Hemophilia: History, Overview, and Treatment

Lee Ellen Brunson-Sicilia, MHS, MLS(ASCP)CM
Department of Clinical Laboratory Sciences
LSU Health-Shreveport
LBruns1@lsuhsc.edu

Objectives

- Review human hemostasis.
- Discuss hemostatic defects present in hemophilia and the symptoms caused.
- Discuss treatments for hemophilia patients.

Hemophilias, in brief

- Hereditary bleeding disorders
- Deficiencies or defects in proteins involved in blood clotting/coagulation
- Associated with a variety of mutations in genes that control coagulation protein production
- The more decreased the production, the more severe the clinical manifestations.
- Treatments involve replacement of deficient protein and depend on severity of symptoms.

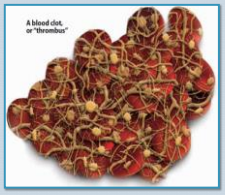
OVERVIEW OF HEMOSTASIS/COAGULATION

Hemostasis defined:

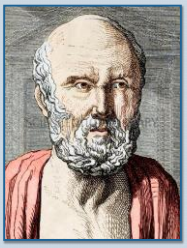
- The property of blood circulation that maintains blood as a fluid within the blood vessels
- The system's ability to prevent excessive blood loss upon injury to vessel(s)

What is a blood clot?

- A gelatinous or semisolid mass of coagulated blood
- Comprised of blood cells (platelets) and fibrin



A little hemostasis history…

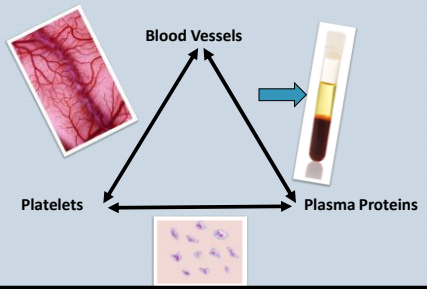


- **Hippocrates – 400BC**
  - Blood of a wounded soldier congealed as it cooled.
  - Bleeding from a small wound stopped as "skin" covered the blood.
  - Bleeding resumed if "skin" was removed.

History, cont.

- 1627 – Mercurialis observed clots in veins at **BODY** temperature.
- 1770 – demonstration that clotting can occur from liquid portion of blood, independent of cells.
- Over time, realization that clotting process is very complex.
- Tests developed to measure clotting time.

Hemostasis involves…



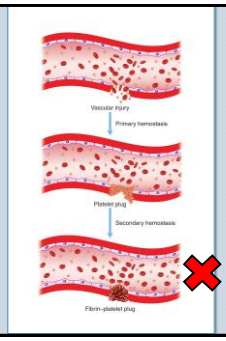
Balance is key!

Hemostasis Overview

- Describes the process involved when blood clots in response to vessel injury.
- Normally, blood flows freely through blood vessels, controlled by physiologic processes.
- Injury severs vessels, causes bleeding.
- Body forms a clot to stop bleeding.
- Clot is broken down when no longer needed.

Three phases of hemostasis

1. **Primary hemostasis** – actions of the blood vessels and platelets (primary platelet plug)
2. **Secondary hemostasis** – actions of protein coagulation factors (secondary fibrin-platelet clot)
3. **Fibrinolysis** – degradation of fibrin clot after cessation of bleeding (degradation of clot)



Types of Bleeding

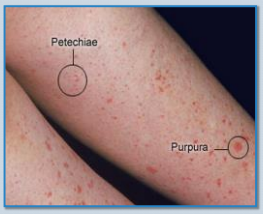
Defects in Primary Hemostasis

- Superficial
- Skin or mucous membranes
  - Epistaxis
  - Gingival mucosa
  - Menorrhagia
  - Petechiae
  - Purpura

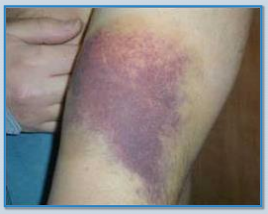
Defects in Secondary Hemostasis

- Internal
- Deeper tissues and joints
  - Hemarthrosis
  - Massive hematomas
  - Deep muscle bleeding
  - Intracranial hemorrhage
  - Excessive bleeding following:
    - Circumcision
    - Dental extraction
    - Intramuscular injections

