BJA

British Journal of Anaesthesia, 117 (S3): iii18–iii30 (2016)

doi: 10.1093/bja/aew358
Review Article

Perioperative management of the bleeding patient

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Abstract

Perioperative bleeding remains a major complication during and after surgery, resulting in increased morbidity and mortality. The principal causes of non-vascular sources of haemostatic perioperative bleeding are a preexisting undetected bleeding disorder, the nature of the operation itself, or acquired coagulation abnormalities secondary to haemorrhage, haemodilution, or haemostatic factor consumption. In the bleeding patient, standard therapeutic approaches include allogeneic blood product administration, concomitant pharmacologic agents, and increasing application of purified and recombinant haemostatic factors. Multiple haemostatic changes occur perioperatively after trauma and complex surgical procedures including cardiac surgery and liver transplantation. Novel strategies for both prophylaxis and therapy of perioperative bleeding include tranexamic acid, desmopressin, fibrinogen and prothrombin complex concentrates. Point-of-care patient testing using thromboelastography, rotational thromboelastometry, and platelet function assays has allowed for more detailed assessment of specific targeted therapy for haemostasis. Strategic multimodal management is needed to improve management, reduce allogeneic blood product administration, and minimize associated risks related to transfusion.

Key words: coagulopathy; direct oral anticoagulants (DOACs); hemostasis & thrombosis; point-of-care testing; thromboembolism; transfusion algorithm

Multiple factors contribute to the complex causes of bleeding in surgical patients that include blood loss, haemodilution, acquired platelet dysfunction, coagulation factor consumption in extracorporeal circuits, activation of fibrinolytic, fibrinogenolytic and inflammatory pathways, and hypothermia.[1,2] Acquired haemostatic defects often present in surgical patients as a result of prescribed oral anticoagulants (warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) and platelet inhibitors (P_2Y_{12} receptor inhibitors-clopidogrel, prasugrel, or ticagrelor). Thus, bleeding after surgery includes both preexisting and/or acquired defects in haemostasis. Congenital bleeding disorders are less common and, hopefully already addressed if a patient presents for surgery. From a preoperative evaluation standpoint, the ISTH bleeding questionnaire is as effective as multiple, laboratory tests for identifying perioperative bleeding risk.[3]

Surgical bleeding is usually characterized by a site of bleeding and confined exclusively to the operative site. Meticulous surgical technique, patience, and good patient selection all contribute significantly to minimizing surgical bleeding in the high-risk patient. The spectrum of available topical haemostatic agents and devices are beyond the scope of this review.[4] **The focus of this review is** microvascular or coagulopathic bleeding as a consequence of abnormal haemostatic mechanisms. While typically manifested as generalizing bleeding within the operative site, this can extend to percutaneous cannulation sites, nasogastric tubes, and urinary catheters.

Management of perioperative bleeding consists of identifying patients at risk, understanding the impact of the operation on haemostasis, institution of allogeneic blood and factor concentrate based therapies, utilizing point-of-care laboratory

Editor's key points

- Perioperative bleeding can involve acquired coagulation abnormalities secondary to haemorrhage, haemodilution, or haemostatic factor consumption.
- Novel approaches for prophylaxis and therapy of perioperative bleeding include use of tranexamic acid, desmopressin, fibrinogen and prothrombin complex concentrate.
- Point-of-care testing of haemostatic function using thromboelastography, thromboelastometry, and platelet function assays allows specific targeted therapy of coagulopathy.

testing, and understanding the limitations of monitoring techniques.[5] Clinically important bleeding can paradoxically evolve into pathologic thrombosis, with the transition of perioperative coagulopathy to hypercoagulability related to the acute phase response. This can be exacerbated by overzealous replacement of deficient procoagulant factors, inattention to deficient anticoagulant factors, and reluctance to initiate needed anticoagulant agents for venous thromboembolic prophylaxis after a recent bleed. Navigating this complex, rapidly changing haemostatic balance exemplifies the value of the perioperative physician with detailed knowledge of haemostasis, anticoagulation, and transfusion medicine. In this review, we address specific and general considerations for various pathophysiological states or circumstances and haemostatic agents and provide algorithmic approaches to bleeding management, in order to place the administration of agents in clinical context.

The following section represents general considerations of haemostasis related to hypothermia and fibrinolysis, which can occur in all patient populations undergoing invasive procedures and require review before approaching the coagulation defects particular to specific patient populations.

General considerations: hypothermia and fibrinolysis

Temperature regulation and the coagulopathy of hypothermia

In controlled circumstances, such as during cardiopulmonary bypass or hypothermic circulatory arrest, hypothermia is used as a neuroprotective mechanism.[6] Inadvertent hypothermia seen with severe trauma, or poorly maintained intraoperative temperature regulation can be associated with worse outcomes. For example, isolated hypothermia of 32.2 °C is associated with a 23% mortality rate, while trauma-induced hypothermia below 32 °C is associated with 100% mortality.[7–8,9] The coagulopathy of hypothermic patients includes dysregulation of coagulation enzyme processes, platelet function, activation of fibrinolysis, and endothelial injury.[10] Bleeding observed at reduced temperatures (33 – 37 °C) often occurs because of defects in platelet adhesion, while at temperatures below 33 °C, both reduced platelet function and coagulation enzyme activity contribute.[11] Active warming should be applied perioperatively if exposed surface area allows. Additionally, hypothermia and acidosis frequently occur together requiring correction of metabolic abnormalities.[11–14]

Fibrinolysis

Activation of the fibrinolytic system is an important mechanism of vascular homeostasis (Figure 1). Mechanistically, plasmin generation is the enzymatic serine protease responsible for fibrinolysis and is formed after the action of t-PA on plasminogen. Plasmin cleaves key coagulation proteins such as fibrin and fibrinogen, but also causes proteolysis of other critical proteins, including fibronectin and von Willebrand factor.[15] In the urogenital tract, hyperfibrinolysis occurs as a result of liberation of the urokinase plasminogen activator system.[16] After cardiopulmonary bypass and/or tissue injury that occurs with surgery or trauma, fibrinolysis is activated and represents an important cause of coagulopathy.[17] In trauma, orthopaedic surgery, and cardiac surgery, multiple studies support the role of antifibrinolytic agent administration in order to decrease bleeding and the need for allogeneic transfusions.[17] These agents can also be used as an adjunct to treating congenital bleeding disorders.[18]

