

Evidence-based treatment recommendations for uremic bleeding

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SUMMARY

Uremic bleeding syndrome is a recognized consequence of renal failure and can result in clinically significant sequelae. Although the pathophysiology of the condition has yet to be fully elucidated, it is believed to be multifactorial. This article is a review of both the normal hemostatic and homeostatic mechanisms that operate within the body to prevent unnecessary bleeding, as well as an in-depth discussion of the dysfunctional components that contribute to the complications associated with uremic bleeding syndrome. As a result of the multifactorial nature of this syndrome, prevention and treatment options can include one or a combination of the following: dialysis, erythropoietin, cryoprecipitate, desmopressin, and conjugated estrogens. Here, these treatment options are compared with regard to their mechanism of action, and onset and duration of efficacy. An extensive review of the clinical trials that have evaluated each treatment is also presented. Lastly, we have created an evidence-based treatment algorithm to help guide clinicians through most clinical scenarios, and answered common questions related to the management of uremic bleeding.

KEYWORDS bleeding time, desmopressin, erythropoietin, uremia, von Willebrand Factor

REVIEW CRITERIA

We searched the MEDLINE and PubMed databases for clinical studies that were written in English. We used MESH terms, including "uremia", "dialysis", "peritoneal dialysis", "deamino arginine vasopressin", "cryoprecipitate coagulum", "recombinant erythropoietin", "estrogens", and "conjugated estrogens", to perform a comprehensive review of all studies evaluating treatment options for uremic bleeding syndrome. These data served as the basis for the evidence-based treatment recommendations offered in this Review.

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INTRODUCTION

Uremic bleeding is a well-recognized complication in patients with renal failure.¹ It was described by Reisman almost 100 years ago in two patients with renal failure from Bright's Disease (a term no longer used but described as acute or chronic nephritis) who experienced severe and generalized bleeding.² The clinical importance of bleeding associated with chronic renal failure itself is, however, difficult to assess, especially as various dialysis techniques, comorbidities and medications are known to affect platelet aggregation and/or the coagulation cascade. When abnormal ecchymosis or bleeding occurs in patients with chronic renal failure, it is, therefore, likely to be multifactorial in nature. This Review describes normal hemostatic and homeostatic processes that prevent unnecessary bleeding, before explaining the pathophysiology of uremic platelet dysfunction and blood loss. Published studies on treatments for uremic bleeding syndrome are discussed, and evidence-based recommendations for the management of bleeding or the risk of bleeding in uremic patients are offered.

NORMAL HEMOSTATIC MECHANISMS

Under normal circumstances, platelets circulate throughout the body in an inactivated or nonadhesive state. A number of agonists can activate platelets. One of the most common is disruption of the vascular endothelium, which evokes a series of biochemical reactions to maintain normal hemostasis. The first set of reactions occurs when a platelet comes into contact with the damaged vascular endothelial surface. Exposure of the damaged endothelial lining permits introduction of collagen (particularly types I, III and VI), fibronectin, thrombospondin, von Willebrand factor (vWF), laminins, and microfibrils, which leads to a change in platelet morphology and provides support for platelet adhesion.³⁻⁶ These changes are also facilitated when activated platelets secrete large quantities of ADP from dense granules. Activated platelets can then also contribute to

adhesion through the release of various adhesive proteins (e.g. vWF, fibrinogen, fibronectin, vitronectin, and thrombospondin) from α -granules.⁷ These changes effect growth of the platelet, facilitating adhesion such that collagen fibers and other platelets can be bound to ultimately form an occlusive plug. Activated platelets also secrete thromboxane A₂ (TxA₂), a well-known and potent platelet aggregator that works to stabilize the friable hemostatic plug.⁸

A second set of reactions involves activation of the coagulation cascade that eventually leads to formation of thrombin.^{9,10} Production of thrombin is crucial to the formation and stabilization of a developing thrombus. Thrombin converts fibrinogen to fibrin monomers.^{11,12} It also facilitates the conversion of factor XIII to factor XIIIa, which is required for clot stabilization.^{13–15} In addition, thrombin binds to protease-activated receptors on platelets, ultimately resulting in upregulation of glycoprotein Ib/IX (GPIb/IX) and glycoprotein IIb/IIIa (GPIIb/IIIa; also known as $\alpha_{IIb}\beta_3$) receptors.^{16–19} GPIb/IX is a particularly important receptor for binding vWF, causing adhesion of platelets to the endothelium.²⁰ Inadequate interaction of GPIb/IX and vWF is thought to contribute to platelet dysfunction seen in uremia.

In addition to these hemostatic mechanisms, there are several homeostatic mechanisms that maintain the balance between clot formation and bleeding. Tissue plasminogen activator, urokinase plasminogen activator, prostacyclin (PGI₂), nitric oxide (NO) and ectoapyrases are released by normal, functioning endothelial cells to maintain a local antithrombotic intravascular surface and degrade ADP.^{21,22}

Another homeostatic mechanism influencing hemostasis is laminar blood flow. This is partially influenced by hematocrit and local endogenous vasodilators, which modulate blood viscosity and vasomotor tone, respectively. A normal hematocrit facilitates the flow of red blood cells midstream, which displaces platelets such that they are closer to the endothelium; consequently, platelets can react quickly to damage to the vasculature.^{23–25} The second aspect of laminar blood flow that influences hemostasis is vessel radius, which is regulated by a number of neurological and chemical mediators including, but not limited to, PGI₂ and NO. Each of the above areas of normal hemostatic regulation is commonly altered in patients with uremia secondary to acute or chronic kidney failure.

PATHOPHYSIOLOGY

It has been known for many decades that uremic bleeding and platelet dysfunction put patients at increased risk of general bleeding. The exact mechanism by which the risk is increased remains largely unknown, but seems to be multifactorial. Understanding of the various dysfunctional components helps to explain the pathophysiology of uremic bleeding and serves as the basis for current approaches to prevention and treatment.

