22.7.5 Acquired coagulation disorders 5546 T.E. Wa

22.7.5 Acquired coagulation disorders 5546 T.E. Warkentin

section 22 Haematological disorders 5546 Gene therapy in haemophilia High KA (2005). Gene transfer for hemophilia: can therapeutic ef- ficacy in large animals be safely translated to patients? J Thromb Haemost, 3, 1682–91. Manno CS, et al. (2006). Successful transduction of liver in hemophilia by AAV-factor IX and limitations imposed by the host immune re- sponse. Nat Med, 12, 342. Murphy SL, High KA (2008). Gene therapy for haemophilia. Br J Haematol, 140, 479–87. Nathwani AC, et al. (2006). Self-complementary adeno-associated virus vectors containing a novel liver-specific human factor IX ex- pression cassette enable highly efficient transduction of murine and nonhuman primate liver. Blood, 107, 2653. Nathwani AC, et al. (2011). Adenovirus-associated virus vector- mediated gene transfer in hemophilia B. N Engl J Med, 365, 2357–65. Thrombotic disease Bucciarelli P, Rosendaal FR, Tripodi A (1999). Risk of venous thrombo- embolism and clinical manifestations in carriers of antithrombin, protein C, protein S deficiency, or activated protein C resistance: a multicenter collaborative family study. Arterioscl Thromb Vasc Biol, 19, 1026–33. Gage B, et al. (2008). Use of pharmacogenetic and clinical factors to pre- dict the therapeutic dose of warfarin. Clin Pharmacol Ther, 84, 326–31. Mannucci PM (2005). Laboratory detection of inherited thrombophilia: a historical perspective. Semin Thromb Hemost, 31, 5–10. Moake JL (2004). Thrombotic thrombocytopenic purpura: survival by ‘giving a dam’. Trans Am Clin Climatol Assoc, 115, 201–19. Nicolaes GA, Dahlbäck B (2003). Congenital and acquired activated protein C resistance. Semin Vasc Med, 3, 33–46. Shih AW, Crowther MA (2016). Reversal of direct oral anticoagulants: a practical approach. Hematology Am Soc Hematol Educ Program, 2016(1), 612–19. Genetic databases Ensembl. http://www.ensembl.org National Center for Biotechnology Information (NCBI). http://www. ncbi.nlm.nih.gov/ UCSC Genome Browser. http://genome.ucsc.edu 22.7.5 Acquired coagulation disorders T.E. Warkentin ESSENTIALS Acquired disorders of coagulation may be the consequence of many underlying conditions, and although they may share abnormality of a coagulation test, for example, a prolonged prothrombin time (PT), their clinical

effects are diverse and often opposing. General clinical approach Diagnosis—most acquired disorders of coagulation can be identi- fied by screening haemostasis tests, including (1) PT; (2) activated partial thromboplastin time (APTT); (3) thrombin clotting time; (4) fibrin degradation products (FDPs), including (5) the cross-linked fibrin assay (D-dimer); and (6) complete blood count with examin- ation of a blood film. Few bleeding disorders give normal results in all these tests, but disorders predisposed to thrombosis as a result of deficiency of natural anticoagulants (e.g. antithrombin, protein C, and protein S) or certain mutations (e.g. factor V Leiden) must be specifically sought. Treatment—patients with coagulopathies who are bleeding or who require surgery are usually treated with blood products such as platelets and frozen plasma. Other treatments used in par- ticular circumstances include (1) vitamin K—required for the post-translational modification of factors II, VII, IX, and X as well as the anticoagulant factors, protein C, and protein S; (2) cryoprecipitate— used principally for the treatment of hypofibrinogenaemia; (3) con- centrates of specific factors—used in isolated deficiencies (e.g. of factors VIII, IX, XI, VII, or fibrinogen); (4) antifibrinolytic agents
(e.g. ε-aminocaproic acid and tranexamic acid); (5) desmopressin (1-deamino-8-d-arginine vasopressin (DDAVP))—increases factor VIII and von Willebrand factor. Prohaemorrhagic coagulation disorders Vitamin K deficiency—most haemostatic factors are produced exclu- sively by the liver, including the vitamin K-dependent factors II, VII, IX, and X, deficiency of which can be caused by (1) malabsorption of fat-soluble vitamins, or (2) coumarin overanticoagulation—minor bleeding episodes occur in about 6 to 10% of patients per year and major bleeding episodes in 1 to 3%. Liver disease—abnormalities include a disproportionately pro- longed PT, reduced/normal fibrinogen levels, and/or pancytopenia (indicating hypersplenism) in an appropriate clinical setting. Disseminated intravascular coagulation (DIC)—clinical manifest- ations range from generalized haemorrhage to widespread micro- vascular thrombosis, predisposing to multisystem organ dysfunction and ischaemic limb necrosis. Initiated by numerous triggers, for ex- ample, the extrinsic coagulation pathway (tissue factor) or interleukin- 6 in the context of systemic inflammation. May be caused by a wide variety of conditions, including trauma and cardiogenic shock, in- fection/septic shock, obstetric complications, acute haemolysis, immunological disorders, and vascular anomalies. The presence of DIC is often indicated by abnormal coagulation tests associated with thrombocytopenia and red cell abnormalities on examination of the blood film: FDPs and fibrin D-dimers are usually greatly increased. Immunoglobulin-mediated factor deficiency—(1) acquired factor VIII deficiency—this is suggested by the occurrence of bleeding, either spontaneously or after minor trauma, in association with a prolonged APTT and a normal PT, with mixing experiments with normal pooled plasma indicating the presence of an inhibitory antibody. The condi- tion is of unknown cause in 50% of cases, with the remainder associated with other autoimmune disorders (e.g. systemic lupus erythematosus), lymphoid and other malignancies, penicillin treatment, or the post- partum state. Aside from treatment with DDAVP (mild bleeding) or purified human factor VIII (or VIIa) concentrates (severe bleeding), patients with high antibody titres may require immunosuppressive therapy (e.g. prednisone ± cyclophosphamide, rituximab). (2) Other acquired coagulation-factor deficiencies caused by antibodies. Other acquired coagulation-factor deficiencies—these include (1) haemodilution and massive transfusion; (2) heparin and

 acquired heparin-like anticoagulants; (3) coagulopathies sec- ondary to plasma cell dyscrasias; (4) hyperfibrinolysis—which may be a result of thrombolytic therapy, malignancy, cardiopulmonary bypass procedures, or advanced liver

disease; and (5) heterogeneous coagulopathies induced by venoms (snake bites). Prothrombotic coagulation disorders Heparin-induced thrombocytopenia—caused by IgG antibodies which recognize complexes of platelet factor 4 and heparin, typ- ically leading to a fall in the platelet count beginning 5 to 10 days after starting the drug (but more abruptly in patients who have re- cently been exposed to it). Thrombosis is caused by several factors, including activation of platelets and stimulation of tissue factor ex- pression on monocytes. Clinical manifestations include (1) venous thrombosis (deep vein thrombosis (including venous limb gangrene), pulmonary embolism); (2) arterial thrombosis (major limb artery thrombosis, stroke, myocardial infarction). Protamine administered after cardiac surgery (to reverse heparin anticoagulation) can trigger acute thrombocytopenia and thromboembolic complications in a patient with platelet-activating antiprotamine/heparin antibodies. Adenocarcinoma-associated chronic DIC—metastatic adenocar- cinoma and other tumours may be associated with a prothrombotic state and large vessel thromboses. Tissue factor and prothrombotic cysteine proteases have been found in tumour extracts. Heparin is the preferred treatment; coumarins (e.g. warfarin) can cause venous limb gangrene in a limb with deep vein thrombosis. Antiphospholipid antibody syndrome—caused by antibodies that
are usually directed against protein cofactors such as β2-glycoprotein I and prothrombin. Clinical manifestations include intermittent throm- boses and (rarely, but most dramatically) sudden life-threatening arterial occlusions. Lupus anticoagulant activity is shown by dem- onstrating inhibition of phospholipid-dependent coagulation assays (most commonly by prolongation of the APTT), with antiphospholipid antibodies also detected by enzyme-immunoassay using purified phospholipids as the target antigen (e.g. anticardiolipin antibody assay). Most patients require long-term anticoagulation. Other conditions associated with microvascular thrombosis—these include disorders predominantly affecting small venules, for ex- ample, (1) coumarin-induced skin necrosis; (2) coumarin-induced venous limb gangrene; (3) symmetric peripheral gangrene; and (4) purpura fulminans; in contrast, (5) thrombotic microangiopathy (e.g. thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome) typically affects arterioles.
Introduction A coagulopathy is a disorder associated with an abnormal coagula- tion assay result, such as a prolonged prothrombin time (PT) (often expressed as the international normalized ratio (INR)), activated par- tial thromboplastin time (APTT), or thrombin clotting time (TCT). Coagulopathies can be associated with either bleeding or throm- bosis, and have many causes (Table 22.7.5.1). The importance of the clinical context is illustrated by two contrasting patient scenarios that have in common a prolonged international normalized ratio (INR) (6.0; usual therapeutic range, 2.0–3.0) during oral anticoagulant therapy: one patient has a life-threatening intracranial haemorrhage complicating warfarin therapy given for a prosthetic heart valve; in contrast, another patient, who was treated for deep vein thrombosis (DVT) complicating heparin-induced thrombocytopenia (HIT) has the limb-threatening complication of warfarin-induced venous limb gangrene, caused by microvascular thrombosis. Table 22.7.5.2 lists common screening tests for coagulopathy. Only a few coagulopathies give normal results in all these screening assays (e.g. α2-antiplasmin deficiency, factor XIII deficiency, mild von Willebrand’s disease including type 2A von Willebrand’s syn- drome associated with monoclonal gammopathy or aortic stenosis). Agents for treating acquired disorders of coagulation Blood products are usually indicated for the treatment of patients with coagulopathies who are bleeding or who require a major inva- sive procedure. Fresh frozen plasma or frozen plasma Fresh frozen plasma is plasma that is frozen within 8 h of collec- tion; it contains all the haemostatic factors at concentrations be- tween 0.7 and 1.0 U/ml. Frozen plasma is plasma frozen within 24 h of collection, and is similar to fresh frozen

plasma, except that it contains significantly less factor VIII; however, isolated VIII defi- ciency is treated with factor VIII concentrate (rather than plasma), and so for virtually all clinical situations where fresh frozen plasma use is appropriate, frozen plasma can be given instead (this is be- cause factor VIII is an acute phase reactant, and is usually not sig- nificantly reduced in most coagulopathic disorders). Accordingly, either fresh frozen plasma or frozen plasma can be used to treat coagulopathy of liver disease, haemodilution from massive trans- fusion, and disseminated intravascular coagulation (DIC). In some jurisdictions, frozen plasma has replaced fresh frozen plasma, and the latter product is no longer available. For a 70 kg adult with a 3 litre plasma volume, 1 litre of frozen plasma (or fresh frozen plasma) will increase the coagulation factors by about 0.25 U/ml. In most patients, this should lead to levels greater than the minimum required for adequate haemostasis (>0.30 U/ml for most factors). Repeat frozen plasma transfusion (e.g. 500 ml every 6 h) may be ne- cessary if the haemostasis defect is ongoing. Frozen plasma is being supplanted by cryosupernatant as a replacement fluid for throm- botic thrombocytopenic purpura (TTP). Solvent/detergent-treated plasma, in which most blood-borne pathogens are inactivated (but not nonenveloped viruses such as hepatitis A, parvovirus B19, or the agent that causes Creutzfeldt–Jakob disease, a potential blood-borne pathogen), has become available, but is limited by its high cost. Cryoprecipitate This contains fibrinogen (0.10–0.25 g/unit), factors VIII and XIII, von Willebrand factor (VWF), and fibronectin. Its principal indica- tion is the treatment of hypofibrinogenaemia, where it increases fi- brinogen levels using just one-quarter of the volume of blood product compared with fresh frozen plasma. Cryoprecipitate is appropriate for patients with significant hypofibrinogenaemia, for example, DIC, primary fibrinolysis, and congenital hypofibrinogenaemia. For a bleeding patient whose fibrinogen level is about 0.5 g/litre, 10 U of cryoprecipitate would probably increase the fibrinogen to above

