Acquired bleeding disorders

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Bleeding disorders are divided into two broad categories, i.e. inherited, discussed in part 1 of this CME series, and acquired, which is the subject of discussion in the current issue. In contrast to inherited haemorrhagic disorders, where generally a single haemostatic abnormality is found, multiple haemostatic defects are commonly present in acquired haemorrhagic diseases. Bleeding is often a presenting manifestation of systemic disease and requires a multidisciplinary team approach. Iatrogenic causes of abnormal haemostasis are of particular importance to the emergency physician. This CME article aims to provide an approach to the diagnosis and management of acquired bleeding disorders encountered in general practice.

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Acquired bleeding disorders encompass a heterogeneous group of conditions with varied and often complex aetiologies. Clinical evaluation of patients presenting with a bleeding disorder often provides clues as to whether the abnormality resides in coagulation factors, platelets or blood vessels. A detailed history and complete physical examination are therefore imperative for meaningful interpretation of laboratory tests, as complex haemostatic derangements may accompany specific clinical scenarios. Interpretation based solely on laboratory tests may be misleading.

For discussion purposes, acquired bleeding disorders are divided into the following groups: (*i*) clotting factor deficiencies; (*ii*) abnormalities of platelet number or function; (*iii*) vascular defects; or (*iv*) various combinations of the three abovementioned disorders. The last group includes liver disease, disseminated intravascular coagulation (DIC) and chronic kidney disease.

Basic laboratory tests (partial thromboplastin time (PTT), international normalised ratio (INR), full blood count (with peripheral blood smear assessment)) and accurate clinical information form a basis for further investigations. To this end, an algorithmic approach is incorporated to serve as a guide (Fig. 1).

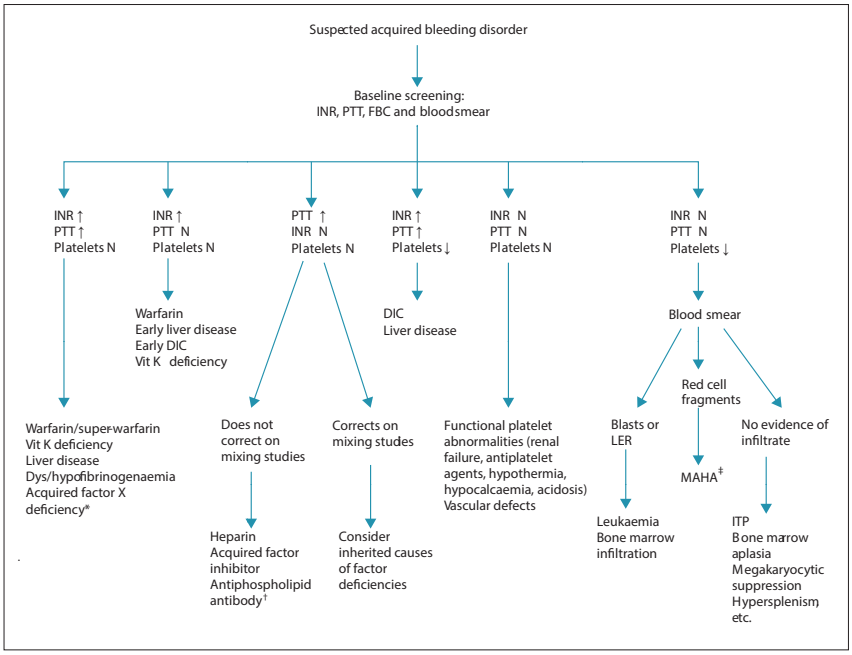

*Fig. 1. Laboratory approach to a suspected acquired bleeding disorder. (LER = leuko-erythroblastic blood reaction (signifying possible bone marrow infiltration); INR = international normalised ratio; PTT = partial prothrombin time; N = normal; FBC = full blood count; DIC = disseminated intravascular coagulation; vit = vitamin; MAHA = microangiopathic haemolytic anaemia; ITP = immune thrombocytopenia.) (*Associated with amyloidosis; †Antiphospholipid antibodies usually cause thrombosis, not bleeding; however, rare instances of prothrombin deficiency can be associated with bleeding; ‡Except for DIC.)*

