Acquired Hemostatic Disorders

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Stefano Barelli, Sabine Blum, and Anne Angelillo-Scherrer

7.1 Introduction

Hemostatic disorders may be inherited or acquired. Acquired hemostatic disorders comprise thrombocytopenia and platelet dysfunction, coagulation factor deficiencies, excessive anticoagulation, and hemorrhagic complications due antiplatelet drugs, anticoagulation, and thrombolysis. Blood disorders associated with myeloproliferative neoplasms and disseminated intravascular coagulation (DIC) can cause both bleeding and thrombosis. Heparin-induced thrombocytopenia (HIT), antiphospholipid antibody syndrome, and thrombotic microangiopathies are conditions that cause thrombocytopenia, but they are more frequently responsible for thrombosis than for bleeding (Fig. 7.1). The present chapter focuses on acquired disorders (congenital coagulopathies are presented in Chap. 6). Antiplatelet and anticoagulant drug complications are presented in Chap. 8.

7.2 Thrombocytopenia

7.2.1 Acquired Thrombocytopenia

Acquired thrombocytopenia is the most common cause of thrombocytopenia. In the absence of a platelet function disorder, spontaneous bleeding may occur when the platelet count is <10–20 G/L of blood. Thrombocytopenia may result from decreased platelet production in cases of bone marrow infiltration by neoplastic cells, acute alcohol toxicity, infections, and vitamin B12 or folate deprivation. It may also be drug induced. Thrombocytopenia can be isolated or part of a more general process such as bone marrow failure, acute leukemia, DIC, chronic liver disease, or

S. Barelli • S. Blum • A. Angelillo-Scherrer (✉)
Service of Hematology, Lausanne University Hospital (CHUV),
CH-1011 Lausanne, Switzerland
e-mail: stefano.barelli@chuv.ch; sabine.blum@chuv.ch; anne.angelillo-scherrer@chuv.ch

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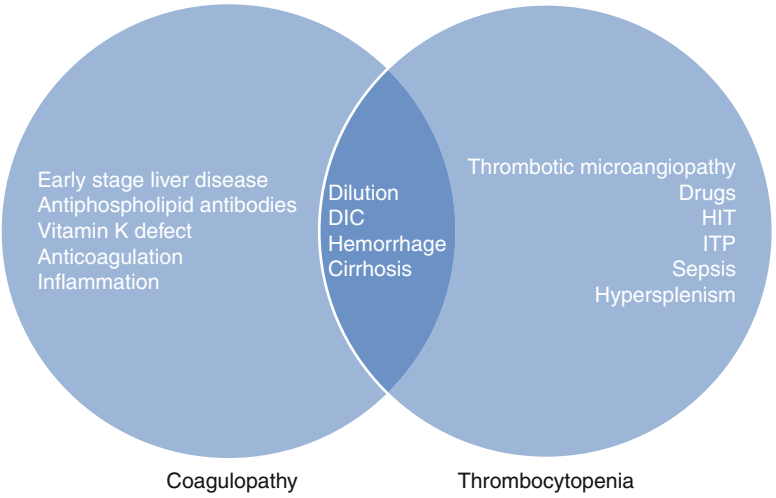

Fig. 7.1 The critically ill patient. *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *ITP* immune thrombocytopenia

thrombotic microangiopathy. The causes of thrombocytopenia can be classified by taking into account the clinical setting, such as outpatient versus inpatient (Table 7.1).

HIV infection often results in thrombocytopenia, and immune thrombocytopenia (ITP) occurs in about 40 % of HIV-infected patients and 2.6 % of hepatitis C patients. Thrombocytopenia is a common feature of sepsis, where it probably results from a combination of impaired platelet production and platelet consumption.

Primary ITP is an autoimmune disorder and the most common cause of isolated thrombocytopenia. Thrombocytopenia is caused by autoantibodies, directed against platelet antigens, which increase the clearance of circulating platelets and decrease platelet production by bone marrow megakaryocytes. Bleeding symptoms such as intracranial hemorrhage are uncommon except in severe ITP. First-line therapy is usually given when platelet counts are <30–50 G/L; it consists of glucocorticoid therapy at 1 mg/kg/day and/or intravenous immunoglobulins at 2 g/kg for 2–5 days (Provan et al. 2010). Tranexamic acid – an antifibrinolytic drug – may be administered together with a platelet transfusion, particularly when bleeding occurs at the mucosal level. Splenectomy, rituximab, and thrombopoietin receptor agonists are second-line therapies.

