Bleeding in Uremia

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Introduction

Bleeding episodes substantially contribute to morbidity and mortality in patients with end-stage renal disease. Here, uremia with the accumulation of uremic toxins plays an important pathogenic role [1]. In particular, an impaired function of platelets, the disturbed interaction between the vessel wall with its endothelium and its extracellular matrix with the platelets, and anemia are all involved in the complex problem of the increased bleeding tendency in uremic patients [1, 2]. Bleeding episodes occur in 24–50% of patients on hemodialysis (HD) [3–5]. A hospital-based analysis reported an approximately twofold increased risk of bleeding in patients with renal failure [6]. Furthermore, bleeding events and access site bleeding requiring transfusion were significantly associated with degrees of renal insufficiency in patients undergoing percutaneous coronary intervention [4]. Clinically, an increased bleeding tendency in patients with renal failure may present as gastrointestinal bleeding, bleeding from cannulation sites, retinal hemorrhage, subdural hematoma, epistaxis, hematuria, ecchymosis, purpura, bleeding from the gums, gingival bleeding, genital bleeding, hemoptysis, telangiectasia, or hemarthrosis [4, 5].

Anticoagulants, particularly direct oral anticoagulants (DOACs) with their potential to accumulate in patients with renal failure, may further interfere with this system, thus promoting bleeding episodes in such patients [7]. While DOACs were associated with a non-statistically significant decreased risk for major bleeding compared to vitamin K antagonist in patients with eCrCL (estimated creatinine clearance) <50 mL/min, they differ from each in their relative risk, with only apixaban and edoxaban being associated with a decreased risk while rivaroxaban and dabigatran are not [8].

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Pathophysiology of Bleeding in Patients with Uremia

Clot Formation and Platelets

Patients with advanced chronic kidney disease seem to have an increased clot strength [9–11]. Furthermore, the clot formation is delayed and lysis is decreased in these patients, which is associated with increased fibrinogen levels. A delayed clot formation may predispose to bleeding complications in patients with advanced chronic kidney disease, while the increased clot strength and decreased breakdown may be related to thrombosis [6, 12]. This increased clot strength seems to be associated with increased levels of fibrinogen in patients with advanced chronic kidney disease [13]. This could be a compensatory mechanism to regulate the deranged hemostasis in these patients [10, 14]. Thus, increased levels of fibrinogen and increased clot strength could be also responsible for the thrombotic events in chronic kidney disease patients. Patients on hemodialysis on the other hand have a decreased clot strength and increased lysis as compared to chronic kidney disease patients not on dialysis. This could be related to the decreased levels of fibrinogen and von Willebrand factor (VWF) or increased tissue plasminogen activator levels after dialysis [15, 16].

However, platelet function itself is also heavily disturbed in uremia [1, 8]. This is emphasized by the observation that platelet function returns to normal after successful kidney transplantation [17]. The pathogenesis of bleeding complication is believed to be multifactorial, including an acquired platelet function disorder characterized by reduced integrin activation and aggregation in response to agonist stimulation [18]. On the other hand, a study in patients with chronic kidney disease undergoing percutaneous coronary

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intervention showed that the prevalence of high residual platelet reactivity for ADP was higher among patients with more severe chronic kidney disease (CKD G 3–5) [19]. High residual platelet reactivity was not associated with major cardiocirculatory events in a 2-year follow-up of these patients. Interestingly bleeding risks were significantly lower in patients with high residual platelet reactivity for ADP.

Uremic toxins such as phenol, phenolic acid (impairment of primary aggregation to ADP), and guanidinosuccinic acid (inhibition of the second wave of ADP-induced platelet aggregation) influence platelet function [20–22] although a correlation between the bleeding time and the concentration of the dialyzable uremic metabolites was not detected so far [23]. However, dialysis improves platelet function and reduces the bleeding risk [24–28]. Urea itself does not seem to interfere with platelet function [29]. Platelet components such as α-granules [25, 30] have an increased ATP/ADP ratio and a reduced content of serotonin in uremia. Furthermore, the thrombin-triggered release of ATP together with an increased calcium content and a disturbed intracellular calcium flux could contribute to the impaired platelet function in uremia [25]. The disturbed arachidonic acid and prostaglandin metabolism with an impaired synthesis and/or release of thromboxane A2 leads to a reduced adhesion and aggregation of platelets contributing to bleeding episodes [25, 31], which can be reversed by dialysis [32]. In addition, ultrafiltrates collected from uremic patients inhibited platelet-activating factor synthesis that could account for the decreased platelet activity [33]. Furthermore, circulating fibrinogen fragments have been demonstrated that can also interfere with hemostasis as they competitively bind to the glycoprotein (GP) IIb/IIIa receptor on platelets resulting in a decreased adhesion and aggregation potential of platelets [34]. Oxidative stress and inflammation also have a profound effect on platelet function [35].