 Table 22.7.5.1 Acquired coagulopathies that cause bleeding or thrombosis Acquired coagulopathies Comment Prohaemorrhagic disorders Vitamin K deficiency or pharmacological antagonism by coumarin Reduced levels of vitamin K-dependent procoagulant factors (II (prothrombin), VII, IX, X) Liver disease Multiple factor deficiencies, especially factors XI and XII (although VIII levels are usually normal/elevated); low fibrinogen levels can indicate hyperfibrinolysis Severe haemodilution/massive transfusion Multiple factor deficiencies; concomitant DIC in some patients Acute DIC: haemorrhagic Certain forms of DIC, e.g. acute head trauma, placental abruption, can lead to bleeding secondary to generalized coagulopathy, especially with fibrinogen depletion Acquired coagulation factor inhibitor (autoimmune) Anti-VIII autoantibodies are most common Direct oral anticoagulants (anti-IIa (antithrombin), anti-Xa) Dabigatran (direct thrombin inhibitor) tends to prolong the APTT; in contrast, the direct Xa inhibitors, rivaroxaban and edoxaban, tend to prolong the INR, although apixaban has minimal effect on the INR Heparin and related drugs Marked APTT prolongation with heparin overdose (extreme overdose also prolongs INR); low molecular weight heparin overdose only minimally prolongs APTT Heparin-like anticoagulants Rare; associated with plasma cell disorders; minimal or no prolongation in APTT Paraprotein-induced coagulopathies See text and Box 22.7.5.3 Hyperfibrinolysis Associated with prostate adenocarcinoma, advanced liver disease, post-thrombolytic therapy, after cardiac surgery, or aortic aneurysm Snake venom See text and Table 22.7.5.6 Prothrombotic disorders Heparin-induced thrombocytopenia (HIT) Strong association with venous and arterial thrombosis; about 10 to 20% of patients have decompensated DIC (elevated INR, low fibrinogen, and/or microangiopathic blood film) Protamine-induced thrombocytopenia (PIT) Potential explanation for post-cardiac surgery thrombocytopenia and

thrombosis in susceptible patient with platelet-activating antiprotamine/heparin antibodies (which could be present if preoperative heparin is given to diabetic patient receiving protamine–insulin) Chronic DIC secondary to adenocarcinoma Strong association with venous and arterial thrombosis; improves with (low molecular weight) heparin; predisposes to coumarin-induced microthrombosis (see later in table), especially venous limb gangrene (acral limb necrosis with associated DVT) Acute DIC associated with symmetric peripheral gangrene or purpura fulminans Certain forms of DIC, e.g. cardiogenic or septic shock, are associated with microthrombosis and acral ischaemic limb necrosis, especially in setting of ‘shock liver’ (acute ischaemic hepatitis) Antiphospholipid syndrome (APS) Prolonged APTT due to ‘lupus anticoagulant’ (‘nonspecific inhibitor’); associated with venous and arterial thrombosis, spontaneous abortions, thrombocytopenia Coumarin-induced necrosis Central skin or acral limb necrosis resulting from microvascular thrombosis; pathogenesis includes depletion of vitamin K-dependent natural anticoagulant, protein C, in setting of hypercoagulability Thrombotic microangiopathy (TMA) Thrombocytopenia and microangiopathic haemolysis (red cell fragmentation), platelet–VWF microthrombi within arterioles; elevated INR and APTT are occasionally seen Table 22.7.5.2 Screening haemostasis tests Assay Comment Prothrombin time (PT), often expressed as international normalized ratio (INR) Screen for deficiency of factors VII, X, V, II, and/or fibrinogen (e.g. vitamin K deficiency/coumarin therapy, liver disease) Activated partial thromboplastin time (APTT) Screen for deficiency of factors VIII, IX, X, V, II, contact factors, and/or fibrinogen; monitor certain anticoagulants, e.g. heparin, lepirudin, argatroban Thrombin clotting time (TT or TCT) Screen for hypofibrinogenaemia and/or presence of heparin; some TCT assays are also sensitive to FDPs Serum fibrin(ogen) degradation products (FDPs) Requirement to clot blood sample can lead to false-positive results due to incomplete blood clotting (e.g. residual heparin) Cross-linked fibrin assay (D-dimer) Detects fibrin degradation products generated after thrombin, factor XIII, and plasmin have acted upon fibrinogen (marker for DIC and/or thrombosis) Paracoagulation assay (e.g. protamine sulphate test) Positive paracoagulation assay often means DIC is clinically significant and may require blood products or anticoagulant therapy Bleeding time Assesses primary haemostasis, i.e. VWF- mediated platelet adhesion to endothelium with secondary aggregation of platelets within haemostatic plug, now replaced in many centres by platelet function analyser (PFA100) Complete blood count; blood film examination Platelet enumeration, and assessment of causes for thrombocytopenia, e.g. red cell fragments indicating microangiopathy

 1.0 g/litre, although a lower than expected increment could occur if the patient had a higher volume of distribution (e.g. a cirrhotic patient with ascites). Where available, fibrinogen concentrates (see later) are increasingly being used for treatment of hypofibrinogenaemia. Specific factor concentrates These are available for use in patients with an isolated deficiency in certain factors, such as VIII or IX. Prothrombin complex con- centrates (PCCs) contain the vitamin K-dependent factors (ei- ther three-factor PCCs containing procoagulant factors II, IX, and X, or four-factor PCCs that additionally contain factor VII), and four-factor PCC is appropriate for the rapid reversal of severe coagulopathy related to coumarin use. Activated PCC (e.g. factor VIII inhibitor bypassing activity (FEIBA)) and factor VIIa are other specialized concentrates with specific uses, for instance, to manage a bleeding patient with an acquired factor VIII inhibitor. Certain other isolated factor deficiencies can be managed by specific factor concentrates, such as recombinant factor VIIa, factor XI, factor XIII, and fibrinogen. Protein C concentrates are available in some juris- dictions for treatment of congenital protein C deficiency. Pharmacological therapies These include the antifibrinolytic agents ε-aminocaproic acid and

tranexamic acid. ε-Aminocaproic acid and tranexamic acid bind to the lysine-binding sites of plasminogen; paradoxically, although increasing the susceptibility of plasminogen to proteolysis by plasminogen acti- vator, these lysine analogues also prevent plasminogen from binding to fibrin, thus impeding fibrinolysis. Oral dosing for ε-aminocaproic acid is about 7 g (100 mg/kg) initially, followed by 3.5 g (50 mg/kg) every 4 h; similar doses are used for intravenous administration. For tranexamic acid, 1.0 to 1.5 g is given every 8 h by mouth; the dose is reduced to between 0.5 and 1.0 g every 8 h if given intravenously (higher dosing is appropriate if given prior to cardiac surgery). Both drugs are avail- able in 500-mg capsules. These drugs are appropriate for the treatment of hyperfibrinolysis, for instance, bleeding following thrombolytic therapy or associated with cardiac or hepatic surgery. These drugs are generally contraindicated in patients with DIC, however, as blocking secondary fibrinolysis could lead to microvascular thrombosis. Desmopressin Desmopressin or 1-deamino-8-d-arginine vasopressin (DDAVP), a synthetic vasopressin analogue, leads to an increase in factor VIII and VWF levels that peak between 45 and 90 min after intravenous infusion (0.3 μg/kg in 50 ml normal saline over 20–30 min; maximum dose, 20 μg). Although repeat DDAVP can be given at 12- to 24-h intervals, the drug becomes less effective over time (tachyphylaxis) as endothelial stores of VWF are depleted, limiting the usual number of injections to no more than three with any treatment course. Flushing, tachycardia, mild hypotension, free-water retention (leading to dilutional hyponatraemia), and angina are occasional side effects. Prohaemorrhagic acquired coagulation disorders Vitamin K deficiency disorders Vitamin K-dependent coagulation factors Vitamin K is required for the post-translational modification of six haemostatic factors, four with procoagulant activity (factors II, VII, IX, and X), and two with anticoagulant activity (protein C and protein S). The physiological relevance of a seventh factor, factor Z, remains unclear. The enzyme vitamin K-dependent γ- glutamylcarboxylase adds a carboxyl group to each member of a cluster of glutamyl residues, thereby forming the γ-carboxyglutamyl residues crucial for enabling these six haemostatic factors to interact with phospholipid membranes in a calcium-dependent fashion. During this γ-carboxylation reaction, the reduced form of vitamin K is oxidized to vitamin K epoxide; oral anticoagulants inhibit the enzyme complex (vitamin K epoxide reductase complex) that regen- erates the reduced form of vitamin K. Diet and absorption of vitamin K Vitamin K1 (phylloquinone) is exclusively derived from plants; vitamin K2 (menaquinone) is synthesized by bacteria. Green, leafy vegetables, such as broccoli, lettuce, cabbage, and spinach, are very good dietary sources of vitamin K (100–500 μg/100 mg). Vitamin K is fat-soluble, and absorption occurs primarily in the small bowel. Serum vitamin K concentrations are only between 150 and 800 pg/ ml and, as hepatic storage is limited (half-life is just a few days), a regular daily intake of about 0.1 to 0.5 μg/kg is required. Although bacterial synthesis is not a major source of vitamin K in humans, anti- biotic treatment nevertheless predisposes to vitamin K deficiency. Vitamin K deficiency Malabsorption of fat-soluble vitamins caused by biliary tract disease, or primary bowel disorders such as coeliac or inflammatory bowel disease, can cause vitamin K deficiency. An inadequate diet, par- ticularly when combined with antibiotic therapy, is another cause. Indeed, coagulopathy can arise during a brief period of decreased intake (e.g. 1 week postoperatively). A disproportionately prolonged PT/INR in the appropriate clin- ical setting suggests vitamin K deficiency (Table 22.7.5.3). The diag- nosis is usually confirmed by assessing the response to vitamin K administration. Compared with the treatment of a coumarin over- dose, small amounts of vitamin K are effective, for example, 1 mg vitamin K given orally or by slow intravenous infusion (over at least 30 min to minimize risk of an anaphylactoid reaction). For serious bleeding, frozen plasma, fresh frozen plasma, or especially PCCs provide a more rapid (but transient) correction of the coagulopathy.

