
Core Curriculum

Essentials of anticoagulation in hemodialysis

Karl-Georg FISCHER

Department of Medicine, Division of Nephrology and General Medicine, University Hospital Freiburg, Freiburg, Germany

Abstract

Numerous acquired hemostatic abnormalities have been identified in renal insufficiency. Hemodialysis procedures add to these disturbances as they repetitively imply turbulent blood flow, high shear stress, and contact of blood to artificial surfaces. This nonphysiological environment leads to activation of platelets, leukocytes, and the coagulation cascade, resulting in fouling of the membrane and ultimately in clotting of fibers and the whole hemodialyzer. Anticoagulation in hemodialysis is targeted to prevent this activation of coagulation during the procedure. Most agents inhibit the plasmatic coagulation cascade. Still commonly used is unfractionated heparin, followed by low-molecular-weight heparin preparations with distinct advantages. Immune-mediated heparin-induced thrombocytopenia constitutes a potentially life-threatening complication of heparin therapy requiring immediate switch to nonheparin alternative anticoagulants. Danaparoid, lepirudin, and argatroban are currently being used for alternative anticoagulation, all of which possess both advantages and limitations. In the past, empirical strategies reducing or avoiding heparin were applied for patients at bleeding risk, whereas nowadays regional citrate anticoagulation is increasingly used to prevent bleeding by allowing procedures without any systemic anticoagulation. Avoidance of clotting within the whole hemodialyzer circuit is not granted. Specific knowledge of the mechanisms of coagulation, the targets of the anticoagulants in use, and their respective characteristics constitutes the basis for individualized anticoagulation aimed at achieving full patency of the circuit throughout the procedure. Patency of the circuit is an important prerequisite for optimal hemodialysis quality.

Key words: Hemodialysis, coagulation, heparins, danaparoid, argatroban, lepirudin

INTRODUCTION

Adequate anticoagulation in hemodialysis procedures relies on knowledge of the basic principles of hemostasis and notably the clotting cascade. Hemostatic abnormalities in renal insufficiency as well as activation of clotting on artificial surfaces further require attention. These as-

pects are discussed in the first part of this review, followed by the second part, which focuses on the principles of anticoagulation and the currently available main anticoagulants used in routine hemodialysis procedures.

PRINCIPLES OF COAGULATION

Hemostasis can be defined as a process of fibrin clot formation to seal a site of vascular injury without resulting in total occlusion of the vessel. To this end, a complex array of multiple processes including both cellular elements and numerous plasma factors with enzymatic activity is arranged (1) to activate clotting rapidly, (2) to limit

Correspondence to: K.-G. Fischer, MD, PhD, Department of Medicine, Division of Nephrology and General Medicine, University Hospital Freiburg, Freiburg Medical School, Hugstetter Strasse 55, D-79106 Freiburg, Germany.
E-mail: karl-georg.fischer@uniklinik-freiburg.de

and subsequently terminate this activation, and (3) to remove the clot by fibrinolysis in the end.

The initial hemostatic response to stop bleeding is the formation of a platelet plug at the site of vessel wall injury. Platelets are activated by a multitude of stimuli, the most potent of which are thrombin and collagen. Upon activation, platelets adhere to the subendothelial matrix, aggregate, secrete their granule content, and expose pro-coagulant phospholipids such as phosphatidylserine. Platelet-derived membrane microvesicles markedly increase the phospholipid surface on which coagulation factors form multimolecular enzyme complexes with pro-coagulant activity. Hence, platelet activation also leads to propagation of plasmatic coagulation.

The coagulation process has long been viewed as a “cascade” of proteolytic reactions ultimately resulting in fibrin clot formation.^{1,2} In this, 2 different mechanisms to initiate clotting, i.e., the extrinsic and intrinsic pathway, were defined, ultimately leading to a common pathway of coagulation. Whereas this concept fits well with the screening laboratory tests prothrombin time and activated partial thromboplastin time (aPTT), it does not sufficiently explain certain clinical observations, which challenge the view of 2 independent pathways of activation in vivo. Here, a model of cell-based hemostasis was proposed comprising of 3 overlapping stages of initiation on tissue-factor (TF)-bearing cells, amplification on platelets, and propagation on the activated platelet surface.^{3,4}