Since CRASH-2 was published in 2010,[19] meta-analyses recommend antifibrinolytic use (mostly tranexamic acid) in abdominal bleeding[20] and trauma, while on-going major studies are being conducted for gastrointestinal bleeding (HALT-IT trial)[21] and postpartum haemorrhage (WOMAN trial).[22] The use of tranexamic acid (TXA) is increasing and additional data are forthcoming. Despite initial concerns about aprotinin, this agent is now being reintroduced in many European markets.[23]

While we will not discuss postpartum haemorrhage in detail, three major considerations are emerging for managing bleeding parturients: routine use uterotonics, aggressive fibrinogen replacement, and prevention of excessive fibrinolysis, as recently reviewed.[24,25]

Antifibrinolytic agents: lysine analogues

The two antifibrinolytic agents administered clinically include epsilon aminocaproic acid (EACA) and TXA.[26] While both medications competitively inhibit plasminogen conversion to the active protease plasmin,[27] only TXA has been shown to inhibit higher plasma concentrations of plasmin.[28,29] Although most of the data for the antifibrinolytic lysine analogues are with TXA, EACA continues to be extensively utilized in the USA.[30] Although multiple studies (primarily meta-analyses of randomized-controlled trials) have shown that lysine analogues decrease bleeding in cardiac surgical patients, there are limited prospective safety data regarding the use of antifibrinolytic agents. Most dosing studies include total EACA doses of 20 to 30 g per patient, or total TXA doses from 2 to 25 g, mainly from 2 to 8 g.[26]

An increase in the incidence of seizures after cardiac surgery from 1.3% to 3.8% has been temporally associated with higher-dose TXA use.[31] The mean age of patients in this report was ~70 yr, and open chamber surgery, with possible air entrainment, was a risk factor.[31] Mechanistically, TXA enhances neuronal excitation by antagonizing inhibitory gamma-aminobutyric acid (GABA)[32] and glycine[33] neurotransmission at the receptor level, an established cause of seizures. This side-effect was not noted in prospective trials, which were notably underpowered for this outcome. Seizure activity has not been described in patients receiving EACA. For other indications such as orthopaedic, trauma and obstetric indications, the data are mostly for patients receiving a total of 2 g of TXA, where seizures have rarely been reported.