Coumarin overanticoagulation Oral anticoagulants (e.g. coumarins such as warfarin and phenprocoumon) are widely used to prevent and treat thrombosis via their vitamin K antagonism. An INR target range between 2.0 and 3.0 is appropriate for most clinical indications, although a higher therapeutic range (INR 2.5–3.5) is appropriate for patients at very high risk for thrombosis (e.g. with mechanical prosthetic heart valves). Bleeding is the major complication of coumarin, with minor and major bleeding episodes occurring in about 6 to 10% and 1 to 3% of patients per year respectively; the intracranial haemorrhage rate is between 0.25 and 1% per year. Changes in diet or alcohol con- sumption, poor patient compliance, and the introduction of new drugs (Table 22.7.5.4) can cause bleeding by producing coumarin overanticoagulation. In contrast, recurrent gastrointestinal or urinary tract bleeding at therapeutic levels of anticoagulation often indicates an occult gastrointestinal or renal lesion, respectively.

section 22 Haematological disorders 5550 The treatment of nontherapeutic (elevated) INRs depends on the clinical setting. Oral vitamin K use is appropriate in many non- urgent conditions as it avoids the risk of anaphylactoid reactions to intravenous use, and has more predictable effects than subcutaneous injection. Much larger and prolonged vitamin K dosing (100– 150 mg/day) is required to treat accidental or deliberate overdoses of long-acting second-generation rodenticides (‘superwarfarins’), such as brodifacoum. Table 22.7.5.3 Results of screening haemostasis assays in various clinical settings PT/INR APTT Fibrinogen TCT Fibrin D-dimers, fibrin monomers Platelets Vitamin K deficiency or antagonism (coumarin) ↑↑ ↑ N N N N Liver disease N, ↑, ↑↑ N, ↑ ↓, N N, ↑ N, ↑, ↑↑ N, ↓, ↓↓ Heparin N, ↑a ↑↑ N ↑↑ N N, ↓b LMWH, danaparoid N N, sl↑ N N, sl↑ N N Thrombin inhibitors (argatroban, dabigatran) N, ↑ ↑, ↑↑ ↓c, N ↑↑ N N Factor Xa inhibitors (rivaroxaban, edoxaban, apixaban) N d, ↑ N, ↑ N N N N Thrombolytic therapy sl↑ N ↓, ↓↓ ↑, ↑↑ ↑, ↑↑ N, ↓ Renal disease N N N N N N, sl↓ Acute DIC ↑, ↑↑ N, ↑, ↑↑ ↑e, N, ↓, ↓↓ N, ↑, ↑↑ ↑↑ ↓, ↓↓ Chronic DIC N, ↑ N, sl↑ N, ↓ N, ↑ ↑, ↑↑ N, ↓, ↓↓ Primary fibrinolysis N, sl↑ N, sl↑ ↓, ↓↓ ↑, ↑↑ ↑, ↑↑ ↓, N Lupus anticoagulant N, ↑f Ng, ↑, ↑↑ N N N N, ↓, ↓↓h Factor VIII inhibitor N ↑, ↑↑ N N N N Haemodilution ↑ ↑, ↑↑ ↓, ↓↓ ↑, ↑↑ N ↓ a An elevated PT/INR secondary to heparin indicates very high heparin levels (e.g. dosing used in cardiac surgery, overdose). b Unfractionated heparin is associated with early, mild, transient thrombocytopenia secondary to weak platelet-activating effects (nonimmune heparin-associated thrombocytopenia); thrombocytopenia that begins 5 or more days after starting UFH or LMWH can indicate HIT. c Thrombin inhibitors can spuriously indicate low fibrinogen levels due to interference with certain fibrinogen assays. d Apixaban has the least effect on the INR among the commercially available direct factor Xa inhibitors. e Elevated plasma fibrinogen levels despite DIC-associated fibrinogen declines can occur when DIC complicates inflammatory disorders with hyperfibrinogenaemia. f An elevated INR can indicate hypoprothrombinaemia. g A normal APTT can be found if the laboratory chooses to use an APTT reagent that is insensitive to lupus anticoagulant activity. h Many patients with antiphospholipid syndrome have concomitant thrombocytopenia; severe thrombocytopenia can indicate catastrophic antiphospholipid syndrome (CAPS). Table 22.7.5.4 Drugs, food, and dietary supplement interactions with warfarin by level of supporting evidence and direction of interaction Potentiation of warfarin’s anticoagulant effect Inhibition of warfarin’s anticoagulant effect Anti-infectives: amoxicillin/clavulanateb, azithromycinb, ciprofloxacina, clarithromycinb, cotrimoxazolea, erythromycina, fluconazolea, isoniazida, itraconazoleb, levofloxacinb, metronidazolea, miconazole oral gela, miconazole vaginal suppositorya, ritonavirb, tetracyclineb, voriconazolea Anti-infectives: dicloxacillinb, griseofulvina, nafcillina, ribavirina, rifampicina, ritonavirb Cardiovascular: amiodaronea, aspirinb, clofibratea, diltiazema, fenofibratea, fluvastatinb,

propafenonea, propronolola, quinidineb, ropiniroleb, simvastatinb, sulfinpyrazone (biphasic with later inhibition)a Cardiovascular: bosentanb, cholestyraminea Analgesics/anti-inflammatories and immunologics: acetaminophenb, aspirinb, celecoxibb, dextropropoxypheneb, interferonb, phenylbutazonea, piroxicama, tramadolb Analgesics/anti-inflammatories and immunologics: azathioprineb, mesalaminea CNS drugs: alcohol (if concomitant liver disease)a, citaloprama, chloral hydrateb, disulfiramb, entacaponea, fluvoxamineb, phenytoin (biphasic with later inhibition)b, sertralinea CNS drugs: barbituratesa, carbamazepinea, chlordiazepoxideb GI drugs and food: cimetidinea, fish oila, grapefruitb, mangoa, omeprazolea GI drugs and food: high vitamin K content foodsa, avocadoa, soy milkb, sucralfateb Herbal supplements: boldo-fenugreeka, danshenb, don quaib, lycium barbarum Lb, PC-SPESb, quilinggaoa, Herbal supplements: ginsengb Other drugs: anabolic steroidsa, fluorouracil,b gemcitabineb, levamisole/fluorouracilb, paclitaxelb, tamoxifenb, tolterodineb, zileutona Other drugs: chelation therapyb, influenza vaccineb, mercaptopurinea, multivitamin supplementb, raloxifeneb CNS, central nervous system; GI, gastrointestinal. Level of causation: a highly probable, b probable. See Ageno et al. (2012) for other drugs for which level of causation is listed as ‘possible’ and ‘highly improbable’. Modified from Ageno et al. (2012). Oral anticoagulant therapy. Antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-based Clinical Practice Guidelines. Chest, 141 (Suppl), e44S−e88S.

22.7.5 Acquired coagulation disorders 5551 Urgent reversal of coumarin anticoagulation When urgent reversal of coumarin anticoagulation is required (e.g. life-threatening bleeding or need for surgery within 6 h), blood prod- ucts should be given in addition to intravenous vitamin K. Although either frozen plasma or fresh frozen plasma are options, four-factor PCCs (containing factors II, VII, IX, and X), where available, are strongly preferred, as reversal can be achieved more reliably, and with much lower volumes of blood product, compared with plasma (Box 22.7.5.1). Direct oral anticoagulant overanticoagulation Direct oral anticoagulants (DOACs), which either inhibit thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, edoxaban), are now available; these variably prolong the PT (or INR) and PTT, have half- lives of approximately 12h (assuming normal renal function), and (except for dabigatran) have no specific antidotes. Bleeding risk is increased in the elderly and in patients with renal dysfunction. Life- threatening bleeding should be managed by general measures (dis- continuing the anticoagulant, red cell transfusions) and, possibly, by specialized prohaemostatic therapies such as four-factor PCC or acti- vated PCC (e.g. FEIBA) or recombinant factor VIIa (e.g. in our centre, we use as off-label therapy 2000 units of four-factor PCC for an adult with life-threatening bleeding associated with a DOAC that inhibits factor Xa) (Box 22.7.5.1). Haemodialysis has been reported to re- duce dabigatran levels. Idarucizumab, a dabigatran-binding antibody fragment, is approved by the Food and Drug Administration in the United States of America when reversal of the anticoagulant effects of dabigatran is needed for emergency surgery/urgent procedures or in life-threatening or uncontrolled bleeding. Liver disease Most haemostatic factors are produced exclusively by the liver. Exceptions include factor VIII (hepatic and extrahepatic synthesis), VWF (endothelium, megakaryocytes), and several factors produced by endothelium (e.g. plasminogen activator and plasminogen acti- vator inhibitor type I (PAI-1)). Box 22.7.5.2 lists the multiple effects on haemostasis caused by liver disease. Often, bleeding is primarily related to anatomical factors, such as oesophageal varices or gastric/duodenal ulcers, though reduced hepatic synthesis of coagulation factors can be a contributing factor. Increased susceptibility to DIC via superadded illness (e.g. bacterial peritonitis), impaired clearance of activated coagulation factors, and hyperfibrinolysis are other fac- tors. The key role of

acute ischaemic hepatitis (‘shock liver’) in ex- plaining microthrombosis is discussed later in this chapter. A prolonged PT/INR is the most frequent laboratory abnormality (Table 22.7.5.3). The fibrinogen level is usually normal or increased; when hypofibrinogenaemia occurs, it generally indicates severe liver disease or hyperfibrinolysis. Fibrin(ogen)-degradation product (FDP) (also known as fibrin split product) and fibrin D-dimer levels Box 22.7.5.1 Management of bleeding or need for urgent surgery in patients receiving vitamin K antagonists Indications 4-factor prothrombin complex concentrate (PCC) is indicated for treat- ment of severe or life-threatening acute bleeding associated with war- farin (or other vitamin K antagonists [VKAs]) OR for rapid reversal of warfarin [or other VKAs] for urgent surgical procedures (generally, when surgery is required in less than 6 hours). PCC has also been used for treatment of severe or life-threatening acute bleeding associated with factor Xa inhibitors (apixaban, rivaroxaban, or edoxaban). Dosing (VKA reversal) Dosing for target INR ~1.5 Patient INR Dose of 4-factor PCC* INR 2–3 20 IU/kg INR 3–6 30 IUkg INR >6 40 IU/kg

- Add 10 IU/kg for target INR < 1.2.
- Also give vitamin K 5–10 mg IV over 30 minutes; may repeat in 12–24 hours.
- Under normal circumstances the PCC dose should not exceed 3000 IU (maximum infusion speed, 8 mL/min).
- For severe acute bleed with unknown INR, give 2000 IU.
- For vials containing 500 IU, round dose to the nearest 500 IU (e.g., 2780 IU rounds up to 3000 U administered).
- 4-factor PCC refers to product containing (procoagulant) factors II, VII, IX, and X; in contrast, 3-factor PCC contains factors II, IX, and X, but not factor VII. Dosing (Factor Xa inhibitor reversal) Give 4-factor PCC, 2000 IU. Relative contraindication Patients with heparin-induced thrombocytopenia (HIT) or suspected HIT (product contains heparin). Source data from McMaster University, Department of Medicine (Hematology and Thromboembolism), Clinical Protocols (and Reversals): Prothrombin Complex Concentrate, at: http://fhs.mcmaster.ca/medicine/ hematology/anticoag_octoplex.htm. Box 22.7.5.2 Causes of bleeding and thrombosis in liver disease Predispose to bleeding • Effects of portal hypertension:

— Oesophageal varices (bleeding site)

— Splenomegaly (thrombocytopenia) • Decreased thrombopoietin production (thrombocytopenia) • Decreased procoagulant factor synthesis • Abnormal coagulation factor synthesis:

— Dysfibrinogenaemia (increased sialic acid content)

