HAEMOPHILIAS AND VON WILLEBRAND DISEASE

HAEMOPHILIAS ARE BLEEDING DISORDERS DUE TO DEFICIENCY IN ONE OF THE CLOTTING FACTORS PRESENT IN THE CLOTTING CASCADE → MOST COMMON ARE HAEMOPHILIA A (FACTOR VIII DEFICIENCY) AND HAEMOHILIA B (FACTOR IX DEFICIENCY)

VON-WILLEBRAND DISEASE (VWD) IS A RELATED HEREDITARY DEFICIENCY OF VON WILLEBRAND FACTOR (VWF)

TYPICALLY PRESENT IN EARLY LIFE, BUT PATIENTS WITH MILD FORMS MAY BE UNAWARE OF A BLEEDING DISORDER UNTIL STRESSED BY SIGNIFICANT TRAUMA OR DEVELOPMENT OF ANOTHER HAEMOSTATIC DISORDER

PATTERN OF BLEEDING SUGGESTS AETIOLOGY:

- **EASY BRUISING, GINGIVAL BLEEDING, EPISTAXIS, HAEMATRUIA, GI BLEEDING OR MENORRHAGIA LIKLEY A PLATELET PROBLEM**
- **PATIENTS WITH SPONTANEOUS DEEP BRUISES, HAEMARTHROSIS, RETROPERITONEAL BLEEDING OR INTRACRANIAL BLEEDING ARE MORE LIKLEY TO HAVE A COAGULATION FACTOR DEFICIENCY**
- **VWD WILL PRESENT WITH FEATURES OF BOTH PLATELET DYSFUNCTION AND COAGULATION DEFICIENCY**

HAEMOPHILIA:

- A disorder of coagulation caused by a deficiency in a circulating plasma protein
- Haemophilia A → deficiency in factor VIII, 1 in 10,000 males
- Haemophilia B → deficiency in factor IX, 1 in 25,000 males
    - These two forms make up 99% cases and are clinically indistinguishable from one another
    - Both are x-linked disorders, hence they are overwhelmingly a disease of men, with women typically being asymptomatic carriers
    - One-third of Haemophilia A and 1/5 of new cases of haemophilia B arise from spontaneous gene mutation
- Individuals with factor activity levels below 1% are classified as having SEVERE DISEASE → experience severe, spontaneous bleeding episodes and bleeding post-trauma that is difficult to control
- Levels of 1-5% → moderate severity, may bleed spontaneously but most often bleed related to traumatic event
    - Levels of 5-40% constitute mild disease and they only bleed post trauma
- BLEEDING IS THE MAJOR COMPLICATION OF HAEMOPHILIA
    - In the past, many haemophiliacs had high rates of HIV and hepatitis due to blood-borne transmission prior to adequate screening of blood donors

CLINICAL FEATURES:

- Both types of haemophilia are characterised by easy bruising and recurrent bleeding into the joints and muscles
- Any trauma or surgery results in prolonged and difficult to control bleeding

Table 230-1 Common Bleeding Manifestations in Patients with Hemophilia

Site	Comments
Hemarthroses	Leads to joint destruction and chronic arthropathy if not adequately treated.
Hematomas	Bleeding into soft tissues or muscle; this bleeding can dissect along fascial planes; most dangerous in the neck (airway compromise), limbs (compartment syndromes), eye (retro-orbital hematoma), spine (epidural hematoma), and retroperitoneum (iliopsoas bleeds and massive blood loss).
Mucocutaneous bleeding	Spontaneous bleeding **uncommon** from the oropharynx, GI tract, epistaxis, or hemoptysis; delayed bleeding after dental extractions is common.
Central nervous system	Intracranial bleeding is the **most** common cause of hemorrhagic death in hemophiliacs of all age groups, with a reported 34% mortality; subdural hematomas occur spontaneously or with minimal trauma.
Hematuria	Common, usually not serious, and the source is rarely found.
Pseudotumor	Erosion into adjacent bone that resemble bone cysts. These result from unresolved or undertreated hematomas; usually have to be removed surgically.