Drug-induced thrombocytopenia is common and may be caused by marrow suppression as well as immune or nonimmune thrombocytopenia. A list of potentially offending drugs can be found on http://www.ouhsc.edu/platelets/ditp.html. In immune-mediated drug-induced thrombocytopenia, platelet counts recover promptly after treatment interruption, usually 5–10 days after the withdrawal of the drug (Stasi 2012). The correct diagnosis is a challenge when the substance causing the thrombocytopenia is not a drug but is in a beverage, food, or herbal remedy (Stasi 2012). Glucocorticoid therapy 1 mg/kg/day is administered when platelets are <10 G/L and if bleeding is not severe. In case of severe bleeding, treatment

Table 7.1 Causes of thrombocytopenia with regard to the clinical setting

Outpatients
ITP
Drug-induced thrombocytopenia
Infections (HIV, hepatitis C, CMV, other recent viral infections, Helicobacter pylori)
Hypersplenism
Autoimmune disorders
Hematological malignancies
Bone marrow failure
Chemotherapy-induced thrombocytopenia
Chronic DIC
Inherited thrombocytopenia
Common variable immunodeficiency
Inpatients
Inpatients in ICU or with multisystemic illness
Infections
Drug-induced thrombocytopenia
Acute or chronic DIC
Liver disease
HIT
Bone marrow disorders, including hematological malignancies
TTP/HUS
Macrophage activation syndrome
Chemotherapy-induced thrombocytopenia
Dilutional thrombocytopenia
Posttransfusion purpura
Inpatients with cardiac disease
HIT
Cardiopulmonary bypass
Intra-aortic balloon pump/ECMO
GPIIb/IIIa inhibitors
Other drug-induced thrombocytopenia
Dilutional thrombocytopenia
Patients in the emergency department
ITP
Drug-induced thrombocytopenia
Alcohol toxicity
Bone marrow disorders
DIC
Liver disease
Chemotherapy-induced thrombocytopenia
TTP/HUS
Pregnancy/postpartum patients
Gestational thrombocytopenia
ITP
HELLP syndrome
Preeclampsia
Abruptio placentae
TTP/HUS

Adapted from Aird and Mark (2002), Stasi (2012)
ITP immune thrombocytopenia, *DIC* disseminated intravascular coagulation, *HIT* heparin-induced thrombocytopenia, *TTP/HUS* thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, *ECMO* extracorporeal membrane oxygenation, *HELLP syndrome* hemolysis, elevated liver enzymes, and low platelets

combines platelet transfusion with intravenous immunoglobulins and high-dose glucocorticoids. Patients often suffer from petechial hemorrhages and urinary or gastrointestinal tract bleeding. Intracranial bleeding is rare.

GPIIb/IIIa inhibitors are antiplatelet agents that may also induce thrombocytopenia (see Chap. 8). HIT is detailed below (Sect. 7.2.2). Emergency surgery in the context of thrombocytopenia can be performed if a platelet transfusion is provided immediately before surgery. If necessary, additional platelet concentrates can be administered during and after surgery. When appropriate, specifically if the surgical procedure involves mucosae, the treatment can be completed with tranexamic acid.

7.2.2 Heparin-Induced Thrombocytopenia

HIT is a "clinical-pathological syndrome" occurring during heparin therapy. HIT is caused by IgG antibodies that bind platelet receptors and recognize PF4-heparin complexes. Because the IgG antibodies activate platelets and induce platelet clearance, they are responsible for a decrease in platelets and a prothrombotic state during heparin therapy. Previous exposure to unfractionated heparin (UFH) and, less frequently, to low-molecular-weight heparin (LMWH) is necessary for the initiation of the process.

Few patients with suspected HIT have true HIT. The diagnosis requires a clear clinical picture and laboratory confirmation of platelet-activating antibodies. Even if anti-PF4-heparin antibodies are easily detectable using enzyme immunoassays (EIAs), only a minority of these antibodies are truly platelet activating, respecting an "iceberg model"; these platelet-activating properties are best detected by activation or aggregation assays.

The following steps are recommended to avoid overdiagnosing HIT (Warkentin 2011):

- *Assessment of pretest probability with the 4Ts scoring system*: the score is a simple clinical tool to help decide whether further investigation and a change of anticoagulation is appropriate (Table 7.2).
- *Laboratory testing*: this should be ordered only if the 4Ts score is intermediate or high. EIAs are widely available and highly sensitive, but not sufficiently specific for platelet-activating antibodies. All positive EIA results need to be confirmed by activating or aggregation assays (serotonin-release assay or heparin-induced platelet activation test).

One mainstay of HIT treatment is the discontinuation of all forms of heparin treatment and the administration of an alternative anticoagulant. Anti-vitamin K anticoagulants (AVK) are contraindicated as an initial treatment due to their transient procoagulant properties (reduction of protein C level). Half of those individuals identified as having HIT concomitantly face the risk of a thrombosis; therefore, an ultrasound screening of the lower limbs is recommended. The risk of thrombosis remains elevated for at least 30 days after heparin therapy and as long as the platelet count has not returned to the normal range.

Table 7.2 4T pretest HIT scoring system

4Ts	2 points	1 point	0 points
Thrombocytopenia	PC fall >50 % and platelet nadir $\geq 20 \times 10^9$/l	PC fall 30–50 % or platelet nadir $10–19 \times 10^9$/l	PC fall <30 % and platelet nadir $<10 \times 10^9$/l
Timing of platelet count fall	Clear onset between days 5–10 or PC fall ≤1 day (prior heparin exposure within 30 days)	Consistent with 5–10 days fall but not clear (e.g., missing PC); onset after day 10; or fall ≤1 day (prior heparin exposure 30 –100 days ago)	PC fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis; acute ischemic reaction post intravenous UFH bolus	Progressive or recurrent thrombosis: non-necrotizing (erythematous) skin lesions; suspected thrombosis (not proved)	None
Other causes for thrombocytopenia	None apparent	Possible	Definite

Adapted from Lo et al. (2006)
Pretest score 6–8 = high probability, 4–5 = intermediate probability, 0–3 = low probability
PC platelet count, *UFH* unfractionated heparin

- There are two alternative classes of anticoagulants for HIT treatment:
  (1) Antithrombin-dependent activated factor X (Xa) inhibitors, such as sodium danaparoid. Anticoagulant activity can be easily monitored by anti-Xa activity measurement. Their long half-life is a disadvantage in perioperative contexts.
  (2) Direct thrombin inhibitors, such as argatroban, have a short half-life. Monitoring can be performed by measuring activated partial thromboplastin time and specific antithrombin (IIa) activity.

