5) Hemostasis & Bleeding Disorders – Dr. Anwar

Hemostasis means arrest of bleeding. It is achieved by a highly integrated process that involves the blood vessels, the platelets and a number of plasma proteins, which are collectively responsible for coagulation and fibrinolysis. One can imagine the complicated nature of this system by the dual function of rapidly stopping bleeding from a localized vessel injury while simultaneously maintaining an uninterrupted blood flow in the neighboring vascular network.

Hemostasis is arbitrarily divided to three stages:
(*) Formation of a “primary hemostatic plug” by the blood vessels and platelets
(*) Formation of a “fibrin clot” through the interaction of soluble coagulation factors
(*) Fibrinolysis through the interaction between the components of the fibrinolytic system.

**BLOOD VESSELS:** Following injury, small blood vessels contribute to the primary hemostatic response in two ways. First, there will be a reflex transient vasoconstriction, which is later maintained by 5-HT released from the platelets. Secondly, their walls contain sub–endothelial microfibrils and collagen, to which platelets escaping from the lumen will adhere to start the formation of primary hemostatic plug. These same sub–endothelial fibres also initiate the process of clotting by activating the contact factors (XII & XI).

**ENDOTHELIAL CELLS:** Blood does not clot inside the blood vessels because of the endothelial cells (EC), which act as a barrier between the blood and the sub–endothelial fibres. They are also active in preventing intravascular coagulation by producing Prostacyclin and Nitric Oxide (endothelium–derived relaxing factor, EDRF), both having strong vasodilatory properties and anti–aggregatory effects on platelets. Thrombomodulin, an integral part of the ECs, converts thrombin from a powerful pro–coagulant to an essential anticoagulant; this is achieved by activating protein C. ECs also produce AT III with its anticoagulant effect against activated clotting factors.

von Willebrand’s factor (vWF), which carries the clotting portion of factor VIII, is also produced in the endothelial cells. vWF is an essential part of primary plug formation by making adhesion between the platelets and sub–endothelial microfibrils possible. ECs also produce tissue plasminogen activators that promote fibrinolysis.

**PLATELETS:** These are by far the most important cells in the body! Understanding the true nature of the platelets in the future could solve most of our problems with myocardial infarctions and other types of ischemic arterial thrombosis that are the leading causes of death all around the world. Platelets are fragments of the cytoplasm of the megakaryocytes that are produced in the bone marrow. They are non–nucleated, biconvex, trilamellar cells containing variety of important cellular elements.

Electron–dense granules contain ADP, ATP, calcium and serotonin.
α–granules contain growth factor, fibrinogen, factor V & VIII:vWF, fibronectin, beta–thromboglobulin, heparin antagonist (PF4) and thrombospordin. Platelets also contain lysosomes, mitochondria, glycogen, etc. Platelets provide the backbone for the adsorption of clotting factors during hemostasis. The plasma membrane Platelet Factor 3 (PF3) is the site of receptors for clotting factors and aggregating agents.
The platelet count ranges between 150 and 400 thousand per μL. Platelet life span is around ten days. Platelet diameter is 2–4 μm and the mean platelet volume is 5 to 8 fL. Normally one third of all platelets in the body are pooled in the spleen, especially the young ones. In splenomegaly, up to 90% of the platelets could be imprisoned in the spleen causing thrombocytopenia.

The process of hemostasis starts with the vessel wall injury and exposure of the platelets and clotting factors to the sub–endothelial microfibrils and collagen. Platelet adhesion to the vessel wall plugs the gap and stops the bleeding. For the full effect of this plug, platelets have to go through a number of stages, each of which is of vital importance in the formation of primary hemostatic plug. Platelet adhesion is not a passive process and needs the presence of special glycoprotein receptors (GP Ib & GPIIb/IIIa) on the surface of platelets and the presence of vWF in the plasma. Absence of GP Ib results in a rare disease called “Bernard–Soulier syndrome” and lack of vWF causes a relatively common bleeding problem called von Willebrand disease.

Within seconds of their “adhesion”, platelets “change their shape” from disc to a spiny sphere which is followed by “release reaction” that reaches its peak in 3 to 5 minutes. Release reaction means releasing contents of the platelet granules that result in recruitment of more platelets to the site of vessel injury. One of the substances released is 5-HT, which maintains the vessel wall constriction. GPIIb/IIIa is also important in aggregating the platelets together and its deficiency causes a disease called Glanzmann disease.