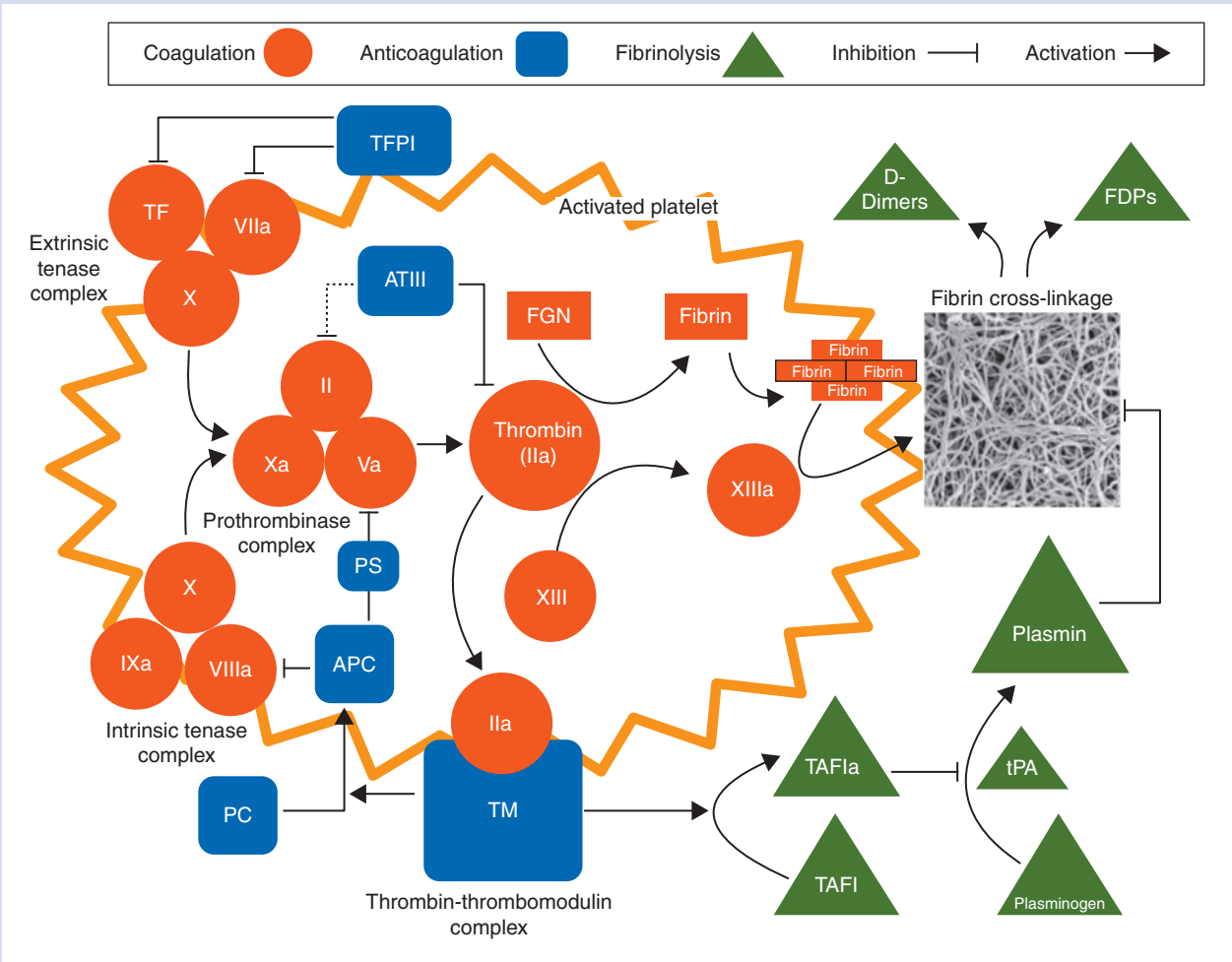

Fig 1 Interplay between coagulation, anticoagulation, and the fibrinolytic systems. In a simplified model, coagulation factors are illustrated upon the activated platelet surface. Through the activation of factor X (Xa) via intrinsic (Factor IXa, VIIIa) and extrinsic tenase (Xase) complexes, factors Xa and Va convert factor II (prothrombin) to factor IIa (thrombin). Thrombin then cleaves fibrinogen into fibrin. Fibrin polymerization is facilitated by the activation of factor XIII that forms cross links leading to clot stabilization. Factor II, VII (not pictured), IX (not pictured) and X are targeted for repletion with prothrombin complex concentrate (PCC) administration. Factor VIIa is targeted for repletion with administration of recombinant factor VIIa (rFVIIa). Simultaneously, anticoagulants negatively modulate clot formation. Antithrombin III (ATIII) modulates factor IIa (primarily) and factor Xa (secondarily), but ATIII-dependent inhibition of factor IXa, XIa, and VIIa-TF complex occurs to a lesser extent (not pictured). Other important anticoagulants include TFPI-modulation of Tissue Factor and factor VIIa, and Activated Protein C (APC) which, through activation of protein S, inhibits factor Va, weakening the prothrombinase complex and impairing thrombin generation. Upstream, APC inhibits factor VIIIa of the intrinsic Xase complex. Factor IIa complexes with Thrombomodulin (TM) to activate PC. Of note, the thrombin-TM/PC/PS system is primarily localized to the endothelium but can be expressed on platelets and monocytes. This complex initiates thrombin-activatable fibrinolysis inhibitor (TAFI), which prevents plasmin production by inhibiting tissue-plasminogen activator and through direct inhibition of plasminogen (not pictured). Plasmin is a serine protease and, as the primary driver of fibrinolysis, results in clot destabilization, degradation of fibrin cross linkage, and production of fibrin degradation products, which include D-dimers. Plasmin triggers platelet activation (not pictured) thereby competing with TAFI at the local level. TF, Tissue Factor; PC, Protein C; PS, Protein S; TFPI(a), Tissue-Factor Pathway Inhibitor (activated); ATIII, Antithrombin III; FGN, Fibrinogen; TM, Thrombomodulin; FDPs, Fibrin Degradation Products; tPA, tissue-Plasminogen Activator.

Coagulation abnormalities in different patient populations

Trauma

The coagulopathy of trauma is a complex pathophysiologic state that results in diffuse, microvascular bleeding.[34,35] Approximately 40% of trauma-related mortality is associated with profound coagulopathy.[36] Management of major bleeding requires repair of the underlying cause after surgery or trauma, volume resuscitation with blood products, and diagnosis and management of the ongoing coagulation defects.[37] Initial retrospective analyses from military trauma reported repletion of intravascular volume using predetermined ratios of fresh frozen plasma (FFP), platelet concentrate (PC), and red blood cells (RBCs) at 1:1:1 reduced mortality in patients with major bleeding.[38–42] To prospectively evaluate this strategy, Holcomb and colleagues[43] reported that with severe trauma and major bleeding, early administration of FFP, PC, and RBCs in a 1:1:1 ratio compared with a 1:1:2 ratio, did not significantly decrease mortality at 24 h or 30 days. They also reported more patients in the 1:1:1 group achieved haemostasis and with less mortality from exsanguination at 24 h (9.2% vs 14.6%;