Platelet–Vessel Wall Interactions

A decreased amount of GPIb on platelets [4] together with the insufficient binding of VWF and fibrinogen to activated platelets from uremic patients can reduce the function of the GPIIb/IIIa complex that is important for the binding of platelets to the vessel wall in order to stop bleeding. In addition, a functional defect in VWF–platelet interaction can be related to an increased bleeding tendency in uremic patients [36, 37].

Moreover, vasoactive substances such as nitric oxide (NO), inhibiting platelet aggregation through the formation of cGMP, or prostacyclins, which modulate vascular tone, can also play a role in defective hemostasis in uremia. Plasma levels of prostacyclin, NO generation of platelets, and the concentration of NO metabolites, which is also related to the lower hemoglobin levels (see below), are increased in the plasma of uremic patients, thus contributing to dysfunctional hemostasis with an increased bleeding risk [38, 39].

Anemia

Anemia can promote bleeding episodes in uremic patients as it directly influences the bleeding time [40–42]. In anemia platelets flow in the middle of the bloodstream due to the lower number of erythrocytes. This impairs the interaction between platelets and the vessel wall resulting in a prolonged bleeding time. And erythrocytes significantly improve platelet adhesion and aggregation in in vitro flow chamber systems, and negative correlations have been found between hematocrit and bleeding time. Furthermore, the low number of erythrocytes with a reduced hemoglobin amount leads to a reduced scavenging of NO [43], thus decreasing ADP and thromboxane A2 release via an enhanced activation of guanylyl cyclase [44] with increased cGMP levels. This inhibits platelet aggregation and inactivation of prostacyclin [45]. Consistently, erythropoietin treatment has a beneficial effect on the bleeding time, but not platelet activation, in renal failure patients [18].

Drugs

Drug–platelet interactions have fundamental effects on platelet function and thus on bleeding disorders, which is also the case in patients with uremia. Antibiotics such as third-generation cephalosporins and β-lactam antibiotics play a role under these circumstances [46, 47]. β-Lactam antibiotics interact with platelets through an interference with ADP receptors. These effects are related to dose and duration of the therapy. Acetylsalicylic acid has been shown to significantly prolong the bleeding time in patients with renal failure [48]. Furthermore, other nonsteroidal anti-inflammatory drugs also alter platelet function through the inhibition of cyclooxygenase, although this is reversible after discontinuation of the drug.

As many anticoagulants are eliminated by the kidney, they can accumulate if their dose is not adapted to the patient's renal function [7]. Anticoagulants that can accumulate in patients with renal impairment include low-molecular-weight heparins (LMWHs), direct factor Xa inhibitors like danaparoid and fondaparinux, and the DOACs such as rivaroxaban, edoxaban, or apixaban as well as the direct thrombin inhibitors refludan and dabigatran. Interestingly, the effect of vitamin K antagonists such as phenprocoumon or warfarin could be aggravated in patients with end-stage renal disease as these patients can develop a vitamin K deficiency [49].

Discussions on the use of the different anticoagulants at different stages of chronic kidney disease are presented in a comprehensive recent review [50].

Management of Bleeding in Patients with Uremia

Management of bleeding in patients with uremia encompasses substances, blood compounds, and procedures that can be used alone or partly in combination (see Table 19.1). However, it must be emphasized that while treating bleeding episodes in uremic patients with potential comorbidities, clot formation is promoted that could lead to other clinical problems in terms of thrombus formation or embolism at other sites (i.e., myocardial ischemia, fistula occlusion).

Table 19.1 Management of bleeding in uremic patients

	Dose	Comment
Dialysis	Individually adequate	PD with better platelet aggregation than HD
Erythropoietin	40–150 U/kg	Target Hb 10.5–11.5 g/dL (see text)
Vasopressin analogues	0.3–0.4 µg/kg as a single dose s.c.	Tachyphylaxis; repeat doses are not effective
	0.3–0.4 µg/kg over 30 min. i.v.	
Conjugated estrogens	0.6 mg/kg/day i.v. for 5 days	Effect lasts 4–5 days
	50 mg/kg/day p.o.	
	50–100 µg/day (patch)	
Fresh frozen plasma	2–3 units	Contains all coagulation factors; use in patients with vitamin K antagonist overdose
Cryoprecipitate	Bags (n) = 0.2 × weight (kg) → provide about 100 mg/dL fibrinogen	Use in hypofibrinogenemia (fibrinogen <1 g/L)
	Standard dose: 10 units; repeat if needed	
Factor VIIa	90 µg/kg i.v. bolus every 2 h until hemostasis	Successful use documented in case reports
	Continue every 3–6 h after hemostasis achieved according to clinical judgment	
Platelet transfusion	1 apheresis unit or equivalent	Emergencies; alloimmunization in transplant candidates possible
Tranexamic acid	20 mg/kg every 48 h i.v.	Not over longer time periods; accumulation in renal failure
	10 mg/kg every 48 h p.o.	

