

# Uremic Bleeding: Pathophysiology, Diagnosis, and Management

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**A**lmost all patients with uremia, the clinical syndrome of advanced renal failure, have a bleeding diathesis. This predisposition becomes especially problematic when these patients undergo invasive procedures such as surgery, biopsy, or catheter placement. Moreover, many of the clinical presentations of uremic bleeding involve life-threatening conditions (**Table 1**), including pericardial tamponade, intracranial bleeding, and gastrointestinal bleeding. In hemodynamically unstable patients with uremia, the massive occult bleeding that can occur in these conditions is particularly troubling and should remain a central concern in the evaluation of such patients.

Symptoms of uremic bleeding can be markedly severe in patients with either intracranial or gastrointestinal bleeding.<sup>1</sup> Subdural hematomas, for example, can produce symptoms that mimic those of dialysis disequilibrium syndrome.<sup>2</sup> In patients with renal failure, gastrointestinal bleeding occurs with greater frequency and is associated with a higher mortality than in the general population; in fact, hemorrhaging of the upper gastrointestinal tract is the second leading cause of death in patients with acute renal failure.<sup>3</sup>

This article will review the underlying pathophysiology and diagnosis of uremic bleeding. Preventive and therapeutic management of the disorder will also be discussed.

## **PATHOPHYSIOLOGY OF UREMIC BLEEDING**

The normal physiologic response to vessel injury begins with local vasoconstriction. Primary hemostasis requires 3 critical steps: (1) platelet adhesion, (2) granule release, and (3) platelet aggregation.<sup>4</sup> In the first step, endothelial cells secrete von Willebrand's factor (vWF), which binds to subendothelial structures and receptor molecules of platelet glycoprotein (GP) Ib; in this way platelets are attached to the sites of endothelial disruption. In the second step, platelet adhesion triggers release of various mediators, including adenosine diphosphate (ADP) and thromboxane A<sub>2</sub>, which stimulate further aggregation and vasoconstriction. Fibrinogen binds platelets to each other, but activation of re-

ceptor molecules of the platelet GPIIb-IIIa complex is essential both to enable this binding to occur and to support irreversible adhesion to surface-bound vWF.<sup>5</sup> In the final step, platelet interaction with coagulation factors leads to generation of thrombin, which activates fibrinogen to produce fibrin, thus forming fibrin clots.<sup>6</sup>

The platelet dysfunction characteristic of uremia is multifaceted (**Table 2**). Platelet count is usually within the normal range or slightly low in patients with uremia. It has been suggested that these patients have a complex platelet dysfunction and an abnormal platelet-vessel wall interaction.<sup>7</sup> Radioligand studies have indicated that the binding of fibrinogen to ADP-stimulated platelets in uremic media is impaired.<sup>8</sup> Notably, the ability of the vessel wall to generate the potent antiaggregatory substance prostacyclin (prostaglandin I<sub>2</sub>) increases in uremia; moreover, endothelial cells seem to generate an abnormal complex of coagulation factor VIII (antihemophilic factor) and vWF. Finally, the largest polymers of vWF, which are primarily responsible for the adhesion process, are deficient in patients with uremia, although the serum level of vWF in these patients is usually high or within the normal range.

Some studies have found a defective interaction between vWF and the GPIIb-IIIa complex that is responsible for decreased spreading of uremic platelets that adhere to the subendothelium.<sup>5,8,9</sup> Platelets from patients with uremia exhibit abnormal adhesive function; a reduced aggregating response to ADP, epinephrine, and collagen; and an altered arachidonic acid metabolism. Numerous biochemical changes in platelets have been reported, including a decrease in serotonin and ADP levels, an increase in the cyclic adenosine monophosphate level, and a decreased ability to generate thromboxane A<sub>2</sub>.<sup>10-12</sup>

Anemia exacerbates the bleeding tendency in patients with uremia, most likely because of deranged radial

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**Table 1.** Clinical Presentations of Uremic Bleeding\*

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Petechiae, purpura, ecchymoses
Epistaxis
Bleeding after invasive procedures (eg, surgery, catheter placement, biopsy)
Hemorrhagic pericarditis (eg, pericardial tamponade)
Hemorrhagic pleural effusion
Gastrointestinal hemorrhage
Intracranial bleeding (eg, from a subdural hematoma or subarachnoid hemorrhage)
Retroperitoneal bleeding (spontaneous or occurring after invasive radiology)
Spontaneous subcapsular hematoma of the liver
Ocular hemorrhage
Uterine hemorrhage

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\*Arranged in approximate order of frequency.

