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22.7.2 Evaluation of the patient with a bleeding tendency 5509 matrix. U-PA associates with the urokinase plasminogen-activator receptor (u-PAR). Antiplasmin Antiplasmin is the physiological inhibitor of plasmin. It has a mo- lecular mass of about 58 kDa and is synthesized in the liver. As an in- hibitor, it has three major functions: to inhibit plasminogen binding to fibrin; to inhibit the proteolytic activity of plasmin; and to bind to fibrin in a covalent manner by the action of factor XIIIa. By binding to fibrin, antiplasmin competitively inhibits the binding of plas- minogen to fibrin. However, when plasminogen within the fibrin clot is converted to plasmin, the latter is protected from inhibition by antiplasmin. On the other hand, free plasmin formed in the cir- culation is rapidly inhibited. TAFI TAFI is also known as plasma procarboxypeptidase B, and it is ac- tivated to carboxypeptidase B by large amounts of thrombin in a reaction dependent upon thrombomodulin. TAFI down-regulates fibrinolysis after clot formation and serves as an important regula- tory mechanism for the fibrinolytic system. TAFI acts primarily by reducing the number of high-affinity plasminogen binding sites on fibrin, the end result of which is decreased fibrinolysis. The fibrinolytic and coagulation systems are closely interrelated. Under normal conditions, fibrin clot formation is always accom- panied by fibrinolysis. The formation of the fibrin clot that contains both tPA and plasminogen results in formation of plasmin within the clot so that clot lysis eventually ensues. It also appears that ac- tivated factor XI and factor XII enhance fibrinolytic activity. The action of the protein C system to decrease thrombin formation down-regulates the TAFI which would favour increased fibrin- olysis. Although much is still unknown, it is generally accepted that both the coagulation and fibrinolytic systems are related to the gen- eral process of inflammation involving several other host defence mechanisms. FURTHER READING Cines DB, et al. (1998). Endothelial cells in physiology and in the pathophysiology of vascular diseases. Blood, 91, 3527–61. Collen D (1999). The plasminogen (fibrolytic) system. Thromb Haemost, 82, 259–70. Coughlin SR (2005). Protease-activated receptors in haemostasis, thrombosis and vascular biology. J Thromb Haemost,

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22.7.2 Evaluation of the patient with a bleeding tendency Trevor Baglin ESSENTIALS An apparent bleeding tendency is a common clinical problem, with presentation varying from acute unexpected bleeding during or im- mediately after surgery or dental extraction, to spontaneous unusual or excessive bruising, purpura, epistaxis, or a chronic haemorrhagic tendency. Long-standing bleeding symptoms suggest a lifelong con- dition, whereas recent-onset bleeding suggests an acquired disorder. If a bleeding disorder has been diagnosed and characterized in an- other family member, then the cause of bleeding may be easily iden- tified, but the absence of a family history does not exclude a heritable disorder. The commonest cause of an acquired bleeding disorder is antithrombotic therapy. Investigations for bleeding disorder include full blood count and film (severe bleeding rarely occurs in the absence of trauma with a platelet count of more than 20 to 30 × 109/litre), prothrombin time (PT), activated partial thromboplastin time (APTT), fibrinogen level, reptilase time (useful for determining if a prolonged APTT is due to heparin), individual factor assays, mixing studies (can indicate if pro- longation of PT or APTT is likely due to a factor deficiency or an in- hibitor), platelet function analysis, and (rarely) bleeding time. Aside from general supportive care, specific therapy can be given when a defined haemostatic abnormality is identified. Drugs that cause bleeding should be stopped. Overanticoagulation due to a vitamin K antagonist can be reversed with vitamin K and/or prothrombin complex concentrate; dabigatran and be reversed

 with idarucizumab; and factor Xa-inhibitors may be reverse with andexanet alfa where this is approved for use. Vitamin K should also be given to critically ill patients and those with liver disease. Early and sufficient blood product support should be given to those with massive blood loss and/or dilutional coagulopathy. Judicious use of fresh frozen plasma and platelets is required in patients with severe coagulopathy such as disseminated intravascular coagulation while the underlying condition is being treated. Patients with overt haem-

atological disorders will require specialist care. Introduction An apparent bleeding tendency is a common clinical problem. A comprehensive history is needed to assess the nature and extent of the bleeding, to guide clinical examination, and to logically pri- oritize investigations. An acquired bleeding tendency is much more common than a heritable genetic disorder and the most common cause of an acquired bleeding disorder is antithrombotic therapy, particularly oral anticoagulant therapy. Some patients who bleed ab- normally during or after surgery have a mild underlying heritable haemostatic defect and so an important aspect of assessment is to determine if there is a heritable defect with late clinical presentation. Effective treatment depends on identifying the underlying cause of bleeding and anticipating when it is likely to be of clinical import- ance so that preventive therapy can be given at times of risk to pre- vent excess bleeding. Clinical assessment Presentation of a bleeding disorder varies from acute unexpected bleeding during or immediately after surgery to spontaneous un- usual or excessive bruising, purpura, epistaxis, or other bleeding developing over several months. With increasing use of pharma- cological thromboprophylaxis in both medical and surgical in- patients and increasing indications for long-term antithrombotic therapy, it is imperative to consider drug-induced bleeding during the initial evaluation of abnormal bleeding. In all cases a comprehensive history is needed. Most heritable disorders of haemostasis are mild, for example, von Willebrand's disease (VWD), and abnormal bleeding may not become manifest until there is a haemostatic challenge, such as surgery or menstruation. Therefore, an important aspect of the assessment of a patient with an apparent acquired bleeding disorder is to determine if it is genuinely of recent onset. The major issues to be determined are as follows: • Is haemostatic capacity reduced or is there a nonhaematological cause for bleeding? • If haemostatic capacity is reduced, is it due to a heritable defect with late clinical presentation or is it the result of a newly acquired defect? • If newly acquired, is it due to an anticoagulant or antiplatelet drug? • If not due to reduced haemostatic capacity then what are the likely circumstances that resulted in abnormal bleeding? Taking a history Assessing haemostatic capacity The main purpose of the history is to establish a clinical impres- sion, or profile, which indicates whether haemostatic capacity is normal or not and if there is a likely explanation for bleeding. Simple bruising, epistaxis, or menorrhagia has low positive and negative predictive value in isolation and unless a systematic history is taken with consideration of the 'overall picture' one can easily be misled into excluding or misdiagnosing a disorder. Rarely is it possible to absolutely exclude a disorder or make a positive diagnosis exclu- sively on the historical information. However, the history is critical, for example, there are some patients who definitely bleed after sur- gical challenges and yet the mechanism of their bleeding disorder cannot be characterized by laboratory investigations. Nevertheless, such patients should be considered to have a bleeding disorder and empirical treatment to reduce bleeding before surgical procedures should be planned. In contrast, patients with borderline abnormal laboratory tests but with no clinical bleeding tendency at times of haemostatic challenge should not be diagnosed as having a bleeding disorder. This scenario is frequently encountered when interpreting von Willebrand protein and factor XI results as there is a poor cor- relation between these factor levels and bleeding tendency in indi- viduals from families with a familial bleeding tendency. Recurrent bleeding from a single site suggests a structural abnormality. Bleeding at many different sites suggests a haemostatic defect. Severity and pattern of bleeding The circumstances of the bleeding episode should be carefully as- sessed. Was bleeding spontaneous or provoked, for example, by trauma or surgery? Was the degree of bleeding excessive or the pattern of bleeding unusual? Did bleeding result in anaemia, pos- sibly requiring transfusion? Was the site of bleeding unusual, for example, a joint bleed in an adult with no previous history of ab- normal bleeding? Was there bleeding with previous haemostatic challenges

