Treatment of Bleeding in Dialysis Patients

Miriam Galbusera,* Giuseppe Remuzzi,*† and Paola Boccardo*
*Mario Negri Institute for Pharmacological Research, Bergamo, Italy, and †Unit of Nephrology and Dialysis, Azienda Ospedaliera, Ospedali Riuniti di Bergamo, Bergamo, Italy

ABSTRACT

Bleeding is a common and potentially serious complication of acute and chronic renal failure. The pathogenesis of bleeding in uremia is multifactorial; however, the major role is played by abnormalities in platelet–platelet and platelet–vessel wall interaction. Platelet dysfunction is partially due to uremic toxins present in circulating blood. Despite decreased platelet function, abnormalities of blood coagulation and fibrinolysis predispose the uremic patients to a hypercoagulable state carrying the risk of cardiovascular and thrombotic complications. Dialysis improves platelet abnormalities and reduces, but does not eliminate, the risk of hemorrhage. Hemodialysis can even contribute to the bleeding through the continuous platelet activation induced by the interaction between blood and artificial surfaces and the use of anticoagulants. Correction of anemia improves hemostasis in uremic patients. Therapeutic management of bleeding in patients with uremia is discussed.

Bleeding is a common and potentially serious complication of acute and chronic renal failure (1). The most common bleeding complications in uremia are petechial hemorrhages, blood blisters, and ecchymoses at the site of fistula access puncture or temporary venous access insertion. Gastrointestinal bleeding occurs with greater frequency and is observed in up to one third of uremic patients. Low-grade gastrointestinal bleeding may be even more common. The causes of bleeding are usually peptic ulcers, hemorrhagic esophagitis, gastritis, duodenitis, and gastric telangiectasias (2,3). Other bleeding complications reported in chronic uremia are subdural hematoma, spontaneous retroperitoneal bleeding, spontaneous subcapsular hematoma of the liver, intraocular hemorrhage, and, now rare, hemorrhagic pericarditis with cardiac tamponade (1).

With the advent of modern dialysis techniques and the use of erythropoietin to correct anemia, the incidence of severe hemorrhages has been definitively reduced. However, bleeding diathesis still represents a problem for uremic patients, particularly during surgery or invasive procedures such as biopsies.

Normal Hemostasis

Hemostasis is a complex process composed of three phases—primary hemostasis, coagulation, and fibrinolysis—that are closely linked to each other. They control blood fluidity and rapidly induce hemostatic plug formation at the site of vascular injury.

Primary hemostasis is due to interactions between platelets and adhesive proteins and the vessel wall (4). Normal vascular endothelium is a thromboresistant surface that possesses antiplatelet, anticoagulant, and profibrinolytic properties, but after vascular injury, platelets are rapidly recruited to form the hemostatic plug.

The mechanism of platelet adhesion is mainly mediated by the interaction of two platelet receptors, glycoprotein Ib (GPIb) and the activation-dependent receptor glycoprotein IIb–IIIa (GPIIb–IIIa) complex, with the adhesive molecules von Willebrand factor (VWF) and fibrinogen (5). In the circulation the initial contact is dependent on the binding of VWF (bound to collagen on the exposed subendothelium or to P-selectin on activated endothelial cells) with GPIb on platelets. This interaction favors the rolling of platelets on the endothelial surface, initiates platelet activation and triggers conformational change in the GPIIb–IIIa complex that facilitates binding with fibrinogen and VWF. Following the adhesion step platelets undergo a shape change and release the content of the granules liberating substances such as ADP, thromboxane, VWF, fibrinogen, thrombin, serotonin, and epinephrine that cause further platelet activation and aggregation as well as vasoconstriction. The process of platelet adhesion is counteracted by the protease ADAMTS13 that cleaves the VWF thus blocking thrombus growth (6).

Coagulation (4) is divided into the intrinsic pathway, initiated by contact with negatively charged surfaces, and the extrinsic pathway initiated by tissue factor (TF). In the coagulation cascade the key event is the activation of the extrinsic pathways promoted by TF, a cell membrane protein that is exposed at the site of vascular

Address correspondence to: Paola Boccardo, Mario Negri Institute for Pharmacological Research, Via Gavazzeni 11, 24125 Bergamo, Italy, or e-mail: boccardo@marionegri.it.
Seminars in Dialysis—Vol 22, No 3 (May–June) 2009 pp. 279–286
DOI: 10.1111/j.1525-139X.2008.00556.x

injury, which leads to the formation of the TF/VIIa complex. This complex, in turn, may activate both FIX and FX. FXa activates FV to FVa, leading to the FXa/FVa complex that is capable of converting prothrombin to thrombin. Once formed, thrombin activates FVIII, FV, FXI, and converts fibrinogen to fibrin. Finally, the thrombin-activated FXIIIa forms fibrin polymers. Thrombin also stimulates positive feedback that activates platelets and produces thrombin bursts leading to maintenance of fibrin formation.

The coagulation cascade is controlled by several anticoagulatory mechanisms including antithrombin, the protein C system, the TF pathway inhibitor, and glycosaminoglycans. Antithrombin III inhibits thrombin, FXa, and FIXa, and its action is greatly accelerated by heparin and heparin-like glycosaminoglycans present on endothelial surface. Thrombomodulin is a thrombin receptor expressed by endothelial cells that, after the formation of the thrombin/thrombomodulin complex, activates protein C, which, together with its cofactor protein S, inactivates both FVa and FVIIIa. Another anticoagulant localized on the endothelium is the TF pathway inhibitor that inhibits FXa and the TF/FVIIa complex.

Fibrinolysis is a regulated mechanism that, through the proteolytic degradation exerted by plasmin, leads to fibrin dissolution (7). Fibrinolysis is activated by the action of tissue plasminogen activator, urokinase, or by the contact system that converts plasminogen to plasmin. Plasmin cleaves FV, FVIII, fibrinogen, and the GPIb receptor on platelets. Fibrin and fibrinogen degradation products interfere with fibrin formation and impair platelet function by GPIIb–IIIa complex occupancy. Plasminogen activator inhibitors (PAI-1 and -2), plasmin inhibitors (alpha-1-antiplasmin, alpha-2-macroglobulin), and thrombin activatable fibrinolysis inhibitor (TAFI) are the molecules that counteract fibrinolysis.

Pathophysiology

The pathogenesis of bleeding in patients with uremia is considered multifactorial (Table 1) and has been the subject of much debate since the 1970s. However, the major defects involve primary hemostasis because platelet–platelet and platelet–vessel wall interactions appear to be of crucial importance. Abnormalities of blood coagulation and fibrinolysis are less consistent and are more indicative of a hypercoagulable state than a hemorrhagic condition.

