BLEEDING DISORDERS
Platelet Disorders
Petechiae, HSP
Kasabach- Merritt, TAR
Thrombocytopenia absent radius syndrome (TARS)

- Rare autosomal recessive disease
- Clinical presentation
  - Thrombocytopenia
  - Absent radius
  - Congenital heart disease – TOF, ASD, VSD
  - Other
    - Eosinophilia
    - Milk protein allergy
    - Leukemoid reaction
    - Intellectual disability

Outcome:
Platelet number improve in the first year. Transfusion support for bleeding.
- Platelet destruction
  - Immune
    - ITP
    - Drugs
  - Non-Immune
    - TTP
    - HUS
    - DIC
    - Infection
    - Cardiac
Acute ITP

- Usually acute onset; immune mediated; post viral
- Peak 2-5 years of age,
- PE –no lymphadenopathy (LN), hepatosplenomegaly.
- CBC- other cell lines normal, large plts on smear
- Treat if plt< 10,000 or wet ITP,
- Treat- IVIG best response, 48-72 hours; blocks Fc receptors, SE
  - Anti-D (WInRho)- Rh+, hemolysis, quick response
  - Steroids good response, block phagocytosis, reduces antibodies, SE, inexpensive, need BM
- BM- Increased megakaryocytes, otherwise normal
- Chronic- If >6 months, F>M, older, unpredictable prognosis
Allo-Immune Thrombocytopenia

- Allo or Iso-Immune: Normal platelet count in mother
- Similar to Rh disease; PL A1 antigen/ Zw-a negative mother.
- 97% of population is PL A1 positive
- Sensitization early in pregnancy
- Plt function defect because Anti-PL-A1 interferes w/aggregation.
- Severe bleeding more likely; first born affected
- Recovery in 2-3 weeks
- Mother’s washed (PLA1 neg) platelets; IVIG; Ultrasound; Steroids
Hemolytic uremic syndrome

• Background
  – Non-immune
  – Microangiopathic hemolytic anemia
  – *E. coli* O157:H7 is a very common cause
  – *Shigella dysenteriae* type I is another cause

• Clinical presentation
  – Usually children between 4 months and 2 years
  – Infection with gastrointestinal symptoms—vomiting and often bloody diarrhea
  – Development of oliguria, hypertension, renal failure
BERNARD-SOULIER SYNDROME

- Autosomal recessive
- Severe platelet dysfunction
- Thrombocytopenia
- Giant platelets
- Markedly prolonged bleeding time
GLANZMANN THRBOATHENIA

- Autosomal recessive
- Abnormal function of GPIIb/IIIa complex (fibrin receptor)
- Severe platelet dysfunction → prolonged bleeding time
- Normal platelet count
- Aggregation studies show abnormal or absent aggregation
- Treatment
  - Platelet transfusion

Hermansky-Pudlak Syndrome
- Common in Puerto-Rican
- Oculocutaneous albinism
- Moderately severe bleeding
Kasabach-Merrit Syndrome

- Vascular tumor
  - Thrombocytopenia
  - Hemolytic anemia
  - Coagulopathy
- Do not regress spontaneously
- Very aggressive
- Can be fatal
COAGULATION DISORDERS
**Normal**

- Factor VIII/vWF complex
- vWF
- VIII:C
- Gene for VIII:C
- Gene for vWF
- vWF carrier protein protects VIII:C from degradation. It is released by activated thrombin.

**Haemophilia A**

- Gene defect
- Defective synthesis of VIII:C

**von Willebrand disease**

- Gene defect
- Rapid degradation of VIII:C in the absence of vWF.
HEMOPHILIA

- X-linked recessive
  - Factor VIII (Hemophilia A) – 85%
  - Factor IX (Hemophilia B) – 10-15%
- Bleeding may start from birth
- Classifications
  - Severe hemophilia <1%
  - Moderate hemophilia 1-5%
  - Mild hemophilia >5%
- Clinical Presentation
  - Easy bruising
  - Intramuscular (deep) hematomas – localized pain and swelling

X-linked recessive
- Primarily boys
- Girls are typically asymptomatic carriers

Normal values for FVIII assays are 50-150%
HEMOPHILIA

• Clinical Presentation
  - Hemarthroses
    • Hallmark of hemophilia
    • Ankle most common
    • Knee and elbow increasing frequency with age

• Laboratory
  - PTT is usually 2-3 times upper limit of normal
  - PT, bleeding time, platelet count normal
  - Specific assay for factor VIII or IX will confirm the diagnosis
<table>
<thead>
<tr>
<th>Factor VIII:C</th>
<th>Severity</th>
<th>Bleeding tendency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1%</td>
<td>Severe</td>
<td>Spontaneous joint/muscle bleeds</td>
</tr>
<tr>
<td>1–5%</td>
<td>Moderate</td>
<td>Bleed after minor trauma</td>
</tr>
<tr>
<td>&gt;5–40%</td>
<td>Mild</td>
<td>Bleed after surgery</td>
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</tbody>
</table>
HEMOPHILIA