For didactic purposes, the process of plasmatic fibrin generation is described based on the classical concept of a coagulation cascade, which comprises the sequential and often overlapping activation of proenzymes or zymogens to active enzymes, resulting in a stepwise amplification. Its activation occurs by initiation of the extrinsic or the intrinsic pathway (Figure 1). The *extrinsic* pathway is initiated by expression of TF, e.g., due to endothelial damage. Tissue factor is a cofactor for the production of activated factor VII (FVIIa). The TF–FVIIa complex (the extrinsic “X-ase” or tenase) activates factor X and factor IX. In vivo, clotting is primarily initiated by this TF pathway.⁵ The *intrinsic* pathway, also termed the contact activation pathway, is thought to be prominently involved in activation of clotting on artificial surfaces such as hemodialysis membranes, but recent data challenge this assumption.⁶ Here, contact with negatively charged surfaces leads to activation of high-molecular-weight kininogen (HMWH), prekallikrein, and factor XII in an ordered fashion (Figure 1). Activated factor XII (FXIIa) activates FXI and FXIa activates factor IX. Factor IXa and factor VIIIa form the intrinsic “X-ase” enzyme complex, which activates factor X to FXa. Therefore, the exogenous

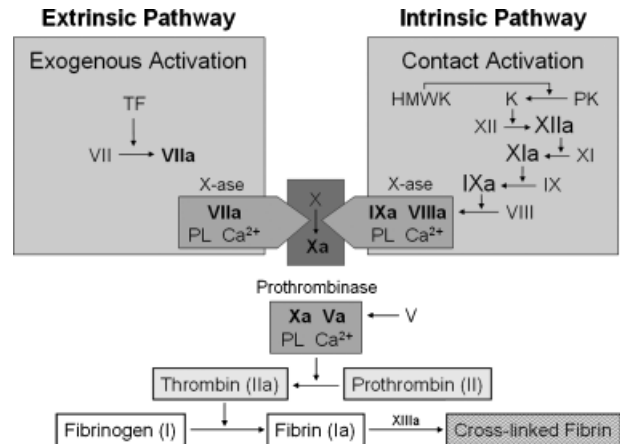


Figure 1 Plasmatic coagulation cascade. Extrinsic and intrinsic pathway of activation converge, as both result in enzyme complexes converting factor X to Xa. Factor Xa is part of the prothrombinase complex, which activates prothrombin to thrombin. Thrombin is the final key enzyme converting soluble fibrinogen to insoluble fibrin.

and contact activation pathway both converge in production of FXa, which is the central activator of the subsequent common pathway. The FXa and FVa form the prothrombinase complex, which converts prothrombin (FII) to the active protease thrombin (FIIa) with enormous efficiency. Finally, thrombin converts the soluble fibrinogen into insoluble fibrin, which is then stabilized by FXIIIa to form stable clots. Assembly and function of the aforementioned enzyme complexes require anionic phospholipid surfaces and calcium ions.

The coagulation process is terminated by the circulating enzyme inhibitors antithrombin and TF pathway inhibitor. Upon clot formation, thrombin binds to thrombomodulin. Owing to the subsequent conformational change, the substrate specificity of thrombin no longer allows for activation of platelets or cleavage of thrombin. Instead, thrombin then activates the anticoagulant protein C pathway, thus terminating its own production and activation. Concerning fibrinolysis, the reader is referred to current textbooks on hemostaseology.

HEMOSTATIC ABNORMALITIES IN RENAL INSUFFICIENCY

The accumulation of uremic toxins causes complex disturbances of the coagulation system. Uremia can lead to an increased bleeding tendency, e.g., due to platelet dysfunction,⁷ which is further enhanced with use of anticoagulants during extracorporeal blood purification procedures. In contrast, clot formation and development of

thrombosis can also occur at increased rates in dialysis patients: pulmonary embolism is more frequent in dialysis patients than in age-matched controls.⁸ Patients on chronic intermittent hemodialysis frequently suffer from vascular access thrombosis,⁹ the risk of which is increased in polytetrafluoroethylene grafts compared with arteriovenous fistulas.¹⁰ Further, numerous hemostatic abnormalities have been found, which may account for the increased risk of thrombosis in end-stage renal disease (ESRD) patients, a few of which are subsequently mentioned: Patients with chronic renal failure have a high prevalence of systemic inflammation and diffuse endothelial damage that may cause hypercoagulability.^{11,12} Activation of platelets and monocytes has also been detected.¹³ Uremic patients with thrombotic events show significantly higher platelet-derived microparticle counts than patients without thrombotic events.¹⁴ Antithrombin levels as well as antithrombin activity can be reduced.^{15,16} In patients with ESRD, deficiencies of the anticoagulant proteins C and S have been observed.^{9,15,16} Activated protein C resistance can occur⁹ or activity of the anticoagulant protein C can be decreased by inhibitors.^{9,17} Activation of the TF coagulation pathway has been found.¹³