TABLE 1. Mechanisms affecting hemostasis in uremia

Platelet abnormalities (reduction in: dense granule content, intracellular ADP and serotonin, and release of the platelet α-granule protein and β-thromboglobulin; enhanced intracellular c-AMP; defective cyclooxygenase activity; abnormalities in mobilization of platelet Ca++, arachidonic acid metabolism, and ex vivo platelet aggregation)
Defects in platelet–vessel wall interaction (abnormal platelet adhesion, altered von Willebrand factor, increased formation of vascular PGI_2)
Abnormal production of nitric oxide
Uremic toxins
Anemia (altered blood rheology, defective platelet diffusivity, decreased release of ADP by erythrocytes, erythropoietin deficiency)
Drug treatment (anticoagulants, antiplatelet agents, nonsteroidal antiinflammatory drugs, β-lactam antibiotics, third-generation cephalosporins)

Platelet Abnormalities

Moderate thrombocytopenia is a common finding in uremic patients (8) suggesting inadequate platelet production or over consumption (9). However, thrombocytopenia 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) (10,11) or from heparin (used as anticoagulant to inhibit clotting) that occasionally may induce thrombocytopenia by an immunologic mechanism (12). In addition, a reduced percentage of reticulated platelets has been reported in patients undergoing hemodialysis (13). In uremia the mean platelet volume may also be decreased causing a reduction in the circulating platelet mass, a finding that is inversely related to the bleeding time.

Thrombocytopenia in uremia may, of course, be a manifestation of the disorder producing the uremia or due to unrelated coexistent disorders. For example, major decreases in platelet count are present in patients with renal failure associated with hemolytic uremic syndrome/thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, eclampsia, and renal allograft rejection.

Numerous biochemical changes in platelets have been reported in uremia. Dense granule content is decreased in uremic platelets (14,15), and a storage pool defect, with reduction in platelet ADP and serotonin, is present. Decreased subnormal platelet ATP release in response to stimulation with thrombin (14) indicates a defect in granule secretion, confirmed by studies showing impairment in the release of the α-granule proteins and β-thromboglobulin in platelets from dialysis patients (16). Intraplatelet cyclic AMP is enhanced in uremic patients (17), and the regulation of adenylate cyclase may also be abnormal (18), possibly contributing to defective platelet aggregation and adhesion to injured vessels. Platelet dysfunction has been also attributed to the prostaglandin-forming enzyme cyclooxygenase and to abnormal Ca^{++} mobilization in platelet leading to an impairment of Ca^{++}-dependent platelet function (19,20). Because platelet defects are partially corrected by dialysis, uremic toxins such as urea, phenol, and guanidinosuccinic acid (GSA) have been casually related to uremic platelet dysfunction.

Several abnormalities of the platelet–platelet interaction have also been reported. Defective platelet aggregation in vitro in response to various stimuli such as ADP, epinephrine, collagen, and thrombin is documented in a great number of studies, although the degree of impairment of platelet aggregation in uremia varies considerably. In several reports platelet aggregation was found to be normal or increased (reviewed in Ref. 8). In addition, defective platelet thromboxane A_2 (TxA_2) production, in response to endogenous and exogenous stimuli

(21,22), is not correctable by thrombin (22). In a subpopulation of uremics, irreversible platelet aggregation does not occur in response to platelet-activating factor (PAF) (23). This abnormality is independent of plasma factor(s) but is probably due to the platelets' reduced capacity to form TxA_2 in response to PAF.

Abnormalities in the platelet contractile system, including reduced association of the cytoskeleton with alpha-actin and tropomyosin, have been reported in platelets from uremic patients. Cytoskeletal proteins are less than normal in resting uremic platelets and, after stimulation with thrombin, actin incorporation is significantly reduced (24).

Several studies have pointed out that the platelet–vessel wall interaction is impaired in uremic patients (25–27). This abnormality is attributable to an impaired function of the platelet GPIIb–IIIa complex receptor accounting for the decreased binding of the two main adhesive proteins circulating in human blood, VWF and fibrinogen, to the stimulated uremic platelet (28). Removal of substances present in uremic plasma improved the binding capacity of GPIIb–IIIa complex suggesting that the platelets' defective function may be attributable to uremic toxins or to receptor occupancy by fibrinogen fragments present in uremic blood (28,29). The impaired GPIIb–IIIa complex activation in uremia may explain aggregation defects as well as reduced VWF-dependent adhesion and thrombus formation (25–27).

No consistent evidence of quantitative or qualitative abnormalities of VWF have been reported in uremia (26,30,31). However, a functional defect in the VWF–platelet interaction may have a role because cryoprecipitate (a plasma derivative rich in VWF) and desmopressin (a synthetic derivative of antidiuretic hormone that releases autologous VWF from storage sites) significantly shorten the bleeding time in these patients.

In addition, molecules such as prostacyclin (PGI_2) and nitric oxide (NO) that inhibit platelet function and modulate the vascular tone affecting platelet–vessel wall interaction are increased in uremia (32,33). The guanidino compound related to arginine guanidinosuccinate accumulates in plasma of uremics, and is involved in the generation of NO (33). In an experimental model of chronic uremia the effect of estrogens on bleeding time was completely reversed by the NO precursor l-arginine (34), suggesting that the effect of estrogens on primary hemostasis in uremia might be mediated by changes in the NO synthesis pathway.

Role of Anemia

In flowing systems, red blood cells increase platelet–vessel wall contact by displacing platelets away from the axial flow and toward the vessel wall, and enhance platelet function by releasing ADP (35) and inactivating PGI_2. Hemoglobin is a scavenger of NO (36) and decreases in available hemoglobin in anemia may contribute to platelet dysfunction. These mechanisms may explain why in uremic patients bleeding time is shortened after partial correction of anemia by red blood cell transfusions (37) or administration of recombinant human erythropoietin (rhEPO) (38,39). There is evidence that bleeding time is inversely related to the hematocrit in uremia (37) as well as in other types of anemia. Anemia, initially mild, is a constant feature of acute and chronic renal failure, and factors that contribute to the anemia are shortened survival of the red cell, failure of the erythroid marrow, repeated blood loss during dialysis and, more importantly, defective secretion of erythropoietin. There is good evidence that substances present in uremic serum, including polyamines, parathyroid hormone, and various cytokines can inhibit erythropoiesis (40).