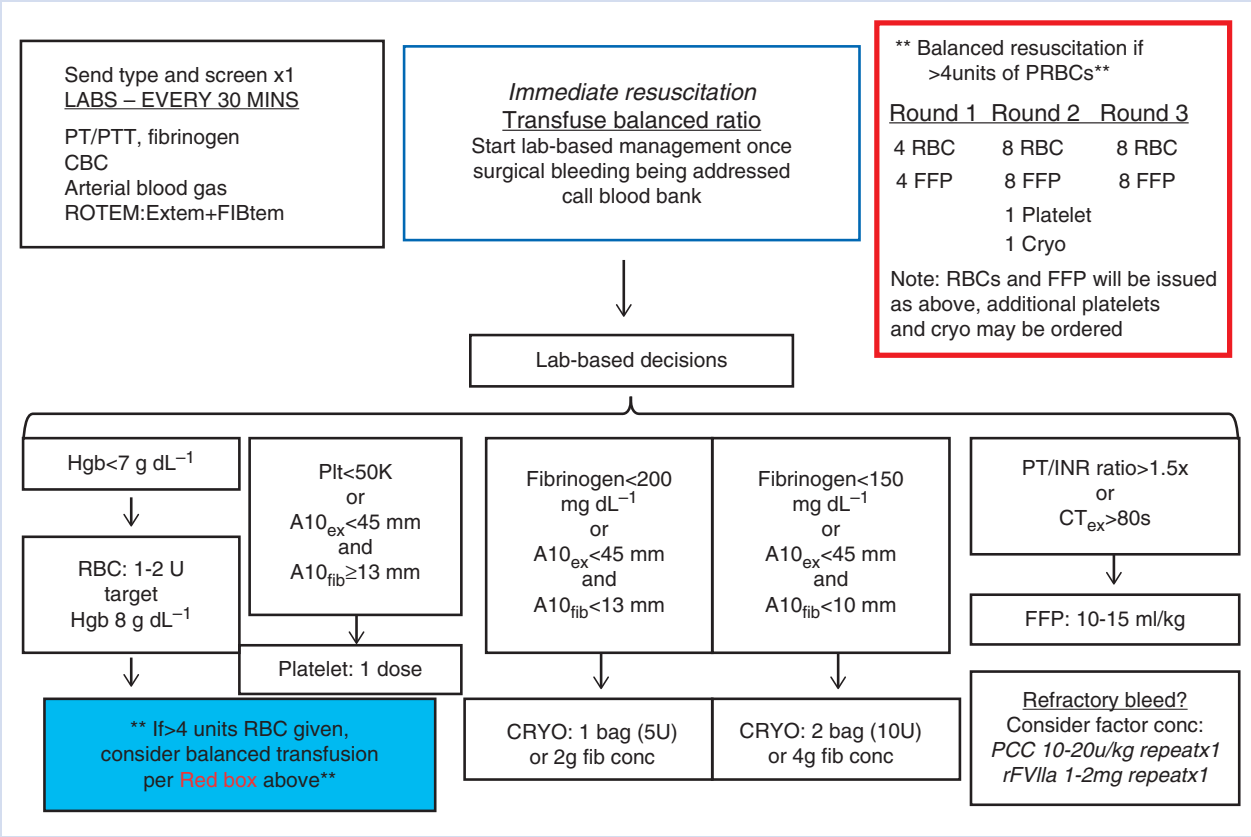

Fig 2 Transfusion algorithm for intraoperative bleeding during noncardiac surgery. Focus on a laboratory-based, viscoelastic testing paradigm, with opportunities for intervention based on clinical decision-making. Our protocol advocates antifibrinolytic therapy, correction of acidosis, and correction of acute hypocalcaemia. Inside the redbox, our balanced ratio recommendations are presented if the patient has been transfused four units of blood and intraoperative haemorrhage is ongoing. Consideration is given to low-dose factor concentrate usage (PCCs, rFVIIa) if bleeding is refractory to balanced resuscitation and algorithmic options. *Figure modified from a draft version of our local massive transfusion protocol.* CBC, complete blood count; Cryo, cryoprecipitate; FFP, fresh frozen plasma; Hgb, haemoglobin; RBC, red blood cell; PLT, platelet count; T & S, type and screen; PCC, prothrombin complex concentrates.

$P = 0.03$). Although use of FFP and PC in the 1:1:1 group was higher, transfusion related complications including multiorgan failure were similar.[43] While evidence supports the 1:1:1 approach, it is not conclusive, and the optimal ratio of FFP:PC:RBCs is still not clear.[44–50] Extension of this principle into the arenas of civilian trauma and massive surgical blood loss has been guided by local massive transfusion protocols, as illustrated in Figure 2, but high-volume transfusions are associated with complications. Without massive bleeding criteria, defined as <10 Units of packed RBCs within 12 h of admission, FFP transfusion is associated with acute lung injury (ALI).[46,51–54] FFP is associated with a dose-dependent relationship with both transfusion associated circulatory overload (TACO) and transfusion-related acute lung injury (TRALI).[53,55] While 1:1:1 transfusion might be appropriate for out-of-hospital resuscitation, such complications support refining these protocols when gross exsanguination has been surgically or manually controlled. Use of viscoelastic coagulation tests (e.g. ROTEM© and TEG©) offers guided coagulopathy treatment that also includes antifibrinolytic agents, cryoprecipitate and factor concentrates.[5,56,57] In our transfusion algorithm for adult *noncardiac* surgery (Figure 2), initial steps include utilization of laboratory data in parallel with packed RBCs. Discussion of specific components within this algorithm is described in separate sections in this review. Briefly, although haemoglobin targets vary depending upon patient injuries and comorbidities, a value of >8 g dl^{-1} is targeted. Platelet concentrate, cryoprecipitate (generally for hypofibrinogenaemia but occasionally administered in patients with known von Willebrand factor or Factor XIII deficiency), and FFP are also administered. Once 4 units of packed RBCs have been transfused, attention is turned to the red box insert within the algorithm, and balanced resuscitation is performed according to blood and blood products given (i.e., Round 1, 2, 3, etc.). Of note, PC and fibrinogen are administered early in this algorithm based on laboratory data, as they are crucial to haemostasis. Fibrinogen remains the first component to reach critically low values during haemorrhage.[58] If refractory bleeding is noted in our algorithm, consideration is given to administration of factor concentrates. Viscoelastic testing has been recently advocated in severely-injured trauma patients, in order to help guide antifibrinolytic therapy in the setting of systemic, post injury hyperfibrinolysis, physiologic/normal fibrinolysis, or hypofibrinolysis/fibrinolytic shutdown.[59] The European Task Force for Advanced Bleeding in Trauma has provided a guideline document in order to manoeuvre through the expansive possibilities related to coagulopathic management in the trauma patient.[60]

Chronic liver disease and orthotopic liver transplantation

Haemostatic changes seen with end-stage liver disease are complex, resulting from reduced concentrations of pro- and anti-coagulant proteins, plasmin-related qualitative platelet dysfunction from defective thromboxane A_2 synthesis, storage pool deficiency, platelet glycoprotein Ib abnormalities,[61–63] and platelet sequestration.[64] Platelet function defects, however, are attenuated by the exaggerated concentrations of von Willebrand Factor (vWF), resulting from deficiency of the hepatically synthesized protease ADAMTS 13.[65] Relative plasminogen activator inhibitor (PAI-1 and 2) deficiency reduces t-PA clearance increasing fibrinolytic potential. Reduced thrombin activatable fibrinolysis inhibitor (TAFI) and alpha-2 antiplasmin further exacerbate this.

During surgery, with reperfusion of the donor liver, hyperfibrinolysis can occur as a result of extensive release of t-PA into the circulation. As a result, these patients can benefit from treatment with antifibrinolytic agents, while taking care to avoid hypercoagulation.[66–69] As previously discussed, viscoelastic testing has been utilized in severely-injured trauma patients in order to help guide antifibrinolytic therapy.[59] With that said, the rationale for utilizing viscoelastic testing might not be the best approach guide to antifibrinolytic use in hepatic failure patients undergoing orthotopic liver transplantation.[70] The balance between bleeding and clotting varies, with the potential for hepatic artery or portal vein thrombosis upon reperfusion and postoperatively coexisting with severe coagulopathic bleeding, especially in the dissection phase of liver transplantation.

Cirrhosis impairs synthesis of all procoagulant factors (except factor VIII produced by endothelium) and often co-exists with vitamin K deficiency,[71] as reflected by prolongation of the prothrombin time (PT), which is highly sensitive to concentrations of factor VII. Although PT and activated partial thromboplastin time (aPTT) are widely used as a monitor in cirrhotic patients, they do not reflect the overall status of pro- and anticoagulant deficiency or excessive fibrinolysis. More current efforts to identify relevant biomarkers, focus on pro-inflammatory cytokines such as monocyte chemoattractant protein-1.[72] Neither PT or aPTT correlate well with bleeding after surgery, liver biopsy or other potentially haemorrhagic procedures in patients with cirrhosis,[73–76] which are better evaluated by more global tests, such as viscoelastic testing or the endogenous thrombin potential (ETP).[77,78] Decreased concentrations of protein C, antithrombin and factor II result in only a 25% reduction in thrombin generation in cirrhotics, reflecting a steady state, with almost "matching" anticoagulant and procoagulant deficiencies.[78] This precarious balance is lost after major stress responses such as infection or blood loss, with haemodilution resulting in profound deficiencies and extreme coagulopathy. Of note, viscoelastic testing commonly demonstrates normal coagulation profiles in these settings.[79]

These findings question the usefulness and safety of targeting PT correction with procoagulants such as plasma, rFVIIa or prothrombin complex concentrate (PCC).[80–82] An ongoing multicentre, randomized, controlled trial is studying the utility of PCCs with respect to reducing allogeneic RBC transfusion, during orthotopic liver transplantation in cirrhotic patients with INR $\geq$ 1.5 (PROTON Trial; Netherlands Trial Register: 3174).[83] In our opinion, focusing on fibrinogen and platelet supplementation makes more sense in this setting.