— Decarboxylated vitamin K-dependent factors • Decreased clearance of plasmin, plasminogen activators, and fibrin (ogen) degradation products • Vitamin K malabsorption • Platelet dysfunction • Increased susceptibility to adverse hepatic effects of alcohol or other drugs • Decreased α2-antiplasmin synthesis (predisposes to hyperfibrinolysis) Predispose to thrombosis • Decreased natural anticoagulant synthesis (e.g. protein C, antithrombin) • Decreased clearance of activated coagulation factors • Physician reluctance to prescribe antithrombotic therapy

section 22 Haematological disorders 5552 are often increased; thus, the laboratory picture can resemble that of DIC even in a patient who is otherwise clinically stable. Management of hepatic coagulopathy should include a trial of vitamin K (e.g. 10 mg once daily for 3 days), although this will not benefit most patients. Frozen plasma (or fresh frozen plasma) may be given to bleeding patients with a prolonged INR, or who require major invasive procedures. Retrospective studies suggest that minor invasive procedures (e.g. paracentesis and pleurocentesis) can usu- ally be performed safely with an INR as high as 1.8. For patients suspected to have significant fibrinolysis, antifibrinolytic therapy can be tried. PCCs should only be used in emergencies, given their prothrombotic potential in this group of patients. Platelet transfusions usually provide minimal increase in the platelet count in patients with platelet sequestration caused by hypersplenism. DDAVP improves haemostasis in patients with prolonged bleeding time secondary to hepatic platelet dysfunction. Haemodilution and massive transfusion Coagulopathies occur in most patients who receive crystalloids, col- loids, or red cell concentrates following trauma, surgery, or fluid re- suscitation for other major illnesses. In many patients, no bleeding results despite moderate abnormalities in the INR, APTT, TCT, and platelet count. The reason is that all the individual coagulation fac- tors remain at haemostatically effective levels, even though the la- boratory assays are abnormal when all the factor levels are uniformly reduced. Massive transfusion is defined as the transfusion of blood prod- ucts equivalent to the patient's total blood volume within 24 h. Red cell concentrates do not provide significant amounts of platelets or coagulation factors. Thus infusions of platelets, frozen plasma (or fresh frozen plasma), and, sometimes, cryoprecipitate are often needed as well. Massive transfusion protocols that timely admin- ister blood using a predetermined ratio, for example, plasma, plate- lets, and red blood cells in a 1:1:2 ratio (i.e. 5 units of frozen plasma, 1 pack platelets (5 units), and 10 units of red blood cells) may be life- saving. Disseminated intravascular coagulation DIC is a group of clinicopathological syndromes characterized by widespread activation of coagulation; there results intravascular gen- eration of thrombin, formation of fibrin, and reactive fibrinolysis. Clinical consequences range from coagulation factor and platelet depletion, resulting in generalized haemorrhage, to widespread microvascular thrombosis, predisposing to multisystem organ dys- function or limb necrosis. 'Acute' DIC, caused by septicaemia, trauma, and obstetrical complications, is most frequent; 'chronic' DIC, typ- ically caused by malignancy, is often associated with a dramatic hypercoagulable state (Table 22.7.5.5). Although DIC is usually a sys- temic process, sometimes a localized abnormality (such as a vascular malformation or aortic aneurysm) leads to the regional activation of coagulation and results in the depletion of haemostatic factors. DIC is usually triggered by the extrinsic coagulation pathway: tissue factor and factor VIIa (Fig. 22.7.5.1). The proinflammatory cytokine interleukin-6 (IL-6) is a principal mediator of DIC in septicaemia and other systemic inflammatory responses, and impairs natural anticoagulant and fibrinolytic pathways. For example, a sustained increase in PAI-1 impairs plasmin formation despite intravascular fibrin generation. Diagnostic and treatment approach to DIC One or more prolonged clotting times and thrombocytopenia in a pa- tient with one of the disorders listed in Table 22.7.5.5 suggests DIC. However, similar test results are seen in patients following major sur- gery, emphasizing the need to interpret the laboratory data in the ap- propriate clinical context. Typically, cross-linked fibrin degradation products, such as D-dimers, are greatly increased in DIC. Sometimes, specialized haemostasis assays are useful, for example, protein C and antithrombin activity levels in DIC complicated by shock liver and symmetrical peripheral gangrene/purpura fulminans. The cornerstone of management is treating its underlying cause and providing supportive measures. For bleeding patients, replace- ment of depleted haemostatic factors with

frozen plasma (or fresh frozen plasma), cryoprecipitate (or fibrinogen concentrate), and platelet transfusions may be needed. Heparin may benefit patients with large-vessel thrombosis or acral ischaemia. The routine use of vitamin K and folate will avoid coagulation and platelet count disturbances in some patients. Trauma and shock Tissue injury due to trauma, burns, or hypoperfusion (e.g. cardiogenic shock) can cause DIC. Head injury in particular can result in DIC with hypofibrinogenaemia, probably because of intravascular release of tissue thromboplastin from injured brain. Acute ischaemic hepatitis (shock liver) The combination of acute ischaemic hepatitis ('shock liver') and DIC (e.g. secondary to cardiogenic or septic shock) can explain is- chaemic limb gangrene despite palpable or Doppler-identifiable Table 22.7.5.5 Main causes of disseminated intravascular coagulation Acute DIC Trauma, burns Cardiogenic shock Infection, especially septic shock Obstetrical complications: • Placental abruption • Amniotic fluid embolism • Pre-eclampsia/eclampsia • Puerperal sepsis Malignancy, promyelocytic leukaemia Allergic reactions Severe heparin-induced thrombocytopenia Severe haemolysis Envenomation (e.g., snake bite) Chronic DIC Malignancy, especially metastatic adenocarcinoma Obstetrical complications: • Dead fetus syndrome Chronic liver disease Vascular anomalies: • Giant haemangioma (Kasabach–Merritt syndrome) • Aortic aneurysm

22.7.5 Acquired coagulation disorders 5553 peripheral arterial pulses. The term 'symmetrical peripheral gan- grene' is used when tissue necrosis primarily affects the distal ex- tremities (invariably, the feet; in one-third of patients, fingers/hands as well). When there is additional nonacral skin necrosis, the term 'purpura fulminans' is applicable. Acral (distal extremity) necrosis results from microthrombosis (capillaries, venules, arterioles). The pathophysiology includes (a) acute DIC; (b) depletion of nat- ural anticoagulants, protein C and antithrombin, secondary to in- creased consumption (DIC) and decreased synthesis (shock liver); and (c) poor acral blood flow secondary to hypotension. A major role for vasopressor therapy in causation of limb necrosis is probably overstated. Ischaemic limb necrosis typically begins approximately 2 to 5 days after onset of shock liver; thus, preceding 'shock liver' can be regarded as a 'warfarin equivalent' (as coumarin-induced microthrombosis too usually begins approximately 2 to 5 days after starting warfarin or another coumarin anticoagulant). Infection Gram-negative and Gram-positive bacteria can cause DIC, either from procoagulant bacterial components (e.g. endotoxin and Staphylococcus aureus toxin) or via the host response to infection (e.g. interleukin-6). The clinical spectrum ranges from prom- inent thrombocytopenia with minimal activation of coagulation, to marked coagulation factor and natural anticoagulant depletion. Certain infections, such as meningococcaemia and Capnocytophaga canimorsus (from dog bites), sometimes produce severe acquired consumptive protein C and/or antithrombin deficiency (usually with concomitant shock liver), which leads to widespread ischaemic necrosis of the extremities (symmetric peripheral gangrene) and elsewhere (purpura fulminans). Postvaricella purpura fulminans can be caused by acquired antiphospholipid antibodies that inter- fere with protein S. Obstetrical complications Acute DIC can be caused by thromboplastin-like materials re- leased during placental abruption or amniotic fluid embolism. Pre-eclampsia too can be accompanied by DIC, although there can be clinical and laboratory overlap with other life-threatening compli- cations of pregnancy (e.g. fatty liver of pregnancy and HELLP syn- drome (haemolysis, elevated liver enzymes, low platelets)). Bleeding due to hypofibrinogenaemia is often prominent in pregnancy- associated DIC. Chronic DIC can be caused by fetal death. Acute haemolysis Haemolysis caused by incompatible blood transfusions, certain infec- tions (e.g. Clostridium perfringens septicaemia), or microangiopathic disorders such as TTP and HELLP, can sometimes be associated with DIC. Immunological disorders (including HIT) Severe

allergic reactions (e.g. anaphylaxis), transplant rejection, glom- erulonephritis, and other vasculitic disorders are sometimes associated with DIC. Severe HIT can also be associated with overt DIC; in such patients, APTT-monitored therapies (e.g. argatroban, bivalirudin) can fail because the concomitant HIT-associated coagulopathy re- sults in supratherapeutic APTT levels upon beginning anticoagulant therapy, which leads to inappropriate dose interruptions/reductions and associated treatment failure (‘APTT confounding’). Vascular anomalies Giant haemangiomas cause overt DIC in about 25% of those affected (Kasabach–Merritt syndrome). Although activation of coagulation and fibrinolysis is localized to the vascular anomaly, depletion of haemostatic factors produces a clinical and laboratory profile indis- tinguishable from DIC. Eradication of haemangioma by radiation, embolization, or surgery is curative. Medical therapies have included heparin, antifibrinolytic drugs (combined with cryoprecipitate to thrombose the vascular tumour), glucocorticoids, and interferon. DIC also occurs in about 0.5 to 1% of patients with abdominal aortic aneurysms, which usually contain adherent thrombi. Immunoglobulin-mediated factor deficiency Coagulation factor inhibitors are usually IgG antibodies that bind to specific coagulation factors, and either neutralize their Tissue factor + factor VIIa Factor XIII Platelet activation THROMBIN Fibrinogen Increased thrombin generation via tissue factor Impaired natural anticoagulant mechanisms Factor IXa (factor VIII) Factor Xa (factor V) PC system X-FDPs (D-dimer) PLASMIN Impaired fibrinolysis via increased PAI-1 Plasminogen Plasminogen activator PAI-1 X–FDPs X–FDPs ATIII B A TFPI + + + + C Soluble fibrin Cross-linked (X) fibrin α2AP Fig. 22.7.5.1 Pathogenesis of thrombosis in DIC. (a) DIC is usually triggered by tissue factor, which activates coagulation by complexing with factor VIIa, ultimately resulting in the generation of thrombin. (b) Impaired natural anticoagulant mechanisms (e.g. excessive consumption of natural anticoagulants, or cytokine-mediated downregulation of natural anticoagulant pathways) predispose to microvascular thrombosis. (c) Impaired fibrinolysis via increased PAI-1 leads to greater microvascular thrombosis. Sometimes, hyperfibrinolysis is caused by increased plasminogen activator release, or low levels of α 2-antiplasmin. α 2AP, α 2-antiplasmin; ATIII, antithrombin III; fDPs, fibrinogen degradation products; FDPs, fibrin degradation products; PAI-1, plasminogen activator inhibitor type 1; PC, protein C; TFPI, tissue-factor pathway inhibitor.

section 22 Haematological disorders 5554 activity (most coagulation factor inhibitors) or result in accel- erated clearance (e.g. antiprothrombin antibodies associated with the antiphospholipid antibody syndrome). Acquired in- hibitors against coagulation factors are rare in otherwise normal (nonhaemophiliac) individuals. Even the most common auto- immune coagulation factor deficiency (factor VIII) has an esti- mated incidence of only 1 per 1 000 000 per year. Acquired factor VIII inhibitor Acquired factor VIII deficiency should be suspected in a patient with spontaneous bleeding, or bleeding following minor trauma, that oc- curs in association with a prolonged APTT and a normal PT/INR (Table 22.7.5.3). Most commonly, muscle or cutaneous haematomas occur, but life-threatening retroperitoneal or intracranial haemor- rhages are described; haemarthrosis is uncommon (cf. congenital haemophilia). The disorder occurs most commonly in older people (median age 60 years), affects men and women equally, and is idio- pathic in 50% of cases. Other autoimmune disorders (e.g. systemic lupus erythematosus), lymphoid and other malignancies, penicillin treatment, or the postpartum state, have been observed in some pa- tients. About 20% of patients die of bleeding, often from their initial bleeding episode. A rapid screening test for a coagulation factor inhibitor is per- formed by repeating the APTT after mixing patient plasma 50:50 with normal pooled plasma. An inhibitor is suggested by a prolonga- tion time more than 4 s over the control, although some inhibitors require a 2-h incubation at 37°C to show inhibition.