Von Willebrand factor

The first, and an important, factor contributing to uremic bleeding is dysfunctional vWF. This adhesion molecule is recognized by thrombin-upregulated GPIb/IX receptors, especially in the presence of increased vascular shear rates.^{20,21,26} Binding of vWF to these receptors initiates a series of intracellular biochemical reactions, eventually resulting in TxA₂ production. The interaction between vWF and GPIb/IX also facilitates activation of GPIIb/IIIa receptors, permitting further platelet aggregation.²⁷

In patients with uremic platelet dysfunction, there is thought to be a functional defect associated with vWF; either decreased binding affinity for GPIb/IX receptors or reduced expression of GPIb/IX receptors on platelets.²⁰ Weakened interaction between vWF and GPIb/IX receptors impairs PIP₂ breakdown and alters cytosolic calcium concentrations, resulting in decreased production of TxA₂ and ADP. There is also potential for decreased functionality of factor VIII, which is normally carried in the blood by vWF. Several studies have measured levels of the vWF–factor-VIII complex as a surrogate for factor VIII levels. These studies have reported normal or elevated levels of vWF–factor-VIII complex in patients with chronic renal failure, indicating a functional defect in one or both components rather than a decrease in the concentration of the complex.^{16,28,29}

Cyclic adenosine monophosphate

Patients with prolonged bleeding times secondary to renal dysfunction have higher PGI₂ levels compared with normal controls.³⁰ PGI₂, a well known vasodilator and inhibitor of platelet aggregation, modulates production of cyclic AMP (cAMP) through activation of adenylyl cyclase.^{21,22} It is believed that the increased levels of cAMP disrupt the breakdown of PIP₂ and alter calcium mobilization such that levels of TxA₂ and ADP are ultimately reduced.²¹

Cyclic guanosine monophosphate

Levels of cyclic GMP (cGMP) in uremic patients are increased as a result of higher concentrations of NO generated by platelets.³¹ It is postulated that patients with chronic renal dysfunction have elevated levels of tumor necrosis factor alpha (TNF- α) and interleukin 1 β , which can induce NO synthase, leading to increased NO concentrations.^{31,32} Human umbilical vein and human microvascular endothelial cells produce NO *in vitro* when exposed to plasma from dialysis patients.^{1,33} Increased NO levels activate guanylyl cyclase leading to elevated levels of cGMP, which also reduce TxA₂ and ADP levels.

Uremic toxins

Patients with impaired kidney function progressively retain approximately 92 known uremic retention solutes, commonly referred to as uremic toxins.³⁴ Uremic toxins commonly associated with uremic bleeding include, but are not limited to, urea, creatinine, guanidinosuccinic acid (GSA), phenolic acids and methylguanidine. Accumulation of these toxins interferes with essential biological and biochemical functions.^{34–37} In particular, urea has been shown to inhibit various enzymes in the urea cycle.^{38,39} As a result of excess urea, L-arginine (an intermediate in the urea cycle) is shunted from the urea cycle. It then transfers an amidine group to aspartic acid, eventually forming GSA.³⁸ L-Arginine is also widely believed to induce NO synthesis, which further stimulates guanylyl cyclase as described above.¹ Finally, GSA and phenolic acid inhibit ADP-induced platelet aggregation, contributing to the complex nature of dysfunctional platelet aggregation in uremia.^{40,41}

Anemia

Patients with chronic renal failure commonly experience anemia resulting from decreased erythropoietin (EPO) production and reduced longevity of red blood cells.^{42,43} The deficiency of circulating red blood cells causes platelets to travel in a more-midstream position, further away from the subendothelium, making it less likely that platelets will react when damage to the vasculature occurs. Red blood cells also release ADP and TxA₂, so a low red blood cell count might lead to decreased platelet aggregation.⁴⁴ Hemoglobin could also have an important role; it has a high affinity for NO, but in the anemic state there is less hemoglobin available to scavenge NO.⁴⁵ NO contributes to activation

of guanylyl cyclase, increasing cGMP levels and further impairing platelet aggregation as described above.

The impaired interactions and dysregulated intracellular pathways in uremia ultimately result in decreased production of TxA₂, less ADP-mediated aggregation, reduced release of adhesive proteins, growth modulators and coagulation factors from platelet α -granules, and fewer changes in platelet morphology, all of which are necessary for adequate formation of a platelet plug.

ASSESSMENT

Patients with uremic bleeding typically present with ecchymoses, purpura, epistaxis and bleeding from venipuncture sites. These patients can also present with gastrointestinal or intracranial bleeding.⁴⁶ While diagnosis of uremic bleeding is still based on clinical symptoms of bleeding, evaluation of bleeding time is the most useful test to assess clinical bleeding in uremic patients.⁴⁷ Bleeding time is measured by making a small incision on the ear lobe, finger, upper arm or thigh and recording the time from the first drop of blood to the last. Normal bleeding time can range from 1–7 minutes. Azotemic indices such as blood urea nitrogen and creatinine do not correlate as well with clinical bleeding as does bleeding time. Mild thrombocytopenia might also be observed in patients with uremic bleeding; however, platelet levels rarely fall below 80×10^3 cells/mm³ and cannot alone account for the severity of bleeding in these patients. Other measures of hemostasis such as prothrombin time and activated partial thromboplastin time typically remain normal.

PREVENTION BY DIALYSIS

As with any medical condition, prevention should always be considered for uremic bleeding. Despite preventive efforts, abnormal bruising or bleeding can still occur, reflecting the multifarious nature of uremic bleeding. Fortunately, dialysis has beneficial effects on common complications other than bleeding in patients with chronic kidney disease.

Dialysis is a necessary component of the management of patients with significantly impaired renal function. One important role of dialysis is the removal of metabolic by-products and uremic retention solutes. Uremic retention solutes have varied physicochemical properties that influence their susceptibility to removal by

dialysis. These solutes can be divided into the following three categories: small water-soluble compounds, larger 'middle-sized' compounds, and protein-bound compounds. High-flux dialysis membranes (e.g. those with a large pore size) are required to remove large retention solutes; these compounds are not efficiently removed via traditional dialysis methods.⁴⁸ Proteomic analysis indicates that high-flux membranes remove substantially more polypeptides with a molecular weight greater than 5 kDa than do low-flux membranes.⁴⁹

Until recently, intradialytic kinetics of small water-soluble guanidine compounds, including guanidine, creatinine, creatine, methylguanidine, GSA and guanidinoacetic acid, were assumed to be similar to those of urea. Eloot *et al.*, however, determined that the volume of distribution of these compounds (except GSA) was markedly higher than that of urea, a characteristic that reduces the efficiency of their removal by dialysis.⁵⁰ It has been suggested that removal of these compounds requires longer or more-frequent dialysis sessions. Binding of these compounds to protein might also influence the effectiveness of dialysis as a treatment and/or preventive measure for uremic bleeding.