such as surgery, trauma, dental extraction, and menstru- ation? Bleeding symptoms over a long time period suggest a lifelong bleeding condition while recent-onset bleeding suggests an acquired disorder, although a mild lifelong condition can be unmasked at times of haemostatic stress such as surgery. Purpura Purpura describes bleeding into the skin. The extent of bleeding may be small (petechiae) or larger (bruising, also called ecchymoses). Bruising is common in patients with reduced haemostatic capacity but is also very common in patients who have no apparent defect of haemostasis. Very extensive bruising, particularly over soft areas that are not likely to be traumatized, and very large bruises in the absence of trauma (>5 cm diameter), are more likely in patients with reduced haemostatic capacity. Bruising over bony areas does not necessarily indicate an abnormality and many normal children fre- quently have several bruises over their knees and shins. When bruising is the result of a bleeding disorder, the pattern of bleeding may be suggestive of the type of underlying disorder, for example, ecchymoses suggesting coagulation factor deficiencies such as classical haemophilia or liver disease and petechiae sug- gesting thrombocytopenia or a vessel wall defect. However, these

 distinctions are not absolute; for example, thrombocytopenia may present with large bruises rather than petechiae. Thrombocytopenia causes petechiae, typically when the platelet count is less than 20 × 109/litre. Petechiae may occur when there is platelet dysfunction or with vascular purpura, either of which can be congenital or ac- quired. Petechiae are unusual with low von Willebrand protein levels but may occur in some individuals with low levels when antiplatelet drugs are prescribed or when there is an increase in hydrostatic pres- sure, for example, in the arm after application of a blood pressure cuff (Hess' test or Rumpel–Leede test). Epistaxis Nosebleeds are common in children in the absence of a bleeding dis- order. They also occur in some adults with allergic rhinitis. Repeated bleeding from the same nostril suggests a local cause. Lifelong re- current epistaxis can occur in VWD, haemophilias, and hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome). Recent-onset epistaxis in adults may be due to an acquired disorder such as thrombocytopenia but is surprisingly uncommon in adults with lifelong bleeding disorders such as the haemophilias and VWD. Gingival bleeding Gum bleeding in the absence of any other abnormal bleeding is usu- ally due to gingivitis requiring improved dental hygiene. Rarely is isolated gingival bleeding due to an underlying disorder. Menorrhagia Menorrhagia is a common problem and not specific for a bleeding disorder. Recent-onset menorrhagia in older women is likely to be due to a gynaecological cause. The main problem in assessing men- orrhagia is subjectivity. For example, many women with VWD do not complain of heavy periods because they consider their own ex- perience as 'normal'. It is important to determine the pattern, for ex- ample, bleeding for several days with clots and particularly bleeding that interrupts normal lifestyle such as absence from work, is more likely to be abnormal and may be due to an underlying haemostatic defect. Very prolonged menorrhagia, rather than heavy bleeding, is more likely to be gynaecological. Dental extraction Bleeding after dental extraction is variable in the normal population. Bleeding lasting more than an hour, rebleeding, or late bleeding re- quiring suturing on more than one occasion suggests a bleeding dis- order. Bleeding after extraction requiring blood transfusion even on one occasion suggests a bleeding disorder. Prolonged bleeding after dental extraction is typical with low von Willebrand factor (VWF) levels and rebleeding is typical of haemophilia. Surgery It is important to ask specifically about all operations including cir- cumcision and tonsillectomy. Abnormal bleeding during surgery or in the postoperative period may be due to antithrombotic therapy, such as warfarin or aspirin, that was not stopped. Abnormal sur- gical bleeding may be the first