Clotting factor deficiencies

Coagulation factor inhibitors

Coagulation factor inhibitors are antibodies that neutralise specific coagulation factors. These antibodies can develop against any factor in the coagulation cascade, but factor VIII (FVIII) is most frequently involved, and may develop in patients with inherited haemophilia A as an immune response to factor-replacement therapy, or spontaneously as auto-antibodies, resulting in the bleeding condition termed acquired haemophilia. The presence of inhibitors is suspected in a patient with abnormal bleeding without any prior bleeding diathesis, or when a patient with known haemophilia has more extreme bleeding

than usual or fails to achieve haemostasis after factor replacement. Prolongation of the screening clotting assays, i.e. INR and/or PTT, with failure to correct on mixing with normal plasma, should alert the attending clinician to the presence of an inhibitor.

Factor inhibitors in inherited haemophilia A and B

This has been discussed in part 1 of this series.[1]

Acquired haemophilia A

Acquired haemophilia A (AHA) is a rare (~1 per million of the population per year), potentially life-threatening auto-immune bleeding disorder due to inhibiting auto-antibodies (inhibitors) against endogenous FVIII. Although documented as a rare condition, AHA is probably under-diagnosed. Mortality in cases of AHA exceeds 20% in patients >65 years of age and those with comorbid disease, such as underlying malignancies. Although death directly due to excessive bleeding is not common, it does contribute to morbidity, thereby increasing the duration and cost of hospitalisation (e.g. delayed wound healing and increased transfusion requirements). Immune modulation therapy to eradicate the inhibitor also contributes significantly to cost and mortality. In contrast to inherited haemophilia, AHA affects both males and females and is most common in the elderly (median age 64 - 78 years). AHA can, however, occur in younger patients in relation to pregnancy and auto-immune diseases. Most cases are idiopathic, but underlying precipitating causes include pregnancy, auto-immune diseases (most commonly rheumatoid arthritis), infection, malignancy and drugs (e.g. interferon alpha). Research suggests that the breakdown of immune tolerance to FVIII is due to both genetic and environmental factors. The majority (94.6%) of patients present with bleeding, which can either be spontaneous or provoked, e.g. after surgery. The site of bleeding is most commonly subcutaneous, followed by the gastrointestinal tract, intramuscular sites and genito-urinary tract. Bleeding in other sites (intracranial and retroperitoneal) can occur, but in contrast to congenital haemophilia, joint bleeding is infrequent. Because of the second-order (non-linear) kinetics of the anti-FVIII antibodies in AHA, FVIII levels are not predictive of bleeding risk and patients can have serious bleeding despite having only modestly reduced laboratory-determined FVIII activity levels.

Inhibitors to other coagulation factors

Inhibitors to other coagulation factors, i.e. fibrinogen, FII, FV, FVII, FIX, FX, FXI, FXIII and von Willebrand factor, do occur but are rare. Correct identification and quantification are, however, indicated for appropriate therapy. As with haemophilia A, these inhibitors develop either in patients with congenital deficiencies related to exposure to replacement therapy or spontaneously in people without a prior bleeding disorder. As with AHA, precipitating factors for spontaneous development of inhibitors include infections, drug exposure, auto-immune diseases, blood transfusions and underlying malignancies.[2]

Diagnosis

Depending on the position of the affected factor in the coagulation cascade, the screening assays, i.e. PTT and/or INR, will be prolonged. Other causes of prolonged screening tests, such as lupus anticoagulant and anticoagulant drugs, e.g. heparin, should be excluded prior to identification and quantification of the coagulation factor inhibitor.

