AN ILLUSTRATED GUIDE TO MEETING THE CHALLENGES OF TREATING HEMOPHILIA

PROPHYLACTIC TREATMENT

Should be used whenever feasible
FOR ALL BLEEDS

Should be
STARTED EARLY
to prevent joint damage

OPTIMIZE PROPHYLAXIS TREATMENT

3%-5%
A 1% factor trough level is too low
TARGET TROUGH LEVELS ARE ATTAINABLE

More tools are available to
OPTIMIZE TREATMENT
including better treatments and alternate dosing schedules

WFH GUIDELINES FOR THE MANAGEMENT OF HEMOPHILIA, 3RD EDITION

PROPHYLAXIS BEST PRACTICES

USE NEW TREATMENTS to optimize prophylactic treatment

- Prophylaxis is superior to episodic treatment
- New treatments have made it possible to increase the target for factor trough levels to 3%-5%
- New treatments are making early treatment initiation easier, especially if central venous access is not required

prophylaxis should be INDIVIDUALIZED

- The most important indicator of efficacy is bleeding frequency (especially for joint and muscle bleeds)
- Bleeding frequency should be the basis for clinical decision making and is a predictor of long-term musculoskeletal outcomes
- Individualized prophylactic therapy should be based on pharmacokinetic-guided dosing

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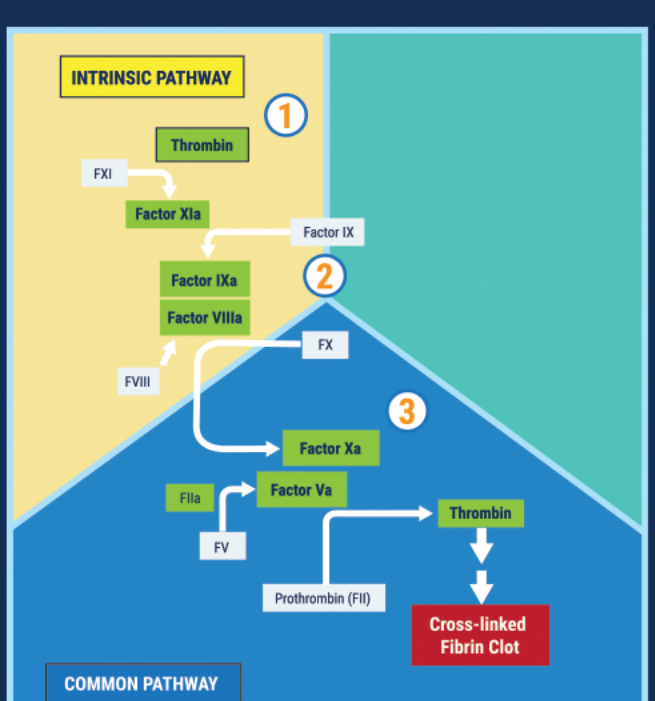
REVIEW OF THE INTRINSIC AND EXTRINSIC PATHWAYS

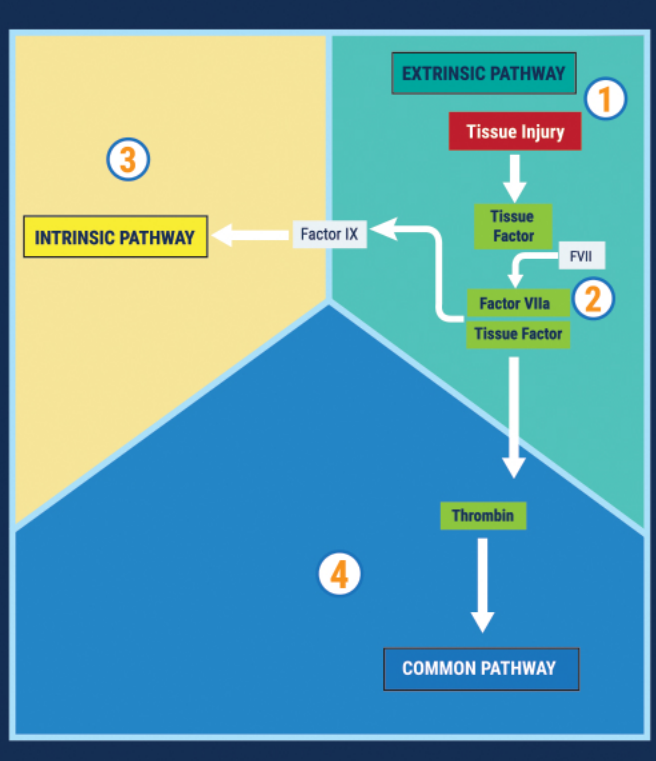
Restoring homeostasis after an injury requires the localized formation of an impermeable platelet and fibrin plug. This brief refresher reviews the major steps and components of the coagulation cascade that are emerging therapeutic targets. For a more complete review of clotting and hemostasis, see Monroe and Hoffman 2006.