Before hematological referral, the following aspects should be assessed (Warkentin 2011):

1. The overall likelihood of HIT.
2. The indication for therapeutic anticoagulation.
3. The renal/hepatic function.
4. The type of surgical procedure planned.

Further reading on HIT management can be found in (Selleng et al. 2007) and in the Clinical Practice Guideline on the management of HIT on www.hematology.org/practice/guidelines.

7.3 Acquired Platelet Dysfunction

Whereas inherited platelet dysfunction is rare, acquired platelet dysfunction is common. Platelet function may be affected by drugs, such as antiplatelet drugs or antidepressants, or by systemic disorders like uremia, liver failure, and myelodysplastic or myeloproliferative disorders.

In case of bleeding, platelet transfusion may be required. Desmopressin is a vasopressin analog that favors release of von Willebrand factor (vWF) from tissue stores (mainly endothelial cells) and may be used in acquired platelet disorders such as uremia. Desmopressin is administered at the dose of 0.3 μg/kg, intravenously in 50 mL of saline over 30 min or subcutaneously (Mannucci and Tripodi 2012). Recombinant activated factor VII (rFVIIa) may be used in the context of hemorrhagic complications (Franchini et al. 2008).

7.4 Acquired Multifactorial Deficiencies

Acquired multifactorial deficiencies are common and may result from vitamin K deficiency, liver disease, or DIC.

7.4.1 Vitamin K Deficiency

A lack of vitamin K impairs posttranslation γ-carboxylation of vitamin K-dependent proteins: factors II, VII, IX, and X, as well as proteins C, S, and Z. Vitamin K deficiency is frequent in neonates, to whom it should be provided systematically to prevent bleeding. In adults, vitamin K deficiency is mainly due to malabsorption as well as vitamin K metabolism impairment by VKA, antibiotics, or rodenticides.

7.4.2 Chronic Liver Disease

The hemostatic process is a complex interplay between the endothelium, platelets, coagulation factors, and the fibrinolytic system. It is balanced by prohemostatic and antihemostatic drivers; however, in chronic liver disease (CLD), this balance is altered (Fig. 7.2) (Lisman and Leebeek 2007). Most procoagulant factors decrease in parallel to the anticoagulant factors (Tripodi and Mannucci 2011). Thrombin – the pivotal factor of coagulation – is synthesized in amounts comparable to healthy subjects, but its generation is reduced by thrombocytopenia. In CLD, prohemostatic factors that are not exclusively synthesized by the liver have unusually high levels (vWF, which restores platelet adhesion to endothelium, and factor VIII, which drives thrombin generation). Tissue plasminogen activator levels are increased due to enhanced release by activated endothelium and/or by decreased hepatic clearance.

In CLD, simple defects are the result of complex pathological processes (Lisman and Leebeek 2007; Roberts et al. 2010):

- Thrombocytopenia: reduced megakaryopoiesis (reduced thrombopoietin, coinfection, alcohol abuse, folate deficiency, and medication), splenic sequestration, viral infections, primary biliary cirrhosis, or DIC
- Defective platelet function: acquired storage pool defect, defective transmembrane signal transduction, decreased levels of functional platelet receptors, or reduced hematocrit, and dyslipidemia

