Management of acquired coagulopathy in acute paediatrics

Sarah L Morley

Correspondence to
Dr Sarah L Morley, NHS Blood and Transplant and Cambridge University Hospitals NHS Trust, Cambridge Blood Centre, Long Road, Cambridge CB2 0PT, UK; sarah.morley@nhsbt.nhs.uk

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ABSTRACT

Acquired coagulopathy is a relatively uncommon occurrence in acute paediatrics but when it occurs is usually associated with significant underlying pathology and often with critical illness. It can be caused by a number of disease processes but infection, blood loss, iatrogenic causes and liver dysfunction are among the commonest. The blood coagulation cascade is complex and intersects with many other physiological pathways. It is also subject to developmental changes, and 'normal' coagulation and haemostasis change considerably during early life. The diagnosis of abnormal coagulation and when treatment should be initiated is influenced both by age and developmental status and limited by the range of tests routinely available to clinicians. Treatment has predominantly involved transfusion of plasma products (usually fresh frozen plasma and cryoprecipitate) but a number of pharmaceutical and human-derived options are now available. Although plasma products are less frequently transfused than red cells or platelets, their use continues to increase and has not followed the reducing usage of other blood components. This article discusses the aetiology of coagulopathy, describes the commonly available diagnostic tests and outlines the evidence available to guide paediatricians when treating acutely ill children with acquired coagulopathy.

INTRODUCTION

Coagulopathy is often a marker of serious illness in acute paediatrics, but its clinical impact can be variable and difficult to predict. The tests available to confirm its presence and monitor severity have been developed with specific monitoring goals in mind (eg, monitoring of anticoagulation therapies) and are not ideal systems for reviewing global haemostasis during ill health. Their limitations almost certainly stem from the multiple influences on haemostasis that include endothelial function, immune activation and platelet function as well as the more commonly monitored plasma proteins. In paediatrics, additional complexity is added by 'developmental haemostasis', whereby the immature haemostatic system yields different normal ranges in standard tests during early life.

Treatment for coagulopathy largely depends upon plasma-based components, which carry most of the potentially adverse effects associated with transfusion of red cells and platelets. The Serious Hazards of Transfusion (SHOT) Haemovigilance scheme has also highlighted that there is a relatively higher risk of adverse events for transfused children as compared with adults.[1] For this reason, treatment guidelines have focused on using these components appropriately and promoting restrictive transfusion practices. Despite these guidelines, use of plasma-based transfusion therapies have continued to increase in paediatrics. The reason for this increased usage is unclear but seems likely to continue.

In recent years, driven by evidence from military medical teams dealing with severe blunt and penetrating injuries, there has been a specific interest in increased plasma usage in very severe trauma and massive blood loss. Additionally, novel and established pharmaceutical agents have been promoted as plasma-sparing agents in severe bleeding and coagulopathy. In particular, recombinant activated factor VII (NovoSeven, Novo Nordisk, Denmark) has been increasingly used 'off-label' in massive haemorrhage. The relevance of these strategies for acutely ill children has yet to be established.

This article discusses the diagnosis, monitoring and novel and established treatments available to the paediatrician caring for acutely ill children with suspected coagulopathy.

THE COAGULATION SYSTEM

The coagulation system is a series of dynamic pathways composed of plasma proteins and membrane-bound components that lead to clot formation. A simplified schematic of these pathways is illustrated in figure 1. The coagulation cascade has been described as two pathways, the contact activation (or intrinsic) pathway and the tissue factor (or extrinsic) pathway, which lead to thrombin formation. Thrombin is the start of the final common pathway that leads to the formation of insoluble fibrin gel from fibrinogen. The tissue factor pathway is the route through which coagulation occurs in most circumstances. Tissue factor is not normally expressed on endothelial cells but is prominent on the cells of the subendothelium (especially fibroblasts) and so is exposed when vessel wall damage occurs. Endothelial cells and monocytes can also be driven to express tissue factor when damaged or exposed to inflammatory mediators (eg, tumour necrosis factor or endotoxin). Very little tissue factor is required to initiate this process, as amplification is provided by the contact activation pathway and activated platelets. The contact activation pathway predominantly provides amplification or regulation of coagulation but is also initiated through exposed collagen on damaged tissue interacting with FXII. Although the clotting factors that make

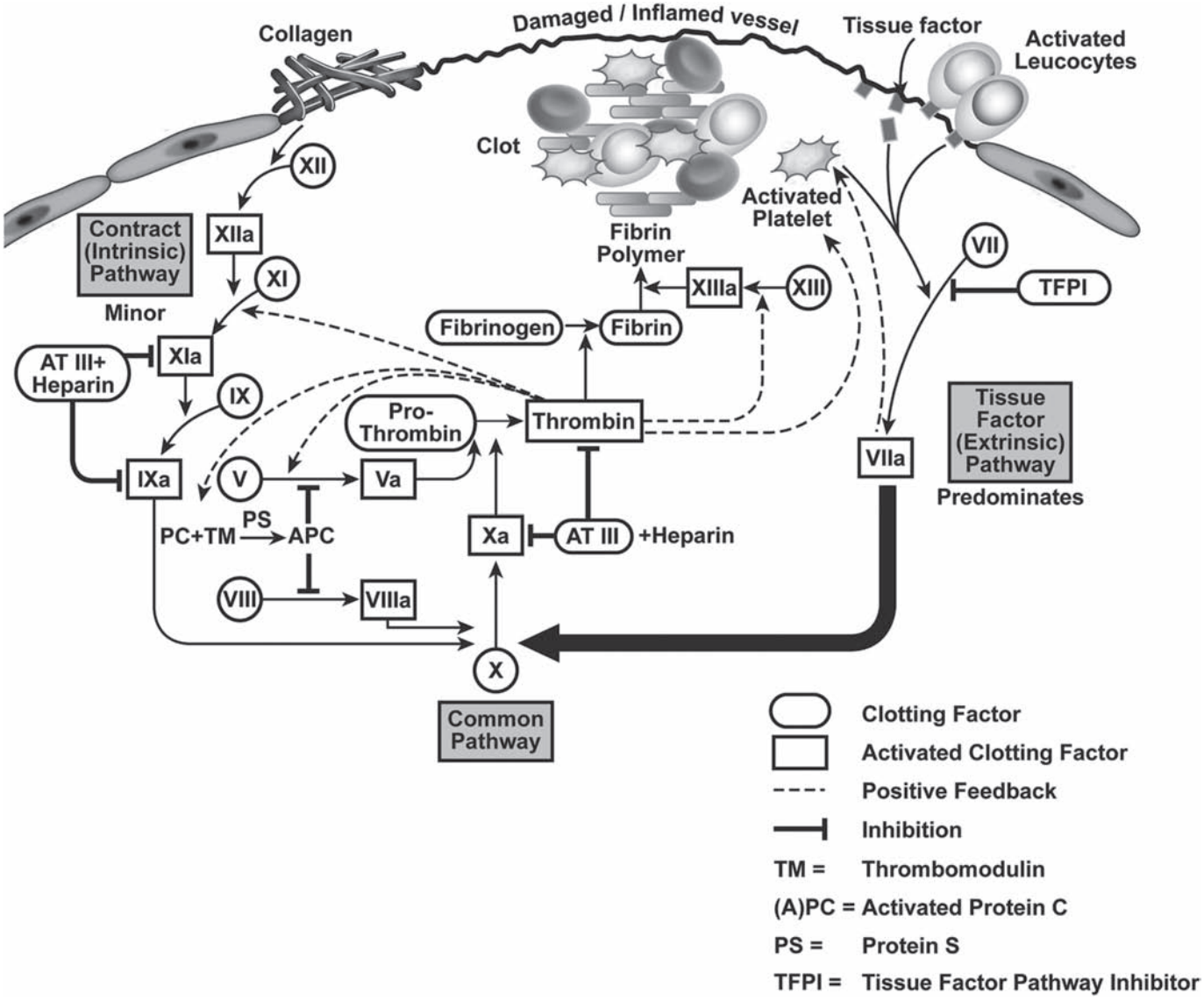

Figure 1 Pathways of the human coagulation system.

