SECTION 17

# Acute Kidney Injury and Organ Crosstalk

CHAPTER 102

## Bleeding and Hemostasis in Acute Renal Failure

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**OBJECTIVES**

This chapter will:

1. Review the physiology of primary hemostasis, coagulation, and fibrinolysis.
2. Discuss the pathogenesis of bleeding in uremia and acute renal failure.
3. Examine the causes of venous and arterial thrombosis in uremia and acute renal failure.

### PHYSIOLOGIC HEMOSTASIS

Physiologic hemostasis is the result of a complex series of events that take place to stop bleeding at the site of injury while maintaining normal blood flow in nondamaged circulation sites. Hemostasis consists of three phases—primary hemostasis, coagulation, and fibrinolysis—which are closely connected to one another (Fig. 102.1).

#### Primary Hemostasis

Primary hemostasis is due to interactions between platelets, adhesive proteins, and the vessel wall. Vascular endothelium is a naturally antithrombotic surface that possesses antiplatelet, anticoagulant, and profibrinolytic properties. Vascular injury, however, determines a switch in endothelium properties, which in turn leads to platelet recruitment, activation, and aggregation to form the hemostatic plug.[1]

The first step of this process, platelet adhesion at the injury site, is mediated by the interaction between platelet adhesion receptors and the extracellular matrix components von Willebrand factor (VWF) and collagen. VWF is a glycoprotein that normally is stored in granules of endothelial cells and platelets, which can also be found circulating in blood. When VWF is released in the bloodstream, it adheres to endothelial cellular membranes as ultra-large multimers that are cleaved subsequently by the protein ADAMTS-13, which prevents spontaneous platelet adhesion and activation. Moreover, VWF also binds to subendothelial matrix proteins, such as collagen.[2]

The platelet transmembrane complex GPIb-V-IX interacts with VWF and determines platelet rolling on the endothelium through P-selectin interaction, and platelet activation by actin cytoskeleton reorganization.[3] Another essential receptor required for platelet adhesion and activation is GPVI, which binds to subendothelial collagen when this component is unmasked by endothelial injuries.[4]

Integrins are present on the surface of platelets in their inactive form while in the steady state. Platelet activation causes a conformational change in $\alpha_{IIb}\beta_3$ (also termed GPIIb/IIIa, the most important of these receptors), which enables it to bind several ligands, such as fibrinogen, VWF, and collagen, thus promoting platelet aggregation.[5] Platelet activation promotes further platelet activation and aggregation through the release of various mediators (e.g., adenosine diphosphate, thromboxane, serotonin) in a feedback activation process. Notably, thrombin (the terminal protease of the coagulation cascade) also facilitates platelet activation through the cleavage of two protease-activated receptors (PAR1 and PAR4).[6]

#### *Coagulation*

Coagulation is divided into the *intrinsic pathway*, initiated by contact with negatively charged surfaces, and the *extrinsic pathway*, initiated by tissue factor (TF).

The coagulation cascade is started by blood vessel disruption and the exposure of subendothelial cells to circulating factors. Subendothelial cells expose TF, which binds factor VII, promoting its proteolysis and leading to the formation of TF–factor VIIa complex. This complex in turn may activate factor IX and factor X.

Factor Xa activates factor V to factor Va, leading to the formation of the factor Xa–factor Va complex, which is