Platelet membrane is very important in hemostasis because it produces a number of prostaglandins from arachidonic acid released from phospholipids in their membrane. Arachidonic acid, through the action of the important enzyme cyclo-oxygenase, produces cyclic endoperoxides like thromboxane A2 (TX A2). TX A2 contributes to hemostasis by causing vasoconstriction, platelet adhesion, aggregation and more release reaction.

As mentioned earlier, platelet also contributes to coagulation by providing a membrane phospholipid called PF3. This factor in the presence of calcium ion, ADSORB many of the coagulation factors and thus enhances clotting on the top of the hemostatic plug.

**COAGULATION:** Clotting factors are present in plasma in inactive precursor forms. These are converted to active forms by an enzyme amplification cascade reaction. There are two pathways for blood coagulation, intrinsic and extrinsic. They both converge on a common pathway that produces the final clot. Although there are many links between these two pathways, deficiency of any factor can cause bleeding problems because optimal hemostasis requires the presence of the clotting factors in optimum amounts.

Classical teaching stresses that the **intrinsic pathway** starts by activation of the contact factors by the sub–endothelial microfibrils and collagen. Factor XII, XI and High molecular weight kininogens are contact factors that use the surface of platelets (PF3) to consolidate the primary
plug. After their activation, they activate factor IX that will ultimately convert factor X to active factor X through the help of a very important activated factor VIII, PF3 and calcium. Factor VIII is important because its deficiency causes hemophilia A. Factor IX deficiency causes Christmas disease.

It is important at this point to mention that factor VIII is composed of two portions. A very big portion, which is called vWF and is responsible for platelet adhesion and a small portion, which is called anti–hemophilia factor or factor VIII clotting (VIII:c) factor which is vital for coagulation. Deficiency of vWF causes von Willebrand disease and deficiency of factor VIII:c causes hemophilia A. One should not forget that vWF is important to carry the clotting factor and in extreme deficiency of vWF a hemophilia picture can also be seen.

The **extrinsic pathway** or tissue factor pathway results from liberation of factor III (tissue factor) to the circulation. This factor is widely distributed in the body but is found in especially high concentration in brain, lungs and placenta. Tissue factor in the presence of factor VII and calcium rapidly converts factor X to active factor X and thus bypass the intrinsic system. While it might take seconds for factor X activation through the extrinsic system, the intrinsic system is a slow process taking minutes.

At this point, it is important to mention the advances that have happened in our understanding of the coagulation process. Actually the cascade mechanism of activating factor XII and then downward is not as true as we believed it. Factor XII (Hageman Factor) has minimal effect on clotting and its deficiency does not cause bleeding. It is the initial thrombin burst, generated through the extrinsic pathway by the Tissue Factor that back–activates factor XI, which in turn sets up the cascade amplification. Mr. Hageman actually died of thrombosis although his APTT was very high! It is now known that Factor XII has fibrinolytic properties through plasminogen activation. Loss of this effect might be behind vulnerability of Factor XII deficient patients to thrombosis.

In the **common pathway**, factor Xa generated through either pathway will convert prothrombin to thrombin in the presence of factor V, PL3 and calcium.

**Thrombin** is the most important part of the clotting cascade. Once it is produced it can play in many scenes and activate numerous substances, including factors VIII, V and XI. Unless it is down regulated, it can clot all the blood in the body in the matter of seconds. Ten ml of plasma can generate enough thrombin to clot all the blood in the body in 30 seconds. Understanding all the ramifications of its action is vital to the understanding of hemostasis. Thrombin first converts fibrinogen to fibrin that is the final product of coagulation. Fibrin so produced is weak and need thrombin to activate factor XIII that cross–links the fibrin strands together to produce a strong stable clot. As mentioned, thrombin should down–regulate itself, otherwise it can cause catastrophic degree of intravascular coagulation. With the cooperation of thrombomodulin on the surface of the endothelial cells,
it activates protein C, which with the help of protein S, can inactivate activated factors V and VIII. Besides, fibrinolysis is also activated by thrombin through the production of plasminogen activators.

It is clear from the above account that Calcium is essential for many stages in the clotting cascade. Calcium removal by anticoagulants like citrate results in an uncoagulable blood. Citrate is used in the blood bank to prevent clotting during storage for the purpose of transfusion.

**Fibrinolysis**: The fibrinolytic system is very important in that it plays a role in removing fibrin from intravascular and extravascular sites. Fibrin degradation is brought about by “plasmin”. Plasmin is produced from “plasminogen” which is the inactive from present in circulation. Plasminogen is converted into plasmin by a number of activators (tissue plasminogen activator, streptokinase and urokinase) and inhibited by a number of inhibitors. Epsilon Amino Caproic Acid and Tranexamic Acid are antifibrinolytic agents used in practice to suppress fibrinolysis in bleeding patients with weak clots.