The most common laboratory observation in AHA is a prolonged PTT that does not correct with mixing with normal plasma after incubation, together with a normal INR, thrombin time and platelet count.[2,3]

Management

Management of patients with acquired inhibitors entails: (*i*) control of bleeding with haemostatic agents, as for inherited haemophilia patients with inhibitors (part 1);[1] (*ii*) eradication of the inhibitor with immune modulating agents (e.g. corticosteroids and rituximab); and (*iii*) treatment of the underlying pathogenic disease process. Thrombotic complications, including myocardial infarctions and cerebrovascular accidents, can occur in relation to haemostatic agent administration.[2-6]

Vitamin K deficiency

Vitamin K is responsible for gammacarboxylation of FII, FVII, FIX and FX, as well as for proteins C, S and Z. Gammacarboxylation enables binding to phospholipid membranes via Ca^{++} bridges. Vitamin K deficiency is encountered in various clinical scenarios and causes include: haemorrhagic disease of the newborn (currently termed vitamin K deficiency bleeding), reduced dietary intake, prolonged antibiotic use, cholestatic liver disease, malabsorption, and drugs, e.g. anticonvulsants and warfarin. The mode of therapy is oral or intravenous vitamin K, and patients with severe bleeding are treated with fresh-frozen plasma (FFP) or prothrombin complex concentrate (PCC).

Anticoagulation and antiplatelet agents

Warfarin

Warfarin, a coumarin derivative, inhibits the enzyme vitamin K epoxide reductase and thereby impairs production of vitamin K-dependent coagulation factors, i.e. FII, FVII, FIX and FX, as well as proteins C, S and Z. Patients treated with coumarin derivatives have reduced concentrations of these coagulation factors, with consequent increased risk of bleeding that is amplified when the INR is supratherapeutic (particularly >5). Other factors that increase the bleeding risk include advanced age, a prior history of bleeding, previous stroke, hypertension, other drugs associated with a bleeding risk (such as non-steroidal anti-inflammatory drugs (NSAIDs)), and abnormal liver or renal function.

Management of warfarin-associated bleeding depends on the severity of bleeding, the level of the INR and the indication for anticoagulation. For over-warfarinisation without bleeding, stoppage of warfarin with possible oral vitamin K administration is usually sufficient. However, if this is accompanied by significant bleeding, reversal of anticoagulation with factor replacement becomes necessary (Table 1).[7]

As for patients scheduled for surgery, anticoagulant reversal must be done before surgery to restore normal coagulation status.

Heparin

Heparin is an anticoagulant that works by binding to and potentiating the activity of antithrombin, which then inhibits thrombin. Heparin is used for the treatment and prevention of thrombosis.

High doses of heparin can cause severe bleeding. In this event, discontinuation of heparin is usually sufficient owing to its short half-life of 8 hours. If rapid reversal of heparin effect is required, protamine sulphate is very effective for unfractionated heparin, but only reverses ~60% of the antifactor Xa activity of low-molecular-weight heparin, and has negligible effects on fondaparinux and danaparoid (a mixture of anticoagulant glycosaminoglycans used to treat heparin-induced thrombocytopenia).[8,9]

Non-vitamin K antagonist oral anticoagulants

Non-vitamin K antagonist oral anticoagulants (NOACs) include thrombin inhibitors, e.g. dabigatran, and FXa inhibitors, e.g. rivaroxaban and apixaban. Outcomes of major bleeding are no worse than with

Table 1. Management of over-warfarinisation

INR 4.0 - 5.0 and no significant bleeding	Omit one dose
	Decrease weekly dose by ~10 - 20% and re-check in 5 -7 days
INR 5.0 - 9.0 and no significant bleeding	Stop warfarin therapy
	Oral vitamin K 1.0 - 2.5 mg (0.1 - 0.25 mL Konakion) if the patient is at high risk of bleeding*
	Monitor INR every 2nd day until in therapeutic range
	Vitamin K may need to be repeated
	Decrease weekly dose of warfarin by 20% once INR therapeutic range has been reached
INR >9.0 and no significant bleeding	Stop warfarin therapy
	Give oral vitamin K 2.5 - 5.0 mg (0.25 - 0.5 mL Konakion)*
	Vitamin K may need to be repeated
	Monitor INR daily until therapeutic range has been reached
	Decrease weekly dose of warfarin by 20% once INR is in the therapeutic range
Prolonged INR and significant bleeding	Stop warfarin therapy
	Administer PCC 50 U/kg or FFP 15 - 20 mL/kg or Bioplasma FDP
	Administer vitamin K 1.0 - 2.0 mg IVI slowly (can be repeated)
	Monitor INR daily