presentation of a mild or moderate heritable bleeding defect if there has been no previous haemostatic challenge, for example, a male having their first operation. It is useful to try and determine if the bleeding was just local, which might be due to a local anatomical reason such as a failed suture, or if there was evidence of more generalized bleeding such as oozing from the wound or bruising at venepuncture or venflon sites. Increasingly, patients are prescribed low-dose heparin (nowadays usually low molecular weight heparin) to prevent venous thrombosis and in a minority of patients this can unmask a mild bleeding tendency, such as that associated with low VWF levels. In most patients, low-dose heparin does not appreciably increase surgical bleeding. However, it is important to review the drug charts from the time of the oper- ation to ensure that the correct dose of heparin was given and that no other drugs that might cause bleeding were administered.
Bleeding in unusual sites Bleeding in an unusual site sometimes suggests a specific diag- nosis. Joint bleeding rarely occurs when there is normal haemostatic capacity. It usually indicates severe coagulation factor deficiency, such as severe congenital factor VIII or IX deficiency or overdose with an oral vitamin K antagonist (VKAs) with an international normalized ratio (INR) in excess of 8.0. Umbilical stump bleeding in the neonate is typical of severe congenital factor XIII deficiency, although the condition is very rare (one per million of the popula- tion). Intracerebral bleeding in an otherwise healthy neonate neces- sitates exclusion of severe congenital factor VIII or IX deficiency, factor XIII deficiency and severe thrombocytopenia such as occurs in fetomaternal alloimmune thrombocytopenia (FNAIT). Family history of bleeding If a bleeding disorder has been diagnosed and characterized in an- other family member then the cause of bleeding may be easily iden- tified. The absence of a family history does not exclude a heritable disorder. The penetrance of VWD is incomplete, and new mutations account for one-third of new patients with haemophilia A.
Drug history The most common cause of an acquired bleeding disorder is antithrombotic therapy. Increasingly, low-dose heparin for inpatient thromboprophylaxis and oral anticoagulant (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) and antiplatelet drugs (aspirin, clopidogrel, prasugrel, ticagrelor, cangrelor, nonsteroidal anti- inflammatory drugs) in both inpatients and outpatients are respon- sible for bleeding. Clinical examination Skin The skin should be inspected in its entirety for evidence of bleeding, noting the distribution (bony or soft areas), pattern (random or sug- gestive of nonaccidental injury), and size (petechiae or ecchymoses). Senile purpura occurs predominantly on the extensor surfaces of the hands and arms and the face. The lesions tend to persist for sev- eral weeks becoming increasingly dark. Senile purpura is due to skin atrophy and resultant blood vessel fragility. Senile purpura is not as- sociated with an underlying systemic bleeding disorder. Purpura occur with amyloid, which may cause bleeding due to capillary fragility as a result of amyloid infiltration, or rarely an acquired deficiency of factor X. Vessels are extremely fra- gile and bleed with very minor trauma. Amyloid may also cause

 proteinuria and excess bleeding may complicate renal biopsy in these patients. Some of these patients also have myeloma, causing thrombocytopenia. Petechiae with a perifollicular distribution occur in scurvy, which may also present with more widespread bleeding into joints, gastrointestinal bleeding, and intracerebral bleeding. Other features include xerostomia, keratoconjunctivitis sicca, and hyperkeratosis. Dental decay is common in patients with scurvy. Treatment with vitamin C results in improvement within hours. Scurvy may be the cause of bleeding in elderly patients with a very poor diet. Purpura occurs with infections including meningococcal septi- caemia and diphtheria, chickenpox, measles, and the haemor- rhagic fevers of Ebola virus and Lassa fever. Purpura fulminans describes necrotic skin lesions which occur with overwhelming infection and the development of disseminated

intravascular coagulation (DIC). Allergic purpura may follow exposure to chemicals and toxins. Henoch–Schönlein purpura is the most common allergic purpura and involves principally skin, joints, gastrointestinal tract, and kid- neys. It typically occurs in children after an upper respiratory tract infection due to streptococcus. The rash consists of purpuric papules over the shins, thighs, and buttocks, sometimes with small ulcers, and the rash is associated with arthritis, nephritis, and abdominal pain. IgA-containing immune complexes are deposited in the vessel walls. Mixed cryoglobulinaemia in patients with hepatitis C infection can produce extensive purpura in association with arthropathy and glomerulonephritis. Psychogenic purpura refers to unexplained bruising with pre- ceding pain in association with anxiety. It has also been referred to as 'auto-erythrocyte sensitization' following reports that subcuta- neous injection of the patient's own red cells can induce the lesions. However, it is uncertain if this is a genuine clinical sign. Telangiectasia may occur in the skin and the mucous membranes. In patients with hereditary haemorrhagic telangiectasia, they occur predominantly in the skin of the hands and fingertips and are evident on the lips. The lesions blanch on pressure in contrast to purpura. Telangiectasias also occur in pregnancy and liver disease, usually on the face and chest. Rarely, large cavernous haemangiomas or aortic aneurysms can cause local consumption of coagulation factors and platelets resulting in a systemic bleeding disorder. Skin hyperelasticity, scars, papules, and plaques may indicate a collagen vascular disorder. Ehlers–Danlos syndrome, Marfan syn- drome, pseudoxanthoma elasticum, and osteogenesis imperfecta are associated with a bleeding tendency due to abnormal platelet– vessel wall collagen interaction. Unusual scars may be due to a dysfibrinogenaemia, Ehlers–Danlos syndrome, or pseudoxanthoma elasticum. Long-term steroid therapy and Cushing disease cause skin atrophy and bruising typically on the extensor surfaces of the hands and arms and on the thighs. Mucosa Telangiectasias are dilated small vessels that may be found in the skin and in the mucous membranes of the respiratory, gastrointes- tinal, and urinary tracts, vagina, eye, liver, and brain in patients with hereditary haemorrhagic telangiectasia (Osler–Weber–Rendu syndrome). Recurrent epistaxis and gastrointestinal bleeding cause iron deficiency. Musculoskeletal Severe haemophilia A (factor VIII deficiency) and B (factor IX defi- ciency) are characterized by repeated spontaneous bleeds into joints, muscles, and soft tissue. The most common joints that bleed are the an- kles, knees, hips, and elbows. Acute haemarthrosis presents as an acutely swollen painful joint resulting in joint immobilization. Repeated bleeds into a joint (target joint) produces chronic haemophilic arthropathy with features of both osteoarthritis (mechanical pain on movement) and rheumatoid arthritis (inflammatory pain at rest). Muscle haema- tomas occur in the iliopsoas, gluteal, calf, and forearm muscles and are more insidious than joint bleeds. Compartment syndrome can com- plicate large bleeds and fibrosis and contractures produce dysfunction and deformity. Large haematomas can cause pseudotumours, par- ticularly when there is chronic rebleeding. These large, expanding soft tissue cysts produce mass effects including neuropathy and bone ero- sion and may produce chronic fistulas. Splenomegaly Splenomegaly can cause hypersplenism with thrombocytopenia. Patients with myeloproliferative disorders may have impaired platelet function. Essential thrombocythaemia is a myeloproliferative dis- order which is particularly associated with impaired platelet func- tion but both bleeding and thrombosis occur. In patients with very high platelet counts, there can be increased consumption of von Willebrand protein causing an acquired von Willebrand syndrome. Patients with polycythaemia are particularly prone to chronic gastrointestinal bleeding. Splenomegaly may be due to portal hyper- tension in patients with liver disease. In these patients, bleeding may be due to thrombocytopenia, platelet dysfunction, coagulation factor deficiency, and production of dysfunctional factors. In add- ition, there may be local bleeding sites such as

