ACQUIRED BLEEDING DISORDERS

IN GENERAL TERMS → BLEEDING RELATED TO PLATELETS USUALLY PRESENTS AS PETECHIAE AND MUCOSAL BLEEDING, WHEREAS BLEEDING RELATED TO COAGULATION DEFECTS PRESENT AS SPONTANEOUS OR EXCESSIVE BLEEDING

ACQUIRED PLATELET DEFECTS:

- Circulating platelets provide an important initial defense against bleeding
- Acquired defects can either be:
    - QUANTITATIVE (i.e. decreased number of circulating platelets or thrombocytopaenia)
    - QUALITATIVE (poorly functioning platelts
- Quantitative deficits are caused by DECREASED PRODUCTION, INCREASED DESTRUCITON, SPLENIC SEQUESTRATION, PLATELET LOSS OR A **COMBINATION OF ALL OF THESE**

Table 228-1 Pathophysiology of Acquired Thrombocytopenia

Mechanism	Associated Clinical Conditions
Decreased platelet production	Marrow infiltration (tumor or infection)
	Viral infections (rubella, HIV, others)
	Drugs (**Table 228-2**)
	Radiation
	Vitamin B_{12} and/or folate deficiency
Increased platelet destruction	Idiopathic thrombocytopenic purpura
	Thrombotic thrombocytopenic purpura
	Hemolytic uremic syndrome
	Disseminated intravascular coagulation
	Viral infections (HIV, mumps, varicella, Epstein-Barr virus)
	Drugs (heparin, protamine)
Platelet loss	Excessive hemorrhage
	Hemodialysis, extracorporeal circulation
Splenic sequestration	Sickle cell disease, cirrhosis

- Most commonly manifested by NON-PALPABLE PETECHIAE, but can also result in:
    - Purpura
    - Mucosal bleeding (gingival, epistaxis)
    - Menorrhagia
    - Haemoptysis
    - Haematuria
    - Haematochezia
        - DEEP TISSUE BLEEDING IS LESS COMMON
- When platelet levels DECREASE BELOW 10, the risk of spontaneous bleeding becomes concerning (especially ICH)

- Other risk factors for bleeding:
    - Age
    - Comorbid illnesses (especially renal disease, liver, connective tissue diseaes, PUD, HT)
    - Fall risk
- With the exception of a few causes, platelet tranfusion should be strongly considered when counts fall below 10.
- The initial priority in treatment of the bleeding patient is securing circulatory stability

THROMBOCYTOPAENIA FROM ↓'D PLATELET PRODUCTION:

- Aetiology of thrombocytopaenia is DIVERSE
- In neonates/infants ➔ CMV, rubella may be causative
- In the older child or adult, IF MULTIPLE CELL LINES ARE AFFECTED, THE DIFFERENTIAL INCLUDES:
    - Aplastic anaemia
    - Marrow infiltration from lymphoma, leukaemia or myelofibrosis
- DRUG HISTORY IS CRUCIAL:

Table 228-2 Drugs That Produce Thrombocytopenia or Impair Platelet Function

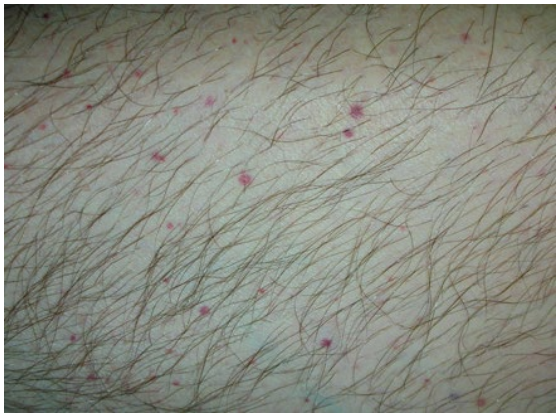
Produce Thrombocytopenia	Impair Function (prolong bleeding time)
Heparin 4+	Aspirin
Gold salts 4+	NSAIDs
Sulfa-containing antibiotics 4+	Glycoprotein IIb–IIIa agents: ticlopidine and clopidogrel
Quinine and quinidine 4+	
Ethanol (chronic use) 4+	Penicillins and cephalosporins
Aspirin 3+	Calcium channel blockers
Indomethacin 3+	β-Adrenergic blockers: propranolol
Rifampin 2+	Nitroglycerin
Abciximab and eptifibatide 2+	Antihistamines
Thiazides and furosemide 2+	Phenothiazines
Acyclovir 2+	Cyclic antidepressants
Procainamide 2+	
Digoxin 2+	
Cimetidine and ranitidine 2+	
Phenytoin and valproate 1+	
Penicillins/cephalosporins 1+	