Dialysis

Dialysis improves platelet functional abnormalities and reduces, but does not eliminate, the risk of hemorrhage. The interaction between blood and artificial surfaces may induce chronic activation of platelets leading to platelet exhaustion and dysfunction. It has been documented that plasma levels of the potent NO inducers tumor necrosis factor-α and interleukin-lβ increase during dialysis (41,42); these cytokines are generated in vivo by monocytes during hemodialysis with complement-activating membranes. Acetate-containing dialysate, endotoxin and its fragments, and other bacterial toxins that can cross the dialysis membranes may increase the production of cytokines which increases NO synthesis. The finding that NO synthesis may decrease during a dialysis session indicates that, under optimal conditions with minimal or no cytokine activation, hemodialysis corrects the exaggerated NO synthesis, possibly by removing some dialyzable NO-releasing substances.

Heparin, used to obtain systemic anticoagulation, can occasionally induce platelet activation and thrombocytopenia (12).

Role of Drugs

In uremia there is an increased risk of bleeding complications caused by drug treatment. β-Lactam antibiotics, that apparently act by perturbing platelet membrane function and by interfering with ADP receptors (43), raise the risk of bleeding due to their accumulation in uremic patients (44). The prolonged bleeding time and the abnormal platelet aggregation are related to the dose and duration of treatment, and are promptly reversible after discontinuation. Third-generation cephalosporins may also inhibit platelet function and lead to marked disturbance of blood coagulation (45).

The administration of acetylsalicylic acid (ASA) to prevent vascular access thrombosis (46) or platelet activation on dialysis membranes (47) is another risk factor for bleeding in uremic patients. The beneficial effect of ASA can be achieved with a moderate dose (160 mg/day) that inhibits platelet TxA_2 generation without affecting vascular PGI_2 formation (46). However, this dose of ASA may have a much greater effect on bleeding time in uremic patients than in healthy subjects (48); this effect does not appear to be related to the increased susceptibility of cyclooxygenase in uremic platelets. ASA seems to have two distinct inhibitory

effects on platelet function in uremia: a transient effect that interferes with one of the determinants of bleeding time, and a lasting effect due to the irreversible blocking of platelet cyclooxygenase (48). The prolongation of bleeding time caused by ASA may, in part, account for the frequency of gastrointestinal bleeding in uremic patients (49). Nonsteroidal antiinflammatory drugs such as indomethacin, ibuprofen, naproxen, phenylbutazone, and sulfinpyrazone also inhibit platelet cyclooxygenase and disturb platelet function but, in contrast to ASA, the inhibitory effect of these compounds is readily reversible as the blood concentration of the drugs falls upon cessation of administration (50).

Abnormalities of Coagulation and Fibrinolysis and Thrombotic Tendency

Despite their well-documented hemorrhagic tendency, uremic patients have an activated coagulation system that is more prominent in those who are treated by hemodialysis. Abnormalities such as enhanced platelet aggregability, increased levels of plasma fibrinogen, FVIII:C and VWF and decreased protein C anticoagulant activity and protein S, elevated plasma lipoprotein(a), increased plasma homocysteine, and the presence of lupus anticoagulant have all been found (reviewed in Ref. 8). Contradictory results have been obtained regarding the fibrinolytic system indicating both a decreased activity (9,51) and an activation of fibrinolysis after a hemodialysis session (52,53). This probably reflects a secondary fibrinolytic response to the fibrin deposition that occurs if the overall fibrinolytic activity is depressed. Dialysis partially corrects the coagulation and fibrinolytic abnormalities found in uremia.

Uremic patients on hemodialysis are exposed to thrombotic complications related to their vascular access. Percutaneous cannulation, central vein catheters, and native vein or prosthetic arteriovenous fistula are all associated with thrombotic occlusion.

ADAMTS13 activity is reduced in uremia (54), an abnormality that favors thrombosis. With severe deficiency of this protease—due to congenital or immune-mediated deficiency—thrombotic thrombocytopenic purpura may occur (55). A complete ADAMTS13 deficiency has been found also in a subgroup of patients with the atypical form of hemolytic uremic syndrome (55).

Laboratory Assessment

To identify patients at risk of hemorrhagic complications several tests have been used to establish which abnormal laboratory findings in uremia correlate best with an increased likelihood of clinically significant bleeding. Coagulation screening tests such as activated partial thromboplastin time, prothrombin time, and thrombin time are generally normal in uremia (56). No good correlation has been found between blood urea nitrogen or creatinine and clinical bleeding (56). The cutaneous bleeding time (normal values: 1–7 minutes) is the best laboratory hallmark of clinical bleeding caused by uremia (57). Bleeding time is an index of the primary phase of hemostasis, that is, the interaction of the platelet with the blood vessel wall, and the formation of the platelet plug.

TABLE 2. Guidelines for the management of bleeding in dialysis patients

The adequacy of dialysis should be appropriately checked for all patients with hemorrhagic complications or undergoing major surgery
It is also advisable to use alternatives to routine heparinization for 1 or 2 months in patients who have experienced severe hemorrhages (such as major gastrointestinal bleeding, hemorrhagic pericarditis, subdural hematomas) or who have undergone recent cardiovascular surgery
Acute bleeding episodes may be treated with desmopressin at a dose of 0.3 μg/kg, intravenously (added to 50 ml of saline over 30 minutes) or subcutaneously. Intranasal administration of this drug at a dose of 3 μg/kg is also effective and well tolerated
A favorable effect of cryoprecipitate on bleeding time has not been uniformly observed; we do not recommend its use
The effect of desmopressin lasts only a few hours and loses efficacy when repeatedly administered, major limitations in its use
In persistent chronic bleeding, hemostatic treatment with a long-lasting effect should be utilized
The most appropriate way treatment is with conjugated estrogens given by intravenous infusion in a cumulative dose of 3 mg/kg as daily divided doses (i.e., 0.6 mg/kg for five consecutive days)
Blood or red blood cell transfusions should be administered to patients whose hematocrit is $< 30\%$; a hemostatic effect of red blood cell transfusion is achieved above this level. If time pressure is not great, treatment with erythropoietin and, usually, iron is efficacious as well

Therapeutic Strategies

The approach to uremic bleeding must be considered in two contexts: the prevention of bleeding in patients at high risk because of invasive procedures or surgery, and the treatment of patients with active bleeding. The strategy depends on the urgency of the situation, the severity of uremia, and the previous therapy employed (Table 2).