INR = international normalised ratio; PCC = prothrombin complex concentrate; FFP = fresh-frozen plasma; FDP = freeze-dried plasma; IVI = intravenous infusion.
*Oral vitamin K should be administered with caution to patients with prosthetic heart valves.

vitamin K antagonists. Three NOAC reversal agents are in various stages of development, i.e. idarucizumab for thrombin inhibitors, andexanet for FXa inhibitors, and ciraparantag for all NOACs.[10]

Antiplatelet agents

Aspirin exerts its antiplatelet effect by irreversibly binding to the enzyme cyclo-oxygenase. Other antiplatelet agents include NSAIDs and adenosine diphosphate (ADP) receptor inhibitors, such as clopidogrel (Plavix). Mild bleeding and bruising may occur in response to trauma or surgery, but are likely to be exacerbated with coexisting medical conditions, such as haemophilia, renal disease and leukaemia. More severe spontaneous bleeds, e.g. from the gastrointestinal tract, occur less frequently. The effect of aspirin and clopidogrel lasts for 5 - 7 days, i.e. the entire lifespan of the platelet.

Abnormalities of platelet number

Platelet defects are typically associated with mucocutaneous bleeding, with the severity depending on the degree of the thrombocytopenia. In general, the risk of bleeding is low when platelets are >80 × 10^9/L, and significantly increased when the platelet count is <20 × 10^9/L (where spontaneous bleeding may occur). Platelet transfusion is indicated in all bleeding patients to maintain a platelet count of 50 - 100 × 10^9/L (depending on the site of blood loss), as well as in selected patients with a platelet count <20 × 10^9/L as bleeding prophylaxis. Causes of thrombocytopenia are divided into: (*i*) central (production failure); and (*ii*) peripheral (reduced survival). These are summarised in Table 2, and some of the more important causes are discussed below.

Immune thrombocytopenia

Immune thrombocytopenia (ITP) is an acquired, auto-immune disorder with the formation of antiplatelet antibodies against platelets and megakaryocytes, resulting in increased destruction and inadequate production of platelets.[11,12]

The term ITP refers to immune thrombocytopenia and no longer to the older term idiopathic thrombocytopenic purpura. The threshold for ITP and for clinical thrombocytopenia is defined as a platelet count <100 × 10^9/L.[13]

The incidence of ITP is ~3 - 4.5/100 000/year.[14,15] In South Africa (SA), primary ITP predominantly affects young females.[16] In Europe, however, the median age is 57 years, with a rising incidence with advancing age (>60 years) and a less marked gender difference.[14,15]

The presentation of ITP may be acute or insidious. Three phases of ITP are recognised: (*i*) newly diagnosed (0 - 3 months from diagnosis); (*ii*) persistent (3 - 12 months); and (*iii*) chronic (>12 months).[13] Most adult patients go on to develop chronic ITP. Spontaneous remissions occur in 5 - 11% of adults, mostly in the first year after diagnosis.[17] ITP may be primary (~80% of cases), with no identifiable cause, or secondary (~20% of cases), due to a number of causes. In SA, a paradigm shift has been noted, with an increasing number of patients with secondary ITP, largely due to HIV infection.[16]

Primary ITP is a diagnosis of exclusion. Secondary causes need to be excluded, including infections (e.g. HIV), auto-immune disorders (e.g. systemic lupus erythematosus), drugs (e.g. rifampicin, quinine and heparin), and lymphoproliferative disorders (e.g. chronic lymphocytic leukaemia, and lymphoma). In the classic patient with primary ITP (young female, isolated thrombocytopenia, no abnormalities on the peripheral smear such as fragments or atypical cells), a bone marrow aspirate and trephine biopsy (BMAT) is not indicated.[18] However, in patients with a suspected secondary cause, or in whom the presentation is atypical, or in individuals >60 years of age, a BMAT must be performed.