In all studies of dialysis for prevention or treatment of uremic bleeding, dialysis has had an uncertain effect on platelets and coagulation. Platelet function has been shown to both worsen and improve after dialysis, making it difficult to interpret the efficacy of other treatment options for uremic bleeding.^{51–54} Dialysis, particularly 48 h of weekly peritoneal dialysis, has been shown to maintain normal *in vitro* platelet aggregation as measured by light transmission platelet aggregometry.³⁶ More equivocally, hemodialysis has been shown in some studies to improve platelet numbers, platelet factor 3 availability and activity, prothrombin consumption index and clot retraction, and to reduce clinical bleeding.^{37,55,56} A study by Nenci *et al.*, however, indicated that hemodialysis was inferior to peritoneal dialysis;⁵⁷ *in vitro* aggregation of platelets from patients undergoing peritoneal dialysis was superior to that of patients receiving hemodialysis. Hemodialysis patients showed no improvement in platelet aggregation compared with uremic patients not receiving dialysis. The mechanisms underlying the inferiority of hemodialysis in improving platelet function have not been fully elucidated,

but possibly include the requirement for heparin during hemodialysis (thereby increasing the risk of bleeding), the removal of compounds necessary for coagulation, platelet loss if cuprophane dialysis is used (not seen with polyacrylonitrile dialysis), disruption of platelet cytoskeleton organization by repeated platelet stress, a decrease in the percentage of RNA-rich platelets, and a reduction in the percentage of available reticulated platelets.^{37,58–60}

The limitations of most of the studies on dialysis for prevention or management of uremic bleeding (listed in Table 1) are lack of clinically useful end points, inadequate sample sizes, or poor randomization techniques.^{36,37,55–57} For example, the study performed by Stewart and Castaldi assessed actual clinical bleeding episodes (which completely resolved with dialysis) and bleeding time, while others assessed only laboratory measures of platelet function.^{36,37,55–57} In the Stewart and Castaldi study, bleeding time was measured using the Ivy method (which was not used in other studies of uremic bleeding) and was defined as having normalized when less than 9 min. The investigators found that bleeding time normalized during 30% of dialysis sessions. Other methods that have been used to assess platelet function primarily evaluate platelet aggregation by light transmission aggregometry; some trials showed improvement in this parameter in patients receiving dialysis. The studies listed in Table 1 are, however, all at least 25 years old, which makes it difficult to extrapolate and apply the results to current dialysis technology. In addition, light transmission aggregometry is primarily a research technique that is not presently useful in clinical practice. Frequent dialysis remains the standard of care for many complications associated with chronic kidney disease but its impacts on the prevention and treatment of uremic bleeding are still largely unknown.

TREATMENT

Treatments for uremic bleeding target the various factors that seem to have a role in platelet dysfunction. Interventions can exert acute (within 6 h) or delayed (within several weeks) effects, and this should be taken into consideration when they are used for a given clinical scenario. Of the interventions presented in this section, EPO could be considered for prevention as well as for treatment.

Table 1 Dialysis for prevention and treatment of uremic platelet dysfunction.

Reference	Study design	Sample size and characteristics	Intervention	Results
Lindsay <i>et al.</i> (1976) ³⁶	Prospective, single center, controlled	Patients with end-stage renal disease receiving peritoneal dialysis ($n = 18$) compared with a historical cohort of healthy volunteers, nondialyzed patients with chronic renal failure and patients receiving hemodialysis at home or in hospital	Peritoneal dialysis (48 h/week in twice weekly sessions) for an average duration of 10 months	ADP-induced platelet aggregation similar between healthy controls, patients with mild renal impairment (serum creatinine < 6 mg/100 ml) and those receiving peritoneal dialysis Platelet adhesion impaired in patients receiving peritoneal dialysis ($P < 0.02$) or hemodialysis in hospital ($P < 0.025$) compared with controls
Stewart and Castaldi (1967) ³⁷	Prospective, single center	Predialysis patients with severe renal failure and mild or severe bleeding ($n = 17$)	9 patients had peritoneal dialysis only, 7 patients had hemodialysis only, 1 patient had both peritoneal and hemodialysis	Complete resolution of clinical bleeding Ivy bleeding time returned to normal (< 9 min) in 6 of 20 cases Platelet adhesion and prothrombin consumption index improved from abnormal baseline values ADP-induced platelet aggregation improved in the 7 patients for whom results were available
Rabiner (1972) ⁵⁵	Prospective, single center	Uremic patients ($n = 25$)	Dialysis	Platelet factor 3-A time normalized in 5 of 25 patients and decreased in 12 of 25
Lindsay <i>et al.</i> (1978) ⁵⁶	Prospective, single center, controlled	Stable patients receiving hemodialysis (12–15 m ² h/week) in twice weekly sessions ($n = 27$)	Hemodialysis frequency increased to 12–15 m ² h/week in thrice weekly sessions	Platelet aggregation similar between patients receiving thrice weekly hemodialysis and healthy controls Platelet aggregation inferior to that of controls in patients receiving twice weekly hemodialysis
Nenci <i>et al.</i> (1979) ⁵⁷	Prospective, single center, controlled	Patients receiving hemodialysis ($n = 13$) or peritoneal dialysis ($n = 11$), renal transplant recipients ($n = 5$), nondialyzed patients with renal failure ($n = 13$) compared with healthy controls ($n = 24$)	Hemodialysis or peritoneal dialysis for patients in appropriate groups	Platelet aggregation similar in patients receiving peritoneal dialysis and healthy controls Platelet aggregation similar in patients receiving hemodialysis and untreated uremic patients

Erythropoietin

Patients with chronic kidney disease often suffer from anemia caused by decreased production of EPO by the kidneys. Recombinant human EPO, commonly used to correct anemia, might also help to stem uremic bleeding by several different mechanisms. First, recombinant human EPO stimulates division and differentiation of erythroid progenitor cells, thereby inducing erythropoiesis. This increase in the number of circulating red blood cells displaces platelets closer to the vascular endothelium, decreasing response time to vascular damage. The net result is a reduction in bleeding time.^{61–63} Second, recombinant human EPO increases the number of reticulated platelets, which seem to be more metabolically active.^{64,65} Third, recombinant human EPO enhances platelet aggregation as well as interaction between platelets and the subendothelium.^{61–63} Fourth, recombinant human EPO might also improve platelet signaling through tyrosine phosphorylation, which enhances the response of platelets to activating stimuli.⁶⁶ Finally, hemoglobin acts as

a scavenger of NO;⁴⁵ therefore, if hemoglobin levels were to be increased using recombinant human EPO, it is proposed that NO levels would drop, resulting in less effective stimulation of guanylyl cyclase and reduced production of cGMP. Although some of these mechanisms are not well defined, they could be of benefit in the prevention and treatment of uremic bleeding (as seen in several trials; see Table 2).^{61–64,67} Adequate dialysis might minimize the required dose of recombinant human EPO, which would reduce costs.^{68,69} This effect might not occur beyond a Kt/V (index of urea clearance) of 1.33.

Recombinant human EPO regimens of 40–150 U/kg intravenously three times a week have been studied for prevention or treatment of uremic bleeding.^{61,62,64} The goal of treatment with recombinant human EPO, regardless of the dose used, is a hematocrit greater than 30% to decrease bleeding time to a normal or near-normal value.^{61–63} Assuming normal iron stores and baseline hematocrit, achieving a hematocrit greater than 30% can take up to 9 weeks in uremic

Table 2 Recombinant human erythropoietin for uremic platelet dysfunction.

