Management of Platelet Derived Bleeding Disorders

- Paul Wisniewski, DO
- Trauma Director
- Surgical Critical Care Fellowship Director

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Cutting Edge
Surgical Medical Group

Disclosures

- None

Learning Objectives

- **Understand the pathophysiology of platelet dysfunction in trauma and uremia,**
- **Identify diagnostic strategies for platelet disorders in trauma and uremia:**
- **Evaluate management options for platelet disorders in trauma and uremia:**
- **Assess the impact of platelet dysfunction on hemorrhagic complications in trauma and uremia:**

Platelets

- Essential for clotting and to stop the bleeding
- Without platelets there is no stable clot formation
- Weak clots
- Platelets are the most scares blood product
- Has to be kept at room temperature
- Only good for 5 days
- Highest infection risk
- Pooled platelets (6 pack = six donors)
- Each bag is 6 donor = 6 units

Three A's of Platelets

1. **Activation (via Cyclooxygenase and ADP)**
    - **Activation** is the initial response of platelets when they encounter damage to the vascular wall. Platelets respond to **collagen**, **thrombin**, **ADP**, and other agonists.
    - **Cyclooxygenase (COX-1)** is a critical enzyme that produces **thromboxane A2 (TXA2)** from arachidonic acid. Thromboxane A2 is a potent platelet agonist that promotes further platelet activation, increases calcium influx, and leads to the expression of the **GPIIb/IIIa** receptor.
    - Additionally, **ADP** (released from platelets or from the damaged vascular wall) binds to **P2Y12 receptors** on platelets, further promoting platelet activation by enhancing their responsiveness to other stimuli like thromboxane A2.

Adhesion (via ADP and vWF)

- Once activated, **platelets adhere** to the exposed subendothelial matrix, primarily through their **GPIb/IX/V complex** interacting with **von Willebrand factor (vWF)**, which binds to collagen at the site of injury. This process is crucial for anchoring the platelets at the site of vascular damage.
- **ADP** also contributes to this phase by amplifying platelet activation locally, making the platelets more sticky and capable of interacting with the matrix and each other. However, **adhesion** itself is primarily driven by the vWF-platelet interaction.

Aggregation (via GPIIb/IIIa)

- In the **aggregation** phase, platelets that are adhered to the site of injury now bind to each other. This is facilitated by **GPIIb/IIIa receptors**, which are activated during platelet activation (via **thromboxane A2** and **ADP**).
- **Fibrinogen** binds to the activated **GPIIb/IIIa receptors** on adjacent platelets, linking them together to form a stable **platelet plug**. This aggregation is a critical step in forming a hemostatic plug and halting bleeding.

Summary of Platelets

Activation:

Triggered by agonists like **collagen**, **thrombin**, and **ADP**.

Cyclooxygenase (COX-1) produces **thromboxane A2**, which amplifies activation.

ADP activates the **P2Y12 receptor**, further promoting platelet activation and responsiveness.

Adhesion:

Platelets **adhere** to the subendothelial matrix through **vWF** interacting with **GPIb/IX/V** complex on the platelet surface.

ADP enhances platelet adhesion by promoting activation and making platelets "stickier."

Aggregation:

Platelet aggregation occurs via **GPIIb/IIIa receptors**, which bind to **fibrinogen** and link platelets together to form a plug.

This process is the final step in sealing the vascular injury and stopping bleeding.

Drugs and Their Effects on Each Phase:

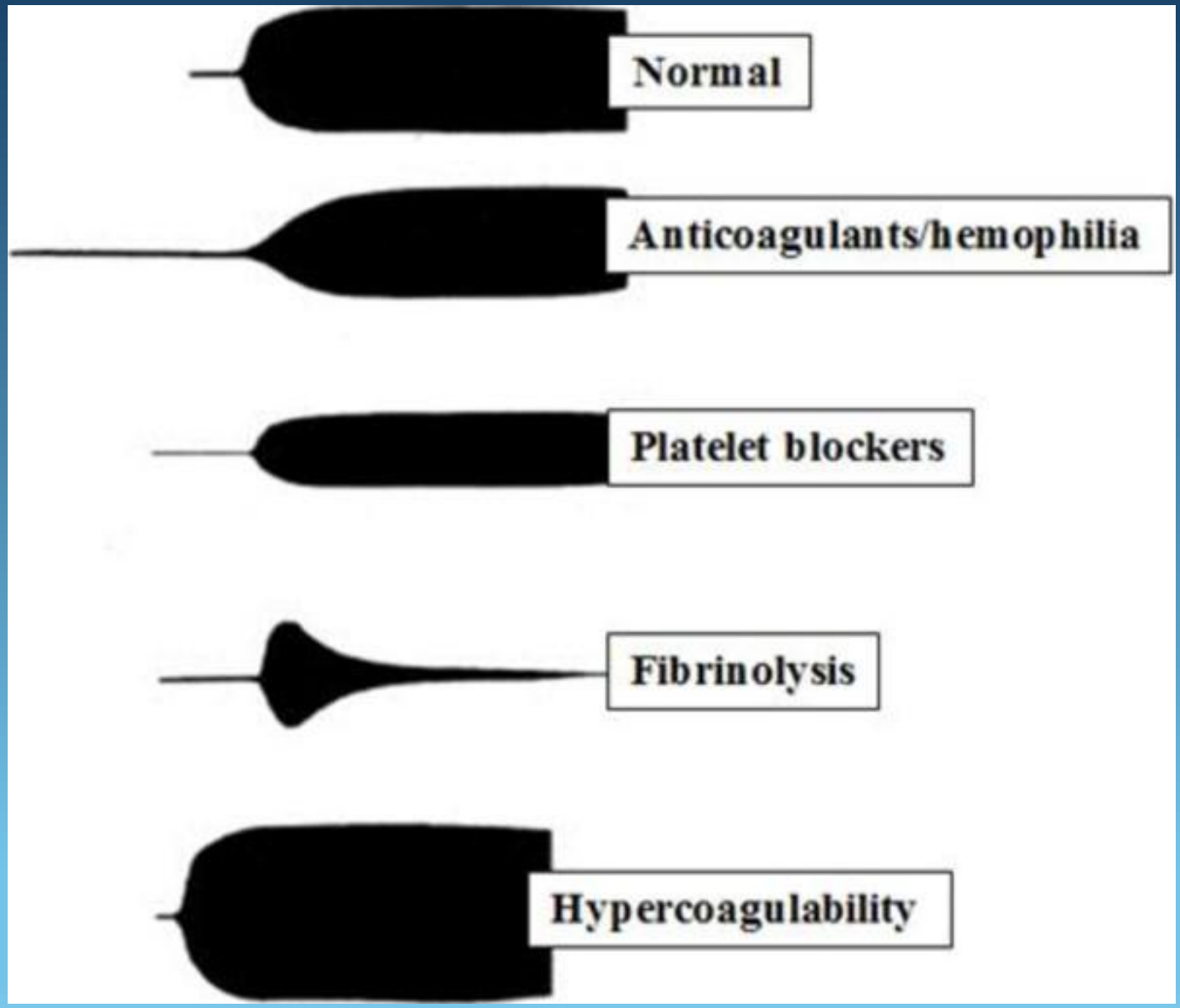
Platelet Function	Drug Class	Drug Examples	Mechanism of Action
	COX-1 Inhibitors	Aspirin	Inhibits **COX-1**, blocking thromboxane A2 production and platelet activation.
	P2Y12 Receptor Antagonists	Clopidogrel, Ticagrelor	Inhibit ADP binding to **P2Y12 receptors**, reducing platelet activation.
	vWF Enhancer	Desmopressin (DDAVP)	Stimulates vWF release, improving platelet adhesion in vWD.
Aggregation	GPIIb/IIIa Inhibitors	Abciximab, Eptifibatide	Block **GPIIb/IIIa** receptor, preventing platelet aggregation.

TEG Tracing for Platelets That Do Not Function Properly (e.g., Due to Aspirin, Uremia)

- **R time**: Normal, since platelet count is often not affected.
- **K time**: Prolonged. Even though the platelet count is normal, dysfunctional platelets are unable to aggregate properly, leading to prolonged clot formation.
- **Alpha angle**: Decreased. This reflects the impaired ability to form a clot because of dysfunctional platelets.