Confirmation is obtained by a specific factor assay showing reduced levels of factor VIII; inhibitor quantitation is most often performed by the Bethesda assay, in which various dilutions of patient plasma are mixed with normal plasma and incubated for 2 h at 37°C: a Bethesda unit is de- fined as the reciprocal of the plasma dilution that yields a 50% reduc- tion in residual factor VIII activity in the test system. Unfortunately, the Bethesda assay tends to underestimate the amount of inhibitor in nonhaemophiliac patients with acquired factor VIII inhibitors. Therapy of bleeding depends upon its severity and the amount of inhibitor present, if known. For patients with minor bleeding, detectable factor VIII levels, and low inhibitor levels (<5 Bethesda units), desmopressin (DDAVP) can be tried. Peak factor VIII levels occur between 45 and 90 min post DDAVP, and repeat levels should be measured to assess efficacy. In other patients with low inhibitor levels but with more severe bleeding, purified human factor VIII concentrates are usually effective. One approach is to give an ini- tial intravenous bolus of 100 U/kg, followed by a continuous infu- sion of factor VIII at 10 U/kg per h, with factor VIII levels measured again 4 to 6 h later. Careful clinical and laboratory assessment for response is needed, since inhibitor levels may have been under- estimated, or higher inhibitor levels stimulated by factor VIII use. Either PCCs or recombinant factor VIIa can be given for patients refractory to human factor VIII. Activated PCC (e.g. FEIBA or Autoplex) are more effective than nonactivated PCCs, but con- comitant antifibrinolytic therapy should be avoided to reduce risk of thromboembolic complications. Recombinant factor VIIa may be preferable for perioperative management, since the risk for inducing postoperative thrombosis is probably lower. In desperate situations, extracorporeal immunoadsorption using staphylococcal protein A may be helpful in removing the antibodies. Spontaneous disappearance of the inhibitor occurs in about 10 to 30% of patients, most commonly in the patient who developed her inhibitor postpartum. Nevertheless, the unpredictable clin- ical course, and the potential for life-threatening bleeding, means that immunosuppressive therapy should be given to most patients. The most widely adopted treatment is with corticosteroids (pred- nisolone, 1 mg/kg daily) in combination with cyclophosphamide (1–2 mg/kg daily), which eradicates the inhibitor in about 70% of cases. A more recent alternative is the anti-CD20 monoclonal antibody rituximab, which has been used successfully in many autoimmune conditions; the regimen consists of four separate intravenous infusions (375 mg/m2 each), given at weekly intervals. Other options include combination chemotherapy (prednisone, cyclophosphamide, vincristine); ciclosporin; or high-dose intra- venous IgG (1 g/kg for 2 days, or 0.4 g/kg for 5 days). Even partial remission can help reduce bleeding. Women with postpartum factor VIII inhibitors usually develop remission within 30 months, and only rarely develop recurrent factor VIII inhibitors with later pregnancies. They also may be less likely to respond to corticoster- oids or other immunosuppressive therapy. Other acquired coagulation factor deficiencies Hypoprothrombinaemia This should be suspected in patients with the antiphospholipid anti- body syndrome, particularly if bleeding occurs or the PT/INR is prolonged. Typically, these pathogenic antifactor II antibodies are non-neutralizing, and therefore mixing patient plasma 50:50 with normal pooled plasma can produce correction of the APTT, in con- trast to other coagulation factor inhibitors. Thrombin inhibitors These are rare, but may cause severe bleeding. More often, pa- tients have antibodies that react preferentially against bovine thrombin: these are formed following the use of ‘fibrin glue’, which contains various bovine clotting factors. Patients have prolonged PT/INR, APTT, and TCT (especially using bovine thrombin). However, it is more likely that any bleeding is the result of clinically significant antibovine factor V antibodies. Factor V inhibitors Rarely, IgG antibodies against factor V arise spontaneously or following treatment with topical bovine thrombin used at sur- gery. Fresh frozen plasma usually does not provide enough factor V to treat bleeding; however, platelet transfusions can be ef-

fective, as platelet activation causes factor V to be released into haemostatic plugs. Factor XIII inhibitors These inhibitors, which sometimes occur in association with iso- niazid therapy, cause bleeding via impaired factor XIII-mediated cross-linking of fibrin. Factor XIII should be measured in a patient with unexplained bleeding and normal results of screening coagu- lation assays. Factor X inhibitors Factor X inhibitors are a rare cause of bleeding in patients with pro- longed PT/INR and APTT. The differential diagnosis also includes

22.7.5 Acquired coagulation disorders 5555 amyloidosis of the AL (amyloid light chain) variety, caused by ad- sorption of factor X to amyloid fibrils. Factor IX inhibitors In nonhaemophiliac patients, factor IX inhibitors are rare and usu- ally associated with autoimmune disease. Treatment includes PCCs or purified factor IX, and immunosuppression. The differential diag- nosis of acquired, isolated, factor IX deficiency includes the neph- rotic syndrome (urinary loss of factor IX). Factor XI inhibitors These rare inhibitors are most often observed in association with systemic lupus erythematosus, and usually do not cause bleeding or require specific treatment. Factor VII inhibitors Factor VII inhibitors are extremely rare, and usually do not cause bleeding or require treatment. The diagnosis is suggested by an iso- lated prolonged PT/INR in the absence of coumarin or vitamin K deficiency. Acquired von Willebrand syndrome Rarely, bleeding is caused by a severe acquired deficiency of VWF, most often in the setting of a monoclonal gammopathy, benign or malignant. Typically, there is disproportional deficiency of the largest VWF multimers due to antibody-mediated clearance (acquired type 2A von Willebrand syndrome). Aortic stenosis and obstructive cardiomyopathies are other causes of type 2A von Willebrand syndrome: this explains why aortic valve re- placement can cure Heyde's syndrome (aortic stenosis associ- ated with recurrent gastrointestinal haemorrhage secondary to angiodysplasia). Heparin and acquired heparin-like anticoagulants Bleeding is a complication of heparin treatment, particularly when the APTT is above the therapeutic range. In patients with massive accidental or deliberate heparin overdose, intravenous protamine can be given to treat bleeding complications. Rarely, patients with spontaneous bleeding and prolonged APTT and TCT measurements have circulating heparin-like anticoagu- lants. Usually associated with plasma cell myeloma and other plasma cell dyscrasias, the coagulopathy does not necessarily respond even to large-dose protamine infusion, and fatal haemorrhage can ensue. Circulating dermatan sulphate glycosaminoglycan appeared to ex- plain the bleeding in a patient with renal failure. Coagulopathies secondary to plasma cell dyscrasias Plasma cell myeloma, macroglobulinaemia, and other plasma cell dyscrasias such as primary amyloidosis can cause various coagulopathies (Box 22.7.5.3). Usually, the TCT is prolonged, most often because of paraprotein-induced interference with fibrin polymerization. A distinct syndrome is monoclonal paraprotein- associated acquired von Willebrand syndrome type 2A, in which high-dose intravenous IgG corrects VWF levels for several days or a few weeks (helpful for managing acute bleeding or before surgery). In some patients, apheresis can improve haemostasis by quickly reducing paraprotein levels, as antineoplastic chemo- therapy is initiated. Hyperfibrinolysis Activation of fibrinolysis occurs normally when fibrin clots are formed during physiological or pathological haemostasis. However, primary fibrinolysis (Table 22.7.5.3) is sometimes the major cause for bleeding, and requires specific treatment. Thrombolytic therapy About 0.5 to 0.7% of patients with myocardial infarction who re- ceived thrombolysis with either streptokinase or tissue plasminogen activator develop an intracranial haemorrhage. The thrombolytic agent should be stopped immediately in any such patient, and they should receive cryoprecipitate and an antifibrinolytic drug (e.g. tranexamic acid); platelets and frozen plasma (or fresh frozen plasma) can help to increase factor V and VIII levels that may have been reduced by

plasmin generated by thrombolysis. It can take between 24 and 36 h for fibrinogen levels to recover after stopping thrombolytic therapy. Malignancy Cancer-associated DIC usually causes a hypercoagulable state. However, promyelocytic leukaemia and prostatic adenocarcinoma are two malignancies commonly associated with prominent hyperfibrinolysis. Laboratory abnormalities include prolonged PT/ INR, APTT, TCT, and hypofibrinogenaemia. The use of all-trans- retinoic acid during induction chemotherapy of promyelocytic leukaemia has reduced the frequency of life-threatening bleeding. Antifibrinolytic therapy can control bleeding in cancer-associated hyperfibrinolysis. Cardiopulmonary bypass surgery Excess bleeding, defined as more than 1 litre per procedure, is a common problem following heart surgery utilizing cardiopul- monary bypass (extracorporeal circulation). About 20% of all red cell concentrates in the United States of America are given for cardiac surgical bleeding. About 5% of patients require urgent resternotomy for critical rates of blood loss (defined as >500 ml in the first 1 h;

> 400 ml/h in the first 2 h; >300 ml/h in the first 3 h; or >1 litre in 4 h). Re-exploration reveals bleeding vessels in two-thirds of patients; the remainder have diffuse oozing. Thrombocytopenia, transient platelet dysfunction, and hyper fibrinolysis are the principal haemostatic defects. Typically, the platelet count falls by between 30 and 60% mainly from haemodilution, al- though platelet losses from bleeding and within the extracorporeal perfusion device also occur. The thrombocytopenia persists for 3 to Box 22.7.5.3 Haemostatic abnormalities associated with dysproteinaemias • Interference with fibrinogen polymerization • Isolated factor deficiency:

— Factor X, fibrinogen, or α2-antiplasmin deficiency (amyloidosis)

— Acquired von Willebrand syndrome (monoclonal gammopathy) • Hyperviscosity (compromising vascular integrity) • Circulating glycosaminoglycan (heparin-like inhibitor) • Thrombocytopenia secondary to:

— marrow failure (disease or treatment related)