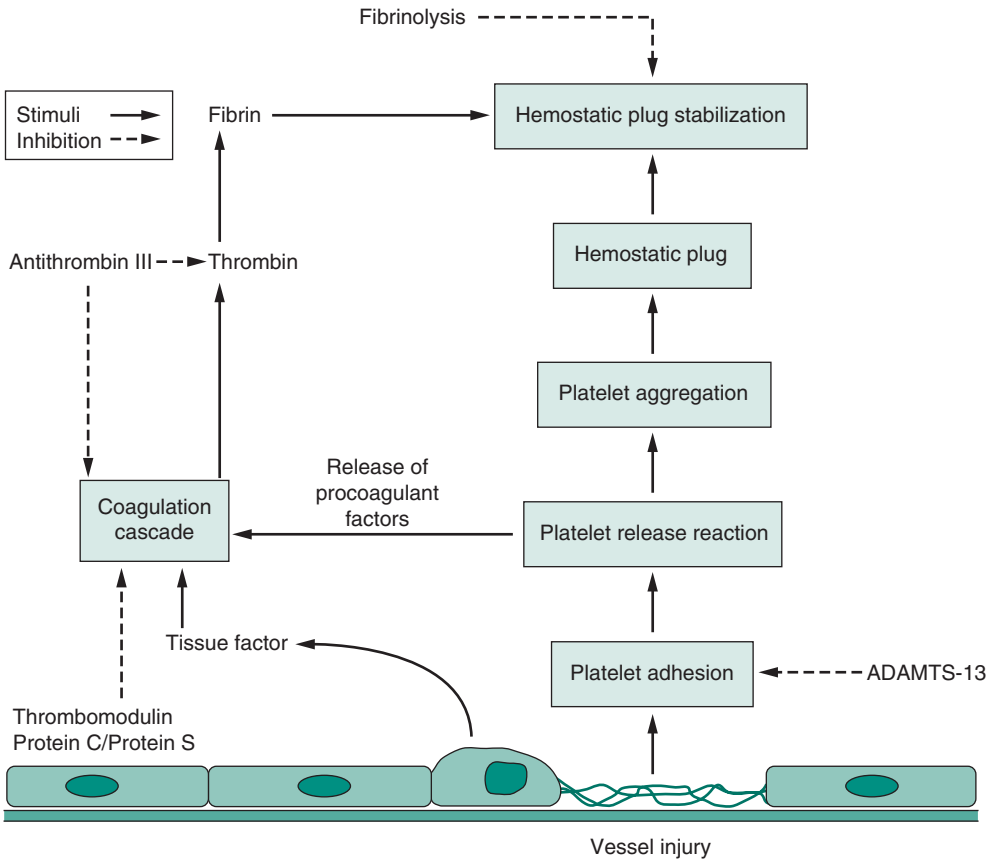


**FIGURE 102.1** Overview of hemostasis.

capable of converting prothrombin (factor II) to thrombin. Factor IXa binds factor VIIIa, which further promotes the activation of factor X. Thrombin then may activate factors VIII, V, and XI and separate factor VIII from VWF, thus enhancing prothrombinase activity. Once formed, thrombin cleaves the fibrinogen molecule to create fibrin monomers that are cross-linked to form polymers through the action of thrombin-activated factor XIIIa.[7]

In recent years the factor XI-factor XII intrinsic pathway, which classically was thought of as a simple amplification loop for the coagulation cascade initiated by the TF, has been reevaluated: new evidence suggests that this pathway is triggered in parallel with the extrinsic pathway through different stimuli, which include collagen and polyphosphates.[8]

There are several anticoagulatory mechanisms for tightly controlling the coagulation cascade. These systems can be divided roughly into two categories: circulating protease inhibitors (e.g., antithrombin and tissue factor pathway inhibitor), which act as inhibitors of coagulation factors by binding to their active sites, and the enzymatic protein C/protein S pathway.

Antithrombin (AT) is one of the most important circulating inhibitors of thrombin formation, which exerts its function through the inhibition of factors IXa, Xa and IIa. The ability of AT to inhibit its targets is accelerated greatly by heparin and heparin-like glycosaminoglycans present on the endothelial cell surface.

Tissue factor pathway inhibitor (TFPI) is another protease inhibitor that is located either in platelets, on the microvascular endothelium, or in a circulating form associated with lipoproteins. TFPI exerts its anticoagulation function by inhibiting factor Xa and the transient TF/FVIIa/FXa complex.

Thrombin is also inhibited by thrombomodulin, a thrombin receptor expressed by endothelial cells. Thrombin-bound thrombomodulin together with the endothelial protein C receptor (EPCR) activates protein C. Activated protein C is then complexed with its cofactor protein S, which in turn proteolytically inactivates factor Va and factor VIIIa, thus preventing the activation of factor X and II. The protein C/protein S pathway is necessary to prevent clot formation on healthy endothelial cells that present thrombomodulin.[9]

## Fibrinolysis

Fibrinolysis is a regulated mechanism that aims to remove blood clots during wound healing and prevent coagulation in intact vascular beds. The activation of fibrinolysis is achieved by converting plasminogen to plasmin through the action of either tissue plasminogen activator (tPA), which is released by activated endothelial cells, or urokinase plasminogen activator (uPA), which is produced mainly by macrophages and monocytes. Once produced, plasmin cleaves factor V, factor VIII, fibrinogen, and the GPIb-V-IX on platelets. Finally, fibrin and fibrinogen degradation products (FDPs) interfere with fibrin formation and impair platelet function through $\alpha_{IIb}\beta_3$ complex occupancy.

Fibrinolysis is controlled primarily by three serine protease inhibitors, plasminogen activator inhibitors 1 and 2 (PAI-1 and PAI-2) and α2-antiplasmin (A2AP). Other inhibitors include α2-macroglobulin, C1-esterase inhibitor,

thrombin-activated fibrinolysis inhibitor (TAFI), and members of the contact pathway of the coagulation cascade.[10]

# PATHOPHYSIOLOGY

## Bleeding

Bleeding is a common and potentially severe complication of acute and chronic renal failure. The clinical manifestations vary, ranging from ecchymoses, epistaxis, bleeding from the gums and venipuncture sites, to overt, life-threatening gastrointestinal bleeding. The advent of modern dialysis techniques has reduced but not eliminated the risk of hemorrhage. Bleeding has been reported in up to half of patients on continuous renal replacement therapy (CRRT), with varying incidence depending on the study cohort and the type of anticoagulation used.[11,12] In a recent series of 252 patients with dialysis-dependent acute renal failure (ARF) in the intensive care setting, major all-cause bleeding was observed in 26% of patients on CRRT and in 23% of patients on intermittent hemodialysis (IHD).[13]

The pathogenesis of acute renal failure–related bleeding is considered multifactorial and includes elements that can be divided roughly into three categories: uremia-related factors, dialysis-related factors, and critical care-related factors.[14] Bleeding tendency in uremic patients has been evaluated extensively, with abnormalities in platelet-platelet and platelet-vessel wall interaction playing a major role. Unfortunately, most studies have been done in patients with chronic renal failure, and it is not clear whether these findings can be extrapolated to acute renal failure. Pathologic conditions that frequently accompany ARF in the intensive care setting, such as sepsis, liver failure, disseminated intravascular coagulation, major surgery, severe trauma, thrombotic microangiopathies, and hypovolemic/cardiogenic shock may aggravate the bleeding tendency observed in such patients. In addition, anticoagulation regimens for renal replacement therapy may contribute further to hemostatic abnormalities.