PD peritoneal dialysis, *HD* hemodialysis

Dialysis

Uremic toxins contribute to the bleeding tendency in patients with end-stage renal disease. The removal of uremic toxins by dialysis improves platelet function with a reduced risk of bleeding [24–28]. On the other hand, hemodialysis itself can enhance the bleeding tendency, due to the intradialytically administered anticoagulants (i.e., heparin) but also due to continuous platelet activation at the dialyzer membrane resulting in a decreased platelet activity [28, 51, 52]. Furthermore, an activation defect of the platelet GPIIb/IIIa complex could be involved in the bleeding tendency of some patients related to hemodialysis [24] as the expression of the GPIIb/IIIa receptor on thrombocytes is higher in peritoneal dialysis [53], which has been shown to maintain in vitro platelet aggregation better as compared to hemodialysis [54]. Moreover, peritoneal dialysis was associated with better platelet aggregation as compared to hemodialysis [55]. The reasons include apart from anticoagulant administration during hemodialysis also the removal of pro-coagulation factors, platelet loss related to the dialyzer, disruption of platelet cytoskeleton, a decrease of RNA-rich platelets, and a reduction of reticulated platelets [56]. Furthermore, a better elimination of middle molecules could be responsible for the advantages of peritoneal dialysis with respect to hemodialysis [54]. However, it is not known how actual dialysis procedures such as hemodiafiltration (HDF) compare to peritoneal dialysis as also HDF effectively eliminates middle molecules. Of note, hemodialysis and peritoneal dialysis could also promote coagulation [57, 58].

Future studies should analyze the effect of modern dialysis techniques (i.e., HDF) or an increase in dialysis time on the bleeding tendency of uremic patients.

Erythropoietin

Chronic kidney disease, particularly in advanced stages, is associated with anemia due to the lack of erythropoietin (EPO). As anemia is associated with an increased bleeding tendency in uremia, the administration of erythrocytes [59] or EPO [60, 61] reduces the bleeding time as well as bleeding episodes. Administration of recombinant erythropoietin leads to an increased number of erythrocytes, thus shifting platelets more to the vessel wall where they can interact with injured sites and stop bleeding [61–63]. Furthermore, the number of reticulated platelets with an increased metabolic activity is higher after the administration of EPO [64, 65], the platelet aggregation and the platelet interaction with the

sub-endothelium is higher [61–63], and erythropoietin improves platelet signaling through tyrosine phosphorylation [66]. Additionally, the scavenging capacity of NO is improved with higher hemoglobin levels after EPO therapy resulting in a lower stimulation of guanylyl cyclase with reduced production of cGMP leading to an improved platelet aggregation (see above) [43].

EPO at a dose of 40–150 U/kg intravenously three times a week has been studied in uremic bleeding [61, 63, 64]. A hematocrit greater than 30% is associated with a normalization of the bleeding time [61–63]. The effect occurs rather slowly after 7 days. However, EPO can be beneficial also in an acute setting as it can improve platelet function by increasing the number of GPIIb/IIIa receptors on platelets as well as increasing thrombin-induced phosphorylation of platelet proteins [62, 63, 66]. Thus, it can be used in acute bleeding episodes but also as a prophylaxis.

However, problems exist with the target parameter: the 2012 KDIGO (Kidney Disease Improving Global Outcomes) guidelines for the management of anemia in patients with renal failure refer to the hemoglobin level as the target parameter for the guidance of the EPO therapy which should be ≤11.5 g/dL as higher hemoglobin levels were associated with an increased incidence of myocardial infarction and a higher mortality [67]. The hematocrit is more variable and should be used with caution as a target parameter. Furthermore, a potential deficit of iron should also be treated before the administration of EPO can be effective. Thus, EPO should be used with caution in patients with bleeding episodes only if anemia is present with a hemoglobin below 10.5 g/dL and normal iron stores.