Cirrhotics are twice as likely to suffer venous thromboembolism than the general population,[84] presumably when anticoagulant concentrations are further depleted and procoagulant constituents predominate. Portal vein thrombosis can occur in cirrhotics with specific prothrombotic coagulation factor mutations that include factor V Leiden and prothrombin G20210A,[85] especially with commonly elevated concentrations of vWF and factor VIII.[86] Antithrombin concentrate can restore the balance between pro- and anti-coagulants through direct modulation of clot formation (Figure 1).[87] In a retrospective, observational study of laparoscopic splenectomy, 4% of cirrhotics receiving antithrombin III (ATIII) suffered portal vein thrombosis compared with 36% who did not.[88] ATIII supplementation is also considered after liver transplant, to minimize allograft thrombosis, but high quality data are limited.

Cardiopulmonary bypass and cardiac surgery

Coagulation abnormalities encountered during cardiac surgery are multifactorial and include preoperative antiplatelet agents, heparin reversal with protamine, acquired platelet dysfunction after cardiopulmonary bypass (CPB), haemodilution, and loss of clotting factors and platelets. Although off-pump cardiac surgery avoids the effects of CPB discussed below, other causes of coagulopathy still apply. CPB induces a complex pathophysiologic state, with pathophysiologic changes that are potentially similar to sepsis and a systemic inflammatory response.[89,90] In a more severe form, coagulopathy after prolonged CPB can produce a consumptive coagulopathy, leading to clinically significant bleeding and/or thrombosis with factor consumption.[91] Excessive thrombin generation and activation of tissue factor causes endothelial dysfunction (predisposing to microvascular thrombosis), with concomitant coagulopathy developing as a result of consumption of both pro- and anti-coagulant proteins (especially fibrinogen and antithrombin), deposition and loss of platelets, and potent activation of fibrinolysis.[92,93] Laboratory findings pathognomonic for diffuse intravascular coagulation (DIC), characterized by decreased platelet counts, low fibrinogen, increased PT, PTT, and D-dimer concentrations, also commonly occur in patients after CPB.[92,93] One important difference is that D-dimer concentrations might not be elevated after cardiac surgery because of routine administration of antifibrinolytics.[94] Acquired ATIII deficiency can occur in cardiac surgical patients as a result of multiple causes that include preoperative heparin administration, haemodilution, and consumption. Low concentrations of ATIII that range from 20% to 50% commonly occur in cardiac surgical patients associated with CPB.[95,96] Ongoing studies are evaluating the role of ATIII supplementation during support with extracorporeal membrane oxygenation (ECMO) and in cardiac surgery.[97,98]

Our group has developed a transfusion algorithm for cardiac surgery (Figure 3), adopted from similar concepts related to trauma-induced coagulopathy (Figure 2), while incorporating the concepts highlighted above. In our algorithmic approach, laboratory data, including viscoelastic testing with ROTEM© (assays for determination of extrinsic pathway coagulation deficiencies – EXTEM©, and determination of fibrinogen-platelet interaction - FIBTEM©), platelet count, and fibrinogen values, are obtained once rewarming is initiated on CPB. If hypofibrinogenaemia is noted and the EXTEM© Clotting Time is > 80 s, consideration is given to administration of four units of FFP during CPB, followed by administration of cryoprecipitate upon separation from CPB. Other management modalities are illustrated, and clinically important bleeding is determined along the way, in order to determine further laboratory investigation and focus administration of deficient coagulation components.

