# Treatment of Bleeding in Dialysis Patient

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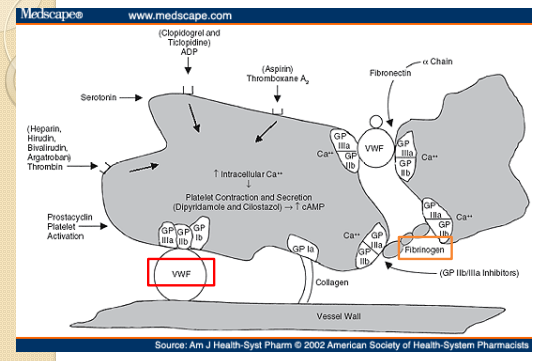
## Introduction

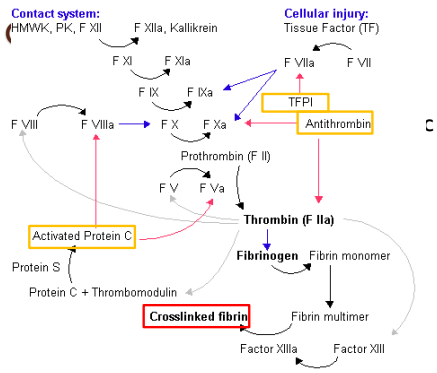
- Bleeding is a common and potentially serious complication of acute and chronic renal failure.
- **Most common**: bleeding at the site of fistula access puncture or temporary venous access insertion.
- **GI bleeding**: is observed in up to 1/3 of uremic patients.
- Other: subdural hematoma, spontaneous retroperitoneal bleeding, spontaneous subcapsular hematoma of the liver, intraocular hemorrhage, and, hemorrhagic pericarditis with cardiac tamponade

## Normal Hemostasis

- Hemostasis:

1. Primary hemostasis
2. Coagulation
3. Fibrinolysis




## Pathophisiology

- The pathogenesis of bleeding in patients with uremia is considered multifactorial.

- TABLE 1. Mechanisms affecting hemostasis in uremia
- ***Platelet abnormalities*** (reduction in: dense granule content, intracellular ADP and serotonin, and release of the platelet a-granule protein and b-thromboglobulin; enhanced intracellular c-AMP; defective cyclooxygenase activity; abnormalities inmobilization of platelet Ca++, arachidonic acid metabolism, and ex vivo platelet aggregation)
- ***Defects in platelet–vessel wall interaction*** (abnormal platelet adhesion, altered vonWillebrand factor, increased formation of vascular PGI2)
- ***Abnormal production of nitric oxide***
- ***Uremic toxins***
- ***Anemia*** (altered blood rheology, defective platelet diffusivity, decreased release ofADP by erythrocytes, erythropoietin deficiency)
- ***Drug treatment*** (anticoagulants, antiplatelet agents, nonsteroidal antiinflammatory drugs, b-lactam antibiotics, third-generation cephalosporins)

## Platelet abnormalities

- Moderate **thrombocytopenia** is a common finding in uremic patients: severe enough to cause bleeding is very rare.
- The **hemodialysis procedure** may itself cause thrombocytopenia through the interaction of blood with membranes that may activate complement (e.g., cuprophane) or from heparin that occasionally may induce thrombocytopenia by an immunologic mechanism.

## Role of anemia

- RBCs:

1. Increase platelet–vessel wall contact
2. Enhance platelet function by releasing ADP and inactivating PGI2

- Hb: a scavenger of NO
- These mechanisms may explain why in uremic patients bleeding time is shortened after partial correction of anemia by red blood cell transfusions or administration of EPO.

## Dialysis

- Dialysis improves platelet functional abnormalities and reduces, but does not eliminate, the risk of hemorrhage.
- The interaction between blood and artificial surfaces: may lead to platelet exhaustion and dysfunction.
- Heparin: occasionally induce platelet activation and thrombocytopenia

## Role of drugs

- **b-Lactam antibiotics**: act by perturbing platelet membrane function and by interfering with ADP receptors, raise the risk of bleeding due to their accumulation in uremic patients.
- **Third-generation cephalosporins**: inhibit platelet function and lead to marked disturbance of blood coagulation
- **NSAID:** inhibit platelet cyclooxygenase and disturb platelet function

- **Aspirin**

1. The beneficial effect of aspirin can be achieved with a moderate dose (160 mg/ day) that inhibits platelet TxA2 generation without affecting vascular PGI2 formation.
2. This dose of aspirin may have a much greater effect on bleeding time in uremic patients than in healthy subjects
3. A lasting effect due to the irreversible blocking of platelet cyclooxygenase

## Laboratory assessment

- Activated partial thromboplastin time, prothrombin time, and thrombin time are generally normal in uremia.
- No good correlation has been found between BUN or creatinine and clinical bleeding.
- The **cutaneous bleeding time** (normal values: 1–7 minutes) is the best laboratory hallmark of clinical bleeding caused by uremia.