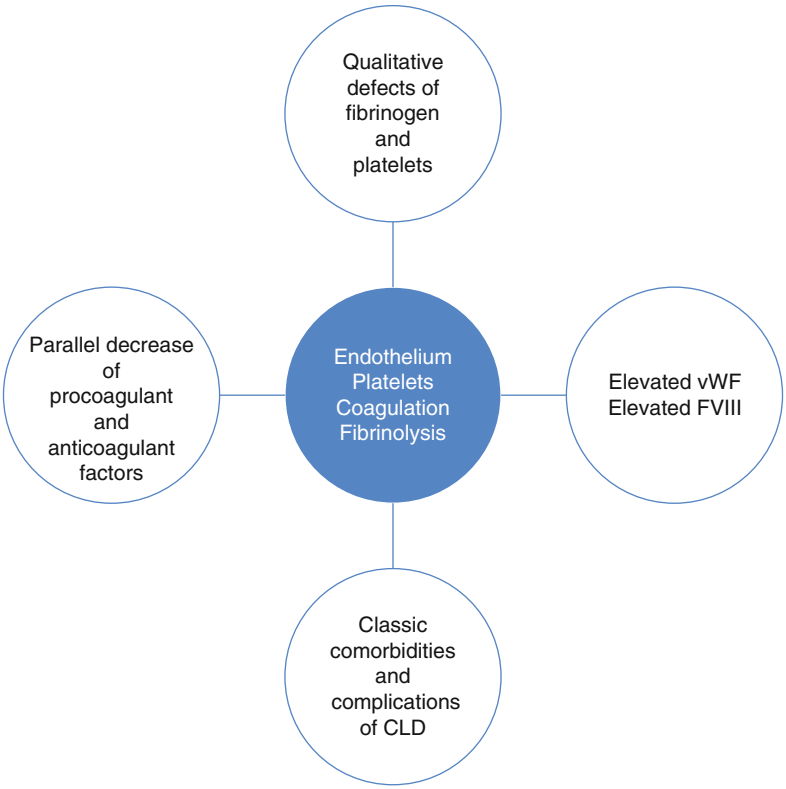

Fig. 7.2 Hemostasis in chronic liver disease (*CLD*). *vWF* von Willebrand factor, *FVIII* factor VIII

- Low or defective coagulation factors: reduced hepatic synthesis function, vitamin K deficiency, DIC, dysfunctional circulating fibrinogen, and altered fibrin polymerization due to excessive sialic acid content

In CLD, the laboratory pattern sometimes resembles the DIC pattern, but DIC should always be suspected in the presence of a trigger (e.g., sepsis) with evolving hemostatic abnormalities (consumption of factors and platelets).

7.4.2.1 Management

The correction of a coagulopathy in a non-bleeding patient is not required (Roberts et al. 2010; Gines et al. 2012). Conservative measures such as vitamin K substitution are recommended for the optimization of hemostasis in CLD. Predicting bleeding complications in CLD patients is challenging. The clinician should base her/his evaluation on three indicators:

1. Patient

   The majority of hemorrhages are due to the rupture of portosystemic varices (Lisman and Leebeek 2007). Bacterial infections, vitamin K deficiency (low dietary intake, loss of intestinal bacterial flora after antibiotherapy, intra-/extrahepatic cholestasis), and renal failure increase the tendency to bleed.

2. Laboratory values

   Current routine coagulation tests offer only limited help in the proper evaluation of the state of hemostatic balance in CLD (Tripodi and Mannucci 2011). For example, a prolonged prothrombin time (PT) does not necessarily indicate that the CLD patient is naturally anticoagulated, and a borderline PT could underestimate the risk of bleeding. Emerging global coagulation tests better reflect the interplay of all the factors involved in hemostasis (thrombin generation tests, thromboelastography) (Roberts et al. 2010).

3. Type of bleeding or surgery

   Acute variceal bleeding is mainly the consequence of anatomical changes and depends on the Child-Pugh score and endoscopic features. It is best treated with fluid resuscitation, pharmacological treatment, and endoscopy. For elective surgical procedures (paracentesis, central venous catheter insertion, or liver biopsy), the potential need for transfusion must anticipated. Transfusions should target a hemoglobin level of >70–80 g/l and platelet counts >50 G/L. Prophylactic transfusion of fresh frozen plasma (FFP) is associated with a risk of volume overload, infection, and transfusion-related acute lung injury (TRALI). This makes the use of prothrombin complex concentrates (PCC) more appropriate. There is no advantage to using recombinant FVIIa (Bosch et al. 2008).

7.4.3 Disseminated Intravascular Coagulation

DIC is a generalized coagulation process secondary to increased thrombin generation and fibrin deposition. Microvascular thrombi lead to organ dysfunction. Consumption of platelets and coagulation factors lead to bleeding (Levi and Ten Cate 1999; Levi et al. 2002). DIC is a systemic process without a specific anatomical localization. Due to its bad prognosis, DIC is also known as the acronym for "Death Is Coming." Interleukin-6 and tumor necrosis factor-α play pivotal roles in thrombin generation.

DIC can develop acutely or remain chronic. Acute DIC occurs in patients with sepsis, after surgery, trauma, or an incompatible blood transfusion, as an obstetrical complication, or as a complication of acute promyelocytic leukemia. Chronic DIC is more common in solid malignancies but can also be observed in large aortic aneurysms.

The principal triggers of DIC are listed below and can be memorized with the acronym "LAST HOME":

- Liver failure
- Angiopathy (macro and micro)
- Sepsis/severe inflammation
- Trauma (head trauma, fat embolism, tissue destruction)
- HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets syndrome)
- Obstetric events (amniotic fluid embolism, *abruptio placentae*)

- Malignancies (myeloproliferative neoplasms, solid tumors)
- Exogenous materials (drugs, transfusion products, toxins, prosthetic materials)

DIC is probably the main mechanism underlying thrombocytopenia in intensive care units. Independent of the severity and the cause of illness, DIC is a marker for severe homeostatic disturbance and predicts a fatal outcome (Vanderschueren et al. 2000).

7.4.3.1 Diagnosis

DIC is not a disease in itself, but a syndrome (Levi et al. 2002). Several clinical conditions mimic the hemostatic pattern of DIC. Overall, DIC should be suspected when a patient presents with:

- An underlying medical or surgical condition compatible with DIC
- Multiple organ failure
- Bleeding and/or thrombotic diathesis
- Thrombocytopenia associated with multiple coagulation factor deficiencies and hyperfibrinolysis (low fibrinogen, high D-Dimers, fibrin degradation products, and fibrin monomer levels).