### *Thrombocytopenia*

Reduced circulating platelet numbers can be observed in ARF patients as a result of uremia,[15,16] which causes inadequate platelet production and overconsumption.[17] Mean platelet volume may also be decreased in uremic patients, causing a reduction in the circulating platelet mass that is related inversely to bleeding time. Nevertheless, the platelet count is rarely below $80 \times 10^9$/L,[15,18] a number considered adequate for normal hemostasis. Still, other conditions may additionally aggravate thrombocytopenia through either platelet consumption or reduced production; these include sepsis, viral infections, hematinic deficiency, disseminated intravascular coagulation, cirrhosis, autoimmune diseases, adverse reactions to drugs, and thrombotic microangiopathies. As a matter of fact, thrombocytopenia has been reported in about 20% of medical patients and in about 30% of surgical patients admitted to intensive care units.[19] In the case of ARF requiring renal replacement therapy, some degree of platelet fragmentation as a result of mechanical stress because of hemodialysis procedures has also been reported. Finally, thrombocytopenia may also derive from the anticoagulation regimen used to inhibit clotting in the extracorporeal circuit. If heparin is used, this may occasionally precipitate an immunologic condition known as heparin-induced thrombocytopenia[20]; however, this condition is associated with thromboembolic events rather than bleeding. In patients at risk of bleeding, alternative means to routine heparinization can be used to avoid clotting in the extracorporeal circulation during hemodialysis. Heparin-free strategies developed specifically for anticoagulation in patients at high risk of bleeding include hemodialysis without anticoagulation and regional anticoagulation with citrate. The use of anticoagulants during renal replacement therapy is discussed in other chapters.

### *Platelet Abnormalities*

A wide variety of platelet abnormalities have been reported in patients with severe renal impairment (Box 102.1), including subnormal dense granule content, impaired release of the platelet α-granule proteins and β-thromboglobulin, reduced capacity to form thromboxane $A_2$, reduction in serotonin and ADP, and elevation of cyclic AMP. Platelet dysfunction has also been attributed to alterations in the prostaglandin-forming enzyme cyclooxygenase and to abnormal $Ca^{2+}$ mobilization in platelets, leading to the impairment of $Ca^{2+}$-dependent platelet function.

Because this platelet defect is corrected partially by dialysis, uremic toxins such as urea, phenol, and guanidinosuccinic acid (GSA) have been related causally to uremic platelet dysfunction. Several studies have pointed out that the platelet-vessel wall interaction is impaired in uremic patients.[21–23] This anomaly is attributable to impaired function of the platelet $\alpha_{IIb}\beta_3$ complex receptor, accounting for the decreased binding of the two main adhesive proteins circulating in human blood, VWF and fibrinogen, to stimulated uremic platelets.[24] The impaired $\alpha_{IIb}\beta_3$ complex activation in uremia may explain aggregation defects, as well as reduced VWF-dependent adhesion and thrombus formation.[21–23] A functional defect in the VWF-platelet interaction may also play a role because, in these patients, cryoprecipitate (a VWF-rich plasma derivative) and desmopressin (a synthetic hormone that releases VWF from storage sites) significantly reduces the bleeding time.

In addition, molecules such as prostacyclin ($PGI_2$) and nitric oxide (NO) that inhibit platelet function and modulate vascular tone, affecting platelet-vessel wall interaction, are increased in uremia.[25] GSA accumulates in the plasma of patients with uremia and is involved in the generation of NO. GSA's effect of stimulating NO release provides a biologic explanation for data showing that GSA was the only uremic toxin that consistently inhibited platelet

**BOX 102.1**

**Platelet Abnormalities in Renal Failure**

- Subnormal dense granule content
- Reduction in intracellular ADP and serotonin
- Impaired release of the platelet α-granule proteins and β-thromboglobulin
- Enhanced intracellular cAMP
- Abnormal mobilization of platelet $Ca^{2+}$
- Abnormal platelet arachidonic acid metabolism
- Abnormal ex vivo platelet aggregation in response to different stimuli
- Defective cyclooxygenase activity
- Abnormality of the activation-dependent binding activity of $\alpha_{IIb}\beta_3$ complex

*ADP,* Adenosine diphosphate; *cAMP,* cyclic adenosine monophosphate.

function to such a degree that it was referred to as a key factor in uremic bleeding. Recent evidence points towards uremic toxins having a causative role in the alteration of platelet transcriptome: uremia has been shown to alter the mRNA platelet content and consequently protein expression, thus impairing platelet function.[26]

Although dialysis improves platelet dysfunction through the removal of uremic toxins, hemodialysis *per se* can contribute to the hemostatic abnormalities observed because the interaction between blood and artificial surfaces may induce the chronic activation of platelets. The consequent release of platelet-derived proteins can induce platelet exhaustion, leading to their dysfunction. It has been demonstrated that plasma levels of the potent NO inducers tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) rise during dialysis.[27,28] IL-1β and TNF-α are generated in vivo by circulating monocytes during hemodialysis with complement-activating membranes. The increased production of cytokines may also be triggered by intact endotoxin, endotoxin fragments, and other bacterial toxins that may cross dialysis membranes, as well as by acetate-containing dialysate. As a result of the massive release of cytokines during dialysis, NO synthesis increases. Thus the capacity of the dialysis procedure to remove uremic toxins is counterbalanced by its effects on platelet activation and NO synthesis. On the other hand, some evidence suggests that NO synthesis does not increase during the course of a dialysis session; instead, it decreases. This finding indicates that under optimal hemodialysis conditions with no or minimal cytokine activation, hemodialysis corrects the exaggerated NO synthesis, possibly by removing some dialyzable NO-releasing substances from uremic plasma.