These complex hemostatic abnormalities have been linked not only to thrombosis but also to progressive atherosclerosis, a frequent condition in ESRD patients.^{12,15} Hypercoagulability increases as renal function declines.¹² Recently, in 16 subjects on maintenance HD, deficiencies in protein C, protein S, antithrombin, and activated protein C resistance were completely corrected within months after renal transplantation.⁹ Hypercoagulability in ESRD patients therefore essentially represents an acquired and reversible condition. During the hemodialysis treatment, markers of a procoagulant state increase further despite the use of anticoagulants.^{12,15,18} Although the clinical relevance of this subclinical thrombus formation is unclear, some authors suggest that an increase in heparin dose by 50% compared with standard recommendations may be warranted.¹⁸ For further details on thrombogenesis in hemodialysis patients, the reader is referred to a recent review.¹⁹

ACTIVATION OF THE COAGULATION CASCADE IN THE EXTRACORPOREAL CIRCUIT

Hemodialysis causes turbulent blood flow and high shear rates.²⁰ Turbulent blood flow and high shear stress activate platelets directly. Shear is one major pathway of platelet-induced hemostasis and thrombosis.²¹ At slow blood flow, platelets can bind to fibrinogen adherent to

the artificial surface via their GPIIb/IIIa receptor. Receptor binding and thrombin formation due to contact activation result in the release of platelet secretion products, platelet aggregation, and activation of the coagulation cascade. In HD leukocytes and platelets coaggregate,^{22,23} an effect that in part appears to be membrane-dependent.²⁴ Coaggregation is followed by activation of both cell types. On adhesion to artificial surfaces, granulocytes release the contents of their granules.²⁵ Granulocytes and monocytes express TF, a potent activator of the coagulation cascade.

In addition to cellular activation, contact of blood with artificial surfaces induces profound activation of plasmatic coagulation.²⁶ Clotting on artificial surfaces is thought to mainly occur via the intrinsic (contact activation) pathway described above. The degree to which the coagulation cascade is activated is determined by the blood flow and the local concentration of factor XIIa. In addition to the intrinsic pathway, extracorporeal blood purification procedures also activate the extrinsic (TF) pathway of coagulation.⁶

Within the extracorporeal circuit, not only the dialyzer but also other components are thrombogenic. The needles or catheters used for vascular access, the tubing, and the arterial and venous bubble traps all contribute to thrombogenesis. The arterial and venous bubble traps are very thrombogenic, because blood flow is slower and in some areas even stasis of blood may be present. In addition, the interface of air and blood and the turbulences in the bubble trap are known inducers of the coagulation cascade. Further risk factors for premature occlusion of the extracorporeal circuit are slow blood flow, high hematocrit, and blood transfusions into the extracorporeal circuit.

STANDARD ANTICOAGULATION IN HEMODIALYSIS

Routine anticoagulation for extracorporeal blood purification procedures is performed by agents interfering with the plasmatic clotting cascade. Knowledge of the specific characteristics of the agents in use is a prerequisite of adequately tailoring the anticoagulant prescription to the patient's clinical condition and the setting in which hemodialysis treatment is required.

According to their specific characteristics, anticoagulants for hemodialysis procedures can be divided into different subgroups. Here, 3 major features should be known: (1) Anticoagulants may differ by their chemical composition. For example, heparins and danaparoid are glycosaminoglycans, the direct thrombin inhibitor lepirudin is a large polypeptide, and the small direct thrombin

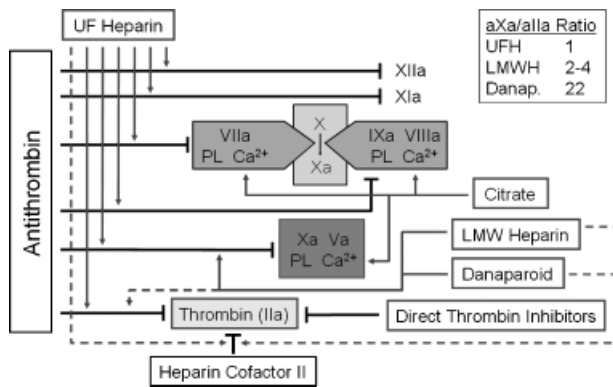


Figure 2 Targets of selected anticoagulants within the coagulation cascade. Antithrombin and heparin cofactor II inhibit key factors in the clotting cascade. Unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and danaparoid are indirect agents increasing the activity of the natural inhibitors. Direct thrombin inhibitors block thrombin. Citrate chelates calcium and thereby inhibits all steps of the coagulation cascade.

inhibitor argatroban is a synthetic derivative of arginin. (2) Anticoagulants may exert their inhibition of the clotting cascade indirectly by binding to physiological anticoagulants. This is the case for the heparins and danaparoid, whose action mainly depends on the presence of antithrombin. In contrast, the direct thrombin inhibitors do not require natural cofactors for their action. (3) Anticoagulants may differ in their targets within the clotting cascade or may exert different inhibitory potency for the same target. For example, by definition, unfractionated heparin (UFH) inhibits FXa and FIIa with equal potency, whereas danaparoid predominantly inhibits FXa. Figure 2 depicts the targets of selected anticoagulants within the clotting cascade.