MA (Maximum Amplitude): Decreased. Despite normal platelet numbers, the platelets are unable to aggregate effectively, leading to a reduced clot strength

TEG Reference

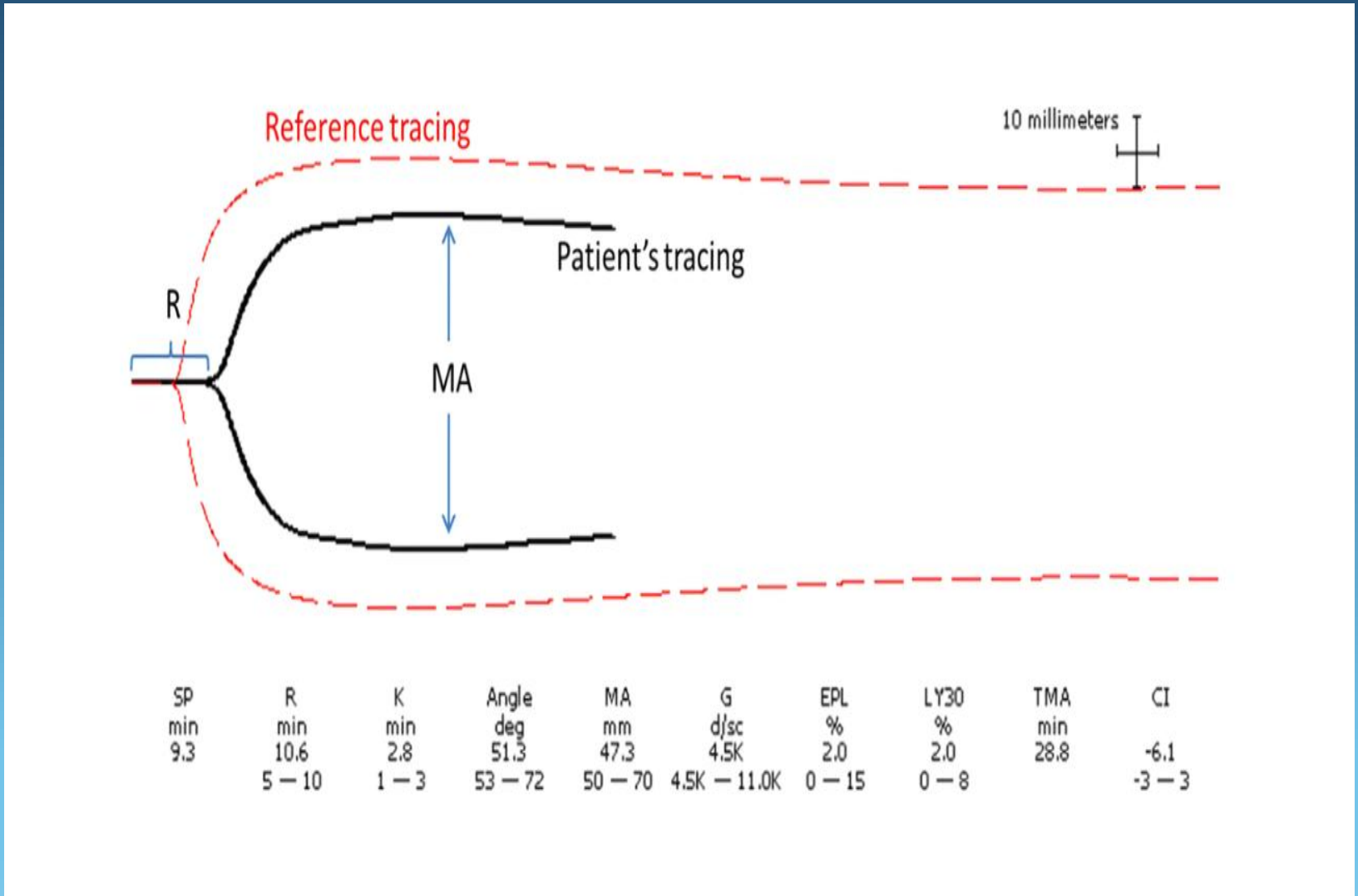


TEG Tracing for Thrombocytopenia (Low Platelet Count)

- **R time**: Prolonged. Fewer platelets are available to initiate clot formation, which delays the time to fibrin formation.
- **K time**: Prolonged. With low platelet numbers, it takes longer to build up enough strength to form a stable clot.
- **Alpha angle**: Decreased. This reflects the slower rate of clot formation, as the platelets are insufficient to rapidly form a strong clot.
- **MA (Maximum Amplitude)**: Decreased. There are fewer platelets to aggregate and form a solid clot.

- The curve will show **a prolonged and less steep clot formation phase**, with a significantly **lower MA**.