up these pathways are found in plasma, almost all the reactions in the cascade occur on the surface of platelets, endothelial cells or other blood cells. Normal endothelium cannot support coagulation because it carries neutral phospholipids on its surface. Disruption of endothelial cell function leads to loss of neutral phospholipids and exposure of negatively charged phospholipids that do support coagulation. Negatively charged phospholipids are also released by activated platelets. Calcium is an important cofactor for many coagulation factor reactions. Fibrinolysis is initiated through the clotting pathways (via thrombin) and is triggered by release of tissue plasminogen activator from damaged endothelial calls.

Vitamin K is an essential factor to a hepatic γ-glutamyl carboxylase that adds a carboxyl group to glutamic acid residues on factors II, VII, IX, X, protein S and protein C. If vitamin K is not available proteins formed in vitamin K absence are produced and are unable to contribute to coagulation.

The clotting cascade contains a number of anticoagulants that help to prevent excessive clot formation. Protein C is activated by thrombin into activated protein C (aPC) and forms a complex with thrombin, thrombomodulin and protein S. This complex downgrades activated factors VIIIa and Va making them inactive. Antithrombin (AT) III is a constantly active enzyme that can inactivate all the factors dependent on vitamin K. It has low activity but in the presence of heparin (which acts as a catalyst) its activity increases 1000-fold. In the circulatory system the heparin role is probably fulfilled by naturally occurring heparin-like compounds (glycosaminoglycans) on the surface of endothelium. The low molecular weight heparins have a preferential role in inactivation of factor Xa rather than the wider panel inhibited by conventional heparin. Tissue factor pathway inhibitor limits the downstream effects of tissue factor by inhibiting factor VIIa (when bound to tissue factor) and also Xa and thrombin.

Table 1 Causes of disseminated intravascular coagulation

Sepsis and severe infections
Gram-negative organisms (including *Neisseria meningitidis*, *Haemophilus influenza*, coliforms)
Gram-positive organisms (including group B Streptococcus)
Viruses (including Dengue fever)
Rickettsiae (including Rocky mountain spotted fever, typhus)
Malaria
Fungal infections (including Aspergillus, Histoplasmosis)
Tissue injury
Massive trauma/surgery and crush injury
Tissue infarction/hypoperfusion
Fractures with fat emboli
Asphyxia and profound shock
Extensive burns
Electrocution
Malignancy
Acute leukaemias (including acute promyelocytic, acute monoblastic or myelocytic leukaemia)
Solid tumours
Toxins
Snake or insect venoms
Recreational drugs
Microangiopathic processes
Thrombotic thrombocytopenic purpura
Haemolytic-uraemic syndrome
Giant haemangioma (Kasabach–Merritt syndrome)
Hereditary or acquired thrombotic disorders
Protein S or C deficiency
Miscellaneous
Acute haemolytic transfusion reactions and other intravascular haemolysis
Acute thrombosis
Graft rejection
Obstetric
Amniotic fluid embolus
Placental abruption
Pre-eclampsia

CAUSES OF ACQUIRED COAGULOPATHY IN CHILDREN

Disseminated intravascular coagulation

Disseminated intravascular coagulation (DIC) is a pathological process that can occur in a number of settings (see table 1) and is characterised by systemic unregulated activation of the pathways leading to blood clotting. The resulting fibrin clots can cause organ compromise in their own right but also cause excessive consumption of coagulation factors and platelets leading to a bleeding tendency, which may cause secondary organ damage. The initial activation may be caused by proinflammatory cytokines released from endothelial and mononuclear cells. Tissue factor is usually expressed only on subendothelial tissues but in sepsis tissue factor expression is induced on endothelial cells and blood mononuclear cells and activates the extrinsic coagulation pathway indiscriminately. The antithrombotic factors (such as ATIII and protein C) are consumed and down-regulated and fibrin degradation may be impaired, leading to further increases in fibrin deposition. Platelets are activated and incorporated in the microthrombi, and thrombocytopenia occurs where platelet consumption is excessive. Purpura fulminans is a severe form of DIC characterised by extensive skin and tissue infarction and necrosis. It is most commonly a feature of meningococcal disease but has been reported in chickenpox (where it may be due to an acquired protein S deficiency) or other bacterial infections.

Trauma/massive transfusion

Traumatic coagulopathy occurs in severely injured trauma patients and a similar syndrome can develop in patients massively transfused after surgery or non-traumatic haemorrhage. As many as 25% of patients with severe traumatic injury are coagulopathic at the time of hospital admission and the presence of coagulopathy correlates with mortality.[2] Many factors contribute to coagulopathy in this setting. The initial insult is tissue injury and shock/hypoperfusion which have been shown to lead to anticoagulation due to increased soluble thrombomodulin in early trauma and also hyperfibrinolysis.[3] The coagulopathy is then potentially worsened in severe trauma by high-volume crystalloid and colloid resuscitation, which leads to coagulation factor dilution with inflammation and further endothelial activation.[2] The dilution may be further exacerbated by transfusion with red cells (in the absence of fresh frozen plasma (FFP) and platelets). Subsequent acidosis, hypocalcaemia and hypothermia can contribute to the coagulopathic state. Eventually, the resulting clotting factor imbalances and platelet and endothelial activation may then lead to DIC and consumptive coagulopathy. Recent work in very severe combat trauma has suggested that expectant treatment based on early replacement of clotting factors and platelets may reduce the occurrence of severe coagulopathy and improve outcomes, and is discussed in more detail below. Aggressive transfusion strategies may be most appropriate for the most severe trauma where prediction tools identify a high risk of bleeding and massive transfusion. Reducing potentiating factors such as hypothermia, electrolyte imbalances and acidosis is intuitively likely to be beneficial, although reversal of these factors after they have occurred has not produced improvement in outcomes.

Vitamin K deficiency

Vitamin K deficiency is rare in otherwise well children because a normal diet contains more than adequate vitamin K and intestinal flora produce an excess of vitamin K_2. Infant formulae provide vitamin K supplementation as do most specialist feeds and total parental nutrition formulations. However, children with chronic malnourishment and especially those taking broad spectrum antibiotics may become deficient in vitamin K. Newborn infants up to 6 months of age (especially those that are breastfed) are particularly at risk and this risk is increased if prophylactic vitamin K was not given at delivery.[4] Other groups in whom vitamin K deficiency may

be relevant are those with cholestatic liver disease, pancreatic insufficiency (eg, cystic fibrosis), malabsorption syndromes, malignancy and prolonged antibiotic use. One study identified adult patients with clinically significant vitamin K deficiency after as little as 1–3 weeks of poor nutrition in the context of abdominal surgery, infection or antibiotic treatment,[5] and evidence of vitamin K deficiency was found in 43% (15/35) of adults on admission to intensive care.[6] Vitamin K deficiency presents with bleeding, ecchymoses and oozing from puncture sites. Internal bleeding is rare in isolated vitamin K deficiency. Vitamin K deficiency commonly causes an initial rise in prothrombin time (PT) followed by a rise in activated partial thromboplastin time (aPTT). Vitamin K can be measured directly as can the decarboxylated forms of vitamin K dependent factors (proteins formed in vitamin K absence) where the diagnosis is in doubt. In most cases, however, these measurements are not undertaken as treatment with vitamin K in suspected cases is usually straightforward and accompanied by few potential side effects.