Patients with ITP may be asymptomatic (where the platelet count is usually >30 × 10^9/L) or may present with bleeding, which is typically of the mucocutaneous type. The incidence of major bleeding events, such as intracranial haemorrhage and cavity bleeding, is low. The platelet count remains the best known predictor of bleeding events in ITP. Lymphadenopathy and hepatosplenomegaly are generally not encountered in primary ITP and, if present, indicate another cause or secondary ITP.

The decision to initiate treatment is primarily based on whether the patient is symptomatic (bleeding) and the level of the platelet count (<30 × 10^9/L). The goal of treatment is to stop the bleeding and increase the platelet count to a safe level and not necessarily to achieve a normal platelet count.

Therapeutic agents used in the treatment of ITP are presented in Table 3.

Corticosteroids (CS) are the mainstay of treatment in newly diagnosed ITP. Prednisone is the preferred initial treatment. Alternative CS include dexamethasone and methylprednisolone.

Table 2. Causes of thrombocytopenia

Spurious (*in vitro* laboratory artefact)
Platelet clumping
A clotted sample
Reduced survival
Immune thrombocytopenia
Primary (idiopathic)
Secondary (infection, drugs,*† auto-immune disease, lymphoproliferative disorder)
Micro-angiopathic haemolytic anaemia
Disseminated intravascular coagulation
Thrombotic thrombocytopenic purpura
Haemolytic uraemic syndrome
HELLP syndrome/pre-eclampsia
Hypersplenism
Production failure
Hypoplastic/aplastic anaemia
Inherited
Acquired
Bone marrow infiltration/replacement
Malignancy
Granulomatous inflammation
Myelofibrosis
Ineffective megakaryopoiesis
Vitamin B_{12} or folic acid deficiency
Drugs, e.g. folate antagonists, such as methotrexate and trimethoprim
Infection, such as HIV
Myelodysplastic syndrome
Direct megakaryocyte suppression
Drugs, e.g. thiazides, tolbutamide
Alcohol
Viral infection of megakaryocytes, e.g. CMV, HIV
Thrombopoietin deficiency
Liver disease

HELLP = haemolysis, elevated liver enzymes, low platelets; CMV = cytomegalovirus.
*Including cephalosporins, ciprofloxacin, clarithromycin, fluconazole, penicillins, sulfamethoxazole and vancomycin.
†>50 drugs have been associated with definite evidence of immune-mediated thrombocytopenia.

Table 3. Therapeutic agents and dosing schedules employed in the treatment of immune thrombocytopenic purpura in adults

Treatment	Agent	Dose	Duration
First line	Prednisone	1 - 2 mg/kg/day orally/IVI	2 - 3 weeks, then tapered over 4 - 6 weeks
	Dexamethasone	40 mg/day orally/IVI	4 days
	Methylprednisolone	1 g/day IVI	3 days
	Immunoglobulin (IV Ig)	1 g/kg/day IVI	1 - 2 days
		or 400 mg/kg/day	3 - 5 days
Second line	Azathioprine	1 - 2 mg/kg/day orally	Maximum dose 150 mg/day
	Mycophenolate mofetil	1 000 mg bid	Minimum 4 weeks
		or 500 mg qid orally	
	Cyclophosphamide	1 - 2 mg/kg/day orally	Up to or >4 months if necessary
	Danazol	200 mg bid up to qid orally	At the discretion of the clinician
	Vincristine	1 - 2 mg IVI weekly	Up to a total of 6 mg
	Rituximab	375 mg/m^2 IVI weekly	4 weeks
	Romiplostim	3 - 10 mg/kg/week subcutaneously	>1 year

IVI = intravenous infusion; IV Ig = intravenous immunoglobulin.

Platelet transfusions are reserved for patients with severe thrombocytopenia with active bleeding or recent onset of 'red purpura', such as oral haemorrhagic bullae. Platelet transfusion is not indicated in patients without bleeding, irrespective of the severity of the thrombocytopenia.

