• Blood coagulation can be divided into three parts:
• (1) primary hemostasis, consisting of the
  ***vascular constriction
  *** platelet plug formation
  as a first line of defense of the body against bleeding;
• (2) fibrin formation, as a result of the activation of various coagulation proteins, which
  ultimately results in the generation of thrombin and subsequent fibrinogen to fibrin conversion; and
• (3) removal of fibrin (fibrinolysis)
1) PRIMARY HEMOSTASIS:

- **Vascular constriction; after truma of the vessels**
  - During the activation of the platelets and via a series of enzymatic reactions, **arachidonic acid** is converted into several eicosanoids, such as thromboxane A2 and various prostaglandins. These mediators may exert a **vasoconstricting** action and thus promote further activation of primary hemostasis. Another consequence of platelet activation is the release of various proteins from platelet storage granules, including:
    - (1) several platelet agonists (such as ADP and serotonin),
    - (2) coagulation factors (such as von Willebrand factor and coagulation factor V),
    - (3) heparin binding proteins (such as platelet factor 4 and beta-thromboglobulin), and
    - (4) proteins with activity as a growth factor or chemokine (such as platelet-derived

Thromboxane and serotonin are strong vasoconstrictor
After disruption of the integrity of the vessel wall, platelets adhere to the (sub)endothelium by means of their surface membrane glycoprotein receptor Ib. The ligand between this receptor and the vessel wall is the circulating protein named von Willebrand factor. As a consequence, the platelet becomes activated, which results in the expression of the platelet membrane surface receptor glycoprotein IIb/IIIa. Subsequently, platelets may aggregate with each other through this receptor, using circulating fibrinogen as a ligand. Red blood cells appear to play an important role in platelet adhesion and aggregation, potentially because of their physical capability to facilitate platelet transport to the surface. Therefore, adequate function of primary hemostasis is dependent on a sufficiently high hematocrit.
FIGURE 4.1. Platelet adherence to endothelium occurs via interaction of the platelet receptor and von Willebrand factor (top). This mechanism results in activation and expression of additional platelet receptors, which may aggregate via fibrinogen to other platelets (bottom).
2) FIBRIN FORMATION:

- The principal route of activation of blood coagulation is via the tissue factor–factor VII pathway (the former “extrinsic system”).
- Tissue factor is a membrane-associated glycoprotein that is not in contact with the blood under physiological circumstances.
- Tissue factor is present at subendothelial sites and becomes exposed to the blood upon disruption of the normal architecture of the blood vessel.
- Alternatively, tissue factor can be expressed by endothelial cells or by mononuclear cells in response to certain stimuli, such as inflammatory mediators.
• After exposition of tissue factor to blood, a complex between tissue factor and factor VII occurs, upon which factor VII is converted into its active form (factor VIIa). The tissue factor–factor VII(a) complex subsequently binds and activates factor X, resulting in factor Xa. Once factor Xa is formed, it converts prothrombin (factor II) to thrombin (factor IIa). This enzymatic reaction requires the presence of factor V as a cofactor, and is most efficient in the presence of a suitable phospholipid surface, such as that provided by the activated platelet.
• **An alternative route for factor Xa activation by the tissue factor–factor VIIa complex is by the activation of factor IX.** The importance of this “secondary” pathway for activation of coagulation is best illustrated by the striking hemorrhagic diathesis of patients with a deficiency of factor VIII or IX (hemophilia A and B, respectively; the incidence of hemophilia A and B is 1:10,000 and 1:70,000, respectively). A **third amplifying pathway** of the blood coagulation system consists of the activation of factor XI by thrombin. Factor Xla subsequently activates factor IX, resulting in further factor Xa and thrombin generation.
• **Thrombin is the key enzyme in the activation of coagulation.**

  The presence of thrombin is **not only essential** for the conversion of fibrinogen into fibrin, but thrombin is also able to **activate various coagulation factors and cofactors**, thereby strongly facilitating its own formation.

• In addition, thrombin is a very strong activator of platelet aggregation.

• The formation of cross-linked fibrin is the ultimate step in the coagulation cascade. To further stabilize the clot, cross-linking of fibrin takes place by thrombin-activated factor XIII.