We recommend using the scoring system of the International Society on Thrombosis and Haemostasis (ISTH) to easily identify overt DIC (Taylor et al. 2001) (Table 7.3).

7.4.3.2 Management

Treatment options should target the cause of DIC and aim to improve the patient's condition rather than the laboratory values (Levi et al. 2009; Thachil and Toh 2012; Wada et al. 2013).

Transfusion of blood components is indicated ONLY during active bleeding or in periprocedural situations. Target blood component levels are:

- Platelets >50 G/L in case of active bleeding and >20 G/L in patients with a high risk of bleeding. Platelet concentrates can be administered.
- PT or aPTT <1.5 times the upper limit of the normal range. FFP should be privileged. PCC may be considered in actively bleeding patients if FFP transfusion is impossible.
- Fibrinogen >1.5 g/l. The administration of fibrinogen concentrate or cryoprecipitate may be recommended in actively bleeding patients with fibrinogen levels persistently <1.5 g/l despite FFP replacement.

Table 7.3 Diagnosis of disseminated intravascular coagulation (DIC)

	0	1	2
PLT [G/L]	>100	<100	<50
FBN [g/l]	>1	<1	
D-dimers [µg/l]	<200	200–3,200	>3,200
PT [%]	>55	55–40	<40

Adapted from Taylor et al. (2001)
A score >5 indicates overt DIC. An underlying disorder known to be associated with DIC is mandatory for the use of this score
PLT platelet, *FBN* fibrinogen, *PT* prothrombin time

When using anticoagulant drugs, LMWH is preferable to UFH; however, it is worth noting that there is no direct evidence of the effects of anticoagulants on DIC.

- Therapeutic doses of UFH or LMWH can be considered in cases of DIC with a predominance of thrombosis.
- Prophylactic anticoagulation with UFH or LMWH is recommended in critically ill, non-bleeding patients to prevent venous thromboembolism (VTE).

Antifibrinolytic agents (e.g., tranexamic acid) may be beneficial in several DIC processes because DIC leads to hyperfibrinolysis. These processes include:

- Trauma if bleeding persists despite FFP transfusion
- Massive postpartum hemorrhage

7.4.3.3 Conclusion

Critically ill patients are at risk of developing DIC, and thus this diagnosis should be assessed as early as possible.

Platelet count and simple coagulation tests (PT, fibrinogen level, or D-dimers) are of great value in identifying overt DIC and following its process.

7.5 Acquired Coagulation Factor Deficiencies

Inhibitors are autologous antibodies to coagulation factors that can develop in different clinical circumstances, such as acquired hemophilia A in the peripartum or in the context of lymphoproliferative neoplasms (alloantibodies only develop in the context of factor substitution for hemophilia A or B). In theory, it is possible to develop an inhibitor to any given coagulation factor; however, inhibitors to FVIII and vWF (see Sect. 7.6) are the most frequent. Patients with acquired FVIII deficiency (also called "acquired hemophilia A") present a broad spectrum of clinical signs ranging from superficial bruising to life-threatening bleeding. The incidence of acquired FVIII deficiency is 1.4/million/year (Collins 2012). The main treatment consists in treating the underlying clinical problem, if it can be clearly identified, for example, as a lymphoproliferative syndrome. If this is not possible, in most of the cases, the hematologist will initiate an immunosuppressive treatment with corticosteroids, monoclonal anti-CD20 antibodies (rituximab), or cyclophosphamide, or a combination of those therapies. However, no treatment will correct the targeted coagulation factor immediately. Should a surgical procedure be necessary, adequate hemostasis must be reached using a treatment that bypasses the targeted coagulation factor. Invasive procedures should thus be avoided when possible. One drug used to overcome the inhibitors of coagulation factors is rFVIIa (NovoSeven®). It bypasses factors VIII and IX and directly activates factor X, which then activates prothrombin to thrombin. Another possible bypassing agent is factor VIII inhibitor bypassing activity (FEIBA®). Both agents seem to have about the same effect on hemostasis (Baudo et al. 2012). Standardized laboratory assays cannot monitor responses to either of these agents. The performances of thrombelastography and thrombin generation, as well as the interpretation of aPTT graphs, are promising indicators, but are not yet standardized (Pivalizza and Escobar 2008). If neither hemostatic agent succeeds in stopping the hemorrhagic process, one option for rapid inhibitor

eradication is immunoadsorption. This technique is neither a standard procedure nor is it available in most hospitals. Most surgical experience has come from hemophilia patients with inhibitors, but bleeding patterns can differ significantly compared to patients with acquired hemophilia and the same aPTT or antibody levels.

The recommended prophylaxis for surgery in patients with FVIII inhibitors is 90–150 μg/kg of rFVIIa every 2–6 h, with increasing time intervals after the first or second postoperative day. Alternatively, a continuous infusion of 50 μg/kg/h can be administered (Huth-Kuhne et al. 2009; Baudo et al. 2010), but it must be noted that no trials have compared continuous and bolus treatment or different dosages. Following major surgery, the alternative treatment is FEIBA® with a recommended loading dose of 100 IU/kg followed by 200 IU/kg every 8 h for 3 days and then a tapering of the daily dose to 150–100 IU/kg for 9–17 days (Tjonnfjord 2004).