Low Platelets



SP	R	K	Angle	MA	G	EPL	LY30	TMA	CI
min	min	min	deg	mm	d/sc	%	%	min	
9.3	10.6	2.8	51.3	47.3	4.5K	2.0	2.0	28.8	-6.1
	5 — 10	1 — 3	53 — 72	50 — 70	4.5K — 11.0K	0 — 15	0 — 8		-3 — 3

Von Willebrand Disease

Types of Von Willebrand Disease (vWD)

Von Willebrand Disease (vWD) is a genetic bleeding disorder caused by a deficiency or dysfunction of **von Willebrand factor (vWF)**, a clotting protein that plays a critical role in platelet adhesion and stabilization of clotting factor VIII. There are three main types of vWD, classified based on the nature of the defect in **vWF** and its associated clinical presentation.

Von Willebrand Disease (vWD)

Von Willebrand Disease (vWD)

Definition

Von Willebrand disease is the most common inherited bleeding disorder, caused by defects in the **von Willebrand factor (vWF)**, which plays a critical role in platelet adhesion and stabilization of factor VIII in the coagulation cascade.

Symptoms

- Mucocutaneous bleeding (nosebleeds, gum bleeding)
- Easy bruising
- Heavy menstrual bleeding (menorrhagia)
- Post-surgical or post-traumatic bleeding

Type 1 Von Willebrand Disease (vWD)

- **Frequency**: The most common and mildest form of vWD, accounting for about **70-80%** of cases.
- **Pathophysiology**: **Partial deficiency** of von Willebrand factor (vWF). In this type, there is **reduced quantity** of vWF, but the **function of the vWF** is typically normal.
- **Clinical Presentation**:
  - Mild bleeding tendency, such as easy bruising, frequent nosebleeds, heavy menstrual bleeding (menorrhagia), and prolonged bleeding after surgery or dental work.
  - Typically presents in childhood or adolescence but can be diagnosed later in life.

Type 1 Von Willebrand Disease (vWD)

Laboratory Findings:

- **vWF antigen** (quantity) is reduced, typically between **30-50%** of normal.
- **Ristocetin cofactor activity** (which measures the functional activity of vWF) is also decreased, but it is usually greater than **30%**.
- **Factor VIII levels** may be mildly decreased, since vWF stabilizes FVIII.

Treatment:

- **Desmopressin (DDAVP)** can be used in most patients to stimulate the release of stored vWF, temporarily increasing vWF and factor VIII levels.
- In some cases, **vWF-containing factor concentrates** may be necessary if DDAVP is ineffective.

Von Willebrand Disease

. Type 2 Von Willebrand Disease (vWD)

- Type 2 vWD is divided into **subtypes (2A, 2B, 2M, and 2N)**, each associated with different defects in the **function** of vWF. The hallmark of Type 2 is **dysfunctional vWF**, where the vWF is present but does not function properly in platelet aggregation or factor VIII binding.

Von Willebrand Disease

- **Treatment**:
  - **DDAVP** is not effective in **Type 2** due to the excessive platelet binding.
  - **Factor concentrates** containing both vWF and factor VIII are typically used in Type 2A, Type 2M, and Type 2N. For **Type 2B**, platelet transfusions may be required in severe cases.
  - Cryoprecipitate

Von Willebrand Disease

Type 3 Von Willebrand Disease (vWD)

- **Frequency**: The **rarest and most severe** form of vWD.
- **Pathophysiology**: There is a **complete absence of von Willebrand factor** (both vWF antigen and function). This results in **severe bleeding** because vWF is critical for platelet adhesion to damaged blood vessels and for stabilizing factor VIII.
- **Treatment**:
  - **Desmopressin (DDAVP)** is ineffective because there is no vWF to release.
  - **vWF-containing factor concentrates** are required for treatment and may be used for prophylaxis in bleeding-prone patients.

Von Willebrand Disease

Type of vWD	vWF Levels	Factor VIII Levels	Key Features	Treatment
Type 1	**Reduced** (mild)	Mildly reduced (often normal)	Mild bleeding, easy bruising, menorrhagia	DDAVP, vWF-containing factor concentrates
Type 2A	Abnormal **multimers**	Mildly reduced	Mucocutaneous bleeding, loss of high-molecular-weight multimers	vWF-containing factor concentrates
Type 2B	Abnormal **multimers**	Mildly reduced	Thrombocytopenia, increased platelet binding	Avoid DDAVP, vWF-containing factor concentrates
Type 2M	Normal **multimers**	Mildly reduced	Defective platelet aggregation, normal vWF antigen	vWF-containing factor concentrates
Type 2N	Normal **multimers**	Low (Factor VIII)	Similar to hemophilia A	vWF-containing factor concentrates
Type 3	**Undetectable**	**Severely low**	Severe bleeding (hemarthrosis, muscle hematomas)	vWF-containing factor concentrates (lifelong use)

Trauma-induced bleeding disorders

Trauma-induced bleeding disorders arise from both **direct platelet injury** and **disseminated intravascular coagulation (DIC)** due to acute injury, surgery, or shock. These conditions can result in impaired platelet function due to mechanical damage, shock-induced platelet dysfunction, or coagulopathy associated with trauma.

