Bleeding disorders

- Vascular abnormalities
- Platelet disorders
- Clotting factor abnormalities
- DIC
Hemostasis

BV Injury

Blood Vessel Constriction

Platelet Activation

Coagulation Activation

Primary hemostatic plug

Plt-Fusion

Tissue Factor

Reduced Blood flow

Stable Hemostatic Plug

Thrombin, Fibrin

Neural
Hemostasis

Platelets & vessel wall (Primary hemostasis)
- Thrombocytopenia
- Von willibrands disease
- Drug induced platelet dysfunction

Coagulation & thrombosis (Secondary hemostasis)
- Hemophilia A
- Hemophilia B
- Vitamin K deficiency
- Other coagulation factors (Deficiency (v, vii, x, xiii), Protein c, s, antithrombin III)

Antiplatelets
- Aspirin
- Thienopyridines (ticlopidine, clopidogrel)
- GpIIa/IIIb antagonists (abciximab, eptifibatide, tirofiban)

Anticoagulant
- Heparin (UF, LMWH)

Fibrinolytic drugs
- STK, Urikinase, TPA
# Primary vs secondary hemostasis

<table>
<thead>
<tr>
<th>Clinical manifestation</th>
<th>Defects of primary hemostasis</th>
<th>Defects of secondary hemostasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>immediate</td>
<td>Delayed -hrs/days</td>
</tr>
<tr>
<td>site</td>
<td>Superficial mucosal bleed</td>
<td>Deep –joints, muscle,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hematoma, hemarthrosis</td>
</tr>
<tr>
<td>Physical finding</td>
<td>Petechiae, ecchymosis</td>
<td></td>
</tr>
<tr>
<td>Treatment response</td>
<td>immediate, local Measures</td>
<td>Require sustain</td>
</tr>
<tr>
<td></td>
<td>effective</td>
<td>Systemic therapy</td>
</tr>
</tbody>
</table>
Disorders of Hemostasis

- **Vascular disorders** –
  - Scurvy, easy bruising, Henoch-Schonlein purpura.

- **Platelet disorders**
  - **Quantitative** - Thrombocytopenia
  - **Qualitative** - Platelet function disorders – Glanzmans, von Willebrand disease

- **Coagulation disorders**
  - **Congenital** - Haemophilia (A, B)
  - **Acquired** - Vitamin-K deficiency, Liver disease

- **Mixed/Consumption:** DIC
HSP/Anaphylactoid purpura

- Self limited type of vasculitis
- Children & young adults
- Purpuric /urticarial rash on extensor surface of arms, legs & buttocks
- Polyaarthralgias/arthritis
- Colicy abdominal pain
- Hematuria (focal glomerulitis)
- Coagulation parameters are normal
- Treatment – glucocorticoids (symptomatic)
Thrombocytopenia

**Decreased marrow production**  
eg  
Marrow aplasia, infiltration with malignant cells, **drugs**

**Splenic sequestration**  
eg  
portal hypertension, splenic infiltration with tumor cells, myeloproliferative & lymphoproliferative disorders

**Accelerated destruction**  
**HUS**  
Immunological - viral (dengue), bacterial infection  
Drugs , Idiopathic - **ITP**
**ALGORITHM FOR THROMBOCYTOPENIA EVALUATION**

1. **Platelet count < 150,000/μL**
   - **Hemoglobin and white blood count**
     - Normal
     - Abnormal
       - **Bone marrow examination**
       - **Peripheral blood smear**
         - **Platelets clumped**: Redraw in sodium citrate or heparin
         - Normal RBC morphology; platelets normal or increased in size
         - Fragmented red blood cells
           - **Microangiopathic hemolytic anemias** (e.g., DIC, TTP)
           - Consider:
             - Drug-induced thrombocytopenia
             - Infection-induced thrombocytopenia
             - Idiopathic immune thrombocytopenia
             - Congenital thrombocytopenia

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Drugs causing thrombocytopenia

- **Chemothreapeutic agents**  Carboplatin, alkylating agents, anthracyclines, antimetabolites
- **Antibiotic**  sulfonamides, penicillins, cephalosporins
- **Heparins** –  UF
- **Antihypertensive** –  thiazide diuretics, ACE inhibitors
- **Alcohol**

Best proof of drug induced etiology is a prompt rise in platelet count when suspected drug is discontinued.