Plasmin degrades fibrin into small fragments called fibrin(ogen) degradation products (FDP) & D–Dimers. FDP is increased in hypercoagulability states when fibrinolysis is secondarily activated as in DIC and pulmonary embolism.

Understanding hemostasis is important to understand the bleeding disorders. As we mentioned, blood vessels and platelets are responsible for the production of the primary hemostatic plug. Clotting factors are important in the production of the stable hemostatic clot. Without clotting, the primary plug is fragile and will be washed away, resulting in delayed bleeding. Clotting factor deficiency causes deep–seated bleedings usually to the joints, muscles, retroperitoneum and other parts of the body that are under physical stress. Abnormalities of blood vessels and platelets result in a purpuric type of bleeding that usually affects the skin and mucus membranes. The bleeding caused by failure of the primary hemostatic plug is very much different from that resulting from clotting factors deficiencies. A hemophiliac usually suffers from repeated bleeding to the joints which finally cripples him if not properly covered with factor VIII:c. Patients with platelet problem or vascular abnormalities have bleeding from the vagina, gastrointestinal tract and skin because of problem with the primary plug formation. This result in prolonged uninterrupted, rather than delayed, bleeding. If we assume that two patients will undergo dental extraction, one with hemophilia and another one with von Willebrand disease, which is a primary hemostatic plug defect, then the von Willebrand patient will continue oozing postoperatively while the hemophiliac might stop bleeding temporarily because his primary hemostatic mechanism is intact. When time comes for the plug to become stable by clotting, the defect uncovers itself and the fragile clot washes away causing delayed bleeding.

The tests used to differentiate bleeding due to clotting factor deficiencies and purpuric types of bleeding are different. Clotting screen, using prothrombin, activated partial thromboplastin and thrombin times (PT, APTT & TT) tests the integrity of the coagulation cascade. Bleeding time,
using a special small standardized instrument called Simplate, tests the blood vessel wall integrity and the platelet count and function.

I. VASCULAR BLEEDING DISORDERS

Fortunately, bleeding disorders due to vessel wall abnormalities are not common in daily practice, although they can be seen more commonly during student examinations!

Few conditions warrant discussion under this title.

**HEREDITARY HEMORRHAGIC TELANGIECTASIA:** This condition is characterized by small vascular malformations, which usually appear after adulthood on the face, lips, tongue and on palmar and plantar surfaces. They are permanent marks that blanch on pressure because they are composed of dilated blood vessels. Purpura, on the other hand, results from bleeding into the skin and do not blanch on pressure. Bleeding into GIT from these telangiectasias can result in iron deficiency anemia and bleeding in the brain can cause CVA.

**EHLERS-DANLOS SYNDROME:** This form of purpura is due to deficiency of the skin collagen that is essential for platelet adhesion. These patients also display hyper-extensible joints, thin, easily-torn paper-like skin with poor healing.

**MARFAN’S SYNDROME & OSTEOGENESIS IMPERFECTA** will be dealt with during the medicine course.

**BACTERIAL, VIRAL & RICKETSIAL INFECTIONS** can all cause vascular bleeding. This can result from toxic damage to the endothelium or through immune complex hypersensitivity. In meningococcal septicemia, DIC also contributes the fulminant nature of the bleeding.

**HENOCH-SCHONLEIN PURPURA** is a well-recognized allergic vasculitic syndrome that usually follows an upper respiratory infection by few weeks. It usually affects children and presents with symmetrical lower extremity rash. Patients may also complain from fever, joint involvement, abdominal pain and hematuria.

**Drugs** (e.g., Allopurinol) and food can also cause allergic vasculitis and purpuric bleeding.

**ATROPHIC PURPURA** is a feature of **SENILE PURPURA** (which typically present as ecchymoses on the extensor surface of the wrist in elderly people) and **CUSHING’S SYNDROME & STEROID THERAPY.**

**SCURVEY, PARAPROTEINEMIA AND AMYLOIDOSIS** can all cause bleeding problems because of changes in the vessel structure.

**OTHER CONDITIONS ASSOCIATED** with vascular bleeding are simple easy bruising, factitious and fat embolism.

II. PLATELET BLEEDING DISORDERS

An adequate number of normally functioning platelets is not only essential for the primary arrest of bleeding after obvious injury, but also to prevent spontaneous leakage of red cells from apparently uninjured vessels. Failure of these two aspects of hemostasis is expressed respectively by a prolonged bleeding time and the
spontaneous appearance of purpuric lesions, both hallmarks of platelet disorders.