Liver disease

The coagulopathy of liver disease is multifactorial. The liver is the main site of synthesis of most coagulation factors and so production is impaired as is modification of the vitamin K dependent factors. The coagulation and fibrinolytic systems are activated, as are platelets. Clotting factors may be sequestered in ascitic fluid. Associated immunodeficiency leads to intercurrent infections and inflammation. Coagulation screening tests are usually prolonged (initially PT but also aPTT and thrombin time (TT)), platelet count is low and bleeding time prolonged. Factors V, VII and, in end-stage disease, fibrinogen are often decreased. FVIII levels may be normal as it can be synthesised outside the liver. Fibrin degradation products and D-dimers are often increased. Treatment of the coagulopathy of liver disease can be difficult and should largely be undertaken to control bleeding and to prevent haemorrhage during procedures. Liver failure leads to poor tolerance of high fluid volumes and replacement of factors can be difficult. Clotting factors are also often rapidly consumed and coagulopathy recurs. Vitamin K is a key treatment in many cases and should be given regularly. FFP usage often results in poor correction of clotting abnormalities in these cases and patients with liver failure often poorly tolerate the large volume of plasma products that may be required.[7]

Cardiopulmonary bypass/extracorporeal membrane oxygenation

Children undergoing cardiopulmonary bypass (CPB) are at risk of both thrombotic and haemorrhagic complications. Most children undergoing CPB will have normal haemostasis before the procedure. On initiation of CPB a significant haemodilution occurs, although this can be reduced by using size-appropriate, low-volume circuits. Unfractionated heparin is usually used to prevent clotting in the circuit and close assessment of aPTT, activated clotting time or thromboelastography are required to titrate the dose. The oxygenator membranes stimulate the contact activation coagulation pathway and also lead to release of inflammatory mediators. Tissue damage associated with surgery leads to tissue factor exposure and further inflammation. The fibrinolytic system is activated during CPB and D-dimer concentrations increase. Excessive fibrinolysis has been linked to bleeding complications, and antifibrinolytic drugs became a commonplace until recent concerns about thrombosis supervened. CPB also causes platelet activation and thrombocytopenia and a prolonged bleeding time may occur.

Acquired inhibitors

Inhibitors of coagulation factors occur most commonly in those receiving coagulation factor treatment for haemophilia or other factor deficiencies. A detailed discussion of their management is outside the scope of this article. However, although rare, a number of coagulation factor inhibitors have been reported in other settings. These include anti-von Willebrand factor (anti-vWF) antibody in patients with Wilms tumour, prothrombin inhibitors in systemic lupus erythematosus, FVIII inhibitors in autoimmune disease and following infection and a variety of factor inhibitors (usually transient) after CPB or major surgery. Patients with unexplained bleeding not likely to be due to DIC or other identifiable causes should be referred for assessment by a paediatric haematologist.

INVESTIGATION OF COAGULOPATHY

A number of different tests are available to paediatricians to assess coagulation. No individual test can provide a comprehensive assessment of this complex system and a number of assays are usually combined to give the best possible information. Table 2 outlines the most frequently used assays and their advantages and disadvantages. The most commonly used tests (PT, aPTT and TT) were designed to assess coagulation in the context of factor deficiencies in patients with clinical bleeding. Their relevance in assessing blood coagulability in the acute clinical setting is debated. They assess only plasma-based components of the coagulation system and take no account of the contribution of the endothelium and blood cells.

Normal ranges

Determining the extent of coagulopathy requires reliable testing. The haemostatic system develops in utero and evolves over the first few months of life, leading to maturational differences in the

Table 2 Outline of screening tests available to paediatricians treating acutely ill children

Test	Method	Pathways involved	Abnormalities detected	Interpretation difficulties in children
PT (prothrombin time) (Quick)	Time to clot platelet-poor plasma after addition of tissue factor, calcium and phospholipid	Tissue factor or extrinsic (V, VII, X) and common (fibrinogen, prothrombin) coagulation pathways. Usually not prolonged until levels of one or more factors <30% normal	Factor VII deficiency Fibrinogen defects Warfarin Liver dysfunction	PT sensitivity/specificity varies between systems and reagents Age-dependent values
INR (international normalised ratio)	Derived from the PT and designed to account for interlaboratory differences in PT assay (see text)			Age-dependent values as for PT. INR will be derived against control values for adult plasma and thus neonatal and infant values will commonly fall outside the expressed normal ranges
aPTT (activated partial thromboplastin time)	Time to clot platelet-poor plasma with addition of kaolin (or similar reagent) followed by calcium and phospholipid	Contact activation or intrinsic (V, VIII, IX, X, XI, XII) and common (fibrinogen, prothrombin) coagulation pathways. Usually not prolonged until factor VIII level <35% normal	Deficiencies in factors XII, XI, IX and VIII and the common pathway. Not very sensitive for mild deficiency Heparin	Sensitivity/specificity very variable according to the assay system Age-dependent values
Fibrinogen	Kinetic assay for clottable fibrinogen. The Clauss method is recommended in the UK		Low fibrinogen prolongs TT, aPTT and PT and makes them uninterpretable	Normal levels 1–4 g/l
TT	Time to form fibrin gel when thrombin added to platelet-poor plasma	Measures fibrin formation	Low/dysfunctional fibrinogen Thrombin inhibitors (eg, heparin or fibrin degradation products)	
D-dimers	Agglutination test for factor XIII crosslinked fibrin subunits. D-dimers are small fibrin degradation products	Demonstrates that plasmin has digested fibrin clot	DIC Thrombosis Liver dysfunction	Not well characterised for children
Specific factor assays	Assays are available for all known clotting factors. Predominantly kinetic assays based on either PT or aPTT but some immunoassays	Not usually indicated unless one of the screening tests is abnormal except if suspicion of von Willebrand disease, factor XIII deficiency or dysfunctional fibrinogen		
Thromboelastography/rotational thromboelastometry	Whole blood is placed in a cuvette and agitated. Mechanical or optical assessment of the speed of clot formation and lysis and clot strength and elasticity is performed	All coagulation pathways, platelet function and fibrinolysis	Usually used at the bedside in anaesthesia or CPB to globally assess clot formation. Has been recommended for use in trauma/massive transfusion[41]	Bedside test ideally requires experienced operators and careful quality control. Utility is best documented in CPB as predictor of bleeding[42]

CPB, cardiopulmonary bypass; DIC, disseminated intravascular coagulation; TT, thrombin time.

- TP (Quick) N dès J5
- Fibrinogène N dès J5
- PTT N dès 3-6 mois !
- ATIII N dès 6 mois !

levels of many coagulation factors. This inevitably also leads to differences in the normal ranges of coagulation screening tests for premature and term infants as compared with adults.