For emergency treatment, intravenous immunoglobulin (IV Ig) and IV/oral CS should be used in combination with platelet transfusions. Emergency splenectomy may rarely be necessary in such patients.

For persistent ITP, treatment options include CS and second-line immunosuppressive agents (such as azathioprine and mycophenolate

mofetil) as steroid-sparing drugs. If these prove unsuccessful, other second-line agents, such as cyclophosphamide, danazol and vincristine, may be considered. Alternative drugs include rituximab and thrombopoietin-receptor agonists (TPO-RAs). The choice of second-line therapies depends on the experience of the clinician, efficacy and safety of the drug, availability, cost and patient preferences.

Chronic ITP refers to disease that continues for >12 months. It is likely that the patient has been on intermittent CS and/or other immunosuppressive or second-line therapy, with a variable clinical response. The three major treatment options for chronic ITP include splenectomy, TPO-RAs and rituximab. Each of these options has advantages and disadvantages and treatment must be individualised to the patient.

Splenectomy is the most definitive therapy for ITP and is effective for persistent and chronic ITP after failure of CS therapy. It is recommended that splenectomy be delayed for at least 6 months (preferably 12 months) from diagnosis, as there is a chance of spontaneous remission in 5 - 11% of cases.[17] The overall response rate is 70 - 90% (complete response 50 - 60%, partial response 20 - 30%). The efficacy of open splenectomy and laparoscopic splenectomy is similar. However, laparoscopic splenectomy has fewer surgical complications, including less postoperative pain, earlier diet tolerance and shorter hospital stay. The risk of overwhelming post-splenectomy infection is increased 1.4-fold in the first year after the procedure. Vaccination against *Streptococcus pneumoniae, Neisseria meningitides* and *Haemophilus influenzae* is recommended 2 weeks prior to the procedure.[19,20] If relapse occurs post splenectomy, accessory splenic tissue (splenunculi) should be excluded. In two recent local studies it was indicated that splenectomy is beneficial and may be considered as the preferred second-line therapy in chronic ITP and failed CS therapy, especially in the SA public health sector.[16,21]

Two TPO-RAs are currently available for use in ITP, romiplostim and eltrombopag. These agents are effective in both splenectomised and non-splenectomised patients, with a response rate of up to 88%. To maintain durable remission, treatment is usually required for months to years before discontinuation. Currently, the high cost of TPO-RAs prohibits their use in the public health sector.[22,23]

Rituximab is an anti-CD20 monoclonal antibody, with an off-label indication in patients with ITP.[24] Remission with rituximab occurs in up to two-thirds of patients but is durable in only one-third. However, the combination of rituximab and high-dose dexamethasone has shown a response rate of 71%, with a durable remission rate of 57%.[25] A higher risk of infection is anticipated with the use of rituximab.

Locally, there is an increase in secondary ITP, particularly in association with HIV.[16,21] The presentation of secondary ITP is identical to that of primary ITP, except for an increased likelihood of cytopenias and association of lymphadenopathy and hepatosplenomegaly.

The acute management of secondary ITP is identical to that of primary ITP, with the important proviso that the underlying cause be specifically treated (e.g. institution of antiretroviral therapy if patients are HIV-positive, removal of offending drug). With HIV, there is a potentially higher risk of infection, which may be exacerbated by immunosuppressive drugs and splenectomy. Although the duration to platelet recovery is slower in HIV-seropositive patients with ITP, the overall response to treatment is similar to that in the HIV-negative counterpart.[16] Splenectomy has been shown to be effective and safe, irrespective of the HIV status of the patient, and remains an appropriate second-line treatment for ITP.[21]

Micro-angiopathic haemolytic anaemia

Micro-angiopathic haemolytic anaemia (MAHA) encompasses a group of entities that are associated with red cell fragmentation haemolysis and thrombocytopenia (Table 4). Although MAHA may be complicated by thrombocytopenia-related blood loss, the risk of bleeding is significantly higher among patients with DIC. In contrast, bleeding is an unusual complication in thrombotic thrombocytopenic purpura (TTP), despite the thrombocytopenia often being very severe ($<10 \times 10^9$/L).

