K DEFICIENCY	ABx therapy Malnutrition Cholestasis and biliary obstruction Warfarin Malabsorption disease (celiac, resection)	Decreased port-translational modification of: **VII, IX, X, prothrombin** **Protein C, Protein S**	Mild deficiency: prolonged PT Severe deficiency: prolonged PT **and** aPTT In most deficiencies: corrects with NML plasma mix Decrease levels of all VitK-dependent factors	IM Vit K FFP: if severe bleeding
LIVER DISEASE	Hepatitis Cirrhosis	Decreased synthesis of ALL FACTORS (including **fibrinogen**)	PT **and** aPTT are prolonged Global decrease in factor activity	Not responsive to VitK therapy

		Focal bleeding Associated with underlying disease Gastric ulcers, esophageal varices	Does not correct with NML plasma mix	FFP: transient control
DISSEMINATED INTRAVASCULAR COAGULATION (DIC)	The underlying process is excessive release of TF into systemic circulation → intravascular coagulation AND fibrinolysis Sepsis Malignancy, Leukemias (APML) Liver Disease Amniotic Embolus Surgery Shock	All factors AND platelets are consumed This results in bleeding and thrombosis of the microvasculature Morbidity due to ischemic infarction of various tissues	Thrombocytopenia Schistocytes (microangiopathy) PT and aPTT prolonged Elevated FDP Elevated D-dimer Depressed fibrinogen Depressed antithrombin Depressed α2-antiplasmin	Tx underlying disease FFP infusion Replace platelets
COAGULATION INHIBITORS	**VIII inhibitors** Hemophilia:isoantibodies to replaced factors Non-hemophilia: autoantibodies **Heparin** **Direct Thrombin Inhibitors**	May result in acquired hemophilia with similar presentation	Low-dose heparin: aPTT prolonged High-dose heparin: both aPTT **and** PT prolonged Does not correct in mixing study	Bypass factors: activated VII
INHERITED PLATELET DYSFUNCTION				
GLANZMANN'S THROMBASTHENIA	**Deficiency of GpIIb/IIIa** AR iheritance	Dysfunctional platelet aggregation	Abnormal PFA-100 findings Increased collagen-ADP time Increased collagen-epinephrine	
BERNARD-SOULIER SYNDROME	**Deficiency of GpIb** AR inheritance	Dysfucntional platelet adhesion (via Vwf) Typically associated with **thrombocytopenia** and increased **MPV**		
THROMBOCYTOPENIA				
IDIOPATHIC THROMBOCYTOPENIC PURPURA (ITP)	Autoimmune Abs against patelet GPs → phagocytosis in liver and spleen (similar to autoimmubne hemolytic anemia)	**Peds:** acute disease, spontaneous resolution **Adults**: chronic relapsing variant May cause neonatal thrombocytopenia	Thrombocytopenia NML PT and aPTT (unless associated with WM and autoimmune hemolytic anemia)	Corticosteroids IVIG Splenectomy Rituximab Romiplostim (TPO agonist)

DRUG-INDUCED THROMBOCYTOPENIA	ABx: PCNs and sulfonamides Quinines Rifampin Heparin (HIT): results in a thrombotic state	May occur via immune complexes or direct binding of the drug on platelet surface	Thrombocytopenia	Discontinue medication
THROMBOTIC THROMBOCYTOPENIC PURPURA (TTP)	AutoAbs to ADAMTS13 → no cleavage of large vWF monomers → increased platlet adhesion and aggregation in microvaaculature → thrombi with vWF → microangiopathy → ischemic necrosis **With coagulopathy: DIC**	Thrombocytopenia Fever MAHA (hemolytic anemia) Neurologic Deficits Renal Failure	Schistocytes Intravascular Hemolytic Anemia Increased LDH, hemoglobinuria Reticulocytosis NML PT and aPTT	Plasma exchange transfusion Corticosteroids
HEMOLYIC UREMIC SYNDROME	EHEC Shigella Inherited	Similar to TTP, with major renal involvement Prodrome: gastroenteritis with bloody diarrhea	Schistocytes Intravascular Hemolytic Anemia Increased LDH, hemoglobinuria Reticulocytosis	Typically self-limited disease
PLATELT SEQUESTRATION	Splenomegaly (myeloproliferative disorders) Portal HTN		Thrombocytopenia	
MARROW FAILURE	Aplastic anemia Leukemias Myelodysplastic Sydrome		Pancytopenia	
ACQUIRED PLATELT DYSFUNCTION				
UREMIC PLATELT DYSFUNCTION	CKD Uremic toxins interfere with platelet function			Dialysis Increase Hct (EPO) Conjugated estrogens DDAVP
ANTI-PLATELT THERAPY	Aspirin ADP-receptor antagonists GpIIb/IIIa antagonists		Abnormal PFA-100 Typically NML PT and aPTT	

PATHOPHYSIOLOGY OF SYSTEMIC THROMBOTIC DISEASE

Disorder	Etiology	Pathophysiology and Presentation	Lab Findings and Diagnosis	Treatment
THROMBOEMBOLISM				
ARTERIAL THROMBOEMBOLISM	**Arterial Atherosclerotic Disease** **Risk Factors** *Arterial thrombosis* CAD RFs (age, smoking, DM II, HTN, dyslipidemia, family history) + inflammation (acute phase reactants: fibrinogen, VIII, CRP, TNF-α, IL-1, IL-6) *Arterial and venous thrombosis* Homocysteinemia, HIT, LAC, antiphospholipid syndromes	Plaque → turbulent flow → platelet activation → thrombosis ALSO loss of the anti-coagulative properties of endothelium **ACS** **TIA** **Ischemic stroke** **PAD**	**Platelet-rich "white" clots**	**Thrombolytics** in obstructive crisis **Anti-platelet therapy**
VENOUS THROMBOEMBOLISM	**Multigenic Disorder** **Clinical Risk Factors** *Venous Stasis* Immobilization, obesity, CHF, post-phlebitic syndrome, age *Endothelial Injury* Trauma (e.g. pelvic and lower extremity surgery), pregnancy, smoking *Hypercoagulability* LAC and antiphospholipid syndromes OCs (estrogen) Adenocarcinoma HIT Polycythemia Vera Essential Thrombocytosis	Thromboembolic events typically occur when a clinical risk factor is superimposed on an underlying genetic predisposition **DVT** **Pulmonary Embolism**	**Stratified fibrin-rich "red" clots** Typically demonstrating lines of Zahn **Dx of DVT** Elevated D-dimer High sensitivity, low specificity Contrast Venography MRI venography Doppler U/S **Dx of pulmonary embolism** V/Q scan Spiral thoracic CT Pulmonary angiography	**Anticoagulation**

	Genetic Risk Factors *Major RFs* 20-fold increase in VTE risk Antithrombin III deficiency Protein C deficiency Common, may result in neonatal purpura fulminans Protein S deficiency *Minor RFs* 5-fold increase in VTE risk Factor V Leiden Heterozygotes have 5-fold risk. Homozygotes have 50-fold risk. Prothrombin G20210A Increased expression of prothrombin (mutation in 3' UTR)			