EHC Webinars

European von Willebrand Disease Community

Von Willebrand disease

Topic on focus

ERN-EuroBloodNet

VWD in the emergency room

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EHC european haemophilia consortium

Advocating for people with haemophilia and congenital bleeding disorders

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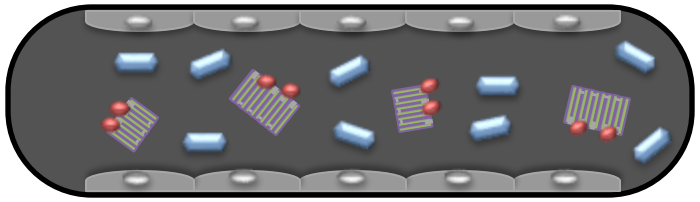
Conflicts of interest

Conflict	Disclosure
Research support	-
Director, Officer, Employee	-
Shareholder	-
Honoraria	-
Advisory committee	Biomarin, CSL Behring, Roche, Sanofi, SOBI
Educational meetings/Symposia	Takeda/Spark

Patients learning objectives

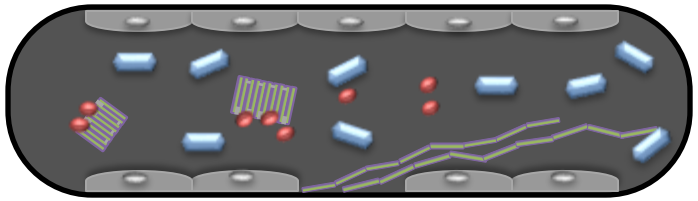
1. von Willebrand factor role in hemostasis
2. First aid
3. Challenges in obtaining pain relief medications
4. Difficulties in accessing clotting factors
5. Identifying patients with von Willebrand disease (VWD) in emergency settings (registries, patient lists, medical IDs, or medical records
6. Guidelines for consulting a hematologist
7. 24h monitoring patients with VWD in the hospital after a trauma

Role of VWF in primary haemostasis

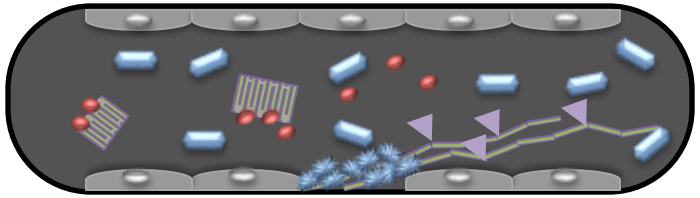


VWF circulates as a loosely coiled protein complex under **basal conditions of low shear stress**

VWF adheres to the site of vascular injury via exposed collagen, causing a conformational change of VWF

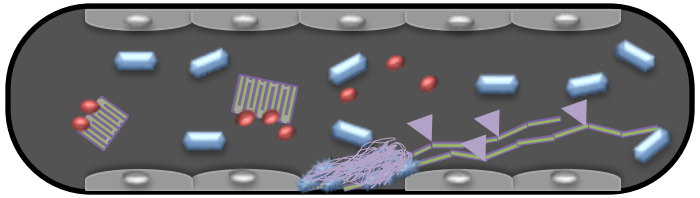


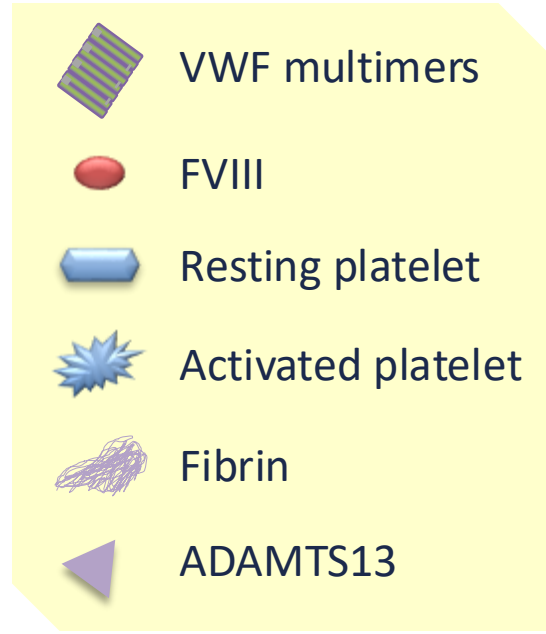
Vascular injury



Upon **unfolding of VWF**, binding sites for platelets and ADAMTS13 become accessible