Reference	Study design	Sample size and characteristics	Treatment	Results
Vigano <i>et al.</i> (1991) ⁶¹	Prospective, randomized, controlled	Patients with end-stage renal disease receiving hemodialysis ($n=20$), hemoglobin <8.06 g/dl (5 mmol/l) and bleeding time >15 min	Recombinant human EPO (50 U/kg i.v. thrice weekly) administered after hemodialysis, titrated by 25 U/kg every 4 weeks until bleeding time normalized	After 12 weeks, recombinant human EPO (150–300 U/kg/week i.v.) normalized bleeding time in patients who achieved a packed cell volume of at least 30% ($P<0.01$)
Zwaginga <i>et al.</i> (1991) ⁶²	Prospective, nonrandomized, multicenter	Patients with anemia and chronic renal failure receiving hemodialysis ($n=21$)	Group 1 ($n=13$): EPO 16 U/kg/week i.v. doubled every 2 weeks to a maximum dose of 256 U/kg/week by week 12; dose was then adjusted to maintain hematocrit until week 20 Group 2 ($n=8$): EPO 240 U/kg/week for 12 weeks; if target hematocrit was not attained, then EPO dose was increased every 2 weeks by 120 U/kg/week until week 20	Group 1: bleeding time decreased after 20 weeks in 11 of 13 patients Group 2: bleeding time decreased after 20 weeks in 6 of 8 patients Platelet adhesion and aggregation improved in both groups
Cases <i>et al.</i> (1992) ⁶³	Prospective, single center	Protocol 1: patients with renal failure receiving hemodialysis ($n=19$) Protocol 2: subset of 14 of patients (as above) to evaluate platelet function	Recombinant human EPO (40 U/kg i.v. thrice weekly) increased by 40 U/kg every 4 weeks until hematocrit exceeded 30%	Mean bleeding time decreased from 20.5 min to 14.3 min ($P<0.01$) after 9.1 ± 3.5 weeks of treatment (mean dose of recombinant human EPO 65 ± 23 U/kg) Correlation between bleeding time and hematocrit was $r=-0.351$ ($P<0.05$)
Tassies <i>et al.</i> (1998) ⁶⁵	Prospective, controlled, single center	Patients with end-stage renal disease receiving hemodialysis ($n=12$) compared with controls ($n=24$)	EPO (40 U/kg i.v. thrice weekly); three doses in total	Increased number of reticulated platelets after 1 week compared with baseline ($13.1 \pm 4.6 \times 10^9/l$ vs $6.6 \pm 2.6 \times 10^9/l$; $P<0.01$) Significant increase in ADP-induced and ristocetin-induced aggregation ($P<0.01$)
Eschbach <i>et al.</i> (1992) ⁶⁷	Prospective, multicenter	Patients receiving hemodialysis ($n=24$) compared with controls ($n=22$)	EPO (i.v. every other day for 4 days) at doses of 15 U/kg ($n=4$), 50 U/kg ($n=5$) or 150 U/kg ($n=15$)	Chronic uremia does not alter response to EPO There is a dose-dependent response to EPO of hematocrit

Abbreviations: EPO, erythropoietin; i.v., intravenously.

patients.⁶³ It is important, however, to understand that beneficial effects on platelets can occur as soon as 7 days after initiation of treatment, as a result of an increase in the number of reticulated platelets.⁶⁵ Recombinant human EPO can be beneficial in the acute setting by improving both platelet adhesion and aggregation.^{62,63}

In conclusion, recombinant human EPO can be used as prophylaxis for uremic bleeding, and also (in combination with other treatment options) during acute bleeding episodes.

Cryoprecipitate

Cryoprecipitate is a blood product rich in factor VIII, vWF and fibrinogen that is commonly used in various bleeding diatheses. The mechanism of action of cryoprecipitate has not been fully elucidated, but it is postulated that this

precipitant might increase the proportion of functional clotting factors in a patient's plasma (Table 3).^{70,71} Cryoprecipitate is a reasonable therapeutic option in uremic patients at high risk of bleeding or with active bleeding. Cryoprecipitate should have a beneficial effect on bleeding time within the first 4–12 h in most patients. Dosing is 10 bags of American-Red-Cross-prepared cryoprecipitate given intravenously over 30 min. Each bag contains variable amounts of factor VIII and fibrinogen. One advantage of using cryoprecipitate is the fast onset of action (approximately 1 h).⁷⁰ Disadvantages include risk of post-transfusion hepatitis, HIV, fever, and allergic reaction. Rare but severe reactions include anaphylaxis, pulmonary edema and intravascular hemolysis. The response in uremic patients can be unpredictable.^{70,71}

Table 3 Cryoprecipitate for uremic platelet dysfunction.

Reference	Study design	Sample size and characteristics	Treatment	Results
Janson <i>et al.</i> (1980) ⁷⁰	Prospective, single center	Bleeding time >15 min in patients with uremia and uncontrolled bleeding or impending surgery (<i>n</i> = 7)	10 bags i.v. American-Red-Cross-prepared cryoprecipitate	Decreased bleeding time in all patients 4 h postinfusion (71% of patients achieved a bleeding time <7 min) Surgery without bleeding complications was performed on 5 patients
Triulzi and Blumberg (1990) ⁷¹	Retrospective, single center	Patients with acute or chronic renal failure, bleeding time >15 min, platelets >100,000/ μ l (<i>n</i> = 5)	10 bags i.v. American-Red-Cross-prepared cryoprecipitate	Decreased bleeding time in 2 patients (normalization after 2–4 cryoprecipitate doses) No reduction in bleeding time in 3 patients

Abbreviation: i.v., intravenously.

Table 4 Desmopressin for uremic platelet dysfunction.

Reference	Study design	Sample size and characteristics	Treatment	Results
Mannucci <i>et al.</i> (1983) ¹⁹	Retrospective, double blind, placebo controlled	Patients with chronic renal failure receiving hemodialysis with prior history of bleeding and bleeding time >10 min (<i>n</i> = 12) Patients with increased bleeding time undergoing surgery (<i>n</i> = 9)	One dose (0.3 μ g/kg i.v.) DDAVP versus placebo One dose (0.3 μ g/kg i.v.) DDAVP	Bleeding time normalized in 5 of 12 patients 1 h postinfusion, 2 of 12 patients 4 h postinfusion, and 1 of 12 patients 8 h postinfusion No excessive blood loss during surgery
Kohler <i>et al.</i> (1989) ^{73,a}	Prospective, randomized, double blind, placebo controlled	Patients receiving hemodialysis for indication of unknown etiology with bleeding time >15 min (<i>n</i> = 8)	One dose (0.4 μ g/kg subcutaneous) DDAVP	Bleeding time reduced in 7 of 8 patients and normalized in 2 of 8 patients Significant increase in concentration of von Willebrand factor
Watson and Keogh (1982) ⁷⁴	Prospective, single center	Patients with chronic renal failure and bleeding time >12 min (<i>n</i> = 12; 4 receiving hemodialysis, 3 receiving peritoneal dialysis)	One dose (0.4 μ g/kg i.v.) DDAVP	Bleeding time normalized in 6 of 12 patients 1 h postinfusion, 3 of 12 patients 2 h postinfusion, but 0 of 5 patients 24 h postinfusion

^aOnly patients with uremia in this study are reported. Abbreviations: DDAVP, desmopressin (1-deamino-8-D-arginine vasopressin); i.v., intravenously.