oesophageal varices. General aspects of examination In addition to identifying signs that may indicate the likelihood and type of a bleeding disorder, it is important to consider broader aspects. For example, is a patient anaemic due to iron deficiency as a consequence of chronic gastrointestinal blood loss? Patients with severe bleeding disorders who have been treated with human- derived blood products, in particular pooled products that have not been virally inactivated, may have chronic infections including hepatitis C and HIV. Chronic liver disease, opportunistic infections, and other complications may be evident. Bleeding as a result of liver failure, renal failure, or paraproteinaemia should be considered. In children, the possibility of nonaccidental injury should be con- sidered, particularly with multiple bruises around the head and neck, or a pattern of bruising in keeping with gripping or shaking. The retina should be examined for haemorrhages. In a drowsy pa- tient or a patient with raised intracranial pressure or an acute focal neurological deficit, there is the possibility of an intracranial bleed. Investigations Laboratory tests Coagulation tests include: • prothrombin time (PT) • activated partial thromboplastin time (APTT)

22.7.2 Evaluation of the patient with a bleeding tendency 5513 • fibrinogen level • thrombin time (TT) • reptilase time (RT) • factor assays • mixing studies • platelet function analysis Coagulation tests are typically performed on plasma that has been separated from a venous blood sample by centrifugation. Thrombin generation takes place on phospholipid surfaces (provided by plate- lets normally) and so an artificial lipid preparation is added as the platelets are removed by the centrifugation. Most routine clotting tests use the time taken for a clot to appear as the endpoint of the assay. Blood is usually taken into tubes containing citrate, which che- lates calcium and thereby prevents clotting. After centrifugation, the plasma is isolated and recalcified during the clotting assay. Clotting tests are indicated in patients with a personal or family history of bleeding. They are not generally indicated as routine preoperative screening tests as they have very low sensitivity and specificity for surgical bleeding in unselected patients. Furthermore, a prolonged APTT on a ‘screening sample’ is most likely to be due to contact factor deficiency or an incidental lupus anticoagulant, neither of which will cause bleeding in a patient with no personal bleeding his- tory but may lead to an unnecessary delay in surgery or an inter- ventional procedure. Preoperative assessment of bleeding risk is better determined by identification of a personal or family bleeding history, which should then be investigated accordingly with specific tests including coagulation factor assays, von Willebrand protein level and function, and platelet count and function. Assessment of haemostasis The history is of primary importance in determining if haemostatic capacity is genuinely reduced. A ‘bleeding score’ derived from that used to quantify bleeding in patients with VWD can be a useful tem- plate for ensuring that a systematic history is taken from patients with an apparent bleeding tendency (Table 22.7.2.1). There is no ab- solute score that indicates an unequivocal diagnosis of a bleeding disorder but the higher the score, the more likely there is an under- lying tendency to bleeding. Blood count and film examination Bleeding tendency increases with thrombocytopenia with a platelet count of less than 80 × 109/litre but severe bleeding rarely occurs in the absence of trauma with a platelet count greater than 20 to 30 × 109/litre. Film examination is mandatory when a bleeding disorder is suspected. Pseudothrombocytopenia due to platelet clumping can lead to an erroneous diagnosis of true thrombocytopenia if the film is not examined for clumps. Conversely, a normal platelet count may be occasionally reported in patients with true thrombo- cytopenia, the normal count being an artefact, for example, due to the presence of a cryoglobulin. In these patients, the thrombo- cytopenia is readily apparent from examination of the blood film. Abnormal platelet morphology

may suggest an underlying heritable platelet defect such as Bernard–Soulier syndrome, May–Hegglin abnormality (MYH9-related disease), or a grey platelet syndrome. Alternatively, a leukaemia or an acquired myeloproliferative dis- order or myelodysplastic syndrome may be apparent from the blood count and film examination. Prothrombin time The PT is the time taken in seconds for a fibrin clot to form after recalcification and addition of thromboplastin (a preparation of tissue factor which is the protein that activates factor VII). The normal PT is about 11 to 14 s, depending on the type of thromboplastin used. The PT is prolonged by: • oral anticoagulant therapy (typically warfarin) • direct oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban, edoxaban) • vitamin K deficiency • liver disease • DIC • dilutional coagulopathy (massive blood transfusion) Anticoagulant therapy with oral VKAs is monitored by the INR. The INR is derived from the PT ratio and is a standardized method of reporting which permits comparability between laboratories. It is inappropriate to use the INR for any purpose other than measuring the intensity of oral anticoagulant therapy with a VKA (such as war- farin|). For all other purposes, the PT or PT ratio should be used. The PT and APTT are variably prolonged by DOACs with the PT being more sensitive to factor Xa inhibitors (rivaroxaban, apixaban, edoxaban) and the APPT more sensitive to thrombin inhibitors (dabigatran). However, these tests cannot be used to quantify the anticoagulant effects of DOACs and should be considered qualita- tive at best. The INR is not used to monitor these drugs as it is for VKA. Laboratories should be aware of the sensitivity of their own assays to each drug. It is likely that coagulation tests will be per- formed on patients taking DOACs as part of clinical assessment (e.g. admission to the accident and emergency department), and the re- sults might wrongly be interpreted if it is not known that the patient has taken one of these drugs. Activated partial thromboplastin time The APTT is the time taken in seconds for a fibrin clot to form after recalcification and exposure to a contact factor activator, such as kaolin. The normal APTT is about 32 to 38 s, depending on the type of contact factor activator used. The APTT is prolonged by: • unfractionated heparin (low molecular weight heparin has min- imal effect at therapeutic levels) • oral anticoagulant therapy (variably) • vitamin K deficiency (mildly, the PT is more sensitive) • liver disease (mildly, the PT is more sensitive) • DIC • dilutional coagulopathy (massive blood transfusion) • severe and moderate deficiencies of clotting factors VIII, IX, or XI. • lupus anticoagulant activity due to antiphospholipid antibodies • contact factor deficiency (including factor XII and prekallikrein, none of which cause bleeding) A low factor XII level produces a marked prolongation of the APTT but deficiency is not associated with any bleeding tendency. This re- flects the fact that the APTT is a nonphysiological test which while useful for screening for deficiency of some clotting factors (VIII, IX, and XI) does not actually reflect physiological haemostasis.