• Treatment
  – Factor replacement
    • Mild to moderate bleeding – raise factor to 35%-50%
    • Severe or life threatening hemorrhage – raise level to 100%
  – Lifelong prophylaxis usually started with first joint hemorrhage
  – DDAVP may be sufficient in mild forms of hemophilia
  – Avoidance of high risk behavior

• Complications
  – Severe hemorrhage
  – Arthropathy
Figure 22.16 Severe arthropathy from recurrent joint bleeds in haemophilia. The aim of modern management is to prevent this from occurring.
Management
Recombinant FVIII concentrate for haemophilia A
recombinant FIX concentrate for haemophilia B.
given by prompt intravenous infusion whenever there
is any bleeding.
Raise to 30%
minor bleeds and simple joint bleeds.
Raise to 100%
Major surgery or life-threatening bleeds then
maintained at 30–50% for up to 2 weeks to prevent secondary haemorrhage.
regular infusion
usually 8–12-hourly for FVIII,
12–24-hourly for FIX, or by continuous infusion) and by
closely monitoring plasma levels.
Avoid
Intramuscular injections,
aspirin and non-steroidal anti-inflammatory drugs
should be avoided in all patients with haemophilia.
Prophylactic FVIII is given to all children with severe haemophilia A to further reduce the risk of chronic joint damage by raising the baseline level above 2%.

**Primary prophylaxis** usually begins at age 2–3 years.
given two to three times per week.
Desmopressin (DDAVP) may allow mild haemophilia A to be managed without the use of blood products. It is given by infusion and stimulates endogenous release of FVIII:C and von Willebrand factor (vWF). Adequate levels can be achieved to enable minor surgery and dental extraction to be undertaken. DDAVP is ineffective in haemophilia B.
**Box 22.5 Complications of treatment of haemophilia**

**Inhibitors, i.e. antibodies to FVIII or FIX**
- Develop in 5–20%
- Reduce or completely inhibit the effect of treatment
- Require the use of very high doses of factor VIII or bypassing agents (e.g. FVIIa) for treating bleeding
- May be amenable to immune tolerance induction

**Transfusion-transmitted infections**
- Hepatitis A, B and C
- HIV
- ?Prions

**Vascular access**
- Peripheral veins – may be difficult to cannulate
- Central venous access devices may become infected or thrombosed.
von Willebrand disease

- Family of bleeding disorders caused by an abnormality of the von Willebrand factor (vWF), carrier protein for Factor VIII
  - can range from almost undetectable to severe bleeding propensity
- vWF binds on platelets to its specific receptor *glycoprotein Ib* and acts as an adhesive bridge between the platelets and damaged subendothelium at the site of vascular injury
  - i.e. causes platelets to stick
- vWF also protects FVIII from degradation
von Willebrand disease

- Type 1 (70-80% of vWFD) is quantitatively less of qualitatively normal vWF
  - autosomal dominant, variable penetrance
  - generally mild, can be asymptomatic and vary with time

- Type 2A and 2B (~15%) have qualitatively abnormal vWF
  - autosomal dominant
  - moderate severity

- Type 3 most severe, low vWF and Factor VIIIc in plasma, vWF absent on platelets
  - autosomal recessive, consanguinity an issue
  - possible mild disease in heterozygotes
von Willebrand disease

- **History**–
  - often mild bleeding (e.g. bruising, epistaxis, primary menorrhagia)

- **Lab**–
  - CBC us. normal, prolonged bleeding time, PT normal, aPTT variably increased
  - vWF and Factor VIII variably decreased

- **Treatment**–
  - often, none needed
  - DDAVP increases vWF and Factor VIII
  - Factor VIII plasma concentrates for severe
VON WILLEBRAND DISEASE (vWD)

- Keywords
  - Recurrent, prolonged mucocutaneous bleeding
  - Family history of mucocutaneous bleeding

- Study of choice
  - vWF assay activity or vWD Panel

(vWF) Carrier protein for factor VIII

Von Willebrand factor (vWF)

Promote platelet adhesions and aggregation
VON WILLBRAND DISEASE

Treatment

- Based on subtype and trial of DDAVP
  - Type 1 usually treated with DDAVP (most common type)
    - DDAVP 0.3 microgram/kg increases the level of vWF and factor VIII 3-5 fold
  - Type 2B and 3 primarily treated with FVIII: vWF concentrates
  - Platelet type treated with platelet transfusions
Thrombophilia

- Clinical presentation
  - A child present with a clot

- Causes
  - Inherited
    - Protein C deficiency
    - Protein S deficiency
    - Anti-thrombin deficiency
    - Factor Leiden mutation
  - Acquired
    - Cancer
    - Antiphospholipid antibodies
    - Central venous catheter