— autoimmune thrombocytopenia • Platelet dysfunction

section 22 Haematological disorders 5556 4 days, followed by recovery of the platelet count to values exceeding the preoperative baseline. Marked prolongation of the bleeding time (>30 min) quickly improves to under 15 min shortly after surgery, and to normal several hours later. Some platelet function defects are ‘extrinsic’ and reversible (e.g. hypothermia, heparin), whereas others indicate longer-lasting ‘intrinsic’ changes (surface glycopro- tein deficiency, acquired granule depletion). Preoperative treatment with aspirin, clopidogrel, or ticagrelor also increases bleeding; un- like with aspirin or clopidogrel, platelet transfusions are not usually effective for bleeding associated with ticagrelor. The importance of hyperfibrinolysis in postcardiac surgical bleeding is highlighted by meta-analysis of studies of high-dose aprotinin, a plasmin inhibitor derived from bovine lung: a two-thirds reduction in blood transfusion, and 50% reduction in resternotomy. However, aprotinin is now infrequently used because of concerns regarding its adverse effect

profile. Other antifibrinolytic drugs that reduce bleeding include the lysine analogues, tranexamic acid (e.g. 10 mg/kg bolus before cardiopulmonary bypass; then 1 mg/kg per h, although dosing regimens vary widely) and ε-aminocaproic acid (total dose up to 20 g). Although these therapies are usually given before cardiopulmonary bypass, they may also provide benefit when used postoperatively for bleeding patients. Management of postcardiac surgical bleeding also includes blood transfusions, especially platelets and frozen plasma, although their benefit is unproven. Residual heparin, including heparin 'rebound', can respond to additional protamine. Desmopressin probably is in- effective. No universally accepted algorithm for management exists. Liver disease Hyperfibrinolysis complicating liver disease is discussed elsewhere. Venom-induced coagulopathies (snake bites) Envenomations can harm or kill humans generally through sys- temic effects (e.g. profound hypotension) (see also Chapter 10.4.2). Sometimes, however, life-threatening coagulopathies result. Snake bites In the United States of America, about 8000 bites from venomous snakes occur each year, resulting in 10 to 20 deaths. This relatively low mortality reflects the less lethal character of New World snakes, as well as the victim's usual close proximity to medical facilities and antivenin therapy. Pit vipers (rattlesnakes, copperheads, cotton- mouths, massasaugas) account for 99% of snakebite poisonings in the United States of America. Worldwide, annually over 100 000 people are estimated to die from snakebite, many in India. Although death usually results from multiple mechanisms (such as circulatory shock, rhabdomyolysis, renal failure, pulmonary failure, and neuro- toxicity), bleeding is sometimes the major factor. Venoms contain multiple digestive enzymes with a broad spec- trum of activity that can include effects on human haemostasis (Table 22.7.5.6). Within a species, haemostatic effects of envenom- ation vary with snake age, diet, and other factors. North American rattlesnakes typically cause the 'defibrination syndrome'; despite even profound hypofibrinogenaemia, bleeding is uncommon. In contrast, venom from Old World vipers frequently cause generalized activation of the coagulation system (DIC), with a greater chance of bleeding or microvascular thrombosis. Bleeding can also result from platelet inhibitors present within venom; for example, the platelet fibrinogen receptor antagonist echistatin (from Echis carinatus), or 'haemorrhagins' such as jararhagin (from Bothrops jararacussu) that damage endothelium. Immediate treatment of a snake bite includes efforts to limit the venom spread (immobilizing and placing a constriction band prox- imal to the bite site). Rapid transport to medical facilities is crucial since antivenin therapy is the mainstay of treatment. Antivenin treatment is indicated for patients with significant pain or swelling, as well as suspected or proven haemostasis abnormalities, as these indicate envenomation rather than a 'dry bite'. Hypersensitivity testing to the antivenin should be performed to rule out pre-existing hypersensitivity to horse serum. The treatment of snake bite is dis- cussed in Chapter 10.4.2. Coagulation studies should include complete blood count (including platelets), PT/INR, APTT, TCT, fibrinogen, and FDPs. Abnormal results indicate envenomation, and are an indication for antivenin therapy. The bedside assessment of defibrination involves placing a few millilitres of blood in a clean, dry test tube at room temperature for 20 min; incoagulable blood indicates defibrination. Usually, blood products should only be given to patients with bleeding. A small clinical trial found that heparin was ineffective in patients with DIC caused by a Russell's viper bite. Laboratory and therapeutic uses of snake venoms Snake-venom fractions are useful for certain laboratory assays. For example, the thrombin-like enzyme batroxobin (reptilase, Bothrops atrox and moojeni), cleaves fibrinopeptide A from fibrinogen even in the presence of heparin. Thus, a prolonged reptilase time indicates hypofibrinogenaemia even in heparin-containing plasma. Ecarin activates prothrombin irrespective of its γ-carboxylation status; thus, it can be used to detect proteins induced by vitamin K ant- agonists to document vitamin K deficiency or dysprothrombinaemia. An ecarin clotting time

is superior to the APTT for monitoring therapy with hirudin (no longer marketed) or other direct thrombin inhibitors (e.g., argatroban). Differences in phospholipid dependency of venom prothrombin activators have led to the use of a Textarin/ ecarin ratio to detect lupus anticoagulants; a ratio over 1.3 is a sensitive and relatively specific test for lupus anticoagulants. Russell's viper venom contains a potent activator of factor X (RVV- X); the dilute Russell's viper venom time (dRVVT), performed by adding RVV-X and diluted rabbit brain phospholipid to test plasma prior to recalcification, measures the rate of formation and activity of the phospholipid-dependent prothrombinase complex in produ- cing thrombin. The dRVVT is thereby prolonged in the presence of a lupus anticoagulant. A commercially available protein C activator (Protac) from Agkistrodon contortrix contortrix (the southern copperhead) has greatly simplified assays for protein C activity, as well as in screening for defects in the protein C anticoagulant pathway. The defibrinogenating snake venom ancrod (Arvin, derived from the Malayan pit viper Calloselasma [Agkistrodon] rhodostoma), which proteolyses fibrinopeptide A, was formerly used for manage- ment of HIT, acute stroke, thrombotic nephropathy, and priapism. The inability to control thrombin generation is a potential drawback of this therapy. Batroxobin (Defibrase) is another defibrinogenating venom that has seen limited clinical applications.

22.7.5 Acquired coagulation disorders 5557 Prothrombotic-acquired coagulation disorders Some acquired coagulation disorders are characterized by an in- creased risk for thrombosis, rather than bleeding. Accordingly, the appropriate treatment usually involves anticoagulant therapy, even if there are abnormal coagulation or platelet count values. Macrovascular thrombosis Some acquired coagulation disorders typically cause thrombosis in large veins and arteries, although small-vessel thrombi can also result. Heparin-induced thrombocytopenia HIT is caused by IgG antibodies that recognize multimolecular com- plexes of platelet factor 4 (PF4) and heparin. Thrombosis results from IgG-induced platelet activation (via platelet Fc receptors), resulting in the generation of procoagulant, platelet-derived microparticles, tissue factor expression by monocytes, and inactivation of heparin by PF4 released from platelets. Increased thrombin–antithrombin complex levels indicate DIC in almost all patients with this condi- tion, although a prolonged INR and/or APTT and/or low fibrinogen level occurs in only approximately 20% of cases. Typically, the fall in platelet count begins 5 to 10 days after starting heparin ('typical-onset' HIT); however, in patients who received heparin within the past 5 to 100 days, the platelet count can fall abruptly upon resuming heparin therapy ('rapid-onset' HIT), be- cause of residual circulating antibodies. HIT occurs in approxi- mately 0.2% of heparin-treated patients (but up to 5% of certain high-risk populations: e.g. postoperative orthopaedic patients re- ceiving unfractionated heparin for over 1 week). HIT is less frequent in patients initially treated with low molecular weight heparin or fondaparinux. HIT antibodies are remarkably transient; moreover, HIT does not usually recur with future heparin exposure, although Table 22.7.5.6 Venom-induced coagulopathies (selected examples) Animal source of venom Main biological effects (trivial name of venom component in bold) Comments Main distribution Venomous snakes Family Viperidae Subfamily crotalinae (pit vipersa) Crotalus adamanteus (Eastern diamondback rattlesnake) Crotalase: cleaves FPA, but not FPB, from fibrinogen (decreased fibrinogen, plasminogen; increased FDPs) 'Thrombin-like' based upon fibrinopeptide A cleavage, but does not activate platelets or factor XIII; despite 'defibrination syndrome', bleeding is uncommon USA (coastal plain from Florida to Mississippi) Crotalus atrox (Western diamondback rattlesnake) Catroxobin: cleaves FPA from fibrinogen; other fibrinogenase activities Also causes defibrination syndrome, usually without bleeding; venom also contains catrocollastatin-C (platelet inhibitor) USA (California to Arkansas); Mexico Calloselasma

[Agkistrodon] rhodostoma (Malayan pit viper) Ancrod: cleaves FPA from fibrinogen Purified ancrod previously used as an antithrombotic agent Southeast Asia Subfamily viperinae (true vipersa) Echis carinatus (saw-scaled viper) Ecarin: activates prothrombin and platelets Causes DIC, often with bleeding; most common cause of snake-bite mortality in the African savannah India, Africa, Asia Daboia russelli (Russell's viper, formerly, Vipera russelli) Russell's viper venom: activates factor X Causes DIC, often with bleeding; venom also causes direct nephrotoxicity Far East Bothrops jararacussu (jararacucu, lance-headed pit viper) • Botrocetin: platelet agglutination via VWF; • Jararhagin: haemorrhagin Venom also contains thrombin-like and factor Xa-activating enzymes, and can cause severe bleeding Brazil Family Elapidaeb Notechis scutatus (tiger snake) Notecarin: activates prothrombin Fatal haemorrhage has been reported Australia Family Colubridaec Nonsnake envenomations that cause coagulopathy Lonomia achelous (caterpillar) Proteolysis of factor XIII; reduced fibrinogen, factor V, plasminogen, and increased FDPs also observed Severe bleeding in humans (wound site, mucous membranes, and internal haemorrhage) Venezuela, Brazil Loxosceles reclusa (brown recluse spider) Activation of endothelium, with resulting dysfunction of interactions with PMNs Potential for severe skin lesions; systemic effects (DIC, haemolytic anaemia) occur in small minority of patients Midwest USA Two other families of venomous snakes (Hydrophiidae and Atractaspididae) do not cause coagulopathies. a Pit vipers are New World snakes named for the heat-sensitive pit located between the eye and the nostril that enables the snake to detect warm-blooded prey even in darkness: the three genera of the Crotalidae family that inhabit the USA are Crotalus (rattlesnakes), Agkistrodon (moccasins, including the copperheads and cottonmouths), and Sistrurus (massasaugas and pigmy rattlesnakes). b With the exception of several Australian species, such as taipan, tiger snakes, brown snakes, and black snakes, elapid snake bites usually cause neurotoxicity, and only occasionally result in haemostatic abnormalities. c The colubrid family includes boomslang, vine snake, keel backs, and the South American 'green snake,' which can also cause bleeding.

section 22 Haematological disorders 5558 deliberate re-exposure is usually restricted to special situations (e.g. cardiac or vascular surgery), and only if platelet-activating anti- bodies are no longer detectable. Most patients with HIT develop venous or arterial thrombosis (Fig. 22.7.5.2), most commonly a DVT, pulmonary embolism, major limb artery thrombosis, stroke, or myocardial infarction. Acute or chronic adrenal failure from bilateral adrenal haemorrhagic necrosis (manifestation of adrenal vein thrombosis) has been described. The thrombocytopenia is typically moderate in severity (median platelet count nadir 60 × 109/litre), and in only 10% of patients does the platelet count fall to less than 20 × 10 /litre. In at least 10% of patients, the platelet count never drops below 150 × 109/litre. This degree of thrombocyto- penia in HIT is much less marked than observed in classic immune- mediated drug-induced thrombocytopenia (Fig. 22.7.5.2). Laboratory testing for HIT antibodies includes activation and antigen assays. The former assays detect antibodies via their platelet- activating properties; the best platelet activation assays utilize washed platelets, for example, the serotonin-release assay (SRA) and the heparin-induced platelet activation (HIPA) test. Commercially available antigen assays detect antibodies that bind to surface-immo- bilized PF4 complexed to heparin or polyvinylsulphonate. Antigen assays are more likely to detect clinically insignificant antibodies, with the potential for a false-positive diagnosis of HIT. Recently, automated HIT assays that give results within 30 minutes of plasma preparation have become available. Treatment includes stopping heparin and instituting alternative nonheparin anticoagulation. Coumarin should not be given to pa- tients during the acute (thrombocytopenic) phase of HIT; particu- larly in those with associated DVT, there is substantial risk of limb loss due to