section 22 Haematological disorders 5514 Table 22.7.2.1 International Society on Thrombosis and Hemostasis Bleeding Assessment Tool Symptom −1 0 1 2 3 4 Epistaxis Number episodes/year Average duration Medical attention required? <5 and <10 min

> 5 or >10 min Required medical consultation Packing or cauterization or antifibrinolytic therapy Blood transfusion/replacement therapy or DDAVP Bruising Exposed or unexposed sites Size on average Minimal or no trauma Specify medical attention No or trivial (<1 cm) 1 cm and no trauma Medical consultation required Bleeding from minor wounds Number per year Duration of

average episode Medical attention required No or trivial (<5/year) 5/year or episodes average >5 min Consultation only Surgical haemostasis Blood transfusion/replacement therapy or desmopressin Oral cavity bleeding Tooth eruption Gums, spontaneous Gums, after brushing Bites to lip and tongue Medical attention required No Bleed with at least one of: Tooth eruption Gums (spontaneous) Gums (brushing) Bites to lip/tongue Consultation only Surgical haemostasis or antifibrinolytic Blood transfusion/replacement therapy or desmopressin Post dental extraction Number of extractions Number complicated by bleeding Medical attention required No bleeding in ≥2 extractions None done or no bleeding in 1 extraction Reported, no consultation Consultation only Resuturing or packing Blood transfusion/replacement therapy or desmopressin GI bleeding Ulcer, portal hypertension, haemorrhoids Spontaneous Treatment required No Associated with ulcer, portal HTN, haemorrhoids, angiodysplasia Spontaneous Surgical haemostasis, blood transfusion, replacement therapy, DDAVP, antifibrinolytic Surgery Number of surgeries Number complicated by bleeding Postoperative medical attention No bleeding in ≥2 surgeries None done or no bleeding in 1 surgery Reported, no consultation Consultation only Surgical haemostasis or antifibrinolytic Blood transfusion/replacement therapy or desmopressin Menorrhagia Duration of menstruation Duration of heavy menstruation How often change pads/ tampons on heaviest/ average days What type of feminine product used Medical attention and treatment No Consultation only Antifibrinolytics, pill D&C, iron therapy, ablation Blood transfusion/replacement therapy or desmopressin or hysterectomy

22.7.2 Evaluation of the patient with a bleeding tendency 5515 Postpartum haemorrhage Number of deliveries Number complicated by bleeding Medical attention required No bleeding in ≥2 deliveries None done or no bleeding in 1 delivery Consultation only D&C, iron therapy, antifibrinolytics Blood transfusion/replacement therapy or desmopressin Hysterectomy Muscle haematomas Post trauma and spontaneous Treatment required Never Post trauma or therapy Spontaneous, no therapy Spontaneous or traumatic, requiring desmopressin or replacement therapy Spontaneous or traumatic, requiring surgical intervention or blood transfusion Haemarthrosis Post trauma and spontaneous Treatment required Never Post trauma, no therapy Spontaneous, no therapy Spontaneous or traumatic requiring DDAVP or replacement therapy Spontaneous or traumatic requiring surgical intervention or blood CNS bleeding Subdural or intracerebral Never Subdural, any intervention Intracerebral, any intervention CNS, central nervous system; D&C, dilation and curettage; DDAVP, 1-deamino-8-d-arginine vasopressin; GI, gastrointestinal; HTN, hypertension. Notes on the bleeding score: Mark the highest scoring box for each symptom (mark one box only for each symptom). Sum the score obtained from each of the 12 symptoms. A bleeding score of ≥4 is considered positive. The higher the score, the more likely there is an underlying tendency to bleeding. Standard laboratory tests such as the prothrombin time (PT) and activated partial thromboplastin time (APTT) are insensitive to mild and moderate reductions of levels of coagulation factors which may be clinically significant and cause bleeding. These tests are not influenced at all by levels of von Willebrand factor. Therefore, it is on the basis

of the history that a decision is made on the extent of laboratory testing. The blood count and film, PT, APTT, and platelet count should be measured. If these are normal but the history is suggestive of an underlying bleeding disorder, a more comprehensive laboratory assessment of haemostatic capacity is indicated. Measurement of the platelet count gives no indication of platelet function.