Acquired FV inhibitors are rare, with fewer than 200 cases described in the literature. The resulting tendency to bleed can vary and is not necessarily associated with residual plasma levels (Franchini and Lippi 2011). Both PT and aPTT are prolonged. Most cases have been provoked by exposition to bovine thrombin products, which are used in surgery for localized hemostasis, but the condition can occur in other circumstances (malignancies, autoimmune diseases, etc.). In case of clinical bleeding, platelet transfusion and FFP are the treatments of choice – effective in about 70–80 % of cases (Ang et al. 2009) – as platelets protect FV from circulating inhibitors. Some published cases have described the successful use of rFVIIa (Jeimy et al. 2008; Lebrun et al. 2008; William 2008); others describe plasmapheresis and immunoadsorption as effective (Tribl et al. 1995; Fu et al. 1996). High-dose intravenous immunoglobulins also seem to rapidly increase FV levels (Buclin et al. 1992; de Raucourt et al. 2003).

Acquired FXIII inhibitors have been described. They can occur in patients using large doses of antibiotics or other drugs, suffering from autoimmune diseases or monoclonal gammopathies, or even spontaneously (Otis et al. 1974; Milner et al. 1977; Ahmad et al. 1996; Luo et al. 2010). As with all acquired factor deficiencies due to inhibitors, eradication of the inhibitor would be the ideal treatment for FXIII inhibitors. In case of bleeding or emergency surgery, treatment options are limited as FXIII is the last factor in the coagulation cascade stabilizing the fibrin clot. Replacement therapy with FFP has been tried, but has not been reliably successful. FXIII concentrate (Fibrogammin®) can increase FXIII levels with doses between 50 and 150 IU/kg (Luo and Zhang 2011), but there have been reports of unsuccessful results (Miesbach 2005). In one case with severe hemorrhages, rFVIIa and tranexamic acid were provided in addition to FXIII concentrate (Boehlen et al. 2013). Immunoglobulin infusions take several days to become effective; the same is true for rituximab treatment, which takes even longer.

7.6 Acquired von Willebrand Syndrome

Acquired von Willebrand syndrome (AvWS) is a rare disorder, but probably more frequent than we might expect. It is normally associated to an underlying disorder, such as lymphoproliferative or myeloproliferative neoplasms, other malignancies,

Table 7.4 Treatment of acquired von Willebrand syndrome

First choice in AvWS	Second choice in AvWS
Intravenous immunoglobulins 2 g/kg on 2 days (not if monoclonal IgM) with expected effect after 12–72 h	Desmopressin
Haemate P® 30 IU/kg before and 20–30 IU/kg 2 h into surgery, postoperative 20–30 IU/kg 3×/day for 5 days	Plasma exchange (3–4 l/day)
Antifibrinolytic drugs if a site with high fibrinolytic activity	rFVIIa 90 µg/kg

Refs. Federici et al. (2000), Maddox et al. (2005), Tiede et al. (2011)
AvWS acquired von Willebrand syndrome, *rFVIIa* recombinant activated factor VII

aortic stenosis (also when part of the Heyde syndrome), or, more rarely, autoimmune diseases. In these conditions vWF is eliminated more rapidly, either due to autoantibodies or to absorption on the surface of platelets or malignant cells. Infused vWF and FVIII concentrates will also rapidly be eliminated, if the underlying condition has not been treated. The same holds true when desmopressin is administered to increase endogenous vWF and FVIII. Table 7.4 summarizes treatment option for AvWS. Anecdotal reports mention the efficacy of plasma exchanges with 3–4 l/day of FFP for several days (Bovill et al. 1986; Silberstein et al. 1987; Federici et al. 2000; Maddox et al. 2005). This method can be useful, but it is not feasible for emergency procedures. It is recommended that emergency patients receive immunoglobulins intravenously (2 g/kg, if possible divided into 2 doses, infused 24 h apart). However, this treatment is ineffective in patients with AvWS in a monoclonal IgM setting (Federici et al. 2000). Factor improvement occurs 12–72 h after treatment and can last from days to weeks (Tiede et al. 2011). In cases showing no factor correction or cases of emergency surgery, 30–100 IU/kg of Haemate P® can be infused before surgery and 20–30 IU/kg two hours into surgery. In the postoperative setting, 20–30 IU/kg of Haemate P® 3 times daily for 5 days seems to be an adequate treatment (Maddox et al. 2005; Tiede et al. 2011). If the response to Haemate P® is diminishing, a further dose of 1 g/kg of immunoglobulins can be given intravenously. rFVIIa is another possibility to control bleeding, administered at the usual dosage of 90 µg/kg. However, there is currently only a limited experience of this treatment. Antifibrinolytic drugs, such as tranexamic acid, can be used in surgery on sites with a high fibrinolytic activity, such as the gastrointestinal tract or the oral cavity, but they are contraindicated in patients with macrohematuria.

During surgery, normal factor levels should be aimed for; in the postoperative setting, plasma levels of at least 50 % seem to be sufficient (Frank et al. 2002).