Coagulation factors that are reduced in the neonatal period (as compared with adults) include FII, FVII, FIX, FX, FXI and FXII and these reductions are exaggerated in preterm infants. FVII increases to near adult levels by day 5 of life but the other factors gradually increase over the first 6 months. The rapid rise in FVII brings the PT, which is prolonged in newborns, to close to adult values by day 5. The international normalised ratio (INR) is a test derived from PT and was designed to compensate for the variation in PT caused by different reagents and analysers, allowing anticoagulant dosage to be monitored using different laboratory systems. It is thus affected by changes in PT in the neonatal period and will be higher than the expected adult ranges in preterm infants and newborns. The aPTT is always prolonged at birth and usually reaches adult levels after 3 months of age (although this can be delayed in premature babies). aPTT ranges are also wider in younger children. The TT is mildly shortened in infants under 3 months of age. Fibrinogen levels are similar to adult levels from the time of birth but tend to rise in the first 5 days of life. FVIII is equivalent to adult levels from birth and vWF may be higher than adult levels. From 1 year onwards coagulation parameters are broadly similar to those of the adult.[8]

The coagulation regulators AT, protein C and protein S are almost certainly low in preterm and term infants. They reach adult values by 6 months of age except protein C, which remains low. Infants also demonstrate low fibrinolysis owing to quantitative and qualitative differences in the pathway. Platelet function may also be abnormal in newborns.

Reference ranges are usually defined as a set of values for a specific test and reagent that

includes the values of a given proportion of the population (usually this would be between 5th and 95th centiles—that is, 90% of the population). These ranges are likely to be different for each age group in early life. Providing absolute normal values for neonates and older children is complicated further because each of the analysers and reagents on the market performs slightly differently. This difference can be especially marked for aPTT. Ideally, each laboratory should develop its own normal range for children of each age and gestation. Establishing cohorts large enough to generate these ranges can be difficult and, in reality, many laboratories use published reference ranges such as those generated by Andrew *et al*[9–11] or published in UK guidelines.[12] Many of these ranges were developed two decades ago using equipment and reagents different from those used today. A more recently published analysis using a currently available analyser suggested that aPTT may be relatively prolonged, compared with adults, until later in childhood than the current UK guidelines suggest.[12 13]

For the clinician, the key to interpreting local coagulation screening tests lies in understanding which normal ranges are being quoted and whether they are age and gestation appropriate. A recent national audit in England suggested that the majority of hospitals do not automatically report paediatric coagulation results alongside age-appropriate normal ranges.[14] It is not uncommon for neonatal coagulation results to be produced alongside adult normal ranges (in this case, every neonate might appear to have a prolonged aPTT). Equally, if preterm results are interpreted using term baby ranges, a similar problem could occur.

Sample collection

Coagulation samples should be drawn cleanly to avoid activation through turbulence, exposure to air bubbles or incorporation of tissue fluids. They should ideally not be drawn through heparin containing indwelling lines. The anticoagulant is sodium citrate and this should be present at a known concentration for the assay to be accurate; hence the need for care in filling tubes to the correct level. A high haematocrit can lead to excessive citrate concentration in the remaining plasma. Coagulation screens are most likely to be accurate if completed within 2 h (if stored at room temperature).

Diagnosis of DIC

No single laboratory test is diagnostic for DIC. Patients with DIC will usually have prolonged global tests of coagulation (PT and aPTT) and a falling or low platelet count. They may have evidence of increased fibrin turnover (eg, D-dimers or fibrin degradation products), although these tests may not be performed regularly in children. A single snapshot of blood tests may not be sufficient to diagnose DIC and serial blood sampling may be required to make the diagnosis with certainty. Clinical suspicion coupled with declining platelet count and abnormal coagulation screening are likely to be the most sensitive indicators. The platelet count is a key early indicator of DIC, with thrombocytopenia present in the majority of cases and 50% of cases having a count <50 $\times 10^9$/l.[15] Platelet count correlates closely with markers of thrombin generation because platelets are depleted by thrombin-induced aggregation. Stabilisation of the platelet count may be a sign that the thrombin generation is resolving. Isolated thrombocytopenia is non-specific for DIC as low platelet counts occur in many other clinical settings. Simple scoring systems for DIC have been devised (in adult patients).[16 17] Relatively little research has been undertaken to determine the utility of these scores in children, although Khemani *et al* have shown an association between DIC score and mortality in a group of critically ill children with septic shock.[18] Recent preliminary work in children has also suggested that measurement of protein C level may have potential as an early screening tool for DIC.[19]

MANAGEMENT OF COAGULATION ABNORMALITIES IN ACUTELY ILL CHILDREN

The most important treatment for any coagulopathic patient is that given to control the underlying condition; making the correct diagnosis is key. Many patients will require supportive treatments but the evidence as to when these should be used and how effective they are is relatively sparse, especially in children.

Clinical use of FFP and cryoprecipitate continues to increase despite concurrent reductions in the use of red cells. Very little evidence of clinical efficacy is available to guide FFP usage.[20] FFP is most commonly transfused to children in neonatal or paediatric intensive care or in the perioperative period.[14]

TRANSFUSION THERAPIES FOR COAGULOPATHY

Fresh frozen plasma

FFP is the commonest transfusion therapy in coagulopathy. FFP is plasma produced from whole blood (by centrifugation) or by apheresis and frozen to −40°C to preserve the labile coagulation factors. A single pack of FFP will have been derived from a single donor. FFP usually contains coagulation factors at close to normal blood levels and also contains other plasma proteins, including immunoglobulins and albumin. In the UK more than 90% of FFP is produced from male donors to reduce the risk of transfusion-associated acute lung injury (TRALI).[21] All blood components are leucodepleted to leave a residual white cell count of <5 $\times 10^6$ leucocytes/unit. Leucodepletion reduces the immunogenicity of blood components and also the likelihood of pathogen transmission. FFP can be stored at −30°C for 24 months. It is thawed at 37°C and used promptly after thawing (within 4 h at room temperature or within

24 h if refrigerated). Factor VIII is the only plasma protein for which the biological activity is quality controlled in FFP, although other plasma proteins such as fibrinogen should be present at normal plasma levels.

In the UK FFP is produced in two formulations according to the age of the intended recipient. Leucocyte-depleted FFP from UK donors is provided for those aged ≥16 years (average volume 273 ml with and FVIIIc >0.7 IU/ml and fibrinogen 20–50 g/l). Methylene blue treated, leucocyte-depleted FFP from non-UK donors is provided for those under 16 years of age (volumes 233 or 56 ml with FVIIIc >0.5 IU/ml). The smaller-volume packs are recommended for use in neonates and infants.

FFP (and cryoprecipitate) for children is manufactured from volunteer male donors, imported from the USA and treated with methylene blue and light as a pathogen inactivation method. At least 90% of the methylene blue is removed after processing. The processing of both FFP and cryoprecipitate reduces the coagulation factor content. The level of functional fibrinogen is lower than in standard FFP (60–80%). There are no published studies showing efficacy of methylene blue treated FFP relative to untreated FFP in the treatment of coagulopathy. The use of non-UK plasma is intended to reduce the theoretical risk of variant Creutzfeldt–Jakob disease transmission through transfusion to those not likely to have been exposed to this disease through their diet.

