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

Pathophysiology

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

**Therapeutic strategy**

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

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**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.

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**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

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**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

**Tranexamic acid (TXA)**

- Preventing the binding of plasminogen to fibrin and the activation of plasminogen to plasmin
- Colonic angiodysplasias and spontaneous subdural and cerebral hematomas 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