## Anemia

Anemia is a constant feature of acute and chronic renal failure and is one of the main determinants of the prolonged bleeding time observed in uremic patients. The multiple comorbidities associated with ARF in the intensive care setting, such as bleeding resulting from major trauma or surgery, sepsis, and extracellular volume expansion, may worsen anemia significantly.

Some evidence suggests that bleeding time is inversely related to the hematocrit in uremia.[29,30] An important function of red blood cells within normal circulation is to increase platelet-vessel wall contact by displacing platelets away from the axial flow and toward the vessel wall; they also enhance platelet function by releasing ADP[31] and inactivating $PGI_2$. This erythrocyte activity explains the shortening of the bleeding time seen in uremic patients after partial correction of anemia by red blood cell transfusions[30] or with administration of recombinant human erythropoietin (rhEPO).[32,33] Such considerations could also, theoretically, be applicable also to anemia resulting from other causes, but there are not enough research data in this context.

Many factors contribute to the anemia of uremic patients, including shortened survival of red cells, failure of the erythroid marrow, repeated blood loss during dialysis, and, perhaps most importantly, defective secretion of erythropoietin. In addition, high-quality evidence indicates that substances present in uremic serum, including polyamines, parathyroid hormone, and various cytokines, can inhibit erythropoiesis.[34] The role of erythropoietin deficiency as the primary underlying defect in anemia in renal failure is supported by data showing that partial correction of anemia with rhEPO was sufficient to correct defective primary hemostasis in uremia. A controlled study established the minimum hematocrit that must be achieved with rhEPO to correct prolonged bleeding time in uremic patients.[33] A threshold hematocrit between 27% and 32% must be reached for bleeding time to become normal, or nearly normal, indicating that a partial correction of renal anemia is sufficient for this purpose.

## Anticoagulants

All drugs characterized by renal metabolism and excretion are potentially prone to accumulation and possibly toxicity in case of ARF. Among the drugs responsible for increased susceptibility to bleeding (which also include antiplatelet agents, nonsteroidal antiinflammatory drugs, and β-lactam antibiotics), anticoagulants should receive a special mention. It is widely known that patients with renal failure treated with anticoagulant agents, either vitamin K antagonists (VKAs) or heparins, are more prone to minor and major bleeding events when compared with patients with normal renal function.[35] In particular, low-molecular-weight heparin (LMWH) excretion is carried out by the kidneys, so accumulation is a common phenomenon in patients with severely reduced renal function. As a consequence, a higher rate of bleeding has been observed in patients with a glomerular filtration rate (GFR) below 30 mL/min compared with patients with a higher GFR.[36] Even though VKAs are characterized by a predominant liver metabolism, the anticoagulant effect in patients with a reduced glomerular filtration rate is less predictable than in the general population, with a fourfold increase in the risk of minor and major bleeding.[37]Approved direct oral anticoagulants (DOAs), which at the moment include one thrombin inhibitor (dabigatran) and three factor Xa inhibitors (apixaban, edoxaban, rivaroxaban), have started to change dogmas regarding oral anticoagulation. These agents have very few drug and food interactions compared with VKAs; in addition, their stable and predictable pharmacokinetics make blood testing for monitoring superfluous in most cases. However, available DOAs are subjected to a certain degree of renal clearance (approximately 80% for dabigatran, 50% for edoxaban, 30% for rivaroxaban, and 25% for apixaban), which makes dose adjustment necessary in case of moderate to severe renal impairment. Moreover, in cases of ARF, drug accumulation poses a considerable threat because of the risk of major bleeding; aside from general measures against hemorrhage, drug removal through hemodialysis seems an appropriate option in case of dabigatran accumulation. In a systematic review of 35 cases of dabigatran-associated bleeding, renal replacement therapy (either IHD or CRRT) was effective in reducing drug blood levels, with hemostasis achieved in 70.6% of cases. However, it is notable that a rebound in dabigatran concentration was reported in more than half of cases, suggesting that a prolonged course of RRT could be more effective.[38] Some reports indicate that sustained low-efficiency dialysis (SLED) may lead to more favorable outcomes compared with IHD.[39]

In contrast, dialysis is not effective in case of apixaban or rivaroxaban accumulation, because of their high protein binding (approximately 87% and 95%, respectively). Even though edoxaban has lower protein binding (55%), dialysis does not influence the drug blood levels and thus cannot be considered a suitable countermeasure in case of drug accumulation.[40]

Specific antidotes against DOAs are currently being studied, but only idarucizumab, a monoclonal antibody specific to dabigatran, has been approved for use.

