The blood is a very complex organ in our body and coagulation, in particular, is coordinated by various mechanisms. It is known from experience that in order to truly learn and comprehend the different coagulation processes and disorders, most medical students take much time and great pains. The topic is often regarded as not comprehensible and very abstract. This article is supposed to provide you with a basic overview of the fundamentals of coagulation disorders and clearly introduce to you the plasma coagulation defects in particular.

Bleeding in Patients

There are many diseases that cause increased bleeding tendency aside from just as many diseases that secondarily lead to coagulation disorders. Coagulopathy is a bleeding disorder characterized by impaired clotting of blood. In your clinical routine, you will have different options available to you to narrow down the cause of the bleeding.
A very reasonable approach is the thorough gathering of the patient’s medical history. This will already allow you to collect plenty of information, which will lead your thought process and eventually your actions in the right direction. Precisely, excessive and prolonged bleeding is triggered by an injury, medical conditions and dental procedures. Frequently, a pathologically increased bleeding tendency may be noticed before surgery and have, at times, a very dramatic effect.

In order to prevent you from having to encounter such a situation unprepared, the following will provide you with a basic overview of the physiology and the pathophysiology of hemostasis.

**Physiology and Pathophysiology of Hemostasis**

First here is some background to what actually takes place during coagulation. Hemostasis is the cessation of bleeding by disruption of vascular endothelium. Many components participate in hemostasis to form clots (made up of platelets and fibrin). It basically includes primary and secondary hemostasis:

**Primary hemostasis**

Primary hemostasis starts immediately and physiologically consists of vasoconstriction and the formation of a “white” thrombus. It basically processed by aggregation of platelets and formation of platelet plug. The thrombocytes or platelets are essential to this mechanism and an important component of the thrombus. An injury to or irritation of the vascular wall usually leads to the release of ADP, which, in conjunction with the von Willebrand factor, allows the platelets to adhere.

The platelets form the thromboxane, which promotes platelet aggregation and vasoconstriction. The thromboxane is derived from arachidonic acid of the platelet membranes via cyclooxygenase - the point of attack for acetylsalicylic acid. Serotonin is secreted to activate platelets. Thus, platelets get activated and adhere together to form platelet plug.

**Secondary hemostasis**

Secondary hemostasis is a time-delayed process aiming for the stabilization of the thrombus after platelet aggregation. This stabilization is achieved via fibrin and factor
XIII stabilization but before that can happen, another complex cascade has to be activated.

The plasma coagulation cascade leads to the formation of the prothrombin activator complex, either intrinsically (factors XII, XI, IX, VIII, X and V) or extrinsically (factors III, VII, X and V), which converts prothrombin to thrombin (activated factor II). The activated thrombin splits fibrinogen and the soluble fibrin eventually forms a firm meshwork using the fibrin-stabilizing factor XIII.

**Dissolving fibrin**

Plasmin acts to dissolve fibrin via fibrinolysis in the process of healing of wound healing. Various plasminogen activators convert the inactive plasminogen into active plasmin, which, in turn, eventually splits fibrin.

It is important for you to understand that hemostaseological processes permanently take place in our bodies and create a balance. There is no either or. Small amounts of fibrin are formed and dissolved everywhere and this system allows for small wounds, bleeding or microthromboses to heal well and almost unnoticed.

This system’s balance, however, may be impacted or even pathologically disturbed. These disturbances are either congenital in nature or caused by diseases. This balance may also be influenced by many iatrogenic mechanisms in order to dissolve or even prevent blood clots from forming, for instance.

**Definition of Hemorrhagic Diathesis**

Hemorrhagic diathesis describes pathologically increased bleeding tendency and bleeding may last too long, be too strong or occur without adequate cause. Such bleeding events should always be reason for skepticism on your part and encourage further probing!

In the end, hemorrhagic diathesis may occur on different levels of the aforementioned hemostasis and manifest itself in thrombotic, plasma or vascular disorders. Here, the causes may be congenital but also acquired.

Basically, hemorrhagic diatheses may be divided into three groups according to their clinical signs:

1. **Platelet disorders** account for approximately 70 % of all cases. This is a large and heterogenic group, which is why we will dedicate a separate article to it shortly. It is caused by any disorder of hemostasis of platelet. The causative factors can be kidney or renal disease, chemotherapy, diminished immunity and radiation.
2. **Coagulopathies** caused by plasma irregularities are responsible for approximately 20 % of hemorrhagic diatheses. It is caused by disorders of fibrinolysis triggered by anticoagulant and fibrinolytic drugs, hemophilia, etc.
3. There are also **combined hemostasis disorders** with platelet and plasma components caused by von willebrand’s disease, radiation, etc.

**Diagnosing Coagulation Disorders**

The most important first step is gathering the patient’s medical history and performing a physical examination. Is the patient on (anticoagulant) medication? Is there a family history of bleeding tendency? Does he have or has he had an infection? Is there the
possibility of a malignancy?