Desmopressin

The most common agent used in uremic patients with active bleeding is desmopressin (1-deamino-8-D-arginine vasopressin [DDAVP]). It is predominately used to treat diabetes insipidus, mild type I von Willebrand’s disease, and bleeding associated with hemophilia A. The mechanism of action of DDAVP has not been fully elucidated, but it is believed to exert part of its hemostatic effect by releasing factor VIII from storage sites, potentially increasing the concentration of factor VIII and minimizing the effects of dysfunctional vWF.⁷² Mannucci *et al.* reported that larger vWF–factor-VIII multimers are present in the plasma after infusion of DDAVP, which might reduce bleeding time.^{19,73} Although the clinical effect of larger vWF–factor-VIII multimers is not well known, there is a strong association between their presence and shortening of bleeding time (Table 4).^{19,73,74}

Desmopressin doses for uremic bleeding are approximately 10-fold higher than doses used

for diabetes insipidus, and range from 0.3 μ g/kg to 0.4 μ g/kg intravenously or subcutaneously as a single injection.^{19,73} One important advantage of DDAVP is its rapid onset of action in the setting of acute bleeding caused by uremic platelet dysfunction. The short duration of DDAVP activity could be an advantage; however, bleeding time tended to return towards baseline within 24 h, indicating patients are once again at risk of bleeding. This clinical effect is consistent with currently available literature and should be anticipated. Studies have shown that DDAVP increases vWF–factor-VIII levels and decreases bleeding time within approximately 1 h after infusion or injection.⁷³ This advantage is important for patients needing biopsies or major surgery who might not otherwise have been considered for these procedures because of their prolonged bleeding time.¹⁹ Another advantage of DDAVP over cryoprecipitate is the avoidance of risk of exposure to various blood-borne pathogens. Disadvantages of

DDAVP include reported tachyphylaxis after one dose, headache, facial flushing, and rare thrombotic events.^{19,73} The tachyphylaxis that develops is thought to be caused by depletion of vWF from endothelial stores.²¹ In addition to its short duration of activity, the potential for tachyphylaxis makes consideration of treatments other than DDAVP imperative, especially in patients with active bleeding.

Estrogens

Estrogens are commonly used for hormone replacement therapy, but also have a unique place in the treatment of uremic bleeding. While it is still uncertain how estrogens work to treat patients with prolonged bleeding time secondary to uremia, it has been postulated that the hormones decrease production of L-arginine, which is a precursor of NO.⁷⁵ By decreasing NO concentrations, which seem to be higher in uremia, there is less guanylyl cyclase stimulation and less production of cGMP. This potentially leads to increased production of TxA₂ and ADP, which are crucial contributors to formation of platelet plugs. Although none of the studies in uremic bleeding has assessed the impact of estrogens on coagulation, it is plausible that the capacity of these hormones to decrease antithrombin III and protein S levels, and increase factor VII concentrations, might contribute to the therapeutic effect in this clinical situation.⁷⁶

Currently available data show that conjugated estrogens can safely and effectively improve bleeding time and clinical bleeding in both males and females (Table 5)^{77–84} The dose of conjugated estrogens needed to produce these effects is 0.6 mg/kg intravenously over 30–40 min once daily for 5 consecutive days.^{78–80} The time to onset of action for conjugated estrogens is about 6 h; maximum effect is evident at 5–7 days with a duration of approximately 14–21 days.^{78–80} More data exist to support use of intravenous estrogen, but oral and transdermal therapy have also been shown to be beneficial. The long-lasting effect of conjugated estrogens is important in patients who are scheduled to undergo surgery in the near future, who might not have been surgical candidates because of prolonged bleeding time. Estrogens have also been successfully used in patients with gastrointestinal bleeding, a common complication associated with uremic platelet dysfunction.^{82–84}

EVIDENCE-BASED RECOMMENDATIONS

It is clear from the available literature that much of the evidence supporting treatment recommendations for uremic bleeding comes from studies performed 25–30 years ago. At that time, medical care was different from today; studies were poorly designed, with small sample sizes and inconsistent methods of assessing platelet function that are not currently used in standard clinical practice. Nonetheless, many clinicians today have patients with either active bleeding or a high risk of bleeding because of chronic renal failure. As a result of the complexity of uremic platelet dysfunction and the varying degrees of efficacy of potential treatments, we have proposed an evidence-based management algorithm that can help guide clinicians through most clinical scenarios of uremic bleeding (Figure 1). We have also answered common questions relating to management of uremic bleeding. The responses to and rationale underlying these basic questions are consistent with and supportive of the proposed treatment algorithm. It is important to keep in mind that these recommendations are not a substitute for a clinician's judgment and must be used alongside consideration of extraneous variables that might be contributing to the bleeding.

Should a hemodynamically stable, actively bleeding uremic patient be given recombinant human EPO?

Yes, if the baseline hematocrit is less than 30% and iron stores are normal (strength of recommendation/evidence, IIa/B [see Box 1 for strength of recommendation/evidence scales]).

As a result of the delayed onset of the beneficial effects of recombinant human EPO, patients who are actively bleeding and hemodynamically unstable are unlikely to benefit from administration of this agent in the acute setting. The use of recombinant human EPO, however, has been shown to have a positive impact on uremic bleeding as soon as 7 days after initiation of therapy and early use in hemodynamically stable patients is probably beneficial when baseline hematocrit is less than 30% and iron stores are normal. The dosing would be the same as recommended in the product insert (target hematocrit $\geq 30\%$), as this is the level at which the greatest benefit in reducing bleeding time is apparent. A hematocrit at this level will also facilitate the distribution of platelets towards the endothelium, where adhesion and

Table 5 Conjugated estrogens for uremic platelet dysfunction.