microvascular thrombosis (coumarin-induced venous limb gangrene). Thus, coumarin therapy should be postponed until the platelet count has recovered to at least 150 × 109/litre, and only then cautiously overlapped (over at least 5 days) with an agent that inhibits thrombin (or its generation). Suitable rapidly-acting anticoagulants include danaparoid (a low molecular weight mixture of glycosa- minoglycans with predominant antifactor Xa activity), fondaparinux (a synthetic antithrombin-dependent factor Xa inhibitor modelled after the crucial pentasaccharide sequence within active heparin), argatroban (a synthetic small-molecule direct thrombin inhibitor), and bivalirudin (a synthetic 20-amino acid analogue of hirudin). Argatroban and bivalirudin dose adjustments are generally per- formed using APTT monitoring. In contrast, fondaparinux and danaparoid do not require APTT monitoring, an advantage that avoids potential for 'APTT confounding', which refers to the situation where APTT-monitored therapies (e.g. argatroban and bivalirudin) fail in patients with HIT-associated DIC, as supratherapeutic APTT levels (reflecting HIT-associated coagulopathy rather than indicating overanticoagulation) lead to inappropriate dose interruptions/reduc- tions, with subsequent progression of thrombosis (including micro- vascular thrombosis/limb necrosis). DOACS (e.g., rivaroxaban, 3 10 20 50 100 200 500 1000 5 No. of Patients (arbitrary units, increasing from bottom to top) Bleeding Thrombosis ~10 x 109/L (median) Heparin-induced thrombocytopenia Nadir Platelet Counts (x10−9/L) Shown on a Log10 Scale Drug-induced immune thrombocytopenia ~60 x 109/L (median) Fig. 22.7.5.2 Nadir platelet counts shown on a log10 scale: comparison of heparin-induced thrombocytopenia versus 'classic' drug-induced immune-mediated thrombocytopenic purpura (e.g. caused by quinine or vancomycin). Whereas the latter typically produces severe thrombocytopenia (median platelet count nadir c.10 × 109/litre), heparin-induced thrombocytopenia usually results in mild-to-moderate thrombocytopenia (20–150 × 109/litre in c.80% of patients; median platelet count nadir c.60 × 109/litre). Thrombosis occurs in 50% or more of patients with heparin-induced thrombocytopenia, whereas drug-induced thrombocytopenia manifests as purpura and other mucocutaneous haemorrhage. From Warkentin TE (2007). Drug-induced immune-mediated thrombocytopenia—from purpura to thrombosis. N Engl J Med, 356, 891–3, with permission.

 apixaban) can be used to treat HIT; their fixed dosing regimens avoid this problem of PTT confounding. Among patients with HIT, low molecular weight heparin (LMWH) treatment has a high risk for clinical cross-reactivity, and should be considered a contraindicated treatment for acute HIT. Some patients benefit from selected ad- junctive treatments, such as high-dose intravenous immunoglobulin (which interrupts HIT antibody-induced platelet activation). The dramatic natural history of HIT, with a risk for subsequent throm- bosis of about 50% even after stopping heparin, means that an al- ternative anticoagulant, together with DVT surveillance, should be considered for all patients strongly suspected to have HIT. Future use of heparin and LMWH is usually avoided in patients with a history of HIT (as suitable nonheparin anticoagulant options usually exist); however, the risk of HIT recurrence appears to be low, and for some situations (particularly cardiac and vascular surgery), intraoperative anticoagulation with UFH is recommended, provided that platelet- activating antibodies are no longer present. Protamine-induced thrombocytopenia Recently, a prothrombotic disorder associated with platelet-activating IgG antibodies that recognize protamine/heparin complexes has been reported. Cases have included diabetic patients who developed marked thrombocytopenia and other complications after receiving protamine sulphate to reverse heparin anticoagulation after cardiac surgery; apparent triggers of immunization may have included pre- operative LMWH thromboprophylaxis in the setting of protamine- insulin therapy. Adenocarcinoma-associated chronic DIC Metastatic

adenocarcinoma sometimes presents as venous or ar- terial thrombosis accompanied by DIC. The diagnosis is suggested by an unexpected rise in the platelet count during heparin treatment, followed by an abrupt platelet count fall, together with new or pro- gressive thrombosis, when heparin is stopped, despite therapeutic anticoagulation with warfarin. The clinical situation can mimic HIT ('pseudo-HIT'), but HIT antibodies are absent (or weakly detect- able), and the platelet count recovers during resumption of heparin (Fig. 22.7.5.3). Oral anticoagulants are ineffective, and may even cause venous limb gangrene (discussed subsequently). Heparin, es- pecially LMWH, is the preferred treatment. Tissue factor-containing tumour vesicles, and factor Xa-activating enzymes found in tumour extracts, are two possible explanations for these procoagulant effects of adenocarcinoma. Antiphospholipid antibody syndrome ('lupus anticoagulant') This clinicopathological syndrome is characterized by large-vessel venous and/or arterial thrombosis, recurrent miscarriages, and thrombocytopenia. An associated 'lupus anticoagulant' (or 'non-specific inhibitor') is a prolonged APTT that results from the inter- ference by antibodies against phospholipid-dependent coagulation reactions; these antiphospholipid antibodies are usually directed against protein cofactors such as β2-glycoprotein I and prothrombin. Sometimes a prolonged PT/INR is caused by non-neutralizing antiprothrombin antibodies that cause hypoprothrombinaemia by increased prothrombin clearance. Despite these laboratory abnormalities, bleeding is unusual, since severe thrombocytopenia or hypoprothrombinaemia is un-common. More often, antiphospholipid antibodies are associated with intermittent thrombosis, and patients often require long-term anticoagulation. The explanation for the paradoxical association with thrombosis remains elusive, but it could be caused by antibody interactions with other protein cofactors described (e.g. activated protein C, protein S, and thrombomodulin). Many patients have a thrombocytopenia that is typically mild and intermittent. Other less common complications include cardiac valvulitis and microvascular thrombosis, which can manifest as acrocyanosis, digital ulceration/ gangrene, and livedo reticularis. Rarely, the abrupt onset of life- threatening multiple large- and (especially) small-vessel vascular oc- clusions occurs ('catastrophic antiphospholipid syndrome' [CAPS]); potential treatments include heparin, high-dose corticosteroids, high-dose intravenous immunoglobulin, and/or plasma exchange. Antiphospholipid antibodies are detected by enzyme-immunoassay using purified phospholipids as the target antigen (e.g. the anti cardiolipin antibody assay). Lupus anticoagulant activity is shown by demonstrating inhibition of phospholipid-dependent coagulation assays. Several assays should be performed, as anti-β2 glycoprotein I antibodies especially interfere with the conversion of prothrombin to thrombin (i.e. best detectable by the dilute Rusell's viper venom time), whereas antiprothrombin antibodies interfere most with global coagulation assays (e.g. kaolin clotting time). The coagulation times remain prolonged following mixing with normal plasma; confirm- ation involves adding excess phospholipid to neutralize the effects of the antiphospholipid antibodies. Not all APTT reagents are sensitive to antiphospholipid antibodies, and so these phospholipid-dependent coagulation assays should be performed in the appropriate clinical situation, even if the APTT is normal. The term 'lupus anticoagulant' refers to the frequent occurrence of these antibodies in patients with systemic lupus erythematosus; nevertheless, most patients with the antiphospholipid antibody 400 1000 800 600 Days after starting heparin

- Platelet fall and new PE when UFH held for liver biopsy

5. Clinical and platelet count improvement upon restarting UFH 200 0 0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60 UFH Warfarin Ancrod Negative HIT tests (SRA)

6. R leg phlegmasia and new PE when INR = 6.5
7. Abrupt platelet count fall off heparin
8. Rising platelet count on UFH
9. R leg DVT, PE Pseudo-HIT cycle repeated Recurrent R leg phlegmasia and new PE with an INR = 4.0 UFH UFH Warfarin UFH

Fig. 22.7.5.3 Pseudo-HIT. Adenocarcinoma with thrombocytopenia and phlegmasia cerulea dolens after stopping unfractionated heparin. The timing of thrombocytopenia onset suggested heparin-induced thrombocytopenia prompting the use of an alternative anticoagulant (ancrod). Heparin was restarted when PF4/heparin antibodies were not detected by activation assay (serotonin-release assay (SRA)). Subsequently, heparin discontinuation led to the recurrence of thrombocytopenia and warfarin-associated phlegmasia cerulea dolens (repeat of pseudo-HIT cycle). DVT, deep venous thrombosis; INR, international normalized ratio; PE, pulmonary embolism.

section 22 Haematological disorders 5560 syndrome do not have systemic lupus erythematosus. Some pa- tients have other autoimmune disorders, malignancy, infections, or procainamide treatment, but usually no associated condition is identified (primary antiphospholipid antibody syndrome). Many patients require long-term anticoagulation. Corticosteroids can benefit patients with bleeding caused by hypoprothrombinaemia. Microvascular thrombosis Some disorders of haemostasis are characterized by small-vessel thrombi, affecting either small venules (e.g. coumarin-induced ne- crosis) or capillaries/post-capillary venules (DIC with severe de- pletion of natural anticoagulants, protein C, and antithrombin) or arterioles (e.g. TTP). Coumarin-induced skin necrosis Coumarin-induced skin necrosis (CISN) is characterized by ne- crosis of the skin and underlying subcutaneous tissues that typ- ically begins 2 to 5 days after commencing warfarin or coumarin anticoagulants. CISN results from failure of the protein C natural anticoagulant system to downregulate thrombin generation in the microvasculature. The relatively short half-life of protein C, com- pared with prothrombin, explains the temporal profile of CISN—that is to say, a transient period of disproportionately reduced protein C activity soon after starting coumarin (Table 22.7.5.7). Furthermore, a relatively high proportion of affected patients have a hereditary ab-normality of the protein C anticoagulant pathway, especially protein C deficiency. Other disorders associated with CISN include con- genital deficiency in protein S or antithrombin, factor V Leiden, and HIT. The pathology is a predominantly noninflammatory, small- vessel thrombosis affecting the subcutaneous postcapillary venules and small veins. CISN characteristically affects central (nonacral) sites with sub- stantial underlying fatty tissues, such as the breast, buttocks, hips, and thighs (Fig. 22.7.5.4). Less common areas include the anterior abdomen, flank, back, penis, legs, arms, and face. About 75% of pa- tients are women; one-third have multiple lesions that can be sym- metrical. The earliest features are localized pain, induration, and erythema; over the next few hours, the skin lesions progress to cen- tral purplish or black discoloration, with blistering, subsequently demarcating to full-thickness skin necrosis. CISN is rare (1/10 000 patients treated with warfarin). Prompt reversal of anticoagulation with vitamin K may prevent incipient CISN if recognized early. However, the diagnosis is usually not made until necrosis is established; at this point, it is unknown whether vitamin K, fresh frozen plasma, or protein C concentrates alter its natural history. In patients without HIT, warfarin is usually replaced by heparin. Many patients require surgical treatment, such as skin grafting or tissue amputation. Following recovery, it is usu-ally safe to reintroduce warfarin provided certain precautions are taken, for example, the gradual