Dialysis

Bleeding in uremia is more easily controlled since the introduction of dialysis (58,59). Dialysis by removing uremic toxins (including urea, creatinine, phenol, phenolic acids, and GSA) improves platelet functional abnormalities (60–62). However, 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. The risk of bleeding may be minimized by using alternatives to routine heparinization to prevent clotting in the extracorporeal circulation or, of course, by using peritoneal dialysis.

Peritoneal dialysis is more effective in correcting platelet abnormalities than hemodialysis (63). The reasons for this have not been completely elucidated but probably are, in part, due to the more biocompatible dialyzing membrane, the avoidance of heparin, and a better clearance of toxins whose clearance is largely treatment time dependent (e.g., those that are intracellular or protein bound). However, in some cases, hypoalbuminemia (frequent in peritoneal dialysis) may cause platelet hyper-reactivity which favors thrombosis (64).

Alternative strategies, developed specifically to anticoagulate patients at high risk of bleeding, include 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.

The earliest approach was regional heparinization (65) with heparin given by constant infusion into the inlet line of the dialyzer and protamine sulfate infused simultaneously into the outlet port before the blood returns to the patient. This technique has been abandoned because of a rebound systemic anticoagulation after the completion of dialysis (66) together with technical complexity; low-dose heparin or heparin-free dialysis is now used as an alternative.

Different heparin-free hemodialysis protocols have been developed for patients at high risk of hemorrhages. Typically, the dialyzer is primed with heparinized saline at the start of treatment and flushes of 100–200 ml of saline (every 15 or 30 minutes) through the dialyzer are employed (67,68) during the dialysis session. This procedure needs a blood flow above 250 ml/minute, membranes of low thrombogenicity such as polysulfone and a short treatment time (69); it may be compromised by poor dialysis technique and is associated with biochemical activation of the clotting system (67,68).

Low-molecular-weight heparin binds with antithrombin to enhance inhibition of factor Xa but does not contain the second binding sequence necessary for inhibiting thrombin activity. It is not clear whether LMWH offers any advantage over anticoagulation with unfractionated heparin because only minor differences can be detected; monitoring of anti-factor Xa activity is required (69). Few long-term studies comparing the use of LMWH over unfractionated heparin in routine hemodialysis (70) are available.

Multiple strategies have been described for citrate anticoagulation. In comparative trials this procedure appeared safe and more effective than others in hemodialysis patients with an active (or recently active) bleeding focus (71). Serious and documented complications of citrate anticoagulation involved citrate intoxication, hyperaluminemia, hyperammonemia, hypernatremia, and profound metabolic alkalosis (72).

Dermatan sulfate has also been proposed as an anticoagulant agent during hemodialysis, because it causes less bleeding than heparin in animal models. The lower hemorrhagic property may be due to its reduced effect on platelets (73) and may also be attributed to a moderate prolongation of activated partial thromboplastin time. A comparative short-term clinical study on few patients showed that dermatan sulfate suppresses clot formation during hemodialysis as efficiently as heparin (74), but long-term comparative trials are warranted.

In the search for alternatives to heparin, antiplatelet drugs such as sulfinpyrazone, adenosine, and PGE_1 have been used, but they appear to have no advantage over heparin. ASA and dipyridamole analogs reduce fibrin and cellular deposition on the filter membrane but increase the risk of gastrointestinal bleeding (47). Despite PGI_2 showing some promise (75), adverse reactions such as headache, flushing, tachycardia, and chest and abdominal pain requiring careful hemodynamic monitoring and a physician's supervision (76) limited the use of PGI_2 to patients at high risk of hemorrhage.

Correction of Anemia

Uremic patients are often severely anemic, and the severity of anemia appears to be related to the extent of the prolongation of bleeding time (77,78). Patients with chronic renal failure and prolonged bleeding time consistently benefited from red cell transfusions. The beneficial effect was independent of changes in platelet function tests or in the level of VWF-related properties (77).

The cloning of the human erythropoietin gene (79) has provided clinicians with a powerful tool to correct the anemia associated with renal failure eliminating the dependency upon transfusion (78,80). Treatment with rhEPO induced a progressive increase in hematocrit accompanied by a significant decrease in the bleeding time (38,39). A randomized study established that in uremic patients on rhEPO a threshold hematocrit between 27% and 32% effectively normalized bleeding time (39). Although improvement in platelet adhesion to subendothelium was observed in some studies, no consistent changes in platelet number, platelet aggregability, markers of platelet activation in plasma, platelet TxA_2 formation, platelet adenine nucleotide content, global coagulation test results, antithrombin III, or cross-linked fibrin derivatives were reported (38,81).

Cryoprecipitate and Desmopressin

Cryoprecipitate is a plasma derivative, obtained when plasma is frozen and thawed, 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 use of cryoprecipitate in uremic patients with a bleeding time greater than 15 minutes (82) was based on the observation that cryoprecipitate shortened the bleeding time of patients with platelet storage-pool disease. 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. However, because this therapy carries the risk of transmitting blood-borne diseases, it was largely replaced by other approaches.

A possible therapeutic alternative to cryoprecipitate is desmopressin acetate (1-deamino-8-d-arginine vasopressin, DDAVP), a synthetic derivative of antidiuretic hormone. DDAVP induces the release of autologous VWF from storage sites into plasma, and avoids the risk of transmitting serum hepatitis or other blood-borne diseases through the administration of blood products. DDAVP shortens the bleeding time in 1 hour and its effect lasts 4–8 hours (83). Bleeding time returns to baseline values within 24 hours. In two randomized, double-blind, cross-over trials, DDAVP was effective at a dose of 0.3 μg/kg body weight given intravenously

(83) (in 50 ml of physiologic saline over a period of 30 minutes) or subcutaneously (84). Desmopressin administered by the intranasal route is well tolerated (85). At 10 to 20 times the intravenous dose, intranasal desmopressin (3 μg/kg) shortens the prolonged bleeding time (85) and decreases clinical bleeding. Desmopressin loses its efficacy when repeatedly administered (86), probably due to a progressive depletion of VWF stores in endothelial cells.

Although remarkably free of serious side effects, DDAVP is reported to cause a mild to moderate decrease in platelet count, facial flushing, mild transient headache, nausea, abdominal cramps, and mild tachycardia, water retention, and hyponatremia. Rarely, thrombotic events followed DDAVP administration, particularly in patients with underlying advanced cardiovascular disease. Nonetheless, desmopressin is useful both in the treatment of bleeding and, prophylactically, in the prevention of bleeding during surgery or invasive procedures (87).