Clinically typing blood frequently reveals the location of the hemostasis disorder:

- **Coagulopathies** frequently manifest themselves as large, extensive hematoma and unexplained and easy bruising. This extensive bleeding is usually sharply defined. Affected organs may be, for instance, muscles, joints or the skin.

![Intermediate magnification micrograph of fetal thrombotic vasculopathy. H&E stain. Histopathologically, it is characterized by:](Image)

- **Thrombotic** or **vascular bleeding** is characterized by **petechiae**. A large amount of petechiae is referred to as purpura but there may also be ecchymosis, small bleeding in the skin.

![Petechiae](Image)
Therefore, combined hemostasis disorders may display both types of bleeding. Should you suspect a coagulation disorder, you may be able to narrow down the causes using different tests:

- **The blood count** will provide evidence of changes in platelet count.
- **Prolonged bleeding points** toward a disorder of platelet function or vascular disorder.
- **Partial thromboplastin time (PTT)** reflects the intrinsic plasma coagulation system and the common pathway which is usually between 20 - 35 seconds. PTT may be prolonged with defective or decreasing coagulation factors II, V, VIII, IX, X, XI and XII.
- **Prothrombin time** (thromboplastin time, Quick test) shows the function of the quicker extrinsic coagulation system and the common pathway. In many cases, assays of Factor VIII and IX are indicated. It is measured in percentages and results lower than 70 % are signs of defective or decreased coagulation factors II, VII, IX and X. The Quick test is a laboratory test. In order to obtain comparable results, INR (international normalized ratio) is used in clinical routine.
- **Thrombin time (TT)** is a test to determine the common pathway for formation of blood clots. Active thrombin activates fibrinogen and in cases of fibrinogen deficiency, TT is prolonged. This indicates towards disseminated intravascular coagulation.
- Another option to detect fibrinogen deficiency is to measure reptilase time. Reptilase is a snake venom that may split fibrinogen. In cases of fibrinogen deficiency, reptilase time is prolonged.

**Note:** If you are trying to detect fibrinogen deficiency in patients on heparin, it is best to determine reptilase time. While thrombin activity is directly affected by heparin or hirudin therapy, reptilase is unaffected by it. If PTT is abnormal, it indicates definite history of bleeding, if PT is not normal with or without abnormal PTT, it indicates towards abnormal levels of vitamin K coagulation factors (II, VII, IX, X)

Furthermore, there are other specific tests for different indications:

- **Measuring factor Xa activity** may be used for monitoring therapy in cases of low-molecular-weight heparin therapy (LMWH). PTT is not suitable for LMWH. Therefore, if therapy is to be evaluated, the antifactor Xa levels should be monitored between three and four hours after injecting LMWH. This is indicated for very light-weight or very heavy patients, for patients with renal insufficiency or if bleeding occurs after LMWH administration.
- **D-dimer tests** are often done in cases where thrombosis or a pulmonary embolism must be ruled out. D-dimers are fibrin by products whose levels are elevated during fibrinolysis. It indicates that there is formation of fibrin intravascularly. Elevated d-dimer levels may have many causes. Normal d-dimer levels, however, rule out thrombosis or pulmonary embolism for the most part.

**Definition and Classification of Coagulopathies**

Coagulopathies describe coagulation disorders that impact secondary hemostasis. They are disorders of the coagulation factors.
Coagulopathies may be subdivided into four large groups:

- Coagulation defects
- Consumption coagulopathies
- Immune-mediated coagulopathies
- Hyperfibrinolysis

This subdivision may not only help you better memorize the details but there are also different therapeutic measures necessary.

Coagulation defects

Coagulation defects describe various deficient or defective coagulation factors. These disorders may be congenital in nature but may also be acquired. Congenital coagulation defects are, for instance, von Willebrand syndrome or hemophilia.

Acquired coagulation-factor deficiencies are frequently found in the context of vitamin K deficiency. Vitamin K is known to be involved in factor synthesis II, VII, IX, and X (in 1972) and its absorption is, for instance, reduced by liver disease, vitamin K antagonists such as Coumarin or simply malabsorption.

Consumption coagulopathies (Disseminated intravascular coagulation, DIC)

The term DIC describes a complex condition in the area of plasma coagulation. As the name suggests, disseminated intravascular activation of the coagulation system takes place slowly via various processes along with the formation of multiple microthrombi. It leads to increased production of thrombin and fibrin.

This systemic coagulation activation results in the hyperstimulation of the hemostasis system and the excessive consumption of coagulation factors, antithrombin and platelets.

This results in increased bleeding tendency with a host of possible bleeding complications and even shock. The disseminated microthrombi activate increased fibrinolysis along with proteolysis of other coagulation factors.