Adapted from Lohr JW, Schwab SJ. Minimizing hemorrhagic complications in dialysis patients. *J Am Soc Nephrol* 1991;2:961–75, and Viganò G, Remuzzi G. Prevention and therapeutic management of bleeding in dialysis patients. In: Nissenson AR, Fine RN, editors. *Dialysis therapy*. 2nd ed. Philadelphia: Hanley & Belfus; 1993:124–8.

transport of platelets, decreasing their contact with the endothelium.<sup>10,11</sup> For the average patient undergoing dialysis, blood losses from bleeding in the gastrointestinal tract, from menstruation (for women), from blood draws, and in the dialyzers after each treatment collectively amount to approximately 2.5 L/year.<sup>2</sup> This figure does not include occasional large losses caused by surgical procedures or bleeding from access devices.

Recent studies have suggested that abnormal production of nitric oxide (NO) also is involved in the bleeding tendency in patients with uremia.<sup>3,11,12</sup> A specific inhibitor of NO formation, *N*-monomethyl-L-arginine, completely normalized the prolonged bleeding time of uremic rats.<sup>11,12</sup> NO is a potent vascular relaxing factor that might, to some extent, counter the vasoconstriction after vessel injury.<sup>3</sup> NO also is known to inhibit platelet adhesion to the vascular endothelium by elevating intracellular levels of cyclic guanosine monophosphate. Limited evidence also has been obtained showing that leukocytes might play a role in blood coagulation; leukocytes have the ability to express different types of clot-promoting activities (their so-called *procoagulant activity*).<sup>13</sup>

Given that dialysis transiently improves or even completely corrects prolonged bleeding time and the clinical bleeding tendency, defective hemostasis appears to be caused, at least in part, by dialyzable uremic toxins.

**Table 2.** Factors Involved in the Uremic Bleeding Tendency

**Factors related to the vessel wall**

Decreased production of the largest multimers of von Willebrand's factor

Enhanced nitric oxide production

Enhanced prostacyclin production

**Factors related to platelets**

Abnormal mobilization of calcium ions in platelets

Defective activation of glycoprotein IIb-IIIa receptors

Defective cyclooxygenase activity (reduced ability to generate thromboxane A<sub>2</sub>)

High levels of cyclic adenosine monophosphate

Low levels of serotonin and adenosine diphosphate

**Factors related to the blood**

Anemia

Altered blood rheology (ie, deranged radial transport of platelets)

Altered transfer of adenosine diphosphate from erythrocytes to platelets

Uremic toxins (eg, guanidinosuccinic acid, phenol, phenolic acid, urea)

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Urea, creatinine, guanidinosuccinic acid, phenolic acid, and parathyroid hormone have been studied as possible culprits. Various dialyzable toxins and high circulating levels of parathyroid hormone have all been causally related to platelet dysfunction in uremia. Dialysis, however, might also contribute to the uremic bleeding tendency. The interaction between blood and artificial surfaces might induce chronic activation of platelets, leading to their eventual dysfunction.<sup>11</sup> Heparin used to obtain systemic anticoagulation can, in a minority of patients, induce platelet activation and thrombocytopenia.<sup>11</sup> This occurrence is known as *heparin-associated thromboembolism* or *white clot syndrome*.<sup>14</sup>

**DIAGNOSIS OF UREMIC BLEEDING**

Various tests have been used to assess the bleeding tendency in patients with uremia, but only determination of the bleeding time has been helpful in distinguishing bleeders from nonbleeders.<sup>9,15</sup> Although potentially very valuable, this laboratory test is prone to give both falsely abnormal and falsely normal results when performed with improper technique.<sup>16</sup> When the blood urea nitrogen level is greater than 60 mg/dL or the serum creatinine level is greater than 6.7 mg/dL, bleeding time is significantly prolonged.<sup>17</sup>