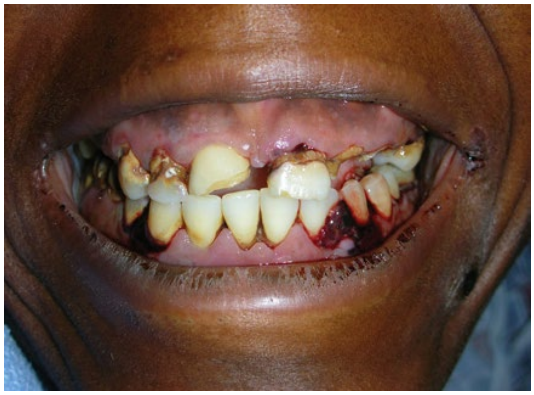
- Chronic alcohol use is a common cause of thrombocytopaenia, but this will generally resolve in 7 days of abstinence in the absence of HYPERSPLENISM from portal hypertension

THROMBOCYTOPAENIA FORM INCREASED PLATELET DESTRUCTION:

- IMMUNE CAUSES OF PLATELET DESTRUCTION:
    - Can be related to medications, infections or autoimmune causes
    - IDIOPATHIC THROMBOCYTOPAENIC PURPURA:

- ITP is an acquired autoimmune disease that results in the rapid destruction of platelets
- Characterised by purpura or petechiae, A NORMAL BONE MARROW and NO OTHER IDENTIFIABLE CAUSE OF THROMBOCYTOPAENIA
- Platelet destruction is mediated by the production of autoantibodies that attach to circulating platelets and these antibody-coated platelets are removed by the reticuloendothelial system
- In some cases, the same antibodies will also bind to THE MEGAKARYOCYTES, limiting the bone marrow response
- Despite the presence of antibodies, THE CIRCULATING PLATELETS **FUNCTION NORMALLY** and many people may not have significant bleeding despite very low platelet counts
- ITP presents in all age groups and may have an acute or chronic course
- ACUTE ITP → more common in younger children and resolves in 1-2 months
- CHRONIC ITP ➔ lasts >3 months, is more common in adults, female predilection and rarely remits spontaneously or with treatment. More likely to exhibit an underlying autoimmune disorder
- Most common sign is DEVELOPMENT OF PETECHIAE OR MUCOSAL BLEEDING (SEE BELOW):





- Otherwise normal physical examination ➔ the presence of lymphadenopathy, hepatosplenomegaly, pallor or hyperbilirubinaemia should suggest an alternative diagnosis → LYMPHOMA, LEUKAEMIA, SLE, HAEMOLYSIS, EBV
- FBC should demonstrate normal cell lines other than platelets
- Diagnosis is based on history, exam, FBC and peripheral smear
- For all patients with ITP:
    - Minimise bleeding risk
    - Avoid use of antiplatelets (including NSAIDS)
    - Avoid unnecessary invasive prodcedures
    - Treat comorbid conditions

        - In those with no symptoms who are otherwise healthy and with platelets >50, NO TREATMENT IS REQUIRED
            - Patients with platelet counts 20-30 or <50 with bleeding generally require treatment
        - CHILDREN WITH PLATELETS <20 WITH BLEEDING OR <10 SHOULD BE GIVEN DRUG TREATMENT WITH CORTICOSTEROIDS OR IVIG
            - Typically initial treatment is PREDNISONE 60-100MG, with a taper after the platelet count reaches normal
            - IVIG 1g/kg/day for 2 days
            - In cases of life-threatening bleeding, appropriate regimens include METHYLPREDNISOLONE 30MG/KG IV FOR THREE DAYS as well as platelets and IVIG ➔ infuse platelets only if needed following the first dose of methylpred as this generally results in a greater rise in the platelet count
                - Infuse red cells as needed
    - DRUG-RELATED CAUSES:
        - Certain medications appear to bind to the platelet membrane ➔ that then stimulates an immune response (see table above)➔ see table above
        - Heparin-induced thrombocytopaenia results in PARADOXICAL HYPERCOAGULABLE STATE due to platelet activation

PLATELET SEQUESTRATION:

- An enlarged spleen can sequester a significant portion of the platelet pool and counts as low as 40 are common in those with marked splenomegaly
- The most common aetiology is cirrhosis with portal hypertension
- Can occur in kids with sickle cell disease as well