• **Synthesis of most of the coagulation factors takes place in the liver.**

• Some **coagulation factors** (II, VII, IX, and X) require the presence of vitamin K for proper synthesis: in the absence of vitamin K, inactive precursor molecules are formed.
3) FIBRINOLYSIS

- Fibrin plays only a **temporary role** and must be removed to **restore normal tissue structure and function**. The enzymatic degradation of fibrin is carried out by the fibrinolytic system, which is partly responsible for the unobstructed flow of blood.

- The pivotal event in the process of **fibrinolysis** is the conversion of the inactive zymogen plasminogen into the active protease plasmin, which cleaves cross-linked fibrin, resulting in the dissolution of a clot.

- Plasminogen activators, of which **tissue-type plasminogen activator (tPA)** and **urokinase-type plasminogen activator (uPA)** are most important, mediate the conversion of plasminogen into plasmin. Both activators are **present in endothelial cells** and may be released by various stimuli, including hypoxia and acidosis, as may occur during thrombotic occlusion. **By protein C**

- Inhibition of the fibrinolytic system may occur at the level of the plasminogen activators by **plasminogen activator inhibitors (such as PAI-1)** or at the level of plasmin by **circulating protease inhibitors**, of which alpha 2 -antiplasmin is the most important one.

- **So An imbalance between activators and inhibitors of the fibrinolytic system, resulting in a net antifibrinolytic state, may contribute to the development of thrombosis.**
The efficacy of postoperative pneumatic calf compression may be based not only on rheological advantages in the venous circulation but also result from the enhanced release of plasminogen activators from the vessel wall upon compression (and venous occlusion), thereby compensating for this fibrinolytic imbalance.

**FIGURE 4.3.** Schematic representation of the fibrinolytic system. Activation of fibrinolysis is indicated with black arrows and inhibition of the system by the open arrows.
NATURAL ANTICOAGULANT MECHANISMS:

• Activation of the coagulation system is regulated at various points.
• Inhibition of the tissue factor–factor VIIa complex may occur by the action of tissue factor pathway inhibitor (TFPI), a surface-associated protease inhibitor.
• Further regulation takes place by the protein C system. Activated protein C, assisted by its essential cofactor (protein S), proteolytically degrades the important cofactors V and VIII. Activated protein C is formed upon activation of circulating protein C by the endothelial cell-bound enzyme thrombomodulin in association with thrombin. Hence, thrombin not only plays a pivotal role in coagulation activation but is also involved in the inhibition of blood coagulation. Both protein C and protein S are vitamin K-dependent proteins.

A situation in which there is normal functional protein C but an impaired sensitivity of factor V to protein C is called activated protein C resistance (APC resistance) and is caused by a point mutation in factor V (factor V Leiden). The prevalence of this mutation is about 3% to 5% in the general population and may account for about 30% of all idiopathic venous thromboembolism.
• A third inhibitory system is formed by antithrombin III: This serine protease inhibitor forms complexes with thrombin and factor Xa, thereby losing their coagulant activity.
• The inhibitory action of antithrombin III on thrombin and factor Xa is strongly amplified in the presence of heparin.
• A (usually hereditary) deficiency of antithrombin III, protein C, or protein S results in a procoagulant state, and patients with these deficiencies are prone to develop thrombosis. This development may occur in particular in situations with an enhanced thrombotic risk, such as the puerperium or postoperatively.
FIGURE 4.2. Schematic representation of the function of blood coagulation in vivo. The principal route of thrombin generation proceeds by the direct activation of factor X by the tissue factor–factor VIIa complex (black arrows). An alternative pathway is formed by the activation of factor IX by the tissue factor–factor VIIa complex and the activation of factor X by this activated factor IX (and cofactor VIII) (shaded arrows). A third amplifying pathway consists of the thrombin-mediated activation of factor XI, which can subsequently activate factor IX and X (open arrows). The point of impact of the three inhibitory systems (antithrombin III, the protein C and S system, and tissue factor pathway inhibitor [TFPI], respectively) are indicated with the dotted lines.
PROHEMOSTATIC AGENT

- ‘pro-hemostatic agents’ may be useful in the prevention and treatment of bleeding in patients with coagulation defects, but also in patients with an a priori normal coagulation system, who experience severe (post-operative) bleeding or are to undergo procedures known to be associated with major blood loss

