Management of Factor Deficiency Disorders

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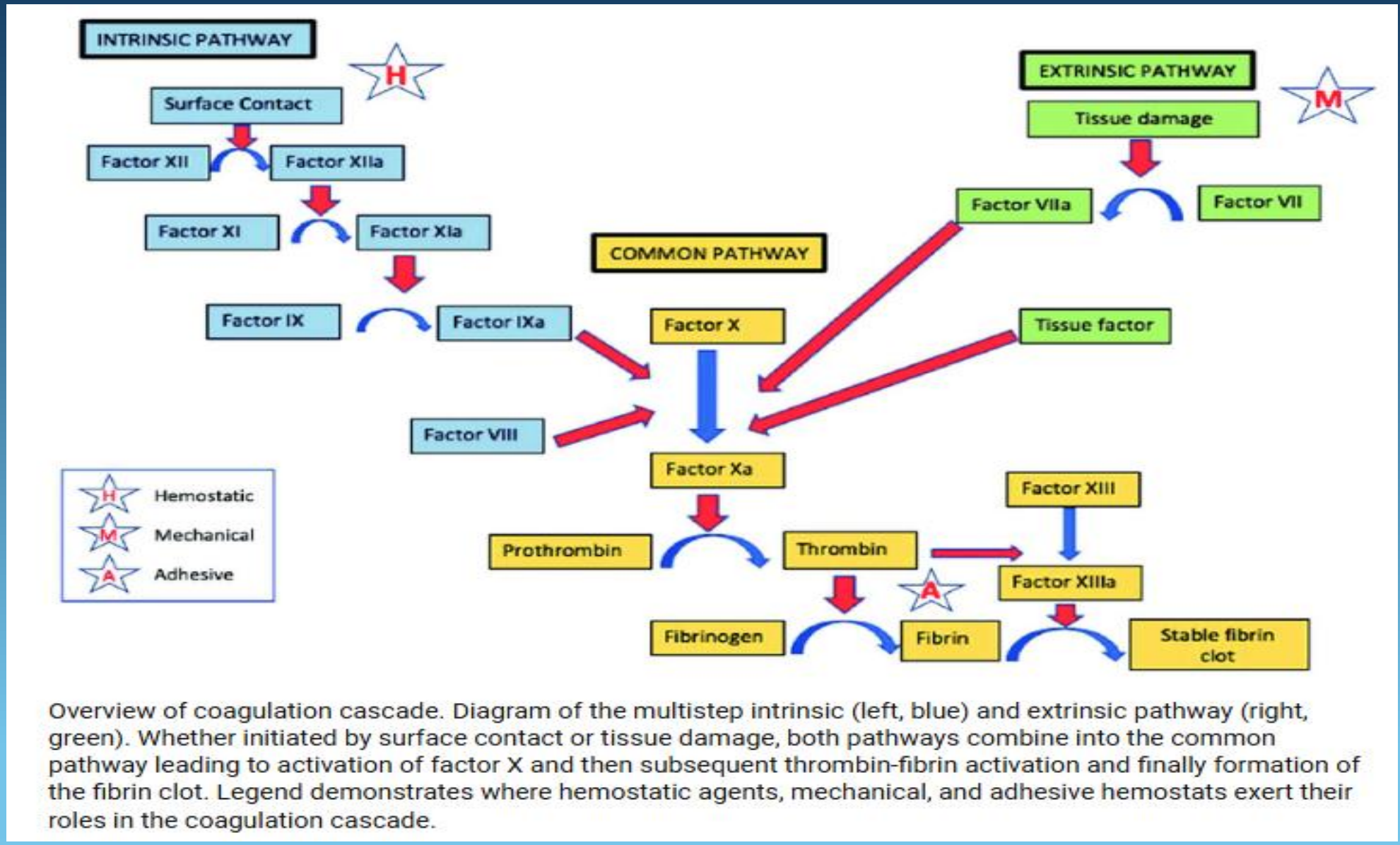
Disclosures

NONE

Learning Objectives

- Evaluate hemostasis as it requires a complex interplay of clotting factors.
- Evaluate deficiencies lead to bleeding diathesis, varying in severity.
- Focus: Factor VIII, IX, XI, XIII, and VII deficiencies.
- Learn the goals for treatment
  - Maintain factor levels to ≥ 50–100% for surgical safety (Poon et al., 2012).

Clotting Cascade



Overview of coagulation cascade. Diagram of the multistep intrinsic (left, blue) and extrinsic pathway (right, green). Whether initiated by surface contact or tissue damage, both pathways combine into the common pathway leading to activation of factor X and then subsequent thrombin-fibrin activation and finally formation of the fibrin clot. Legend demonstrates where hemostatic agents, mechanical, and adhesive hemostats exert their roles in the coagulation cascade.