It is diagnosed by an elevation in PTT, PT, plasma D-dimers and decrease in levels of fibrinogen.

Immune-mediated coagulopathies

Many immune-mediated diseases produce different autoantibodies. These autoantibodies may target the components of the coagulation system, thus creating coagulopathy. A classic representative for these types of diseases is systemic lupus erythematosus.

Hyperfibrinolysis

As previously mentioned, fibrinolysis is regulated by plasminogen. Different mechanisms may cause increased fibrinolysis through excessive plasminogen activation, which, in turn, results in the increased consumption of coagulation factors. This results in more fibrinolytic activity than fibrin formation. The clinical consequence is severe bleeding.

Genetically, there may be a deficiency of alpha-2 antiplasmin but malignant diseases may also be linked to increased fibrinolysis. Fibrinolytic therapy is used in
cases of vascular occlusions. Hyperfibrinolysis may result in dangerous bleeding complications, which is why an indication for fibrinolysis must be researched under any circumstances. Chronic liver disease can be one of its common causes.

Cardiopulmonary bypass surgery or removal of thrombus in arterial or venous thromboembolism can trigger it by the use of fibrinolytic agents.

Consumption coagulopathy may cause secondary increased reactive fibrinolysis and exaggerate the consumption of coagulation factors via proteolysis. Reactive fibrinolysis means that increased fibrinolysis is only activated after preceding thrombus formation.

Therapy for Disorders of Secondary Hemostasis

The goal of therapy is to restore the normal coagulation balance. Here, it is again very important to envision the correct coagulation balance as overtreatment may directly lead to the opposite result meaning increased tendency to clot. Therapeutic indications depend on the individual clinic. In cases of mild disorders, it is frequently appropriate to watch-and-wait, pending surgeries or relevant bleeding, however, must be dealt with more urgently.

The aforementioned definitions lead to different therapy principles:

- In cases of an **underlying disease**, the disease should be treated first. Administering (expensive) coagulation factors, for instance, will hardly benefit the patient if the body continues producing antibodies against them. In this case, immunotherapy should be in the forefront.
- **Intrinsic system disorders** (i.e. hemophilia) may be substituted depending on the individual clinic and necessity.
- **Extrinsic system disorders** may be balanced like intrinsic system disorders. In cases of bleeding requiring treatment that occur during vitamin K antagonist therapy, it makes sense to first discontinue said therapy and administer vitamin K. This may pose a therapeutic dilemma for which there are no clear recommendations. The indication for individual oral anticoagulation must be weighed against the individual bleeding. It should be given in international normalized ratio (INR), which should be <5.
- **Hyperfibrinolysis** may be stopped by administering tranexamic acid. Tranexamic acid inhibits the formation of plasmin.

Increased Tendency to Clot

In order to complete the overall picture of these disorders, it should be mentioned that there are also diseases resulting in an increased tendency to clot. This group includes, for instance, antithrombin deficiency, protein C and S deficiency as well as resistance to activated protein (APC resistance / factor V Leiden mutation). Prothrombin mutations or increased levels of factor VIII are also possible.

Individuals with these diseases frequently suffer from thrombophilia early in life. In cases where young people suffer from, for instance, phlebothrombosis, pulmonary artery thrombosis or cerebral infarction, you should take the group of thrombophilias into consideration!
Review Questions

The answers are below the references.

1. Which of the following types of bleeding are most typical for pronounced thrombocytopenia?
   
   A. Bleeding into body cavities
   B. Bleeding into large joints
   C. Gastrointestinal bleeding
   D. Diffuse petechiae
   E. Extensive bleeding under the skin

2. You care for a 74-year-old retiree with atrial fibrillation in your general practitioner's office. Many attempts at controlling his heart rhythm have failed in the past. You had already convinced your patient years ago that thromboembolism prophylaxis may be appropriate and would now like to find out if prophylactic protection is sufficient. Which parameters do you measure?
   
   A. Partial thromboplastin time
   B. Activated factor X
   C. Anti-factor X levels
   D. Serum phenprocoumon levels
   E. INR of thromboplastin time

3. For years, you have been caring for a now 53-year-old patient in your practice. He now complains of “unusual” bleeding. Apparently, harmless cuts bleed profusely and for a long time, he has noticed extensive bleeding under the skin without being able to recall any injuries. You find normal Hb levels and a normal platelet count. PTT is prolonged and INR elevated, reptilase and thrombin time is prolonged as well while fibrinogen is reduced. What do you suspect is the cause for this coagulation disorder?
   
   A. Thrombocytopathy with normal platelet count
   B. Primary hyperfibrinolysis
   C. Accidental Marcoumar overdose
   D. Vascular hemorrhagic diathesis
   E. Hemophilia type A or B

References

Herold, G. und Mitarbeiter, Innere Medizin, 2014

Correct answers: 1D, 2E, 3B

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