Blood component support in acquired coagulopathic conditions: Is there a method to the madness?

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Acquired coagulopathies are often detected by laboratory investigation in clinical practice. There is a poor correlation between mild to moderate abnormalities of laboratory test and bleeding tendency. Patients who are bleeding due to coagulopathy are often managed with various blood components including plasma, platelets, and cryoprecipitate. However, prophylactic transfusion of these products in a nonbleeding patient to correct mild to moderate abnormality of a coagulation test especially preprocedure is not evidence-based. This article reviews the management of bleeding due to oral anticoagulants and antiplatelet agents, disseminated intravascular coagulation, chronic liver disease, and trauma. Am. J. Hematol. 00:000–000, 2012.

Introduction

Acquired coagulopathies are commonly encountered in clinical practice. Coagulopathies result from consumption of coagulation factors during disseminated intravascular coagulation (DIC), decreased synthesis of coagulation factors due to chronic liver disease and/or vitamin K deficiency, or dilutional effect due to massive transfusion in an exsanguinating patient. Similarly, oral and parental anticoagulation therapy can lead to coagulopathy, with or without bleeding. While these coagulopathies may be detected by routine laboratory testing, not all coagulopathies detected by laboratory testing (especially mild to moderate) are associated with clinical bleeding. Laboratory tests used to detect coagulopathy include prothrombin time (PT), partial thromboplastin time (PTT), fibrinogen, d-dimers, and platelet count.

Without treatment, coagulopathy can cause significant morbidity and mortality in a *bleeding patient*; therefore, immediate correction is paramount. Efficacious management of coagulopathy is best tailored to each patient. While most coagulopathies can be managed by appropriate blood component transfusions, others (such as warfarin reversal) can be managed by replacement therapy for specific factor(s) [1]. Due to a paucity of well-designed clinical trials, management of these coagulopathies is not always evidence-based. Blood transfusion is very safe with regard to known viral infections (e.g., HIV, Hepatitis C, and B); nonetheless, there is always a risk of an unknown pathogen and/or noninfectious complications (e.g., Transfusion Related Acute Lung Injury, TRALI, Transfusion Associated Circulatory Overload, TACO) [2,3]. This manuscript describes, therefore, a rational approach to the management of acquired coagulopathies.

Blood Components

Fresh frozen plasma (FFP) is obtained either by separation of supernatant plasma from a whole blood donation or an apheresis technique. It is immediately frozen within 8 h to preserve heat labile factors V and VIII. The volume of FFP derived from whole blood is approximately 250–325 mL; the volume derived from apheresis is 400–600 mL. The FFP is stored at −18°C for 1 year. The patient's ABO blood group is required for FFP transfusion; in emergency, however, when ABO typing cannot be performed, group AB plasma can be used. Before its release from the blood bank, FFP is thawed at 37°C. FFP can be stored at 4°C for up to 24 h; thereafter, however, it can be relabeled as thawed plasma and kept for another 4 days. All coagulation factors are stable in thawed plasma except for FVIII [4]. Notably, most patients requiring plasma therapy generally have very high levels of FVIII because it is an acute phase reactant.

Cryoprecipitate is obtained by controlled thawing of FFP from −18 to 4°C. Several proteins precipitate out at 4°C. The bag is centrifuged at 4°C to remove cryosupernatant or cryo-poor plasma. Each bag (or unit) of cryoprecipitate has a volume of 10–15 mL and contains at least 250–400 mg of fibrinogen, about 100 units of FVIII and VWF, as well as a significant amount of FXIII and ADAMTS13 [5]. A pool of 10 bags (or units) constitutes a dose of cryoprecipitate for an average adult, whereas in the case of children, one bag of cryoprecipitate per 10 kg body weight is given. ABO matching for adults is not necessary as there is a very small amount of plasma (100–150 mL) in a dose of cryoprecipitate. For transfusion purposes, each unit of cryoprecipitate is thawed and then pooled within the blood bank before dispensing as a single dose, although recently many blood centers are providing prepooled cryoprecipitate where 5–10 units are prepooled and frozen.