The subsequent sections can only give a short overview on each anticoagulant agent or strategy. The information provided therein does not allow for proper use of the respective anticoagulant. Careful evaluation of the information provided by the manufacturer and the dose recommendations given is a prerequisite for their use. For further details on anticoagulation for hemodialysis procedures, the reader is referred to an overview published recently.¹⁹

Unfractionated heparin

Unfractionated heparin preparations constitute a mixture of anionic glucosaminoglycans of varying molecular size (5–40, mean 15 kDa). The main action of heparin on the

coagulation system is indirect due to the binding to antithrombin (“heparin-binding factor I”). Heparin enhances the activity of this natural anticoagulant protein 1000 to 4000-fold. Antithrombin inactivates thrombin, factor Xa, and to a lesser extent factors IXa, XIa, and XIIa. At high doses, heparin also binds to “heparin-binding factor II.” Heparin is ineffective against thrombin or factor Xa if they are located in a thrombus or bound to fibrin or to activated platelets. Because UFH has a narrow therapeutic window of adequate anticoagulation without bleeding, laboratory testing (aPTT or as bedside test “activated clotting time,” ACT) of its effect is required. In addition to increasing the bleeding risk, other side effects of heparin are worsening of osteoporosis and lipid status, allergic reactions such as pruritus, and thrombocytopenia. Immune-mediated heparin-induced thrombocytopenia (HIT) is a rare but life-threatening complication of heparin therapy.^{27,28}

Application of heparin during hemodialysis requires an initial loading dose, followed by a maintenance dose: as an initial loading dose, the European best-practice guidelines for HD recommend administering 50 IU/kg UFH into the arterial access needle.²⁹ The maintenance dose of heparin is 500 to 1500 IU of UFH/hr, given via constant infusion into the arterial line using an infusion pump.²⁹ Alternatively, the maintenance dose can be given as repeated bolus injection. During intermittent HD, the patient is systemically anticoagulated. The ACT is adjusted to 80% above the baseline value. Because the hemodialysis patient is systemically anticoagulated for at least 4 hr, aPTT should be checked before surgical procedures after dialysis. Heparin requirements during HD are determined by patient-related factors, the amount of heparin adsorption to the membrane of the dialyzer, and the thrombogenicity of components of the extracorporeal circuit.

Table 1 lists the dose recommendations for use of UFH for intermittent HD. The recommendations should be considered as guidelines and not followed uncritically in any individual patient.

Low-molecular-weight heparin (LMWH)

Low-molecular-weight heparin preparations comprise a mixture of anionic glucosaminoglycans with a smaller size (molecular weight: 4–8 kDa) compared with UFH. The LMWH also bind to antithrombin. However, because of the short chain length of LMWH, antithrombin/LMWH complexes have less affinity to thrombin, resulting in a reduced inhibition of thrombin compared with UFH. The inhibitory effect on factor Xa vs. thrombin is 1:1 for UFH but 2.5:1 or 3:1 in LMWH, depending on the individual