FFP and cryoprecipitate should be administered using a standard blood giving infusion set with a 170–200 µM filter. Children should be given FFP of the same ABO group whenever possible but can be given FFP from different groups if necessary. Non-group-specific plasma should always be given only when authorised by the local transfusion laboratory. Group O plasma should usually only be given to group O recipients. Group O FFP should not be used in infants or neonates who are not group O because the relatively large volumes required can lead to passive immune haemolysis. FFP and cryoprecipitate do not need to be matched for rabbit haemorrhagic disease. FFP and cryoprecipitate do not need to be irradiated as they are not associated with graft versus host disease, they are also not required to be cytomegalovirus negative as they do not transmit this virus.

Cryoprecipitate

Cryoprecipitate was originally developed as the first practical method of preparing a concentrated treatment for haemophilia. It is prepared by controlled thawing of frozen plasma to precipitate high molecular weight plasma proteins.

Cryoprecipitate is produced by thawing a single donation of FFP at 4°C. The precipitated portion is then frozen to –30°C. The cryoprecipitate prepared from a single donor unit contains 80–300 IU of factor VIII and vWF, and 300–600 mg of fibrinogen in a volume of 20–50 ml. It is produced as single units for children or as pools of five for older children and adults. It can be stored at –30°C for 24 months. It is thawed at 37°C and should be used within 4 h when thawed. Methylene blue treated cryoprecipitate is now provided for children younger than 16 years in the UK.

A typical adult dose is two pools of 5 units (equivalent to 10 single donor units). One such treatment administered to an adult would typically raise the plasma fibrinogen level by about 1 g/l. For children, the initial recommended dose is 5 ml/kg body weight[22] and further treatment should be guided by repeat clinical assessment and laboratory testing. A standard blood giving infusion set with a 170–200 µM filter should be used. It should be ABO compatible where possible.

Solvent-detergent treated FFP

This commercial product (Octaplas, Octapharma AG, Switzerland) is prepared from large pools of 300–5000 European plasma donations treated with a solvent and detergent to remove lipid-enveloped viruses (eg, HIV and hepatitis B and C). The concentrations of coagulation factors are tightly controlled, although some factors such a protein S may be reduced compared with standard FFP (solvent detergent (SD) plasma is not recommended in protein S deficiency). It is provided in 200 ml bags with fibrinogen 2.7 g/l and factor VIII >0.5 IU/ml. It is prepared by ABO group and administered according to the same guidelines as for FFP.

In common with other plasma products solvent-detergent treated FFP (SD FFP) should not be given to patients with IgA deficiency who are prone to hypersensitivity reactions. SD FFP is the product recommended in the UK for patients with thrombotic thrombocytopenic purpura who require high doses in plasma exchange. SD FFP has a good safety record for transfusion-transmitted viral and bacterial infection and a low incidence of TRALI and allergic reaction. Despite the additional safety measures taken to remove pathogens in SD FFP, concerns still remain about use of blood components derived from large donor pools as the risk of transmitted infection (particularly of novel pathogens) may be increased.

Fibrinogen concentrate

Fibrinogen concentrate (HaemocomplettanP/RiaSTAP, CSL Behring, USA) has been marketed for a number of years for the treatment of congenital hypofibrinogenaemia. It is currently distributed on a named patient basis only in the UK. In certain European countries it has been used for management of acquired hypofibrinogenaemia and has been advocated by some researchers as a fibrinogen replacement therapy for patients requiring massive transfusion[23] or cardiac/vascular surgery. It is produced from pooled human plasma by fractionation and undergoes viral reduction and inactivation steps. It has a fibrinogen concentration of around 20 mg/ml which is similar

to, or higher than, that of cryoprecipitate. Little research is available to guide its use in acquired coagulopathy and it cannot be currently recommended for routine treatment, apart from treatment of congenital hypofibrinogenaemia.

Evidence base for FFP and cryoprecipitate transfusion

Although FFP is widely used, there are few well-founded indications. In general, FFP usage is considered to be either therapeutic or prophylactic. Therapeutic use is where active bleeding is occurring (usually but not exclusively in the presence of known abnormal coagulation tests). Prophylactic use of FFP is treatment of abnormal coagulation parameters in the absence of active bleeding and may be undertaken to prevent spontaneous haemorrhage or to prevent haemorrhage due to a planned invasive procedure. A large systematic review of randomised trials involving FFP has highlighted the dearth of evidence supporting either therapeutic or prophylactic use. In particular, evidence for prophylactic use is extremely weak.[20] Numerous small trials have been undertaken in many clinical settings but few were adequate to detect meaningful outcomes and those that were adequate did not show any clear evidence in favour of prophylactic FFP use.

Most guidelines suggest that plasma should only be transfused in the case of active bleeding, or where there is a high risk of bleeding, and not based on abnormal coagulation screens alone.[17 24] Use of FFP may be recommended in the non-bleeding patient with abnormal coagulation parameters where certain invasive procedures are about to be undertaken, but there is little evidence to support efficacy for this indication. Holland and Brooks[25] have reviewed international guidelines and demonstrated that most recommend that the threshold for FFP transfusion should require a coagulopathy with PT/aPTT >1.5 times normal (it would be usual for this to be 1.5 times the mid-point of the relevant age-appropriate normal range—in some laboratories this may approximate to an INR >1.5 depending on the assay used). There is also clear international evidence that clinicians do not comply with these guidelines, and commonly transfuse patients with borderline coagulation tests. Their own work (in a relatively small retrospective series of adult and paediatric patients) suggested that there was little change in INR following FFP transfusion for patients whose pretransfusion INR was <1.7.

A small number of trials have provided evidence suggesting a lack of clinical benefit for FFP in specific clinical settings. One study that is particularly relevant for paediatricians was a study conducted in the north of England, which demonstrated that prophylactic FFP did not prevent intraventricular haemorrhage or improve developmental outcome at 2 years in preterm infants.[26] In that study infants were randomised without reference to coagulation screening. Systematic reviews have failed to confirm any positive role for FFP in preventing bleeding and reducing transfusion requirements following CPB in cardiac surgery.[20 27] Massicotte *et al* have recently demonstrated a lack of association between abnormal coagulation parameters (INR >1.5) and bleeding and transfusion during liver transplantation. In their group of patients the avoidance of FFP transfusion was associated with a decreased requirement for red cell transfusion perioperatively, possibly owing to the effect of hypervolaemia.[28]

Very little evidence is available to guide the use of cryoprecipitate. Most guidelines recommend that a severely reduced fibrinogen level (<1 g/l) that persists despite treatment with FFP can be treated with cryoprecipitate where active bleeding is occurring or predicted.[17 24 29]

Correct dose of FFP

There is relatively little evidence supporting appropriate FFP dosage. Current UK guidelines suggest that an initial dose of 15 ml/kg is appropriate, although a range of 10–20 ml/kg is commonly used.[22 24] Sensibly, in older children, the dose should be rounded down to the nearest whole unit to minimise donor exposure. A follow-up coagulation screen is essential in all cases to ensure that the desired correction of laboratory parameters has been achieved.

In many cases it is likely that multiple FFP doses may be required. The work of Holland and Brooks[25] suggests that a cumulative dose of 21 ml/kg is likely to be required to achieve a target INR of 1.7 from a starting INR of 3. To achieve an INR of 1.3 from the same starting point 50 ml/kg is likely to be needed. In severe cases the transfusion strategy should be tailored to ensure that the likely cumulative dose is delivered with minimum donor exposure and serial monitoring of blood loss and coagulation parameters should be undertaken.