Vasopressin Analogues

Bleeding disorders can be treated with desmopressin (1-deamino-8-D-arginine vasopressin, DDAVP) in patients with end-stage renal disease [37]. Most studies analyzed the bleeding time that cannot properly predict the bleeding tendency in uremic patients [56]. However, also with the in vitro closure time test, the beneficial effects of desmopressin on primary hemostasis could be demonstrated [68]. A prospective non-controlled study in uremic patients on antiplatelet drugs demonstrated that a single dose of desmopressin before invasive procedures could improve platelet function measured by collagen/epinephrine closure time of PFA-100™ and was also well tolerated [69]. Furthermore, it can be also used as a prevention of bleeding episodes in such patients (i.e., renal biopsies, endoscopy, and surgery). It is administered at a dose of 0.3–0.4 μg/kg as a single dose subcutaneously or over 30 min intravenously. Both administration routes can effectively restore primary hemostasis in uremic patients [70]. So far no data exist on orally administered desmopressin although it should also be theoretically effective. Due to its rapid onset, it is recommended as the first-line treatment in uremic patients with active bleeding [56]. However, its effect reaches its maximum after 4–6 h and has nearly vanished after 8–24 h [37]. Even after one dose, tachyphylaxis might occur; thus its duration of activity is rather short [56] and treatment should not be repeated after one dose [56]. In patients with antiplatelet drugs [69] as well as heparin, desmopressin can also reduce the prolonged bleeding time [71]. Its mechanism of action is an increase of VWF, factor VIII, and tissue plasminogen activator (tPA) from storage sites mediated via the activation of vasopressin V2R receptors on endothelial cells. Plasminogen activator inhibitor 1 (PAI-1) level is diminished due to tPA release and tPA and PAI-1 complex formation. Furthermore, functional protein C level is also decreased in patients with uremia after administration of desmopressin [5, 72, 73]. Furthermore, it increases the expression of GPIb on platelets [72]. This minimizes the effects of dysfunctional VWF and leads to larger VWF multimers that reduce bleeding time [74, 75].

Conjugated Estrogens

Bleeding episodes can be also treated with conjugated estrogens in patients with uremia [76–80]. A double-blind randomized crossover study revealed that the administration of estrogens (0.6 mg/kg/day i.v. for 5 days) leads to a reduced bleeding time as well as an increased platelet activity in patients on hemodialysis [81]. The therapeutic effect was achieved for 7–14 days after treatment where the effect starts already 6 h after administration of the substance. An oral dose of 50 mg/kg/day leads to a measurable reduction of the bleeding time 2 days after administration and lasts for approximately 4–5 days [72, 82]. Furthermore, a transdermal estradiol patch with a dose of 50–100 μg/day can be applied twice a week [83]. This approach is also suitable for longer treatment periods as it was used for 2 months during this study. Even transdermal doses ≤50 μg daily might be effective [84]. Successful treatment of nasal bleeding has also been achieved with topical intranasal estrogens in patients with von Willebrand disease and hemophilia [85].

An increase of platelet reactivity could be mediated through the increase of β-thromboglobulin and thromboxane B_2 as well as an increased synthesis of VWF and factor VIII together with a reduction of protein S levels [5]. Furthermore, uremia is associated with an increased generation of endothelium-derived NO [86], which can be prevented by estrogens [87]. Estrogens need more time until the therapeutic effect begins, while its duration is substantially longer in comparison to desmopressin [76].

Fresh Frozen Plasma, Cryoprecipitate, and Factor VIIa

Cryoprecipitate contains substantial amounts of VWF, factor VIII, fibrinogen, factor XIII, and fibronectin and thus can immediately correct defects in primary hemostasis. However, this effect will last for only 4–12 h [5, 36, 45]. It should be used only in emergency situations where a rapid correction of hemostatic defects is needed, particularly if hypofibrinogenemia with fibrinogen levels <1 g/L is present [72]. However, the effect in patients with end-stage renal disease is difficult to predict [36, 37, 88]. Infections, anaphylactic reactions, and volume overload could be adverse reactions in patients with renal failure [5, 72]. In contrast to cryoprecipitate, fresh frozen plasma contains all coagulation factors and should be used in patients with severe bleeding due to warfarin or phenprocoumon therapy where cryoprecipitate is not effective due to its low content in vitamin K-dependent coagulation factors [89].

Moreover, some case reports describe the use of recombinant activated factor VII (rFVIIa) for treatment of bleeding in uremic patients [90–93]. This approach seems attractive, as it should act only locally at the site of bleeding [94]. Thus, it has been successfully used also in a patient with bleeding after a kidney biopsy [94]. However, due to the lack of studies, only little experience exists with the use of rFVIIa in uremic patients.