A **platelet-fibrin plug** is formed and bleeding ceases

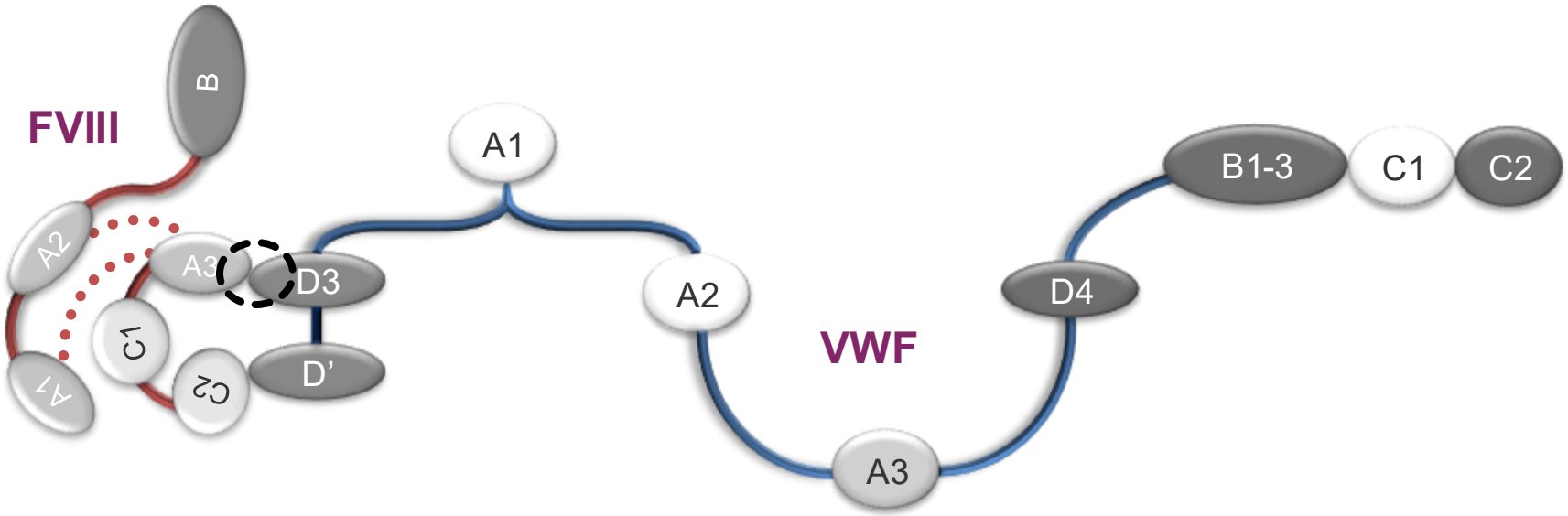




Nichols WL, et al. Haemophilia. 2008;14:171–232; Denis CV, Lenting PJ. Int J Hematol. 2012;95:353–361

Role of VWF in secondary haemostasis

FVIII is noncovalently bound to the D'-D3 region of VWF (dotted lines)



VWF forms a complex with FVIII in circulation, which stabilises and protects FVIII from degradation and localizes it to the site of the platelet plug to bring about the formation of a clot