Ratio of transfused blood components in massive transfusion

Work undertaken in military trauma centres dealing with severe battlefield injuries has led to a growing literature suggesting that earlier use of plasma and platelets alongside red cell transfusions (to mimic the proportions in whole blood) should be used to prevent coagulopathy and thrombocytopenia in severe trauma. The concept of 'damage control resuscitation' and the transfusion theories that contribute to it have recently been reviewed by Holcomb and Spinella.[30] Briefly, this strategy employs 'hypotensive' early resuscitation with early corrective surgery. Fluid resuscitation is minimised and, in particular, crystalloid use is restricted and is replaced by aggressive transfusion strategies to correct coagulopathy and thrombocytopenia to reduce further blood loss. Advocates of this transfusion strategy

would usually recommend its use only in patients expected to require massive transfusion.

Suggestions for the precise ratio of blood components that is optimal vary. Some authors advocate a 1:1 ratio of plasma:red blood cells (RBCs) (and some a 1:1:1 ratio RBCs:plasma:platelets), although others have suggested simply that a higher ratio of plasma is used (eg, 1:2 plasma:RBCs is preferable to low ratios—eg, 1:8). A retrospective military study showed a substantial reduction in mortality in cases treated with high plasma ratios.[30a] The recommendation that RBCs and FFP should be used in a 1:1 ratio in this setting to provide the equivalent of whole blood is poorly researched in children but has been studied in the setting of adult military and civilian severe trauma.

The practical application of this strategy is not entirely straightforward. Using UK components, RBCs and FFP are both formulated so that each unit is the equivalent of that which would be derived from a single whole-blood donation. It should be noted that the standard adult platelet pack (whether pooled buffy coat platelets from whole-blood donation or derived by apheresis) is the equivalent of the platelets from four whole-blood donations containing on average 240 × 10^9 platelets in 250 ml. The apheresis-derived units provided for neonatal and paediatric use contain around 60–70 × 10^9 platelets in 50 ml. It would thus be necessary to moderate platelet doses accordingly and to monitor platelet counts to determine therapeutic doses for individual cases.

Until more data are available, caution should be exercised in using fixed ratios of blood components for all except early resuscitation of the most severe trauma/haemorrhage cases as all blood products carry risks that may outweigh therapeutic benefit if used in excess. Such strategies should also be regarded as 'resuscitation' in the most acute sense and as soon as haemorrhage is controlled and the patient's clinical status has stabilised, then titration of products based on blood testing should be reinstituted to reduce the risks of overtransfusion of any individual component.

Adverse effects of plasma transfusion

The SHOT group collates reports of adverse events associated with transfusion in the UK. Their 2008 report found that 7.1% (74 of 1040) of adverse events occurred in children <16 years of age with 3.0% (31 of 1040) <1 year of age and 1.9% <4 weeks of age. Events in children are still disproportionately high, as compared with adults, for the number of transfusions undertaken. The number of adverse events reported continues to increase but the number of deaths related to transfusion in all age groups is declining year on year. In all age groups FFP was responsible for only 11% (33/300) of acute transfusion reactions; in children this figure was 4% (1/25). The commonest acute transfusion reactions with FFP were allergic reactions and febrile reactions. There were no transfusion-transmitted infections reported to SHOT associated with FFP in 2008.

TRALI occurs within 6 h of the precipitating transfusion and usually presents as a non-cardiogenic pulmonary oedema with shortness of breath, hypoxia and diffuse infiltrates on chest x-ray. It may be difficult to recognise as many children receiving FFP will have pre-existing lung and cardiovascular disease. It is usually associated with anti-leucocyte antibodies either anti-HLA or antineutrophil antibodies from the donor that bind to the leucocytes of the recipient. Since it is antibody mediated it is most commonly induced by FFP but can occur with any products containing residual plasma (including platelets and red cells). The antibodies are most commonly generated in the donor by exposure to neonatal antigens during pregnancy and are generally found in male subjects only after transfusion or transplant. At present, all FFP provided to under 16s should be from male donors and in 2008 89% of all FFP produced in the UK for adults was male donor derived. The UK blood services are aiming for 100% male donor FFP by the end of 2009. TRALI is now less common in the UK and no cases were reported in children <16 years during 2008, although it is likely that TRALI is under-reported.

PHARMACEUTICAL TREATMENTS

Vitamin K

Patients suspected to have vitamin K deficiency should receive supplementation using the most appropriate route according to the urgency of the situation. Where urgent correction is required (in those who have severe coagulopathy or overt bleeding) then the intravenous route is preferred (although serious anaphylactoid reactions have occurred and can cause haemodynamic instability); the oral route can be used where absorption is not impaired and a slower correction is tolerable. Correction of coagulopathy with vitamin K is rapid (2–6 h for parenteral and 6–8 h with oral administration). It would be reasonable to consider vitamin K supplementation as a first-line treatment for coagulopathy in any chronically unwell child where malabsorption, malnutrition, hepatic insufficiency have occurred or abdominal surgery has been carried out or broad-spectrum antibiotic therapies used. Although not usually a substitute for correction of clotting factors in the acutely bleeding child, vitamin K supplementation may help to reduce coagulopathy and minimise transfusion in patients in whom bleeding may occur. Vitamin K may be especially helpful in young breast-fed infants, especially if there is uncertainty about administration of prophylactic vitamin K in the newborn period. The current UK guidelines produced by the British Committee for Standards in Haematology recommend that children in intensive care be given intravenous vitamin K 0.3 mg/kg (maximum dose 10 mg) three times weekly to prevent vitamin K deficiency. This guideline is based upon evidence from small

trials conducted in adults and has not been fully validated in children.[6 24]

Recombinant factor VIIa

Recombinant factor VIIa is a relatively new product that was originally licensed as a treatment for bleeding in patients with haemophilia who are unable to respond to treatment owing to antibodies to factor VIII or IX. Initial case reports suggested that factor VIIa can be helpful in patients with prolonged or excessive bleeding due to surgery or trauma and also in patients with intracranial haemorrhage. In recent years unlicensed use of factor VIIa has increased dramatically and it has been incorporated in many hospitals' guidelines for major haemorrhage, even though the evidence for its use in this setting is poor. A recent systematic review assessed 17 randomised controlled trials undertaken using VIIa.[31] These included studies of prophylactic use to prevent bleeding in haemorrhage-prone routine surgery, emergency treatment of ongoing haemorrhage and lastly, treatment of early intracranial haemorrhage. The review was unable to establish a clear indication of benefit in either prophylaxis for haemorrhage-prone procedures or therapeutic use in refractory haemorrhage. Those studies that did suggest benefit were unable to establish cost effectiveness.

A recent randomised controlled trial of two dose regimens of FVIIa compared with placebo showed a reduction in overall haemorrhage volume in the treatment groups but no reduction in the percentage of patients with poor outcome (defined as severe disability or death).[32] There are also significant concerns about the risk of thromboembolic events following FVIIa administration. Birchall *et al* found an overall risk of thromboembolic events of 8% for the treatment group versus 5% in the placebo group for the 17 studies included in their review. These events occurred despite the exclusion of patients with a previous history of thromboembolic disease. The most serious thromboembolic events (myocardial infarction and ischaemic stroke) were only reported in patients receiving FVIIa in these studies (none were reported in placebo groups).[31] Mayer *et al*[32] showed a similar frequency of thromboembolic events in each of their cohorts studied during intracranial haemorrhage but arterial thromboembolism was significantly more common in the higher-dose treatment arm than placebo (9% vs 4%; p=0.04).