QUALITATIVE PLATELET ABNORMALITIES:

- Several disease processes can cause acquired qualitative or functional abnormalities of platelets

Table 228-3 Clinical Conditions Associated with Qualitative Platelet Abnormalities
Uremia
Liver disease
Disseminated intravascular coagulation
Antiplatelet antibodies (idiopathic thrombocytopenic purpura, systemic lupus erythematosus)
Cardiopulmonary bypass
Myeloproliferative disorders (thrombocytosis, polycythemia vera, chronic myeloid leukemia, acute lymphocytic or myelogenous leukemia)
Dysproteinemias (multiple myeloma, Waldenström macroglobulinemia)
von Willebrand disease (congenital or acquired)

- In myeloproliferative diseases, platelets are often dysfunctional even if count is normal
- Consider infusion of platelets at much higher levels of platelet count
- THROMBOCYTOSIS ➔ can be seen in many disorders ➔ inflammatory state, malignancy, polycythaemia and post-splenectomy
- DRUG-INDUCED QUALTITATIVE PLATELET DYSFUNCTION:

Table 228-4 Duration of Antiplatelet Activity

Drug	Onset	Duration of Effect
Aspirin	1 h	Up to 7 d
Most NSAIDs	1 h	1 d
Piroxicam	1 h	2 d
Ticlopidine or clopidogrel	1–2 d	4–7 d

ACQUIRED BLEEDING DISORDERS:

LIVER DISEASE:

- Acute and chronic diseases of the liver can be associated with many haemostatic abnormalities
- Hepatocytes synthesise all coagulation factors except FACTOR VIII
- Malabsorption syndromes can occur with processes that interfere with the absorption of fat-soluble vitamins, including impaired bile acid metabolism can led to coagulation issues
- Thrombocytopaenia in severe liver disease is most caused by portal hypertension, which leads to congestive hypersplenism and splenic sequestration
- Patients with significant liver disease have INCREASED FIBRINOLYSIS as a result of decreased synthesis of α-2 plasmin inhibitor ➔ mildly elevated D-dimer and FDP
- Can be difficult to distinguish liver disease from DIC ➔ but prolongation of PT and decreased fibrinogen in liver disease is A POOR PROGNOSTIC SIGN
- Patients with liver disease and coagulation abnormalities without significant bleeding generally require CLOSE OBSERVATION ONLY
- VITAMIN K SHOULD BE GIVEN TO ALL PATEINTS WITH LIVER DISEASE AND ACTIVE BLEEDING
    - Also give FFP, especially if pending a procedure
    - Consider cryoprecipitate

RENAL DISEASE:

- Haemostatic abnormalities are commonly present in patients with renal disease related to abnormalities in clotting factors and quantitative and qualitative platelet dysfunction
- Retention of uraemic toxins causes inhibition of platelet aggregation

- Acute bleeding can be treated with dialysis, transfusion of RBC
    - Platelet infusions alone are generally ineffective because the infused platelets quickly acquire the uraemic defect ➔ only indicated in life-threatening bleeding

DISSEMINATED INTRAVASCULAR COAGULATION:

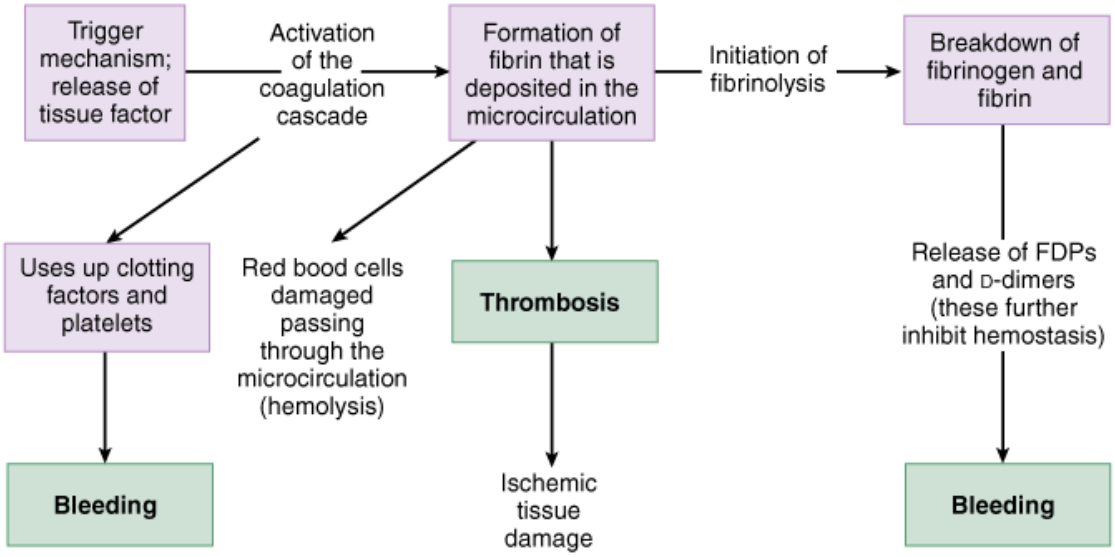
- DIC is an acquired syndrome characterised by INAPPROPRIATE AND WIDESPREAD ACTIVATION OF THE COAGULATION SYSTEM RESULTING IN INTRAVASCULAR FIBRIN FORMATION
- Can be acute and life-threatening or chronic and compensated
- ASSOCIATED WITH WIDE VARIETY OF DISORDERS