Simplified Explanation: Human Coagulation Pathways

The clotting system is like an emergency response team that stops bleeding. There are **three main parts** to the clotting cascade:

1. **Intrinsic Pathway**
2. **Extrinsic Pathway**
3. **Common Pathway**

- They all work together to form a **fibrin clot** and stop bleeding.

Extrinsic Pathway ("Fast and First Responder")

- Triggered by **external injury** to blood vessels (like a cut).
- When tissue is damaged, **Tissue Factor (TF)** is released.
- Tissue Factor binds to **Factor VII**, turning it into **VIIa** (activated form).
- Factor VIIa + Tissue Factor activate **Factor X** (start of the common pathway).

Easy memory:

➡️ "Extrinsic = External injury = Tissue Factor + Factor VII"

- **Speed:** Very rapid response — buys time for the intrinsic pathway to join in.

Intrinsic Pathway ("Reinforcement and Amplifier")

- Triggered by **damage inside the blood vessel** or exposure of collagen.
- Uses **factors already present in the blood** ("intrinsic").
- Starts with **Factor XII** activating **Factor XI**, which then activates **Factor IX**.
- **Factor IXa + Factor VIIIa** (with calcium and phospholipids) also activate **Factor X**.

Easy memory:

➡️ "Intrinsic = Internal injury = Collagen exposure = Factors XII, XI, IX, VIII"

- **Speed:** Slower to start, but powerful — amplifies clot formation.

Common Pathway ("Final Clot Maker")

- Both intrinsic and extrinsic pathways meet here at **Factor X**.
- **Factor Xa + Factor Va** convert **Prothrombin (Factor II)** to **Thrombin (Factor IIa)**.
- **Thrombin** converts **Fibrinogen (Factor I)** to **Fibrin**, which forms the mesh that makes a stable clot.
- Thrombin also activates platelets and more factors to strengthen the clot.

Summary Table

Pathway	Trigger	Key Factors	Role
Extrinsic	External trauma, tissue damage	Tissue Factor, Factor VII	Rapid response to injury
Intrinsic	Vessel wall damage, collagen exposure	Factors XII, XI, IX, VIII	Amplifies clot formation
Common	Activation by either pathway	Factors X, V, II (Prothrombin), I (Fibrinogen)	Produces thrombin and stable fibrin clot

Professional Takeaways :

The **extrinsic pathway** stops bleeding quickly at the site of injury.

The **intrinsic pathway** boosts the clot and makes it stronger.

The **common pathway** finishes the job by making **thrombin**, which creates a stable fibrin clot.

How Platelets Fit Into the Clotting Cascade

Think of platelets as the "construction crew" of clot formation. While the clotting cascade is a series of chemical reactions (**enzymes activating enzymes**), platelets provide the **physical platform** and **mechanical strength** of the clot.

Here’s how they work together:

1. Vessel Injury Happens

1. Blood vessel damage exposes **collagen** and **von Willebrand factor (vWF)**.
2. Platelets rush to the scene and **stick to the exposed collagen**, helped by vWF (platelet adhesion).

2. Platelet Activation

1. Once activated, platelets become "adhered."
2. Activated platelets change shape (they spread out), release chemical signals (ADP, thromboxane A2), and recruit more platelets to pile onto the injury site (**platelet aggregation**).

3. Platelet Plug Formation

1. Activated platelets form a temporary **platelet plug** — this is the first step to stop bleeding (but it's not stable yet).

Step-by-Step Integration of Platelets in Clotting

1. **Platelets Provide a Surface for the Clotting Cascade**
    1. Platelets expose **negatively charged phospholipids** on their surface.
    2. This creates a perfect landing pad for clotting factors to assemble and activate each other efficiently.
    3. Especially important for **intrinsic pathway factors** (like VIIIa, IXa) and the **common pathway** (activation of Factor X and prothrombin to thrombin).
2. **Thrombin Supercharges Platelets**
    1. Thrombin (from the common pathway) does two key things:
        1. Converts **fibrinogen to fibrin**, weaving a mesh over the platelet plug.
        2. Further **activates platelets**, making them even stickier and enhancing clot stability.
3. **Fibrin + Platelets = Stable Clot**
    1. The fibrin meshwork traps red blood cells and more platelets, **turning the loose platelet plug into a strong, stable clot.**

Professional Takeaway :

- Platelets are not part of the clotting cascade enzymes, but they are essential partners.
- They form the initial **platelet plug** and provide the surface for clotting factor reactions.
- **Without platelets, even perfect factor levels won't produce a stable clot.**
- Treatments like **Desmopressin (DDAVP)** work partly by increasing platelet adhesion (through vWF release)!