7.7 Coagulation Impairment Secondary to Drug Therapy

7.7.1 Opioid Abuse

In cases of chronic opioid abuse, morphological and rheological platelet changes can occur. An accumulation of free fatty acids can induce these changes (Zvetkova et al. 2010).

7.7.2 Antiplatelet Drugs and Anticoagulants

See Chap. 8

7.7.3 Antidepressant Drugs

Selective serotonin reuptake inhibitors (SSRIs) are known to have an influence on platelet function. In combination with oral anticoagulation therapy such as warfarin, the bleeding risk is even higher (Cochran et al. 2011). This holds true only for SSRIs and serotonin and norepinephrine reuptake inhibitors (SSNRIs). Other antidepressants do not increase the risk of bleeding when given concomitantly with warfarin, and the classic tricyclic antidepressants do not seem to alter platelet function.

SSRIs are known to alter platelet aggregation (Sarma and Horne 2006) and increase the risk of gastrointestinal bleeding (Dalton et al. 2003). Platelet aggregation is altered by different mechanisms, such as the inhibition of the serotonin transporters (Abdelmalik et al. 2008) and the depletion of serotonin inside the platelets (Dalton et al. 2003), but also by decreasing platelet count (Ataoglu and Canan 2009). Before elective surgery, it would be suitable to discontinue the use of these drugs to allow normal platelet function. In emergency surgery platelet concentrates should be given only in case of bleeding, as not every patient under SSRIs will show a tendency to bleed.

7.7.4 Thrombolytic Drugs

Thrombolysis is performed by intravenous or intra-arterial administration of plasminogen activators, such as recombinant tissue plasminogen activator (rTPA), in order to induce blood vessel recanalization. Cerebral hemorrhage is the most severe complication of thrombolysis.

Recommendations for the prevention of complications due to thrombolysis are (Trouillas and von Kummer 2006):

- Respect the guidelines regarding the contraindications to thrombolysis.
- Do not prescribe LMWH during the 24 h following thrombolysis.
- Avoid UFH immediately after thrombolysis.
- Analysis of hemostasis should be performed before and 2 h after the start of thrombolysis with a blood count and determination of the levels of fibrinogen and fibrinogen degradation products or D-dimers.

7.8 Malignancies

A recent retrospective analysis has shown an “unacceptably” high risk of thrombotic events in patients with malignancies (Moore et al. 2011). Venous events include deep vein thrombosis (DVT), pulmonary embolism (PE), and visceral/

splanchnic and cerebral vein thrombosis. Some patients may also present superficial vein thrombosis. Venous malignancy per se is a risk factor for DVT (Prandoni et al. 2005). About 10 % of patients with idiopathic DVT have an underlying malignancy. Arterial events comprise stroke, myocardial infarction, and arterial embolism.

The activation of coagulation in patients with a malignancy is caused by the acute-phase reaction, anticancer treatments, and prothrombotic properties of tumor cells. The latter induce tissue factor, protease-activating factor X, plasminogen activator inhibitors which lead to impaired fibrinolysis and cytokines targeting the endothelium, leukocytes, and platelets. The whole process is influenced by the stage of the disease, invasive procedures (e.g., central venous catheter), and the patient's profile (inherent thrombophilia).

7.8.1 Diagnosis

Indicators of a possible undiscovered malignant process in a patient with DVT are:

- No apparent classic risk factors for DVT
- Recurrent DVT
- Bilateral involvement
- A high level of D-dimers (>4,000 mg/l) at presentation
- DVT in a patient younger than 60 years old

The stage of malignancy influences the thrombotic pattern: arterial embolism can be seen in ongoing chemotherapy or in the presence of a nonbacterial endocarditis; DIC can be found in metastatic disease.

7.8.2 Management

For patients with cancer, the initiation of antithrombotic prophylaxis is particularly recommended in:

- Metastatic disease
- Surgical procedure
- Placement of a central venous catheter
- Inflammatory and/or infectious conditions

UFH and particularly LMWH are the cornerstones of DVT prophylaxis. Oral anticoagulation by VKA is difficult to manage because of pharmacokinetic concerns (poor nutrition, co-medication, or liver dysfunction), hemorrhagic concerns (thrombocytopenia secondary to chemotherapy, to radiotherapy, or to medullar spread of cancer), or surgical concerns (long half-life imposing reversal by factor concentrates in case of emergency).

7.8.3 Conclusions for Clinical Practice

These conclusions are based on guidelines of the American College of Chest Physicians http://www.chestnet.org/accp/guidelines.

For patients with a high risk of VTE who are undergoing abdominal or pelvic surgery for cancer, but who do not otherwise exhibit a high risk for major bleeding complications, extended pharmacological prophylaxis with LMWH is recommended (4 weeks).

In patients with DVT of the leg and/or a PE and active cancer, treatment with LMWH is recommended over VKA therapy. In patients with DVT and cancer who are not treated with LMWH, VKA is suggested over dabigatran or rivaroxaban as a long-term therapy.

In patients with acute DVT and/or PE and a contraindication to anticoagulation (hemorrhage, surgery, or thrombocytopenia), the use of an inferior vena cava filter is recommended (see also Chap. 8). A conventional course of anticoagulant therapy should be considered as soon as the risk of bleeding resolves.