Although the total volume of platelets in the body is not much, their function is so important that a thorough discussion of platelet normal values is timely. Assuming a normal platelet count of 150,000 to 400,000/uL or 150 to 400 billion/L and a mean platelet volume of 5 to 8 femtoliter, it means that the total volume of platelets per liter of blood can be calculated by a simple arithmetic multiplication:

\[
\text{Total volume per liter} = \text{individual mean platelet volume (MPV)} \times \text{numbers per liter}
\]

Taking an average platelet count of 250 billion/L and an MPV of 8 fl, then the average platelet mass per liter is \( (250 \times 10^9) \times (8 \times 10^{-15})/L = 2000 \times 10^{-6}L = 2 \text{ mls} \)

That means in every liter of blood there are 2 mls of platelets.

Plateletcrit can be calculated from this value as 0.2% (0.1 to 0.4% or 0.1 to 0.4 ml/dL).

If we have an average of 2 mls platelet per one liter of blood and the total volume of blood in an average sized adult is 5 liters, then the total volume of platelets in our body is only 10 mls! Not much for cells that rule our destiny.

It is important from these calculations to realize that it is not only the platelet count, which is important, but also the plateletcrit, which is dependent on the platelet number, and mean platelet volume (MPV). Today's machines give values for platelet numbers, MPV and plateletcrit. Students should familiarize themselves to look at all these values when evaluating a patient with low platelet count.

**Thrombocytopenia (TP)**

Thrombocytopenia (TP) means reduced platelet count below 150 thousand per uL. TP could result from impaired production, increased consumption or both.

**The causes of TP are:**

**Φ DEFECTIVE PLATELET PRODUCTION**
- Aplastic Anemia
- Leukemias & malignant marrow infiltration
- Viral Infections
- Chemotherapy, Radiotherapy, etc.
- Megaloblastic Anemia
- Alcoholism
- Various Hereditary TP.

**Φ LOSS OF PLATELETS FROM CIRCULATION**
- Splenomegaly
- Massive Transfusion

**Φ DECREASE PALTELET SURVIVAL**

- Immune destruction:
  - (a). Immune Thrombocytopenic Purpura (ITP).
  - (b). Drug Induced TP
  - (c). Evans’ Syndrome (ITP + AIHA)
  - (d). SLE & other autoimmune-diseases
  - (e). Lymphomas
  - (f). Neonatal TP

- Non-Immune Consumption:
  - (DIC) Disseminated Intravascular Coagulation
  - (TTP/HUS) Thrombotic Thrombocytopenic Purpura/Hemolytic Uremic Syndrome
  - Acute Infections
Immune Thrombocytopenic Purpura is a common cause of thrombocytopenia that is caused by the production of anti-platelet antibodies. These IgG antibodies can cause premature destruction of the platelets by the cells of reticuloendothelial system, commonly in the spleen. Because there is no diagnostic test for ITP, it is usually defined as thrombocytopenic purpura in the absence of underlying diseases or drug toxicity and with increased or normal number of megakaryocytes in the bone marrow. The blood smear shows reduced platelet count with giant forms. This condition was quite common where I practiced in Saudi Arabia with 168 patients followed up in my department by the time I left in 2004.

There are two main types of ITP; an acute self-limiting type that usually affects children and a chronic from that usually affects young adult females.

<table>
<thead>
<tr>
<th></th>
<th>ACUTE “Childhood”</th>
<th>CHRONIC “Adult”</th>
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<tbody>
<tr>
<td>Peak age</td>
<td>2 to 6 years</td>
<td>20 to 40 years</td>
</tr>
<tr>
<td>Sex (M/F) incidence</td>
<td>1:1</td>
<td>1:3</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>Preceding Infection</td>
<td>Common</td>
<td>Unusual</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>Often &lt; 20,000/uL</td>
<td>Usually &gt; 20,000/uL</td>
</tr>
<tr>
<td>Spontaneous Remission</td>
<td>More than 80%</td>
<td>Less than 20%</td>
</tr>
<tr>
<td>Usual Duration</td>
<td>2 to 4 weeks</td>
<td>Months/usually years</td>
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Acute ITP in children usually starts abruptly within few weeks after an acute viral infection. The peak age incidence is around three years. The platelet count tends to be very low and usually below 20,000/uL. The child may present with extensive skin purpura, superficial bleeding and epistaxis. Apart from the bleeding, which is seldom sufficient or chronic to cause severe anemia, the child is usually in a good general health. Spleen might be just palpable in ITP although this is not essential for diagnosis. A very important diagnostic parameter is increased numbers of megakaryocytes in the bone marrow indicating that the low platelet count is from peripheral destruction. Sometimes megakaryocytes might not be increased and look normal. Bone marrow examination should be done to rule out leukemias and confirm the diagnosis of ITP. Some authorities doubt the necessity of marrow examination in typical cases without other elements of marrow failure.