Conjugated Estrogens

Patients with gastrointestinal or intracranial bleeding, or those undergoing major surgery, who require long-lasting hemostatic competence, may benefit from the use of conjugated estrogens. The anecdotal observation of diminished gastrointestinal bleeding in uremic patients treated with conjugated estrogens and the improved hemostasis in von Willebrand's disease during pregnancy led to investigations of the effect of estrogens on the bleeding tendency in uremia (31,88).

One oral dose of 25 mg of a conjugated estrogen preparation normalizes bleeding time for 3–10 days with no apparent ill effects (89). A controlled study showed that conjugated estrogens, given intravenously at a cumulative dose of 3 mg/kg divided over five consecutive days, produced a long-lasting reduction in the bleeding time in uremics. At least 0.6 mg/kg estrogen was needed to reduce bleeding time (89), and four or five infusions spaced 24 hours apart were needed to reduce the bleeding time by at least 50%. Low-dose transdermal estrogen (estradiol 50–100 μg/24 hours) applied as a patch twice weekly reduces recurrent gastrointestinal bleeding with a parallel improvement of bleeding time and no side effects (90). The therapeutic activity cannot be ascribed to an effect on VWF multimeric structure, platelet aggregation in response to different stimuli (ADP, arachidonic acid, calcium ionophore A23187) or platelet TxB_2 generation. The effect of conjugated estrogens on bleeding time in uremic rats is antagonized by giving the animals the NO precursor, l-arginine (34); this suggests that conjugated estrogens exert their hemostatic effect by interfering with the NO synthetic pathway. In the same model, estrogens return plasma nitrate almost completely to normal, further confirming a direct involvement of NO in the hemostatic effect of these molecules.

The estrogens were safe and well tolerated making them a reasonable alternative to cryoprecipitate or desmopressin in the treatment of uremic bleeding, especially when a long-lasting effect is required.

Tranexamic Acid

Tranexamic acid (TXA), an anti-fibrinolytic lysine analog, stabilizes hemostatic clots by preventing the binding of plasminogen to fibrin and the activation of plasminogen to plasmin; it shortens bleeding time in uremic patients (91,92). TXA was effective in controlling chronic bleeding from colonic angiodysplasias (93) and spontaneous subdural and cerebral hematoma in dialysis patients (94) and, as adjunctive therapy, in treating major upper gastrointestinal bleeding in dialysis patients (95). Because TXA may accumulate in renal insufficiency and there is no evidence that it is more effective than commonly used therapies, intravenous TXA could be considered only in the acute setting when no satisfactory responses have been obtained with other treatments (96).

Recombinant Activated Factor VII

Recombinant activated factor VII (rFVIIa) induces hemostasis by enhancing thrombin generation on thrombin-activated platelet surfaces at the site of vascular injury and leading to a stable clot resistant to premature fibrinolysis (97,98). This product was originally developed for the treatment of hemorrhages in patients with hemophilia associated with antibodies inactivating factor VIII or IX (97). Only a few anecdotal reports of successful use of rFVIIa for treatment of bleeding in uremic patients are available (99–102). Recent studies indicate variable efficacy of rFVIIa treatment in clinical conditions different from hemophilia (103), together with an increased risk of thromboembolic events in patients in whom rFVIIa was used on "off-label" basis (104). Despite promising results, controlled clinical trials are needed to establish the efficacy, safety, and dose of rVIIa treatment in clinical setting other than hemophilia.

Conclusion

The association between a bleeding tendency and uremia has been demonstrated repeatedly. Although modern dialysis techniques and the use of erythropoietin to correct anemia have reduced its frequency, bleeding is still a potentially life-threatening complication in uremic patients and limits surgery and invasive procedures.

The pathogenesis of uremic bleeding is multifactorial and is not completely elucidated. However, it has been attributed mainly to abnormalities of primary hemostasis, particularly platelet dysfunction and impaired platelet–vessel wall interaction. Despite the hemorrhagic tendency, abnormalities of coagulation and fibrinolysis predispose uremic patients to a hypercoagulable state.

The current management includes an adequate dialysis schedule, and red cell transfusions or rhEPO for patients with severe anemia. Acute bleeding episodes may be treated with desmopressin, which is rapidly effective at least on bleeding time. Patients with gastrointestinal or intracranial bleeding or those undergoing major

surgery may benefit from conjugated estrogen infusions, which are ideal for the treatment of dramatic bleeding because of their long-lasting effect.

