Bleeding and thrombosis

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Bleeding and thrombosis

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Update Info

Intended Learning Outcomes

Bleeding and thrombosis

1. Describe the physiology of normal coagulation
2. Describe common bleeding disorders in the critically ill and discuss the appropriate treatment with surgery, haemostatic interventions, blood components and pharmacological agents
3. Interpret traditional laboratory tests of coagulation and point of care assessment of coagulation
4. Diagnose and manage thrombotic disorders that occur in the critically ill
5. Discuss traditional antithrombotic drugs and new oral anticoagulants
6. Discuss management of anticoagulation and bleeding associated with novel technologies in organ support

eModule Information

Relevant Competencies from CoBaTrICE

Bleeding and thrombosis
• **3.1** Manages the care of the critically ill patient with specific acute medical conditions

1. Introduction

Critically ill **patients** are inherently at risk of thrombotic events due to severity of illness, immobilization and altered coagulation. Less frequently, patients are admitted to the emergency room with haemorrhagic shock or from the operating room with a coagulopathy. Knowledge of normal haemostasis and disorders of coagulation are paramount to achieving optimal outcomes. The incidence of drug-induced and circuit-induced coagulopathies is increasing with the advent of new pharmacological agents and novel modes of organ support aimed at prolonging life. We discuss aetiology and management of thrombotic and bleeding events in critical care patients.

2. Normal Haemostasis

When vessel injury occurs, a series of events results in wound sealing and prevention of bleeding. These include generation of a platelet plug, activation of the coagulation cascade and formation of a stable cross-linked fibrin clot. Strict local control mechanisms localise the clot to the site of injury.

> **Note**
>
> Platelet recruitment and activation are the initial events that occur following vascular endothelial injury

First, platelets adhere to the site of tissue damage, become activated and spread on the exposed subendothelial surface to form large platelet aggregates. This process is critically dependent upon VWF, a large protein that facilitates platelet binding to exposed collagen. Platelets adhere weakly at first. Then, platelet interactions with collagen and vWF facilitate stable platelet adhesion. Once anchored at the site of injury, platelet activation results in the release of mediators such as adenosine diphosphate (ADP), serotonin and thromboxane A2, which activates more platelets. Activated platelets provide an important phospholipid (PL) surface for the activation of the coagulation pathways leading to the formation of fibrin.

> **Note**
>
> Next, the tissue factor-dependent extrinsic pathway is activated, resulting in propagation of the coagulation cascade.

Simultaneously, the tissue factor (TF)-dependent, or the extrinsic pathway of blood coagulation begins. This occurs when TF on the surface of leukocytes and insubendothelial matrix is exposed. Blood coagulation is initiated by the complex of activated factor VII (FVIIa) and TF, which catalyzes the activation of factor X (FX) and factor IX (FIX) (Figure 1).

Under normal circumstances, TF is not exposed to blood, however this may occur following vascular injury or following induction of cellular TF expression. For example, TF expression can be induced in peripheral blood monocytes in response to bacterial lipopolysaccharide exposure or sepsis.

> **Note**
>
> An amplification process, the contact – or “intrinsic pathway” – is activated by components of the injured vasculature

Coagulation may also be activated by the contact – or “intrinsic” – “pathway” (Figure 1). In this pathway, components entirely contained within the vasculature (including high molecular weight kininogen, pre-kallikrein and FXII) initiate blood coagulation, resulting in activation of FXI. The result of this pathway is FXIa-mediated FIX activation, which activates FX.

FXa activates prothrombin to generate thrombin. Thrombin then cleaves fibrinogen to generate fibrin, the main protein constituent of the final blood clot. This causes fibrin to polymerize forming an insoluble fibrous mesh, which incorporates platelets and VWF. This fibrin “clot” is stabilized by FXIII, which is activated by thrombin and covalently cross-links fibrin. Thrombin also feeds back and activates FV and FVIII. This results in rapid amplification of thrombin generation due to generation of powerful cofactors in the coagulation cascade - (Figure 1). Thrombin also activates other pro-coagulant and anticoagulant clotting factors and platelets.

Note

Thrombin cleaves fibrinogen to generate fibrin, the main component of the ‘fibrin mesh’

Once formed, a tightly regulated process known as fibrinolysis breaks down the stable blood clot. In this process, plasminogen is activated to plasmin, which in turn degrades fibrin. The two major plasminogen activators are tissue plasminogen activator (tPA) and urokinase plasminogen activator (uPA). Plasminogen activator inhibitor (PAI)-1, PAI-2 and α2-antiplasmin inhibit fibrinolysis.

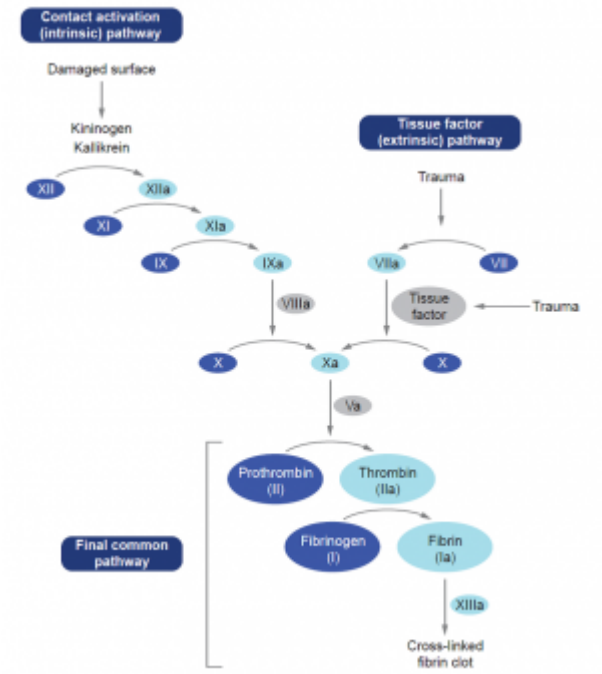

Figure 1 :The coagulation cascade

During blood coagulation, protease-cofactor complexes assemble on a negatively charged membrane surface. The extrinsic tenase complex (TF/FVIIa), the intrinsic tenase complex (FVIIIa/FIXa) and the prothrombinase complex (FVa/FXa) are the three major enzyme complexes, which assemble during coagulation. All of these complexes require the presence of Ca_2 + and phospholipid in order to function. The end result of blood coagulation is the formation of a fibrin clot. XII, factor XII, etc.; XIIa, activated factor XIIa , etc.

During blood coagulation, coagulation proteins assemble on a negatively charged membrane surface. Blood coagulation enzymes require the presence of Ca_2+ and phospholipid in order to function. The end result of blood coagulation is the formation

of a fibrin clot.

Note

Calcium is an important co-factor in the extrinsic, intrinsic and prothrombin tenase pathways, deficiency of which can contribute to coagulopathy.

Coagulation is tightly regulated. The healthy vessel lining (endothelium) is intrinsically anticoagulant. Also, blood coagulation is tightly regulated by various anticoagulant pathways, including antithrombin (AT) and the protein C pathway. AT inhibits thrombin, FIXa, FXa and FXIa. Heparan sulphate and heparin molecules interact with AT and enhance its anticoagulant function. Protein C is activated to activated protein C (APC) by thrombin bound to a cell surface receptor.

APC inhibits coagulation by cleaving the powerful cofactors FVa and FVIIIa, in the presence of protein S. In addition, APC has recently been shown to possess signalling properties that mediate anti-inflammatory, anti-apoptotic and endothelial barrier protective effects.

In summary, normal coagulation requires firstly platelet activation and aggregation. Almost simultaneously, the coagulation cascade is activated. The combined effect of the intrinsic and extrinsic pathways form prothrombinase, which cleaves prothrombin to thrombin. Thrombin cleaves fibrinogen to generate fibrin, the main component of the “fibrin mesh”. This fibrin mesh stabilizes the previously formed platelet plug.

In text References

(Furie and Furie. 2008)

References

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3. Coagulation Tests

3. 1. Prothrombin Time and INR:

Prothrombin time (PT) is used to test the activity of coagulation factors in the extrinsic pathway (tissue factor TF and factor VII) and final common pathway (factors X and V, prothrombin and fibrinogen). To account for local differences in TF preparations used in the PT test, the results are often expressed as an INR. The INR is the ratio of the patient PT compared with a normal control raised to the power of the International Sensitivity Index. A specific index is assigned to each batch of locally produced TF, which compares its performance to an international standard.

The following are causes of a prolonged prothrombin time (PT):

- Warfarin therapy
- Vitamin K deficiency
- Severe liver failure
- Deficiencies of extrinsic pathway factors (TF, FVII)
- Deficiencies of common pathway factors (FX, FV, prothrombin and fibrinogen)
- Antiphospholipid antibodies with anti-prothrombin activity

> **Note**
>
> Prothrombin Time (PT) is used to test the activity of coagulation factors in the extrinsic pathway and common pathway

INR is commonly used to monitor the therapeutic effect of Warfarin. Warfarin is a vitamin K antagonist (VKA). It inhibits vitamin K epoxide reductase, an enzyme required for reduction of the oxidised form of vitamin K. Reduced vitamin K is a cofactor in the gamma carboxylation of clotting factors II, VII, IX and X. Protein C and S are also impacted by VKA. Inactivation of these clotting factors prolongs PT. INR is commonly used to monitor the therapeutic effects of Warfarin.

> **Note**
>
> Warfarin therapy results in decreased hepatic production of factors II, VII, IX and X

3. 2. Activated Partial Thromboplastin Time

The activated partial thromboplastin time (APTT) is used to test the activity of coagulation factors in the intrinsic and common pathways. Phospholipid and negatively charged particulate matter (silica, celite, kaolin) are added to plasma to generate a fibrin clot. Abnormalities in the intrinsic (prekallikrein, high-molecular-weight kininogen and factors XII, XI, IX and VIII) and common (factors X and V, prothrombin and fibrinogen) pathways prolong the APTT.

The following are causes of a prolonged APTT:

- Heparin therapy (or heparin contamination of sample)
- Haemophilia A (deficiency of FVIII)
- Haemophilia B (deficiency of FIX)
- Haemophilia C (deficiency of FXI)
- Antiphospholipid syndrome (‘lupus anticoagulant’)
- von Willebrand disease (severe)

> **Note**
>
> APTT is used to test the activity of coagulation factors in the intrinsic and common pathways

3. 3. Fibrinogen Levels

Adequate fibrinogen levels are required for formation of the fibrin mesh. Fibrinogen levels often fall in patients with diffuse bleeding as seen in disseminated intravascular coagulopathy and dilutional coagulopathy following massive blood transfusion. Both PT and APTT are likely to be prolonged when fibrinogen levels are decreased.

3. 4. Thrombin Time

The thrombin time (TT) measures the rate of conversion of fibrinogen to polymerised fibrin after the addition of thrombin to plasma.

The following are reasons for a prolonged TT:

- Heparin therapy (or heparin contamination of sample)
- Thrombin inhibitors (hirudin, argatroban, danaparoid)

- Hypofibrinogenaemia
- Fibrinogen degradation products (FDPs) and D-dimers
- High concentrations of serum proteins that interfere with fibrin polymerisation (e.g. multiple myeloma, amyloidosis).

3. 5. Activated Clotting Time

The activated clotting time (ACT) is used to monitor the anticoagulant effect of higher doses of heparin that are sufficient to infinitely prolong the APTT.

> **Note**
>
> ACT is used to monitor anticoagulation during cardiopulmonary bypass most often with an ACT goal of four times the preheparin ACT

3. 6. Fibrinogen Degradation Products and D-Dimers

Elevated FDPs are indicative of lysis of fibrinogen and non-cross linked fibrin, whereas increased D-dimers indicate lysis of already cross-linked fibrin. High concentrations of FDPs have an anticoagulant effect by inhibiting fibrin polymerisation and platelet function

Patients in Intensive Care may have a variety of coagulation abnormalities. These may be present at admission or develop during their stay. All abnormalities should be reviewed and a diagnosis considered. These are some common abnormalities that may be seen (the list is not exhaustive):

- Patients with a prolonged PT but a normal APTT have a problem in the extrinsic system (factor VII). The common causes of this include warfarin therapy, chronic liver failure and vitamin K deficiency
- Patients with a normal PT but prolonged APTT have a problem confined to the intrinsic pathway. The common causes of this include heparin therapy or contamination, antiphospholipid antibodies, haemophilia A and von Willebrand disease
- If the PT and APTT are both prolonged, the problem is likely to be an inherited defect in the final common pathway or a more complex acquired disorder of multiple pathways
- If both the PT and APTT are normal and the patient has diffuse clinical bleeding, the causes include thrombocytopenia, platelet dysfunction or von Willebrand disease.

@ **Communication**

Consult the haematology service for bleeding in patients with persistent prolongation of coagulation times.

3. 7. Thromboelastography

Thromboelastography (TEG), has been advocated as a more clinically relevant monitor of both coagulation and anticoagulation to other tests of coagulation. The ‘reaction time’ (r) represents the time taken for initial fibrin formation. The r-time is affected by heparin, warfarin, hypofibrinogenemia and hypercoagulability. Recent advances include the addition of tissue factor to TEG (rapid TEG), to accelerate results. The addition of heparinase (hTEG) allows assessment of clot stability during heparin therapy.

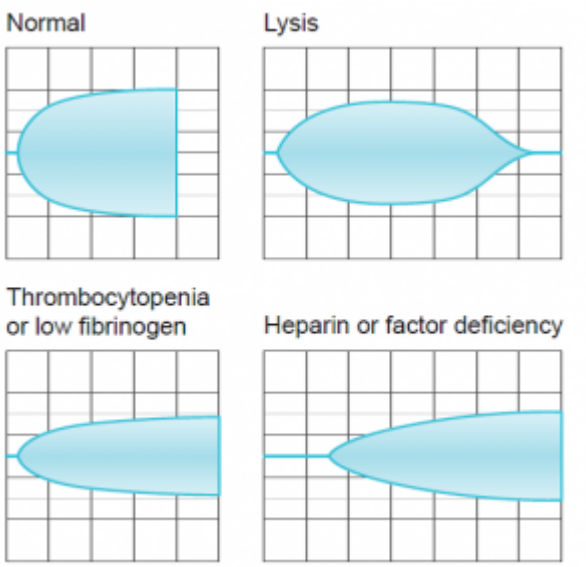

Figure 2: Thromboelastography

4. Thrombocytopenia in the Intensive Care Unit

4. 1. Introduction to thrombocytopenia

Thrombocytopenia is common in the critically ill population and is defined as a platelet count below the 2.5th percentile of the normal platelet count distribution. Individual laboratory reference ranges may vary in the precise definition of this lower limit. A systematic review of 24 studies enrolling 6894 patients from medical, surgical, mixed, cardiac and trauma intensive care units (ICUs) reported thrombocytopenia on admission to the ICU in 8.3-67.6% of patients. The incidence of thrombocytopenia acquired while in the ICU ranged from 13.0% to 44.1%.