Platelet Transfusion

Platelet transfusions are immediately effective in reducing the bleeding risk for approximately 4–5 h [5]. This approach should be used in emergency situations if immediate correction is warranted or if the pharmacologic approach is not effective. In transplant candidates a risk of alloimmunization, although low, exists [5].

Tranexamic Acid

Tranexamic acid inhibits fibrinolysis by forming a reversible complex with plasminogen and preventing its conversion to plasmin [5]. It can be administered orally or intravenously [72, 95]. Tranexamic acid effectively stops cerebral, gastrointestinal, or angiodysplasia-associated bleedings of the colon in patients on hemodialysis [96–98]. However, as it is eliminated via the kidneys, the dose should be limited to 20 mg/kg every 48 h i.v. or 10 mg/kg every 48 h p.o. [72]. Thus, tranexamic acid should not be administered over longer time periods. Single doses of tranexamic acid can be combined with other compounds in uremic patients in order to control bleeding.

Summary

Uremia develops in patients with end-stage renal disease without an adequate renal replacement therapy. Bleeding episodes are a significant clinical problem in such patients. They could be of mild character but could also result in fatal outcomes. The increased bleeding tendency in uremia results from an impaired function of platelets and a disturbed platelet–vessel wall interaction. Furthermore, anemia and anticoagulants/antiplatelet drugs contribute to the increased risk of bleeding in these patients. Management of bleeding episodes in uremic patients includes an adequate dialysis for the removal of uremic toxins that could interfere with the function of platelets and the correction of anemia with EPO in order to increase the number of red blood cells that shift platelets more to the vessel wall where they can interact with sites of injury as well as a better capacity to scavenge NO through increased amounts of hemoglobin. Furthermore, estrogens can be administered that alter VWF, factor VIII, compounds of the arachidonic acid metabolism, and the production of NO. Desmopressin improves platelet function through the release of VWF and factor VIII. In severe cases, also fresh frozen plasma or rFVIIa can be administered. Moreover, tranexamic acid that inhibits the conversion of plasminogen to plasmin can be given. In severe bleeding episodes, also combinations of the above therapeutic approaches can be considered (Table 19.1).

References

1. Boccardo P, Remuzzi G, Galbusera M. Platelet dysfunction in renal failure. Semin Thromb Hemost. 2004;30(5):579–89.
2. Jalal DI, Chonchol M, Targher G. Disorders of hemostasis associated with chronic kidney disease. Semin Thromb Hemost. 2010;36(1):34–40.
3. Kaufman JS, et al. Randomized controlled trial of clopidogrel plus aspirin to prevent hemodialysis access graft thrombosis. J Am Soc Nephrol. 2003;14(9):2313–21.
4. Moal V, et al. Impaired expression of glycoproteins on resting and stimulated platelets in uraemic patients. Nephrol Dial Transplant. 2003;18(9):1834–41.
5. Pavord S, Myers B. Bleeding and thrombotic complications of kidney disease. Blood Rev. 2011;25(6):271–8.
6. Parikh AM, et al. Venous thromboembolism in patients with reduced estimated GFR: a population-based perspective. Am J Kidney Dis. 2011;58(5):746–55.
7. Dager WE, Kiser TH. Systemic anticoagulation considerations in chronic kidney disease. Adv Chronic Kidney Dis. 2010;17(5):420–7.
8. Raccah BH, et al. Major bleeding and hemorrhagic stroke with direct oral anticoagulants in patients with renal failure: systematic review and meta-analysis of randomized trials. Chest. 2016;149(6):1516–24.
9. Chapman MP, et al. Thrombelastographic pattern recognition in renal disease and trauma. J Surg Res. 2015;194(1):1–7.
10. Holloway DS, et al. Thrombelastography of blood from subjects with chronic renal failure. Thromb Res. 1987;45(6):817–25.