More than 80% of children with acute ITP will remit spontaneously and permanently and no treatment is usually indicated other than reassurance of the family and avoidance of injury. Many reputable places now treat all children with ITP because of the 1% incidence of cerebral bleeding.

In contrast to acute childhood ITP, the disease in adults (chronic adult ITP) behaves differently. It predominantly affects young adult women and usually has an insidious onset without an obvious precipitating cause. The biggest problem with ITP in adults is its tendency for chronicity. The disease might go on for months if not years or lifetime. The spleen is a definite culprit in this type of ITP as it is responsible for the production of the antibodies that sensitize the platelets; platelet-coated antibodies are then destroyed by the splenic macrophages. No wonder splenectomy is so effective in the treatment of these patients.
Thrombocytopenia leads to a positive feedback stimulation of the bone marrow to produce more platelets. The marrow diagnostically shows increased numbers of megakaryocytes with predominance of early forms. Platelets produced by these young megakaryocytes tend to be larger than normal (giant) with more hemostatic granules. That is why these patients do not bleed extensively despite low platelet counts. A common mistake in the management of these patients is to give them platelet concentrate as a primary measure. These patients produce tens of times more platelet than an average person (although this view is challenged lately “2007”) and do not need platelet transfusion. It is more important to suppress the autoimmune production of antibodies by steroid than giving them platelets. It extreme emergency, massive platelet transfusion might be warranted.

Platelets are very important part in the formation of the primary hemostatic plug and their reduction or malfunction can cause superficial purpuric type of bleeding. Purpura means purple spots of hemorrhage in the skin or the mucus membrane. If these spots are tiny they are called “Petichae”. Larger ones of up to 0.5 cm in diameter are called “purpura”. “Bruises” are larger skin hemorrhages that might extend to inches in diameter. More superficial and extensive skin bleeding might be called “ecchymosis”. In severe thrombocytopenia, subcutaneous “hematomas” might be the presenting feature. Mucus membrane bleeding can cause epistaxis, menorrhagia or GIT bleeding.

As mentioned above, Steroid is the mainstay of treatment. In children, intravenous immunoglobulin should be given initially. Splenectomy is the treatment of choice in more chronic cases. In refractory cases even chemotherapy might be used. Occasional patients do not respond to any treatment and live with their very low platelets for years.

III. COAGULATION DISORDERS

Majority of clotting disorders are inherited. These are not common disorders but they are important because the life-long burden, which they impose on those who inherit them, can now be considerably lightened by treatment. Unfortunately even this statement is historically wrong because many hemophiliacs died from HIV infection due to overzealous blood product transfusion.

The various clotting defects are due to inherited mutations of the genes responsible for the synthesis of the specific proteins, which are the clotting factors.

HEMOPHILIA (A): Legg, in 1872, defined Hemophilia as “A congenital and lifelong tendency to hemorrhage into muscles and joints”. This is still one of the best definitions for the disease.

Hemophilia is the most common hereditary disorder of blood coagulation. The inheritance is sex linked (it is the third commonest X-linked disorder). One fourth of patients have no family history and presumably result from fresh spontaneous mutation. The incidence of hemophilia is in the order of 1 in 10,000 population (1 in 5,000 male births). Hematologically, I was carrying of one million population in the Asir of Saudi Arabia, and nearly had one hundred patients in nearly eleven families. That meant that the incidence was just right.

The defect in hemophilia is an absence or low level of plasma factor VIII clotting activity (VIII:c). It appears likely that there is either defective synthesis of this part of the factor VIII or synthesis of a structurally abnormal molecule. In this disorder there is a normal amount of the big portion of factor VIII, which is called von Willebrand Factor (vWF) and is involved in platelet-vessel wall interaction.
CLINICAL FEATURES OF HEMOPHILIA: This failure of the hemostatic mechanism leads to deep-seated bleeding (joints, muscles, brain, retroperitoneum, etc) rather than the superficial purpura of thrombocytopenia, vessel wall abnormalities or vWD.

Hemophiliacs usually present with bleeding, especially after circumcision, which is usually the first hemostatic challenge to these male infants in this part of the world. Recurrent painful bleeding into the joints (hemarthrosis) is the hallmark of hemophilia. This gradually leads to progressive deformity and crippling.