Sometimes prolongation of bleeding time does not result from uremia itself. For example, high doses of penicillins, cephalosporins, and related antibiotics (eg, penicillin G, carbenicillin, ticarcillin, ampicillin, moxalactam) cause prolongation of bleeding time and interfere with platelet function by binding to platelets and blocking recognition of platelet-membrane agonist receptors.<sup>17</sup> Propranolol and other  $\beta$ -adrenergic blockers also induce a mild qualitative platelet defect in some patients by an unknown mechanism.

The damage caused by aspirin to platelets is irreversible. Aspirin inactivates the cyclooxygenase enzyme in platelets. Because platelets do not carry the necessary organelles and nuclear information to regenerate this enzyme, prolonged bleeding time usually persists for 8 to 10 days, which is roughly equal to the life of a thrombocyte in the circulation. Desmopressin can reverse the adverse effect that aspirin has on bleeding time.<sup>6</sup> Alcohol, which by itself does not affect bleeding time, enhances aspirin's ability to prolong bleeding time.<sup>16</sup> Nonsteroidal anti-inflammatory drugs also can cause platelet dysfunction, and the duration of this dysfunction is related to the half-life of the drugs in the serum.

#### **PREVENTION OF UREMIC BLEEDING**

It is safer to prevent uremic bleeding than it is to treat it. A complete coagulation profile that includes bleeding time should be obtained before any invasive procedure is attempted in patients with uremia. Bleeding tendencies related to hepatic failure or other causes should be corrected. If bleeding time is prolonged, desmopressin should be administered before invasive procedures, especially in high-risk patients. Physicians should be selective about the type and technique of the surgical procedure used, in order to minimize trauma. In the process of line placement, for example, horizontal searching movements under the skin with a trochar needle should be avoided, because this action might cause rupture of many small subcutaneous venules.

Patients with uremia who are to undergo elective surgery should be advised to avoid aspirin and other nonsteroidal anti-inflammatory drugs for at least 1 week prior to the operation.<sup>16</sup> The adequacy of renal replacement therapy should be checked. Because patients who do not receive adequate dialysis tend to bleed more, patients receiving dialysis should have an adequate session before surgery, preferably without the use of heparin. Alternatives to standard heparin administration during dialysis include heparin anticoagulation with protamine reversal, minimal use of heparin, use of prostacyclin, and regional citrate anticoagulation. If heparin

must be used, the surgeon should be informed of its dosage and the time it is given. Even if regional heparinization is used, rebound heparin effect should be expected during surgery.<sup>2</sup>

Prior to surgery, a threshold hematocrit between 27% and 32% must be reached if bleeding time is to become normal or nearly normal. Autologous blood storage for possible autotransfusion during the perioperative period should be considered, especially for patients who are kidney transplant candidates, to avoid sensitization and risk of infections.

Dialysis patients usually receive therapy with recombinant human erythropoietin and tend to have iron deficiency because of the high rate of iron utilization. Consequently, iron stores should be checked and replaced, if needed, prior to any surgical procedure. Patients who are receiving erythropoietin treatment and are maintaining relatively normal hematocrit levels usually do not have bleeding problems during the perioperative period.

Invasive procedures in infected areas should be avoided, because infection increases the bleeding tendency; it is very difficult to control bleeding in an infected area until the infection is eliminated. Using only aseptic techniques will eliminate infectious complications and the necessity for antibiotic treatment, which can cause platelet and vascular dysfunctions.

If initial creation of a native arteriovenous fistula for dialysis is proficient, many complications from further access placement procedures will be avoided. Synthetic grafts used for dialysis access are more prone to thrombosis and infection and have shorter lives than do native fistulas; thus, the number of access procedures required in patients with synthetic grafts is much higher.