Common risk factors for thrombocytopenia identified in multivariate analyses include:

- Increasing severity of illness
- Severity of organ dysfunction
- Sepsis
- Renal failure

4. 2. Diagnostic approach to thrombocytopenia

The diagnostic approach to thrombocytopenia in the critically ill patient differs to that in a healthy outpatient. The aetiology may be difficult to ascertain, as thrombocytopenia can be a manifestation of an underlying multi-systemic disorder or as a consequence of a treatment.

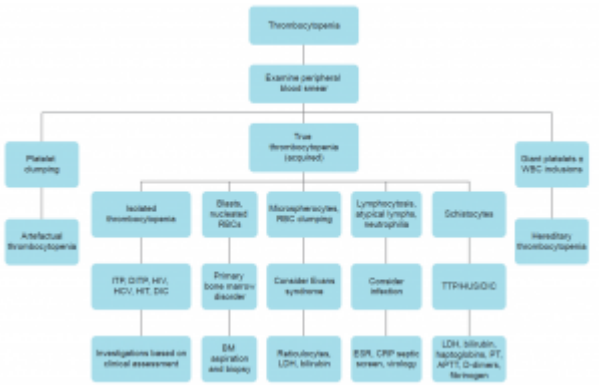

Figure 3: Diagnostic approach to

thrombocytopenia.

Figure 3: APTT, activated partial thromboplastin time; BM, bone marrow; CRP, C-reactive protein; DIC, disseminated intravascular coagulation; D-ITP, drug-induced immune thrombocytopaenia; ESR, erythrocyte sedimentation rate; HCV, hepatitis C virus; HIT, heparin-induced thrombocytopenia; HIV, human immunodeficiency virus; HUS, haemolytic uraemic syndrome; ITP, immune thrombocytopenia; LDH, lactate dehydrogenase; PT, prothrombin time; RBC, red blood cell; TTP, thrombotic thrombocytopenic purpura; WBC, white blood cell.

A low platelet count can occur as a result of increased peripheral platelet destruction, decreased bone marrow synthesis, haemodilution or platelet sequestration. Occasionally, a low platelet count may be artefactual due to preanalytical sampling issues or platelet ‘clumping’. Consequently, where unexpectedly low platelet counts are reported, a repeat sample should be requested and/or a blood smear examined.

Note

Thrombocytopenia may be due to decreased platelet production, increased destruction, sequestration, haemodilution or a laboratory error.

Rarely, where thrombocytopenia is accompanied by microangiopathic haemolytic anaemia, a diagnosis of a thrombotic microangiopathy should be considered. This spectrum of disorders is characterised by the presence of red blood cell fragments on the peripheral blood smear (Image 1) and may be accompanied by renal impairment, fever and/or neurological signs and symptoms.

The extreme end of the microangiopathic hemolytic anemia spectrum include the diagnoses of Thrombotic Thrombocytpenic Purpura (TTP) and Haemolytic Uremic Syndrome (HUS). These are life threatening conditions with mortality > 90% in the absence of specific treatment. ADAMTS-13 levels are used different between TTP and HUS with a ADAMTS-13 levels < 10% is supportive of TTP and mandates urgent plasmapheresis. This intervention in a time manner can has reduced mortality from TTP to approximately 10%.

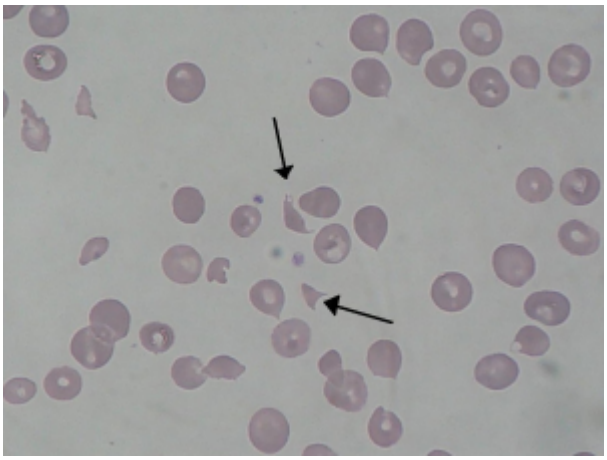

Figure 4: Blood smear with schistocytes (indicated by arrows).

Platelet sequestration may occur in congestive splenomegaly due to portal hypertension (as a consequence, for example, of liver cirrhosis) and is characterised by redistribution of platelets from the circulating pool to the splenic pool. In massive transfusion with red cells or crystalloid, dilution may result in a fall in platelet count.

4. 3. Approach to the thrombocytopenic patient

***History and Physical Examination**:*

In assessing the patient with thrombocytopenia, it is important to elicit the temporal profile of the thrombocytopenia and whether associated bleeding or thrombosis is a feature. Comorbidities should be noted, including liver disease, autoimmune disorders, malignancy and recent chemotherapy.

There are some important elements in a patient history that might point toward a bleeding diathesis. These include a patient or family history of:

- Spontaneous epistaxis
- Early bruising
- Haemarthrosis
- Prolonged bleeding post dental extraction
- Current herbal remedies
- Excessive bleeding post previous surgical procedure

Particular attention should be given to the presence or absence of documented infection, as sepsis is a major cause of thrombocytopenia in the ICU. Recent surgery (particularly cardiothoracic surgery) and/or insertion of devices associated with abnormal blood flow (including an intra-aortic balloon pump or left ventricular assist device) may be particularly relevant. Moreover, ICU patients develop thrombocytopenia following pulmonary artery catheterisation more frequently than non-catheterised control subjects.

Note

Sepsis is the most common reason for a low platelet count in the critically ill

A medication history should make note of drugs known to cause thrombocytopenia (including heparin, cephalosporins, linezolid and trimethoprim-sulfamethoxazole, carbapenams) and those that may worsen associated bleeding complications, including aspirin and non-steroidal anti-inflammatory drugs. As noted above, and as discussed in detail separately, anticoagulants may both potentiate bleeding or, in the

case of heparin, may be relevant in the direct pathogenesis of thrombocytopenia (HIT). The frequency of drug-induced thrombocytopenia in critically ill patients is approximately 20% and may be immune-mediated.

> **Note**
> Drug induced thrombocytopenia accounts for 20% of all causes of a low platelet count in the ICU

Recent travel, alcohol intake and family history of bleeding/thrombocytopenia should also be elicited. The physical examination should examine the pattern of bleeding, if any. A generalised microvascular bleeding pattern may represent systemic associated coagulopathy.

A recently diagnosed associated thrombotic event, particularly if it occurred at an unusual site, in a patient who has recently commenced heparin increases the clinical pretest probability of HIT. A full cardiorespiratory, neurological and gastrointestinal examination should be performed, including a specific evaluation of spleen size.

Thrombocytopenia in pregnancy demands special attention. Conditions associated with pregnancy-associated thrombocytopenia – including gestational thrombocytopenia, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome and preeclampsia – require specific monitoring and therapy in consultation with a maternal-foetal specialist. Severe maternal thrombocytopenia may have significant potential associated maternal and foetal complications, particularly at the time of labour and delivery. Written care pathways jointly agreed by ICU, obstetric and haematological care providers should be carefully implemented.

In text References

(Stasi 2012)

Laboratory findings:

A peripheral blood smear is an important initial investigation in the critically ill patient with thrombocytopenia. Correct interpretation may allow prompt recognition and treatment of a potentially fatal process such as a thrombotic microangiopathy and permits exclusion of platelet clumping as a cause of artefactual thrombocytopenia.

> **Note**
> A peripheral blood smear is an important initial investigation in a patient with thrombocytopenia

- Sepsis is the most common cause of a low platelet count in the critically ill. Findings on the peripheral blood smear consistent with infection include neutrophilia, toxic neutrophil granulation, lymphocytosis and atypical lymphocytes.

- Giant platelets in the presence or absence of white cell inclusion bodies may raise the possibility of a hereditary thrombocytopenia.
- Red blood cell fragments (schistocytes), particularly when in large number, raise the possibility of a thrombotic microangiopathy (including thrombotic thrombocytopenic purpura (TTP) and haemolytic uremic syndrome (HUS)).
- The identification of blasts or other morphologically abnormal cells may suggest an underlying bone marrow disorder.

Important

> The presence of schistocytes on peripheral blood smear is suggestive of TTP/HUS or DIC. These are life-threatening pathologies requiring urgent interventions to include plasmapheresis. Urgent consultation with a senior haematologist is required!

In addition to the blood smear, other initial investigations should include a renal and liver profile and a full infection screen including inflammatory markers and blood cultures. As DIC is a common cause of thrombocytopenia in the ICU, a prothrombin time (PT), activated partial thromboplastin time (APTT), plasma fibrinogen and D-Dimer assay should be performed. A suspected thrombotic microangiopathy should prompt measurement of lactate dehydrogenase, bilirubin and haptoglobins.

References

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4. 4. Management of Thrombocytopenia

Identification and treatment of the underlying pathogenesis is the cornerstone of management. Medications suspected of contributing to thrombocytopenia should be discontinued following risk-benefit assessment.

Platelet transfusion, where indicated, may serve as a useful diagnostic tool. Failure to detect a significant rise in platelet count 30-60 minutes after platelet transfusion suggests peripheral destruction and points towards an immunogenic or drug induced aetiology. Platelet transfusion should be considered in patients who are actively bleeding, or those requiring an invasive procedure with a high associated bleeding risk, where the pre-procedure platelet count is $<50\times10^9$ /L. Observational data supports the transfusion of platelets in those with a platelet count is less than 10×10^9 /l as spontaneous intra-cerebral haemorrhage is most common in these patients

There are some considerations relevant (but not limited to) patients in intensive care with thrombocytopenia:

- Placement of central venous catheters in the thrombocytopenic patient is associated with an increased risk of bleeding which may be decreased with the use of ultrasonic guidance.
- Neuraxial procedures including lumbar puncture or epidural catheter insertion is strongly discouraged when an absolute platelet count is <70–80×10^9 /L.
- For thrombocytopenic patients at high risk of haemorrhage without liver failure, citrate may be considered as anticoagulant management for intermittent and continuous renal dialysis.

See ESICM Module in Renal Replacement Therapy

In general, platelet transfusion is recommended before insertion or removal of large bore intravascular devices such as dialysis catheters and removal of intra-aortic balloon pumps although strong evidence to support this practice is lacking.

Prophylactic platelet transfusion should be avoided if possible where the underlying pathogenesis is associated with a high thrombotic risk. These conditions include TTP, HUS and HIT. Discussion with a senior colleague and a haematologist is warranted in this situation.

> **Important**
> Prophylactic platelet transfusion should be avoided in TTP/HUS, catastrophic antiphospholipid syndrome and HIT.

Antithrombotic prophylaxis should be continued unless the bleeding risk is excessive, except when the platelet count is <30×10^9 /L or there is a major risk of haemorrhage.

If immune thrombocytopenia is suspected or diagnosed, first-line treatment may consist of intravenous immunoglobulin and/or high-dose steroids. Finally, in the rare setting of TTP, plasma exchange should be considered, following multidisciplinary assessment including haematological input.

In text References

(Hui et al. 2011; Van der Linden et al. 2012; Greinacher and Selleng. 2010)

> **References**

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5. Heparin-Induced Thrombocytopenia (HIT)

5. 1. Introduction

Heparin-induced thrombocytopenia (HIT) is an antibody-mediated adverse drug reaction induced by platelet-activating antibodies against multi-molecular complexes of platelet factor 4 (PF4) and heparin. HIT is associated with a high risk of thromboembolic complications. HIT with thrombosis (HITT) may be associated by potentially life-threatening complications including pulmonary embolism (PE), ischaemic limb necrosis necessitating limb amputation, acute myocardial infarction and stroke.

> ★ **Important**
>
> HITT is a life-threatening condition that requires a high index of suspicion, a thoughtful diagnostic process and early consultation with a senior haematologist with a special interest in coagulation!

> @ **Communication**
>
> If a diagnosis of HIT is suspected, advice from a senior haematologist should be sought, as screening tests have high positive rates and alternative anticoagulants to heparin may have severe side effects

Common risk factors for developing HIT:

1. Heparin specific:
    - UFH
    - Larger dosage
    - Longer duration of exposure
2. Patient specific:
    - Cardiac patient
    - Orthopaedic patient
    - Elderly patient.

> **Note**
>
> UFH is associated with a 10-fold higher risk of HIT development than LMWH

A patient’s individual risk of developing HIT may be modulated by the type and dose of heparin received and by patient-specific factors. UFH use, for example, is associated with a 10-fold higher risk of HIT development than LMWH. Moreover, the risk of HIT in

cardiac and orthopaedic patients receiving UFH is estimated to be approximately 1–5%, whereas medical and obstetric patients have a risk of approximately 0.1–1.0%.

The most common complication of HIT is venous thrombosis. Published data suggest that up to 50% of patients with documented HIT who do not receive alternative anticoagulant therapy may develop DVT or PE. Arterial thrombotic events may also complicate HIT and are more common in cardiovascular patients. HIT is associated with significant mortality risk, usually because of thrombotic complications. Other rare clinical sequelae include necrotic skin lesions at the site of heparin injection and adrenal haemorrhagic necrosis.

Infrequently, manifestations of HIT may develop after heparin is discontinued. This phenomenon, known as delayed-onset HIT occurs at a median of 10–14 days after heparin withdrawal and may be associated with disseminated intravascular coagulation (DIC).

As a general rule, an abrupt fall in platelet count over 1–2 days is suggestive of a immunologic cause, whereas a gradual fall over a week is likely to be caused by a consumptive coagulopathy or bone marrow failure.
HIT is an immunogenic mechanism in which, typically, immunoglobulin G (IgG) antibodies formed following exposure to heparin, bind PF4/heparin complex on the surface of platelets with resultant platelet activation and aggregation.

Note

HIT is an immunogenic phenomenon!

5. 2. Pathophysiology

Heparin exposure leads to the formation of IgG antibodies that recognise multi-molecular complexes of positively charged PF4 and negatively charged heparin on the platelet surface. IgM and IgA, in rare circumstances can play a role. Heparin binding induces a conformational change in PF4. This conformational change results in neoepitope exposure and development of IgG antibodies that recognise and bind to PF4/heparin complex on the platelet surface. Therefore, platelet activation and aggregation occurs. This process is likely to contribute significantly to the observed prothrombotic clinical phenotype. However, the precise molecular mechanisms underlying thrombosis development remains incompletely elucidated (Figure 5).