Table 1 Anticoagulation during intermittent hemodialysis

	Indication	Dose	Comment
<i>Unfractionated heparin (UFH)</i> Standard heparin	Patient with normal bleeding risk	Initial loading: 50 IU/kg MD: 500 to 1500 IU/hr	Target ACT: 80% above baseline, depending on dialyzer used
Low heparin (with maintenance dose)	Patient with increased bleeding risk	Initial loading 10 to 25 IU/kg MD: 250 to 500 IU/hr	Target ACT: 40% above baseline in venous line
Very low heparin (without loading or maintenance dose)	Patient with very high bleeding risk or active bleeding	Rinse dialyzer with 5000 to 20,000 IU of heparin, flush system with 0.5 to 2 L of saline. Intermittently rinse with normal saline.	Target ACT: no change from baseline. Keep blood flow \geq 250 mL/min
<i>Low-molecular-weight heparin (LMWH)</i>	Improvement of lipids possibly: less osteoporosis, less pruritus, less hair loss, less blood transfusions compared with UFH		Monitoring requires measurement of anti-factor Xa-activity in venous line (aPTT and ACT are unreliable)
<i>Dosing of selected drugs (according to the manufacturers' information)</i> Dalteparin		<i>In patients with a low bleeding risk:</i> either 85 anti-Xa-IU/kg as bolus (HD up to 5 hr) or initial bolus 30 to 35 IU/kg; MD: 10 to 15 IU/kg/hr (target anti-Xa-level: \geq 0.5 IU/mL) <i>In patient with a high bleeding risk:</i> initial bolus 5 to 10 IU/kg; MD: 4 to 5 IU/kg/hr (target anti-Xa-level: 0.2 to 0.3 max. 0.4 IU/mL)	
Enoxaparin		100 anti-Xa-IU/kg as single bolus (if clots are formed: repeat 50 to 100 anti-Xa-IU/kg) <i>In patients with a high bleeding risk:</i> 50 anti-Xa-IU/kg with use of double lumen catheter 75 anti-Xa-IU/kg with use of single lumen catheter <i>With a normal bleeding risk and dialysis up to 4 hr:</i> < 50 kg, 2850 anti-Xa-IU as single bolus 50 to 69 kg, 3800 anti-Xa-IU as single bolus > 70 kg, 5700 anti-Xa-IU as single bolus 4500 IU as single bolus into arterial line increase by 500 IU for next HD, if clots visible; decrease by 500 IU for next HD, if prolonged bleeding after HD at arterio-venous fistula	
Nadroparin			
Tinzaparin			

<i>Heparinoid substance</i> Danaparoid	In HIT type II	Rinse system with 750 IU Bolus weight adjusted Before 1st HD Before 2nd HD Before 3rd and following HD treatments: measure anti-factor Xa-level; target in venous line: up to 0.5 to 0.8 IU/mL, adjust dose accordingly: anti-Xa < 0.3: anti-Xa 0.3 to 0.35: anti-Xa > 0.35	<55 kg 2500 IU 2000 IU 2000 IU 2000 IU 1500 IU	>55 kg 3750 IU 3750 IU
<i>Direct thrombin inhibitors</i> Hirudin				
Lepirudin	In HIT type II	Dose applies to high-flux-dialyzer: 1st HD: bolus: 0.1 mg/kg; for subsequent HDs dose depends on aPTT before HD: bolus: 0.05 to 0.1 mg/kg 250 µg/kg loading dose before HD MD: 1.7 to 3.3 µg/kg × min (in normal liver function)		High risk of bleeding complications; no antidote available; target hirudin levels: 0.5 to 0.8 µg/mL target aPTT 50 to 75 s
Argatroban	In HIT type II			Target aPTT: 1.5 to 3 × mean of normal range
Citrate	In patients with high bleeding risk	3 mmol citrate/L blood flow (e.g., 50 mmol/hr at a blood flow of 250 mL/min) Ca ²⁺ -infusion: blood flow into venous line		Target ACT: 200 to 250 s in venous line use no calcium and low sodium in dialysate adjust according to target > 1 mmol/L ionized Ca ²⁺ in arterial line

ACT=activated clotting time; aPTT =activated partial thromboplastin time; HIT =heparin-induced thrombocytopenia; MD=maintenance dose.

LMWH preparation. Several LMWH preparations have been marketed, which differ in their chemical and pharmacokinetic properties. Despite not being interchangeable, LMWH preparations share the following common features: (1) The anticoagulant effect (anti-Xa activity) of LMWH in patients with normal renal function is highly correlated with body weight, allowing use of a fixed dose per kilogram body weight. Laboratory monitoring is not necessary in patients with normal renal function. (2) In renal failure, dosing has to be reduced. (3) If monitoring is performed, anti-factor Xa activity needs to be measured, while aPTT and ACT are not reliable.^{30,31} Recently, a modified Xa-ACT has been demonstrated to measure reliably the anticoagulant effect of LMWH preparations within a point-of-care setup.³¹ If anti-factor Xa activity is measured, a level of >0.5 IU/mL is recommended in the venous line of the extracorporeal circulation. In patients at high risk of bleeding, a lower anti-Xa activity may be sufficient to prevent clotting of the dialysis circuit. (4) LMWH are much less likely to induce HIT type II. A more detailed description of common features of LMWH has been given elsewhere.¹⁹

Table 1 lists dose recommendations for use of LMWH for intermittent HD as provided by the manufacturers. The recommendations should be considered as guidelines and not followed uncritically in any individual patient.

ALTERNATIVE ANTICOAGULATION IN HIT

A moderate decline in platelet count is frequently observed after commencing HD. However, thrombocytopenia during heparin therapy may hint at immune-mediated HIT, which constitutes a potentially life-threatening complication. This requires immediate diagnostic and appropriate therapeutic measures.^{27,28}

Heparin-induced thrombocytopenia type I

Within the first 2 to 3 days of heparin therapy, a modest reduction in platelet count ($<100,000$ /mL) is frequently seen. This is not due to an immunologic reaction but is caused by a direct heparin-induced degranulation of platelets. This type of thrombocytopenia (HIT type I) is regarded as harmless. Platelet count increases even though heparin therapy is continued.