- PLATELETS, PLASMA, AND COAGULATION FACTOR CONCENTRATES
Platelet transfusion may be considered in patients with severe thrombocytopenia and bleeding or a risk for bleeding. Platelet concentrates usually contain a mixture of the platelet preparation of the blood donation from six donors (6 units). After platelet transfusion, the platelet count should rise by at least $5 \times 10^9 /l$ per unit of platelets transfused.
<table>
<thead>
<tr>
<th>Platelet count $&lt;10 \times 10^9/l$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count $&lt;50 \times 10^9/l$ with demonstrated bleeding or a planned surgical/invasive procedure</td>
</tr>
<tr>
<td>Documented platelet dysfunction (e.g., prolonged bleeding time) with (microvascular) bleeding or undergoing a surgical/invasive procedure and (assumed) insufficient efficacy of other interventions (e.g., desmopressin)</td>
</tr>
<tr>
<td>Bleeding patients or patients undergoing a surgical procedure who require more than 10 U of packed red cells</td>
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**FRESH FROZEN PLASMA**

- contains all coagulation factor and may be used to replenish congenital or acquired deficiencies in these factors. For more specific therapy, or if the transfusion of large volumes of plasma is not desirable, fractionated plasma of purified coagulation factor concentrate is available.

- **Prothrombin complex concentrates (PCCs)** contain the vitamin K-dependent coagulation factors II, VII, IX, and X. Hence, these concentrates may be used if immediate reversal of coumarin therapy is required.

- **Cryoprecipitate** is fractionated plasma that contains mainly von Willebrand factor, factor VIII, and fibrinogen. However, because of problems in the production of cryoprecipitate, particularly with regard to standards to prevent the transmission of infectious agents, in most parts of the Western World cryoprecipitate is not readily available.

- **Purified concentrates** containing only that specific factor are available for a selected number of clotting factors. These concentrates are particularly useful in cases of isolated (usually congenital) deficiency of a single clotting factor, such as factor VIII concentrate for the treatment of hemophilia A.

- Clotting factor concentrates derived from plasma are of human origin. Potentially, these carry the risk of transmission of blood-borne diseases. Despite all current measures to prevent this complication, these risks are not fully eliminated. Hence, the use of these products should be limited as much as possible, especially if no strict indication is present or an alternative treatment is available.
| Table 4.3. Suggested Transfusion Guidelines for Fresh Frozen Plasma |

| Correction of multiple or specific coagulation factor deficiencies in bleeding patients or if a surgical/invasive procedure is planned |
| Congenital deficiencies of a specific factor (provided specific factor concentrates are not available, e.g., factor XI) |
| Acquired deficiencies, e.g., related to liver disease, massive transfusion, or disseminated intravascular coagulation |
| Volume replacement in case of severe bleeding to avoid massive transfusion of gelatin or crystalloid solutions |
| Thrombocytopenic thrombotic purpura |
• Deamino-D-arginine vasopressin (DDAVP, desmopressin) is a vasopressin analogue that induces release of the contents of the endothelial cell-associated Weibel–Palade bodies, including von Willebrand factor. Hence, the administration of DDAVP results in a marked increase in the plasma concentration of von Willebrand factor (and associated coagulation factor VIII). DDAVP can be administered by different routes (intravenously, subcutaneously, and intranasally) but is usually administered by intravenous administration, resulting in an immediate prohemostatic effect. **DDAVP is used for the prevention and treatment of bleeding in patients with von Willebrand disease or mild hemophilia**. It is also used in patients with an impaired function of primary hemostasis, such as those with uremia, liver cirrhosis, or aspirin-associated bleeding.
• Given that activation of coagulation in vivo predominantly proceeds by the tissue factor–factor VII(a) pathway, recombinant factor VIIa has been developed as a prohemostatic agent and has recently become available for clinical use. Although no thrombotic complications of recombinant factor VIIa treatment have been reported thus far, the safety of this strategy in a general population remains to be established.
MONITORING OF BLOOD COAGULATION

• For **proper function of primary hemostasis**, a platelet count of at least 30 to 50 *10^9 is required.

• The function of the primary hemostatic system may be tested by **performance of the bleeding time**. However, clinical studies have shown that there is **no correlation between the result of the bleeding time and the occurrence and intensity of perioperative bleeding**.