Straining during defecation after placement of a catheter can initiate or cause recurrence of bleeding around the catheter site. Therefore, efforts should be made to ensure that patients undergoing catheter placement for dialysis are not constipated. It is likely that constipated patients would bleed more often and longer than nonconstipated patients. Patients with catheters in their groins for the purpose of emergent dialysis should never be allowed to sit and should not ambulate, because they are at very high risk for developing a massive hematoma in the groin.

#### **TREATMENT OF UREMIC BLEEDING**

##### **Adequate Dialysis**

Dialysis has been the standard therapy for uremic bleeding. However, it might not be adequate to correct bleeding time.<sup>15</sup> Hemodialysis corrects prolonged

bleeding time in only 30% to 50% of the cases.<sup>6</sup> Patients undergoing peritoneal dialysis generally have fewer bleeding problems.<sup>6,17</sup>

### **Mechanical Pressure**

For overt bleeding sites, prolonged mechanical pressure over the area that is bleeding might in itself be sufficient to control bleeding, if the bleeding time is not too prolonged. The site of bleeding should be elevated above the level of the heart. The head of the bed should be elevated to decrease the pressure in central veins. Large catheters, such as hemodialysis catheters, should not be removed, because their removal can result in the creation of a large hole through which blood can extravasate easily, not to mention that the patient would lose vascular access for dialysis. Dressings soaked with blood can be weighed to assess the amount of bleeding, and heparin should be avoided during dialysis until bleeding stops.

### **Management of Anemia**

If present, anemia should be corrected in patients with uremic bleeding. As bleeding continues, worsening anemia contributes to the bleeding tendency. In the acute setting, transfusions of packed red blood cells might be needed to correct the anemia. However, the risk associated with transfusions is significant. Transfusions of blood or blood products can have a number of adverse effects: (1) transmission of viral infections; (2) formation of coagulation factor inhibitors and immune complexes; and (3) anaphylaxis caused by IgA deficiency.<sup>6</sup> For long-term therapy of uremic anemia, intravenous or subcutaneous administration of recombinant human erythropoietin, 35 to 50 U/kg body weight 3 times per week, is the current treatment of choice.<sup>17</sup>

### **Administration of Desmopressin**

According to a study, desmopressin (1-deamino-8-D-arginine vasopressin) normalized bleeding time in 75% of patients with chronic renal failure.<sup>6</sup> The largest multimeric form of vWF was investigated under appropriate laboratory conditions and found to be reduced or absent in the plasma of patients with uremia; the intraplatelet vWF content was half the normal value.<sup>18</sup> These findings might explain the beneficial effect of therapeutic agents that either replace or stimulate the release of large vWF multimers. Desmopressin increases the levels of coagulation factor VIII and vWF in a dose-dependent manner.<sup>6</sup> It similarly increases the level of the largest vWF polymers in the blood, as well as the plasminogen activator level. Other hemostatic factors are not affected. The peak response of factor

VIII occurs almost immediately after infusion of the drug; vWF reaches its peak 30 to 60 minutes later.<sup>6</sup>

Although the exact mechanisms involved in increasing the levels of factor VIII, vWF, and plasminogen activator are not clear; antidiuretic vasopressin ( $V_2$ ) receptors are thought to be involved. Desmopressin produces little or no vasoconstriction, no increase in blood pressure, and no contractions of the uterus or gastrointestinal tract, all of which are related to stimulation of  $V_1$  receptors. Additionally, one study showed a further reduction in protein C activity after the infusion of desmopressin, but the role of this change in the correction of the uremic bleeding is not clear.<sup>19</sup>

Desmopressin can be administered intravenously or subcutaneously at a dose of 0.3  $\mu\text{g}/\text{kg}$  or intranasally at a dose of 30  $\mu\text{g}/\text{kg}$ . An intravenous route is most likely preferable when a marked and consistent increase in factor VIII and vWF is required for prophylaxis or for treatment of severe hemorrhaging. Desmopressin is usually infused in 50 mL normal saline over a 30-minute period. Subcutaneous administration gives comparable results, but at least 6 mL of fluid is required to deliver an adult dose of desmopressin by this route. After desmopressin administration, bleeding time shortens considerably in 2 to 4 hours, but the effect of desmopressin disappears within 6 to 8 hours. Thus, although desmopressin can obviate the need for blood products in many uremic patients, its hemostatic actions tend to be short-lived.