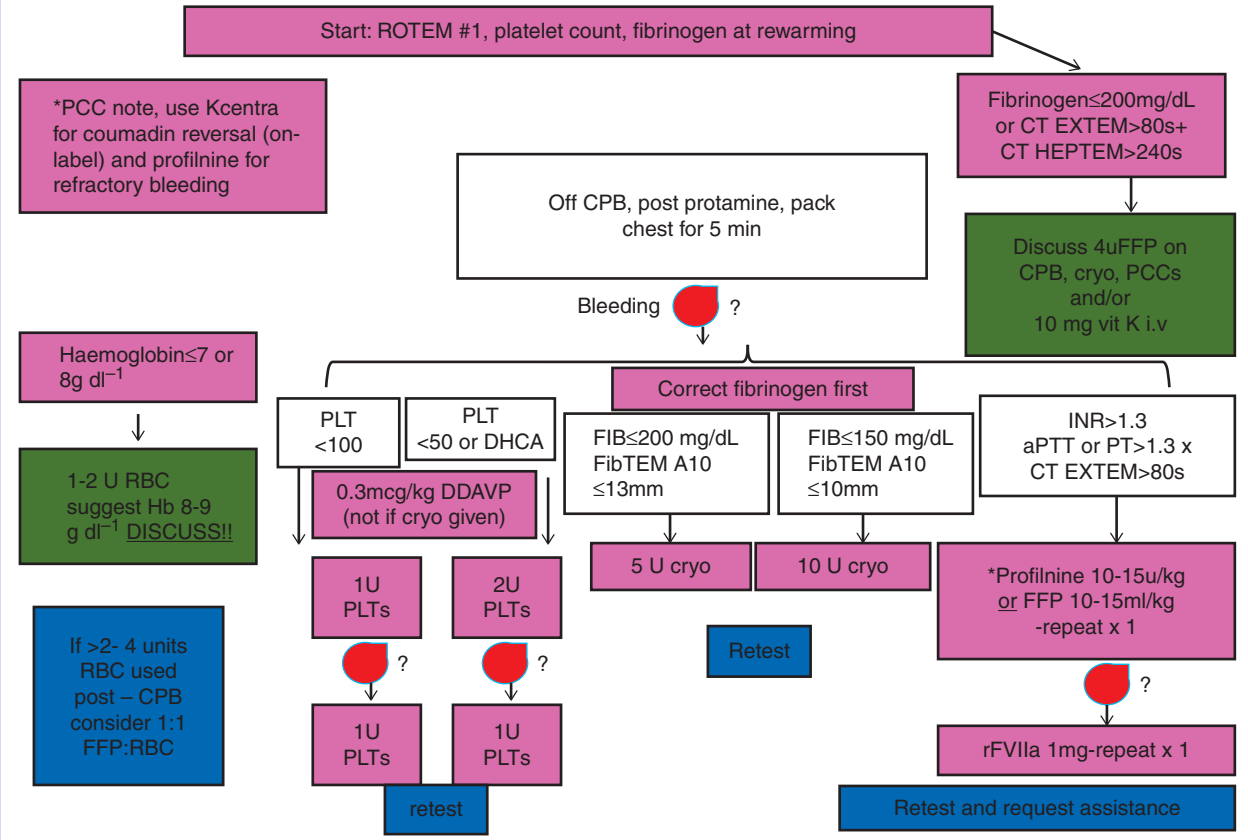

Fig 3 Transfusion Algorithm for intraoperative bleeding during cardiac surgery. In this laboratory, viscoelastic testing (ROTEM©) paradigm, samples are sent upon body temperature rewarming during CPB. Our algorithm directs the correction of hypofibrinogenaemia (using the Klaus Fibrinogen assay or FibTEM© A10 values and thrombocytopenia. Patients whom have undergone hypothermic circulatory arrest and the ensuing platelet dysfunction of hypothermia, receive platelet concentrate transfusion depending on platelet value during on-CPB rewarming values, when temperatures are >33 °C. Notably, because of established institutional practices, a first set of haemostasis blood samples are sent to the laboratory on CPB, and in order to account for heparin effect, HEPTEM© is sent in addition to EXTEM©. Thus, if HEPTEM© is >240 s, then it is presumed the added prolonged clotting time is as a result of additional factor deficiencies and requires FFP administration. A HEPTEM© CT <240 s indicates manufacture-established values after heparin antagonism. This value aids the practitioner in deciding on FFP administration while on CPB, in order to avoid delayed initiation of coagulation management after separation from CPB. Consideration is also made to post-CPB PCC administration, as PCC usage on CPB might be less useful owing to the larger volume of distribution and potential deposition of PCC factors onto CPB filters. With opportunities for clinical observation and laboratory values for deciding further clinical intervention, various deficiencies are managed through such blood, plasma, and factor concentrate administration. Antifibrinolytic therapy is standard practice for our cardiac surgical patients that require CPB. Notably, we have internally tested our 5U-pack of cryoprecipitate and have found fibrinogen concentration to range between 1.5-2.5 grams. We recommend a similar assessment locally within each hospital to help with best practice. *Figure modified from a draft version of our local cardiac surgery transfusion protocol.* AT III = Antithrombin III; CT = Clotting time; CPB = cardiopulmonary bypass; Cryo = Cryoprecipitate; FFP = fresh frozen plasma; FIB = Fibrinogen concentration; Hb = Haemoglobin; PCCs = Prothrombin complex concentrate; PLT = platelet count; RBC = Red blood cell; rFVIIa = Recombinant activated factor VIIa; U = unit.

Pharmacological haemostatic agents

A review of allogeneic blood products and dosing is beyond the scope of this article. Outside of the massive trauma setting, their use is guided by laboratory testing. In average adults, one unit of RBCs increases haemoglobin concentrations by ~1g dl^{-1}, one adult dose of platelets increases platelet count by ~25-35x10^9 l^{-1}, and a typical dose of 10-20 ml kg^{-1} plasma raises factor levels by ~10%. Cryoprecipitate is discussed separately below.

Desmopressin

Desmopressin (DDAVP) is the V2 analog of arginine vasopressin that releases vWF multimers from endothelial stores.[99] vWF is a critical protein that facilitates platelet adherence, by acting as a protein bridge between platelet glycoprotein Ib receptors and damaged vascular subendothelium. DDAVP decreases bleeding times in mild haemophilia A or von Willebrand disease, but beyond these indications, and despite widespread perioperative use, efficacy is limited.[100] DDAVP is administered intravenously at doses of 0.3 mcg kg^{-1}, and should be infused over 15-30 min to avoid changes in bp or cardiac chronotropy.[101] Despite 18 trials of desmopressin in 1295 patients undergoing cardiac surgery, only minimal reduction of perioperative blood loss (~115 ml) was reported.[102,103] The benefit of administering DDAVP in these patients is unclear, especially with concomitant use of vasopressin.

Coagulation factor concentrates

Although allogeneic blood products are the basis of coagulopathy management, they require cross matching, have well

documented transfusion reactions and other risks, require blood bank management, and can be limited by availability and need for transport from the blood bank. Factor concentrates, including fibrinogen concentrates and PCCs, are evolving as a way to replace or reduce allogeneic blood product administration.[104–106] Several factor concentrate based algorithms have been described favourably.[107,108]

Fibrinogen

Fibrinogen is a critical haemostatic factor for the development of effective local clot in surgical patients, and for managing perioperative bleeding in cardiac surgical patients.[106,109–111] Normal fibrinogen concentrations are 200-400 mg dl^{-1} in the nonparturient, but can be > 400 mg dl^{-1} during the third trimester of pregnancy. While the target fibrinogen concentration in a bleeding patient is not known, bleeding increases for each 100 mg dl^{-1} decrease in fibrinogen concentration in parturients,[112] and fibrinogen concentrations decrease in proportion to increased blood loss after cardiac surgery.[113,114] Many society guidelines suggest a transfusion trigger of 100 mg dl^{-1} of fibrinogen, based on the threshold of 80-100 mg dl^{-1} that begins to affect the PT or aPTT, despite the absence of *in vivo* clinical evidence for this recommendation. European guidelines have recommended targeting low normal concentrations (~200 mg dl^{-1}) since at least 2010.[60,115] To achieve this, 3-4 g fibrinogen concentrate or 15-20 single donor units of cryoprecipitate have been recommended in the bleeding patient, ideally targeted by laboratory data.