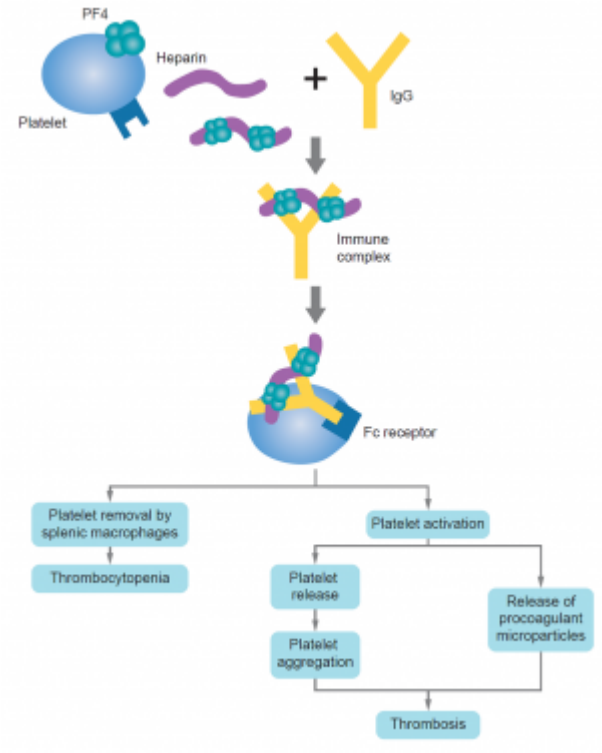

Figure 5: Pathophysiology of HIT

5. 3. Clinical Syndrome

Thrombocytopenia (defined as a platelet count below the lower limit of the laboratory reference range) is the most common clinical manifestation of HIT and occurs in 85% to 90% of affected patients. In confirmed HIT, the platelet count characteristically begins to drop at day 5-10 after heparin has been commenced. This syndrome is known as 'typical onset HIT'.

'Rapid-onset HIT' refers to an abrupt platelet count fall (within 24 hours) that occurs in patients who already have circulating HIT antibodies because of recent exposure to heparin, usually within the previous 30 days but occasionally within 100 days.

'Acute HIT' may mimic an anaphylactoid reaction and may be associated with fever, chills, hypertension, tachycardia, dyspneoa and chest pain within 30 minutes of heparin administration.

Thrombosis may manifest as skin necrosis at heparin injection sites. In up to 25% cases of confirmed HITT, thrombosis precedes onset of thrombocytopenia.

Notes

- Clinical Presentations of HIT

- ‘Typical-onset’ HIT: platelet count characteristically begins to fall at day 5–10 after heparin has been commenced
- ‘Rapid-onset’ HIT: platelet counts fall abruptly within 24 hours in patients exposed to heparin in the previous 30–100 days
- ‘Acute HIT’ usually occurs within 30 minutes of heparin administration and mimics an anaphylactoid reaction
- ‘Delayed-onset’ HIT: platelet count falls a median of 10–14 days after heparin withdrawal.

Important

The diagnosis of HIT in the postoperative cardiac patient possess a diagnostic conundrum as there are many reasons for thrombocytopenia seen in cardiac patients and laboratory tests for HIT have a very high false positive rate!

5. 3. 1. Cardiac surgery

In the period following cardiac surgery, up to 50% of patients may have positive heparin/PF4 antibody tests. These test results are frequently available before the results of functional assays (see below). In contrast, only approximately 1–5% of patients who have undergone cardiac surgery develop the clinicopathological syndrome HIT.

Note

50% of postoperative cardiac surgery patients will have positive heparin/PF4 antibody test results

The low positive predictive value of antigen assays in this population should be considered when evaluating such a patient, particularly as thrombocytopenia is a relatively common occurrence in the immediate period following cardiothoracic surgery and cardiopulmonary bypass.

Typically, the platelet count would be expected to return to near normal in a continual fashion by postoperative day 4. Recovery of platelets after surgery followed by a secondary fall during postoperative days 5–14 or thrombocytopenia that persists for >4 days post operatively is associated with a higher clinical likelihood of HIT.

5. 4. Clinical diagnosis:

HIT is a clinicopathological diagnosis based on both clinical findings and the presence of platelet activating antibodies directed at the heparin/PF4 complex. Definitive laboratory testing may not be available at the time of clinical decision-making. Pre-test clinical probability scores have been developed and clinically validated. One such clinical probability score is the 4T score (Table 1).

Currently published clinical data suggest that patients with a low 4T score have a very low probability of HIT (0–3%). However, potential limitations of the 4T score include modest interobserver agreement and relatively poor positive predictive value (9–17%).

	Score = 2	Score = 1	Score = 0
Thrombocytopenia Compare the highest platelet count within the sequence of declining platelet counts with the lowest count to determine the per cent of platelet fall **(Select only one option)**	• >50% platelet fall AND nadir of ≥20 AND no surgery within the preceding 3 days	• >50% platelet fall BUT surgery within preceding 3 days OR • Any combination of platelet fall and nadir that does not fit criteria for Score 2 or Score 0 (e.g. 30-50%platelet fall or nadir 10-19)	• <30% platelet fall • Any platelet fall with nadir <10
Timing (or platelet count fall or thrombosis) Day 0 = first fay of most recent heparin exposure **(Select only one option)**	• Platelet fall day 5-10 after start of heparin • Platelet fall within 1 day of start of heparin AND exposure to heparin within past 5-30 days	• Consistent with platelet fall days 5-10 but not clear (e.g. missing counts) • Platelet fall within 1 day of start of heparin AND exposure to heparin in past 31-100 fays	• Platelet fall ≤ day 4 without exposure to heparin in past 100 days
Thrombosis (or other clinical sequelae) **(Select only one option)**	• Confirmed new thrombosis(venous or arterial) • Skin necrosis at injection site • Anaphylactoid reaction to IV heparin bolus • Adrenal haemorrhage	• Recurrent venous thrombosis in a patient receiving therapeutic anticoagulants • Suspected thrombosis (awaiting confirmation with imaging) • Erythematous skin lesions at heparin injection sites	• Thrombosis suspected
Other cause for Thrombocytopenia **(Select only one option)**	• No alternative explanation for platelet fall is evident	**Possible other cause is evident:** • Sepsis without proven microbial source • Thrombocytopenia associated with initiation of ventilator • Other	**Probable other cause present:** • Within 72 hours of surgery • Confirmed bacteraemia/fungaemia • Chemotherapy or radiation in past 20 days • DIC due to non-HIT cause • PTP • Platelet count <20 AND given a drug implicated in causing D-ITP • non-necrotizing skin lesions at LMWH injection site(presumes DTH) • other

DIC, disseminated intravascular coagulation; D-ITP, drug-induced immune thrombocytopenia; DTH, xxxx; HIT, heparin-induced thrombocytopenia IV, intravenous; LMWH, low-molecular-weight heparin PTP, post transfusion purpura.
A) Timing of clinical sequelae, such as thrombocytopenia, thrombosis, or skin lesions.
B) Two points if necrotizing heparin-induced skin lesions even if thrombocytopenia not present
C) Drugs implicated in D-ITP: relatively common: glycoprotein IIb/IIIa antagonists(abciximab, eptifibatide, tirofiban); quinine, quinidine, sulfa antibiotics, carbamazepine, vancomycin; less common: actinomycin, amitriptyline, amoxicillin/piperacillin/nafcillin, cephalosporins(cefazolin, ceftazidime, ceftriaxone), celecoxib, ciprofloxacin, esomeprazole, fexofenadine, fentanyl, fucidic acid, furosemide, gold salts, levofloxacin, metronidazole, naproxen, oxaliplatin, phenytoin, propranolol, propoxyphene, ranitidine, rifampin, suramin, trimethoprim. Note: this is a partial list

Table 1: 4T score (Warkentin TE, Linkins LA. Non-necrotizing heparin-induced skin lesions and the 4T's score. J Thromb Haemost. 2010;8:1483-5. Linkins LA, et al. Thromb Haemost. 2010 Jul;8(7):1483-5

5. 5. Laboratory diagnosis of HIT

Laboratory assays for HIT fall into two broad categories: antigen assays that detect the presence of HIT antibodies and functional assays that detect evidence of platelet activation by HIT antibodies in the presence of heparin. In general, antigen assays that detect HIT antibodies are very sensitive but of variable specificity and frequently poor positive predictive value as a consequence.

Functional assays that detect platelet activation, such as the serotonin release assay and heparin-induced platelet activation, are sensitive and specific for HIT because they only detect antibodies that are capable of activating platelets. These assays are technically difficult to perform, requiring a source of human platelets from suitable donors.

Notes

!Reference List Missing

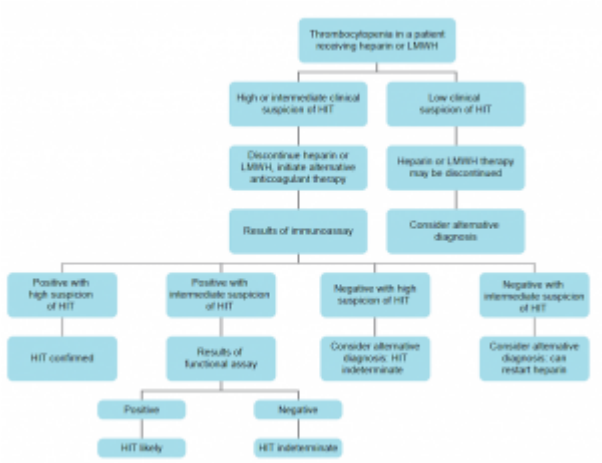

Figure 6: Algorithm for suggested diagnosis and initial management of HIT

HIT : heparin-induced thrombocytopenia

LMWH: low-molecular-weight heparin.

5. 6. Management of heparin-induced thrombocytopenia and heparin-induced thrombocytopenia with thrombosis

In patients with suspected HIT, all forms of heparin (including heparin flushes and heparin-coated line and catheters) should be discontinued. Moreover, given the high ongoing thrombotic risk, currently published guidelines recommend commencement of an alternative non-heparin anticoagulant (such as the direct thrombin inhibitors lepirudin, bilvalirudin argatroban or the factor Xa inhibitor danaparoid). Consideration should be given to the patient's renal and liver function when selecting an anticoagulant agent for this purpose.

HIT is a disorder associated with a prothrombotic phenotype, despite marked thrombocytopenia. Because of its immunological pathophysiology, platelet transfusion may be associated with a theoretical additional thrombotic risk. Although little direct evidence exists to support this hypothesis, currently published guidelines suggest avoidance of platelet transfusion where possible in patients with HIT. Some observational data support keeping the absolute platelet count greater than 10 x 109/l to reduce the risk of spontaneous intra-cranial haemorrhage

> **Note**
>
> Platelet transfusion should be avoided in HIT unless a patient is bleeding or where an invasive procedure associated with a high bleeding risk is being considered

Transitioning from direct thrombin inhibitor or factor Xa inhibitor therapy to a vitamin K antagonist (VKA) may be challenging and should be guided by a haematologist. Occasionally this transition may fall within the jurisdiction of the intensive care physician.

It is important to note that the duration of the direct thrombin inhibitor overlap should be ≥5 days to allow minimum length of time necessary for VKA (warfarin) therapy to reduce prothrombin levels to those associated with effective anticoagulation. In the setting of concurrent administration of warfarin and argatroban, international normalised ratio (INR) interpretation can be challenging. Advice from senior haematology colleagues should be sought.

> **Communication**
>
> Transition to chronic VKA anticoagulation from direct thrombin inhibitor or factor Xa therapy is challenging and should be guided by a haematologist with an expertise in coagulation.

In text References

(Linkins et al. 2012; Arepally and Ortel. 2006; Cuker and Cines. 2012)

References

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6. Antithrombotic medications in the Intensive Care Unit

6. 1. Introduction

Recent years have seen the development of a range of new pharmacological drugs to prevent thrombotic events. This development has occurred in conjunction with increasingly complicated invasive procedures. Management of bleeding in these patients requires an understanding of the pharmacology of the antithrombotic agents being administered. Increasing use of well-established and new anticoagulant drugs exposes the critical care clinician to intensive care unit (ICU) admissions for bleeding complications related to anticoagulant use.

6. 2. Antiplatelet agents:

6. 2. 1. Aspirin

Aspirin is an irreversible platelet COX inhibitor. Consequently, its platelet inhibitory effect is sustained until the platelet pool is replenished by bone marrow synthesis, a process that can take up to 7–10 days.

Oral aspirin is rapidly absorbed from the stomach and proximal small intestine. Peak plasma concentration is reached within 30 minutes (up to 3–4 hours following ingestion of enteric-coated preparations). The main indication for aspirin is the treatment and prevention of cardiovascular and cerebrovascular events.

Note

Aspirin is an irreversible COX inhibitor

6. 2. 1. 1. Thienopyridines (Clopidogrel, Prasugrel)

Thienopyridines irreversibly block adenosine diphosphate-mediated activation of the platelet P2Y12 receptor.

Clopidogrel is typically administered for the secondary prevention of cardiac events in patients that have required deployment of a coronary stent. Specific to percutaneous coronary intervention post acute coronary syndrome (ACS), clopidogrel is indicated for

up to 12 months after deployment of a bare-metal stent (BMS) as per 2016 AHA/ACC guidelines.

Prasugrel is typically used for the treatment of acute ST-segment elevation myocardial infarction. Prasugrel has a more rapid onset of action than clopidogrel and a greater associated bleeding risk has been reported than with clopidogrel.

> **Note**
>
> Thienopyridines irreversibly block adenosine diphosphate-mediated activation of the platelet P2Y12 receptor. Therefore in the event of urgent surgery consideration should be given to stopping the agent (in discussion with cardiology to assess the risk/ benefit ratio). The drug should be stopped seven days before surgery. For elective surgery, consideration should be given to waiting until the agent can be safely discontinued.

6. 2. 2. Dipyridamole

Dipyridamole in its extended release form is approved as an adjunct to aspirin for stroke prevention. It is a reversible inhibitor of platelet function. Although its half-life is short (approximately 10 hours), it is typically combined with aspirin, an irreversible antiplatelet agent.

6. 2. 3. Glycoprotein (GP) IIb/IIIa inhibitors

Glycoprotein (GP) IIb/IIIa inhibitors are administered parenterally to achieve acute platelet inhibition in the setting of percutaneous coronary intervention. These drugs prevent fibrinogen-mediated platelet aggregation.

Commercially available platelet GP IIb/IIIa inhibitors include abciximab, tirofiban and eptifibatide. Abciximab, a monoclonal anti-GP IIb/IIIa monoclonal antibody, has a short plasma half-life (30 minutes). However, platelet function may remain inhibited for up to 12–24 hours due to persistent receptor binding. Tirofiban and eptifibatide are reversible competitive GP IIb/IIIa inhibitors with very short plasma half-lives.

Side effects or adverse events associated with GP IIb/IIIa antagonists:

- The incidence of major haemorrhage with GP IIb/IIIa antagonists is 10%
- Moderate or severe thrombocytopenia has been reported in association with abciximab in up to 5% and 0.5% of treated patients, respectively, but an association with tirofiban and eptifibatide has not been proven.