DIC is characterised by systemic activation of the coagulation cascade with production of microthrombi in the small vessels of multiple organs, resulting in organ dysfunction and consumption of coagulation factors and platelets.[26] It can manifest with bleeding and/or thromboembolism, depending on the rate of fibrinolysis and coagulation factor consumption relative to the compensatory production of these proteins. Causes of DIC include severe sepsis, obstetric calamities, major trauma and some malignancies (particularly acute promyelocytic leukaemia). All of these can result in systemic coagulation activation, either by exposing procoagulant proteins, or by generating procoagulant cytokines. It is diagnosed by demonstrating evidence of the following:

- consumption of blood clotting factors, leading to prolongation of the INR and/or PTT, with a decreasing fibrinogen level. Fibrinogen is, however, an acute-phase reactant, and is therefore not invariably low in patients with DIC
- consumption of anticoagulant molecules (such as antithrombin)
- accumulation of the products of fibrinolysis (such as D-dimers)
- a decreasing platelet count.

The abovementioned factors are diagnostic in an appropriate clinical setting.

Treatment of DIC is aimed at active management of the underlying cause, and symptomatic management of the associated organ and coagulation abnormalities. Treatment options include FFP and platelet transfusions in the event of bleeding, or low-molecular-weight heparin therapy when thromboembolic phenomena predominate. The use of antifibrinolytic agents is generally not advised owing to the risk of exacerbation of the microvascular thrombotic process, but may be of benefit in patients with hyperfibrinolysis (typified by very low fibrinogen and markedly elevated D-dimer levels). The mortality rate associated with DIC is high, particularly in the presence of pronounced organ dysfunction or severe coagulopathy.

Organ dysfunction

Liver disease

Coagulopathy in patients with liver disease can be difficult to differentiate from laboratory-determined DIC values. Haemostatic abnormalities due to liver disease include:

- thrombocytopenia due to thrombopoietin deficiency, hypersplenism (if enlarged spleen) and possible megakaryocytic suppression (secondary to alcohol or hepatitis B or C infection)
- coagulopathy due to impaired production of clotting factors by the liver, vitamin K deficiency (e.g. alcohol abuse, obstructive jaundice), production of functionally abnormal fibrinogen (dysfibrinogenaemia)
- increased fibrin degradation products due to: (*i*) impaired hepatic clearance; and/or (*ii*) hyperfibrinolysis (impaired clearance of tissue plasminogen activator and decreased production of fibrinolytic inhibitors).

Table 4. Summary of common microangiopathic haemolytic anaemias

Microangiopathic entity	Common features	Causal/risk factors	Management
Disseminated intravascular coagulation	Anaemia and thrombocytopenia Red cell fragmentation Deranged coagulogram (↑ INR and/or PTT, ↑ D-dimers, ↓ fibrinogen and AT levels)	Major trauma Severe infection/sepsis Obstetric accidents Select malignancies Transfusion reaction Giant haemangiomas Liver disease	Treat underlying cause LMWH in early stages* Platelet/FFP/cryoprecipitate infusion if bleeding
Thrombotic thrombocytopenic purpura	Severe anaemia and thrombocytopenia Marked red cell fragmentation ± renal impairment ± fever ± fluctuating neurological manifestations ADAMSTS13 levels may be low	HIV infection Auto-immune disease Drugs (clopidogrel, ticlodipine, quinine) Metastatic adenocarcinoma Allogeneic stem cell/solid-organ transplantation Congenital deficiency of ADAMTS13 (rare)	Plasma exchange/infusion Corticosteroids Treat underlying cause Platelet transfusion C/I unless bleeding
Haemolytic uraemic syndrome	++ Red cell fragmentation Marked renal impairment Moderate anaemia and thrombocytopenia C'3 and C'4 levels may be low in aHUS	Shiga toxin-associated diarrhoeal illness *Shigella dysenteriae* *Escherichia coli* (O157:H7 & O104:H4) aHUS dysregulation of alternate C' pathway Congenital factor H or I deficiency/ antibodies to factor H	Supportive measures A trial of plasma exchange (aHUS) Eculizumab (aHUS) (limited availability) Dialysis – usually for aHUS
HELLP syndrome/pre-ecclampsia	Anaemia and thrombocytopenia Red cell fragments Raised AST/ALT Hypertension Headache and visual disturbance, RUQ pain, pulmonary oedema	Risk of recurrence in subsequent pregnancies	Emergency delivery by caesarean section