**Treatment**  - stop culprit drug (recover within 7-10 days)
  - platelet count <10000 & bleeding
  - glucocorticoids
  - plasmapharesis/platelet transfusion
Heparin-Induced Thrombocytopenia (HIT)

- **Seen in** 3-5% of patients treated with *unfractionated* heparin
- thrombocytopenic after 1-2 weeks of Rx
- **Caused by** IgG antibodies against *platelet factor 4/heparin complexes* on platelet surfaces
- **Exacerbates** thrombosis, both arterial and venous (in setting of severe thrombocytopenia)
  - Antibody binding results in platelet activation and aggregation.
- **Rx** - cessation of heparin
Acute ITP

• Common in children, follows recovery from viral exanthem/URTI

• Sudden onset & thrombocytopenia is often severe.

• 60% recover within 4-6 wks & >90% within 3-6 months

• Mechanism is by formation of immune complex containing viral antigens & formation of antibodies against viral antigens which cross reacts with platelets & lead to their immunological destruction
Chronic ITP

- Common in adults (20-40 yrs) – F/M 3:1
- Insidious onset & persist for several years
- Formation of antiplatelet antibodies synthesized in spleen
- Sensitized platelet are destroyed in spleen
- Clinical features – petechiae, hemorrhage, easy brusing, mucosal bleeding from gums, malena
- Lab – thrombocytopenia, BF-large platelet,
  - marrow - ↑ no of megakaryocyte with large non lobulated single nuclei
  - Platelet survival studies - ↓ life span
  - Coombs test - antiplatelet IgG antibody

Treatment
- <10% cases recover spontaneously
- Steroid prednisolone 60mg/d x 4-6 wks
- Immunosuppressive – danazole,
  - azathioprine, cyclophosphamide, vincristine, vinblastin, cyclosporin
- Splenectomy
- IVIg
<table>
<thead>
<tr>
<th>Feature</th>
<th>Acute</th>
<th>Chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age / Sex</td>
<td>Children</td>
<td>Adult/Female</td>
</tr>
<tr>
<td>Onset</td>
<td>Abrupt</td>
<td>Gradual</td>
</tr>
<tr>
<td>Predisposing Factors</td>
<td>Viral infection/ vaccine</td>
<td>-</td>
</tr>
<tr>
<td>Duration</td>
<td>&lt;2 months</td>
<td>&gt;6mnoths</td>
</tr>
<tr>
<td>Pathogenesis</td>
<td>-</td>
<td>IgG against Platelet GP</td>
</tr>
<tr>
<td>Peripheral smear</td>
<td>Thrombocytopenia &amp; Giant PLTS</td>
<td>Same</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>Normal or ↑Megakaryocytes</td>
<td>Same</td>
</tr>
<tr>
<td>Feature</td>
<td>Acute</td>
<td>Chronic</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>--------------------------------------------</td>
<td>-----------------------------------------</td>
</tr>
<tr>
<td>Tests</td>
<td>Prolonged BT &amp; Normal PT &amp; PTT</td>
<td>Same</td>
</tr>
<tr>
<td>Complication (most dangerous)</td>
<td>Intracranial bleed</td>
<td>Same</td>
</tr>
<tr>
<td>Clinical course</td>
<td>Spontaneous remission</td>
<td>No</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLT. Transfusion</td>
<td>If &lt;20,000</td>
<td>If &lt;50,000</td>
</tr>
<tr>
<td>Splenectomy</td>
<td>No</td>
<td>Yes (refractory cases)</td>
</tr>
</tbody>
</table>
Thrombotic Thrombocytopenic purpura (TTP)