## Thrombosis

ARF patients are at risk of not only minor and major bleeding but also the opposite: venous and arterial thrombosis have been reported with increased incidence in these subjects. In addition, uremic patients are at a higher risk of thrombotic complications with the vascular access as a consequence of hemodialysis. Percutaneous cannulas, arteriovenous shunts, and native vein or prosthetic arteriovenous fistulas are particularly prone to thrombotic occlusion. The incidence of thromboembolism after venous thrombosis is significantly increased (from two- to eightfold, depending on the series) in patients with end-stage renal disease compared with patients with normal renal function.[41,42] Renal impairment is also one of the most important risk factors for postangioplasty or stent thrombosis.[43] Similarly to bleeding, factors related to the increased risk of thrombosis include uremia, dialysis, and critical illnesses.

### Platelet Alterations

Even though platelet alterations in renal failure are related more frequently to bleeding disorders, specific changes may also predispose to thrombosis. Platelets may become activated because of accompanying conditions, such as sepsis and its complications.

Phosphatidylserine, one of the most abundant phospholipids, could play a major role in uremia-associated hypercoagulability. Increased levels of phosphatidylserine can be identified on the surface of platelets in subjects with reduced renal function[44]: this molecule, which is usually located in the inner side of the cellular membrane, acts as a prothrombotic signal through the binding of activated factor V, the enhancement of TF activation, and the facilitation of platelet aggregation.[45]

Some evidence indicates that platelets in uremic blood present increased levels of P-selectin, which facilitates the formation of platelet-leukocyte aggregates and platelet activation. Moreover, the activity of the protease ADAMTS-13 is reduced in uremia, as well as in acute inflammation, cirrhosis, and during the postoperative period.[46] This promotes the persistence of ultra-large VFW multimers on the surface of endothelial cells and thus enhances platelet adhesion and aggregation.

### Inflammation and Endothelial Dysfunction

As discussed in the physiology section, endothelial cells are paramount for hemostasis. Laminar blood flow maintains the endothelium in an antithrombotic condition by inhibiting platelet adhesion and aggregation through the expression of molecules such as NO, anticoagulants, and fibrinolytic agents. In addition, normal flow on the endothelium downregulates oxidative stress molecules and thus inflammatory responses.[47]

Renal failure causes a series of derangements at the endothelial level: hemodynamic factors such as volume overload and hypertension lead to increased shear stress which, coupled with uremia- or inflammation-related molecules, may promote a shift in the endothelium's natural anticoagulant ability.

Regarding the connection between inflammation and coagulation, proinflammatory cytokines are known to activate platelets and enhance TF expression through endothelial cells. This explains why thrombotic events (e.g., vascular access thrombosis, disseminated intravascular coagulation) and clotting of the extracorporeal circuit are observed more frequently in septic patients. However, the direct effect of cytokines may be only a partial explanation for this phenomenon; in recent years, microparticles, small vesicles released from the plasmatic membrane of platelets, endothelial cells and other cellular types after cell activation, apoptosis or exposure to shear stress, have gained increasing attention as pivotal factors in inflammation- and uremia-related hypercoagulability.[48] Microparticles (MPs) may influence coagulation through at least three different mechanisms: first, MPs may contain phospholipids such as phosphatidylserine, whose prothrombotic action was described in the previous paragraph.[49] Second, MPs express TF on their surface and actively release free TF in the bloodstream, thus promoting uncontrolled activation of the extrinsic coagulation pathway.[50] Finally, another tentative mechanism involving micro-RNAs (miRNAs) has been proposed: miRNAs are small, single-strand noncoding RNAs that regulate gene expression at a posttranscriptional level. A growing body of evidence indicates that miRNAs are involved in the control of coagulation: miRNAs have been shown to influence platelet aggregation through the upregulation of the $P2Y_{12}$ receptor, which is essential for the activation of $\alpha_{IIb}\beta_3$. In addition, specific miRNAs have been associated with deep vein thrombosis and markers of hypercoagulability such as D-dimer and activated protein-C in complex with protein-C inhibitor,[51] while specific miRNA expression profiles identified platelets with increased aggregation responses to epinephrine.[52] Recent studies have shown that MPs act as natural carriers of miRNAs between cells,[53] suggesting that miRNAs released upon activation or exposure to stress from different cell types may modulate gene expression in other cells.

The elevation of circulating MPs of endothelial origin has been described in plasma from patients with renal failure, underscoring the degree of endothelial dysfunction observed in this condition.[54,55] Interestingly, other reports have found that the uremic toxin p-cresyl sulfate, a metabolite of tyrosine that accumulates in renal failure, promotes the release of endothelial MPs, causing endothelial dysfunction.[56] A similar action has been described for indoxyl acetate and indoxyl sulfate, compounds that are produced as a result of the tryptophan metabolism of gut bacteria, with subsequent metabolization by the liver. Indolic metabolites are excreted by the kidneys through active secretion by tubular cells and tend to accumulate with decreasing renal function. These molecules have been shown to promote the shedding of MPs with phosphatidylserine from erythrocytes, which in turn act as binding sites for factor Xa and prothrombinase complexes, thus enhancing thrombin production.[57]