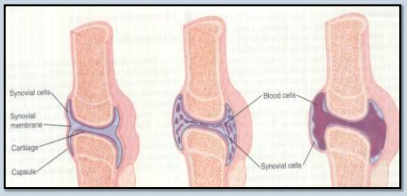
Defects in Primary Hemostasis

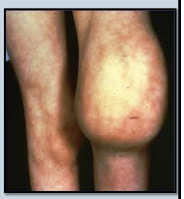


Defects in Secondary Hemostasis

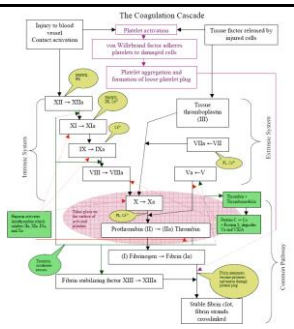


Hemarthrosis

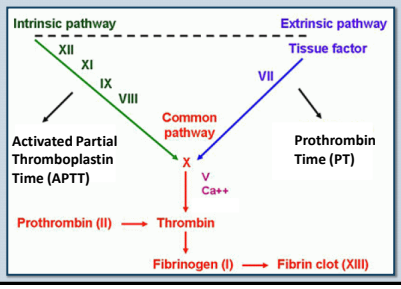




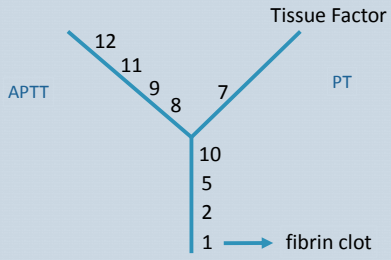
WHAT HAPPENS IN SECONDARY HEMOSTASIS?



Secondary Hemostasis: The Coagulation Cascade



The cascade, simplified…

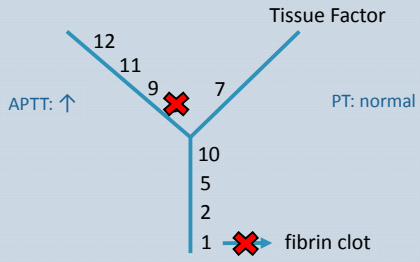


HEMOPHILIAS

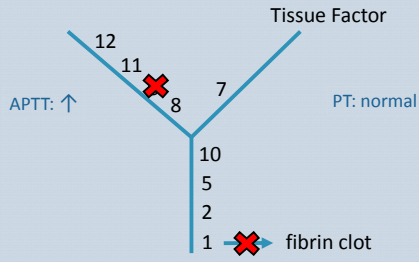
What causes hemophilia?

- Three types—A, B, and C—distinguished by deficient secondary hemostatic protein
  - **Hemophilia A: deficiency of Factor 8 – most common**
  - **Hemophilia B: deficiency of Factor 9**
  - **Hemophilia C: deficiency of Factor 11 – least severe**
- A & B – X-linked recessive: Men affected; women are primarily carriers
- C – autosomal recessive: Men and women affected equally
- Characterized by normal PT and prolonged APTT

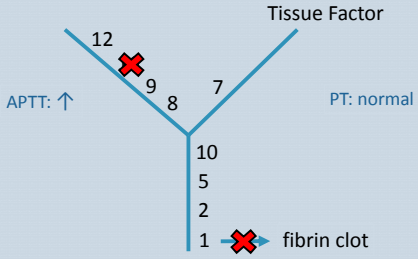
The problem in hemophilia A…



The problem in hemophilia B…

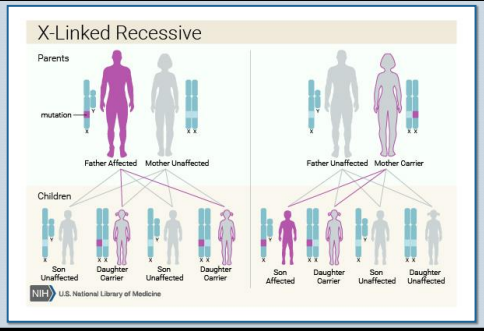


The problem in hemophilia C…



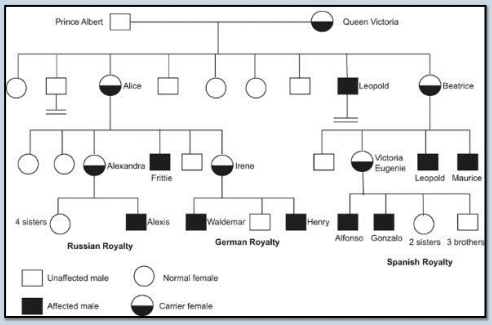
Hemophilia – early history

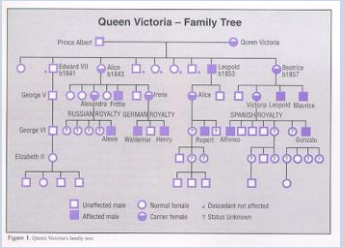
- 2nd century AD – Jewish writings
  - Woman's 3rd son exempt from circumcision if two elder brothers died post-circumcision.
  - A boy forbidden to be circumcised because sons of mother's three sisters died post-circumcision
  - Reports of fatal bleeding after minor surgery in brothers or in maternally related male cousins
- 18th century obituaries and writings
  - Six brothers bled to death after minor injuries; half-siblings by a different mother unaffected
  - A man and two of his sister's sons affected – "bleeders"
- 1820 – "Nasse's Law" – hemophilia only occurs in males but is transmitted through females



"The Royal Disease"

- Queen Victoria was a carrier of Hemophilia B, ruled England 1837-1901
- Had nine children
  - Leopold was affected
  - Alice and Beatrice were carriers
- Caused hemophilia to spread through royal houses of Spain, Germany and Russia





The mechanism becomes clearer

- **1893** – first record of prolonged clotting time of hemophilic blood in tube
- **Prior to 1936,** bleeding tendency was attributed to fragile vessels or platelet defects
- **1936** – Harvard doctors showed that substance extracted from normal plasma could correct clotting problem – "anti-hemophilic factor"

Mechanism, cont.