section 22 Haematological disorders 5516 Fibrinogen level Fibrinogen levels are low in: • DIC • dilutional coagulopathy (massive blood transfusion) • advanced liver disease • following thrombolytic therapy • congenital hypofibrinogenaemia (very rare) Thrombin time The TT is the time taken in seconds for a fibrin clot to form after addition of thrombin. The TT is prolonged by: • unfractionated heparin • direct thrombin inhibitors (dabigatran, argatroban) • hypofibrinogenaemia (see earlier for low fibrinogen levels) • fibrin degradation products (high levels may occur in DIC and after thrombolysis) Reptilase time This is a snake venom-based test. It is prolonged by low fibrinogen levels but not by heparin and so comparison of the TT and RT is useful for determining if a prolonged APTT is due to heparin; a long TT with normal RT indicates heparin. Heparin contamination is common on samples from hospitalized patients, even though the use of heparin flushes and sampling from catheters is often denied by clinical staff. Weak heparin flushes significantly prolong the APPT on samples taken from indwelling catheters. In many cases it is necessary to obtain a venous sample from a fresh venepuncture. Factor assays Individual factor assays are useful in patients with a bleeding his- tory and are guided by PT and APTT results. The cascade model of coagulation is no longer considered to represent the physiological process involved in coagulation. The cascade model was derived from observation of results using the PT and APTT assays but these are not ‘physiological’ tests. While the cascade model may not be ‘physiologically true’, it is still a useful framework for interpreting PT and APTT results. For example, in a patient with a bleeding his- tory with a normal PT and a long APTT (not due to heparin or a lupus anticoagulant), there may be deficiency of factor VIII, IX, or XI (Fig. 22.7.2.1). Table 22.7.2.2 summarizes the interpretation of laboratory investigations. Mixing studies If the PT or APTT are prolonged then a 50:50 mix of patient plasma with normal plasma will indicate if the prolongation is likely due to a factor deficiency (the mix corrects the abnormality) or an in- hibitor, such as heparin or a specific factor inhibitor (the mix does not correct the abnormality). Platelet function analysis Platelet function can be assessed at high and low shear. The platelet function analyser (PFA-100) is an automated technique that meas- ures the ability of platelets to occlude an aperture under conditions of high shear. The test is performed on a citrated blood sample within 4 h of sample collection and is abnormal in the presence of low von Willebrand protein activity or platelet function defects. Thrombocytopenia causes prolonged closure and so the test re- quires a normal platelet count in order to assess platelet function. Platelet function at low shear rate is assessed by platelet aggregation. Prothrombin Thrombin Fibrinogen Fibrin VIIa IX IXa VIIIa X Xa Va XI XIa Tissue factor XIIa Contact factors XII VII APTT PT Common pathway Extrinsic pathway Intrinsic pathway TT Fig. 22.7.2.1 Cascade model of coagulation. APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time.

22.7.2 Evaluation of the patient with a bleeding tendency 5517 Aggregation studies are performed typically on platelet rich plasma prepared by slow centrifugation of citrated blood within 4 h of sample collection. There is a poor correlation with bleeding ten- dency except in specific congenital disorders characterized by severe platelet dysfunction, for example, Glanzmann thrombasthenia and Bernard–Soulier syndrome. • Agonists used for aggregation studies include ADP, collagen, arachidonic acid and adrenaline (epinephrine). • Response to ristocetin is an agglutination response

dependent on induced conformational change of platelet membrane proteins (e.g. glycoprotein Ib–IX–V, promoting interaction with VWF). • Ristocetin-induced platelet agglutination (RIPA) is carried out at high (1.2 mg/ml) and low ristocetin concentrations (0.5 mg/dl). Positive RIPA at 0.5 mg/dl is an abnormal result and is observed in type 2B VWD and with high VWF levels (e.g. pregnancy). Platelet storage pool disorders are characterized by absent platelet α or δ granules. α-Granule proteins include β-thromboglobulin and platelet factor 4 which can be measured by enzyme-linked im- munosorbent assay—these are deficient in α-granule storage pool defects. Nucleotides (ADP/ATP) can be measured by a variety of techniques including high-pressure liquid chromatography and are deficient in δ-storage pool disorders. These analyses are beyond the scope of most haematology laboratories. Many patients with in- herited thrombocytopenias are misdiagnosed as immune thrombo- cytopenia (ITP) but complex laboratory techniques, including flow cytometry and targeted gene sequencing, are required for diagnosis. Bleeding time The bleeding time is used much less frequently now that platelet function analysis at high shear is readily available. The bleeding time does not predict surgical bleeding and is largely no longer con- sidered a test with clinical utility. Other investigations Global tests of haemostasis Further tests of haemostasis which assess the dynamic interaction of the individual components of haemostasis rather than the Table 22.7.2.2 Interpretation of laboratory investigations Coagulopathy PT APTT Fibrinogen TT Platelets (PFA) Heritable VWF—mild N N N N N Abnormal VWF—moderate N N or ↑ N N N Abnormal VWD—severe N ↑ N N N Abnormal VWD—type 2B (rare) N N N N ↓ Abnormal VIII N ↑ N N N N IX N ↑ N N N N XI N ↑ N N N N VII X, V, or II ↑ ↑ N N N N Fibrinogen N N ↓ ↑ N N or abnormal XIII N N N N N N Thrombocytopenia N N N N ↓ Abnormal Glanzmann’s disease N N N N N Abnormal Bernard–Soulier syndrome N N N N ↓ Abnormal Acquired Heparin N or ↑ ↑ N ↑a N N Warfarin ↑ N or ↑ N N N N Aspirin/clopidogrel N N N N N Abnormal Dilutional coagulopathy ↑ ↑ N or ↓ N or ↑ ↓ abnormal Renal disease N N N N N or ↓ Abnormal Liver disease ↑ ↑ N or ↓ N or ↑ N or ↓ N or abnormal DIC ↑ ↑ N or ↓b N or ↑ ↓ abnormal Acquired von Willebrand syndrome N N or ↑ N N N Abnormal Hyperfibrinolysis N or ↑ N or ↑ N or ↓ N or ↑ N N or abnormal Surgical bleeding N N N N N N N, normal. PFA (platelet function analysis on the PFA-100) only performed in selected cases. In cases of complex coagulopathy, PFA is abnormal primarily due to thrombocytopenia. a With heparin, the thrombin time is prolonged but the reptilase time is normal. b With DIC, the level of fibrin degradation products (such as D-dimer) is very high and this interferes with fibrin polymerization which contributes with low fibrinogen levels to the prolonged thrombin time.