### Effect of Uremic Toxins on Coagulation and Fibrinolysis

The activation of coagulation has been demonstrated in uremic patients and is more prominent in those who undergo hemodialysis. Thrombin is formed continuously, as demonstrated by the increased levels of thrombin-antithrombin levels,[58–61] D-dimers,[59,60] and fibrinopeptide A.[59,60,62] Conflicting results have been obtained regarding the fibrinolytic system. Initial reports noted decreased fibrinolytic activity in uremia, either absolute or relative to the extent of activation of the coagulation[17,62]; this finding has been used as an explanation for the hypercoagulable state. Subsequent studies, however, have described the activation of fibrinolysis in uremia, with an increase in plasmin-antiplasmin

complexes[58,63] and fibrinogen and fibrin degradation products,[58,59] together with a decrease in plasminogen activator inhibitor activity after hemodialysis sessions.[61,64] These later findings probably reflect a fibrinolytic response that is secondary to fibrin deposition, which also takes place when overall fibrinolytic activity is depressed.

In patients treated with hemodialysis, the extracorporeal circulation of blood is another important source of hemostasis impairment.[65] Blood-air and blood-dialyzer interfaces are major determinants of hypercoagulability.[66] Other factors concur to increase this effect (e.g., low biocompatibility of the membrane, low blood flows, and hemoconcentration). Strategies to prevent coagulation activation and clotting of the extracorporeal circuit have been developed and are discussed extensively in other chapters.

An additional explanation of such derangements lies, again, in the changes caused by uremic toxins. In addition to the already described prothrombotic activity through MP release, indolic compounds are potent inducers of TF in endothelial cells through their action on the aryl hydrocarbon receptor pathway.[67] Other tryptophan degradation products, kynurenine and its metabolites, are known to accumulate in renal failure, especially in patients who need renal replacement therapy. Preliminary reports show a close association between kynurenines and markers of coagulation activity,[68] but causality has not been demonstrated yet. Hyperhomocysteinemia is an almost constant finding in uremia; this molecule can promote platelet activation, inhibit the protein C system, reduce the endothelial secretion of tPA, and increase TF activity.[45,69] However, clinical studies conducted so far have failed to demonstrate a causal relationship between homocysteine levels and thrombosis.[70]

## CONCLUSION

Bleeding and thrombosis are potentially life-threatening complications of renal failure and uremia that are highly prevalent in the critical care setting. The pathogenesis of bleeding and thrombosis in acute renal failure is multifactorial and includes elements related to uremia, critical illnesses, and hemodialysis. Recent advances in dialysis techniques and an increasing understanding of hemostasis in renal failure have paved the way for interventions to reduce the incidence and mortality of both conditions; however, clinicians should always be aware of the potential risk of coagulopathy when facing acute renal failure.

### Key Points

1. The pathogenesis of bleeding and thrombosis in the setting of acute renal failure is multifactorial.
2. Platelet-platelet and platelet-vessel wall interaction play a major role in the pathogenesis of uremic bleeding.
3. Endothelial dysfunction and uremic toxins have been recognized as pivotal factors for the development of renal failure-related thrombosis.
4. Drugs and comorbidities may precipitate or aggravate bleeding and thrombosis in the setting of acute renal failure.

## Key References


5. Gale AJ. Current understanding of hemostasis. *Toxicol Pathol*. 2011;39:273-280.
14. Oudemans-van Straaten HM. Hemostasis and thrombosis in continuous renal replacement treatment. *Semin Thromb Hemost*. 2015;41:91-98.
19. Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370:847-859.
25. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? *Blood*. 1999;94:2569-2574.
48. Camaioni C, Gustapane M, Cialdella P, et al. Microparticles and microRNAs: new players in the complex field of coagulation. *Intern Emerg Med*. 2013;8:291-296.


A complete reference list can be found online at ExpertConsult.com.