6. 2. 4. Management of bleeding in patients receiving antiplatelet medications:

There are no specific reversal agents for antiplatelet drugs. General haemostatic measures are recommended, including drug discontinuation, administration of tranexamic acid and management of the bleeding source and associated coagulopathy (using human plasma and fibrinogen as necessary). For major or life-threatening bleeding, transfusion of donor platelets may be considered.

Important

There are no specific reversal agents for antiplatelet agents. For major or life-threatening bleeding, transfusion of donor platelets should be considered! However, the recent PATCH study, a randomised controlled trial of platelet transfusion versus no transfusion in patients with spontaneous haemorrhagic stroke showed increased mortality in the platelet transfusion group.

6. 3. Vitamin K antagonists (including warfarin)

Vitamin K antagonists (VKAs) inhibit vitamin K epoxide reductase, an enzyme complex required for reduction of the oxidised form of vitamin K. Reduced vitamin K is a cofactor in gamma carboxylation of procoagulant coagulation factors II, VII, IX and X and anticoagulant proteins C and S. Inhibition of gamma carboxylation of these coagulation factors inhibits their functional activity and achieves therapeutic anticoagulation.

6. 3. 1. Management of bleeding in patients receiving vitamin K antagonist therapy

Four-factor PCC is a blood-derived product that contains coagulation factors II, VII, IX and X. PCC is licensed for the emergency reversal of anticoagulation in the setting of critical haemorrhage or where there is a requirement for urgent intervention in the anticoagulated patient. The dose of PCC is 25–50 IU/kg and should be administered with 5 mg vitamin K. Importantly, the onset to Vitamin K is slower than PCC so PCC is used to facilitate the immediate reversal of warfarin. The duration of action of PCC is short so an additional dose maybe required to cover the time of time of peak action of Vitamin K.

Note

Four-factor prothrombin complex concentrate (25–50 IU/kg) is licensed for the emergency reversal of warfarin therapy

Where PCC is unavailable, human plasma and vitamin K may be administered, although this approach may result in suboptimal

6. 4. Heparin

Heparin binds to antithrombin (AT) and potentiates AT-mediated inhibition principally of thrombin and activated factor X.

6. 4. 1. Unfractionated Heparin

Unfractionated heparin (UFH) is a glycosaminoglycan used as a parenteral anticoagulant in many clinical settings. UFH exhibits a biphasic clearance, including a rapid saturable mechanism believed to be due to cellular elimination and slower non-saturable renal clearance. Because of complex pharmacokinetics, the anticoagulant response to UFH can be difficult to predict. Consequently, the therapeutic effect of heparin requires activated partial thromboplastin time (APTT) (or activated clotting time ACT) measurement. At therapeutic intravenous doses, the plasma half-life of UFH is 45–90 minutes. Upon discontinuation of an UFH infusion, return to baseline APTT typically occurs in approximately 3–4 hours.

In cases where APTT targets are difficult to achieve despite increased dosing of UFH, one should consider anti-thrombin III (AT-III) deficiency and measure an AT-III level. Specific interventions include transfusion of human plasma or recombinant AT-III.

6. 4. 2. Low Molecular Weight Heparin

Low-molecular-weight heparins (LMWHs) are derived from UFH. These agents have lower molecular weights and exhibit lower thrombin inhibitory activity relative to activated factor X than UFH. LMWHs have a more predictable dose-response relationship, longer plasma half-lives and a more favourable benefit-to-risk ratio compared to UFH. These drugs do not typically require monitoring, but have slower offset times, ranging from 12 hours for prophylactic doses to approximately 24 hours for therapeutic doses. LMWH are cleared renally. Consequently, dose adjustments are required in renal failure.

> **Note**
>
> Unlike UFH, dose adjustment is required with LMWH in the setting of renal failure

Measurement of plasma anti-activated factor X may be performed in unusual circumstances where LMWH anticoagulant effect is less predictable, including extremes of body weight (pre-mature neonates), renal impairment and Extra-Corporeal-Life-Support.. Another clinical paradigm the clinician needs to be aware of is the problem of correct interpretation of anti-FXa in the patient with elevated bilirubinaemia.

6. 4. 3. Management of bleeding in patients receiving heparin

In patients receiving UFH, bleeding may occasionally be managed simply by stopping the infusion, in view of the very short plasma half-life. When this measure is insufficient, protamine sulphate should be administered.

Note

1 mg of protamine neutralises 80–100 units of UFH. The calculated amount of UFH should be based on the previous 2 hours

Protamine has a very short plasma half-life (approximately 7 minutes). Therefore, further doses may be required. When given in vast excess to the amount required to reverse UFH, protamine may produce a weak anticoagulant effect and can cause severe allergic reactions including anaphylaxis. Therefore, it is important to calculate the required dose and to administer protamine slowly (over >5 minutes).

Note

Protamine only partially reverses the anticoagulant effect of LMWH

Protamine does not fully reverse the anticoagulant effect of LMWH. However, where LWMH has been administered within 8 hours, protamine should be given at a dose of 1 mg per 100 anti-activated factor X units of LMWH up to a maximum of 50 mg. A second dose of 0.5 mg protamine per 100 anti- activated factor X units may be given if bleeding continues. Where >8 hours have elapsed since the last LMWH dose, smaller doses of protamine may be administered. General haemostatic measures should also be considered.

Important

A phenomenon of ‘heparin rebound’ may occur in postoperative cardiac surgery patients as bleeding may occur with a raised ACT despite reversal with protamine, as the half-life of protamine is much shorter than that of heparin

6. 5. Danaparoid

Danaparoid is a low-molecular-weight heparinoid consisting of a mixture of glycosaminoglycans. It is a more selective activated factor X inhibitor than LMWH. It is occasionally used for anticoagulation in a patient with confirmed heparin-induced thrombocytopenia (HIT). Plasma anti-activated factor X activity may be measured to monitor the anticoagulant effect of danaparoid if required.

6. 5. 1. Management of bleeding in patients receiving danaparoid

There is no specific antidote for bleeding in patients receiving danaparoid. The drug should be discontinued and general haemostatic measures implemented. Plasmapheresis may be considered in the setting of critical or life-threatening bleeding.

6. 6. Fondaparinux

Fondaparinux is a parenterally administered pentasaccharide that acts as an indirect activated factor X inhibitor with a relatively long half-life (17–20 hours with normal renal function and up to 72 hours when creatinine clearance is <30 mL/minute). Like heparin, its anticoagulant effect is dependent upon adequate plasma levels of antithrombin.

6. 6. 1. Management of bleeding in patients receiving fondaparinux

There is no specific antidote for bleeding in patients receiving fondaparinux. Management of bleeding should be through cessation of treatment and general haemostatic measures.

6. 7. Bivalirudin

Bivalirudin is a recombinant hirudin. Its half-life is 25 minutes (although it may approach approximately 3.5 hours in dialysis-dependent patients). It is frequently used in the setting of percutaneous coronary intervention and occasionally during cardiopulmonary bypass in patients with HIT. It is degraded mostly by proteolysis, and only 20% is renally excreted. Its activity is measured by ACT or APTT.

Note

Bivalirudin has been used as an alternative to heparin to anticoagulate for cardiopulmonary bypass in patients with the potential for HIT

6. 7. 1. Management of bleeding in patients receiving Bivalirudin

There is no specific antidote for bivalirudin, but given its short half-life, cessation of treatment and haemostatic measures are often sufficient in a bleeding patient.

6. 8. Argatroban

Argatroban is a reversible direct thrombin inhibitor that is rapidly eliminated via the hepatic cytochrome P450 3A4/5 enzyme. The plasma half-life is 45 minutes. It is approved for the treatment of HIT and is the agent of choice in a patient with HIT and renal insufficiency. Argatroban is usually monitored by APTT. It also prolongs prothrombin time (PT), ACT and thrombin time.

Note

Argatroban is the anticoagulant of choice in a patient with HIT and renal insufficiency

6. 8. 1. Management of bleeding in patients receiving Argatroban

There is no specific antidote for argatroban, but given its short half-life, cessation of treatment and haemostatic measures are often sufficient in the setting of bleeding.

Note

Non-vitamin K antagonist oral anticoagulants. Non-vitamin K antagonist oral anticoagulants (NOACs) can be classified by route of administration and site of action. Rivaroxaban and apixaban are oral agents that function as activated factor X inhibitors. Dabigatran is an oral direct thrombin inhibitor.

6. 9. Dabigatran

Dabigatran is a direct thrombin inhibitor that directly inhibits free and clot-bound thrombin. It has a rapid onset of action, few drug interactions and measurement of anticoagulant effect is very rarely required. It is approved for stroke prevention in patients with non-valvular atrial fibrillation and for venous thromboembolism (VTE) prophylaxis following total hip or knee replacement. Peak plasma drug concentration is reached at 2–3 hours after administration.

Note

Dabigatran prolongs APTT

Dabigatran has a half-life of approximately 12–14 hours in patients with normal renal function. However, in view of its approximately 80% renal excretion, the half-life is prolonged in patients with renal impairment (reaching approximately 22–35 hours where creatinine clearance is <30mL/minute). Dabigatran has relatively low plasma protein binding (35%), which facilitates its partial elimination by haemodialysis.

The APTT is sensitive to dabigatran therapy. However, the relationship of dabigatran to APTT is curvilinear and as a result, APTT correlates poorly with the anticoagulant effect of dabigatran. The effects of dabigatran can be best measured using the thrombin clotting time (TCT). This assay may be used to measure plasma dabigatran levels.

> **Important**
>
> Dabigatran is 35% protein bound. In the setting of excessive bleeding due to dabigatran, haemodialysis may be useful!

6. 9. 1. Management of bleeding in patients receiving Dabigatran

Management of bleeding includes cessation of treatment and general haemostatic measures. In bleeding patients who have taken a dose of dabigatran in the past 2 hours, consideration should be given to oral activated charcoal administration to prevent further absorption.

Haemodialysis, haemofiltration and charcoal haemoperfusion offer the possibility of enhanced clearance of the active drug.

Recently, ‘Idarucizumab’ a humanized antibody fragment, or Fab, designed as a specific reversal agent to dabigatran is licensed for immediate reversal of its anticoagulants effects in the emergent life-threatening setting. It does not affect the coagulation cascade.

> **Note**
>
> Idarucizumab is a humanized antibody fragment used for the immediate reversal of the anticoagulant effects of dabigatran.Rivaroxaban cannot be eliminated by haemodialysis, as over 90% of Rivaroxaban is protein bound.

6. 10. Thrombolytics

Over the years, biological thrombolytics including streptokinase and urokinase have largely been replaced by the recombinant tissue plasminogen activators (rtPAs). Examples of rtPAs used in clinical practice today are alteplase, reteplase and tenecteplase. rtPAs are serine proteases that catalyse the conversion of plasminogen into plasmin. Alteplase is currently the only agent licensed as a thrombolytic in acute stroke. Its use is associated with 6.4% incidence of cerebral haemorrhage in this setting.

Absolute contraindications to thrombolysis include:

- Any prior intracranial hemorrhage

- Known cerebral vascular lesion
- Known malignant intracranial neoplasm
- Ischemic stroke within 3 months
- Suspected aortic dissection
- Active bleeding or bleeding diathesis (except menses)
- Significant closed head or facial injury within 3 months

Note

These is a 6% incidence of cerebral haemorrhage associated with systemic thrombolysis

6. 10. 1. Management of bleeding in patients after thrombolysis

Despite the fact that tPA has a very short half-life, currently published guidelines recommend the following measures in patients with major bleeding (including intracranial haemorrhage):

- Discontinuation of the fibrinolytic drug and of other anticoagulant agents
- Administration of human plasma at a dose of 12ml/kg
- Administration of intravenous tranexamic acid 1g every eight hours
- Fibrinogen should be replaced with cryoprecipitate or fibrinogen concentrate if levels are depleted
- Further therapy should be guided by regular coagulation tests.

In text References

(Levy et al. 2013; Cheng-Ching et al. 2012; Makris et al. 2013)

References

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- Makris M, Van Veen JJ, Tait CR, Mumford AD, Laffan M; British Committee for Standards in Haematology., Guideline on the management of bleeding in patients on antithrombotic agents., 2013, PMID:23116425

7. Interruption of anticoagulant and antiplatelet therapy in the ICU

Occasionally, patients who are receiving antithrombotic therapy will require temporary interruption of therapy. This may arise where a patient receiving anticoagulant or antiplatelet therapy for venous thromboembolism (VTE), atrial fibrillation or ischaemic heart disease requires a surgical procedure. Management of these scenarios has been the subject of several recently published international guidelines.

7. 1. Perioperative management of patients receiving vitamin K antagonist therapy

If local guidelines are available, they should be followed. Alternatively,guidelines published by the American College of Chest Physicians (Douketis et al. 2012) recommend discontinuation of vitamin K antagonists (VKAs) approximately 5 days before an elective procedure where the bleeding risk associated with the procedure precludes continuation of anticoagulant therapy. Recommencement of VKA therapy is recommended 12–24 hours after surgery, assuming adequate haemostasis.

References

- Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R, Perioperative management of antithrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines., 2012, PMID:22315266

7. 2. Bridging of anticoagulant therapy

“Bridging” anticoagulant therapy (typically with LMWH or UFH) is recommended in patents that are at high risk of thrombotic complications, including a subset with high-risk mechanical heart valves, atrial fibrillation or recent VTE. These patients deemed at ‘high risk’ of thromboembolism include those with a prosthetic mitral valve, atrial fibrillation with an associated high CHADS2 score or a venous thromboembolic event in the past 3 months. In all cases, blood products should be available in the event of major haemorrhage in patients receiving bridging therapy.

Where intravenous UFH is selected as bridging therapy, UFH should be discontinued 4–6 hours before surgery and a normal APTT confirmed.

Important

UFH should be discontinued 4–6 hours before surgery and a normal PT and APTT confirmed!

If therapeutic-dose subcutaneous LMWH is used as bridging therapy, the last dose of LMWH should be administered 24 hours prior to surgery, assuming normal renal profile and therefore normal LMWH clearance. Bridging therapy may be omitted in patients deemed at low risk for thromboembolism.

Important

Therapeutic-dose subcutaneous LMWH should be ceased for 24 hours before planned surgery and recommenced 24 hours after surgery in patients with a low-to-moderate bleeding risk and 48–72 hours after surgery in those with a high bleeding risk!

7. 3. Perioperative management of antiplatelet therapy

7. 3. 1. Aspirin

Aspirin is an irreversible inhibitor of platelet function. Recovery of platelet function after discontinuation of aspirin therapy requires replenishment of functional platelets and takes up to 7-10 days.
In patients at moderate to high risk for cardiovascular events who are receiving aspirin therapy and require non-cardiac surgery, aspirin should be continued perioperatively. This also applies to any patient on aspirin therapy scheduled for coronary artery bypass graft (CABG) surgery.
Aspirin may be temporarily discontinued (7-10 days preoperatively) in patients deemed at low risk for cardiovascular events and in patients at risk of bleeding in critical areas such as intracranial, epidural and ocular spaces.