The clinical severity of the disease correlates well with the extent of the coagulation factor deficiency. Severe patients have less than 1% of factor VIII:c and usually present with spontaneous and repeated deep-seated bleeding. Moderate (Factor VIII:c between 1 and 5%) and mild (5-20%) hemophiliacs are less symptomatic but still can bleed extensively after trauma or surgery.

Bleeding into the joint, usually knee, ankle and elbow, causes severe pain, tenderness, warmth and distention. Chronic repetition of this process leads to synovial hypertrophy, degenerative joint changes and mechanical derangement of the articular surfaces. Disuse of the surrounding muscles will lead to atrophy and weakness. The articular surfaces will be lost with demineralization of the bone, bone lipping and osteophyte formation. The final result in poorly treated patients is fixation of the affected joints with flexion deformities. In clinical terms that means crippling of the patient. Incomplete resolution of hemorrhages into soft tissue and bone can cause pseudo-tumor formation. The treatment of hemophilia A is by transfusion of factor VIII concentrate.

HEMOPHILIA (B) or CHRISTMAS DISEASE

This is also a sex-linked inherited coagulation disorder that differs from Hemophilia A by being due to deficiency of factor IX. Presentation is very similar to that of hemophilia A but treatment is with factor IX rather than factor VIII. The incidence is one fifth of that of hemophilia A.

Both hemophilia A & B affect the male sex but are transmitted through female carriers. All the sons of a hemophiliac father are normal but all his daughters are carriers. The chance of inheriting the disease from a carrier mother is one in two for sons; that means half of the sons of a carrier mother are hemophiliacs. The chance of inheriting the gene (becoming a carrier) from a carrier mother is also one in two for daughters. Full female hemophiliacs are rare. Female carriers have around 50% factor VIII:c and are usually asymptomatic.

HEMOPHILIA “A” or “B”

<table>
<thead>
<tr>
<th></th>
<th>VIII, IX Level</th>
<th>% all Hph. A</th>
<th>% all Hph. B</th>
<th>Onset AGE</th>
<th>Neonatal Symptoms</th>
<th>M. &amp; J. Bleed</th>
<th>CNS Bleed</th>
<th>Tooth Extra</th>
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<tbody>
<tr>
<td>SEVERE</td>
<td>&lt; 1%</td>
<td>70%</td>
<td>50%</td>
<td>&lt;1 yr</td>
<td>PCB+++ ICH+</td>
<td>Spont.</td>
<td>High</td>
<td>Usual</td>
</tr>
<tr>
<td>MODERATE</td>
<td>1-5%</td>
<td>15%</td>
<td>30%</td>
<td>1-2 yr</td>
<td>PCB+++ ICH+-</td>
<td>Minor Tr</td>
<td>Mod.</td>
<td>Common</td>
</tr>
<tr>
<td>MILD</td>
<td>&gt; 5%</td>
<td>15%</td>
<td>20%</td>
<td>2-adult</td>
<td>PCB - ICH-</td>
<td>Maj. Tr</td>
<td>Rare</td>
<td>Often</td>
</tr>
</tbody>
</table>

PCB: Post-circumcision Bleeding  ICH: Intra-cranial Hemorrhage
Upward of one third of hemophiliacs do not have excessive post-circumcision bleeding.

**FACTOR VIII**: Prompt, early & sufficient replacement with factor VIII is the mainstay of treatment in hemophilia.

<table>
<thead>
<tr>
<th>Factor VIII</th>
<th>LOW PURITY</th>
<th>INTER. PURITY</th>
<th>HIGH PURITY</th>
<th>ULTRA PURITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA (U/mg Protein) (Specific Activity)</td>
<td>&lt;5</td>
<td>1-10</td>
<td>50-100</td>
<td>3000</td>
</tr>
<tr>
<td>Product</td>
<td>CRYO-PRECIPITATE</td>
<td>Humate-P Profilate-OSD</td>
<td>Alphanate Koate-HP</td>
<td>*Plasma-derived, MoAb-purified *Recombinant F VIII</td>
</tr>
</tbody>
</table>

The amount of factor VIII given depends on the type of bleeding and the half-life of factor VIII.

For **Joint & muscle** bleeding, 50% level (25 U/Kg) is satisfactory. It can be repeated as needed. Rest and immobilization of the joint initially & then physiotherapy after the bleeding stopped are essential.

Bleeding from **oral mucosa** needs 50% level initially. Saliva has fibrinolytic effect and Antifibrinolytic agents are sufficient after the initial dose.

For **Epistaxis**, 100% level is needed initially and then 30% until healing occurs. Local measures are important.