## References


1. Colman R, George J, Hirsh J, et al. *Hemostasis and Thrombosis, Basic Principles and Clinical Practice*. Lippincott Williams & Wilkins; 2001:3-16.
2. Jackson SP, Nesbitt WS, Kulkarni S. Signaling events underlying thrombus formation. *J Thromb Haemost*. 2003;1:1602-1612.
3. Jackson SP, Mistry N, Yuan Y. Platelets and the injured vessel wall– 'rolling into action': focus on glycoprotein Ib/V/IX and the platelet cytoskeleton. *Trends Cardiovasc Med*. 2000;10: 192-197.
4. Nieswandt B, et al. Glycoprotein VI but not alpha2beta1 integrin is essential for platelet interaction with collagen. *EMBO J*. 2001;20:2120-2130.
5. Gale AJ. Current understanding of hemostasis. *Toxicol Pathol*. 2011;39:273-280.
6. Kahn ML, et al. A dual thrombin receptor system for platelet activation. *Nature*. 1998;394:690-694.
7. Ariëns RAS, Lai T-S, Weisel JW, et al. Role of factor XIII in fibrin clot formation and effects of genetic polymorphisms. *Blood*. 2002;100:743-754.
8. Versteeg HH, Heemskerk JWM, Levi M, et al. New fundamentals in hemostasis. *Physiol Rev*. 2013;93:327-358.
9. Oliver JA, Monroe DM, Church FC, et al. Activated protein C cleaves factor Va more efficiently on endothelium than on platelet surfaces. *Blood*. 2002;100:539-546.
10. Chapin JC, Hajjar KA. Fibrinolysis and the control of blood coagulation. *Blood Rev*. 2015;29:17-24.
11. van de Wetering J, et al. Heparin use in continuous renal replacement procedures: the struggle between filter coagulation and patient hemorrhage. *J. Am. Soc. Nephrol. JASN*. 1996;7:145-150.
12. Oudemans-van Straaten HM, Wester JPJ, de Pont ACJM, et al. Anticoagulation strategies in continuous renal replacement therapy: can the choice be evidence based? *Intensive Care Med*. 2006;32:188-202.
13. Pschowski R, et al. Effects of dialysis modality on blood loss, bleeding complications and transfusion requirements in critically ill patients with dialysis-dependent acute renal failure. *Anaesth Intensive Care*. 2015;43:764-770.
14. Oudemans-van Straaten HM. Hemostasis and thrombosis in continuous renal replacement treatment. *Semin Thromb Hemost*. 2015;41:91-98.
15. Ferguson JH, Lewis JH, Zucker MB. Bleeding tendency in uremia. *Blood*. 1956;11:1073-1076.
16. Stewart JH. Platelet numbers and life span in acute and chronic renal failure. *Thromb Diath Haemorrh*. 1967;17:532-542.
17. Panicucci F, et al. Comprehensive study of haemostasis in chronic uraemia. *Nephron*. 1983;33:5-8.
18. Castaldi PA, Rozenberg MC, Stewart JH. The bleeding disorder of uraemia. A qualitative platelet defect. *Lancet*. 1966;2:66-69.
19. Hunt BJ. Bleeding and coagulopathies in critical care. *N Engl J Med*. 2014;370:847-859.
20. Hall AV, Clark WF, Parbtani A. Heparin-induced thrombocytopenia in renal failure. *Clin Nephrol*. 1992;38:86-89.
21. Castillo R, et al. Defective platelet adhesion on vessel subendothelium in uremic patients. *Blood*. 1986;68:337-342.
22. Zwaginga JJ, et al. High von Willebrand factor concentration compensates a relative adhesion defect in uremic blood. *Blood*. 1990;75:1498-1508.
23. Escolar G, et al. Uremic platelets have a functional defect affecting the interaction of von Willebrand factor with glycoprotein IIb-IIIa. *Blood*. 1990;76:1336-1340.
24. Benigni A, et al. Reversible activation defect of the platelet glycoprotein IIb-IIIa complex in patients with uremia. *Am J Kidney Dis*. 1993;22:668-676.
25. Noris M, Remuzzi G. Uremic bleeding: closing the circle after 30 years of controversies? *Blood*. 1999;94:2569-2574.
26. Plé H, et al. Alteration of the platelet transcriptome in chronic kidney disease. *Thromb Haemost*. 2012;108:605-615.
27. Noris M, et al. Enhanced nitric oxide synthesis in uremia: implications for platelet dysfunction and dialysis hypotension. *Kidney Int*. 1993;44:445-450.
28. Herbelin A, Nguyen AT, Zingraff J, et al. Influence of uremia and hemodialysis on circulating interleukin-1 and tumor necrosis factor alpha. *Kidney Int*. 1990;37:116-125.
29. Eknoyan G, Wacksman SJ, Glueck HI, et al. Platelet function in renal failure. *N Engl J Med*. 1969;280:677-681.
30. Livio M, et al. Uraemic bleeding: role of anaemia and beneficial effect of red cell transfusions. *Lancet*. 1982;2:1013-1015.
31. Gaarder A, Jonsen J, Laland S, et al. Adenosine diphosphate in red cells as a factor in the adhesiveness of human blood platelets. *Nature*. 1961;192:531-532.
32. Moia M, et al. Improvement in the haemostatic defect of uraemia after treatment with recombinant human erythropoietin. *Lancet*. 1987;2:1227-1229.
33. Viganò G, et al. Recombinant human erythropoietin to correct uremic bleeding. *Am J Kidney Dis*. 1991;18:44-49.
34. Macdougall IC. Role of uremic toxins in exacerbating anemia in renal failure. *Kidney Int Suppl*. 2001;78:S67-S72.
35. Hetzel GR, Sucker C. The heparins: all a nephrologist should know. *Nephrol Dial Transplant*. 2005;20:2036-2042.
36. Lim W, Dentali F, Eikelboom JW, et al. Meta-analysis: low-molecular-weight heparin and bleeding in patients with severe renal insufficiency. *Ann Intern Med*. 2006;144:673-684.
37. Limdi NA, et al. Kidney function influences warfarin responsiveness and hemorrhagic complications. *J. Am. Soc. Nephrol. JASN*. 2009;20:912-921.
38. Chai-Adisaksopha C, et al. Hemodialysis for the treatment of dabigatran-associated bleeding: a case report and systematic review. *J Thromb Haemost*. 2015;13:1790-1798.
39. Artunc F, et al. Removal of Dabigatran Is Superior by Sustained Low Efficient Dialysis (SLED) Compared to Intermittent Hemodialysis. *Blood Purif*. 2015;39:331-332.
40. Bounameaux H, Camm AJ. Edoxaban: an update on the new oral direct factor Xa inhibitor. *Drugs*. 2014;74:1209-1231.
41. Kumar G, et al. Pulmonary embolism in patients with CKD and ESRD. *Clin J Am Soc*. 2012;7:1584-1590.
42. Parikh AM, et al. Venous thromboembolism in patients with reduced estimated GFR: a population-based perspective. *Am J Kidney Dis*. 2011;58:746-755.
43. Ting HH, et al. Evaluation of long-term survival after successful percutaneous coronary intervention among patients with chronic renal failure. *Am J Cardiol*. 2001;87:630-633, A9.
44. Bonomini M, Dottori S, Amoroso L, et al. Increased platelet phosphatidylserine exposure and caspase activation in chronic uremia. *J Thromb Haemost*. 2004;2:1275-1281.
45. Lutz J, Menke J, Sollinger D, et al. Haemostasis in chronic kidney disease. *Nephrol Dial Transplant*. 2014;29:29-40.
46. Mannucci PM, et al. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. *Blood*. 2001;98:2730-2735.
47. Shashar M, Francis J, Chitalia V. Thrombosis in the uremic milieu–emerging role of 'thrombolome. *Semin Dial*. 2015;28: 198-205.
48. Camaioni C, Gustapane M, Cialdella P, et al. Microparticles and microRNAs: new players in the complex field of coagulation. *Intern Emerg Med*. 2013;8:291-296.
49. Barteneva NS, et al. Circulating microparticles: square the circle. *BMC Cell Biol*. 2013;14:23.
50. Key NS. Analysis of tissue factor positive microparticles. *Thromb Res*. 2010;125(suppl 1):S42-S45.
51. Wang X, et al. Diagnostic potential of plasma microRNA signatures in patients with deep-vein thrombosis. *Thromb Haemost*. 2016;116:328-336.
52. Nagalla S, et al. Platelet microRNA-mRNA coexpression profiles correlate with platelet reactivity. *Blood*. 2011;117:5189-5197.
53. Lindsay CR, Edelstein LC. MicroRNAs in Platelet Physiology and Function. *Semin Thromb Hemost*. 2016;42:215-222.
54. Faure V, et al. Elevation of circulating endothelial microparticles in patients with chronic renal failure. *J Thromb Haemost*. 2006;4:566-573.
55. Gao C, et al. Thrombotic Role of Blood and Endothelial Cells in Uremia through Phosphatidylserine Exposure and Microparticle Release. *PLoS ONE*. 2015;10:e0142835.
56. Meijers BKI, et al. The uremic retention solute p-cresyl sulfate and markers of endothelial damage. *Am J Kidney Dis*. 2009;54:891-901.
57. Gao C, et al. Indolic uremic solutes enhance procoagulant activity of red blood cells through phosphatidylserine exposure and microparticle release. *Toxins (Basel)*. 2015;7:4390-4403.