Peyvandi F, et al. Blood Transfus. 2011;Suppl 2:S3–S8

First aid procedures

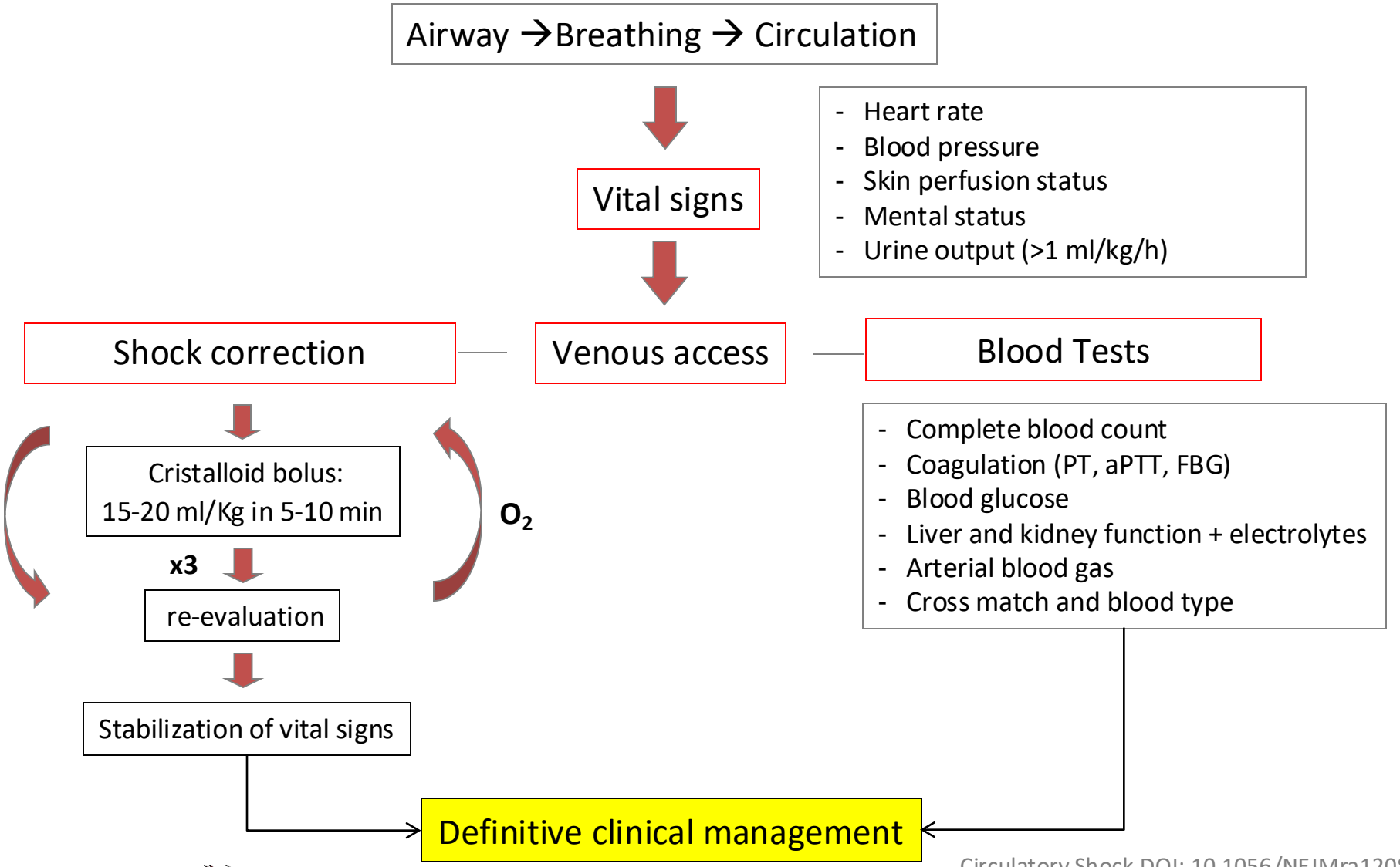
1. Emergency assistance: Ensure Safety

- Evaluate signs of shock and/or internal hemorrage
- Collect precise informations about diagnosis and VWD subtype
- Contact physician of the referral centre (Spoke or HUB centre)

2. In case of an already known patient with a clear diagnosis

- Contact the patient's referring center and in meantime start the treatment
- Plan patient's transfer to the center
- Move the patient to the closer ER or to the hospital suggested by the referring center

Approach in emergency-urgent care



Circulatory Shock DOI: 10.1056/NEJMra1208943

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EHC Webinars Von Willebrand disease

Topic on focus ERN-EuroBloodNet

Consulting a hematologist, including when and how to seek their expertise

- If major surgery is needed

  both FVIII and VWF activity levels have to be checked and kept at ≥0.50 IU/mL before surgery and for at least 3 days after surgery

- Monitoring only FVIII (≥0.50 IU/mL) may be insufficient to avoid life threatening bleedings