**GIT & GUT** bleeding also need 100% level initially and then 30% until healing occurs.

**CNS** bleeding needs 100% level initially and the 50-100% for two weeks.
Surgery & Trauma need 100% initially and 50% until wound healing begins. Level should be kept at around 30% until healing is complete.

**von Willebrand Disease (vWD)**

vWD is a common bleeding problem affecting ~ 1% of the population. It is also due to a factor VIII defect, but it is the big portion of factor VIII (von Willebrand Factor = vWF) that is missing or reduced. vWF is produced by the endothelium and platelets and is under autosomal control rather than being X-linked. That is why vWD can affect both sexes.

This disease was first described in 1926 by von Willebrand and has been found to be different from hemophilia because the bleeding is purpuric rather than deep-seated. This is because factor VIII:vWF is essential in the primary hemostatic plug formation by bridging the platelet to the injured blood vessel wall.

Clinically, bruising and mucus membrane bleeding is common and menorrhagia is characteristic. Hemarthrosis or deep-seated bleeding is not a feature of vWD.

To make matters easier for the student, the bleeding in thrombocytopenia, vessel wall abnormalities and vWD is similar. Hemophilia bleeding is different in being delayed and affecting joints and muscles. In the laboratory, one can differentiate between the two diseases by doing “Bleeding Time”. It is prolonged in vWD but normal in hemophilia. APTT is also prolonged in hemophilia but might be normal in vWD.

vWF is a highly multimeric structure with high, intermediate and low molecular weight multimers. There are three major types of vWD. Partial quantitative deficiency of all the multimers is called Type 1 vWD. Virtual absence of multimers is Type 3, which is usually homozygous and severe. Qualitative defect of the multimers cause Type 2 vWD. Type 2A is caused by deficiency of the high M.Wt. multimers. Increased affinity of the vWF to Platelet GP 1b causes depletion of the high M.Wt multimers and thrombocytopenia, and is called Type 2B. Type 2M is cause by decreased affinity of vWF to platelet GP 1b, leading to normal multimers “hence M designation”. Type 2N “Normandy” is caused by lack of vWF’s desire to carry the VIII:c, hence a hemophilia picture. Platelet-type vWD is caused by decreased affinity of the platelet GP1b to adhere to vWF.

One piece of advice to all students; you should never ever give intramuscular injections to patients with bleeding disorders, because this might lead to muscle hematoma and bruise formation. Advise your patients to reject all intramuscular injections when given by other doctors who are not aware of their diseases. At least, you should not do your patients harm. Also advise them to avoid inadvertent prescription of Aspirin or similar drugs that paralyze the platelets and cause more bleeding tendency.

Although it is not fair to envy these patients, especially the very mild ones, but they seem to be sort of protected from ischemic diseases like cardiac infarction & CVA because of their defective hemostasis!
Treatment of vWD is by DDAVP, vWF-containing FVIII concentrate and antifibrinolytic drugs. Unfortunately, we only have FFP that is not a rich source of vWF. Cryoprecipitate should be avoided because it cannot be virally inactivated.

“DIC”

DISSEMINATED INTRAVASCULAR COAGULATION

The normal hemostasis depends on a highly integrated process that involves the blood vessels, the blood platelets and a number of plasma proteins (clotting factors) that are collectively responsible for coagulation. Defect or deficiency in any one of these parameters will cause bleeding, while TRIGGERING any of these components might cause thrombosis. When thrombosis is intravascular and disseminated, we call it Disseminated Intravascular Coagulation.

*. The most important of these triggering mechanisms are those associated with liberation of factor III (Tissue Factor) into the circulation, which through the extrinsic pathway of coagulation causes quick and widespread coagulopathy. Most of the body tissues, but particularly Brain, Placenta, Red Cells and granules of the leukemic promyelocytes (M3) are rich in such factor; thus crush injuries involving the brain, brain surgery, abruptio placentae & other obstetric complications, M3 and transfusion reactions might be associated with DIC.

*. Widespread vascular injury with disruption of the endothelial cells and exposure of the subendothelial collagen tissues and microfibrils causes contact activation of the intrinsic pathway as well as provoking platelet adherence. SHOCK and SEPSIS are well-recognized causes of DIC through this mechanism. Actually more than half of our DIC patients are due to septicemia, particularly from gram-negative infections. The lipopolysaccharide outer cover of these bacteria (endotoxin) causes release of TNF-α and other cytokines (IL-1, 6 & 8) that cause thrombin generation.

*. Direct activation of prothrombin or factor X may take place after snakebite, pancreatitis or shock, thus causing DIC.