References

1. Remuzzi G: Bleeding disorders in uremia: pathophysiology and treatment. *Adv Nephrol Necker Hosp* 18:171–186, 1989
2. Eiser AR: Gastrointestinal bleeding in maintenance dialysis patients. *Semin Dial* 1:198–202, 1988
3. Doherty CC: Gastrointestinal bleeding in dialysis patients. *Nephron* 63:132–136; discussion 137-139, 1993
4. Stassen JM, Arnout J, Deckmyn H: The hemostatic system. *Curr Med Chem* 11:2245–2260, 2004
5. Ruggeri ZM: von Willebrand factor, platelets and endothelial cell interactions. *J Thromb Haemost* 1:1335–1342, 2003
6. Lopez JA, Dong JF: Cleavage of von Willebrand factor by ADAMTS-13 on endothelial cells. *Semin Hematol* 41:15–23, 2004
7. Fay WP, Garg N, Sunkar M: Vascular functions of the plasminogen activation system. *Arterioscler Thromb Vasc Biol* 27:1231–1237, 2007
8. Joist JH, Remuzzi G, Mannucci PM: Abnormal bleeding and thrombosis in renal disease. In: Colman RW, Hirsh J, Marder VJ, Salzman HW (eds). *Hemostasis and Thrombosis: Basic Principles and Clinical Practice*. Philadelphia: Lippincott JB, 1994:921–935
9. Panicucci F, Sagripanti A, Pinori E, Vispi M, Lecchini L, Barsotti G, Giovannetti S: Comprehensive study of haemostasis in chronic uraemia. *Nephron* 33:5–8, 1983
10. Hakim RM, Schafer AI: Hemodialysis-associated platelet activation and thrombocytopenia. *Am J Med* 78:575–580, 1985
11. Knudsen F, Nielsen AH, Kristensen SD: The effect of dialyser membrane material on intradialytic changes in platelet count, platelet aggregation, circulating platelet aggregates and antithrombin III. *Scand J Urol Nephrol* 19:227–232, 1985
12. Hall AV, Clark WF, Parbtani A: Heparin-induced thrombocytopenia in renal failure. *Clin Nephrol* 38:86–89, 1992
13. Tassies D, Reverter JC, Cases A, Escolar G, Villamor N, Lopez-Pedret J, Castillo R, Ordinas A: Reticulated platelets in uremic patients: effect of hemodialysis and continuous ambulatory peritoneal dialysis. *Am J Hematol* 50:161–166, 1995
14. Di Minno G, Martinez J, McKean ML, De La Rosa J, Burke JF, Murphy S: Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis. *Am J Med* 79:552–559, 1985
15. Eknoyan G, Brown CH 3rd: Biochemical abnormalities of platelets in renal failure. Evidence for decreased platelet serotonin, adenosine diphosphate and Mg-dependent adenosine triphosphatase. *Am J Nephrol* 1:17–23, 1981
16. Kyrle PA, Stockenhuber F, Brenner B, Gossinger H, Korninger C, Pabinger I, Sunder-Plassmann G, Balcke P, Lechner K: Evidence for an increased generation of prostacyclin in the microvasculature and an impairment of the platelet alpha-granule release in chronic renal failure. *Thromb Haemost* 60:205–208, 1988
17. Vlachoyannis J, Schoeppe W: Adenylate cyclase activity and cAMP content of human platelets in uraemia. *Eur J Clin Invest* 12:379–381, 1982
18. Jacobsson B, Ransnas L, Nyberg G, Bergh CH, Magnusson Y, Hjalmarson A: Abnormality of adenylate cyclase regulation in human platelet membranes in renal insufficiency. *Eur J Clin Invest* 15:75–81, 1985
19. Gura V, Creter D, Levi J: Elevated thrombocyte calcium content in uremia and its correction by 1 alpha(OH) vitamin D treatment. *Nephron* 30:237–239, 1982
20. Ware JA, Clark BA, Smith M, Salzman EW: Abnormalities of cytoplasmic $Ca2^{+}$ in platelets from patients with uremia. *Blood* 73:172–176, 1989
21. Smith MC, Dunn MJ: Impaired platelet thromboxane production in renal failure. *Nephron* 29:133–137, 1981
22. Remuzzi G, Benigni A, Dodesini P, Schieppati A, Livio M, De Gaetano G, Day SS, Smith WL, Pinca E, Patrignani P, Patrono C: Reduced platelet thromboxane formation in uremia. Evidence for a functional cyclooxygenase defect. *J Clin Invest* 71:762–768, 1983
23. Macconi D, Vigano G, Bisogno G, Galbusera M, Orisio S, Remuzzi G, Livio M: Defective platelet aggregation in response to platelet-activating factor in uremia associated with low platelet thromboxane A2 generation. *Am J Kidney Dis* 19:318–325, 1992
24. Escolar G, Diaz-Ricart M, Cases A, Castillo R, Ordinas A, White JG: Abnormal cytoskeletal assembly in platelets from uremic patients. *Am J Pathol* 143:823–831, 1993
25. Castillo R, Lozano T, Escolar G, Revert L, Lopez J, Ordinas A: Defective platelet adhesion on vessel subendothelium in uremic patients. *Blood* 68:337–342, 1986
26. Zwaginga JJ, Ijsseldijk MJ, Beeser-Visser N, de Groot PG, Vos J, Sixma JJ: High von Willebrand factor concentration compensates a relative adhesion defect in uremic blood. *Blood* 75:1498–1508, 1990
27. Escolar G, Cases A, Bastida E, Garrido M, Lopez J, Revert L, Castillo R, Ordinas A: Uremic platelets have a functional defect affecting the interaction of von Willebrand factor with glycoprotein IIb–IIIa. *Blood* 76:1336–1340, 1990
28. Benigni A, Boccardo P, Galbusera M, Monteagudo J, De Marco L, Remuzzi G, Ruggeri ZM: Reversible activation defect of the platelet glycoprotein IIb–IIIa complex in patients with uremia. *Am J Kidney Dis* 22: 668–676, 1993