Symptoms

- Excessive bleeding after trauma
- Prolonged or spontaneous bleeding in severe cases
- Mucosal bleeding (nosebleeds, gum bleeding)

Diagnosis

- **Platelet Count**: Often normal, but platelet function may be impaired.
- **Platelet Aggregation Studies**: To assess dysfunction.
- **Thromboelastography (TEG)**: To evaluate clot formation and platelet function during trauma-induced coagulopathy.

Trauma-Induced Platelet Dysfunction

Management

- **First-Line**:
  - **Platelet Transfusion**: For patients with significant thrombocytopenia or platelet dysfunction.
  - **Fresh Frozen Plasma (FFP)**: To correct coagulopathy.
  - **Cryoprecipitate**: In cases of significant fibrinogen depletion.
- **Second-Line**:
  - **Tranexamic Acid**: To prevent fibrinolysis and control bleeding.
  - **Recombinant Activated Factor VII (rFVIIa)**: In severe cases of bleeding

Trauma-Induced Platelet Dysfunction

Management

- **First-Line**:
  - **Desmopressin (DDAVP)**: Stimulates the release of stored vWF (effective in Type 1 vWD).
  - **Von Willebrand Factor Concentrates**: For severe cases, especially Type 2 and Type 3 vWD.
- **Second-Line**:
  - **Estrogen Therapy**: For managing menorrhagia.

Antifibrinolytics: Such as **tranexamic acid** to prevent excessive fibrinolysis

Uremic Bleeding: Pathophysiology, Diagnosis, and Treatment

Introduction

Uremic bleeding is a common complication in patients with chronic kidney disease (CKD), particularly in those with end-stage renal disease (ESRD) or those undergoing hemodialysis. This bleeding disorder is characterized by a bleeding tendency despite normal platelet counts, and it is often described as a form of **platelet dysfunction** rather than thrombocytopenia. Understanding the underlying pathophysiology, diagnostic approach, and treatment strategies is crucial for managing these patients.

Pathophysiology of Uremic Bleeding

Uremic bleeding results primarily from **platelet dysfunction**, and its pathogenesis is multifactorial. Key contributors include:

1. **Impaired Platelet Adhesion and Aggregation**:
    1. In uremia, platelets have reduced **adhesion** to the damaged endothelium and impaired **aggregation**. This is due to a defect in the **glycoprotein Ib/IX/V complex** (involved in platelet adhesion to **von Willebrand factor (vWF)**) and **GPIIb/IIIa** receptors (required for aggregation via fibrinogen).
    2. The interaction between platelets and the subendothelial matrix is compromised, leading to insufficient platelet plug formation.
2. **Defective Platelet Granule Release**:
    1. Platelets in uremic patients have a reduced ability to release granules (e.g., ADP, serotonin, and thromboxane A2), which are necessary for amplifying the platelet response and promoting aggregation.

Pathophysiology of Uremic Bleeding

1. **Altered Plasma Factors**:
    1. Uremic toxins accumulate in the blood, leading to the inhibition of platelet function. These toxins may interfere with **cyclooxygenase (COX)** and **prostaglandin synthesis**, further impairing platelet function.
    2. Increased levels of **urea** in the blood contribute to dysfunctional platelet adhesion and aggregation by affecting platelet receptors and the vascular endothelium.
2. **Increased Fibrinolysis**:
    1. Uremic patients often have elevated levels of **plasminogen activator inhibitor-1 (PAI-1)**, leading to an increased tendency for fibrinolysis and further compromise in hemostasis.
3. **Vascular Endothelial Dysfunction**:
    1. Endothelial dysfunction, a hallmark of uremia, can exacerbate bleeding by impairing the production of **nitric oxide** (NO), which normally acts to modulate platelet aggregation and vasodilation.
    2. Uremic toxins can damage endothelial cells, leading to an imbalance in procoagulant and anticoagulant factors.