Heparin-induced thrombocytopenia type II

From 4 to 10 days after initiating heparin therapy, HIT type II may develop, which is an immune-mediated dis-

ease (now commonly referred to as "HIT" and likewise in the consecutive sections in this review). Antibody formation against the complex of heparin and platelet factor 4 ("HIT antibodies") is the cause of this devastating disease. If HIT is suspected, immediate action has to be taken and all heparin application has to be stopped, even before laboratory test results are available confirming the presence of antibodies. Occasionally, HIT manifests immediately on start of heparin therapy, if the patient had previous contact with heparin. In HIT, thrombocytopenia ($>20,000$ /mL, mean $60,000$ /mL) indicates platelet consumption owing to the disease process. Here, low platelet count is not associated with bleeding complications; instead, venous and arterial thromboembolism may occur. Among the procoagulant abnormalities of the coagulation system, HIT presents with the highest rate of clot formation (50% within 30 days).³² HIT is also called the "white clot syndrome," because characteristic platelet-rich, white arterial thrombi are formed. These may manifest in a dramatic clinical picture with ischemia of one or several limbs and a high mortality rate due to cerebral or myocardial infarctions. However, the majority of thrombi are formed in the venous system including the lungs. The venous manifestations are frequently overlooked or not interpreted as a manifestation of HIT.

Anticoagulation in hemodialysis patients with HIT

If HIT is likely to be present, all applications of heparin have to be stopped, including heparin ointments to the skin or heparin-coated catheters. A "heparin-free dialysis" must not use heparin for initial rinsing. LMWH preparations must also be avoided. Although LMWH induce HIT antibodies less frequently than UFH, they have a high rate of cross-reactivity once UFH has induced HIT antibody formation. As long as the platelet count is low in active HIT, systemic anticoagulation is mandatory to reduce the risk of life-threatening thrombus formation. During this time, it is not sufficient to use, e.g., regional citrate anticoagulation that merely prevents clot formation in the extracorporeal circulation. Established systemic alternative anticoagulation in patients with HIT is performed with danaparoid, lepirudin, or argatroban. Additionally, fondaparinux may become an additional alternative option.

The subsequent sections only can give a short overview on each anticoagulant agent. The information provided therein does not allow for proper use of the respective anticoagulant. Careful evaluation of the information provided by the manufacturer and the dose recommendations

given is a prerequisite for their use. For further details on alternative anticoagulation for hemodialysis procedures in HIT patients including the numerous caveats, the reader is referred to a detailed review published recently.²⁸

Danaparoid

Danaparoid is a heparinoid of low molecular weight (5.5 kDa) consisting of heparan sulfate (83%), dermatan sulfate, and chondroitin sulfate. Danaparoid constitutes the alternative anticoagulant that was most widely used for management of HD in patients with HIT.³³ In 2002, danaparoid was withdrawn by the manufacturer from the U.S. market, whereas it is still available in Canada and the European Community.

The main anticoagulant effect of danaparoid depends on binding to antithrombin and heparin cofactor II. Factor Xa is more selectively inhibited than with the use of LMWH. The activity ratio for factor Xa to thrombin inhibition is 22:1 (compared with 3:1 with LMWH). Danaparoid has a low rate of cross-reactivity against HIT antibodies. During danaparoid treatment, HIT antibodies can be detected in vitro in 10% of cases. In 6.5% of patients with HIT, persistent or repeated thrombocytopenia was observed with use of danaparoid.³⁴ As positive in vitro cross-reactivity is of uncertain clinical significance, attention should focus on platelet count monitoring after starting danaparoid application. A further decline in platelet count, or new fibrin deposits and clot formation within the extracorporeal circuit after application of danaparoid, may indicate clinically relevant cross-reactivity. For monitoring of danaparoid therapy anti-Xa activity has to be measured, and aPTT is not helpful. The half-life of the anti-Xa activity of danaparoid is 25 hr in patients with normal renal function and is further prolonged in uremia. An antidote is not available.

Table 1 lists the dose recommendations for use of danaparoid for intermittent HD as provided by the manufacturer. The recommendations should be considered as guidelines and not followed uncritically in any individual patient. If applied with appropriate care, danaparoid provides adequate anticoagulation for HD of HIT patients with a favorable benefit/risk ratio, even during long-term use. Before invasive procedures, appropriate (repetitive) laboratory measurements have to be carried out in hemodialysis patients on danaparoid treatment.