Table 228-5 Common Conditions Associated with Disseminated Intravascular Coagulation (DIC)

Clinical Setting	Comments
Infection	Probably the most common cause of DIC; 10%–20% of patients with Gram-negative sepsis have DIC; endotoxins stimulate monocytes and endothelial cells to express tissue factor; Rocky Mountain spotted fever causes direct endothelial damage; DIC more likely to develop in asplenic patients or cirrhosis; septic patients are more likely to have bleeding than thrombosis.
Bacterial	
Viral	
Fungal	
Carcinoma	Malignant cells may cause endothelial damage and allow the expression of tissue factor as well as other procoagulant materials; most adenocarcinomas tend to have thrombosis (Trousseau syndrome), except prostate cancer tends to have more bleeding; DIC is often chronic and compensated.
Adenocarcinoma	
Lymphoma	
Acute leukemia	DIC most common with promyelocytic leukemia; blast cells release procoagulant enzymes, there is excessive release at time of cell lysis (chemotherapy); more likely to have bleeding than thrombosis.
Trauma	DIC especially with brain injury, crush injury, burns, hypothermia, hyperthermia, rhabdomyolysis, fat embolism, hypoxia.
Organ injury	May have chronic compensated DIC; acute DIC may occur in the setting of acute hepatic failure, tissue factor is released from the injured hepatocytes. Pancreatitis can activate the coagulation cascade.
Liver disease	
Pancreatitis	
Pregnancy	Placental abruption, amniotic fluid embolus, septic abortion, intrauterine fetal death (can be chronic DIC); can have DIC in *h*emolysis-elevated *l*iver enzymes-*l*ow *p*latelets (HELLP) syndrome.
Vascular disease	Large aortic aneurysms (chronic DIC can become acute at time of surgery), giant hemangiomas, vasculitis, multiple telangiectasias.
Envenomation	DIC can develop with bites of rattlesnakes and other vipers; the venom damages the endothelial cells; bleeding is not as serious as expected from laboratory values.
Acute lung injury or adult respiratory distress syndrome	Microthrombi are deposited in the small pulmonary vessels, the pulmonary capillary endothelium is damaged; 20% of patients with ARDS develop DIC and 20% of patients with DIC develop ARDS.
Transfusion reactions, such as acute hemolytic reaction	DIC with severe bleeding, shock, and acute renal failure.

- PATHOGENESIS:
    - The COMMON PATHWAY is the expression of cytokines and activation of TISSUE FACTOR ➔ leads to thrombin generation and results in small

fibrin clots formed and deposited in the microcirculation, thereby leading to thrombotic occlusion of vessels and eventually end-organ dysfunction
    - Widespread activation of the coagulation system leads to CONSUMPTION OF CIRCULATING PLATELETS AND COAGULATION FACTORS
    - Production of thrombin and fibrin, indirectly activates TPA and the counterregulatory fibrinolytic system ➔ can result in excessive and pathologic bleeding