- Any child who presents with excessive bruising or with significant bleeding in to their joints, muscles or CNS that is spontaneous or out of proportion to the history of trauma should be suspected to have haemophilia
    - CHILD ABUSE IS MUCH MORE COMMON THAN HAEMOPHILIA

DIAGNOSIS:

- IN HAEMOPHILIA:
    - Prothrombin time (which measures the extrinsic pathway), will be NORMAL
    - APTT (which measures the intrinsic pathway), will be ABNORMAL
        - May be normal in those with mild disease
        - Bleeding time will be normal in both forms of haemophilia
- SPECIFIC FACTOR ASSAYS CAN BE DONE

TREATMENT:

- GENERAL PRINCIPLES:
    - EARLY AND COMPLETE FACTOR REPLACEMENT IN THOSE WITH LIFE-THREATENING BLEEDING
    - Spontaneous or traumatic bleeding into the neck, tongue, retropharynx or pharynx has HIGH POTENTIAL FOR AIRWAY COMPROMISE
    - Any patient who presents with altered mental state, localising neurological symptoms or new headache or has blunt head injury REQUIRES IMMEDIATE FACTOR REPLACEMENT FOLLOWED BY URGENT HEAD CT
        - If deficit localises to within the spinal cord, MRI is appropriate

    - Complaints of back, thigh, groin or abdominal pain may have bleeding into the retroperitoneum → patients may complain of hip pain and have difficulty straightening their leg
        - Iliopsoas bleed can cause COMPRESSION OF THE FEMORAL NERVE
    - Simple injuries can progress to compartment syndrome ➔ have high index of suspicion
    - One of the most common manifestations of haemophilia is HAEMARTHROSIS ➔ it is important to note that patients can reliably report when bleeding is occurring, even if subtle. DESPITE MINIMAL FINDINGS, PATIENT CONCERNS SHOULD BE TAKEN SERIOUSLY! Prompt treatment can prevent or reduce long-term sequelae of haemophilic arthropathy
    - If an infant has known haemophilia and is persistently irritable, a thorough search for a source of occult bleeding is warranted
    - PAIN CONTROL NEED TO BE AGGRESSIVELY ADDRESSED AS THESE CONDITIONS ARE VERY PAINFUL
    - CVC should not be placed in haemophiliacs without adequate factor replacement (similar rules apply to LP, ABG)
        - Never give IM injections without factor replacement first
    - Avoid NSAIDs
- FACTOR-REPLACEMENT THERAPY:
    - Effective in controlling haemorrhage in haemophilia
    - There are now TWO OPTIONS ➔ recombinant factor replacement or plasma derived and purified factor replacement
        - Lower rates of infection, but higher risk of DIC and can cause paradoxical clotting
    - When major bleeding occurs in the CNS, GIT, neck, throat, in a large muscle or when severe injury is present ➔ factor replacement levels between 80-100% are necessary and will need to continue for days to weeks

Table 230-3 Initial Factor Replacement Guidelines in Severe Hemophilia				
Site	**Desired Initial Factor Level (%)**	**Hemophilia A Initial Dose (units/kg)**	**Hemophilia B Initial Dose (units/kg)**	**Details**
Skin (deep laceration)	—	—	—	Abrasions and superficial lacerations usually do not require factor replacement. Treat with pressure and topical thrombin.
Deep muscle	40–80	20–40	40–60	Admit, monitor total blood loss, watch for compartment syndrome.
				Duration of replacement: 1–5 d.
Joint (hemarthrosis)	30–50	15–25	30–40	Orthopedic consult may be required for splinting, physical therapy, and follow-up.
				Duration of replacement: 1–3 d.
Epistaxis	40–50	20–25	80–100	Local measures should be used.
				Replacement is given until bleeding resolves.
Oral mucosa	50	25	50	Local measures and antifibrinolytic therapy will decrease need for additional factor replacement (see Special Considerations: Oral and Mucosal Bleeding).
Hematuria	50	25	50	Common and typically not severe. Rest and hydration are important.
GI bleeding	100	50	100	Consultation with a gastroenterologist for endoscopy to locate potential lesion is appropriate.
Central nervous system	100	50	100	Treat before CT.
				Early neurosurgical consultation.
				Lumbar puncture requires factor replacement.

- SPECIAL CONSIDERATIONS:
  - ORAL AND MUCOSAL BLEEDING:
    - Common problem ➔ can clean site of inadequate clot, and add a dry topical thrombin on the bleeding site. Replace factors to 80-100% of normal. Antifibrinolytic agents as adjuncts
  - MILD HAEMOPHILIA A:
    - May not always require factor replacement
    - Can be treated with DESMOPRESSIN, which is believed to cause release of vWF from endothelial storage sites. Can be given intranasally. With repetitive use, stores of factor VIII will be depleted.
  - HAEMATURIA:
    - Rest and hydration are important
    - Replace factors to 50% levels
  - INHIBITORS:
    - These are antibodies against replacement factors and tend to occur most commonly in severe haemophiliacs.
    - They interfere with the effectiveness of factor replacement therapy and can cause anaphylaxis during factor administration
    - Inhibitors occur in 10-25% of haemophilia A and 1-2% of B
    - Options for treatment do exist ➔ CLOSE CONSULTATION WITH HAEMATOLOGY RECOMMENDED