Reference	Study design	Sample size and characteristics	Treatment	Results
Liu <i>et al.</i> (1984) ⁷⁷	Prospective, single center	Patients receiving hemodialysis or peritoneal dialysis with bleeding time >30 min and "abnormal bleeding tendency" (n=6)	Conjugated estrogens (5–50 mg i.v. or oral) in divided doses every 12 h	Reduced bleeding time in 5 patients Bleeding time normalized in 4 patients after 2–5 days of treatment
Livio <i>et al.</i> (1986) ⁷⁸	Randomized, double blind, placebo controlled, crossover	Patients with chronic renal failure and a history of bleeding receiving hemodialysis, with bleeding time >20 min (n=6)	Conjugated estrogen (0.6 mg/kg i.v.) for 5 days (total doses 122–197 mg) or placebo	Reduced bleeding time in all estrogen-treated patients within 6 h
Vigano <i>et al.</i> (1988) ⁷⁹	Prospective, controlled, single center	Patients with chronic renal failure and prolonged bleeding time receiving hemodialysis (n=15) versus healthy controls	Conjugated estrogens (0.3 mg/kg i.v., n=5; 0.6 mg/kg i.v., n=10)	0.3 mg/kg/day dose did not reduce bleeding time in the 5 patients 4–5 daily infusions of 0.6 mg/kg i.v. are needed to prolong reduction of bleeding time
Heistingier <i>et al.</i> (1990) ⁸⁰	Randomized, double blind, placebo controlled, crossover, single center	Patients with end-stage renal disease receiving hemodialysis (n=7)	Conjugated estrogens (0.6 mg/kg/day i.v.) for 5 days	Significant reduction of bleeding time on days 7 and 14 (11 min vs 15 min, P=0.04; and 12 min vs 17 min, P=0.03, respectively) Minimal effect at 21 days, no effect at day 28
Shemin <i>et al.</i> (1990) ⁸¹	Group 1: prospective, single center Group 2: prospective, randomized, placebo controlled, single center	Group 1: actively bleeding patients (n=4) 3 of whom were receiving hemodialysis Group 2: patients without active bleeding receiving hemodialysis (n=10)	Group 1: conjugated estrogens 50 mg PO until bleeding time normalized or for 9 days Group 2: conjugated estrogens 50 mg PO or placebo until bleeding time normalized or for 9 days	Group 1: cessation of bleeding in all patients, bleeding time normalized in 2 and decreased by 50% in 1 Group 2: bleeding time normalized in 3 of 5 patients, bleeding time decreased by <50% in remaining 2 patients
Bronner <i>et al.</i> (1986) ⁸²	Prospective, single center	Patients with active bleeding receiving hemodialysis (n=7)	Norethynodrel/mestranol at varied doses (n=6); ethinyl estradiol (n=1)	Cessation of clinical bleeding during treatment Mean blood transfusion requirements decreased from 1.2 U/month to 0.2 U/month during treatment
Sloand and Schiff (1995) ⁸³	Prospective, single center	Patients with renal insufficiency (n=6) 4 of whom were actively bleeding	17β-estradiol 50 μg/24 h transdermally (n=3); 17β-estradiol 100 μg/24 h transdermally (n=3)	Reduced blood transfusion requirements Improved bleeding time in all patients
Heunisch <i>et al.</i> (1998) ⁸⁴	Case report	One patient with acute renal failure, rectal and nasogastric bleeding	Conjugated estrogen (10 mg/day i.v.) for 7 days	Hemoglobin level remained stable and requirement for blood products ceased Rectal and nasogastric bleeding resolved Patient subsequently died

Abbreviations: i.v., intravenously; PO, by mouth.

aggregation are more likely to be initiated. Patients with uremia secondary to chronic kidney disease will generally require EPO replacement therapy for treatment or prevention of anemia; recombinant human EPO is, therefore, already a standard of care for these patients.

Does recombinant human EPO prevent bleeding caused by uremic platelet dysfunction?

Yes, if the hematocrit is increased to more than 30% (strength of recommendation/evidence,

IIa/B [see Box 1 for strength of recommendation/evidence scales]).

Studies have shown that when the hematocrit is greater than 30%, bleeding time is reduced in most patients because of displacement of platelets such that they are closer to the vascular endothelium. This displacement decreases the time required for adhesion and aggregation in response to damage. The decrease in bleeding time would theoretically help prevent uremic bleeding. It is important to remember the complex nature of, and the multiple factors contributing to, uremic