- CLINICAL FEATURES OF DIC:
    - VARY WITH THE UNDERLYING PRECIPITATING ILLNESS
    - The complications of DIC are:
        - Bleeding
        - Thrombosis
        - Purpura fulminans
        - Multiple organ failure
        - Although haemorrhage and thrombosis may occur simultaneously, USUALLY ONE PREDOMINATES IN AN INDIVIDUAL PATIENT, and the most common manifestation is BLEEDING
        - Thrombotic manifestations ➔ mental state changes, focal ischaemia or gangrene, oliguria, renal cortical necrosis, acute lung injury and ARDS
- LABORATORY FINDINGS:
    - The most commonly observed finding is THROMBOCYTOPAENIA, and a progressive drop in the platelet count is SENSITIVE, BUT NOT SPECIFIC FOR DIC
    - Depletion of clotting factors is reflected by prolonged clotting times
    - Fibrin degradation products and D-dimer may help differentiate DIC from other causes of prolonged clotting times

Table 228-6 Laboratory Abnormalities Characteristic of Disseminated Intravascular Coagulation (DIC)

Studies	Result
Most Useful	
Prothrombin time	Prolonged
Platelet count	Usually low, or dropping
Fibrinogen level	Usually low (fibrinogen is an acute phase reactant, so may actually start out elevated) fibrinogen level <100 milligrams/dL correlates with severe DIC
Helpful	
Activated partial thromboplastin time	Usually prolonged
Thrombin clotting time	Prolonged (not sensitive)
Fragmented red blood cells	Should be present (not specific)
Fibrin degradation products and D-dimer*	Elevated
Specific factor assays	Extrinsic pathway factors are most affected (VII, X, V, and II)
Factor II, V, VII,† X	Low
Factor VIII (acute phase reactant)	Low, normal, high
Factor IX	Low (decreases later than other factors)

Table 228-7 Algorithm for the Diagnosis of Disseminated Intravascular Coagulation

Score global coagulation test results	Calculate score
1. Platelet count	If 5 or greater: compatible with overt DIC
0 if >100,000/mm3	If 4 or less: no overt DIC; repeat in 1–2 d
1 if 50 to 100,000/mm3	
2 if <50,000/mm3	
2. Elevated fibrin degradation products or D-dimer	
0 if no increase	
2 if moderate increase	
3 if large increase	
3. Prolonged prothrombin time	
0 if <3 s prolongation	
1 if between 3–6 s prolongation	
2 if >6 s prolongation	
4. Fibrinogen level	
0 if >100 milligrams/dL	
1 if <100 milligrams/dL	

- TREATMENT OF DIC:
  - Rests on SUPPORTIVE MEASURES AND MANAGEMENT OF THE UNDERLYING ILLNESS
  - Circulatory stabilisation → fluid resuscitation, blood transfusion, inotropes
    - Replacement therapy with platelets, fibrinogen and coagulation factors
      - Should only occur in patients with documented DIC with bleeding or an impending procedure

        - Goal is to raise fibrinogen to 100-150mg/dL with cryoprecipitate
    - ROLE OF HEPARIN IN DIC REMAINS UNCLEAR
        - Usually for patients with documented DIC in whom thromboembolic complications predominate the clinical picture (purpura fulminans) and in patients with chronic DIC and thrombosis (i.e. solid tumours)
        - Antifibrinolytic agents (tranexamic acid) should be used with great caution → associated with serious and fatal thromboembolic events

CIRCULATING INHIBITORS OF COAGULATION:

- Also known as ACQUIRED INHIBITORS OF COAGULATION → antibodies that are directed against one or more of the coagulation factors
- Most inhibitors develop in patients with hereditary bleeding disorders who receive transfusion of plasma products
- TWO MOST COMMON INHIBITORS ➔ FACTOR VIII INHIBITORS, AND ANTIPHOSPHOLIPID ANTIBODIES
- FACTOR VIII INHIBITORS:
    - Most commonly develop in patients with haemophilia A, but can also develop spontaneously in patients with previously normal haemostasis (but this is rare)
    - MORTALITY IS ~22%, and the majority of acquired cases are in the elderly
    - Can develop in association with autoimmune disorders ➔ SLE, RA, UC as well as lymphoproliferative disorders (multiple myeloma, Waldenstrom macroglobulinaemia, MGUS) and inpatients with allergic drug reactions (penicillins, sulfonamides, phenytoin)
    - Lab studies show normal PT, but greatly prolonged APTT and a factor VIII-specific assay will show very low or absent factor VIII activity
    - Treatment is with steroids, IVIG, cytotoxic agents or rituximab to suppress antibody production
        - Consult haematology early with bleeding → options include FACTOR VIII, FACTOR IX COMPLEXES, PURIFIED PROTHROMBIN COMPLEX, RECOMBINANT FACTOR VII, PLASMAPHERESIS