As a result of widespread clotting and thrombosis, coagulation factors and platelets are consumed. So the hallmark of DIC is bleeding due to triggered thrombosis. In many of these patients the blood fails to clot due to gross fibrinogen deficiency. In DIC platelet count will be low; PT, APTT and TT are prolonged. Because of activation of the fibrinolytic process, Fibrin(ogen) Degradation Products “FDP” and D-Dimers are increased.

DIC can be classified into Compensated, Uncompensated and Clinical DIC.

In more chronic syndromes increased synthesis of coagulation factors may result in normal assays and screening test results. Blood film examination may show fragmentation of the red cells due to their damage when they pass through the fibrin strands in small vessels.

TREATMENT OF DIC: DIC does not only mean bleeding; thrombosis might be as important and can cause multiple organ failure.

By far the most important measure is to eliminate the cause of the DIC. This might be achieved by removing the precipitating cause or extinguishing the triggering mechanism. The deficit in platelet, fibrinogen and coagulation factors should then be
Corrected if the bleeding is severe or alarming. Heparin should only be used under special circumstances and under the supervision of the hematologist.

HOW TO EVALUATE A BLEEDING PATIENT IN THE LABORATORY

Defective hemostasis with abnormal bleeding may result from thrombocytopenia, abnormal platelet function or defective coagulation. Vascular causes of bleeding are not common. A number of simple tests are employed to assess the platelet and clotting component of hemostasis.

(1). Full Blood Count & Blood Film Examination:
As thrombocytopenia is the commonest cause of abnormal bleeding, patients with suspected bleeding disorders should initially have a blood count and blood film examination. In addition to establishing the presence of thrombocytopenia, the cause of this may be obvious, e.g., an acute leukemia.

(2). Bleeding Time (BT):
When the platelet count and film examination are normal, especially if the patient presents with purpuric type of bleeding, BT is done to detect abnormal platelet function (or vessel wall abnormalities). This test is very useful to measure the platelet plug formation in vivo. Now with standardized disposable instruments (Simplate) one can accurately measure the efficiency of the primary hemostatic plug formation. After application of 40 mm Hg pressure on the upper arm with a blood pressure cuff, two 1 mm deep, 1 cm long incisions are made in the flexor surface of the forearm skin. Bleeding should stop in less than 9 minutes, and usually around three to five minutes. Prolongation of BT indicates abnormalities of the primary hemostatic plug formation. Thrombocytopenia, abnormal platelet function (e.g., Uremia, MPD, Myeloma, Bernard Soulier Syndrome, Glanzmann’s Disease, etc), vWD, DIC, TTP/HUS and vessel wall abnormalities can prolong the BT.

(3). Coagulation Screening:
A common leftover problem is ordering “clotting” time. This is a very crude test for the clotting mechanism and is not done in any good hospital. It is replaced now by Coagulation Screen that tests different pathways of the coagulation cascade. These screening tests may provide an assessment of the extrinsic and intrinsic systems of blood coagulation and also the central conversion of fibrinogen to fibrin. In general prolongation of the clotting screens beyond normal control plasmas in the test systems indicate a factor deficiency.

THE PROTHROMBIN TIME (PT) measures the extrinsic system of coagulation (Factor VII) as well as factors common to both systems (Factors X, V, Prothrombin and Fibrinogen). Tissue thromboplastin and calcium are added to plasma and the clotting time is recorded. Normal PT is around 12 seconds.

THE ACTIVATED PARTIAL THROMBOPLASTIN TIME (APTT) measures the intrinsic system factors VIII, IX, XI AND XII in addition to factors common to both systems. An activator (Kaolin), a platelet surface substitute (Cephalin) and calcium are added to the test plasma and the clotting time is recorded. Normal APTT is between 30 to 40 seconds.

THROMBIN TIME (TT) measures the time needed to clot the fibrinogen present in the test plasma after adding the thrombin reagent. It is prolonged in fibrinogen deficiency or abnormality. The normal TT is around 10 seconds.

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<thead>
<tr>
<th>DISEASE OR FACTOR DEFICIENCY</th>
<th>PT</th>
<th>APTT</th>
<th>TT</th>
<th>BLEEDING TIME</th>
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<tr>
<td>HEMOPHILIA</td>
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<td>PROLONGED</td>
<td>NORMAL</td>
<td>NORMAL</td>
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<td>Vwd</td>
<td>N</td>
<td>N OR P</td>
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<td>P</td>
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<td>VII</td>
<td>P</td>
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<td>X, V &amp; II</td>
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COAGULATION

TF = Tissue Factor
APC = Active Protein C