Desmopressin, when used every 12 hours as usually recommended, can cause tachyphylaxis.<sup>6</sup> The initial beneficial response is restored when therapy is withheld for 3 or 4 days. Because most bleeding episodes and prophylaxis for minor surgical procedures generally require only 1 dose of desmopressin (or, at most, only a few doses) to be administered, tachyphylaxis does not often hamper clinical use of the drug.<sup>6</sup>

Desmopressin often is used in combination with an antifibrinolytic drug in Europe, but the addition of an antifibrinolytic agent entails the risk of thrombosis.<sup>6</sup> In the predialysis period, patients with chronic renal failure may develop desmopressin-induced water retention, which in turn may increase their likelihood of developing congestive heart failure. In patients undergoing coronary artery bypass surgery, an inhibition of vWF level has been suggested as being preferable to its elevation in order to encourage graft patency.<sup>6</sup>

Some authors have suggested that intranasal administration of low-dose desmopressin (eg, 20  $\mu\text{g}$ ) may be effective as treatment of a bleeding diathesis in children.<sup>20</sup>

### **Cryoprecipitate Infusion**

Infusion of cryoprecipitate that is rich in factor VIII and vWF can shorten the prolonged bleeding time in many patients with uremia.<sup>16</sup> However, the hemostatic response to cryoprecipitate infusion is variable. Some patients with uremic bleeding do not respond at all to this therapy<sup>15</sup>; this observation is consistent with the current concept that the pathogenesis of uremic bleeding is multifaceted. Cryoprecipitate should be reserved for those patients who do not respond to desmopressin or for whom desmopressin is contraindicated. For actively bleeding patients, the recommended dose of cryoprecipitate is 10 bags given over 30 minutes. According to a published report, the nadir value of bleeding time occurred 1 to 12 hours after infusion.<sup>15</sup> As with other blood products, this treatment carries the risk of transmitting infection and causing allergic or rare anaphylactic reactions; there also might be serologic incompatibility because of red cell isoagglutinins.<sup>15</sup>

### **Administration of Conjugated Estrogens**

Conjugated estrogens were introduced recently into the management of uremic bleeding. For patients who require prolonged hemostatic maintenance because of gastrointestinal or intracranial bleeding or major surgery, administration of conjugated estrogens should be considered. Among conjugated estrogens, 17 $\beta$ -estradiol was found to be the most active component in correcting prolonged bleeding time in uremic rats.<sup>13</sup> The dissociation between the short half-life (a few hours) of estrogen in the plasma and the long-lasting effect (weeks) of the drug is remarkable and suggests that the effect of estrogens on primary hemostasis in uremia is mediated by a receptor mechanism. Estrogens enter the cell and bind high-affinity receptor proteins on the cytosol; the resultant estrogen-protein complex is then translocated into the cell nucleus, with subsequent induction of specific messenger RNA and certain specific but unknown proteins.<sup>13</sup>

Platelets do not possess specific receptors for estrogens.<sup>13</sup> There is some evidence that endothelial cells and leukocytes have estrogen receptors, but the exact mechanism by which estrogen treatment corrects the uremic bleeding tendency is still unclear, although a biochemical explanation recently has been proposed.<sup>21</sup> Some authors have claimed that 17 $\beta$ -estradiol corrects abnormal primary hemostasis in uremic rats by limiting vascular endothelial expression of NO-forming enzymes.<sup>21</sup>

Conjugated estrogen infusion (0.6 mg/kg daily) for 5 consecutive days is the current recommended regimen. With this protocol, an initial decrease in bleeding

time is seen approximately 6 hours after the first dose, and the maximum effect can be achieved in 5 to 7 days; bleeding time usually returns to pretreatment levels in 2 to 3 weeks. Because of the delayed onset of action, the effectiveness of this treatment usually is underestimated, so the therapy is not extensively used. Whenever prolonged bleeding control is needed, conjugated estrogen therapy should be started at the same time as therapy with rapidly acting agents such as desmopressin and cryoprecipitate.