7. 3. 2. Thienopyridines

Thienopyridines (including clopidogrel and prasugrel) are associated with a higher potential for bleeding compared with aspirin. When used in combination with aspirin in patients awaiting CABG, thienopyridines should be discontinued ≥5 days before cardiac surgery.

In patients receiving DAPT who require a surgical procedure, , the two important clinical questions an intensivist must ask firstly, what is the indication for the coronary stent, stable ischaemic heart disease (SIDH) or acute coronary syndrome (ACS). The second question is what type of stent was placed, bare metal stent (BMS) or drug

eluting stent (DES)? In SIHD with BMS, DAPT should be continued for at least 1 month and for at least 6 months post DES. The 2016 ACC/AHA guidelines suggest at least 12 months for BMS and DES after acute coronary syndrome.

In patients requiring urgent surgery outside these time limits, it is suggested that DAPT be continued in the perioperative period. Multidisciplinary discussion with senior cardiology, haematology and surgical colleagues is recommended.

7. 4. Perioperative management of non-vitamin K antagonist oral anticoagulants

The recently developed oral direct inhibitors of thrombin or activated factor X have short half-lives and are variably eliminated by the kidneys. Moreover, these agents have rapid onset of effect when recommenced postoperatively. Whereas limited high-quality evidence exists to guide perioperative management of patients receiving these drugs, broad guiding principles include consideration of the bleeding risk associated with the planned surgical procedure and the patient's renal function.

A detailed description of management strategies is included in the references below. However, a suggested management algorithm for the direct thrombin inhibitor dabigatran (Table 3) and the activated factor X inhibitor rivaroxaban (Table 4) is shown.

Table 3: Perioperative management of dabigatran-treated patients who require major procedures.

Renal fuction (CrCl mL/min)	**Half-life (hours)**	**When to discontinue dabigatran before surgery**	
		Standard bleeding risk	High bleeding risk
>80	13(11 - 22)	24 hours	At least 2 days
>50 - =<80	15(12 - 34)	At least 24 hours	At least 2 days
>30 - =<50	18(13 - 23)	At least 2-3 hours	At least 4 days
=<30	27(22 - 35)	>= 4 days seek specialist advice	>= 5 days seek specialist advice

Table 4: Perioperative management of rivaroxaban-treated patients who require major procedures.

Renal fuction (CrCl mL/min)	Half-life (hours)	When to discontinue rivaroxaban before surgery	
		Standard bleeding risk	High bleeding risk
>30	12(11 - 13)	24 hours	>= 2 days
=<30	Unknown	>= 2 days seek specialist advice	>= 4 days seek specialist advice

In text References

(Douketis et al. 2012; Poldermans et al. 2010; Levine et al. 2016)

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8. Massive Transfusion

8. 1. Introduction

Massive haemorrhage is a medical emergency and may complicate obstetric healthcare, trauma, major surgery and the care of patients with gastrointestinal disease or other comorbidities. Haemorrhagic shock from trauma accounts for 80% of deaths in the operating room and 50% of deaths occur in the first 24 hours. Data from large trauma centres show that 40–60% of fatalities occur at the scene or in transit. A “lethal triad” is described in patients with massive haemorrhage:

- Hypothermia
- Acidosis
- Coagulopathy.

The management of massive haemorrhage is usually only one component of the management of the critically unwell patient. Death due to the failure to recognise the risk of massive haemorrhage and the need for urgent transfusion support care has been highlighted by haemovigilance organisations. Factors critical to the successful transfusion management of massive haemorrhage include a major haemorrhage protocol (MHP) delivered by a well-coordinated trained multidisciplinary team of clinical, laboratory and logistical staff.

The initial approach to a patient suffering massive haemorrhage should include:

- An advanced trauma life support (ATLS) protocol should be followed with an A, B, C, D, E approach
- A massive haemorrhage situation should be declared and transfusion should begin as per protocol
- The airway should be secured, adequate ventilation confirmed, and large-bore intravascular access should be obtained. Central venous access may be required if peripheral access is unsuccessful
- A group and cross-match should be sought and blood products made available as per local protocols
- Consideration should be given to directly transferring the patient to the operating theatre for surgical haemostasis and haemodynamic stabilisation

See ESICM module on Airway management

8. 2. Definitions and diagnosis

Definitions of massive haemorrhage vary. Traditionally, massive blood loss was defined as the loss of one blood volume (70 mL/kg in an adult man, 65 mL/kg in an adult woman) within a 24-hour period. Alternative definitions included a 50% blood volume loss within 3 hours or loss of 150 mL/minute. However, blood loss may be occult and the volume underestimated.

> ★ **Important**
>
> Tolerance of blood loss may vary depending on patient-related factors including age, health, drugs and co-morbidities. Particular care must be taken in the assessment of children, pregnant women and patients receiving beta-blocker therapy

Appropriate and early recognition of massive blood loss is required to institute timely and effective interventions and therapy. Predictive scoring systems have been published.

> ★ **Important**
>
> Massive haemorrhage may be defined as bleeding which leads to a systolic pressure less than 90 mmHg and/or heart rate more than 110 beats per minute!

8. 3. Therapeutic goals in massive haemorrhage

European guidelines for the management of bleeding following trauma, originally published in 2007 and updated in 2010 and 2013, are part of a European ‘Stop the Bleeding Campaign’. The acronym STOP stands for:

- Search for patients at risk of coagulopathic bleeding
- Treat bleeding and coagulopathy as soon as they develop
- Observe the response to interventions
- Prevent secondary bleeding and coagulopathy.

The therapeutic goals in massive blood loss of both trauma and other causes are to stop the bleeding and resuscitate in order to reduce morbidity and mortality. Bleeding

may be both surgical and non-surgical i.e. coagulopathic. The causes of coagulopathy are complex and include pre-existing illness and drugs, especially aspirin and warfarin.

Challenge

You should familiarise yourself again with the pharmacology and emergency reversal of commonly prescribed anti-thrombotic drugs

Note

Coagulopathy correlates with shock and temperature. The serum lactate or base deficit measurements should be used to estimate and monitor the extent of shock. The initial body temperature should be maintained >35°C and ionised calcium >0.9 mmol/L.

Methods for controlling the source of bleeding:

- In general, the early control of surgical or traumatic bleeds may include use of a tourniquet, topical haemostatic dressings, direct pressure and fracture stabilisation
- Interventional radiology may play an important role, particularly with pelvic haematomas and rectus sheath haematomas
- Patients presenting with haemorrhagic shock following trauma with unidentified bleeding require immediate further assessment of chest, abdominal cavity and pelvic ring including rapid imaging
- Early surgery is often essential for assessment and definitive management, which includes the control of bleeding.

Important

For an unidentified source of haemorrhage, THINK! “ON THE FLOOR and FOUR MORE”: 1. Thorax 2. Abdomen 3. Pelvis 4. Long bones

Fluid therapy may be initiated with crystalloids in the hypotensive bleeding patient. The use of hypertonic solutions should not be used, according to current resuscitation guidelines. Transfusion support is designed to provide timely haemostatic resuscitation with the early use of tranexamic acid as an antifibrinolytic, the use of red cells instead of crystalloid/colloid therapy and the use of blood products including plasma, platelets and fibrinogen concentrate or cryoprecipitate to prevent or correct coagulopathy.

Most guidelines suggest a staged approach to transfusion support in patients at risk for massive haemorrhage.

- Tranexamic acid. The early (within 3 hours of injury) administration of 1 g of tranexamic acid over 10 minutes followed by an infusion of 1 g over 8 hours.
- A foundation ratio of blood components. In patients with critical bleeding, the immediate application of a ‘foundation ratio’ of blood component therapy. Recent RCT’s support the use of 1:1:1 (RBC:Plasma:Platelets)
- Goal-directed therapy. Adjustments to the foundation ratio of transfusion should be made according to clinical course and laboratory profiles.

Combining goal-directed therapy and an MHP, the following goals should be aimed for:

- Clinical evaluation and treatment plan
- Resuscitate and stop bleeding (C-ABC)
- Normal temperature
- Systolic pressure 80–90 mmHg in the initial phase without brain injury with a mean arterial pressure >80 mmHg in patients with combined haemorrhage and brain injury.
- Urine output >1 mL/kg/hour
- Confirm ABO and rhesus D (RhD) blood groups.

Laboratory parameters to aim for during a massive transfusion:

- Maintain haemoglobin >70–90 g/L (a higher target of 90–100 g/L is suggested for patients with cardio-respiratory disease)
- Maintain platelet count >50×10^9 /L: Give one pool of platelets when the platelet count falls below 75×10^9 /L. A target of 100×10^9 /L may be considered in patients with ongoing bleeding and/or traumatic brain injury
- Maintain prothrombin time (PT) ratio and activated partial thromboplastin time (APTT) ratio ≤1.5. Administer fresh frozen plasma (FFP)/human plasma at a standard dose (up to 12–15 mL/kg) to achieve these targets
- Maintain fibrinogen >1.5 g/L. Administer fibrinogen supplementation (50 mg/kg) if fibrinogen level falls below 1.5 g/L. Give cryoprecipitate at a dose of two 5-pools (administer additional dose if required)
- Normalise serum base excess and lactate.
- Close attention to ionized calcium levels as citrate binding of ionized calcium can lead to a clinically significant fall in the plasma free calcium concentration increased coagulopathy

8. 4. Patient subgroups

Major bleeding may occur in many patient groups. The management for all is based on the approach described above. However, additional recommendations are made for various patient subgroups.

8. 4. 1. Bleeding disorders

Patient with acquired or congenital bleeding disorders should be managed in conjunction with a haematologist.
See Interpretation of abnormal coagulation tests in this module

8. 4. 2. Obstetric haemorrhage

Obstetric haemorrhage remains a leading cause of death worldwide and should be managed in accordance with local and national guidelines. The routine first-line management is optimal obstetric intervention and uterotonic drugs rather than blood. Fibrinogen levels rise during pregnancy and are in the range of 4–6 g/L at delivery. Fibrinogen should be measured and managed early.

8. 4. 3. Gastrointestinal haemorrhage

Recent data suggest a higher 6 week survival and lower rebleeding rates in patients allocated to a restrictive red cell transfusion threshold. The recommended post transfusion target is 70-90g/L.

8. 4. 4. Paediatric haemorrhage

The details of paediatric practice are not covered in this module. The principles of management are the same in children as they are for adults. However the total blood volume in children is greater than 70ml/kg and children can be more difficult to assess and monitor.

Specialist support is required which includes early intubation. Normal laboratory values differ in childhood however fibrinogen levels are broadly similar. The approximate age and weight of the child should be given on the transfusion request form in order to allow the laboratory to select the best component. All transfused components should be prescribed in millilitres and calculated on the basis of weight.

8. 5. Complications of Massive Blood Transfusion

The potential complications of a blood transfusion are:

- Metabolic
- Hypothermia
- Allergic reaction
- Infection.

Massive transfusion can be lifesaving. However, the rapid transfusion of large amounts of stored blood components can also result in serious complications in both the short and long term. The metabolic complications such as hyperkalemia and hypocalcaemia may kill and, for this reason, the patient must be closely monitored and managed (Table 5).

Table 5: Metabolic complications of massive transfusion

Problem	Prevention/treatment
Hypothermia • Impairs homeostasis and reduces 02 delivery to tissues	Keep patient warm, warm fluids including blood through warming device, warm air blanket
Hypocalcaemia • Citrate anticoagulant in FFP and platelets, especially if liver impairment	Maintain ionised calcium >1 mmol/L, give calcium chloride 10% 10 ml over 10 minutes
Hyperkalemia • Red cells stored for 35 days may have potassium level of 5 - 10 mmol/pack	Monitor potassium levels (ECG)

ECG: Electrocardiogram
FFP: Fresh Frozen Plasma

8. 6. Organisational aspects of a massive haemorrhage protocol

A consultant or the most senior clinician should declare a massive haemorrhage situation once a massive haemorrhage is suspected and should assign staffing appropriately.

A communication lead should be appointed, whose sole responsibility is to communicate with laboratory staff and other involved departments. When communicating with the blood laboratory, the lead clinician should indicate the timescale with which blood is needed at the bedside.

Roles should be assigned, as per updated ATLS algorithms, to staff members with the appropriate expertise, e.g. anaesthesiology for securing airway, emergency medicine for intravenous access. Haematology staff should be involved early.

A detailed review of the acute management of haemorrhagic shock can be found in the recommended reading below.

8. 7. Blood Components

8. 7. 1. Red Blood Cells

Red cells are necessary to deliver oxygen at a cellular level. Red cells also improve haemostasis by reducing tissue ischaemia and causing platelet margination.

> ★ **Important**
>
> The optimal target haemoglobin in the management of haemorrhage is unknown and the haematocrit levels in bleeding patients are not reliable

Red cell transfusion is likely to be required when 30–40% of blood volume is lost suddenly. Red cells are rarely indicated at haemoglobin concentrations >10 g/dL, with the exception being patients with congenital cyanotic heart disease. Haemoglobin <6 g/dL is generally considered an obligatory transfusion trigger. The optimal haematocrit to prevent coagulopathy is unknown, but experimental data suggest that haematocrit plays an important role in sustaining haemostasis.

Pre-transfusion procedures are designed to determine the patient's ABO and RhD group and to identify red cell antibodies that could haemolyse transfused cells. Red cells may be released based on a serological cross match or by electronic issue once testing is complete. The approximate time for completion of testing and issue of red cells may take up to 45 minutes. In the emergency situation, blood may be issued before serological testing is complete:

- Group-specific: This is typing blood according to ABO groups, determined by antigens on the red cell surface. The process also involves testing for rhesus antibodies
- Group and cross match: The patient's blood is mixed with a potential donors blood and assessed for cross- reaction.

The risk assessment is the responsibility of the doctor ordering the blood.

In the life-threatening situation, group O red cells must be available for immediate use. Group O RhD negative is the 'universal blood group' for emergency transfusion of red cells. However, supply is limited and RhD negative components should be prioritised for women of childbearing age, i.e. under the age of 50 years.

A RhD-negative female of childbearing age who is administered Rh-positive blood can develop anti-D antibodies and risk the development of haemolytic disease of the newborn in subsequent pregnancies. The frequency of anti-D formation after transfusion of RhD positive blood products to RhD negative patients is 20% for RBCs and <4% for platelets. Group O RhD-positive red cells are an acceptable option in male patients and women deemed beyond childbearing age.

Group-specific blood should be used where possible. Group-specific blood, i.e. ABO and RhD selected blood, is the preferred option for urgent transfusion support. Blood should be available within 10–15 minutes.

Red cells are stored at 4±2°C. Currently, red cells should be transfused within 4 hours of leaving controlled storage conditions. Blood cannot be returned to stock if left outside of temperature control for more than 30 minutes. However, the blood can be used at any time within the 4-hour period.