It is likely that FVIIa treatment will continue to be used as 'rescue treatment' in refractory life-threatening haemorrhage. Clearly, in the majority of cases the ideal situation would be to obtain haemostasis by direct surgical means or by correction of coagulopathy. However, factor VIIa intuitively may have greatest utility in those cases where this is either impractical or the site inaccessible—for example, blunt trauma in the field, diffuse intra-abdominal bleeding, intracranial bleeding or rapid haemorrhage, where blood product provision may be delayed. The thromboembolic risks associated with FVIIa are becoming increasingly apparent. There is no clear evidence that the benefits of FVIIa outweigh the risks in this setting and at present the risk:benefit ratio can only be estimated on an individual basis by the treating doctor. Current adult guidelines recommend that VIIa should only be considered if there is ongoing haemorrhage >300 ml/h (probably equivalent to around 4–5 ml/kg/h in a child) that has not responded to adequate replacement of coagulation factors and platelets, correction of acidosis and where surgical haemostasis is not possible.[33]

Antifibrinolytic drugs

Antifibrinolytic drugs (which reduce the breakdown of fibrin) are used in some surgical centres to reduce postoperative bleeding after major surgery (eg, cardiac or orthopaedic procedures) and may reduce transfusion requirements in this setting.[34] Some authors have advocated their use in cases of severe trauma, although current evidence does not support routine use in this setting. They are not recommended, however, as treatment for coagulopathy, and particularly DIC where cessation of fibrinolysis might be detrimental.[17] Use of these agents in specific cases of DIC with hyperfibrinolysis (diagnosed by high levels of markers of fibrin degradation or thromboelastography) has been reported but such intervention should only be considered under advice from a haematologist expert in the field. The only antifibrinolytic currently licensed for children in the UK is tranexamic acid and its use in children is usually reserved for specific settings (eg, prevention of bleeding following cardiac or orthopaedic surgery, severe menorrhagia, severe epistaxis or excessive bleeding after dental surgery).

Additional pharmacotherapy for DIC

Supportive treatment for DIC is a complicated issue. Where necessary, supportive transfusion of FFP and platelets should be considered as first-line treatment, according to the principles outlined above. In bleeding patients, or those at high risk for bleeding, the platelet transfusion threshold is usually considered to be 50×10^9/l (although local guidelines may vary). Lower thresholds ($10–20 \times 10^9$/l) may be appropriate for those felt to be at low risk for bleeding. Administration of either human-derived/recombinant anticoagulants or drugs such as heparin have been advocated but few have shown benefit in clinical trials. The research relating to these options is discussed briefly below.

Recombinant aPC

Recombinant human aPC (drotrecogin α) has been investigated as a therapeutic intervention for patients with severe sepsis (with and without laboratory evidence of DIC). It has been suggested that restoring the anticoagulant protein C pathway may help to reduce the severity of DIC.

A number of clinical studies have been undertaken in adults and children and are reviewed in detail by Laterre.[35] In 2001 the PROWESS study (a multicentre, randomised, double-blind, placebo-controlled trial in 1690 adults with severe sepsis) showed a 19.4% relative risk reduction (p=0.005) in all-cause mortality for patients given aPC by continuous infusion for 4 days.[36] The incidence of serious bleeding events was higher in the treatment than the placebo group (3.5% vs 2.0%; p=0.06). A more recent randomised, placebo-controlled study in 2640 adults (ADDRESS) has shown that aPC is not beneficial in patients with severe sepsis but at low risk of death.[37] In children a dose-finding study suggested that the pharmacokinetics and safety characteristics of aPC were similar to those in adults.[38] A multicentre, randomised, double-blind, placebo-controlled trial in 477 paediatric patients (term babies to <18 years) with severe sepsis (RESOLVE) was reported in 2007.[39] There was no difference between treatment and control groups in the primary outcome measure (composite time to complete organ failure resolution) or the secondary outcome measure (mortality at 28 days) 17.2% and 17.5% (p=0.93), respectively. Bleeding events occurred in 4.6% in the treatment group and 2.1% in the control group. Likelihood of bleeding with aPC was greater in children younger than 60 days at enrolment. Thus, aPC can reduce mortality in adult patients with severe sepsis at high risk of death but is not recommended for children presenting with severe sepsis.

Antithrombin

A concentrate of AT has been used in some settings in adult patients with DIC. Such administration may demonstrably improve clinical parameters but has not been shown to reduce mortality.[40] Evidence is very limited and thus AT is not recommended for use in DIC at present.

Heparin

In rare cases DIC can present with a predominantly thrombotic picture (eg, arterial or venous thromboembolism or unusual forms of purpura fulminans presenting with widespread skin infarction). Use of heparin has been advocated in these cases. Unfractionated heparin infusion (which is reversible and has a short half-life) with dose adjusted for bodyweight (a starting dose of 10 U/kg/h may be recommended) has been suggested. Close monitoring of aPTT is required with careful clinical assessment for bleeding complications. It should be noted that heparin may not be effective if ATIII levels are low. In general, use of heparin in DIC should be considered only rarely and any treatment should be undertaken only with the assistance of a paediatric haematologist with specific expertise.

In patients where thromboprophylaxis would usually be recommended then prophylactic doses of low molecular weight heparin should be given (according to local guidelines) even where DIC is present unless the patient exhibits active bleeding. Graduated compression stockings should also be used.

SUMMARY

Treatment for acute coagulopathy continues to be based predominantly on plasma products, and use of FFP continues to increase. Evidence suggests that many patients are treated unnecessarily and that when treatment is given it may not positively influence the clinical course. Current UK and international guidelines recommend that plasma products should be reserved for those who are actively bleeding, or who have coagulation tests prolonged to more than 1.5 times normal and are also at high risk of bleeding (eg, before certain invasive procedures). In general, FFP usage for children should be limited to these relatively restrictive recommendations.

Recent evidence suggests that there may be benefit in more liberal use of plasma components in the specific setting of resuscitation during massive haemorrhage. Early use of FFP in severe trauma may help to prevent the development of full-blown coagulopathy and limit ongoing bleeding. Once the immediate resuscitation phase is complete and bleeding is controlled then treatment should return to the usual restrictive guidelines and be based upon coagulation testing. Research in this field has been undertaken almost exclusively in adults and especially in the battlefield setting. It has yet to be confirmed whether liberal use of plasma is helpful in civilian trauma or surgery in children.

When testing for coagulopathy it is important that results are assessed against age-appropriate normal ranges, which may not be routinely provided. Identifying and treating the underlying cause of any coagulation abnormality is also essential. Supplementation of vitamin K is a simple and rapid intervention in patients who may be deficient, and may reduce plasma transfusion. Chronically ill children may be especially at risk and coagulopathy may be prevented in this group by vitamin K prophylaxis. Other pharmaceutical adjuncts may be useful in specific settings, but require specialist advice from a haematologist as side effects may outweigh benefits. Recombinant factor VIIa has been used 'off-label' to treat massive bleeding but it should usually be considered only rarely in severe ongoing blood loss where strenuous attempts to control bleeding and manage coagulopathy have been made.

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REFERENCES

1. **Stainsby D**, Jones H, Wells AW, *et al.* Adverse outcomes of blood transfusion in children: analysis of UK reports to the serious hazards of transfusion scheme 1996-2005. *Br J Haematol* 2008;**141**:73–9.