 amount or function of specific components in isolation are avail- able in some specialized laboratories. These techniques include thromboelastography, thrombin generation, and tests of fibrinolysis. Anatomical imaging Specific bleeding points may be due to structural abnormalities and imaging directly by endoscopy or by CT, magnetic reson- ance imaging, or angiography will be indicated in some patients. Interventional radiology with arterial embolization can be used to stop localized bleeding, for example, from the gastrointestinal tract. Specific issues Drug-induced bleeding The most common cause of an acquired bleeding disorder is anti- coagulant therapy. Approximately 1 in 100 of the United Kingdom population are now receiving long-term oral anticoagulant therapy. Increasingly, patients are being treated with DOACs rather than warfarin. Overanticoagulation with oral anticoagulants (VKA or DOACs) is responsible for most life-threatening bleeds attributable to antithrombotic therapy. Vitamin K antagonists Overanticoagulation due to a VKA such as warfarin is indicated by a high INR, often due to intercurrent illness and antibiotic use. The INR is particularly influenced by the factor VII level which is not the main determinant of bleeding risk. When over-anticoagulaiton due to an oral VKA is

reversed by intravenous vitamin K the INR may correct over several hours but a significant bleeding tendency remains as the factor VII level rises more quickly than the other vitamin K-dependent factors. Therefore, in patients with signifi- cant bleeding, reversal requires a combination of factor replacement (a prothrombin complex concentrate (PCC) containing factors II, VII, IX, and X for immediate and effective reversal of bleeding) and vitamin K (for a sustained reversal when the response to factor re- placement has decayed). Direct oral anticoagulants Overanticoagulation with a DOAC may not be associated with a par- ticularly prolonged PT or APTT and a quantitative assay is required to determine the intensity of anticoagulation with these drugs. A di- lute plasma thrombin time such as the Hemoclot assay is useful for thrombin inhibitors (dabigatran) and drug-specific calibrated anti-Xa assays are required for factor Xa-inhibitors (rivaroxaban, apixaban, edoxaban). There is no evidence that the anticoagulant effect of DOACs can be reversed by administration of plasma-derived factors, including PCC, but their short half-life (<12 h) makes management of bleeding less problematic than that associated with VKA. A spe- cific antidote to dabigatran (idarucizumab, a monoclonal antibody fragment that binds to dabigatran) is licensed, and factor Xa- inhibitors (e.g. andexanet alfa, a truncated form of enzymatically inactive factor Xa which acts as a decoy receptor, binding to and reversing the anticoagulation action of factor Xa inhibitors) are becoming available. Antiplatelet drugs Platelets are integral to thrombin generation and antiplatelet drugs can be considered as anticoagulants, hence their ability to prevent thrombosis. Bleeding risk is in part determined by the potency of antiplatelet activity, for example, the bleeding risk associated with a fibrinogen receptor antagonist (IIb–IIIa inhibitor) is far greater than with aspirin or an ADP receptor antagonist such as clopidogrel. The individual response to antiplatelet therapy is extremely variable and even aspirin or an ADP receptor antagonist may produce a sig- nificant bleeding tendency in some patients. The pharmacological half-life of antiplatelet drugs is determined by the mechanism of in- hibition of platelet function. Aspirin and ADP antagonists irrevers- ibly inhibit platelet function and so recovery is dependent on new platelet production. The lifespan of a platelet is typically 10 days and so 10% of the platelet pool is replaced each day. Once there is 50% replenishment (5 days after stopping therapy), platelet-dependent haemostatic capacity is usually adequate for normal blood coagu- lation. NSAIDs reversibly inhibit platelet function and there is no effect 24 to 48 h after stopping treatment. Surgical bleeding Postoperative bleeding is a common clinical problem. It is essential to examine the drug and infusion charts and check that the dose of any drug that may affect haemostasis is not excessive. It is also imperative to determine if the site of surgery is the only site of bleeding. If this is the case, for example, there is no bleeding from venepuncture sites or an endotracheal tube, and there is no history of previous abnormal bleeding, then depending on the results of coagulation tests it is im- portant to keep the possibility of anatomical surgical bleeding as a likely possibility. In some cases of severe bleeding the patient may have to return to theatre to look for a bleeding point. Severe surgical bleeding may result in a dilutional coagulopathy due to fluid volume replacement or DIC due to hypotensive shock with a severe exacerba- tion of bleeding and a complex secondary coagulopathy. Critically ill patients There are many potential acquired disorders of haemostasis in crit- ically ill patients. A coagulopathy due to vitamin K deficiency oc- curs within a few days in critically ill patients with no oral intake. Parenteral vitamin K supplementation should be used routinely to prevent bleeding in the critical care setting. Many critically ill pa- tients develop DIC. Massive transfusion and dilutional coagulopathy A dilutional coagulopathy resulting in deficiency of clotting factors and platelets will cause abnormal bleeding in patients receiving large amounts of plasma expanders and red blood cells even in the ab- sence of DIC. It is important to give replacement therapy with fresh frozen plasma and platelet

concentrates guided by repeated meas- urement of the PT, APTT, and platelet count. Standardized protocols for the early administration of blood products in patients receiving massive blood transfusion are increasingly used to ensure adequate replacement of clotting factors and platelets in order to prevent or at least limit the development of coagulopathy. Disseminated intravascular coagulation The major manifestations of DIC are end-organ damage due to microvascular thrombosis but the most readily apparent clin- ical manifestation is often bleeding due to the consumptive coagulopathy. DIC is a clinical diagnosis supported by the results of laboratory investigations with a prolonged PT and APTT, a low