initiation of oral anticoagulation. Coumarin-induced venous limb gangrene Venous limb gangrene involves the acral (peripheral) regions of the body—most often the toes, feet, and legs, but sometimes also the fingers, hands, and arms—usually in association with DVT. The severity ranges from an initial stage of phlegmasia caerulea dolens (‘swollen, blue, painful’ limb) to extensive venous limb gangrene re- quiring limb amputation. Two disorders predispose to coumarin- induced venous limb gangrene: HIT and cancer-associated DIC. Recent data suggest that the supratherapeutic INR (typically >3.5) that characterizes venous limb gangrene is caused by a severe re- duction in factor VII, which parallels a severe reduction in protein C activity that explains the microvascular thrombosis underlying this syndrome. Essentially, coumarin interferes with the protein C anticoagulant pathway, while at the same time it is unable to con- trol the increased thrombin generation characteristic of HIT or cancer-associated DIC. Purpura fulminans and symmetrical peripheral gangrene Purpura fulminans is a rare syndrome of DIC and microvascular thrombosis that results in multicentric ischaemic necrosis of the skin and subcutaneous tissues, predominantly affecting the extrem- ities (Fig. 22.7.5.5). The most common cause is overwhelming septi- caemia, especially with meningococcus. A severe, acquired reduction Table 22.7.5.7 Half-lives of vitamin K-dependent procoagulant and anticoagulant factors Procoagulant factors Half-life (h) Anticoagulant factors Half-life (h) Factor II (prothrombin) 60 Protein C 9 Factor X 40 Protein S 40−60 Factor IX 24 Factor VII 4−6 The longer half-life of the major procoagulant vitamin K-dependent factor (factor II, or prothrombin), compared with the major vitamin K-dependent natural anticoagulant factor (protein C), is relevant to the pathogenesis of CISN (see text). ‘Classic’ CISN (central skin necrosis) DVT DVT Venous limb gangrene Fig. 22.7.5.4 Coumarin-induced skin necrosis: ‘classic’ syndrome (usually affecting central tissue sites) and coumarin-induced venous limb gangrene. Typically, an active DVT subtends the distal extremity affected by venous limb gangrene. From Warkentin TE (1996). Heparin-induced thrombocytopenia IgG-mediated platelet activation, platelet microparticle generation, and altered procoagulant/ anticoagulant balance in the pathogenesis of thrombosis and venous limb gangrene complicating heparin-induced thrombocytopenia. Transfus Med Rev, 10, 249–58, with permission.

22.7.5 Acquired coagulation disorders 5561 in protein C activity complicating DIC is the most likely cause for the microvascular thrombosis, and some experts recommend treat- ment with protein C concentrates, if available. Autoantibodies against protein S have been implicated in patients with postvaricella purpura fulminans. In other patients with apparent ‘idiopathic’ purpura fulminans, autoantibodies that interfere with the protein C anticoagulant system have been described. Peripheral symmetric gangrene is a term sometimes used when acral regions of two or more limbs are affected (Fig 22.7.5.5). More recently, a role for acute ischaemic hepatitis (‘shock liver’) in predisposing to microvascular thrombosis and ischaemic limb necrosis/central skin necrosis sec- ondary to natural anticoagulant (protein C, antithrombin) depletion in DIC of critical illness with circulatory shock has been reported. Septicaemia and other systemic inflammatory response syndromes Multiple organ failure often complicates septicaemia and other systemic inflammatory disease syndromes, including adult re- spiratory distress syndrome, fat embolism, and acute pancreatitis. Thrombocytopenia and coagulopathy are common, and some pa- tients have DIC that could contribute to organ dysfunction via microvascular thrombosis. However, a prothrombotic basis for organ failure is usually speculative, as microthrombosis is rarely documented pathologically, and nonthrombotic microvascular dis- turbances that impair tissue oxygen delivery also occur. Thrombotic microangiopathy Thrombotic microangiopathy is a clinicopathological syndrome of microangiopathic haemolysis and thrombocytopenia carrying a risk

for arteriolar occlusion by microaggregates of platelets and VWF, particularly affecting the kidneys and central nervous system. Microangiopathic red cell changes are characteristic, for example, ‘helmet cells’ (schistocytes) and small, triangular red cell fragments. The prototypic illness is TTP, which typically affects adults and is idiopathic. However, familial and secondary forms of TTP also exist. The pathogenesis of TTP involves the formation of platelet–VWF microaggregates in high-shear situations (arterioles). Platelet- bound VWF levels are increased during TTP. Patients with familial TTP have ultralarge multimers of VWF during remission; these very large multimers disappear during active disease. A constitutional deficiency of a VWF-cleaving metalloproteinase (ADAMTS13) has been identified in patients with familial TTP. In many patients with nonfamilial TTP, an IgG autoantibody, which inhibits the VWF- cleaving metalloproteinase, has been identified. The mainstays of treatment for acute TTP are corticosteroids and frozen plasma (or fresh frozen plasma) given by infusion or apheresis. Corticosteroids, often given as prednisone 200 mg/day, may treat the autoimmune component of TTP. Provision of either frozen plasma, or the cryoprecipitate-depleted fraction of plasma (cryosupernatant), has greatly reduced mortality in TTP, likely through several mechan- isms, for example, apheresis helps clear the pathogenic autoantibody and large VWF multimers. The monoclonal antibody rituximab, which recognizes CD20 (surface antigen on B-cell precursors), ap- pears to be effective in many patients with refractory or relapsing TTP. The haemolytic uraemic syndrome (HUS) is a nephrotropic thrombotic microangiopathy with a distinct pathogenesis, including its association with verocytotoxin-producing Escherichia coli usu- ally acquired from eating undercooked meat (hamburger disease). Although the majority of cases of ‘typical’ HUS is post-diarrhoeal (or D+ HUS), the remaining 25% of ‘atypical’ (or D−) HUS lacks a diarrhoeal prodrome, with many patients having a hereditary de-fect in an alternate complement pathway protein, such as gain-of- function mutations in C3 or factor B, or loss-of-function mutations in factor H or factor I. Haemostasis in the newborn Neonatal vitamin K deficiency Haemorrhagic disease of the newborn caused by vitamin K defi- ciency was once a relatively common cause of bleeding during the first week of life, particularly in breastfed infants. Low vitamin K levels in mother’s milk, and insufficient colonization of the newborn bowel by bacteria producing vitamin K, predispose to the inability to meet the infant’s vitamin K requirements (1 μg/kg per day). The routine administration of vitamin K, either 1 mg given intramuscu- larly immediately after birth, or three oral doses of vitamin K, has led to the near disappearance of this problem in developed countries. Bleeding within 24 h of birth can occur in certain high-risk settings, for example, mothers receiving anticonvulsants or warfarin; in these cases, the mother should receive vitamin K, 10 mg by mouth, each day for 2 weeks prior to delivery. Vitamin K deficiency occurring later in infancy despite appropriate neonatal vitamin K prophylaxis can indicate hepatobiliary or bowel disease. Neonatal DIC In neonates, DIC commonly complicates infection, asphyxia, re- spiratory distress syndrome, aspiration of meconium or amniotic fluid, maternal hypertensive syndrome, hypothermia, and brain Protein C and antithrombin deficiency caused by increased consumption (disseminated intravascular coagulation) Detectable pulses on palpation or Doppler signal Nonacral skin necrosis (purpura fulminans) Nonacral skin necrosis (purpura fulminans) Protein C and antithrombin deficiency caused by acute ischaemic hepatitis (“shock liver”) Symmetric peripheral gangrene (acral skin necrosis) with reduced circulation to extremities associated with hypotension or use of vasopressors Fig. 22.7.5.5 Clinical profile of symmetric peripheral gangrene. DIC, disseminated intravascular coagulation; FDP(s), fibrin(ogen) degradation product(s); FPA, fibrinopeptide A; PMNs, polymorphonuclear leucocytes; VWF, von Willebrand factor. Adapted from Warkentin TE (2015). Ischaemic limb gangrene with pulses. N Engl J Med, 373, 642–55.

Society. Reprinted with permission.

section 22 Haematological disorders 5562 injury. This condition poses a significant risk of bleeding or throm- bosis, as the immature liver has an impaired capacity to synthesize coagulation factors, and the mononuclear phagocyte system has a limited ability to clear activated coagulation factors. Treatment is aimed at the underlying cause of the DIC, with blood product given for the bleeding. Neonatal purpura fulminans Purpura fulminans can begin within hours or days following birth, often first affecting the heels or venepuncture sites. The underlying cause is usually a congenital abnormality affecting the protein C anticoagulant system (homozygous deficiency of protein C or pro- tein S). Frozen plasma or protein C concentrates given every few days prevents a recurrence in some patients. FURTHER READING Bakchoul T, Jouni R, Warkentin TE (2016). Protamine (heparin)- induced thrombocytopenia: a review of the serological and clin- ical features associated with anti-protamine/heparin antibodies.
J Thromb Haemost, 14, 1685–95. Bevan DH (1999). Cardiac bypass haemostasis: putting blood through the mill. Br J Haematol, 104, 208–19. Cole MS, Minifee PK, Wolma FJ (1988). Coumarin necrosis—a review of the literature. Surgery, 103, 271–7. Galli M (2013). Treatment of the antiphospholipid syndrome. Auto Immun Highlights, 5, 1–7. George JN, Nester CM (2014). Syndromes of thrombotic micro angiopathy. N Engl J Med, 371, 654–66. Holbrook A, et al. (2012). Evidence-based management of anticoagu- lant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest, 141 Suppl, e152S–84S. Holcomb JB, et al. (2015). Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA, 313, 471–82. Hunt BJ (2014). Bleeding and coagulopathies in critical care. N Engl J Med, 370, 847–59. Janbain M (2015). Acquired hemophilia A: emerging treatment op- tions. J Blood Med, 6, 143–50. Kitchens CS (1992). Hemostatic aspects of envenomation by North American snakes. Hematol Oncol Clin North Am, 6, 1189–95. Levi M, van der Poll T (2014). A short contemporary history of dis- seminated intravascular coagulation. Semin Thromb Hemost, 40, 874–80. Ortel TL, et al. (1994). Topical thrombin and acquired coagulation factor inhibitors: clinical spectrum and laboratory diagnosis. Am J Hematol, 45, 128–35. Sane DC, et al. (1989). Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. Ann Intern Med, 111, 1010–22. Warkentin TE (2001). Venous limb gangrene during warfarin treat- ment of cancer-associated deep venous thrombosis. Ann Intern Med, 135, 589–93. Warkentin TE (2007). Drug-induced immune-mediated thrombocytopenia—from purpura to thrombosis. N Engl J Med, 356, 891–3. Warkentin TE (2011). Fondaparinux treatment of acute heparin- induced thrombocytopenia confirmed by the serotonin-release assay: a 30-month, 16-patient case series. J Thromb Haemost, 9, 2389–96. Warkentin TE (2011). How I diagnose and manage HIT. Hematol Am Soc Hematol Educ Program, 2011, 143–9. Warkentin TE (2015). Ischemic limb gangrene with pulses. N Engl J Med, 373, 642–55. Warkentin TE (2019). High-dose intravenous immunoglobulin for the treatment and prevention of heparin-induced thrombocytopenia: a review. Exp Rev Hematol. Warkentin TE, Greinacher A (2013). Heparin-induced thrombocyto- penia, 5th edition. CRC Press, Boca Raton, FL. Warkentin TE, Pai M, Linkins LA (2017). Direct oral anticoagulants for treatment of HIT: update of Hamilton experience and literature review. Blood, 130, 1104–13. Warkentin TE, et al. (1995). Heparin-induced thrombocytopenia in pa- tients treated with low-molecular-weight heparin or unfractionated heparin. N Engl J Med, 332, 1330–5. Warkentin TE, et al. (1997). The pathogenesis of venous limb gangrene associated with heparin-induced thrombocytopenia. Ann Intern Med, 127, 804–12. Warkentin TE, et al. (2015). Warfarin-induced venous limb ischemia/ gangrene complicating cancer: a novel and clinically distinct syn- drome.

Blood, 126, 486–93.

Revision #1
Created 2026-01-22 16:42:48 UTC by Omar Ayman
Updated 2026-01-22 16:42:48 UTC by Omar Ayman