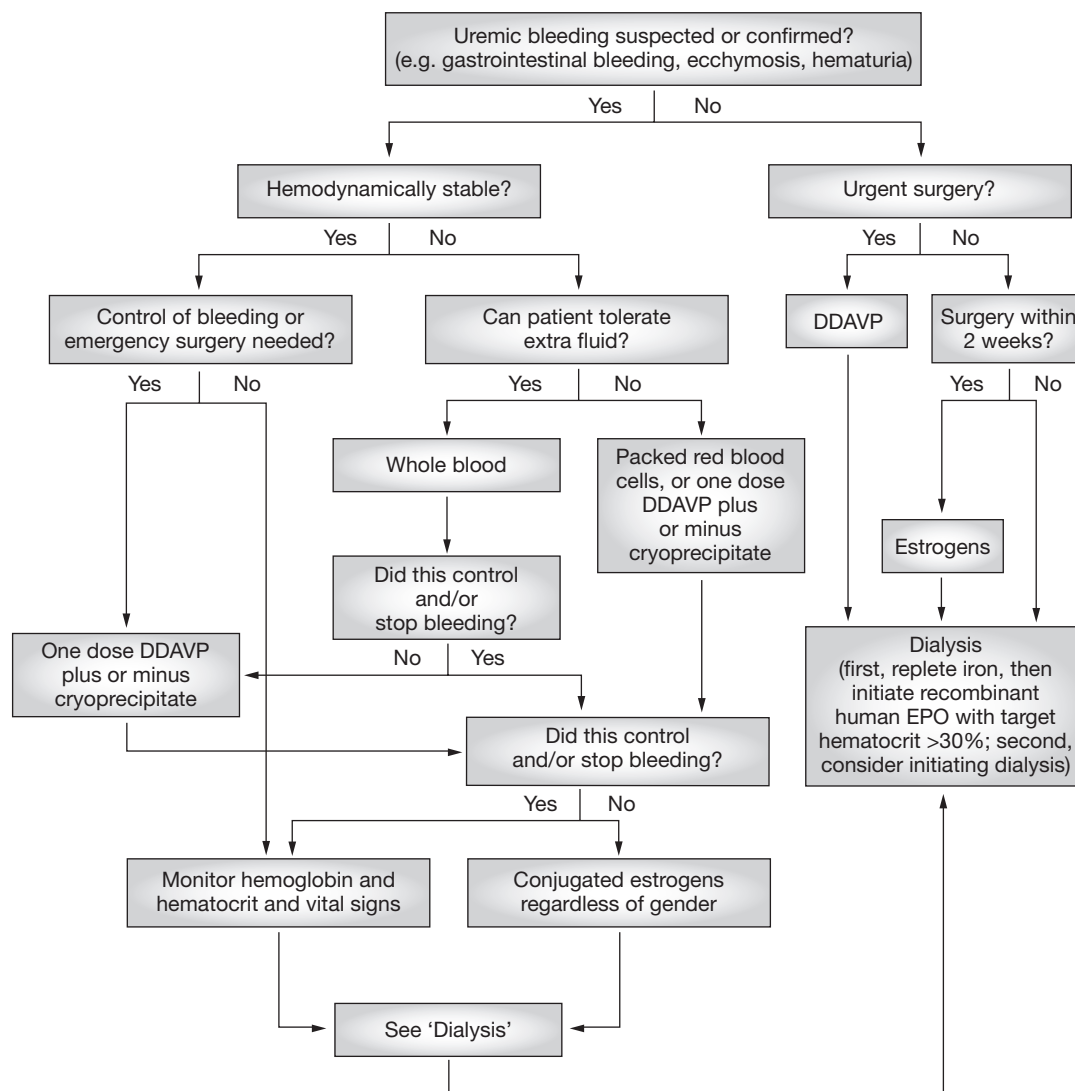


Figure 1 Algorithm for the management of uremic platelet dysfunction. If at any stage in the algorithm the patient with uremic platelet dysfunction should start to actively bleed, the clinician should return to the top of the algorithm. This algorithm is not intended to replace sound clinical judgment or prevent additional consideration of patient factors that could influence management decisions. Abbreviations: DDAVP, desmopressin (1-deamino-8-D-arginine vasopressin; single doses of 0.3–0.4 $\mu\text{g}/\text{kg}$ body weight intravenous); EPO, erythropoietin.

platelet dysfunction. Use of recombinant human EPO should, therefore, be only one part of a clinician's strategy for preventing uremic bleeding. As stated above, patients with chronic kidney disease might require recombinant human EPO to treat or prevent anemia, and this agent is therefore already a standard of care in this population.

Will dialysis offer any acute benefit to a uremic patient with active bleeding?

Yes (strength of recommendation/evidence, IIa/B [see Box 1 for strength of recommendation/evidence scales]).

There are limited data on the efficacy of dialysis in actively bleeding uremic patients. Results, however, are promising. A small study showed complete resolution of clinical bleeding in all patients who were actively bleeding prior to dialysis.³⁷ Frequent dialysis might also improve indices of platelet aggregation and bleeding time in some patients, theoretically contributing to cessation of bleeding. Dialysis is the standard of care for patients with renal failure; it will facilitate removal of uremic retention solutes in plasma, but should be used in combination with other treatments (Figure 1).

Box 1 Scales of strength of recommendation and strength of evidence.

Strength of recommendation

Class I: Recommended—the given test or treatment is useful and should be performed or administered.

Class IIa: Recommended in most cases—the given test or treatment is generally considered to be useful and is indicated in most cases.

Class IIb: Recommended in some cases—the given test or treatment might be useful and is indicated in some, but not most, cases; generally reserved as a ‘last resort’ option.

Class III: Not recommended—the given test or treatment is not useful under any circumstances and should be avoided.

Strength of evidence

Category A: Evidence based on:

- meta-analyses of randomized controlled trials with homogeneity with regard to the direction and degree of results between individual studies
- at least three well-executed randomized controlled trials involving large numbers of patients from more than one center; often includes data from an international population

Category B: Evidence based on:

- few (1 or 2) well-executed randomized controlled trials involving large numbers of patients
- meta-analyses of randomized controlled trials with conflicting conclusions with regard to the direction and degree of results between individual studies
- randomized controlled trials involving small numbers of patients OR with significant methodological flaws (e.g. bias, high drop-out rate, flawed analysis)
- nonrandomized studies (e.g. cohort, case-control, observational)

Category C: Evidence based on:

- expert opinion or consensus from specialists within field of study
- published case reports or case series
- anecdotal evidence

Category D: Unknown, or no appropriate evidence to support or reject

Does dialysis prevent uremic platelet dysfunction?

Possibly (strength of recommendation/evidence, IIa/B [see Box 1 for strength of recommendation/evidence scales]).

Studies^{36,37,55–57} support the conclusion that dialysis—in particular, peritoneal dialysis—improves platelet function, as it can result in measures of platelet aggregation returning to normal values (comparable to those of healthy controls). Patients had pre-existing uremic platelet dysfunction, and the goal of the studies was to determine if platelet function could be normalized by dialysis. Studies support a target serum creatinine concentration of less than 6 mg/100 ml to maintain normal platelet function. Data indicate that peritoneal dialysis can normalize platelet function, but it is not known if hemodialysis or peritoneal dialysis can prevent the first occurrence of uremic platelet dysfunction.

Can estrogen be administered to male uremic patients with active bleeding?

Yes (strength of recommendation/evidence, IIb/B [see Box 1 for strength of recommendation/evidence scales]).

All of the studies of estrogen discussed in this Review included male patients. No adverse effects of the hormone were reported, other than hot flashes. Most of the studies that evaluated estrogens limited duration of administration to five consecutive days. Adverse effects of long-term administration of conjugated estrogens in males, therefore, remain unknown and administration of this hormone for more than 5 days cannot be recommended.

Should estrogen be administered orally, transdermally or intravenously?

Intravenously (strength of recommendation/evidence, IIa/B [see Box 1 for strength of recommendation/evidence scales]).

Oral, transdermal and intravenous routes of administering conjugated estrogens to manage uremic platelet disorder have all been evaluated. Each of these routes has been associated with decreased bleeding time. Nevertheless, intravenous administration has been studied most frequently and seems to be the preferred route. Studies of intravenous conjugated estrogens at doses of 0.6 mg/kg/day reported decreased bleeding time. We therefore recommend intravenous administration over oral and transdermal routes.

What dose of estrogen most effectively prevents or treats bleeding in uremic patients?

The most effective dose of estrogen depends on the route of administration (strength of recommendation/evidence, IIa/A/B [see Box 1 for strength of recommendation/evidence scales]).

Three studies evaluating patients with uremic bleeding using a dose of 0.6 mg/kg/day conjugated estrogens intravenously all detected a decrease in bleeding time.^{78–80} Lower doses have also been evaluated and shown to be ineffective.⁷⁹ When treating a patient with oral conjugated estrogens, doses of 50 mg/day, for an average of 7 days, have been shown to be effective. Transdermal estrogen has been effective when administered at doses of 50–100 µg/day. As stated above, all tested routes of administration and doses decreased bleeding time; however, 0.6 mg/kg/day intravenously has been the most frequently studied protocol with reproducible results.

Are conjugated estrogens preferable to estrogen–progesterone combination products?

Yes, however combination products have been shown to be effective (strength of recommendation/evidence, IIa/B [see Box 1 for strength of recommendation/evidence scales])

Conjugated estrogens have been much more extensively studied than estrogen–progesterone combination products, which have been evaluated in one study. Bronner *et al.* evaluated combination products and showed cessation of bleeding and decreased requirement for blood transfusions.⁸² No other studies have been performed to determine if these results are reproducible. After reviewing trials that tested estrogens for treatment of uremic bleeding, we recommend the use of conjugated estrogens 0.6 mg/kg/day intravenously rather than combination products.

Should DDAVP be first-line therapy in a uremic patient with bleeding?