aHUS = atypical haemolytic uraemic syndrome; RUQ = right upper quadrant; INR = international normalised ratio; PTT = partial thromboplastin time; LMWH = low-molecular-weight heparin; AT = antithrombin; HELLP = haemolysis/elevated liver enzymes/low platelet count; ++ = moderate to severe; + = mild to moderate; FFP = fresh-frozen plasma; AST = aspartate transaminase; ALT = alanine transaminase; C' = complement; C/I = contraindicated.
*Particularly useful if the dominant clinical manifestations are thrombotic.

As there is a concomitant depletion of both pro- and anticoagulant molecules in patients with synthetic dysfunction of the liver, bleeding manifestations are often not as severe as would be anticipated from the degree of the laboratory derangements. However, associated renal dysfunction or infection can predispose to bleeding. In particular, gastrointestinal bleeding from oesophageal varices is a concern in patients with portal hypertension, requiring reduction of the portal pressure and ligation of the varices. Coagulation factor, fibrinogen and platelet replacement therapy may be needed, but caution should be exercised against liberal use of FFP in liver disease, as the plasma volume expansion may elevate portal pressure and thereby paradoxically increase the risk of variceal bleeding.[27] Bleeding due to hyperfibrinolysis, diagnosed with viscoelastic tests such as the thromboelastogram (TEG), can respond to antifibrinolytic agents, e.g. tranexamic acid.

Renal disease

Numerous haemostatic disturbances are observed in renal disease, which may predispose to a hypo- or hypercoagulable state. There is no superior pathogenic factor to determine whether a patient would be prone to bleeding or thrombosis, where the dynamics of events are often influenced by comorbid factors.[28] Tendency to bleed is caused by platelet dysfunction (due to accumulation of toxic metabolites, fibrinogen degradation products, anaemia, drugs, etc.) and decreased FXI/XII level. Desmopressin and/or antifibrinolytics are generally effective in controlling uraemic bleeding.

Vascular defects

Acquired vascular bleeding disorders include the following:

Scurvy. Vitamin C promotes peptidyl hydroxylation of procollagen, and its deficiency causes abnormal collagen formation with defective perivascular support. This predisposes to capillary fragility and mucocutaneous bleeding. Treatment is with vitamin C 200 mg daily.

Henoch-Schönlein purpura. This idiopathic disorder is primarily a disease of children, but may occur at any age, and is characterised by abdominal colic, arthritis, nephritis and palpable purpura. Biopsy of the skin shows an acute immune-related vasculitis and complement/immunoglobulin complexes. Treatment entails supportive care and steroids in more severe cases.

Paraproteinaemia and amyloidosis. The mechanism of bleeding is multifactorial, including interference with coagulation factor levels/function, impaired platelet aggregation and deposits of light chain/amyloid fibrils in cutaneous blood vessels, with increased vessel fragility. Cryoglobulins may similarly deposit in dermal vessels and cause vasculitis and purpura. Management entails treatment of the underlying condition.

Senile purpura. In the elderly there is loss of subcutaneous collagen and elastin fibres. Bruising is usually induced by minor trauma.

Conclusion

Acquired bleeding disorders encompass a heterogeneous group of conditions with varied aetiologies. A detailed history and complete physical examination are imperative for meaningful interpretation of laboratory tests and appropriate treatment. Bleeding is often a presenting manifestation of systemic disease and therefore necessitates a multidisciplinary team approach.

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