While the exact fibrinogen content of each unit of cryoprecipitate is unknown, in a 70 kg adult, a 5-unit bag of cryoprecipitate increases fibrinogen by approximately 25-35 mg dl^{-1}.[116] This approximate incremental increase might be reduced in the event of ongoing haemorrhage. In mainland Europe, fibrinogen concentrates are used for fibrinogen repletion as cryoprecipitate is not readily available. Fibrinogen concentrates lack other components of cryoprecipitate such as vWF and factors VIII and XIII.[106] In a prospective study, patients randomized to fibrinogen concentrate as a first line therapy had a significantly lower rate of any allogeneic blood product transfusions, including packed RBCs and FFP.[117] Conversely, fibrinogen concentrate was not effective after aortic reconstruction surgery, possibly attesting to the multifactorial nature of this coagulopathy and a complexity that confounds a single agent panacea.[118]

Prothrombin complex concentrates. Prothrombin complex concentrates (PCCs) are purified coagulation factors that include procoagulant factors II, VII, IX and X and anticoagulant proteins C, S and Z in variable concentrations; minimal antithrombin and heparin are present in some preparations, as recently reviewed.[5] The use of PCCs for the emergent or urgent vitamin K antagonist anticoagulants reversal is extensively reported in guidelines.[105,119] Currently, there is extensive and increased use for off-label applications, include reversing direct oral anticoagulants (DOACs) such as apixiban, dabigatran, rivaroxaban, and edoxaban, and for treating refractory bleeding in surgical patients.[108,120–122] Initially developed as a source of factor IX in haemophilia B,[5] PCCs were used in activated form as a bypassing agent for haemophiliacs, with alloantibodies or inhibitors to purified or recombinant factor VIII (haemophilia A) or factor IX (haemophilia B). Factors VIII and IX are bypassed with activated PCCs, which enhance factor Xa production through the extrinsic tenase complex, which feeds into the prothrombinase complex and restores downstream thrombin generation (Figure 1). Of note factor VIIa was developed from activated PCCs.[5]

Recombinant activated factor VIIa. Recombinant FVIIa (rFVIIa, Novoseven®, Novo Nordisk, Denmark) is approved in most countries for treating bleeding episodes in patients with haemophilia A or B with inhibitors, congenital Factor VII deficiency, and Glanzmann's thrombasthenia who are refractory to platelet transfusions, with or without antibodies to platelets; and for treating bleeding for perioperative management in adults with acquired haemophilia. In these examples, rFVIIa is effectively used as a bypassing agent at doses of 90-120 mcg kg^{-1} and infusions. Conversely, off-label dosing is unknown, with lower doses (~20 mcg kg^{-1}) increasingly favored,[123,124] and rFVIIa is still included in guidelines for refractory bleeding.[125,126* 127,128] It is important to have other coagulation substrates present for optimal efficacy of generated FXa; predictors of rFVIIa-treatment failure include evidence of coagulation substrate deficiency, haemodilution, or consumption, leading to altered laboratory measurements (INR > 2.0, platelet count < 80 x 10^9 L^{-1}, fibrinogen < 100 mg dl^{-1}).[128] High thromboembolism rate (> 20%),[129] a complication rate of 44%,[128] and a mortality of 32%[128] are also described in retrospective evaluations of registries for refractory bleeding patients. Prospective trials report a lower incidence of thrombosis, but high rFVIIa doses increase the risk of arterial, but not venous, thromboembolic events, especially among the elderly.[130] Recent large reviews of nonsurgical, noncardiac and cardiac surgical patients, demonstrated effectiveness.[131] A modest increase in thromboembolic risk was seen with both therapeutic (RR 1.21; 95% C.I. 0.93 – 1.58) and prophylactic use (RR 1.32; 95% CI 0.84 – 2.06).[132]

The overenthusiastic initial adoption of rFVIIa was subsequently tempered by thromboembolism complications.[130,132,133] We can apply this knowledge to PCC use in refractory bleeding by addressing substrate repletion and minimizing dosage (10-15 IU kg^{-1}; Figures 2 and 3). Failure to address platelet, fibrinogen, Factors II, VIII, IX or X deficiencies in patients with severe haemorrhage can limit the effectiveness of rFVIIa or PCC to restore thrombin generation and fibrin clot formation.[5]

Protamine

Protamine, isolated from salmon sperm, is a highly basic nuclear histone, that binds DNA to provide structural integrity. Its molecular weight is ~5000 Da with ~70% arginine residues that result in its highly basic nature. Protamine binds to the acidic heparin molecule via a simple acid-base interaction,[134] but only partially antagonizes low-molecular-weight heparin (LMWH) activity. Excess protamine should be avoided when antagonizing heparin as it can contribute to coagulopathy[135] by inhibiting factor V activation and platelet activity.[136] To better match the pharmacokinetic profile of heparin slowly released from poorly perfused tissues, such as adipose tissue after CPB (heparin rebound), a protamine infusion of 25-50 mg h^{-1} can significantly reduce blood loss after cardiac surgery.[137] Heparin concentrations during rebound usually range from 0.1 to 0.3 IU mL^{-1}, which is at the low end of the therapeutic range. The activated clotting time (ACT) is poorly sensitive as a measure of heparin at such low concentrations.

Direct oral anticoagulants

Direct oral anticoagulants (DOACs) represent a class of orally administered factor inhibitors approved for anticoagulation in patients with venous thromboembolic disease and stroke prevention in patients with nonvalvular atrial fibrillation. As the prevalence of patients taking DOACs continues to increase, so

does the importance of understanding how to best antagonize the anticoagulant effect of these agents. Although the reader is directed elsewhere for review of approaches to management of bleeding in these patients,[138] general efforts using PCCs or aPCCs remain unproved with unknown dosing regimens. Additionally, specific antidotes are currently available or under development, as follows.

Specific antidotes for direct oral anticoagulants

Recently, idarucizumab (Praxbind™, Boerhinger Ingelheim, Germany) was approved for antagonism of dabigatran, a direct thrombin inhibitor (DTI) within the class of the direct oral anticoagulants (DOACs). Concentrations of unbound dabigatran remained low at 24 h in 79% of the patients, and for most operative normal haemostasis was restored. One thrombotic event occurred within 72 h after idarucizumab administration in a patient in whom anticoagulants had not been reinitiated.[139]

Factor Xa inhibitors are another subclass of DOACs without an approved antagonism agent. Andexanet alfa (Portola Pharmaceuticals, South San Francisco, California, USA) is a modified, recombinant derivative of Factor Xa with the serine on the FXa-active site mutated to alanine, inactivating the serine protease activity and thus removing its ability to cleave prothrombin to thrombin.[140,141] The membrane-binding domain of plasma-derived Factor X has also been deleted, precluding inclusion of andexanet into the prothrombinase complex. This "decoy molecule" sequesters FXa inhibitors, rapidly reducing free plasma concentration and neutralization anticoagulant effect. Andexanet alfa binds to antithrombin complexed with LMWH, fondaparinux, rivaroxaban, apixaban and edoxaban. The short half-life of andexanet alfa relative to FXa inhibitors can be insufficient to correct coagulopathy, particularly in the setting of renal dysfunction or older age,[142] although interim reports from a clinical trial are encouraging.[143] Other antagonism agents in development include PER977.[144] But antagonism of anticoagulation incurs a thrombosis risk that will have to be balanced with bleeding and will likely need to be addressed once haemostasis is achieved.[141] Despite the potential for these specific antagonism agents, a multimodal approach to coagulation management is needed during management of bleeding related to DOACs, which might necessitate coagulation factor concentrate administration.