• Most frequently used screening tests for blood coagulation are the
  • prothrombin time (PT)
  • activated **partial thromboplastin time (aPTT)**.

• these tests are useful to screen for **deficiencies of single or multiple coagulation factors**.

• In addition, the **PT is used to monitor coumarin treatment**, whereas the **aPTT is most frequently used to monitor the intensity of heparin anticoagulation**.
Coagulation tests must be performed on plasma rather than serum, because clotting factors are removed during serum preparation along with the clotted cellular elements.

While the PT and aPTT provide an overall assessment of clot formation, they do not provide information about fibrin crosslinking or clot dissolution and will thus be insensitive to abnormalities of factor XIII function or abnormal fibrinolysis.

Clotting times — Clotting times measure the time it takes plasma to clot when various substances are added. The citrate in the blue top collection tube chelates calcium in the collection tube so that coagulation is unable to proceed, because calcium is required for assembly of coagulation factor complexes on activated cell surfaces or phospholipids. Sufficient calcium to overcome the chelator is added back to the sample at the time of test initiation, along with a source of phospholipid and an initiator (tissue factor for the prothrombin time [PT]; silica or diatomaceous earth for the activated thromboplastin time [aPTT]). The precise composition of PT and aPTT reagents is proprietary and generally not disclosed. PT instrument reagent systems are standardized using the international normalized ratio (INR).
PROTHROMBIN TIME (PT) AND INR

- The prothrombin time (PT) measures the time it takes plasma to clot when exposed to tissue factor, which assesses the extrinsic and common pathways of coagulation.
- The PT test is performed by recalcifying citrated patient plasma in the presence of tissue factor and phospholipid and determining the time it takes to form a fibrin clot. The result is measured in seconds and reported along with a control value and/or an INR.
- In most laboratories, the normal range is approximately 11 to 13 seconds.
- The INR is dimensionless. It is calculated as a ratio of the patient’s PT to a control PT obtained using an international reference thromboplastin reagent developed by the World Health Organization (WHO), using the following formula:\[ \text{INR} = \frac{\text{Patient PT}}{\text{Control PT}}^\text{ISI} \]
- The control value for the PT is the mean normal PT for the laboratory determined from ≥30 fresh, normal plasmas handled identically to patient material. The ISI (international sensitivity index) is based on an international reference thromboplastin reagent; however, it is useful to have the ISI value confirmed within each laboratory for each PT reagent and instrument to account for effects of handling and equipment performance [12,13].
• Unlike the PT, the results of the INR will be similar on a blood sample tested in any laboratory using any thromboplastin reagent/instrument system when calibrated correctly. This allows comparison of the patient’s testing performed at different times and/or locations, which is of great benefit for warfarin monitoring. Use of the INR is also extremely valuable for research studies because it allows investigators to compare the degree of anticoagulation of patients from different institutions.

• **Uses of the PT/INR** — Clinical uses of the PT include the following:
  
  • Evaluation of unexplained bleeding
  
  • Diagnosing disseminated intravascular coagulation
  
  • Obtaining a baseline value prior to initiating anticoagulation
  
  • Monitoring warfarin therapy
  
  • Assessment of liver synthetic function
  
  • As noted above, the INR was developed to allow patients receiving warfarin at steady state to compare values obtained at different times and from different laboratories. The INR is also commonly used as a surrogate for the PT in assessing integrity of the extrinsic and common pathways in bleeding patients (figure 1) and to assess end-stage liver disease as part of the model for end-stage liver diseases (MELD) score.
• The aPTT test is performed by recalcifying citrated plasma in the presence of a thromboplastic material **that does not have tissue factor activity (hence the term partial thromboplastin)** thereby initiating coagulation via **the intrinsic clotting pathway**.

• The normal range for the aPTT varies but in most laboratories, the normal range is approximately 25 to 35 seconds.

• There is **no standardization of the aPTT test across different reagent/instrument systems analogous to the INR for the PT**. Thus, aPTT values from different laboratories cannot be compared directly.

• For heparin monitoring, it is recommended that each laboratory establish the therapeutic range by determining the aPTT range that corresponds to 0.2 to 0.4 units/mL by protamine titration or 0.3 to 0.7 anti-factor Xa units/mL.