2. **Brohi K**. Diagnosis and management of coagulopathy after major trauma. *Br J Surg* 2009;**96**:963–4.
3. **Brohi K**, Cohen MJ, Ganter MT, *et al.* Acute coagulopathy of trauma: hypoperfusion induces systemic anticoagulation and hyperfibrinolysis. *J Trauma* 2008;**64**:1211–17; discussion 1217.
4. **Van Winckel M**, De Bruyne R, Van De Velde S, *et al.* Vitamin K, an update for the paediatrician. *Eur J Pediatr* 2009;**168**:127–34.
5. **Alperin JB**. Coagulopathy caused by vitamin K deficiency in critically ill, hospitalized patients. *JAMA* 1987;**258**:1916–19.
6. **O'Shaughnessy D**, Allen C, Woodcock T, *et al.* Echis time, under-carboxylated prothrombin and vitamin K status in intensive care patients. *Clin Lab Haematol* 2003;**25**:397–404.
7. **Argo CK**, Balogun RA. Blood products, volume control, and renal support in the coagulopathy of liver disease. *Clin Liver Dis* 2009;**13**:73–85.
8. **Lippi G**, Franchini M, Montagnana M, *et al.* Coagulation testing in pediatric patients: the young are not just miniature adults. *Semin Thromb Hemost* 2007;**33**:816–20.
9. **Andrew M**, Paes B, Milner R, *et al.* Development of the human coagulation system in the healthy premature infant. *Blood* 1988;**72**:1651–7.
10. **Andrew M**, Paes B, Milner R, *et al.* Development of the human coagulation system in the full-term infant. *Blood* 1987;**70**:165–72.
11. **Andrew M**, Paes B, Johnston M. Development of the hemostatic system in the neonate and young infant. *Am J Pediatr Hematol Oncol* 1990;**12**:95–104.
12. **Williams MD**, Chalmers EA, Gibson BE. The investigation and management of neonatal haemostasis and thrombosis. *Br J Haematol* 2002;**119**:295–309.
13. **Monagle P**, Barnes C, Ignjatovic V, *et al.* Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thromb Haemost* 2006;**95**:362–72.
14. **Allard S**, Stanworth SJ, Raja A. National comparative audit of the use of fresh frozen plasma in adults. *Blood Matters* 2009;**28**:6–8.
15. **Spero JA**, Lewis JH, Hasiba U. Disseminated intravascular coagulation. Findings in 346 patients. *Thromb Haemost* 1980;**43**:28–33.
16. **Taylor FB** Jr, Toh CH, Hoots WK, *et al.* Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost* 2001;**86**:1327–30.
17. **Levi M**, Toh CH, Thachil J, *et al.* Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol* 2009;**145**:24–33.
18. **Khemani RG**, Bart RD, Alonzo TA, *et al.* Disseminated intravascular coagulation score is associated with mortality for children with shock. *Intensive Care Med* 2009;**35**:327–33.
19. **Samransamruajkit R**, Hiranrat T, Prapphal N, *et al.* Levels of protein C activity and clinical factors in early phase of pediatric septic shock may be associated with the risk of death. *Shock* 2007;**28**:518–23.
20. **Stanworth SJ**, Brunskill SJ, Hyde CJ, *et al.* Is fresh frozen plasma clinically effective? A systematic review of randomized controlled trials. *Br J Haematol* 2004;**126**:139–52.
21. **Chapman CE**, Stainsby D, Jones H, *et al.* Ten years of hemovigilance reports of transfusion-related acute lung injury in the United Kingdom and the impact of preferential use of male donor plasma. *Transfusion* 2009;**49**:440–52.
22. **Gibson BE**, Todd A, Roberts I, *et al.* Transfusion guidelines for neonates and older children. *Br J Haematol* 2004;**124**:433–53.
23. **Fenger-Eriksen C**, Lindberg-Larsen M, Christensen AQ, *et al.* Fibrinogen concentrate substitution therapy in patients with massive haemorrhage and low plasma fibrinogen concentrations. *Br J Anaesth* 2008;**101**:769–73.
24. **O'Shaughnessy DF**, Atterbury C, Bolton Maggs P, *et al.* Guidelines for the use of fresh-frozen plasma, cryoprecipitate and cryosupernatant. *Br J Haematol* 2004;**126**:11–28.
25. **Holland LL**, Brooks JP. Toward rational fresh frozen plasma transfusion: The effect of plasma transfusion on coagulation test results. *Am J Clin Pathol* 2006;**126**:133–9.
26. Randomised trial of prophylactic early fresh-frozen plasma or gelatin or glucose in preterm babies: outcome at 2 years. Northern Neonatal Nursing Initiative Trial Group. *Lancet* 1996;**348**:229–32.
27. **Casbard AC**, Williamson LM, Murphy MF, *et al.* The role of prophylactic fresh frozen plasma in decreasing blood loss and correcting coagulopathy in cardiac surgery. A systematic review. *Anaesthesia* 2004;**59**:550–8.
28. **Massicotte L**, Beaulieu D, Thibeault L, *et al.* Coagulation defects do not predict blood product requirements during liver transplantation. *Transplantation* 2008;**85**:956–62.
29. **Roseff SD**, Luban NL, Manno CS. Guidelines for assessing appropriateness of pediatric transfusion. *Transfusion* 2002;**42**:1398–413.
30. **Holcomb JB**, Spinella PC. Optimal use of blood in trauma patients. *Biologicals* 2010;**38**:72–7.
30a. **Borgman MA,** Spinella PC, Perkins JG, *et al*. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma* 2007;**63**:805–13.
31. **Birchall J**, Stanworth SJ, Duffy MR, *et al.* Evidence for the use of recombinant factor VIIa in the prevention and treatment of bleeding in patients without hemophilia. *Transfus Med Rev* 2008;**22**:177–87.
32. **Mayer SA**, Brun NC, Begtrup K, *et al.* Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* 2008;**358**:2127–37.
33. **Stainsby D**, MacLennan S, Thomas D, *et al.* Guidelines on the management of massive blood loss. *Br J Haematol* 2006;**135**:634–41.
34. **Henry DA**, Carless PA, Moxey AJ, *et al.* Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. *Cochrane Database Syst Rev* 2007;**4**:CD001886.
35. **Laterre PF**. Clinical trials in severe sepsis with drotrecogin alfa (activated). *Crit Care* 2007;**11**(Suppl 5):S5.
36. **Bernard GR**, Vincent JL, Laterre PF, *et al*. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med* 2001;**344**:699–709.
37. **Abraham E**, Laterre PF, Garg R, *et al*. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med* 2005;**353**:1332–41.
38. **Barton P**, Kalil AC, Nadel S, *et al.* Safety, pharmacokinetics, and pharmacodynamics of drotrecogin alfa (activated) in children with severe sepsis. *Pediatrics* 2004;**113**:7–17.
39. **Nadel S**, Goldstein B, Williams MD, *et al.* Drotrecogin alfa (activated) in children with severe sepsis: a multicentre phase III randomised controlled trial. *Lancet* 2007;**369**:836–43.
40. **Warren BL**, Eid A, Singer P, *et al.* Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA* 2001;**286**:1869–78.
41. **Spinella PC**, Holcomb JB. Resuscitation and transfusion principles for traumatic hemorrhagic shock. *Blood Rev* 2009;**23**:231–40.
42. **Essell JH**, Martin TJ, Salinas J, *et al.* Comparison of thromboelastography to bleeding time and standard coagulation tests in patients after cardiopulmonary bypass. *J Cardiothorac Vasc Anesth* 1993;**7**:410–15.

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Sarah L Morley

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