8. 7. 2. Fresh Frozen Plasma (FFP)/Solvent Detergent Plasma (Octoplas)

Large-volume transfusion of crystalloid or red cells results in a dilutional coagulopathy due to coagulation factor deficiency. Human plasma is available as solvent detergent plasma (Octoplas) or FFP. If an estimated blood loss of one blood volume is suspected, plasma should be infused at volumes of 12–15 mL/kg, depending on severity of haemorrhage. If the patient's blood group is unknown, group AB plasma or group A plasma products with low anti-B titres may be administered in the emergency setting.

> **Note**
>
> Dilutional coagulopathy may be prevented by early infusion of human plasma and platelets

8. 7. 3. Fibrinogen

Fibrinogen levels fall early and a critical level of <1 g/L may be reached following a 150% blood volume loss. Coagulation profiles should be monitored frequently. If fibrinogen remains low (<1.5 g/L) despite transfusion of human plasma, cryoprecipitate or fibrinogen concentrate should be administered.

> **Note**
>
> 1 L human plasma contains approximately 2–5 g of fibrinogen whereas 200 mL cryoprecipitate contains 3–4g of fibrinogen

Cryoprecipitate also contains factors VIII and XIII and von Willebrand factor. It is a blood component which is not routinely pathogen activated.

Fibrinogen concentrate is an alternative source of fibrinogen, but it is not currently licensed for use in acquired coagulopathies in the UK. It is a plasma fraction, which has been subject to pathogen inactivation and is used extensively within Europe, usually given at a dose of 3–4 g. The current evidence does not support the superiority of one source of fibrinogen over

8. 7. 4. Platelets

Most haematological societies endorse a platelet count of >75×10^9 /L in an actively bleeding patient. A platelet count <50×10^9 /L can be anticipated when two blood volumes have been replaced by crystalloid or red cells. Empirical platelet transfusion may be required when abnormal platelet function is suspected. Situations with abnormal platelet function include cardiopulmonary bypass, patients with renal dysfunction and those on antiplatelet therapy.

Note

Platelet transfusion through a dedicated platelet-giving set is recommended

Platelet transfusions do not reverse antiplatelet drugs such as clopidogrel and there is no evidence to support use of platelet transfusions to improve outcomes in patients who have recently taken antiplatelet agents.

8. 8. Equipment for blood administration

8. 8. 1. Venous access

Good venous access is required for the optimal management of massive haemorrhage. Access should be large bore and central where possible. Intraosseous devices may be used to give fluids and blood when peripheral or central access is initially not possible. Some authors raise concerns about the risk of mechanical haemolysis where blood has been transfused through an intraosseous device under pressure.

References

- See ESICM module on management of multiple trauma

8. 8. 2. Administration sets

All blood components should be administered using administration sets that incorporate a 170–200-μm filter. There are no requirements to use an additional 40-μm microaggregate filter unless returning salvage red cells. Red cells and plasma may be given using the same administration set. However, it is advised that a fresh giving set is used for platelets in order to reduce platelet loss in the partially occluded filter.

8. 8. 3. Blood warming devices

The use of a blood-warming device is recommended when giving large volumes of red cells or plasma. Red cells are normally stored at 4°C and plasma, once thawed, may still be cool.

Hypothermia can occur if a blood warmer is not used. Acidosis can be induced by lactate released by red cells during storage, as well as the citrate used in red cells as an anticoagulant. When administered in large volumes, these factors contribute to the 'lethal triad' of coagulopathy, acidosis and hypothermia, which is associated with poor survival.

Blood warmers may be integrated with infusion or pressure devices in order to deliver blood rapidly at a near physiological temperature of 37°C. All such devices should be approved for warming blood (check manufacturer recommendations), be regularly maintained and all adverse reports reported as per medical devices.

8. 8. 4. Infusion devices

Rapid infusion devices are increasingly used in centres managing major haemorrhage. These devices may be used with and without a reservoir into which both red cells and plasma can be added and mixed before given as a predetermined bolus. It should be remembered that, when using a reservoir, all the blood units used will need to be linked to that patient even if all of the blood is not used.

8. 9. Logistics of Blood Supply

The storage and supply of blood is subject to legislation with strict quality assurance frameworks. Blood components are stored in carefully controlled temperatures with each component requiring separate conditions. The current storage conditions are summarised in Table 6 below. It is important that platelets are not transported in the same compartment as thawed products or cool red cells.

Table 6: Blood component storage requirements and shelf-life

Component	Storage temperature	Shelf-life	Extended shelf-life
Red cell concentrates	4±2°C	35 days	
FFP	-25°C	2 years	
Platelets	22±2°C	5 days	7 days with bacterial testing
Cryoprecipitate	-25°C	2 years	

FFP: Fresh Frozen Plasma

8. 10. Pharmacological options in massive haemorrhage

8. 10. 1. Tranexamic Acid

Tranexamic acid (TA) is an antifibrinolytic agent that inhibits plasminogen activation and, at high concentrations, inhibits plasmin.

> **Note**
>
> The randomised controlled trial, CRASH-2 in 2010, demonstrated that death was reduced with tranexamic acid

TA was shown to be efficacious and safe in the CRASH-2 trial. Further analysis of the data showed that the benefit was greatest the earlier the TA was given after injury. There may be harm if TA is given >3 hours after injury. The protocol for TA was a loading dose of 1 g over 10 minutes followed by 1 g in 500 mL normal saline over 8 hours.

> **References**
>
>
> - CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet 2010;376:23-32. PMID:20554319
>

8. 10. 2. Aprotinin

Aprotinin is a bovine protein and serine protease inhibitor with multiple effects including an antifibrinolytic action. It is not currently routinely recommended for use in massive haemorrhage due to concerns about safety.

Recombinant activated factor VII

> **Important**
>
> The use of recombinant activated factor VII (rFVIIa) as a treatment option for patients with haemorrhagic shock has been supported in case reports; however, overall, data are lacking

Evidence from more than one randomised controlled trial fails to support the efficacy of rFVIIa for the treatment of bleeding in blunt trauma or penetrating trauma patients. In addition, Levi et al. (2010) reviewed the safety of rFVIIa and found an increased rate of arterial thromboembolism, which increased with patient age. Current guidelines suggest that the use of rFVIIa is not recommended in the management of major haemorrhage unless part of a clinical trial.

However, European guidelines state that rFVIIa should be considered if major bleeding and traumatic coagulopathy persists despite standard attempts to control bleeding. The decision to use rFVIIa should normally be made at consultant level.

Note

The fibrinogen level, calcium, temperature and pH should be normalised prior to administering rFVIIa

8. 10. 3. Prothrombin Complex Concentrate

Prothrombin complex concentrate (PCC) is licensed as an alternative to human plasma for the emergency reversal of anticoagulation due a vitamin K antagonist (warfarin).

PCC may also be clinically useful for reversal of PT in a patient at risk of volume overload. Some centres use PCC in certain clinical situations, such as liver disease and after cardiopulmonary bypass (CPB). The use of PCC carries an increased risk of both venous and arterial thrombosis during the recovery period. Thromboprophylaxis should be started as soon as possible after the bleeding has been controlled.

8. 10. 4. Thromboprophylaxis

Trauma patients and obstetric patients who bleed excessively have a high rate of post-event venous thromboembolism (VTE). Current thromboprophylaxis protocols significantly reduce the rate of VTE. European guidelines suggest mechanical thromboprophylaxis with intermittent pneumatic compression and/or antiembolism stockings as soon as possible. Pharmacological thromboprophylaxis is recommended within 24 hours after bleeding has been controlled

8. 11. Non pharmacological management options

8. 11. 1. Radiologically aided arterial embolization

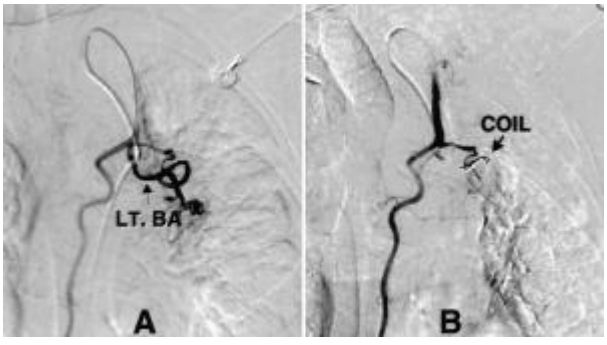

Figure 10: Bronchial Artery Embolisation Chest. 2002;121(3):789-795

Radiologically aided areterial embolisation techniques are becoming more widespread, and successful cessation of bleeding can be achieved with embolisation of bleeding arteries following angiographic imaging. The suitability of such manoeuvres needs to be assessed in the individual case and also depends on availability of an interventional radiologist. The technique can be remarkably effective and may eliminate the need for surgical intervention, particularly in major obstetric haemorrhage.

8. 11. 2. Cell Salvage

The use of intraoperative cell salvage can be remarkably effective at both reducing demand on allogeneic supplies and providing a readily available red cell supply in massive haemorrhage. The technique is often used when blood loss is anticipated to exceed 1000 mL. The indications for cell salvage are detailed in the Association of Anaesthetists of Great Britain and Ireland (AAGBI) guidelines: Blood Transfusion and the Anaesthetist – Intra-operative Cell Salvage. {http://www.aagbi.org/sites/default/files/cell%20_salvage_2009_amended.pdf}

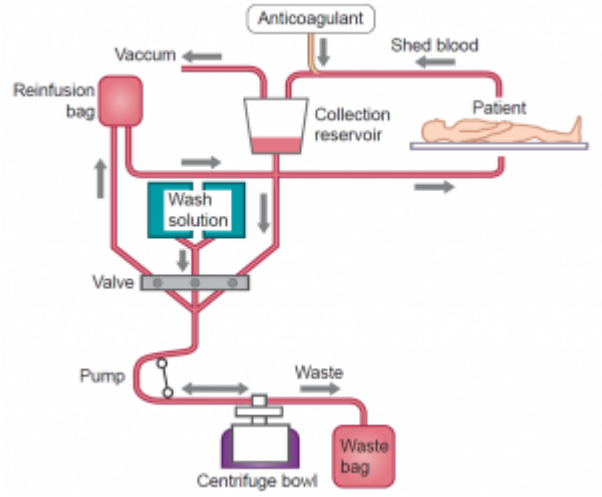

Figure 11: Cell Salvage Circuit

Complications associated with cell salvage include:

- Non-immune haemolysis
- Air embolus
- Febrile non-haemolytic transfusion reactions
- Coagulopathy due to dilution of clotting factors
- Contamination with drugs, cleansing solutions and infectious agents
- Incomplete washing leading to contamination with activated leucocytes, cytokines, and other microaggregates

8. 12. Interpretation of coagulation tests during a massive transfusion

8. 12. 1. Prothrombin Time

The PT is more sensitive than the APTT to low coagulation factors in trauma patients. However, both tests are relatively insensitive test for abnormal haemostasis and a relatively normal result should not necessarily reassure the clinician. The PT can be used to make decisions regarding FFP replacement. It is common practice to correct PT to within 1.5 of normal.

8. 12. 2. International Normalised Ratio

> **Note**
>
> International normalised ratio (INR) is not an appropriate test in massive haemorrhage

INR is standardised for warfarin control and results may be misleading in the context of dilutional and consumptive coagulopathies and liver disease.

8. 12. 3. Activated Partial Thromboplastin Time

The APTT is commonly used to guide blood product replacement to maintain an APTT below 1.5 times normal. However, the APTT can show false positives with both lupus anticoagulant and heparin contamination. For more information please see Coagulation tests.

8. 12. 4. Clauss fibrinogen

Clauss fibrinogen is an easily available test and should be specifically requested if not part of the routine coagulation screen. The Clauss fibrinogen assay should be used in preference to an estimated fibrinogen level because methods based on the PT may give incorrect values in the presence of disseminated intravascular coagulation (DIC), liver disease and other conditions.

Class fibrinogen is more sensitive than the PT and APTT in detecting developing dilutional or consumptive coagulopathy. Levels below 1 g/L in the context of massive haemorrhage are usually insufficient and emerging evidence suggests that a level of at least 1.5 g/L is required.

8. 12. 5. Thromboelastometry

If whole-blood point-of-care testing is used, such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM), then the protocol for blood product usage based on results should be agreed in advance. A Cochrane review found lack of evidence that transfusion guided by TEGTM or by ROTEMTM improved morbidity or mortality in patients with severe bleeding.

Point-of-care testing introduces challenges of standardisation, quality control and staffing, especially in programs with less frequent trauma cases. Currently, there is insufficient evidence to support TEG or ROTEM over serial laboratory testing.

In text References

(Afshari et al. 2011)

References

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8. 13. Controversy and changing practice

8. 13. 1. The age of red cells

There is a controversy as to whether fresher (<14 days) red cells may provide better effect in the critically ill patient. The storage of red cells does result in a ‘storage lesion’, which theoretically may cause adverse effects. However, a pragmatic, randomized, controlled trial conducted at six hospitals in four countries found no significant difference in the rate of death among those who underwent transfusion with the freshest available blood and those who underwent transfusion according to the standard practice of transfusing the oldest available blood.

At the present time, there is not enough evidence to routinely support the use of fresh red cells for resuscitation. However, hospitals providing pre-hospital transfusion may choose to rotate their stock so that the fresh stock is used for ‘shock packs’.

8. 13. 2. Blood samples

The biggest risk in emergency transfusion is the issue and administration of ABO-incompatible blood. One of the commonest causes is ‘wrong blood in tube’. Recent guidelines have advised additional precautions for the issue of group-specific blood. The precautions include the use of two separate blood samples or secure electronic identification (ID) and labelling systems.

8. 13. 3. Component use

The optimal ratio of blood components is controversial. Some centres have adopted a 1:1:1 (red-cell concentrate RCC:FFP:Plts) ratio for resuscitation following military experience. However a large, multi-center RCT comparing 1:1:1 to 2:1:1 showed no difference in 24-hour and 30 day mortality

In text References

(Dzik et al. 2011; British Committee for Standards in et al. 2006; Association of Anaesthetists of Great Britain and et al. 2010; Lal and Shaz. 2013; Spahn et al. 2013; National Institute for Health and Care 2017; Doughty and Allard. 2006; Levi et al. 2010; Heddle et al. 2016; Holcomb et al. 2015)

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9. Management of bleeding and anticoagulation during extracorporeal life support

9. 1. Introduction

The use of extracorporeal life support (ECLS) for the management of refractory hypoxaemia continues to rise. Improved survival is supported by results from observational studies conducted during the influenza A virus subtype H1N1 epidemic and a randomised controlled trial investigating the use of ECLS for treatment of acute respiratory distress syndrome.

Traditional indications for cardiac support via veno-arterial (VA)-ECLS include management of postoperative cardiogenic shock and bridging therapy to cardiac transplantation. Overall mortality is high in patients receiving extracorporeal membrane oxygenation (ECMO), with survival rates of 77% for neonatal respiratory failure, 45% for paediatric cardiac failure, 60% for adult respiratory failure and 32% for adult cardiac failure.