11. Pivalizza EG, Abramson DC, Harvey A. Perioperative hypercoagulability in uremic patients: a viscoelastic study. J Clin Anesth. 1997;9(6):442–5.
12. Lutz J, et al. Haemostasis in chronic kidney disease. Nephrol Dial Transplant. 2014;29(1):29–40.
13. Nunns GR, et al. The hypercoagulability paradox of chronic kidney disease: the role of fibrinogen. Am J Surg. 2017;214(6):1215–8.
14. Velik-Salchner C, et al. The effect of fibrinogen concentrate on thrombocytopenia. J Thromb Haemost. 2007;5(5):1019–25.
15. Sabovic M, et al. The influence of the haemodialysis procedure on platelets, coagulation and fibrinolysis. Pathophysiol Haemost Thromb. 2005;34(6):274–8.
16. Vaziri ND, et al. Blood coagulation, fibrinolytic, and inhibitory proteins in end-stage renal disease: effect of hemodialysis. Am J Kidney Dis. 1994;23(6):828–35.
17. Kennedy C, et al. Successful kidney transplantation normalizes platelet function. Clin Kidney J. 2018;11(4):574–80.
18. Casari C, Bergmeier W. Acquired platelet disorders. Thromb Res. 2016;141(Suppl 2):S73–5.
19. Zhu P, et al. Platelet reactivity in patients with chronic kidney disease undergoing percutaneous coronary intervention. Platelets. 2018:1–7.
20. Horowitz HI. Uremic toxins and platelet function. Arch Intern Med. 1970;126(5):823–6.
21. Horowitz HI, et al. Further studies on the platelet-inhibitory effect of guanidinosuccinic acid and its role in uremic bleeding. Am J Med. 1970;49(3):336–45.
22. 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. 1970;49(3):346–51.
23. Remuzzi G, et al. Bleeding in renal failure: altered platelet function in chronic uraemia only partially corrected by haemodialysis. Nephron. 1978;22(4–6):347–53.
24. Benigni A, et al. Reversible activation defect of the platelet glycoprotein IIb-IIIa complex in patients with uremia. Am J Kidney Dis. 1993;22(5):668–76.
25. Di Minno G, et al. Platelet dysfunction in uremia. Multifaceted defect partially corrected by dialysis. Am J Med. 1985;79(5):552–9.
26. Gawaz MP, et al. Impaired function of platelet membrane glycoprotein IIb-IIIa in end-stage renal disease. J Am Soc Nephrol. 1994;5(1):36–46.
27. Remuzzi G, et al. Altered platelet and vascular prostaglandin-generation in patients with renal failure and prolonged bleeding times. Thromb Res. 1978;13(6):1007–15.
28. Sreedhara R, et al. Defective platelet aggregation in uremia is transiently worsened by hemodialysis. Am J Kidney Dis. 1995;25(4):555–63.
29. Linthorst GE, Avis HJ, Levi M. Uremic thrombocytopathy is not about urea. J Am Soc Nephrol. 2010;21(5):753–5.
30. 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. 1981;1(1):17–23.
31. Smith MC, Dunn MJ. Impaired platelet thromboxane production in renal failure. Nephron. 1981;29(3–4):133–7.
32. Bloom A, et al. Evidence against a platelet cyclooxygenase defect in uraemic subjects on chronic haemodialysis. Br J Haematol. 1986;62(1):143–9.
33. Wratten ML, et al. Uremic ultrafiltrate inhibits platelet-activating factor synthesis. Blood Purif. 1999;17(2–3):134–41.
34. Thekkedath UR, et al. Elevated fibrinogen fragment levels in uremic plasma inhibit platelet function and expression of glycoprotein IIb-IIIa. Am J Hematol. 2006;81(12):915–26.
35. Brunini TM, et al. Platelet nitric oxide synthesis in uremia and malnutrition: a role for L-arginine supplementation in vascular protection? Cardiovasc Res. 2007;73(2):359–67.
36. Janson PA, et al. Treatment of the bleeding tendency in uremia with cryoprecipitate. N Engl J Med. 1980;303(23):1318–22.