58. Mezzano D, et al. Hemostatic disorder of uremia: the platelet defect, main determinant of the prolonged bleeding time, is correlated with indices of activation of coagulation and fibrinolysis. *Thromb Haemost*. 1996;76:312-321.
59. Sagripanti A, et al. Plasma parameters of the prothrombotic state in chronic uremia. *Nephron*. 1993;63:273-278.
60. Ireland HA, Boisclair MD, Lane DA, et al. Hemodialysis and heparin. Alternative methods of measuring heparin and of detecting activation of coagulation. *Clin Nephrol*. 1991;35:26-33.
61. Reber G, Stoermann C, de Moerloose P, et al. Hemostatic disturbances induced by two hollow-fiber hemodialysis membranes. *Int J Artif Organs*. 1992;15:269-276.
62. Lane DA, et al. The significance of fibrinogen derivatives in plasma in human renal failure. *Br J Haematol*. 1984;56:251-260.
63. Nakamura Y, Tomura S, Tachibana K, et al. Enhanced fibrinolytic activity during the course of hemodialysis. *Clin Nephrol*. 1992;38:90-96.
64. Speiser W, et al. Enhanced fibrinolysis caused by tissue plasminogen activator release in hemodialysis. *Kidney Int*. 1987;32:280-283.
65. Romão JE, Fadil MA, Sabbaga E, et al. Haemodialysis without anticoagulant: haemostasis parameters, fibrinogen kinetic, and dialysis efficiency. *Nephrol Dial Transplant*. 1997;12:106-110.
66. Lindhout T. Biocompatibility of extracorporeal blood treatment. Selection of haemostatic parameters. *Nephrol Dial Transplant*. 1994;9(suppl 2):83-89.
67. Gondouin B, et al. Indolic uremic solutes increase tissue factor production in endothelial cells by the aryl hydrocarbon receptor pathway. *Kidney Int*. 2013;84:733-744.
68. Pawlak K, Mysliwiec M, Pawlak D. Hypercoagulability is independently associated with kynurenine pathway activation in dialysed uraemic patients. *Thromb Haemost*. 2009;102:49-55.
69. Cetin O, et al. Hyperhomocysteinemia in chronic renal failure patients: relation to tissue factor and platelet aggregation. *Clin Nephrol*. 2006;65:97-102.
70. Jamison RL, et al. Effect of homocysteine lowering on mortality and vascular disease in advanced chronic kidney disease and end-stage renal disease: a randomized controlled trial. *JAMA*. 2007;298:1163-1170.