Bleeding and thrombosis are the leading causes of morbidity and mortality in this population.

The following section may be generalised to other extracorporeal devices, including extracorporeal renal replacement systems, plasmapheresis, gas exchange devices (including Novolung and veno-venous VV-ECLS) and, finally, mechanical circulatory support devices, including intra-aortic balloon pump (IABP), VA-ECLS, temporary pulsatile or continuous-flow right, left or biventricular assist device (RVAD, LVAD or BiVAD, respectively), implantable ventricular assist device (VAD) and total artificial heart.

9. 2. Overview of extracorporeal life support technology

With the development of covalently bonded heparin-coated circuits, much of the previously published literature is now outdated. The intricacies of ECLS are beyond the scope of this review on bleeding and thrombosis. For a more detailed review on the practicalities of ECLS, please refer to the Extracorporeal Life Support Organization (ELSO) website referenced below.

ECLS involves cannulating major vessels, removing blood from the patient, pumping the blood through an artificial membrane oxygenator that facilitates gaseous exchange and, ultimately, returning the oxygenated blood to the patient.

VV-ECLS (Figure 12) is performed for refractory hypoxaemia due to compromised lung parenchyma and involves cannulation of large central veins.

Note

VV-ECLS is performed for refractory hypoxaemia due to compromised lung parenchyma

VV-ECLS usually involves cannulating the femoral veins using two separate cannulae: an access and a return cannula. A variation of this technique involves use of a single-entry dual lumen cannula inserted in the internal jugular vein under fluoroscopic or echocardiographic guidance.

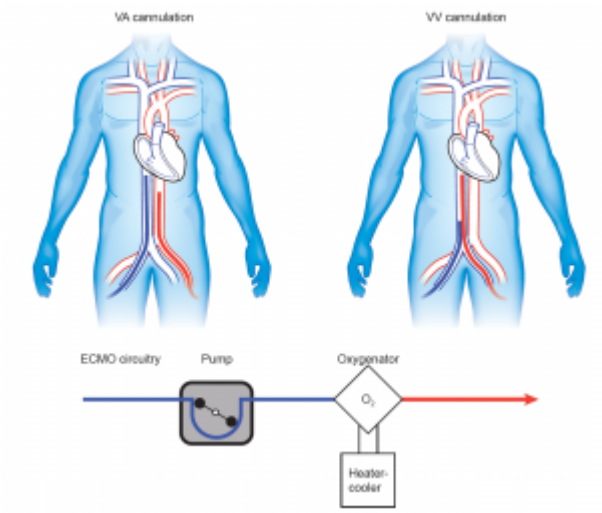

Figure 12: Peripheral veno-arterial (VA)- and veno-venous (VV)-extracorporeal life support circuits.
ECMO, extracorporeal membrane oxygenation;
O2, oxygen.

VA-ECLS is performed for cardiogenic shock. The process involves insertion of an access cannula into a large vein and a return cannula into part of the aorta. Central VA-ECLS is usually performed via a sternotomy for the management of cardiogenic shock after cardiac surgery.

Note

VA-ECLS is performed for cardiogenic shock

Peripheral VA-ECLS (Figure 12) usually involves insertion of an access cannula into a femoral vein with the return cannula inserted into the descending aorta via the femoral artery. A ‘chimney-piece’ inserted during surgical cut-down or T-junction added with the percutaneous approach is required to allow flow to the distal lower limb via a retrograde cannula.

Important

> ECLS induces a hypercoagulable state requiring a ‘partial’ state of anticoagulation within the extracorporeal circuit

ECLS induces a hypercoagulable state as blood is removed from the body in flow rates similar to native cardiac output and must contact many meters of non-biological surfaces. When native blood contacts the non-biological ECLS circuit, a pro-inflammatory and hypercoagulable state is induced that necessitates systemic anticoagulation.

Within seconds of initial blood contact with the non-biological circuit, a layer of fibrinogen, von Willebrand factor (VWF) and fibronectin is adsorbed, followed by platelet adhesion and activation, which promotes systemic thrombus formation. The inflammatory response that occurs in the paediatric population is greater than that observed in adults.

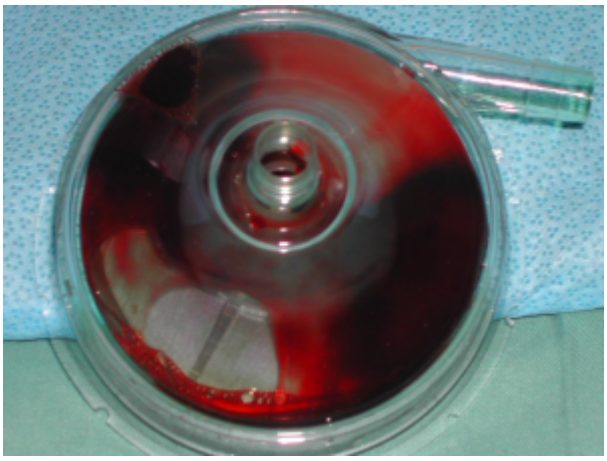

Figure 13: Clot in the head of a centrifugal extracorporeal life support pump.

Clotting in the ECLS circuit can be detected by careful examination with a flashlight by a trained ECLS practitioner and is visible as very dark non-moving areas on circuit surfaces. In general, clots measuring approximately 1–5 mm may simply be observed. It is suggested that clots measuring >5 mm on the side of the return cannula should be removed, by removing that part of the circuit or the entire circuit.

Platelet/fibrin-rich thrombi appear as white areas on the circuit at connectors and stagnant sections. These are clots that have not accumulated red cells, usually because they are in areas of very high flow. Similar to red clots, clots <5 mm may only be observed. For the reasons outlined, ECLS necessitates a ‘partial’ state of anticoagulation with a systemic anticoagulant.

Potential complications of clots in an ECLS circuit are:

- Progressive dysfunction of the oxygenator
- Consumptive coagulopathy
- Embolic events including pulmonary embolism (PE) in VV-ECLS
- Acute pump head failure and death in patients requiring high-flow support.

Other than removal of the clot, the following steps can be taken to address clots in the ECLS:

- A heparin bolus, e.g. (50 IU/kg) may be given to establish a new ACT target of 220 seconds
- Continue to observe the thrombus and the oxygenator performance
- A semi-elective change of the circuit.

9. 3. Anticoagulation of extracorporeal life support circuits

Heparin is the most common anticoagulant used to prevent thrombosis in ECLS circuits. Upon initial cannulation of a patient, a bolus (50–100 IU/kg) of unfractionated heparin (UFH) is given followed by a continuous infusion.

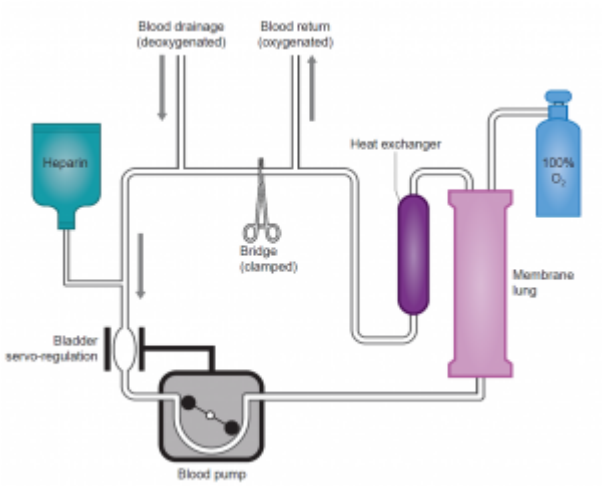

Figure 14: Extracorporeal life support circuit with pre-pump heparin anticoagulation.

Heparin infusion is regulated to maintain the ACT at 1.5 times the upper limit for the specific measurement system. The ACT is the time (in seconds) required for a clot to form in a whole-blood sample in response to an activating reagent.

The ACT is a point-of-care assessment and should be measured hourly after cannulation until stable levels are achieved and at least 4-hourly thereafter. The usual suggested target is 160–220 seconds.

> ★ **Important**
>
> ACT is a point-of-care test that is useful in monitoring anticoagulation of ECLS circuits

The ACT frequently does not correlate well with the plasma activated partial thromboplastin time (APTT) and is affected by the coagulation maturity, platelet dysfunction, hypothermia and diminished plasma antithrombin levels. Factor Xa levels are often used for a more accurate assessment of heparin activity. Factor Xa levels are difficult to interpret correctly in the presence of hyperbilirubinemia

The APTT that will prevent thrombus extension with heparin has been reported as 1.5 times baseline APTT. A typical target range is 50–70 seconds. Heparin doses required to achieve this target are approximately 20–70 IU/kg/hour.

Plasma concentrations of natural anticoagulants including antithrombin (AT) may drop during ECLS and clotting may occur even when large doses of heparin are given. Some centres consider AT replacement to 80–100% of control levels, although few data exist to support this approach.

Another near-patient test, thromboelastography (TEG), has been suggested as a superior monitor of anticoagulation to ACT. The ‘reaction time’ (r) represents the time taken for initial fibrin formation. The r-time is affected by heparin, hypofibrinogenaemia and hypercoagulability. Recent advances include addition of tissue factor to TEG which gives a more rapid result. The addition of heparinase (hTEG) allows assessment of clot stability during a heparin infusion.

9. 4. Bleeding during ECLS

Excess bleeding is the most common reason for unanticipated discontinuation of ECLS. The practitioner must always be aware that catastrophic bleeding may occur.

The initial step in the management of excessive bleeding is restoration of a normal coagulation profile. This involves decreasing the rate of heparin infusion, aiming for an ACT <1.5 times the baseline upper limit, transfusion of human plasma, fibrinogen and an antifibrinolytic agent if bleeding is severe.

Case reports describe the use of recombinant activated factor VII (rFVIIa) for the treatment of a massive bleed. Clinicians need to be aware that a freshly primed circuit should be at the bedside if rFVIIa be used, as a life-threatening thrombotic event may occur soon after administration of rFVIIa.

The most common site of bleeding is at the cannula insertion site. Bleeding can be minimised by delaying administration of a heparin bolus until after dilation of the soft tissue at the entry site.

Note

> The most common site of bleeding is at the cannula insertion site

Tamponading the insertion site with sutures and prolonged compression may be required. Removal of the cannula should always be considered. When going directly from cardiopulmonary bypass to ECLS in the operating room, it is reasonable to wait until the ACT is normal or bleeding stops before starting heparin.

Excessive bleeding may occur at many sites, including mucous membranes and the gastrointestinal tract. These should be dealt with on a specific case-by-case basis.

Aside from exsanguination, intracranial haemorrhage is the most devastating complication of excessive bleeding in ECLS with an incidence of 7–10%. Limited options include stopping anticoagulation completely or discontinuing the ECLS run and returning the patient to high ventilatory and/or inotropic support.

> **Note**
> Intracranial haemorrhage occurs in 7–10% of ECLS runs

Case series exist supporting successful ECLS runs without anticoagulation for extended periods of time. The modern era of heparin-coated catheters and circuits facilitate this conservative approach.

Thrombocytopenia is common in ECLS and is often multifactorial. Circulating platelets adhere to the plastic surfaces and undergo a ‘release reaction’ which attracts other platelets. If the platelet count is <10,000/L, spontaneous bleeding can occur. The ELSO recommends transfusion to maintain platelet counts ≥80×109/L.

> **Important**
> The ELSO recommends transfusion to maintain platelet counts ≥80×109/L.

Heparin-induced thrombocytopenia (HIT) is a rare complication of ECLS. Platelet counts tend to remain below 10×109/L despite repeated platelet transfusions. Expert opinion from a consultant haematologist should be sought before commencing an alternate agent. Such agents are the direct thrombin inhibitors, including argatroban and recombinant hirudin or bivalirudin. A change of circuit is required to a more traditional non-heparin-coated circuit including a specific non- pretreated oxygenator.

Fibrinogen can become depleted during ECLS. Fibrinogen levels should be measured daily and maintained within the normal range by infusion of human plasma or fibrinogen concentrate. There are no studies evaluating use of antifibrinolytics for bleeding on ECLS.

Regarding transfusion triggers for red blood cells (RBCs), the critical haemoglobin for transfusion of RBCs during ECMO is influenced by the level of bleeding, congenital heart disease, myocardial function, preoperative haemoglobin, ECMO flow and neurological status.

Variable practice in anticoagulation was highlighted by ELSO in a cross-sectional survey of 187 centres:

- 72% of respondents reported having a written institutional ECMO protocol for both anticoagulation and blood product management at their institutions
- 59% of respondents reported use of heparin-bonded circuits. UFH was used at all centres
- Only 8% of respondents indicated use of alternative anticoagulation medications
- 97% of respondents reported using serial monitoring of ACT as the preferred method of measuring anticoagulation
- 82% of respondents reported antithrombin III testing, 65% reported anti-activated factor X testing and 43% reported use of TEG during ECMO

Goal ranges for these three tests and interventions triggered by out-of-range values were variable.

ELSO are currently gathering expert opinions to facilitate future guidelines on anticoagulation and bleeding.

In text References

(Görlinger, Bergmann and Dirkmann. 2012; Oliver 2009; Bembea et al. 2013; Extracorporeal Life Support Organization) 2017)

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10. Thrombosis in the ICU

10. 1. Introduction

Admission to hospital for an acute medical illness is associated with an eight-fold increase in thrombosis.

Risk factors for thrombosis include active cancer, previous venous thromboembolism (VTE), reduced mobility, known inherited or acquired thrombophilia, trauma or surgery within the previous month, age >70 years, myocardial infarction or ischaemic stroke, acute infection and obesity.

Conversely, medical or surgical patients may have concomitant major risk factors for bleeding that include gastroduodenal ulcers in the previous 3 months, platelet count $<50\times10^9$ /L, age >85 years, hepatic failure, renal failure and admission to a critical care facility.

The very nature of intensive care medicine exposes patients to invasive monitoring and procedures that requires a risk–benefit assessment of when to institute or withhold thromboprophylaxis.

10. 1. 1. Venous thromboembolism risk assessment

The risk of VTE in patients admitted to the intensive care unit (ICU) varies, depending on their acute illness, premorbid state and ICU-specific exposures and events. Evidence to support routine screening for VTE is lacking. Optimal thromboprophylaxis regimens are poorly characterised due to heterogeneity in published trials. However, for critically ill patients, pharmacological thromboprophylaxis should be instituted versus no prophylaxis.

> ★ **Important**
>
> Critically ill patients are at increased risk for thrombosis and should receive thromboprophylaxis with low-molecular-weight heparin (LMWH), low-dose unfractionated heparin (UFH) or fondaparinux

There is no compelling evidence to support one drug over another. For critically ill patients who are bleeding or at a high risk for bleeding, mechanical thromboprophylaxis should be instituted until the bleeding risk decreases, at which

time pharmacological thromboprophylaxis should be resumed. Thromboprophylaxis should be continued until mobility returns.