• **Uses of the aPTT** — Clinical uses of the aPTT include the following:
  
  • Evaluation of unexplained bleeding
  
  • Diagnosing disseminated intravascular coagulation (DIC)
• Obtaining a baseline value prior to initiating anticoagulation
• ● Monitoring therapy with unfractionated heparin
• ● Monitoring therapy with parenteral direct thrombin inhibitors
• Of note, low molecular weight (LMW) heparins often do not prolong the aPTT.
CLINICAL MANAGEMENT OF COAGULATION ABNORMALITIES AND BLEEDING
Inherited deficiencies of all of the coagulation factors are seen. However, the three most frequent are:

1) factor VIII deficiency (hemophilia A and von Willebrand's disease)
2) factor IX deficiency (hemophilia B or Christmas disease),
3) and factor XI deficiency.

Hemophilia A and hemophilia B are inherited as sex-linked recessive disorders with males being affected almost exclusively.

The clinical severity of hemophilia A and hemophilia B depends on the measurable level of factor VIII or factor IX in the patient’s plasma.

Plasma factor levels less than 1% of normal are considered severe disease, factor levels between 1% and 5% moderately severe disease, and levels between 5% and 30% mild disease.

Patients with moderately severe hemophilia have less spontaneous bleeding but are likely to bleed severely after trauma or surgery. Mild hemophiliacs do not bleed spontaneously and have only minor bleeding after major trauma or surgery.
Patients with severe hemophilia have spontaneous bleeds, frequently into joints, leading to **crippling arthropathies**.

1) Intracranial bleeding

2) Intramuscular hematoma, retroperitoneal hematomas, and gastrointestinal, genitourinary, and retropharyngeal bleeding are added clinical sequelae seen with severe disease.

Since platelet function is normal in hemophiliacs, patients may not bleed **immediately** after an injury or minor surgery as they have a normal response with platelet activation and formation of a platelet plug.
• Approach:
  1) History
  2) Physical examination

Investigations:
  Pre OP clinics
  Follow Guidelines, protocols and policies.

These are done for etiological Factors in bleeding
Patients with hemophilia A or B are treated with factor VIII or factor IX concentrate, respectively.

Recombinant factor VIII is strongly recommended for patients not treated previously and is generally recommended for patients who are both human immunodeficiency virus (HIV) and hepatitis C virus (HCV) seronegative.

For factor IX replacement, the preferred products are recombinant or high-purity factor IX. In general, activity levels should be restored to 30% to 40% for mild hemorrhage, 50% for severe bleeding, and 80% to 100% for life-threatening bleeding.

Alternate treatments should be used and may include porcine factor VIII, prothrombin complex concentrates, activated prothrombin complex concentrates, or recombinant factor VIIa.
VON WILLEBRAND’S DISEASE

• von Willebrand’s disease (vWD), the most common congenital bleeding disorder, is characterized by a quantitative or qualitative defect in vWF, a large glycoprotein responsible for carrying factor VIII and platelet adhesion.

• Patients with vWD have bleeding that is characteristic of platelet disorders such as easy bruising and mucosal bleeding.

• Menorrhagia is common in women.

• vWD is classified into three types. Type I is a partial quantitative deficiency, type II is a qualitative defect, and type III is total deficiency.

• For bleeding, type I patients usually respond well to desmopressin (DDAVP). Type II patients may respond, depending on the particular defect. Type III patients are usually unresponsive. These patients may require vWF concentrates.
DIC or acquired Hypofibrinogenemia is a syndrome and is always secondary to an underlying disorder. The syndrome is characterized by a systemic activation of the blood coagulation system, the generation and deposition of fibrin, microvascular thrombi in various organs, and in many cases the development of multiorgan failure. Depletion of coagulation proteins and platelets resulting from the ongoing activation of the coagulation system may induce diffuse bleeding complications, although micro clot formation may occur in the absence of severe clotting factor depletion and bleeding.