- **1947** – Argentinian doctor showed that transfusion of one hemophilia patient with blood from another could temporarily correct clotting problem in recipient, and vice versa
  - Suggested two different X-linked hemophilias
  - Hemophilia A, Factor VIII deficiency - much more common
  - Hemophilia B, Factor IX deficiency ("Christmas disease")

Hemophilias A & B

- **X-linked recessive**
- Both FVII and FIX play crucial roles in hemostasis
- Clinical features identical in both, distinguished only in lab
  - Specific factor assays
  - Mixing studies with factor-deficient plasma

Hemophilias A&B, cont.

- Thousands of mutations
- 1/3 of cases develop mutation spontaneously
- Symptoms can be severe, moderate or mild
- Hemarthrosis most common feature of severe disease
- Mild deficiencies may go undetected

Severity of hemophilia

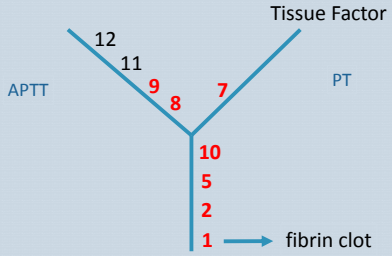
Factor VIII or IX Level, Units/dL	Severity	Symptoms
<1	Severe	Frequent spontaneous hemarthrosis with crippling
		Frequent severe, spontaneous hemorrhage (intracranial, intramuscular)
1–5	Moderate	Bleeding at circumcision
		Infrequent spontaneous joint and tissue bleeds
		Excessive bleeding after surgery or trauma
		Serious bleeding from minor injuries
6–30	Mild	Rare spontaneous bleeds
		Excessive bleeding after surgery or trauma
		Might not be discovered until bleeding episode occurs

Hemophilia C: Factor XI deficiency

- **Autosomal recessive**
- 1 in 100,000 from general population affected
- High prevalence in Ashkenazi Jewish population
- 50% of patients have bleeding problems
  - Hemostatic role of FXI not as crucial
- Prolonged APTT: consider multiple factors
- Best test → factor XI assay

36

The most important factors



Things to consider…

- ABO group O individuals have less Factor VIII
  - Have decreased amounts of von Willebrand Factor
- Estrogen-containing contraceptives increase FVIII levels
- Newborns have lower FIX activity

TREATMENTS FOR HEMOPHILIA

Early Treatments

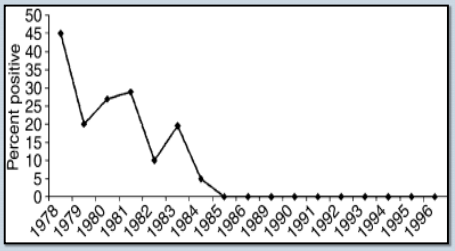
- 1911 – first anti-hemophilic factor preparation
- 1934 – Russell's viper venom – directly activates Factor 10
- 1946 – improved preparations of Factor 8
- 1950s and 1960s – fresh frozen plasma
- 1965 – Judith Pool – discovery of cryoprecipitate

Clotting Factor Concentrates

- 1970s – Filtered clotting factor concentrates introduced
- 1980 – Life expectancy reached age 60
- Demand for plasma rose significantly
- Concentrates pooled from up to 20,000 donors
- Risk of contracting "non-A, non-B hepatitis" viewed as acceptable considering enhanced quality of life and longevity

Hemophilia Setback

- 1980s – First cases of AIDS reported in U.S.
- 1982 – Three cases of hemophilia patients with symptoms resembling AIDS
- 1983 – HIV virus identified
- 1984 – Heat-inactivation of viruses employed in manufacture of factor concentrates; enhanced donor screening programs
- 1981-1984 – 50% of U.S. hemophilia patients infected with HIV
- 1987 – Successful heat-inactivation of non-A, non-B hepatitis virus in factor concentrates



Frequency of human immunodeficiency virus (HIV) infection in US hemophilia patients.

Modern-day Hemophilia Care

- 1977 – Desmopressin: inexpensive, safe treatment for mild hemophilia A cases
- 1992 – Recombinant factor concentrates for hemophilia A
- 1997 – Recombinant factor concentrates for hemophilia B

Complications – Factor Inhibitors

- Antibodies form against infused concentrates post-treatment
- Frequency of treatment increases likelihood of inhibitor formation
- Patients with inhibitors have far worse outcomes than those without
- Various drug modifications to reduce frequency of treatments
  - Increase factor half-life
  - Reduce natural anti-coagulant activity
  - Mimic activity of Factor VIII
- Alternate factor concentrates
- Immune tolerance induction

On the horizon…gene therapy?