10. 1. 2. Mechanical Thromboprophylaxis

Mechanical thromboprophylaxis can be provided by the following methods:

- Graduated compression stockings (GCSs)
- Intermittent pneumatic compression devices (IPCs) (Image 6)
- Venous foot pumps (VFPs).

Figure 15: Intermittent pneumatic compression devices.

These devices reduce venous stasis, a risk factor for VTE, by displacing blood from the superficial to the deep venous system via the perforating veins, thereby increasing the velocity and volume of flow in the deep system.

Of note, pooled data from studies of surgical patients using compression stockings to prevent VTE failed to demonstrate or exclude a beneficial effect on symptomatic deep-vein thrombosis (DVT) or pulmonary embolism (PE).

Stocking use increased the risk of skin breakdown with no effect on rates of limb ischaemia or amputation. Insufficient data exist to support a recommendation of thigh-high stockings over knee-high stockings. A 5% risk of skin breakdown has been reported in stroke patients treated with GCSs.

> **Note**
>
> Pneumatic compression devices reduce DVT risk with no beneficial effect on mortality or PE

A meta-analysis of 22 trials of pneumatic compression devices revealed a reduced DVT risk with no beneficial effect on mortality or PE. When compared to heparin, pooled results failed to show a benefit with IPC in DVT or PE prevention, but fewer bleeding complications were noted.

The combination of IPC and pharmacological prophylaxis has been shown to decrease DVT risk in trials involving post-surgical patients.

10. 1. 3. Pulmonary Embolism

Pulmonary emboli are probable under-diagnosed in the critically ill and should be included in any differential diagnosis of any cardiorespiratory compromise.

A retrospective study of 200 critically ill patients who underwent CT with contrast revealed a 9% incidence of occult PEs on chest imaging performed for a variety of indications. Epidemiological data suggest that 1% of all patients admitted to hospitals die due to acute PE, and 10% of all hospital deaths are PE-related.

Clinical outcome data from large registries and cohort studies suggest that approximately 10% of all patients with acute PE die during the first 1–3 months after diagnosis. Consequently, prevention is of critical importance, where feasible.

10. 1. 3. 1. Classification of pulmonary embolism

The principal pathophysiology associated with morbidity and mortality is the presence of right ventricular (RV) dysfunction and failure resulting from acute RV pressure overload.

The American Heart Association (AHA) has suggested categorisation of acute PE according to severity to predict poorer outcome and to tailor guidelines for therapeutic interventions.

The AHA defines a massive PE as ‘an acute PE with sustained hypotension, pulselessness or profound bradycardia’. Hypotension is defined as a systolic BP <90 mmHg for at least 15 minutes or requiring inotropic support and is not due to a cause other than PE, such as arrhythmia, hypovolaemia, sepsis or left ventricular dysfunction. Persistent profound bradycardia is defined as a heart rate <40 beats per minute with signs or symptoms of shock.

> ★ **Important**
>
> A ‘massive’ PE is an acute PE with sustained hypotension, pulselessness or profound bradycardia!

A submassive PE is defined as an ‘acute PE without systemic hypotension (systolic BP ≥90 mmHg) but with either RV dysfunction or myocardial necrosis’.

> ★ **Important**
>
> A ‘submassive’ PE is an acute PE with RV dysfunction or myocardial necrosis, without systemic hypotension!

RV dysfunction is defined by the presence of any one of the following: RV dysfunction on echocardiography or CT, elevated B-type natriuretic peptide (BNP) or typical ECG changes. Myocardial necrosis is defined as a troponin leak.

The third category is low-risk PE, defined as ‘an acute PE in patients who are normotensive with normal biomarker levels and no RV dysfunction on imaging’.

> ★ **Important**
>
> A ‘low-risk’ PE is an acute PE with normotension, normal cardiac biomarkers and no RV dysfunction on imaging!

The absence of haemodynamic instability tends to favour an improved outcome. The British Thoracic Society has published guidelines and clinical algorithms to aid in the diagnosis of PE. We will focus on high-risk PE as this clinical scenario often mandates referral to intensive care or may occur in the setting of active intensive care.

10. 1. 3. 2. Clinical syndrome

The symptoms of a PE include dyspnoea, diaphoresis, pleuritic chest pain, cough and haemoptysis. Clinical signs of PE include tachypnoea, tachycardia, an accentuated pulmonary component of the second heart sound, pleural rub and fever.

Acute right heart failure in patients with massive PE is indicated by increased jugular venous pressure, a right-sided third heart sound, RV heave and hypotension.

Electrocardiogram (ECG) findings of sinus tachycardia, new-onset atrial arrhythmias, new right bundle-branch block (complete or incomplete), Qr pattern in V1, S1Q3T3, negative T waves in V1 through V4, and ST-segment shift over V1 through V4 have been shown to correlate with worse short-term prognosis in acute PE.
The following ECG (figure 16) shows S1Q3T3 with rSRI in V2 . These findings are highly suspicious for pulmonary emboli.

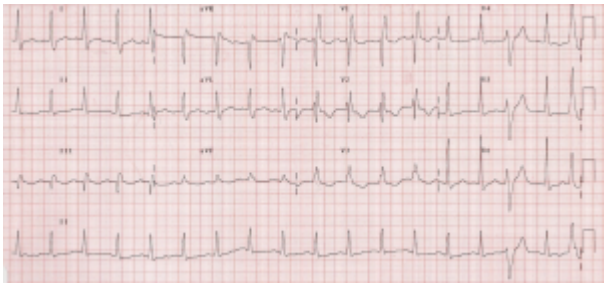

Figure 16: Electrocardiogram

Point-of-care echocardiographic evidence of a pressure-loaded right ventricle, RV free wall hypokinesis in the presence of normal RV apical contractility (McConnell's sign) is highly suggestive of a large PE.

Note

On echocardiography, the presence of RV free wall hypokinesis and normal RV apical contractility is very suggestive a large PE

In the less extreme situation, CTPA with multi-slice CT is the current gold standard in the absence of formal intra-arterial angiography. Figure 17 demonstrates a CTPA with large bilateral pulmonary emboli visible.

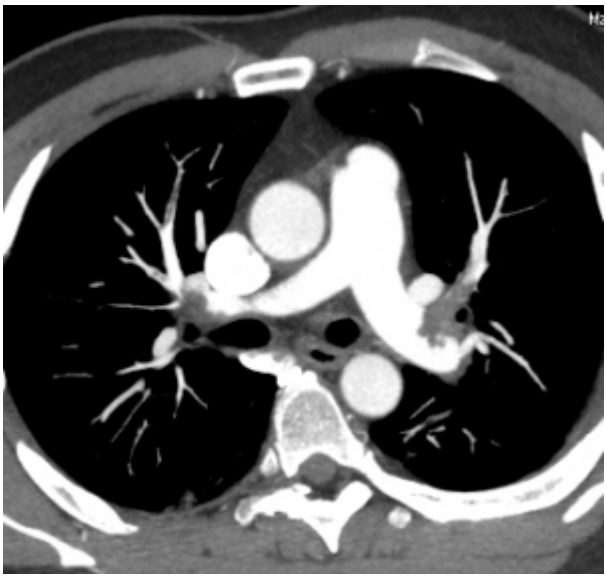

Figure 17: Computed tomography–pulmonary angiogram.

10. 1. 3. 3. Treatment strategies for pulmonary embolism

Thrombolysis for a massive PE, with recombinant tissue plasminogen activator (rtPA) is indicated in the presence of cardiogenic shock as evident by a low systolic BP (outlined in the AHA statement).

When a PE is suspected, patients should immediately receive a weight-adjusted bolus of UFH while awaiting the results of further diagnostic workup.

As soon as PE is confirmed in the setting of hypotension, thrombolysis should be administered without delay in the absence of contraindications. rtPA (alteplase), given as a 100-mg infusion over 2 hours, is considered the treatment of choice for patients with PE.

Pooled data from five trials that included haemodynamically unstable patients have suggested a significant reduction in rates of death or PE recurrence after thrombolysis in this group.

Important

> The role of thrombolytic therapy in patients with submassive PE is unclear and thrombolysis should be reserved for haemodynamically unstable patients!

Retrospective cohort studies and registries have suggested a 36% incidence of major bleeding events and a 4% rate of intracranial/fatal haemorrhage following thrombolysis for PE. Because of potentially devastating complications and lack of benefit in submassive PE, thrombolysis is currently reserved for haemodynamically unstable patients.

Transcatheter procedures may be considered as an alternative to thrombolysis when there are contraindications or when emergency surgical thrombectomy is unavailable or contraindicated.

Catheter-based interventions may also be performed when thrombolysis has failed to improve haemodynamics in the acute setting. The goals of catheter-based therapy include rapidly reducing pulmonary artery pressure, RV strain, and pulmonary vascular resistance with the hope of increasing systemic perfusion and facilitating RV recovery.

Studied techniques include aspiration thrombectomy, thrombus fragmentation and rheolytic thrombectomy, which use a high velocity saline jet to fragment the thrombus, removing debris into an evacuation lumen.

A systematic review of percutaneous therapy alone revealed a clinical success rate of 81%. Catheter-based interventions should only be performed by experienced operators in centres with capabilities to manage cardiac tamponade or pulmonary artery rupture and haemorrhage.

Surgical embolectomy is an alternative strategy in the setting of massive PE. Older case series involving cardiopulmonary bypass reported a mortality rate between 20% and 30% despite surgical embolectomy. A more recent study of 47 patients undergoing surgical embolectomy over a 4-year period reported a 96% survival rate. In experienced centres, surgical embolectomy can be performed off cardiopulmonary bypass and without aortic clamping and cardioplegia.

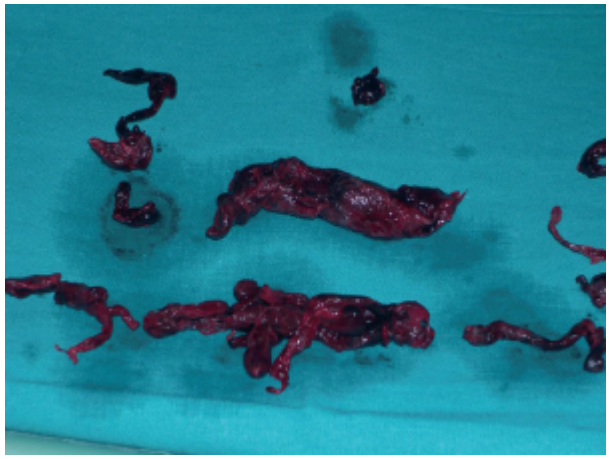

Figure 18: Gross specimen of bilateral pulmonary emboli after surgical thrombectomy.

In the unfortunate scenario of concurrent pathologies of PE and a patent foramen ovale (PFO), a patient may present with a paradoxical embolus or be considered at high risk for paradoxical embolisation on imaging. In the absence of evidence from randomised controlled trials, surgical embolectomy is currently the recommended strategy for thrombus extraction.

10. 1. 4. Ileo femoral Deep Vein Thrombosis

Proximal DVTs are more likely to result in embolisation in comparison to isolated below-knee DVTs. Once confirmed, anticoagulation with UFH, LMWH or fondaparinux should be commenced. Transition to oral anticoagulants usually occurs at general ward level.

In general, anticoagulation may be safely stopped after 3 months in most patients with a first-episode of DVT related to a major reversible risk factor such as recent surgery or trauma. Patients with recurrent DVT or unprovoked DVT should be considered for treatment of indefinite duration, with periodic reassessment of risk and benefit.

For most cancer patients with DVT, first-line therapy should be weight-based LMWH monotherapy for at least 3–6 months, or as long as the cancer or its treatment is ongoing.

10. 1. 4. 1. Vena cava filters

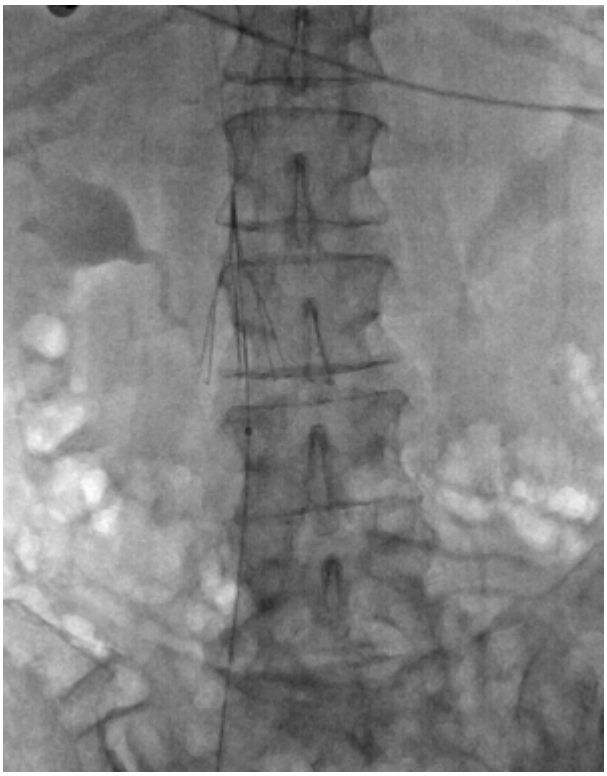

Figure 19: Inferior vena cava filter (in situ).

IVC filters should be considered in patients at high risk for developing PE who have contraindications to anticoagulation. Examples of such clinical circumstances include haemorrhagic stroke and recent surgery.

IVC filters are also used for the treatment of recurrent PE despite adequate anticoagulation and to allow temporary interruption of chronic anticoagulation in high-risk patients with limited ability to tolerate a further PE. In patients with an acute PE, the AHA recommend IVC filter placement in patients with contraindications to anticoagulation or with active bleeding. Anticoagulation should be resumed once contraindication to anticoagulation or active bleeding has resolved.

The PREPIC trial, which included 400 patients with IVC filters, reported a significant reduction in recurrent PE at 12 days and 8 years. However, these beneficial effects were offset by an increased incidence of recurrent DVT with no effect on overall mortality.

Complications of IVC filter insertion include:

- Placement of an IVC filters may be associated with a mortality risk of approximately 0.1%.
- Early complications:
    - Device malposition (1.3%)
    - Pneumothorax (0.02%)
    - Haematoma (0.6%)
    - Air embolism (0.2%)

    - Inadvertent carotid artery puncture (0.04%)
    - Arteriovenous fistula (0.02%).
- Late complications:
    - Recurrent DVT (21%)
    - IVC thrombosis (2–10%)
    - IVC penetration (0.3%)
    - Filter migration (0.3%).

In text References

(Kahn et al. 2012; British Thoracic Society Standards of Care Committee Pulmonary Embolism Guideline Development. 2003; Jaff et al. 2011; Lankeit and Konstantinides. 2011; Arnoult et al. 2013; Decousus et al. 1998; Leacche et al. 2005)

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