Treatment in emergency-urgent care

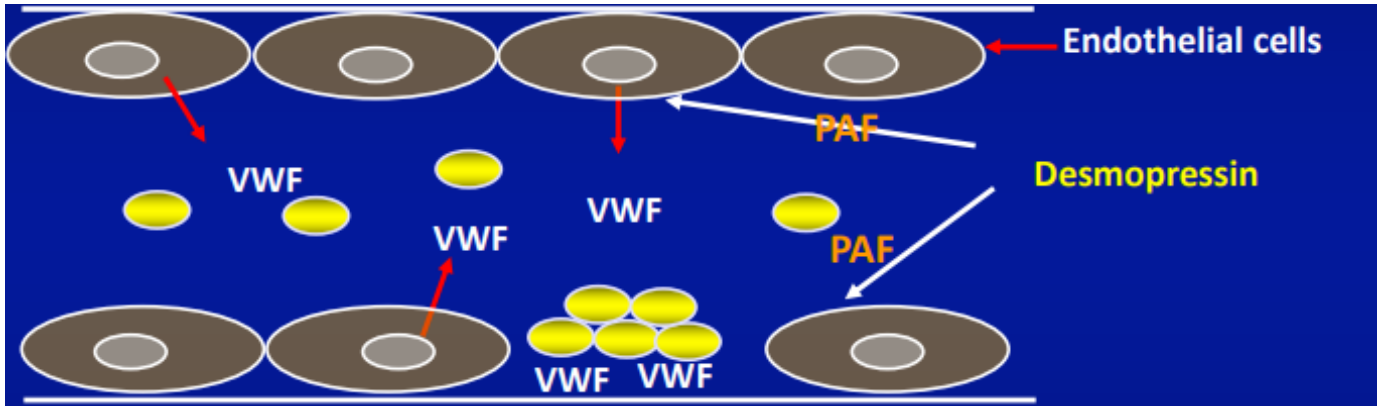
  - VWF concentrates
  - Combined concentrates VWF/FVIII
  - Desmopressin (only if desmopressin trial has previously been performed and not for patients with type 3 and type 2B VWD)

- Major surgery
  - Target: vWF and FVIII ≥0.50 UI/mL for at least 3 days after surgery
- Critical bleeding (cerebral or gastrointestinal)
  - Target: vWF and FVIII ≥1.0 UI/mL with strict monitoring and dose adjustment

- Approximative recovery
  - FVIII: 2% for each UI/Kg
  - vWF: 1,4% for each UI/Kg

Treatment: desmopressin (DDAVP)

- To be tested in type 1 and 2 (NOT TYPE 2B → due to thrombocytopenia)
- Determines the release of endogenous VWF from endothelial cells
- Requires the presence of normal VWF (not type 3)



Treatment: desmopressin (DDAVP)

- When is desmopressin contraindicated?
  - In emergency setting if trial of desmopressin has never been performed
  - Type 3 VWD (lack of efficacy)
  - Type 2B (thrombocytopenia due to ↑ platelet binding)
  - Severe cardiovascular disease

Treatment: VWF concentrates for patients who do not respond to DDAVP

Characteristics	Plasma-derived FVIII/VWF	Recombinant (VonVendi)
Ultra large multimers	Absent	Present
HMW multimers	Variably deficient	Present
Multimer triplet structure	Present	Absent
Carbohydrate structure/ glycosylation of VWF	Normal	Possibly altered glycosylation due to the lack of ABO determinants
VWF:RCo/VWF:Ag	Variable, but typically <1	>1

Product	Manufacturer	Purification	Viral inactivation	VWF:RCo/Ag (ratio)	VWF:RCo/FVIII (ratio)
Alphanate	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72h)	0,47±0,1	0,91±0,2
Factor 8Y	BioProducts Laboratory	Heparin/glycine precipitation	Dry heat (80°C, 72h)	0,29	0,81
Fahndi	Grifols	Heparin ligand chromatography	S/D + dry heat (80°C, 72h)	0,47±0,1	1,04±0,1
Haemate P	CSL Behring	Muliple precipitation	Pasteurization (60°C, 10h)	0,59±0,1	2,45±0,3
Immunate	Baxter	Ion exchange chromatography	S/D vapor heat (60°C, 10h)	0,47	1,1
Wilate	Octapharma	Ion exchange + size ecxchision Chromatography	S/D + dry heat (100 °C, 2h)	-	0,9
Wilfactin	LFB	Ion exchange + affinity	S/D 35nm filtration, dry heat (80°C, 72h)	~0,95	~50

Franchini, M., & Mannucci, P. M. (2016). Von Willebrand factor (Vonvendi®): the first recombinant product licensed for the treatment of von Willebrand disease. *Expert Review of Hematology*, *9*(9), 825–830. https://doi.org/10.1080/17474086.2016.1214070

Castaman, Giancarlo et al. "Principles of care for the diagnosis and treatment of von Willebrand disease." *Haematologica* vol. 98,5 (2013): 667-74. doi:10.3324/haematol.2012.077263

rVWF is another source of treatment with high molecular weight VWF

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Minor surgery – International guidelines

- Suggestion: increasing VWF activity levels to ≥ 0.50 IU/mL with desmopressin or factor concentrate **WITH** the addition of tranexamic acid
- Suggestion: giving tranexamic acid alone in patients with type 1 VWD (baseline VWF activity of > 0.30 IU/mL and a mild bleeding phenotype) undergoing minor mucosal procedures

conditional recommendations (based on very low certainty in the evidence of effects)