Direct thrombin inhibitors

Direct thrombin inhibitors do not require natural cofactors to inhibit the clotting cascade. Instead, they directly

bind to and block thrombin, the final key enzyme within the coagulation process inducing the conversion of soluble fibrinogen to insoluble fibrin. From the different thrombin inhibitors currently available, lepirudin and argatroban are approved for alternative anticoagulation in HIT (in the United States and a number of other countries).

Hirudin

Lepirudin is a recombinant hirudin preparation approved for the treatment of HIT in patients. Lepirudin is difficult to use in patients with renal failure or on dialysis.^{35,36} Because it is mainly eliminated by the kidneys, its half-life is markedly prolonged in renal failure.³⁷ After a single loading dose, the patient may be therapeutically anticoagulated for 1 week or longer. Therefore, bleeding risk is increased especially when interventions or surgery cannot be circumvented. In this regard, adequate hirudin dosing is essential.³⁵ Hirudin dose requirements in critically ill patients on continuous HD are minimal, especially in the case of anuria.³⁸ Bleeding risk can be reduced by applying hirudin as a bolus rather than continuous infusion. In case of bleeding complications, there is no antidote available to antagonize the anticoagulant effect of hirudin. High-volume hemofiltration, but not HD, is effective in reducing hirudin plasma levels.^{39,40} An ultrafiltrate volume of 15% of body weight reduces hirudin plasma levels by 50%.³⁹

Hirudin constitutes a polypeptide and does not show cross-reactivity to HIT antibodies. Yet, up to 74% of patients treated with hirudin for more than 5 days develop anti-hirudin antibodies (aHAb).^{41,42} The presence of aHAb often requires dose adjustments.^{41,43} Recent in vivo studies clearly show that hirudin action is markedly prolonged because aHAb delay its renal clearance even without renal impairment.⁴⁴ In the presence of aHAb, hemofiltration no longer constitutes a rescue measure to reduce hirudin plasma levels rapidly.⁴⁴ This aim may be achieved only by plasmapheresis.

Monitoring of therapy is frequently performed by measuring aPTT (target range 1.5–2.5 of normal). Activated partial thromboplastin time is not ideal for monitoring lepirudin therapy, because it does not linearly increase with lepirudin blood levels and effect; thus, high aPTT levels may correspond to very high lepirudin levels.⁴⁵ Lepirudin levels are more reliably assessed by ecarin clotting time or chromogenic substrate assays.⁴⁵

Table 1 lists the dosing recommendations for use of lepirudin for intermittent HD. The recommendations should be considered as guidelines and not followed

uncritically in any individual patient. Hirudin is a valid alternative anticoagulant for HD procedures in HIT patients, but it should be used with caution and careful monitoring. Especially before invasive procedures, appropriate (repetitive) laboratory measurements have to be carried out in hemodialysis patients on lepirudin treatment.

Argatroban

Argatroban is a potent arginine-derived, synthetic, catalytic site-directed thrombin inhibitor being approved as an alternative anticoagulant for HIT in the United States, Canada, and a number of European countries. It does not cross-react with HIT antibodies. In contrast to hirudin, argatroban is metabolized primarily by the liver, and its half-life is only moderately extended in patients with renal insufficiency.⁴⁶

In a retrospective analysis of 47 HIT patients requiring renal replacement therapy, argatroban provided effective anticoagulation with an acceptable safety profile.⁴⁷ A prospective cross-over study of 12 maintenance HD patients showed different argatroban dosing regimens to be safe and well tolerated.⁴⁸

There are conflicting data concerning the necessity of dose adjustments of argatroban in renal failure.^{49–51} In ICU patients suffering from overt renal and additionally from occult liver insufficiency, dose reductions may be frequently necessary (unpublished observations of the author). Based on this experience, in ICU patients, in our center we start argatroban at a reduced dose, provided there is no acute thrombosis. Careful monitoring and dosing is required. Similar experiences have also been reported by others.⁵⁰ Periodic monitoring of the anticoagulant activity of argatroban is recommended using for example the aPTT, the ECT, or the activated clotting time (ACT).^{48,49}

Argatroban appears to be at least as well suited as lepirudin for anticoagulation of HIT patients requiring HD. Its predominant hepatic elimination favors argatroban for alternative anticoagulation in chronic renal failure. Its role and dosing in ICU patients suffering from acute renal failure remain to be defined.

Table 1 lists the dosing recommendations for use of argatroban for HD. The recommendations should be considered as guidelines and not followed uncritically in any individual patient. In particular, ICU patients often do not require full-dose argatroban. Before invasive procedures, appropriate (repetitive) laboratory measurements have to be carried out in hemodialysis patients on argatroban treatment.