- Diffuse bleeding >> is a classical picture, bleeding from any where , nose , even from the cannula site .
- Severe bleeding from DIC poses a particular problem in trauma patients or during the early postoperative phase.
- Infection is the most common cause of DIC and, in patients with septic shock, DIC is a strong predictor of death. Another cause of DIC is malignancy, although in that setting DIC usually is relatively mild. In contrast, the DIC that accompanies obstetrical catastrophes, such as abruptio placentae or amniotic fluid embolism, is very turbulent but usually self-limiting.
PATHOGENESIS OF DIC DIC is characterized by widespread intravascular fibrin deposition resulting from enhanced fibrin formation and impaired fibrin degradation. Enhanced fibrin formation is caused by tissue factor-mediated thrombin generation and simultaneously occurring depressing of inhibitory mechanisms. That is, the normal counterbalance achieved by the anticoagulation systems (antithrombin III, protein C–protein S) is deranged, possibly due to increased factor consumption. Furthermore, impairment of endogenous fibrinolysis is mainly caused by high circulating levels of PAI-1, the principal inhibitor of plasminogen activation. Thus, deposition of fibrin in the (micro)vasculature is caused by both the formation and its inadequate removal of intravascular fibrin. This inadequate removal is caused by an impaired function of the fibrinolytic system. Ultimately, the remarkable imbalance between coagulation and fibrinolysis results in a net procoagulant state.
For example, injuries resulting in embolization of materials such as brain matter, bone marrow, or amniotic fluid can act as potent thromboplastins that activate the DIC cascade. Additional etiologies include malignancy, organ injury (such as severe pancreatitis), liver failure, certain vascular abnormalities (such as large aneurysms), snake bites, illicit drugs, transfusion reactions, transplant rejection, and sepsis.

**TABLE 4.5. Underlying Surgical Diseases Causing Acute or Chronic Disseminated Intravascular Coagulation (DIC)**

- Septicemia/infections
- Polytrauma
- Malignancies
- Aortic aneurysm
- Brain injury
- Extended liver surgery
- Extracorporeal circulation
- Thermal injury/hypothermia
- Fat embolism
- Peritoneovenous shunt
- Massive transfusion

**FIGURE 4.5.** Schematic representation of the pathogenesis of DIC. Activation of coagulation depends on tissue factor-mediated thrombin generation and a simultaneously occurring depression of the physiological coagulation-inhibitory systems. Impaired function of the fibrinolytic system, caused by high levels of the fibrinolytic inhibitor PAI-1, further contributes to the procoagulant state.
DIAGNOSIS OF DIC

• No single laboratory test or combination of tests allows a definitive diagnosis of DIC. However, the clinical diagnosis can be made reliable by taking into consideration the underlying disease and a combination of laboratory findings. Hence, the diagnosis of DIC is usually based on markers of advanced consumption of coagulation proteins and platelets, that is,

• *** prolonged clotting times (aPTT and PT) and
• *** low platelets, in combination with tests that do not detect the generation but rather the *** degradation of fibrin (fibrin degradation products).
• *** low fibrinogen level, and elevated fibrin markers (FDPs, D-dimer, soluble fibrin monomers)
• Measurement of fibrinogen is commonly performed but has shown to be of no value for the diagnosis of DIC, especially because the acute-phase reactant properties of fibrinogen in many clinical situations may completely obscure ongoing fibrinogen consumption.
scoring system developed by the International Society for Thrombosis and Hemostasis has been shown to have high sensitivity and specificity for diagnosing DIC as well as a strong correlation between an increasing DIC score and mortality, especially in patients with infections.
MANAGEMENT OF DIC

• The most important facets of treatment are relieving the patient’s causative primary medical or surgical problem and maintaining adequate perfusion. If there is active bleeding, hemostatic factors should be replaced with
  • ***FFP, which is usually sufficient to correct the hypofibrinogenemia, although cryoprecipitate, fibrinogen concentrates, or platelet concentrates or factor supplements may also be needed.
  • ***Given the formation of microthrombi in DIC, heparin therapy has also been proposed. Most studies, however, have shown that heparin is not helpful in acute forms of DIC, but may be indicated in cases where thrombosis predominates, such as arterial or venous thromboembolism and severe purpura fulminans.
COAGULOPATHY OF LIVER DISEASE

- The liver plays a key role in hemostasis because it is responsible for the synthesis of many of the coagulation factors. Patients with liver disease, therefore, have decreased production of several key non-endothelial cell-derived coagulation factors as well as natural anticoagulant proteins, causing a disturbance in the balance between procoagulant and anticoagulant pathways. This disturbance in coagulation mechanisms causes a complex paradigm of both increased bleeding risk and increased thrombotic risk. The most common coagulation abnormalities associated with liver dysfunction are thrombocytopenia and impaired humoral coagulation function manifested as prolongation of the prothrombin time and international normalized ratio (INR).
• **The etiology of thrombocytopenia in patients with liver disease** is typically related to
  • 1) hypersplenism
  • 2) reduced production of thrombopoietin
  • 3) immune-mediated destruction of platelets.