Yes (strength of recommendation/evidence, I/A [see Box 1 for strength of recommendation/evidence scales]).

DDAVP has repeatedly been shown to improve bleeding time in patients who are actively bleeding or who are being prepared for surgery. DDAVP improves dysfunctional platelet activity by stimulating release of factor VIII from

endothelial stores and by increasing vWF activity. As a result of its rapid onset of action, DDAVP is commonly used as the first-line agent in patients with active bleeding or those who are about to undergo surgery.

Should DDAVP treatment be repeated if bleeding is not controlled by the initial dose?

No (strength of recommendation/evidence, I/C [see Box 1 for strength of recommendation/evidence scales])

DDAVP administration should not be repeated because of the risk of tachyphylaxis. It is postulated that tachyphylaxis occurs as a result of depletion of factor VIII and vWF endothelial stores. If bleeding has not been controlled after one dose of DDAVP, then consideration should be given to other treatment options such as cryoprecipitate or conjugated estrogens.

Should DDAVP be administered orally or intravenously?

Intravenously (strength of recommendation/evidence, I/B [see Box 1 for strength of recommendation/evidence scales]).

To our knowledge no trial has evaluated oral DDAVP in uremic bleeding. Oral administration of DDAVP might be as beneficial as intravenous therapy, but there are currently no data to support this. At this time, we can recommend only the use of intravenous DDAVP. Trials of oral administration of DDAVP for uremic bleeding should be performed before any recommendation can be made for or against its use.

When should cryoprecipitate be administered to a uremic patient with bleeding?

If the patient is hemodynamically stable but in need of urgent surgery or control of bleeding; also for patients who are hemodynamically unstable and who cannot tolerate extra fluid (see treatment algorithm Figure 1; strength of recommendation/evidence, IIb/B [see Box 1 for strength of recommendation/evidence scales]).

Cryoprecipitate, rich in factor VIII, vWF and fibrinogen, should be reserved for patients who are either actively bleeding or in need of urgent surgery. It is also an important treatment option for patients who have received one dose of DDAVP but have not achieved hemostasis. Before administration of cryoprecipitate, patients should be evaluated to determine if they

Table 6 Summary of relative effects of different treatment options in uremic bleeding.

Treatment option	Prevents uremic platelet dysfunction	Effective for active bleeding	Useful in males and females	Improves platelet adhesion	Improves platelet aggregation	Increases platelet size or number	Reduces bleeding time	Normalizes bleeding time
Dialysis	+	–	+	–	+	+	++	+
Recombinant human EPO	+	+/-	+	+	+	+	++	+
Cryoprecipitate	–	++	+	–	–	–	++	+
Desmopressin	–	+++	+	–	+/-	–	+++	++
Estrogen intravenous	–	+	+	–	+	–	++	+
Estrogen oral	–	+	+	–	+	–	+	+
Estrogen transdermal	–	+	+	–	–	–	+	–

Abbreviation: EPO, erythropoietin.

are able to tolerate the associated increase in intravascular volume. Care should also be given when administering blood products because of the potential for transmission of infectious disease such as hepatitis and HIV.

Is the combination of cryoprecipitate and DDAVP beneficial in uremic bleeding?

Theoretically, yes (strength of recommendation/evidence, IIb/D [see Box 1 for strength of recommendation/evidence scales]).

No study has evaluated the combination of cryoprecipitate and DDAVP. As these two agents have different mechanisms of action, it is proposed that they could be given in combination with additive benefits.

Do omega-3 fatty acids increase the risk of bleeding in patients with uremia?

Not known, but theoretically possible (level of evidence, D [see Box 1 for strength of recommendation/evidence scales]).

There has been growing interest in this question in conditions (other than uremic bleeding) in which the risks of bleeding or blood loss are increased. This interest exists because many patients now use fish oil supplements to treat lipid abnormalities and various inflammatory conditions. When omega-3 fatty acids—whether as supplements or in food—are incorporated into the diet, they can partially replace omega-6 fatty acids in the cell membranes of many cells (erythrocytes, platelets, endothelial cells, lymphocytes, monocytes, granulocytes and fibroblasts, to name but a few). This partial replacement results in competition between

omega-3 and omega-6 fatty acids during production of endoperoxides (e.g. TxA_2 and prostaglandin). Specifically, eicosapentaenoic acid, an omega-3 fatty acid, competes with arachidonic acid at the level of cyclooxygenase and lipoxygenase during production of prostaglandin and leukotriene. As a result of this competition, eicosapentaenoic acid and docosahexaenoic acid, another omega-3 fatty acid, cause a decrease in TxA_2 and an increase in PGI_3 production. Although there is no evidence to support or disprove the risk of this biochemical competition, these effects could theoretically increase a patient's chance of bleeding in the setting of uremic platelet dysfunction.

CONCLUSIONS

Uremic bleeding in patients with chronic renal failure is extremely complex. One factor contributing to this complexity is the incomplete elucidation of the pathophysiology of the condition. As we do not fully understand the mechanisms underlying uremic bleeding, prevention and treatment for many different clinical scenarios are not clearly defined. Treatment options tend to focus on one, perhaps two, aspects of the pathophysiology; their relative effects are summarized in Table 6. EPO works to increase the number of red blood cells, allowing platelets to travel in closer proximity to the endothelium. Cryoprecipitate and desmopressin work to increase the proportion of normal or functional factors that might be dysfunctional in patients with uremic bleeding. Estrogens are thought to work by decreasing NO levels, thereby increasing concentrations of TxA_2 and

ADP. Multiple interventions that simultaneously affect different aspects of the pathophysiology of uremic bleeding might most effectively prevent bleeding in high-risk patients and limit active bleeding in those for whom cessation of blood loss is more pressing. The benefit of early evaluation to identify patients at high risk of bleeding cannot be underestimated. By determining which patients are most at risk, clinicians can utilize dialysis and EPO in the early stages of uremic bleeding, and employ desmopressin, cryoprecipitate and/or estrogens prior to a surgical procedure, thereby possibly preventing bleeding secondary to uremic platelet dysfunction. If a patient presents with uremia, clinicians should remain vigilant for early signs and symptoms of bleeding so that the efficacy of intervention can be maximized.

KEY POINTS

- Pathophysiology of uremic bleeding in patients with chronic renal failure is incompletely elucidated, but probably involves dysfunctional von Willebrand factor, increased levels of cyclic AMP and cyclic GMP, uremic toxins and anemia
- Typical presenting symptoms include ecchymoses, purpura, epistaxis, and bleeding from venipuncture sites; gastrointestinal and intracranial bleeding might also be evident
- Evaluation of bleeding time is the most useful clinical test; normal bleeding time ranges from 1–7 minutes
- Prevention and treatment options include dialysis, erythropoietin, cryoprecipitate, desmopressin and conjugated estrogens, used alone or in combination

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Competing interests

The authors declared they have no competing interests.