29. Sreedhara R, Itagaki I, Hakim RM: Uremic patients have decreased shear-induced platelet aggregation mediated by decreased availability of glycoprotein IIb–IIIa receptors. *Am J Kidney Dis* 27:355–364, 1996
30. Turney JH, Woods HF, Fewell MR, Weston MJ: Factor VIII complex in uraemia and effects of haemodialysis. *Br Med J (Clin Res Ed)* 282:1653–1656, 1981
31. Livio M, Mannucci PM, Vigano G, Mingardi G, Lombardi R, Mecca G, Remuzzi G: Conjugated estrogens for the management of bleeding associated with renal failure. *N Engl J Med* 315:731–735, 1986
32. Remuzzi G, Marchesi D, Livio M, Schieppati A, Mecca G, Donati MB, de Gaetano G: Prostaglandins, plasma factors and haemostasis in uremia. In: Remuzzi G, Mecca G, de Gaetano G (eds). *Hemostasis, Prostaglandins and Renal Disease*. New York: Raven Press, 1980:273–281
33. Noris M, Remuzzi G: Uremic bleeding: closing the circle after 30 years of controversies? *Blood* 94:2569–2574, 1999
34. Zoja C, Noris M, Corna D, Vigano G, Perico N, de Gaetano G, Remuzzi G: l-arginine, the precursor of nitric oxide, abolishes the effect of estrogens on bleeding time in experimental uremia. *Lab Invest* 65:479–483, 1991
35. Gaarder A, Jonsen J, Laland S, Hellem A, Owren PA: Adenosine diphosphate in red cells as a factor in the adhesiveness of human blood platelets. *Nature* 192:531–532, 1961
36. Martin W, Villani GM, Jothianandan D, Furchgott RF: Blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation of rabbit aorta by certain ferrous hemoproteins. *J Pharmacol Exp Ther* 233:679–685, 1985
37. Livio M, Gotti E, Marchesi D, Mecca G, Remuzzi G, de Gaetano G: Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. *Lancet* 2:1013–1015, 1982
38. Moia M, Mannucci PM, Vizzotto L, Casati S, Cattaneo M, Ponticelli C: Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. *Lancet* 2:1227–1229, 1987
39. Vigano G, Benigni A, Mendogni D, Mingardi G, Mecca G, Remuzzi G: Recombinant human erythropoietin to correct uremic bleeding. *Am J Kidney Dis* 18:44–49, 1991
40. Macdougall IC: Role of uremic toxins in exacerbating anemia in renal failure. *Kidney Int Suppl* 59:S67–S72, 2001
41. Noris M, Benigni A, Boccardo P, Aiello S, Gaspari F, Todeschini M, Figliuzzi M, Remuzzi G: Enhanced nitric oxide synthesis in uremia: implications for platelet dysfunction and dialysis hypotension. *Kidney Int* 44: 445–450, 1993
42. Herbelin A, Nguyen AT, Zingraff J, Urena P, Descamps-Latscha B: Influence of uremia and hemodialysis on circulating interleukin-1 and tumor necrosis factor alpha. *Kidney Int* 37:116–125, 1990
43. Shattil SJ, Bennett JS, McDonough M, Turnbull J: Carbenicillin and penicillin G inhibit platelet function in vitro by impairing the interaction of agonists with the platelet surface. *J Clin Invest* 65:329–337, 1980
44. Andrassy K, Ritz E: Uremia as a cause of bleeding. *Am J Nephrol* 5:313–319, 1985
45. Bang NU, Tessler SS, Heidenreich RO, Marks CA, Mattler LE: Effects of moxalactam on blood coagulation and platelet function. *Rev Infect Dis* 4(Suppl.):S546–S554, 1982
46. Harter HR, Burch JW, Majerus PW, Stanford N, Delmez JA, Anderson CB, Weerts CA: Prevention of thrombosis in patients on hemodialysis by low-dose aspirin. *N Engl J Med* 301:577–579, 1979
47. Lindsay RM, Ferguson D, Prentice CR, Burton JA, McNicol GP: Reduction of thrombus formation on dialyser membranes by aspirin and RA 233. *Lancet* 2:1287–1290, 1972
48. Gaspari F, Vigano G, Orisio S, Bonati M, Livio M, Remuzzi G: Aspirin prolongs bleeding time in uremia by a mechanism distinct from platelet cyclooxygenase inhibition. *J Clin Invest* 79:1788–1797, 1987
49. Boyle JM, Johnston B: Acute upper gastrointestinal hemorrhage in patients with chronic renal disease. *Am J Med* 75:409–412, 1983
50. Harker LA, Fuster V: Pharmacology of platelet inhibitors. *J Am Coll Cardiol* 8:21B–32B, 1986
51. Castaldi PA, Rozenberg MC, Stewart JH: The bleeding disorder of uraemia. A qualitative platelet defect. *Lancet* 2:66–69, 1966
52. Reber G, Stoermann C, de Moerloose P, Ruedin P, Leski M: Hemostatic disturbances induced by two hollow-fiber hemodialysis membranes. *Int J Artif Organs* 15:269–276, 1992
53. Speiser W, Wojta J, Korninger C, Kirchheimer JC, Zazgornik J, Binder BR: Enhanced fibrinolysis caused by tissue plasminogen activator release in hemodialysis. *Kidney Int* 32:280–283, 1987
54. Mannucci PM, Canciani MT, Forza I, Lussana F, Lattuada A, Rossi E: Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. *Blood* 98:2730–2735, 2001
55. Galbusera M, Noris M, Remuzzi G: Thrombotic thrombocytopenic purpura – then and now. *Semin Thromb Hemost* 32:81–89, 2006
56. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ: Evidence-based treatment recommendations for uremic bleeding. *Nat Clin Pract Nephrol* 3:138–153, 2007