• The total body platelet mass is often normal in patients with hypersplenism, but a much larger fraction of the platelets is sequestered in the enlarged spleen. Bleeding may be less than anticipated because sequestered platelets can be mobilized to some extent and enter the circulation. Thrombopoietin, the primary stimulus for thrombopoiesis, may be responsible for some cases of thrombocytopenia in cirrhotic patients, although its role is not well delineated. Finally, immune-mediated thrombocytopenia may also occur in cirrhotics, especially those with hepatitis C and primary biliary cirrhosis.

• In addition to thrombocytopenia, these patients also **exhibit platelet dysfunction via defective interactions between platelets and the endothelium**, and possibly due to uremia and changes in endothelial function in the setting of concomitant renal insufficiency.
• 1) Most often, treatment should be withheld for invasive procedures and surgery. Platelet transfusions are the mainstay of therapy; however, the effect typically lasts only several hours. Risks associated with transfusions in general and the development of antiplatelet antibodies in a patient population likely to need recurrent correction should be considered.

2) A potential alternative strategy involves administration of interleukin-11 (IL-11), a cytokine that stimulates proliferation of hematopoietic stem cells and megakaryocyte progenitors. Most studies using IL-11 have been in cancer patients, although some evidence exists that it may be beneficial in cirrhotics as well. Significant side effects limit its usefulness.

• 3) A less well-accepted option is splenectomy or splenic embolization to reduce hypersplenism. In addition to the risks associated with these techniques, reduced splenic blood flow can reduce portal vein flow with subsequent portal vein thrombosis. Results are
COAGULOPATHY OF TRAUMA

- Traditional teaching regarding trauma-related coagulopathy attributed its development to:
  - 1) acidosis >> decrease o2 supplement
  - 2) hypothermia,
  - 3) dilution of coagulation factors. Recent data, however, have shown that over one third of injured patients have evidence of coagulopathy at the time of admission.

- >> acute coagulopathy of trauma (ACoT) is not a simple dilutional coagulopathy but a complex problem with multiple mechanisms. Whereas multiple contributing factors exist, the key initiators to the process of ACoT are shock and tissue injury. Brohi et al have demonstrated that only patients in shock arrive coagulopathic and that it is the shock that induces coagulopathy through systemic activation of anticoagulant and fibrinolytic pathways.
• Local Hemostases:
  • Digital pressure
  • Tourniquet
  • Packing
  • Biological agents that help platelets adhesion
BLOOD TRANSFUSION

- Serological compatibility
- Typing and Cross-Matching:
  - Serologic compatibility for A, B, O, and Rh groups is established routinely. Cross-matching between the donors’ red blood cells and the recipients’ sera (the major cross-match) is performed. **Rh-negative recipients should be transfused only with Rh-negative blood.**
  - However, this group represents only 15% of the population. Therefore, the administration of Rh-positive blood is acceptable if Rh-negative blood is not available. **However, Rh-positive blood should not be transfused to Rh-negative females who are of child-bearing age.**
  - In emergency situations, type O-negative blood may be transfused to all recipients. O-negative and type-specific red blood cells are equally safe for emergency transfusion. **Problems are associated with the administration of four or more units of O-negative blood because there is a significant increase in the risk of hemolysis.** In patients with clinically significant cold agglutinins, blood should be administered through a blood warmer. If these antibodies are present in high titer, hypothermia is contraindicated.
  - Typing and cross matching are difficult inpatients with hemolytic anemia and those with multiple transfusions.
BANKED WHOLE BLOOD

- is rarely available in Western countries.
- With sequential changes in storage solutions, the shelf life of red blood cells is now 42 days. Recent evidence has demonstrated that the age of red cells may play a significant role in the inflammatory response and incidence of multiple organ failure. The changes in the red blood cells that occur during storage include reduction of intracellular ADP and 2,3-diphosphoglycerate (2,3DPG), which alters the oxygen dissociation curve of hemoglobin, resulting in a decrease in oxygen transport.
- Stored RBCs progressively becomes acidotic with elevated levels of lactate, potassium, and ammonia.
RED BLOOD CELLS AND FROZEN RED BLOOD CELLS

• Red blood cells are the product of choice for most clinical situations requiring resuscitation. Concentrated suspensions of red blood cells can be prepared by removing most of the supernatant plasma after centrifugation.