Antiplatelet agents: aspirin and thienopyridine derivatives

Aspirin is used extensively for the secondary prevention of atherothrombotic disease that includes occlusive coronary artery and peripheral arterial disease, and cerebrovascular thromboembolism.[145] Although aspirin has the potential to increase blood loss after major surgery, this probably does not result in increased needs for transfusions and should always be considered for risk *vs* benefit effects.[146] As such aspirin should not be discontinued preoperatively except before neurosurgery procedures. Antagonism of aspirin is rarely necessary 48 h after the last dose and can be achieved by DDAVP[147] or platelet transfusion.

Clopidogrel (Plavix), prasugrel (Efient, Effient), ticagrelor (Brilinta), and cangrelor (Kengreal) belong to the class of thienopyridine derivatives that act by blocking the adenosine diphosphate (ADP) P_2Y_{12} receptor on platelets. Dual antiplatelet therapy with aspirin and clopidogrel is a current standard of care after percutaneous coronary intervention (PCI), however this combination is associated with an increased bleeding risk.[148] Prasugrel and ticagrelor have stronger antiplatelet effect than clopidogrel because of more effective metabolism and less dependence on cytochrome P450 enzymes subject to genetic polymorphisms.[149]

The decision whether or not the interrupt or even antagonize antithrombotic therapy with dual platelet inhibition requires careful thrombotic risk and haemostatic benefit evaluation, especially in patients with recent drug-eluting stent rather than bare-metal stent implantation. Administration of platelet concentrates (~2 units) can correct the haemostatic defect after antiplatelet drugs have been stopped for 12–24 h (free drug can inhibit transfused platelets).[150,151] Ideally, aspirin is restarted 6 h and P_2Y_{12} receptor blockade is restarted 12–48 h after surgery. When continued P_2Y_{12} receptor blockade is desirable, cangrelor infusion can serve as a bridge to surgery.[152] In the actively bleeding patient, testing for platelet dysfunction has been thought to be unreliable as most tests require a relatively normal platelet count and most of the platelet function testing might not work well after the dilutional changes and activation after CPB.[12] However, a recent prospective observational study, illustrated that preoperative ADP-induced platelet aggregability predicted the risk for severe bleeding in cardiac surgical patients treated with preoperative ticagrelor.[153]

Transfusion algorithms and bleeding

Transfusion algorithms represent one of the most important strategies to reduce excess transfusion, and all components of coagulation management outlined in our review have been included in the algorithms presented. Developing a specific therapeutic plan through use of transfusion algorithms has been shown to consistently reduce allogeneic blood administration.[107] It is important to realize that any laboratory testing that discourages empirical blood product administration, is important as part of a multimodal approach to blood conservation and reduction of allogeneic blood product use, while realizing that laboratory values can lag behind the clinical scenario, if blood loss remains rapid.[37,154] Transfusion algorithms generally recommend administration of plasma when bleeding is accompanied by PT or aPTT > 1.5 times normal, platelet transfusions for thrombocytopenia with a platelet count <50,000–100,000, or cryoprecipitate or fibrinogen concentrate when fibrinogen concentrations are < 200 mg dl^{-1} (2 g l^{-1}).[155] The critical role of fibrinogen continues to evolve with most data suggesting the importance of normalizing fibrinogen in bleeding patients. With critical bleeds, and turn over time in standard laboratory testing, point-of-care testing, including rotational thromboelastometry (ROTEM©), thromboelastography (TEG©) and/or platelet function testing, are important.[155] In the actively bleeding patient, testing for platelet dysfunction is unreliable, as most tests need a relatively normal platelet count.[12] With these capabilities and limitations in mind, we have developed transfusion algorithms for both noncardiac (Figure 2) and cardiac (Figure 3) surgical patients in order to guide perioperative management of coagulopathy.

Conclusions

The potential for haemorrhage in trauma and surgical patients represents an ongoing concern for management. Anticoagulation monitoring using point-of-care testing, optimal use of transfusion therapies, adjunct administration of antifibrinolytics and purified and recombinant concentrates, provide

clinicians with the ability to administer vital coagulation therapies to treat haemorrhage. Other key considerations include management of hypofibrinogenaemia, thrombocytopenia and platelet disorders, topical haemostasis, excluding surgical sources of bleeding, and temperature regulation. The integration of the optimal use of pharmacologic agents, allogeneic transfusion, and factor concentrates into a comprehensive perioperative coagulation treatment algorithm for bleeding, is an important therapeutic approach for the management of bleeding in surgical patients.

Authors' contributions

Study conduct: K.G., I.J.W.
Data analysis: K.G., J.H.L., I.J.W.
Writing paper: K.G., J.H.L., I.J.W.
Revising paper: all authors

Declaration of interest

K.G. is a co-investigator in a prospective, open-label study of Andexanet-Alfa in patients receiving Factor Xa inhibitors with acute major bleeding, sponsored by Portola Pharmaceuticals.

J.H.L. serves on steering committees for Boehringer-Ingelheim, CSL Behring, Grifols, and Janssen; consultant to Instrumentation Laboratories and Pfizer.

I.J.W. is the Principal Investigator in a prospective, open-label study of Andexanet Alfa in patients receiving Factor Xa inhibitors with acute major bleeding, sponsored by Portola Pharmaceuticals and has recently received grant support from CSL Behring and Terumo BCT.

Funding

NIH R01HL121232-01 (I.J.W.), Departmental funding (K.G., J.H.L.)

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Handling editor: Hugh Hemmings