- Can give factor VII ➔ this enhances thrombin generation and by binding to activated platelets, it also activates factor X in the absence of tissue factor

Table 230-4 Replacement Therapy for Hemophilia A and B in Patients with Inhibitors

Type of Product*	Hemophilia A Dose	Hemophilia B Dose	Comments
Factor VII concentrates	5000–10,000 units bolus followed by a continuous infusion	Not applicable	Not available in the U.S. Preferred if patient has Factor VII deficiency
Prothrombin complex concentrates; contains factors II, VII, IX, and X; small amount of activation occurs during processing	75–100 units/kg	Approximately 75 units/kg	Thrombotic risk Risk of contamination with other coagulation factors
Octaplex®			
Konyne-80®			
Proplex-T®			
Anti-inhibitor coagulant complex; contains factors II, VII, IX, and X, with Factor VII mainly in an activated form	50–100 units/kg	50–100 units/kg	Thrombotic risk Used in patients with high BIA unit titers and high BIA units antibody response
FEIBA-VH®			
Autoplex-T®			
Recombinant Factor VIIa	90–120 micrograms/kg	90–120 micrograms/kg	No risk of viral transmission
NovoSeven®			
Highly purified Factor IX concentrates	Not applicable	Variable	—
AlphaNine SD®			
Mononine®			
Recombinant Factor IX products	Not applicable	Variable	Product of choice for hemophilia B patients with significant inhibitor activity
BeneFIX®			

VON WILLEBRAND DISEASE:

- vWD is the most common congenital bleeding disorder, present in ~1% of the population
- Classified as below:

Table 230-5 Simple Classification and Treatment of von Willebrand Disease

Type	Frequency	Defect	Treatment
1	70%–80% of cases	All the multimeric forms are present, but in decreased quantity (approximately 20%–50% normal levels)	Desmopressin and, if no response, consider the measures below.
2	10%–15% of cases	The von Willebrand molecule is abnormal and dysfunctional	vWF-containing concentrate or cryoprecipitate if vWF-containing product is not available.
3	<10% of cases	Almost no vWF present	vWF-containing concentrates or cryoprecipitate if vWF-containing concentrate is not available.

- vWF is a glycoprotein that is synthesised, stroed and then secreted by vascular endothelial cells and serves TWO KEY ROLES IN NORMAL HAEMOSTASIS:
    - It is a cofactor for platelet adhesion
    - It is the carrier protein for factor VIII ➔ when vWF is absent, the half-life of factor VIII decreases ➔ hence the clinical presentation is similar to haemophilia
- Circulating vWF does not bind directly to platelets, but when exposed to the subendothelial matrix, it undergoes a structural change, allowing it to bind to PLATELET GLYCOPROTEIN 1B ➔ leads to platelet activation and adhesion to other platelets, as well as to the damaged endothelium

CLINICAL FEATURES:

- Skin and mucosal bleeding symptoms are common in people with vWD ➔ recurrent epistaxis, gingival bleeding, unusual bruising, GI bleeding and menorrhagia in young women
- Haemarthrosis is NOT TYPICAL UNLESS SEVERE DISEASE IS PRESENT

DIAGNOSIS:

- Tests used → bleeding time, APTT, factor VIII activity, vWF antigen and vWF activity
- Prothrombin time should be normal

TREATMENT:

- NON-TRANSFUSIONAL THERAPIES:
    - DESMOPRESSIN ➔ mainstay for most with type I vWD ➔ it induces the release of vWF from storage sites within the endothelium, thus promoting haemostasis. DOSE ➔ 0.3MICROG/KG SC/IV/IN Q12H
        - The response is less with each subsequent dose as vWF storeage sites become depleted
        - Need to fluid restrict to avoid hyponatraemia (ADH effect)
- TRANSFUSIONAL THERAPIES:
    - Plasma derivatives that contain vWF are used for those type I patients who do not respond to desmopressin or have type II or III disease
    - CRYOPRECIPITATE CONTAINS FACTOR VIII AND VWF, BUT HAS HIGHER RISK THAN OTHER BLOOD PRODUCTS FOR VIRAL TRANSMISSION ➔ administration of 10 bags will usually control bleeding
    - Preferred products are factor VIII products that contain multimeric vWF that have undergone viral inactivation processes
    - PLATELETS for those who do not respond to vWF containing plasma products

DISPOSITION AND FOLLOW UP:

- Most patients with vWD who present acutely bleeding can be controlled with desmopressin and local measures

- The unusual patient with almost no vWF activity is treated like a patient with haemophilia