37. Mannucci PM, et al. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. N Engl J Med. 1983;308(1):8–12.
38. Defreyn G, et al. A plasma factor in uraemia which stimulates prostacyclin release from cultured endothelial cells. Thromb Res. 1980;19(4–5):695–9.
39. Kyrle PA, et al. 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. 1988;60(2):205–8.
40. Fernandez F, et al. Low haematocrit and prolonged bleeding time in uraemic patients: effect of red cell transfusions. Br J Haematol. 1985;59(1):139–48.
41. Galbusera M, Remuzzi G, Boccardo P. Treatment of bleeding in dialysis patients. Semin Dial. 2009;22(3):279–86.
42. Howard AD, et al. Analysis of the quantitative relationship between anemia and chronic renal failure. Am J Med Sci. 1989;297(5):309–13.
43. Martin W, et al. Blockade of endothelium-dependent and glyceryl trinitrate-induced relaxation of rabbit aorta by certain ferrous hemoproteins. J Pharmacol Exp Ther. 1985;233(3):679–85.
44. Noris M, et al. Enhanced nitric oxide synthesis in uremia: implications for platelet dysfunction and dialysis hypotension. Kidney Int. 1993;44(2):445–50.
45. Kaw D, Malhotra D. Platelet dysfunction and end-stage renal disease. Semin Dial. 2006;19(4):317–22.
46. Fass RJ, et al. Platelet-mediated bleeding caused by broad-spectrum penicillins. J Infect Dis. 1987;155(6):1242–8.
47. Shattil SJ, et al. Carbenicillin and penicillin G inhibit platelet function in vitro by impairing the interaction of agonists with the platelet surface. J Clin Invest. 1980;65(2):329–37.
48. Gaspari F, et al. Aspirin prolongs bleeding time in uremia by a mechanism distinct from platelet cyclooxygenase inhibition. J Clin Invest. 1987;79(6):1788–97.
49. McCabe KM, Adams MA, Holden RM. Vitamin K status in chronic kidney disease. Nutrients. 2013;5(11):4390–8.
50. Burlacu A, et al. Pros and cons of antithrombotic therapy in end-stage kidney disease: a 2019 update. Nephrol Dial Transplant. 2019;34(6):923–33.
51. Remuzzi G, et al. Platelet function in patients on maintenance hemodialysis: depressed or enhanced? Clin Nephrol. 1982;17(2):60–3.
52. Sirolli V, et al. Cell activation and cellular-cellular interactions during hemodialysis: effect of dialyzer membrane. Int J Artif Organs. 2002;25(6):529–37.
53. Salvati F, Liani M. Role of platelet surface receptor abnormalities in the bleeding and thrombotic diathesis of uremic patients on hemodialysis and peritoneal dialysis. Int J Artif Organs. 2001;24(3):131–5.
54. Lindsay RM, et al. Platelet function in patients on long term peritoneal dialysis. Clin Nephrol. 1976;6(2):335–9.
55. Nenci GG, et al. Effect of peritoneal dialysis, haemodialysis and kidney transplantation on blood platelet function. I. Platelet aggregation by ADP and epinephrine. Nephron. 1979;23(6):287–92.
56. Hedges SJ, et al. Evidence-based treatment recommendations for uremic bleeding. Nat Clin Pract Nephrol. 2007;3(3):138–53.
57. Cardigan RA, et al. Activation of the tissue factor pathway occurs during continuous venovenous hemofiltration. Kidney Int. 1999;55(4):1568–74.
58. Pawlak K, Pawlak D, Mysliwiec M. Association between tissue factor, its pathway inhibitor and oxidative stress in peritoneal dialysis patients. Blood Coagul Fibrinolysis. 2007;18(5):467–71.
59. Livio M, et al. Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. Lancet. 1982;2(8306):1013–5.
60. Moia M, et al. Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. Lancet. 1987;2(8570):1227–9.