In cancer patients who have upper extremity DVT that is associated with a central venous catheter, 3 months of anticoagulation treatment is recommended if the catheter is removed. If the catheter is not removed, anticoagulation treatment should be continued as long as the central venous catheter remains.

7.9 Monoclonal Gammopathies

7.9.1 Mechanism

Monoclonal gammopathies interfere with coagulation through several mechanisms:

- Shear wall stress due to increased blood viscosity.
- Fibrin polymerization with the loss of a harmonious clot structure.
- Autoantibody-like behavior of monoclonal proteins on coagulation factors (thrombin, FVIII, and vWF) with enhanced clearance (e.g., acquired von Willebrand syndrome).
- Absorption of coagulation factors (mostly FX) by subendothelial paraprotein deposits in AL amyloidosis. It is usually associated with a prolonged aPTT (this condition requires a hematologist's expertise).
- Heparin-like activity of certain monoclonal proteins.

7.9.2 Diagnosis

Paraprotein interference with hemostasis can be suspected in the following situations:

- History of lymphoproliferative disorders or plasma cell dyscrasia (chronic lymphocytic leukemia, Waldenström disease, MGUS, multiple myeloma)
- Bleeding complications with normal classic coagulation tests
- New onset mildly prolonged aPTT
- Abnormal primary hemostasis tests such as PFA-100.
- Poor response to Desmopressin
- Etiologic diagnosis of AvWS
- Monoclonal gammopathy

- Essential thrombocytosis
- Severe aortic stenosis (Heyde syndrome triad)

7.10 BCR/ABL-Negative Myeloproliferative Neoplasms

BCR/ABL-negative myeloproliferative syndromes (MPS) can be associated with either hemorrhagic complications or, more often, thrombotic complications, or worse, both.

7.10.1 Thrombotic Complications

Polycythemia vera (PV) and essential thrombocythemia (ET) are two types of MPS that are associated with up to 50 % of thrombotic events (Elliott and Tefferi 2005), with arterial thrombotic events being more common than venous events (Fenaux et al. 1990; De Stefano et al. 2008). The most common events among patients with PV and ET are ischemic strokes (De Stefano et al. 2008). The prevalence of splanchnic and cerebral vein thrombosis is unusually high in patients with MPS, and such events might be the presenting feature of the disease, even before diagnosis (Reikvam and Tiu 2012). Thrombotic risk is higher due to elevated hematocrit with hyperviscosity, thrombocytosis, and leukocytosis (Wolanskyj et al. 2006). Janus kinase 2 (JAK2) mutations can also add to the thrombotic risk through increased red cell adhesiveness (Buss et al. 1985) and altered platelet signaling (Falanga et al. 2007). Patients with MPS are treated with aspirin and/or cytoreduction, according to their risk level.

7.10.2 Hemorrhagic Complications

Most patients with hemorrhagic complications suffer from ET associated with a high platelet count or are patients with secondary bleeding due to anticoagulation for thrombotic risk (De Stefano et al. 2008; Tartaglia et al. 1986). Bleeding in patients with thrombocytosis is normally due to AvWS and occurs when platelets rise over 1000 G/L, in association with the loss of large multimers due to the binding of vWF to platelets (Michiels et al. 2001). Dysfunctional platelets can be a further problem (Elliott and Tefferi 2005; Landolfi et al. 1995).

7.10.3 Treatment

Both thrombotic and hemorrhagic complications can be treated by cytoreduction, such as hydroxyurea treatment, with effect on all blood lineages. A high hematocrit alone can be treated with phlebotomy; a high platelet count alone can be lowered with anagrelide. Another option for lowering peripheral blood cell counts is interferon. Normally, patients with MPS take aspirin on a regular basis. If possible, peripheral blood cell counts should be within normal ranges before surgical

procedures. In emergency, surgery platelet count should be at least $<100 \times 10^9$/l to reduce the risk of bleeding. With regard to thrombotic complications, patients at high risk should receive an appropriate antithrombotic prophylaxis with, for example, LMWH.

7.11 Antiphospholipid Antibody Syndrome

The antiphospholipid antibody syndrome is an acquired autoimmune tendency to thrombosis that is diagnosed when antiphospholipid antibodies are present, together with a history of thrombosis and/or complications during pregnancy. Treatment comprises antithrombotic drugs. In the perioperative setting, the management of antiphospholipid antibody syndrome requires input from a hematologist.

One category of antiphospholipid antibodies, called "lupus anticoagulant," can interfere with in vitro coagulation tests such as PT, aPTT, and ACT. It is important to be aware of the impact of this interference on patient monitoring in the perioperative setting, particularly if a cardiopulmonary bypass must be performed. Interference can be circumvented by using a Hepcon® test or by measuring the heparin concentration by anti-Xa activity tests (Jervis et al. 2009).

7.12 Thrombotic Microangiopathies

Thrombotic microangiopathies are characterized by direct antiglobulin test-negative hemolytic anemia, thrombocytopenia, petechial hemorrhages, fever, and/or renal and neurological complications. Diagnosis of thrombotic microangiopathies may prove difficult, and the input of a hematologist is required to best define perioperative management.

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