Oral administration of conjugated estrogens at a dose of 50 mg daily for 7 days was shown to be effective.<sup>17</sup> However, the length of the beneficial effect was short, and bleeding time again became prolonged within 4 days of the treatment session. One author has recommended that patients with uremia who have prolonged bleeding times be placed on maximal transdermal therapy with estrogen (ie, 100  $\mu$ g/24 h) at least 2 weeks before undergoing any surgery.<sup>22</sup>

### **Administration of Antifibrinolytic Agents**

Oral administration of  $\epsilon$ -aminocaproic acid and tranexamic acid has proved to be extraordinarily effective in achieving oral hemostasis; tranexamic acid, the newer drug, is more potent.<sup>6</sup> Patients with uremia who undergo tooth extractions and minor oral surgery may benefit from these drugs. Both drugs inhibit plasminogen and (to a lesser degree) plasmin activation.

An adverse effect of such antifibrinolytic therapy is the development of thrombi in areas other than the target site.  $\epsilon$ -Aminocaproic acid has been known to cause thrombosis in the glomerular capillaries of the renal pelvis and ureters of patients with upper urinary tract bleeding. Consequently, this agent should not be used to treat hematuria of upper urinary tract origin. Similarly, tranexamic acid is contraindicated in patients with subarachnoid hemorrhage, because it may cause cerebral edema and infarction.<sup>6</sup>

### **Topical Administration of Hemostatic Agents**

In patients with uremia, topical administration of hemostatic agents can be used both for exterior wounds and during surgery. These agents can be used in conjunction with systemic antifibrinolytic therapy to achieve immediate hemostasis at a wound site. Adsorbable collagen hemostat (ACH) is a faster and more effective agent than are thrombin, gelatin foam, and oxidase cellulose. The rapid hemostatic effect of ACH is mediated by its interaction with platelets at the injury site. This bovine collagen product sticks firmly to the bleeding surface, and its fibrillar structure provides a mesh in which platelets become trapped. As platelets interact with the

collagen fibrils, they undergo a release phenomenon, triggering further aggregation and production of fibrin.<sup>6</sup>

ACH has been reported to achieve effective local hemostasis during surgery in patients receiving heparin or aspirin and in patients with coagulation factor deficiencies.<sup>6</sup> ACH creates a slightly more intense and longer-lasting inflammatory response than occurs normally but does not slow the rate or impair the quality of wound healing. The collagen material is resorbed in less than a week.<sup>6</sup>

### Platelet Transfusion

Platelet transfusion is advocated only in cases of uncontrolled hemorrhage in patients with uremia. Shortly after entering a uremic environment, platelets become dysfunctional, so platelet transfusion should be used only in combination with administration of desmopressin, cryoprecipitate, and packed red blood cells.<sup>17</sup>

### Kidney Transplantation

When available as an option, renal transplantation offers the best protection against uremic bleeding by reversing the adverse effects of uremia on the vessel wall, platelets, and other blood components.

### CONCLUSION

The bleeding diathesis of patients with uremia is a significant clinical concern, especially when surgery and other invasive procedures are required. The pathogenesis of the hemorrhagic tendency of these patients is not totally understood, although complex platelet dysfunction with abnormal platelet–vessel wall interaction is thought to have a major role; deficiency of the largest vWF polymers is likewise suspected of playing a part. In most cases, treatment with dialysis is adequate therapy for patients with uremia, yet such therapy sometimes fails to correct their prolonged bleeding time. In these cases, the incidence of uremic bleeding can be decreased in patients by better control of their anemia and by use of agents such as desmopressin, cryoprecipitate, conjugated estrogens, antifibrinolytic agents, and ACH.

Being unduly aggressive in correcting prolonged bleeding time may at times result in clotting at vascular access sites of patients receiving dialysis. The likelihood of perioperative clotting at these sites is already increased because of anesthesia and the potential hypotension associated with it. In managing uremia, physicians must remain attuned to these possibilities in selecting the best treatment for individual patients.

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