Hemophilia A (Factor VIII Deficiency)

Pathophysiology:

- X-linked recessive disorder.
- Deficient/defective Factor VIII disrupts intrinsic pathway (White et al., 2001).

Diagnosis:

- Prolonged aPTT, normal PT.
- Confirm with Factor VIII assay
  - <1% severe,
  - 1–5% moderate,
  - >5% mild) (Srivastava et al., 2020).

Treatment:

- Recombinant Factor VIII or plasma-derived concentrates.
- Emicizumab for prophylaxis (Callaghan et al., 2020).

Surgical Requirement:

- Maintain 80–100% factor activity for major surgery (Srivastava et al., 2020).

What is Emicizumab?

Emicizumab is a **bispecific monoclonal antibody**.
It mimics the function of **Factor VIII** by binding simultaneously to:

- **Activated Factor IX (FIXa)**
- **Factor X (FX)**

This "bridges" the gap that exists in Hemophilia A patients who have low or no functional Factor VIII.
Emicizumab promotes the activation of Factor X by Factor IXa, leading to thrombin generation and clot formation, bypassing the need for native Factor VIII.

Key points:

- **Indication:** Hemophilia A (with or without inhibitors).
- **Administration:** Subcutaneous injection (huge advantage over IV factor replacement).
- **Frequency:** Weekly, biweekly, or even monthly dosing.
- **Clinical Impact:** Reduces bleeding rates significantly — studies report **87% reduction in bleeding episodes** (Callaghan et al., 2020).
- **It is NOT used for Hemophilia B**, only for **Hemophilia A**.

Hemophilia B (Factor IX Deficiency)

Pathophysiology:

- X-linked recessive; "Christmas Disease."
- Deficiency in Factor IX impacts thrombin generation (Lillicrap, 2013).

Diagnosis:

- Prolonged aPTT, normal PT.
- Factor IX activity assay (<1% severe) (Peyvandi et al., 2016).

Treatment:

- Recombinant Factor IX (Alprolix, Idelvion).
- Gene therapy: FDA-approved etranacogene dezaparvovec (Miesbach et al., 2021).
- "Christmas disease" is named after the first patient formally described with Hemophilia B, **Stephen Christmas**, who was diagnosed in 1952 in the UK.

Factor XI Deficiency (Hemophilia C)

Pathophysiology:

- Autosomal recessive.
- Reduced thrombin generation secondary to Factor XI deficiency (Salomon et al., 2008).

Diagnosis:

- Prolonged aPTT; normal PT.
- Confirm with Factor XI assay (Seligsohn, 2009).

Treatment:

- Fresh frozen plasma or Factor XI concentrate (rare).
- Antifibrinolytics (tranexamic acid) adjunctively (Bolton-Maggs, 2003).

Surgical Requirement:

- Maintain ~30–45% activity for major surgery (Salomon et al., 2008).

Factor XIII Deficiency

Pathophysiology:

- Autosomal recessive, rare.
- Deficiency impairs fibrin cross-linking, leading to unstable clots (Muszbek et al., 2011).

Diagnosis:

- Normal PT/aPTT.
- Clot solubility test, Factor XIII assay (<1% severe deficiency) (Dorgalaleh et al., 2013).

Treatment:

- Recombinant FXIII-A (Tretten®).
- Plasma-derived FXIII concentrate.

Factor VII Deficiency

Pathophysiology:

- Autosomal recessive.
- Impairs tissue factor pathway and thrombin generation (Mariani et al., 2006).

Diagnosis:

- Isolated prolonged PT.
- Confirm with Factor VII activity assay (<10% severe) (Peyvandi et al., 2007).

Treatment:

- Recombinant activated Factor VII (rFVIIa, NovoSeven®).
- Plasma-derived concentrates.

Surgical Requirement:

- Maintain ≥ 50% activity for major surgery (Mariani et al., 2006).

Summary of Factor Deficiencies

Factor Deficiency	Surgical Activity Target	Treatment Options
Factor VIII	80–100%	rFVIII, Emicizumab
Factor IX	80–100%	rFIX, Gene therapy
Factor XI	30–45%	FFP, FXI concentrate, TXA
Factor XIII	>50%	rFXIII, Plasma-derived FXIII
Factor VII	≥50%	rFVIIa, Plasma-derived FVII

What is PCC?