57. Mattix H, Singh AK: Is the bleeding time predictive of bleeding prior to a percutaneous renal biopsy? *Curr Opin Nephrol Hypertens* 8:715–718, 1999
58. Eknoyan G, Wacksman SJ, Glueck HI, Will JJ: Platelet function in renal failure. *N Engl J Med* 280:677–681, 1969
59. Larsson SO: On coagulation and fibrinolysis in renal failure. *Scand J Haematol Suppl* 15:1–59, 1971
60. Rabiner SF, Molinas F: The role of phenol and phenolic acids on the thrombocytopathy and defective platelet aggregation of patients with renal failure. *Am J Med* 49:346–351, 1970
61. Horowitz HI, Stein IM, Cohen BD, White JG: Further studies on the platelet inhibiting effect of guanidinisuccinic aid and its role in uremic bleeding. *Am J Med* 49:336–345, 1970
62. Remuzzi G, Livio M, Marchiaro G, Mecca G, de Gaetano G: Bleeding in renal failure: altered platelet function in chronic uraemia only partially corrected by haemodialysis. *Nephron* 22:347–353, 1978
63. Nenci GG, Berrettini M, Agnelli G, Parise P, Buoncristiani U, Ballatori E: Effect of peritoneal dialysis, haemodialysis and kidney transplantation on blood platelet function. I. Platelet aggregation by ADP and epinephrine. *Nephron* 23:287–292, 1979
64. Sloand EM, Bern MM, Kaldany A: Effect on platelet function of hypoalbuminemia in peritoneal dialysis. *Thromb Res* 44:419–425, 1986
65. Gordon LA, Perkins HA, Richards V, Rukes JM, Simon ER: Studies in regional heparinization. II. Artificial-kidney hemodialysis without systemic heparinization; preliminary report of a method using simultaneous infusion of heparin and protamine. *N Engl J Med* 255:1063–1066, 1956
66. Blaufox MD, Hampers CL, Merrill JP: Rebound anticoagulation occurring after regional heparinization for hemodialysis. *Trans Am Soc Artif Intern Organs* 12:207–209, 1966
67. Ivanovich P, Xu CG, Kwaan HC, Hathiwala S: Studies of coagulation and platelet functions in heparin-free hemodialysis. *Nephron* 33:116–120, 1983
68. Casati S, Moia M, Graziani G, Cantaluppi A, Citterio A, Mannucci PM, Ponticelli C: Hemodialysis without anticoagulants: efficiency and hemostatic aspects. *Clin Nephrol* 21:102–105, 1984
69. Fischer KG: Essentials of anticoagulation in hemodialysis. *Hemodial Int* 11:178–189, 2007
70. Saltissi D, Morgan C, Westhuyzen J, Healy H: Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation. *Nephrol Dial Transplant* 14:2698–2703, 1999
71. Flanigan MJ, Von Brecht J, Freeman RM, Lim VS: Reducing the hemorrhagic complications of hemodialysis: a controlled comparison of low-dose heparin and citrate anticoagulation. *Am J Kidney Dis* 9:147–153, 1987
72. Kelleher SP, Schulman G: Severe metabolic alkalosis complicating regional citrate hemodialysis. *Am J Kidney Dis* 9:235–236, 1987
73. Fernandez F, Van Ryn J, Ofosu FA, Hirsh J, Buchanan MR: The haemorrhagic and antithrombotic effects of dermatan sulphate. *Br J Haematol* 64:309–317, 1986
74. Boccardo P, Melacini D, Rota S, Mecca G, Boletta A, Casiraghi F, Gianese F: Individualized anticoagulation with dermatan sulphate for haemodialysis in chronic renal failure. *Nephrol Dial Transplant* 12:2349–2354, 1997
75. Zusman RM, Rubin RH, Cato AE, Cocchetto DM, Crow JW, Tolkoff-Rubin N: Hemodialysis using prostacyclin instead of heparin as the sole antithrombotic agent. *N Engl J Med* 304:934–939, 1981
76. Swartz RD, Flamenbaum W, Dubrow A, Hall JC, Crow JW, Cato A: Epoprostenol (PGI2, prostacyclin) during high-risk hemodialysis: preventing further bleeding complications. *J Clin Pharmacol* 28:818–825, 1988
77. Fernandez F, Goudable C, Sie P, Ton-That H, Durand D, Suc JM, Boneu B: Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. *Br J Haematol* 59:139–148, 1985
78. Gordge MP, Leaker B, Patel A, Oviasu E, Cameron JS, Neild GH: Recombinant human erythropoietin shortens the uraemic bleeding time without causing intravascular haemostatic activation. *Thromb Res* 57:171–182, 1990
79. Lin FK, Suggs S, Lin CH, Browne JK, Smalling R, Egrie JC, Chen KK, Fox GM, Martin F, Stabinsky Z, Badrawi SM, Lai P-H, Goldwasser E: Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci U S A* 82:7580–7584, 1985
80. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW: Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 316:73–78, 1987
81. van Geet C, Hauglustaine D, Verresen L, Vanrusselt M, Vermylen J: Haemostatic effects of recombinant human erythropoietin in chronic haemodialysis patients. *Thromb Haemost* 61:117–121, 1989
82. Janson PA, Jubelirer SJ, Weinstein MJ, Deykin D: Treatment of the bleeding tendency in uremia with cryoprecipitate. *N Engl J Med* 303:1318–1322, 1980
83. Mannucci PM, Remuzzi G, Pusineri F, Lombardi R, Valsecchi C, Mecca G, Zimmerman TS: Deamino-8-d-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med* 308:8–12, 1983
84. Vigano GL, Mannucci PM, Lattuada A, Harris A, Remuzzi G: Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. *Am J Hematol* 31:32–35, 1989
85. Shapiro MD, Kelleher SP: Intranasal deamino-8-d-arginine vasopressin shortens the bleeding time in uremia. *Am J Nephrol* 4:260–261, 1984
86. Canavese C, Salomone M, Pacitti A, Mangiarotti G, Calitri V: Reduced response of uraemic bleeding time to repeated doses of desmopressin. *Lancet* 1:867–868, 1985
87. Mannucci PM: Desmopressin (DDAVP) in the treatment of bleeding disorders: the first 20 years. *Blood* 90:2515–2521, 1997
88. Liu YK, Kosfeld RE, Marcum SG: Treatment of uraemic bleeding with conjugated oestrogen. *Lancet* 2:887–890, 1984
89. Vigano G, Gaspari F, Locatelli M, Pusineri F, Bonati M, Remuzzi G: Dose-effect and pharmacokinetics of estrogens given to correct bleeding time in uremia. *Kidney Int* 34:853–858, 1988
90. Sloand JA, Schiff MJ: Beneficial effect of low-dose transdermal estrogen on bleeding time and clinical bleeding in uremia. *Am J Kidney Dis* 26:22–26, 1995
91. Mezzano D, Panes O, Munoz B, Pais E, Tagle R, Gonzalez F, Mezzano S, Barriga F, Pereira J: Tranexamic acid inhibits fibrinolysis, shortens the bleeding time and improves platelet function in patients with chronic renal failure. *Thromb Haemost* 82:1250–1254, 1999
92. Mezzano D, Munoz B, Pais E, Downey P, Pereira J: Fast decrease of bleeding time by tranexamic acid in uremia. *Thromb Haemost* 83:785, 2000
93. Vujkovac B, Lavre J, Sabovic M: Successful treatment of bleeding from colonic angiodysplasias with tranexamic acid in a hemodialysis patient. *Am J Kidney Dis* 31:536–538, 1998
94. Vujkovac B, Sabovic M: Treatment of subdural and intracerebral haematomas in a haemodialysis patient with tranexamic acid. *Nephrol Dial Transplant* 15:107–109, 2000
95. Sabovic M, Lavre J, Vujkovac B: Tranexamic acid is beneficial as adjunctive therapy in treating major upper gastrointestinal bleeding in dialysis patients. *Nephrol Dial Transplant* 18:1388–1391, 2003
96. Hedges SJ, Dehoney SB, Hooper JS, Amanzadeh J, Busti AJ: Authors' response to "Tranexamic acid and uremic bleeding: evidence-based treatment recommendations." *Nature Clin Pract Nephrol* 3:E3–E3, 2007
97. Roberts HR, Monroe DM, White GC: The use of recombinant factor VIIa in the treatment of bleeding disorders. *Blood* 104:3858–3864, 2004
98. Hedner U, Ezban M: Tissue factor and factor VIIa as therapeutic targets in disorders of hemostasis. *Annu Rev Med* 59:29–41, 2008
99. Revesz T, Arets B, Bierings M, van den Bos C, Duval E: Recombinant factor VIIa in severe uremic bleeding. *Thromb Haemost* 80:353, 1998
100. Moisescu E, Ardelean L, Simion I, Muresan A, Ciupan R: Recombinant factor VIIa treatment of bleeding associated with acute renal failure. *Blood Coagul Fibrinolysis* 11:575–577, 2000
101. Ng HJ, Koh LP, Lee LH: Successful control of postsurgical bleeding by recombinant factor VIIa in a renal failure patient given low molecular weight heparin and aspirin. *Ann Hematol* 82:257–258, 2003
102. Alioglu B, Avci Z, Baskin E, Ozcay F, Tuncay IC, Ozbek N: Successful use of recombinant factor VIIa (NovoSeven) in children with compartment syndrome: two case reports. *J Pediatr Orthop* 26:815–817, 2006
103. Mannucci PM, Levi M: Prevention and treatment of major blood loss. *N Engl J Med* 356:2301–2311, 2007
104. O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM: Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. *JAMA* 295:293–298, 2006