Treatment of Uremic Bleeding

Diagnosis of Uremic Bleeding

The diagnosis of uremic bleeding is clinical but requires supportive laboratory evidence. The key steps in diagnosis are as follows:

1. **Clinical Presentation**:
    1. **Petechiae** and **purpura** (bruising) are common in the skin and mucosal surfaces (e.g., nosebleeds, gingival bleeding).
    2. **Prolonged bleeding times** and **delayed bleeding after minor trauma or surgery**.
    3. **Heavy menstrual bleeding** in women with uremia is also a common presentation.

Treatment of Uremic Bleeding

1. **Platelet Count**: Typically normal (which helps differentiate uremic bleeding from thrombocytopenia).
2. **Bleeding Time (BT)**: Often prolonged, reflecting impaired platelet function.
3. **Platelet Function Tests**: Tests like **platelet aggregation studies** (using agonists like ADP or collagen) or **flow cytometry** to assess platelet receptor function (e.g., GPIb/IX/V, GPIIb/IIIa).
4. **Coagulation Profile**:
    - **Prothrombin Time (PT)** and **Activated Partial Thromboplastin Time (aPTT)** are usually normal.
    - **Fibrinogen levels** and other markers of clotting are typically within the normal range.
5. **Uremic Toxins**: Elevated **urea**, **creatinine**, and other uremic toxins may be measured to assess the degree of renal impairment.

Treatment of Uremic Bleeding

. Desmopressin (DDAVP)

•**Desmopressin (DDAVP)** is an effective treatment for **uremic bleeding**, particularly in patients with **mild-to-moderate uremic bleeding**. DDAVP stimulates the release of **von Willebrand factor (vWF)** and **factor VIII** from endothelial storage sites, improving platelet adhesion to the subendothelial matrix.

•DDAVP is often used **preoperatively** or in cases of **acute bleeding episodes**.

3. Platelet Transfusion

•**Platelet transfusions** are sometimes used in severe cases of uremic bleeding, especially if the patient is undergoing surgery or has significant hemorrhage. However, this is typically a **temporary measure**, as platelet dysfunction often persists despite transfusions.

4. Antifibrinolytic Agents

•**Antifibrinolytics**, such as **tranexamic acid**, may be used to reduce excessive fibrinolysis and stabilize clot formation in some cases.

Treatment of Uremic Bleeding

5.Estrogen Therapy

•For **menorrhagia** in women with uremia, **estrogen therapy** may be considered to improve hemostasis.

6.Other Considerations

•**Erythropoiesis-Stimulating Agents (ESAs)** may be used to manage anemia, a common problem in CKD, but these are not directly involved in bleeding control.

•**Dialysis** may need to be optimized for patients with severe renal failure to improve outcomes.

7. Avoidance of Drugs that Impair Platelet Function

•In patients with uremic bleeding, **NSAIDs** (which inhibit COX-1) and **antiplatelet drugs** (like aspirin and clopidogrel) should be avoided, as they can further impair platelet function and exacerbate bleeding.

Treatment of Uremic Bleeding

Hemodialysis

- **Hemodialysis** remains the mainstay of treatment for uremic bleeding. By removing **uremic toxins** from the blood, dialysis can restore platelet function. Some patients may experience improvement in bleeding time and platelet function after a dialysis session.
- **High-flux dialysis** (which uses larger pores to remove more toxins) may be particularly effective in patients with severe uremia.

Treatment of Uremic Bleeding

1. **Thromboelastography (TEG)**:
    1. TEG can be used to assess overall coagulation function and platelet function. Uremic patients often show **abnormal platelet function** despite normal PT and aPTT.

TEG Tracing for Platelet Dysfunction (e.g., Uremic Bleeding)

- **R time**: Normal or slightly prolonged. Since platelet count is often normal, the initiation of clotting (fibrin formation) is not usually impaired unless other clotting factors are affected by uremic toxins.
- **K time**: Prolonged, reflecting a delay in clot formation due to poor platelet aggregation.
- **Alpha angle**: Reduced. This indicates that clot formation is slower because platelets cannot aggregate properly.
- **MA (Maximum Amplitude)**: Decreased. The overall strength of the clot is reduced because the platelets cannot aggregate effectively.

- The curve will appear **slower and flatter** in the formation phase (after the R time) and **lower in height** than a normal curve due to the reduced platelet aggregation.

Treatment Strategies

Treatment strategies for uremic bleeding primarily aim to improve platelet function and manage underlying uremia. Approaches include both **pharmacologic** and **non-pharmacologic** interventions.

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