Other agents—fondaparinux

Fondaparinux is a fully synthetic pentasaccharide derived from the minimal binding region of heparin to the anti-thrombin molecule and exerts high anti-Xa activity.⁵² Despite not being formally approved, fondaparinux has occasionally been used for alternative anticoagulation in HIT patients. The half-life is longer than with LMWH preparations and is further prolonged in renal failure. Therefore, its dose is to be reduced for anticoagulation in patients with renal insufficiency and for HD procedures. Recently, successful anticoagulation with fondaparinux has been described in a maintenance HD patient with symptomatic HIT.⁵³ The role of fondaparinux for anticoagulation in HD procedures of HIT patients requires further evaluation.

Role of regional citrate anticoagulation in HIT

Regional citrate anticoagulation (for details see below) allows the use of heparin-free HD without systemic anticoagulation. As long as platelet count is decreased in HIT or other laboratory or clinical signs of active disease with thromboembolism are present, extracorporeal anticoagulation alone is insufficient and systemic anticoagulation using hirudin, danaparoid, or argatroban is mandatory. If systemic anticoagulation is no longer indicated, but repeated heparin use should be avoided for a prolonged period of time, regional citrate anticoagulation is an excellent choice to prevent recurrence of HIT.

Alternative anticoagulation in HIT

Low-dose UFH

Even in patients at high risk for bleeding complications, UFH still is the most frequently used agent for anticoagulation during HD, although at a reduced dose. In “low heparin” intermittent HD, the system is rinsed with 2500 to 5000 IU of heparin and subsequently with at least 2 L saline solution to remove the anticoagulant that has not bound to the surface of the artificial polymers. The following hemodialysis treatment uses a low-maintenance dose of heparin in order to maintain the systemic ACT no higher than 40% above baseline.

Heparin-“free” hemodialysis

If the bleeding risk is extremely high (e.g., in patients at risk for intracranial bleeding), maintenance heparin is completely avoided. This is possible if dialysis

membranes with low thrombogenicity (e.g., polysulfone), a short treatment time (2–3 hr), and a high blood flow (>250 mL/min) are used. It may be helpful to rinse the extracorporeal system repeatedly with saline (25–150 mL injected into the arterial line every 15–30 min). This treatment without maintenance dosing is frequently called “heparin-free dialysis.” However, with commencement of the treatment the patient receives a small dose of heparin as the extracorporeal circuit is connected to the patient’s circulation. In addition, during the treatment, adsorbed heparin can be released from the artificial polymers and reach the patient. The amount of heparin is very low and does not elevate aPTT or ACT. However, if the patient has developed HIT antibodies even a small amount of the substance is sufficient to trigger the immunologic process again. Therefore, in case of HIT the so-called “heparin-free dialysis” (applying heparin for recirculation into the tubing system, followed by saline washout) must not be used. Even heparin-coated catheters or dialyzers are not allowed.

Regional citrate anticoagulation

Regional citrate anticoagulation is an interesting alternative method compared with heparin in patients with a high bleeding risk. Citrate infused into the arterial line chelates calcium and magnesium, and thus inhibits the coagulation cascade in the extracorporeal circulation. The deficit in ionized calcium is present only locally in the extracorporeal circulation because, before blood reinfusion, calcium is substituted into the venous line to target normal ionized calcium. Some aspects of citrate anticoagulation necessitate a modification of the dialysis prescription: (1) Citrate is metabolized in the liver to form bicarbonate, and may induce metabolic alkalosis. To compensate for this bicarbonate production, bicarbonate concentration in the dialysate needs to be reduced to avoid metabolic alkalosis. (2) Trisodium citrate may induce hypernatremia. To compensate for sodium infusion, the sodium concentration in the dialysate should be reduced. (3) Dependent on the respective ionized calcium concentration, both the citrate and calcium infusion are to be modified: (a) If in the venous line (before calcium substitution) the concentration of ionized calcium is not low enough, or ACT is too short, the citrate infusion rate should be increased. (b) If ionized calcium in the arterial line (before citrate infusion) is too low, calcium infusion has to be increased to avoid systemic hypocalcemia.

Development of alkalosis is usually not a problem in intermittent HD, as citrate anticoagulation is used for only a few hours per week. In addition, many of the citrate

calcium complexes are removed into the dialysate and are not infused into the patient.

It has been demonstrated that bleeding complications are reduced compared with low-dose heparin.⁵³ Citrate anticoagulation also improves biocompatibility and reduces deposition of blood components on the dialysis membrane compared with UFH or LMWH.^{54,55} A simplified treatment protocol has recently been published and may help to promote this valuable option in HD therapy.⁵⁶

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