61. Vigano G, et al. Recombinant human erythropoietin to correct uremic bleeding. Am J Kidney Dis. 1991;18(1):44–9.
62. Cases A, et al. Recombinant human erythropoietin treatment improves platelet function in uremic patients. Kidney Int. 1992;42(3):668–72.
63. Zwaginga JJ, et al. Treatment of uremic anemia with recombinant erythropoietin also reduces the defects in platelet adhesion and aggregation caused by uremic plasma. Thromb Haemost. 1991;66(6):638–47.
64. Peng J, et al. Aged platelets have an impaired response to thrombin as quantitated by P-selectin expression. Blood. 1994;83(1):161–6.
65. Tassies D, et al. Effect of recombinant human erythropoietin treatment on circulating reticulated platelets in uremic patients: association with early improvement in platelet function. Am J Hematol. 1998;59(2):105–9.
66. Diaz-Ricart M, et al. Erythropoietin improves signaling through tyrosine phosphorylation in platelets from uremic patients. Thromb Haemost. 1999;82(4):1312–7.
67. Besarab A, et al. The effects of normal as compared with low hematocrit values in patients with cardiac disease who are receiving hemodialysis and epoetin. N Engl J Med. 1998;339(9):584–90.
68. Lee HK, et al. Desmopressin improves platelet dysfunction measured by in vitro closure time in uremic patients. Nephron Clin Pract. 2010;114(4):c248–52.
69. Kim JH, et al. Desmopressin improves platelet function in uremic patients taking antiplatelet agents who require emergent invasive procedures. Ann Hematol. 2015;94(9):1457–61.
70. Vigano GL, et al. Subcutaneous desmopressin (DDAVP) shortens the bleeding time in uremia. Am J Hematol. 1989;31(1):32–5.
71. Franchini M. The use of desmopressin as a hemostatic agent: a concise review. Am J Hematol. 2007;82(8):731–5.
72. Horl WH. Thrombocytopathy and blood complications in uremia. Wien Klin Wochenschr. 2006;118(5–6):134–50.
73. Zeigler ZR, Megaludis A, Fraley DS. Desmopressin (d-DAVP) effects on platelet rheology and von Willebrand factor activities in uremia. Am J Hematol. 1992;39(2):90–5.
74. Kohler M, et al. Subcutaneous injection of desmopressin (DDAVP): evaluation of a new, more concentrated preparation. Haemostasis. 1989;19(1):38–44.
75. Watson AJ, Keogh JA. Effect of 1-deamino-8-D-arginine vasopressin on the prolonged bleeding time in chronic renal failure. Nephron. 1982;32(1):49–52.
76. Heunisch C, et al. Conjugated estrogens for the management of gastrointestinal bleeding secondary to uremia of acute renal failure. Pharmacotherapy. 1998;18(1):210–7.
77. Liu YK, Kosfeld RE, Marcum SG. Treatment of uraemic bleeding with conjugated oestrogen. Lancet. 1984;2(8408):887–90.
78. Livio M, et al. Conjugated estrogens for the management of bleeding associated with renal failure. N Engl J Med. 1986;315(12):731–5.
79. Vigano G, et al. Dose-effect and pharmacokinetics of estrogens given to correct bleeding time in uremia. Kidney Int. 1988;34(6):853–8.
80. Zoja C, et al. Prolonged bleeding time and increased vascular prostacyclin in rats with chronic renal failure: effects of conjugated estrogens. J Lab Clin Med. 1988;112(3):380–6.
81. Heistinger M, et al. Effect of conjugated estrogens on platelet function and prostacyclin generation in CRF. Kidney Int. 1990;38(6):1181–6.
82. Shemin D, et al. Oral estrogens decrease bleeding time and improve clinical bleeding in patients with renal failure. Am J Med. 1990;89(4):436–40.
83. Sloand JA, Schiff MJ. Beneficial effect of low-dose transdermal estrogen on bleeding time and clinical bleeding in uremia. Am J Kidney Dis. 1995;26(1):22–6.
84. Gonzalez J, Bryant S, Hermes-DeSantis ER. Transdermal estradiol for the management of refractory uremic bleeding. Am J Health Syst Pharm. 2018;75(9):e177–83.
85. Ross CS, et al. Intranasal oestrogen cream for the prevention of epistaxis in patients with bleeding disorders. Haemophilia. 2011;17(1):164.
86. Remuzzi G, et al. Role of endothelium-derived nitric oxide in the bleeding tendency of uremia. J Clin Invest. 1990;86(5):1768–71.
87. Noris M, et al. 17beta-estradiol corrects hemostasis in uremic rats by limiting vascular expression of nitric oxide synthases. Am J Physiol Renal Physiol. 2000;279(4):F626–35.
88. Triulzi DJ, Blumberg N. Variability in response to cryoprecipitate treatment for hemostatic defects in uremia. Yale J Biol Med. 1990;63(1):1–7.
89. Pantanowitz L, Kruskall MS, Uhl L. Cryoprecipitate. Patterns of use. Am J Clin Pathol. 2003;119(6):874–81.
90. Gielen-Wijffels SE, et al. Successful treatment of severe bleeding with recombinant factor VIIa after kidney transplantation. Intensive Care Med. 2004;30(6):1232–4.
91. Moisescu E, et al. Recombinant factor VIIa treatment of bleeding associated with acute renal failure. Blood Coagul Fibrinolysis. 2000;11(6):575–7.
92. 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. 2003;82(4):257–8.
93. Revesz T, et al. Recombinant factor VIIa in severe uremic bleeding. Thromb Haemost. 1998;80(2):353.
94. Maksimovic B, et al. Treatment of bleeding after kidney biopsy with recombinant activated factor VII. Blood Coagul Fibrinolysis. 2012;23(3):241–3.
95. Sabovic M, et al. The effect of long-term, low-dose tranexamic acid treatment on platelet dysfunction and haemoglobin levels in haemodialysis patients. Thromb Haemost. 2005;94(6):1245–50.
96. 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. 2003;18(7):1388–91.
97. Vujkovac B, Lavre J, Sabovic M. Successful treatment of bleeding from colonic angiodysplasias with tranexamic acid in a hemodialysis patient. Am J Kidney Dis. 1998;31(3):536–8.
98. Vujkovac B, Sabovic M. Treatment of subdural and intracerebral haematomas in a haemodialysis patient with tranexamic acid. Nephrol Dial Transplant. 2000;15(1):107–9.