Remarks:

- Individualized therapy plans are important for patients who may be overtreated when VWF activity is increased to ≥ 0.50 IU/mL by any therapy and addition of tranexamic acid
- Type 1 VWD: desmopressin or VWF or VWF/FVIII concentrates ± tranexamic acid
- Type 2 VWD: VWF or VWF/FVIII concentrates ± tranexamic acid. Generally, does not respond to desmopressin which is contraindicated in type 2B.
- Type 3 VWD: VWF or VWF/FVIII concentrates ± tranexamic acid. Desmopressin is contraindicated because of a lack of efficacy
- For patients at **higher risk of thrombosis**, it may be desirable to **avoid the combination of extended increased VWF and FVIII levels (> 1.50 IU/mL) and extended use of tranexamic acid**
- In dental procedures, consider use of local hemostatic measures

Major surgery – International guidelines

- Suggestion: targeting **both FVIII and VWF activity levels of ≥ 0.50 IU/mL for at least 3 days after surgery**
- Suggestion against using only FVIII ≥ 0.50 IU/mL as a target level for at least 3 days after surgery

conditional recommendations (based on very low certainty in the evidence of effects)

Remarks:

- Keep both trough levels (FVIII and VWF) at ≥ 0.50 IU/mL for at least 3 days or as long as clinically indicated after the surgery (instead of choosing only 1)
- The specific target levels should be individualized based on the patient, type of procedure, and bleeding history as well as availability of VWF and FVIII testing
- The duration of the intervention can vary for specific types of surgeries

International guidelines

CLINICAL GUIDELINES

Blood Adv. 2021;5:301-325.
doi:10.1182/bloodadvances.2020003264

ASH ISTH NHF WFH 2021 guidelines on the management of von Willebrand disease

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Clinical cases - 1

- 20 y/o female with Type 1 VWD and menorrhagia
  - Group 0 pos
  - FVIII 28%, VWF:Ag 26%, VWF:Rco 25%

- Familiarity: her mother with history of prolonged bleeding after minor wounds. No significant bleedings after surgery or delivery
- PBAC score: 435 before oral estroprogestin treatment
- Bleeding Severity Score (ISTH-BAT): 5 (no surgery, no pregnancy, no dental extractions)
- Desmopressin trial:
  - pre FVIII 28% VWF:Ag 25% RCo 24%
  - post-1h FVIII 202% VWF:Ag 157% RCo 145%
  - post-2h FVIII 163% VWF:Ag 154% RCo 145%
  - post-4h FVIII 122% VWF:Ag 136% RCo 134%

Clinical cases - 2

- 37 y/o male with type 2M VWD, low FV and head trauma
  - Group A pos
  - FVIII 33%, VWF:Ag 14%, VWF:RCo <6%
  - 80 Kg
- Car accident with multiple fractures, included skull fracture
  - Treated with plasma-derived concentrate FVIII/VWF (Fahndi) 4500UI with no significant bleeding
  - Then 2000UI for fractures surgical reduction

Clinical cases - 3

- 34 y/o female with type 2B VWD, in pregnancy
  - Group B pos
  - FVIII 89%, VWF:Ag 80%, VWF:RCo 5%
  - 66 Kg
- Previous caesarean delivery in emergency treated with wilfactin and tranexamic acid, without complications
- Indications for next delivery
  - Wilfactin 4500UI 30 minutes before caesarean or epidural anaesthesia + 1000 mg of tranexamic acid 30-60 minutes before caesarean or epidural anaesthesia or during delivery.

Take home messages

Ensure Timely Access to Medications: *Develop strategies to prevent delays in providing pain relief and clotting factors for patients.*
Expert Notes/Recommendations: ……..

Prioritize Early Bleeding Management: *Streamline processes to quickly identify and treat bleeding episodes, ensuring uninterrupted access to necessary clotting factors.*
Expert Notes/Recommendations: ……

Facilitate VWD Patient Identification in Emergencies: *computing resources like patient registries, medical IDs, and electronic or paper medical records to help healthcare providers recognize VWD patients promptly*.
Expert Notes/Recommendations: **……**

Engage Hematology Expertise Effectively: *Define clear protocols for consulting hematologists, including specific situations that require their involvement and the appropriate steps to engage them*.
Expert Notes/Recommendations:……

Implement Post-Trauma Observation Protocols: *Adopt a 24-hour hospital monitoring policy for VWD patients after trauma (e.g., head injuries) to ensure delayed bleeding is detected and treated early.*
Expert Notes/Recommendations:……

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