INTRINSIC PATHWAY



1. Thrombin and FIXa generated from **EXTRINSIC PATHWAY** activation leads to activation of FIX/FVIII on platelets
2. FVIIIa/FIXa activates FV/FX (aka, prothrombinase), triggering the **COMMON PATHWAY**
3. FVa/FXa converts prothrombin to thrombin, which leads to conversion of fibrinogen to fibrin and **CLOT FORMATION**

EXTRINSIC PATHWAY



1. Initiation of the clotting cascade begins with exposure of tissue-factor (TF) in the extravascular space to the vascular space
2. TF complexes with FVII
3. FVIIa activates FIX which goes on to activate the **INTRINSIC PATHWAY**
4. FVIIa also initiates thrombin production through activation of the **COMMON PATHWAY**

OVERCOMING THE VWF HALF-LIFE CEILING

AFFINITY
of recombinant FVIII for VWF can be improved

- Culture in human cells rather than rodent cells ensures full tyrosine sulfation, which is needed for efficient VWF binding
- A single-chain FVIII variant (lonoctocog alfa) has been engineered to improve the FVIII-VWF binding affinity

These strategies have only resulted in
MODEST IMPROVEMENTS
in FVIII half-life

SUBSTITUTION THERAPY:
EMICIZUMAB

EMICIZUMAB SUBSTITUTION THERAPY

- An alternative hemostatic agent that substitutes for FVIIIa in patients with hemophilia A
- Simultaneous binding of FIXa and FX circumvents the need for FVIIIa, allowing FIXa-mediated FX activation
- Administered subcutaneously
- Emicizumab may not provide all the noncoagulation-related benefits of FVIII replacement that may support, for example, long-term joint and bone health and optimal wound healing

HEMOSTATIC REBALANCING:
ANTI-TFPI STRATEGIES

Hemostatic rebalancing with **ANTI-TFPI THERAPY**

- Tissue Factor Pathway Inhibitor (TFPI) downregulates thrombin production through the extrinsic pathway
- Therapies in clinical trials achieve hemostatic rebalancing by removing the negative feedback systems on the extrinsic pathway
- Leading compounds administered subcutaneously
- Anti-TFPI treatments do not rely on FVIII or FIX activities, and therefore have the potential to treat hemophilia A or B, including in patients with inhibitors

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HEMOSTATIC REBALANCING
TARGETING ACTIVATED PROTEIN C

Hemostatic rebalancing with **PROTEIN C INHIBITORS**

- Protein C exerts an anticoagulant effect by inhibiting FVIIIa and FVa, preventing activation of FX and prothrombinase
- Lead compound administered subcutaneously
- Activated protein C inhibitors do not rely on FVIII or FIX activities, and therefore have the potential to treat hemophilia A or B, including in patients with inhibitors

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HEMOSTATIC REBALANCING
THROMBIN GENERATION

Hemostatic rebalancing with **THROMBIN GENERATION**

- Antithrombin (AT) is a small protein that is a major regulator of coagulation that primarily suppresses the activity of thrombin (FIIa) and FXa, but it also has an inhibitory effect on FVIIa and proteases in the intrinsic pathway
- Thrombin generating treatments target AT, relieving its inhibitory effect on thrombin, FXa, and its other targets
- Lead compound administered subcutaneously
- Thrombin generating treatments do not rely on FVIII or FIX activities, and therefore have the potential to treat hemophilia A or B, including in patients with inhibitors

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GENE THERAPIES

Gene Therapy POTENTIAL

Only a **single gene** needs to be replaced

A **single treatment** could reduce lifetime dependence on factor

BARRIERS to overcome

LONG-TERM safety, efficacy, and durability of factor expression unknown

Eligibility due to **pre-existing immunity to viral vectors**

Application in **pediatric populations** and **patients with history of inhibitors**