 fibrinogen and platelet count, and elevated fibrin degradation prod- ucts (such as D-dimer). Persistent oozing from venepuncture sites in patients with sepsis or in obstetric patients suggests DIC. A fi- brinogen level less than 1 g/litre suggests DIC in a patient with an ac- quired severe bleeding disorder not due to dilutional coagulopathy. The most important aspect of treatment is that of the underlying cause (e.g. sepsis), although fresh frozen plasma and platelet concen- trates are used to treat bleeding or prevent haemorrhage associated with planned invasive procedures. A chronic form of DIC occurs in patients with malignancy. ABO blood group-associated low von Willebrand protein levels and von Willebrand disease The most common heritable bleeding tendency is due to a low VWF level. This may be due to genetic mutation of the VWF gene (often designated VWD), or more commonly the effect of epigenetic fac- tors such as blood group O (designated blood group O-associated low VWF level). Regardless, the level of von Willebrand protein ap- pears to be an important continuous variable influencing the coagu- lation phenotype. The first apparent manifestation of this may be excessive surgical bleeding and as a result the patient is considered to have an acquired bleeding disorder. The history may be informative, such as a detailed menstrual history in women. It can be difficult to establish a diagnosis of a mild reduction in von Willebrand protein in the immediate postoperative period as levels rise due to the stress response. Consequently, it is prudent to re-evaluate patients several weeks after an episode of abnormal surgical bleeding. VWF levels should be interpreted in relation to blood group and the clinical cir- cumstances at the time a blood sample was taken. VWF levels rise with age and so a mild bleeding disorder associated with low levels may be attenuated as the patient ages. Thrombocytopenia Many drugs result in a reversible idiosyncratic thrombocytopenia. In most cases, drug-induced thrombocytopenia is mild and does not cause bleeding. Notable exceptions are quinine and gold-induced thrombocytopenia which are severe. An evaluation of drug history and cessation of possibly implicated drugs is essential in patients with acquired bleeding who are found to be thrombocytopenic. Other com- monly used drugs for which there is good evidence for drug-induced thrombocytopenia include amiodarone, atorvastatin, carbamaze- pine, cimetidine, diclofenac, digoxin, ranitidine, co-trimoxazole, and vancomycin. Cytotoxic drugs produce a dose-dependent sup- pression of bone marrow platelet production and thrombocytopenic bleeding is common in oncology practice. Bone marrow suppression and bone marrow failure syndromes, such as aplastic anaemia and myelodysplasia, often result in production of dysfunctional platelets and the bleeding tendency is significantly greater than in patients with thrombocytopenia and an uncompromised marrow, such as occurs in ITP in which the bleeding risk is relatively low. Inherited thrombocytopenias are often misdiagnosed as ITP in adults but correct diagnosis of these disorders is difficult. A family history of thrombocytopenia or a lifelong history of a relatively stable, though low, platelet count is suggestive. The normal platelet count decreases with age and platelet counts less than 150 × 109/litre may be ‘normal’ in older patients. Therefore, abnormal bleeding should not neces- sarily be attributed to a mild reduction in platelet count. Over the age of 65 years the lower limit of

normal is around 120 × 109/litre and by the age of 80 years around 100 × 109/litre. In addition, abnormal bleeding is not usually apparent until the platelet count is below 80 × 109/litre, when platelet function is normal. Thrombocytopenia is common in HIV infection. Gestational thrombocytopenia occurs in 5% of pregnancies but the platelet count is rarely less than 80 × 109/litre and it is not associated with an increased bleeding tendency. Renal disease Bleeding risk increases with the degree of renal impairment and is due to a defect of platelet–vessel wall interaction as well as impaired platelet function. In most patients, laboratory tests of haemostasis are normal. Platelet function tests may give variable results that do not correlate with bleeding risk. The cause of the bleeding is an ac- cumulation of dialysable uraemic toxins including urea and phenols which inhibit platelet function and possibly VWF activity. Anaemia contributes to the bleeding tendency due to a reduction in platelet– vessel wall contact as the haematocrit decreases. Bleeding is most commonly into the skin and mucous membranes and gastrointes- tinal haemorrhage is common. Haemodialysis and peritoneal dia- lysis reduce the bleeding tendency without any appreciable effect on tests of platelet function. 1-deamino-8-d-arginine vasopressin (DDAVP) improves haemostasis. Correction of anaemia by transfu- sion or erythropoietin therapy to maintain the haemoglobin above 100 g/litre is beneficial. Administration of conjugated oestrogens has also been reported to reduce the bleeding tendency. Liver disease The PT and APTT are frequently abnormal in patients with ad- vanced liver disease but correction of abnormalities with fresh frozen plasma is only indicated if there is active bleeding or in an- ticipation of an invasive procedure. The liver is the site of synthesis of the majority of proteins involved in haemostasis. In cirrhosis, there is deficient production of coagulation factors compounded by pro- duction of dysfunctional factors (due to defective post-translational carboxylation) with thrombocytopenia due to portal hypertension with hypersplenism and in some case defective marrow platelet production. Platelet function is defective. In obstructive jaundice, there is production of dysfunctional factors which respond initially to intravenous vitamin K. In acute hepatitis, there is predominantly a consumptive coagulopathy due to DIC. In advanced liver dis- ease and hepatoma, there may be additional dysfibrinogenaemia. Hypofibrinogenaemia with a fibrinogen level less than 1 g/litre occurs with fulminant hepatic failure. Reduced clearance of tissue plasminogen activator may cause hyperfibrinolysis which contrib- utes to bleeding. A variable degree of DIC may be present in patients with chronic liver disease and acute DIC may be precipitated by infection. Transfusion of platelets, fresh frozen plasma, PCC (con- taining factors II, VII, IX, and X), and fibrinogen (or cryoprecipitate as a source of fibrinogen) will depend on individual circumstances. Parenteral vitamin K should always be considered and frequently a trial of therapy is required, for example, 10 mg daily for 3 days. Acquired haemophilia and acquired von Willebrand syndrome Acquired inhibitors are rare and most often autoantibodies. Platelet autoantibodies result in shortened platelet survival and thrombo- cytopenia (ITP). The bleeding manifestations of ITP are variable

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