• The preparation reduces but does not eliminate reactions caused by plasma components. Frozen red blood cells are not currently available for use in emergencies, as the thawing and preparation time is measured in hours. They are used for patients who are known to have been previously sensitized.

• The red blood cell viability is improved, and the ATP and 2,3-DPG concentrations are maintained.
• Platelet Concentrates.
• WBC
• Fresh Frozen Plasma. Fresh frozen plasma (FFP) prepared from freshly donated blood is the usual source of the vitamin K-dependent factors and is the only source of factor V. FFP carries similar infectious risks as other component therapies.
• Cryoprecipitate
• Factor components
INDICATIONS OF BLOOD TRANSFUSION:

• In general, blood loss or low hemoglobin.
• 1) Improvement in Oxygen-Carrying Capacity.
• 2) Treatment of Anemia
• 3) Volume Replacement
Hazards of transfusion:

- 10% of all transfusions
- Less than 0.5% are serious

Non hemolytic reactions

- 1%
- Rise in Temp. more than 1°C

Bacterial contamination

- Allergic reactions
- Respiratory (TACO)
- TRALI
- Hemolytic reactions
ALLERGIC REACTIONS

• Allergic reactions are relatively frequent, occurring in **about 1% of all transfusions**. **Reactions are usually mild and consist of rash, urticaria, and flushing.**

• In rare instances, **anaphylactic shock develops.**

• Allergic reactions are caused by the transfusion of antibodies from hypersensitive donors or the transfusion of antigens to which the recipient is hypersensitive.

• Allergic reactions can occur after the administration of any blood product but are commonly associated with **FFP and platelets.**

• Treatment and prophylaxis consist of the administration of antihistamines. In more serious cases, epinephrine or steroids may be indicated.
RESPIRATORY COMPLICATIONS

• Respiratory compromise may be associated with transfusion-associated circulatory overload (TACO), which is an avoidable complication. It can occur with rapid infusion of blood, plasma expanders, and crystalloids, particularly in older patients with underlying heart disease.

• Central venous pressure monitoring should be considered whenever large amounts of fluid are administered. Overload is manifest by a rise in venous pressure, dyspnea, and cough. Rales can generally be heard at the lung bases.

• Treatment consists of diuresis, slowing the rate of blood administration in sitting position, and minimizing fluids while blood products are being transfused.
THE SYNDROME OF TRALI (TRANSFUSION-RELATED ACUTE LUNG INJURY)

• defined as noncardiogenic pulmonary edema related to transfusion.
• It can occur with the administration of any plasma-containing blood product. Symptoms are similar to circulatory overload with dyspnea and associated hypoxemia. However, TRALI is characterized as noncardiogenic and is often accompanied by fever, rigors, and bilateral pulmonary infiltrates on chest x-ray. It most commonly occurs within 1 to 2 hours after the onset of transfusion but virtually always before 6 hours.
• Treatment of TRALI entails discontinuation of any transfusion, notification of the transfusion service, and pulmonary support, which may vary from supplemental oxygen to mechanical ventilation.
Hemolytic reactions Contd.

1 Acute
   ABO incompatibility
   Fatal in 6% of cases
   Result from laboratory or clerical errors
   Basic problem is destruction of RBCs
   Hemoglobinemia and Hemoglobinuria (usually acidic)
      Deaths occur from DIC and acute renal failure
2 Delayed, 2 to 10 days later
   Extravascular hemolyses leading to anemia and hyperbilirubinemia usually resolved spontaneously.
• What to look for?
  • Pain at the site of transfusion
  • Facial flushing
  • Back and chest pain
  • Associated symptoms (Tachycardia, Hypotension or respiratory distress)
• What to do?
  • Stop transfusion
  • Suspected unit and a sample of recipients blood to be sent to blood bank
  • Adequate hydration
  • Monitoring urinary output
  • Supportive measures
THANK YOU