- Fulminant often lethal disorder initiated by endothelial injury & subsequent release of procoagulant factors eg Vwf
- Cause pregnancy, metastatic cancer, mitomycin C, Chemotherapy, HIV, drugs like ticlopidine

**Clinical feature**
- pentard
  - hemolytic anaemia
  - thrombocytopenia
  - neurological finding
  - renal failure
  - fever

**Treatment**
- Removal/correct ppt factors
- Exchange transfusion/intensive plasmapharesis
- Infusion of fresh frozen plasma

Most patient survive a/c illness recover completely with no residual renal or neurological disease
Hemolytic uremic syndrome (HUS)

- Disease of infancy/early childhood

**Clinical feature**   Tetrad
  
  - fever
  - thrombocytopenia
  - microangiopathic hemolytic anemia
  - a/c renal failure

- Onset is preceded by minor febrile viral illness
- Epidemic related to infection E.coli (0157H7) has been documented

**Treatment**

- No therapy effective
- Symptomatic – dialysis for a/c renal failure
- 5%mortality in children
- 10-15% develop CRF
## Thrombotic Microangiopathies

<table>
<thead>
<tr>
<th>HUS</th>
<th>Feature</th>
<th>TTP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Neurological symptoms</td>
<td>Prominent</td>
</tr>
<tr>
<td>Prominent</td>
<td>Acute Renal Failure</td>
<td>Less prominent</td>
</tr>
<tr>
<td>Children</td>
<td>Age</td>
<td>Adults</td>
</tr>
<tr>
<td>Infection (E.coli O157 : H7)</td>
<td>Cause</td>
<td>Genetic (vWF metalloprotease-ADAMTS 13) deficiency</td>
</tr>
<tr>
<td>Supportive</td>
<td>Rx.</td>
<td>Plasma Exchange</td>
</tr>
<tr>
<td>Good in children</td>
<td>Prognosis</td>
<td>Better with plasma exchange</td>
</tr>
<tr>
<td>Bad in adults</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Von Willibrands disease

- Most common inherited bleeding disorder
- vonWillibrand factor – heterogeneous multimeric plasma glycoprotein
- Facilitates platelet adhesion
- Plasma carrier for factor VIII (antihemophylic factor)
- Normal plasma vWF level is 10mg/l
- Modest reduction in plasma vWF conc. decreases platelet adhesion & cause clinical bleeding
- Mild cases bleeding occurs only after surgery or trauma
- More severely affected patients have spontaneous epitaxis or oral mucosal, git, genitourinary bleeding
<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
<th>Type III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Most common</td>
<td>Less common</td>
<td>Least common</td>
</tr>
<tr>
<td>inheritance</td>
<td>AD</td>
<td>AD</td>
<td>AR</td>
</tr>
<tr>
<td>vWF</td>
<td>&lt;50%</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>RC activity</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Multimer pattern</td>
<td>N</td>
<td>↓</td>
<td>A</td>
</tr>
</tbody>
</table>
Lab

- BT- Prolonged
- N -Platelet count
- Reduced plasma vWF concentration
- Defective platelet aggregation with ristocetin.
- Reduced factor VIII activity
Treatment

- Factor VIII concentrate infusion (cryoprecipitate)
- During surgery/trauma factor VIII conc. Infusion given BD X 2-3 days
- Minor bleeding responds to single infusion
- Desmopressin effective only in type I, can be given intravenously or by an intranasal spray (1.5 mg/mL). The peak activity when given intravenously is approximately 30 min, while it is 2 h when given intranasally. The usual dose is 0.3 g/kg intravenously or 2 squirts (1 in each nostril) for patients >50 kg (1 squirt for those <50 kg).