## Therapeutic strategy

1. Dialysis
2. Correction of anemia
3. Cryoprecipitate and desmopressin
4. Conjugated estrogen
5. Tranexamic acid
6. Recombinant activated factor VII

## Dialysis

- Dialysis by removing uremic toxins (including urea, creatinine, phenol, phenolic acids, and GSA) improves platelet functional abnormalities.
- Dialysis may contribute to bleeding tendency through platelet activation induced by interaction of blood with the artificial surface as well as the use of systemic anticoagulation.

- Peritoneal dialysis is more effective in correcting platelet abnormalities than hemodialysis.
- However, in some cases, hypoalbuminemia (frequent in peritoneal dialysis) may cause platelet hyper-reactivity which favors thrombosis.

- Alternative strategies: regional anticoagulation with heparin and protamine, low-dose heparin, hemodialysis without anticoagulation, the use of low-molecular-weight heparin (LMWH), and regional anticoagulation with citrate.

1. Heparin + Protamine: This technique has been abandoned because of a rebound systemic anticoagulation after the completion of dialysis together with technical complexity.
2. Heparin-free dialysis: associated with biochemical activation of the clotting system
3. LMWH: not clear whether LMWH offers any advantage over anticoagulation with unfractionated heparin because only minor differences can be detected

4. Citrate: safe and more effective than others in hemodialysis patients with an active (or recently active) bleeding focus;
   - ✓ Complication: citrate intoxication, hyperaluminemia, hyperammonemia, hypernatremia, and profound metabolic alkalosis
5. Dermatan sulfate: A comparative short-term clinical study on few patients → dermatan sulfate suppresses clot formation during hemodialysis as efficiently as heparin but long-term comparative trials are warranted.

6. Antiplatelet drugs (eg. sulfinpyrazone, adenosine, and PGE1): no advantage over heparin
7. Aspirin and dipyridamole analogs: reduce fibrin and cellular deposition on the filter membrane but increase the risk of GI bleeding
8. PGI2: showing some promise, but adverse reactions such as headache, flushing, tachycardia, and chest and abdominal pain

## Correction of anemia

- Patients with chronic renal failure and prolonged bleeding time consistently benefited from red cell transfusions.
- EPO: A randomized study established that in uremic patients on rhEPO a threshold hematocrit between 27%and 32%effectively normalized bleeding time.

## Cryoprecipitate

- Cryoprecipitate: rich in VWF, fibrinogen, and fibronectin that has traditionally been used in the treatment of hemophilia A, von Willebrand's disease, hypofibrinogenemia, and dysfibrinogenemia.
- The effect of cryoprecipitate is apparent *1 hour after infusion*, but maximal effects on the bleeding time are obtained 4–12 hours (average: 8 hours) after the infusion. By 24–36 hours, the effect of cryoprecipitate is no longer detected.
- As many as 50% of patients fail to respond to cryoprecipitate.
- Risk of transmitting blood-borne disease

## Desmopressin (DDAVP)

- DDAVP induces the release of autologous VWF from storage sites into plasma.
- DDAVP shortens the bleeding time in 1 hour and its effect lasts 4– 8 hours. Bleeding time returns to baseline values within 24 hours.
- DDAVP was effective at a dose of 0.3 μg/kg body weight IV or SC.
- At 10 to 20 times the intravenous dose, intranasal desmopressin (3 μg/kg) shortens the prolonged bleeding time.

- Desmopressin loses its efficacy when repeatedly administered, probably due to a progressive depletion of VWF stores in endothelial cells.
- Free of serious side effects
- Treatment of bleeding and the prevention of bleeding during surgery or invasive procedures

## Conjugated estrogen

- Long lasting hemostatic competence, such as undergoing surgery or GIB
- One oral dose of 25 mg of a conjugated estrogen preparation normalizes bleeding time for 3–10 days with no apparent ill effects
- In uremics: a cumulative dose of 3 mg/kg IV divided over five consecutive days, produced a long-lasting reduction in the bleeding time

- Low-dose transdermal estrogen (estradiol 50–100 μg/24 hours) applied as a patch twice weekly reduces recurrent GIB with a parallel improvement of bleeding time and no side effects.
- Conjugated estrogens exert their hemostatic effect by interfering with the NO synthetic pathway.

## Tranexamic acid (TXA)

- Preventing the binding of plasminogen to fibrin and the activation of plasminogen to plasmin
- Colonic angiodysplasias and spontaneous subdural and cerebral hematoma in dialysis patients and, as adjunctive therapy, in treating major UGI bleeding in dialysis patients
- Accumulate in renal insufficiency

## Recombinant activated factor VII

- Enhancing thrombin generation on thrombin-activated platelet surfaces and leading to a stable clot resistant to premature fibrinolysis
- Initial → treatment of hemorrhages in patients with hemophilia associated with antibodies inactivating factor VIII or IX

## Conclusion

- Bleeding is still a potentially life-threatening complication in uremic patients and limits surgery and invasive procedures.
- Acute bleeding episode: DDAVP
- GI or intracranial bleeding; undergoing major surgery: conjugated estrogen