PCC stands for **Prothrombin Complex Concentrate**.

It is a medication that contains **concentrated vitamin K–dependent clotting factors**. There are two main types:

1. **3-factor PCC (3F-PCC):**
   Contains factors II, IX, X (low levels of VII).
2. **4-factor PCC (4F-PCC):** *(More commonly used clinically, and this is what Kcentra is!)*
    1. Contains Factors **II, VII, IX, X**
    2. Also includes **proteins C and S**, which are natural anticoagulants and help balance clot formation.
    3. **Kcentra®** is an example of 4F-PCC.

Purpose of PCC

PCC is used to **rapidly reverse anticoagulation**, especially:

- **Warfarin reversal** (Vitamin K antagonist)
- Emergency surgery
- Life-threatening bleeding
- Off-label: reversal of certain direct oral anticoagulants (DOACs), though specific reversal agents (like idarucizumab for dabigatran) are preferred.

Mechanism of Action

Supplies functional vitamin K–dependent factors (II, VII, IX, X).

These factors are essential for the **clotting cascade**, especially the extrinsic and common pathways.

Quickly restores thrombin generation and normal coagulation function.

Administration

Route: Intravenous infusion.

Onset: Very rapid — clotting factor activity improves within minutes to hours.

Often given alongside **intravenous Vitamin K**, which ensures sustained factor production by the liver.

Safety and Risks

Thrombosis: Due to rapid correction of coagulation, there is an inherent risk of blood clots.

DIC risk: Monitor carefully in critically ill patients.

Requires careful dosing, often based on body weight and INR level.

Clinical Note

PCC is **much faster and more efficient than fresh frozen plasma (FFP)** for anticoagulation reversal.

Requires much lower volumes than FFP (useful in patients at risk for fluid overload).

Summary Table

Feature	Description
Full name	Prothrombin Complex Concentrate (PCC)
Types	3F-PCC, 4F-PCC (Kcentra®)
Contents	Factors II, VII, IX, X, proteins C and S (in 4F-PCC)
Main use	Rapid reversal of vitamin K antagonists (warfarin)
Mechanism	Replaces depleted vitamin K–dependent clotting factors
Administration	IV infusion
Risks	Thrombosis, DIC, allergic reactions

FIEBA (sometimes styled as Feiba®)

FEIBA stands for:
Factor **E**ight **I**nhibitor **B**ypassing **A**ctivity.

- **What is it?**
  It is an **activated prothrombin complex concentrate (aPCC)**.
- **Purpose:**
  Used in patients with **hemophilia A or B who have developed inhibitors** (antibodies) against standard factor replacement therapy.
- **How it works:**
  Contains non-activated factors II, IX, X, and **activated factor VII (FVIIa)** — this bypasses the need for Factor VIII or IX by directly promoting thrombin generation and clot formation.
- **Indications:**
  - Bleeding episodes in hemophilia patients with inhibitors
  - Perioperative management in these patients
  - Sometimes off-label in other rare coagulopathies
- **Route:**
  Intravenous
- **Caution:**
  Risk of thrombosis if overdosed or in certain prothrombotic states.

Kcentra®

- **What is it?**
  4-factor prothrombin complex concentrate (4F-PCC).
- **Contents:**
  Factors **II, VII, IX, X**, and proteins **C and S** (natural anticoagulants).
- **Purpose:**
  Primarily used for **rapid reversal of warfarin (vitamin K antagonist)–induced anticoagulation** in adults with:
  - Acute major bleeding
  - Need for urgent surgery or invasive procedures
- **Mechanism:**
  Supplies functional vitamin K–dependent clotting factors to restore normal coagulation.
- **Route:**
  Intravenous
- **Caution:**
  Thrombosis risk, especially in patients with history of clots or disseminated intravascular coagulation (DIC).

Quick Comparison Table

Feature	FEIBA (aPCC)	Kcentra (4F-PCC)
Use	Hemophilia A or B with inhibitors	Warfarin reversal or urgent coagulation restoration
Factors Contained	II, IX, X (inactive), VIIa (active)	II, VII, IX, X (all inactive), proteins C and S
Main Action	Bypasses Factor VIII/IX pathway	Replenishes vitamin K-dependent factors
Route	IV	IV
Risk	Thrombosis, DIC	Thrombosis, DIC
Notes	Used in inhibitor-positive hemophilia	Used for warfarin reversal and DOAC (off-label sometimes)

Clinical Pearl:

FEIBA: Think **hemophilia with inhibitors**.

Kcentra: Think **warfarin reversal and urgent surgery**.

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