Platelets are derived either from whole blood donation (also called random or platelet concentrate) or by apheresis machine. Four to six random units of platelet concentrates are pooled in the blood bank or prepooled at the blood center (called *Acrodose* platelets) and constitute a platelet dose (which is equivalent to one apheresis platelet unit). Generally, both types of platelets are prestorage leukoreduced, thereby significantly reducing chill rigor reactions (due to significant reduction in cytokines), and HLA alloimmunization and are considered CMV safe. Because cold temperature make platelets dysfunctional, they are stored at room temperature on a shaker, which increases risk of bacterial growth (1:2,000–1:3,000) [6]. Hence, their shelf life is limited to 5 days, which contributes to perpetual shortages. Regulations require that the platelets be tested for bacterial contamination. Apheresis and Acrodose units

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TABLE I. Parkland Health and Hospital System: Guidelines for Management of Elevated INR or Bleeding in Patients Receiving Warfarin

INR	Management
Above therapeutic range but < 5 No significant bleeding No surgical intervention needed	Lower or omit dose, monitor INR more frequently, and resume at a lower dose when INR therapeutic; if only minimally above therapeutic range, no dose reduction may be required.
INR ≥ 5, but < 9 No significant bleeding	Omit next one or two doses of warfarin. Monitor INR and reinstitute warfarin at lower dose when INR drops to within therapeutic range. If patient at increased risk of bleeding, consider giving vitamin K 2.5–5 mg PO.
INR ≥ 5, but < 9 Surgery (after 24 hs) or dental extraction at any INR	Vitamin K 2.5–5 mg PO or 1–2 mg IV[a]. Recheck in 24 hr. If still high, give vitamin K 2.5 mg PO or 2 mg IV.
INR ≥ 9 No significant bleeding	Patient should be evaluated by a physician. Hold warfarin therapy and give higher dose of vitamin K (5–10 mg PO) with the expectation that INR will be reduced substantially in 24–48 hr. Monitor more frequently and use additional vitamin K if necessary. Resume therapy at lower dose when INR therapeutic.
Serious/life-threatening bleeding or emergent surgery at any elevation of INR	• Send patient to emergency room or hospital admission • Hold warfarin • Vitamin K 10 mg slow IV infusion and PCC 50 U/kg IV. Check INR 5 min after PCC. • Reassess INR in $\leq$ 6–12 hr. If INR did not correct with PCC + vitamin K, consider 2 U fresh frozen plasma (FFP). • Retreat with PCC and/or vitamin K every 6–12 h as needed.
Intracranial hemorrhage	See Trauma Coumadin Protocol

[a] Vitamin K 1–2 mg may be diluted in 50 ml and administered on general floors.

TABLE II. Prothrombin Complex Concentrate (PCC) for Warfarin Reversal: Coagulation Factor Composition

	FII	FVII	FIX	FX
BEBULIN®	120 U	13 U	100U	139U
PROFILNINE® SD	148 U	11 U	100 U	64 U
BERIPLEX®[a]	128 U	68 U	100 U	152 U
OCTAPLEX®[a]	44–152 U	36–96 U	100 U	72–120 U

[a] Not available in the United States (4 factors PCC).

are subjected to bacterial culture, whereas other means (such as pH testing) are used to detect bacteria in pooled platelets. One dose of platelet contains approximately 250–350 mL plasma. Because platelets express A or B blood group antigens poorly on their surface, ABO matching is not generally practiced and the oldest units on the shelf are dispensed first.

Management of Coagulopathies

Warfarin (vitamin K antagonist, VKA) reversal

An estimated 3 million patients are on warfarin for primary and secondary prevention of venous thromboembolism as well as for the prevention of systemic embolism from atrial fibrillation and patients with prosthetic heart valves [1]. Pharmacologic efficacy of VKA is monitored by international normalized ratio (INR), which is a calculated value derived from prothrombin time. The therapeutic range of INR is 2.0–3.0 for thromboembolism prophylaxis and 2.5–3.5 for patients with mechanical heart valve [7,8].

Warfarin inhibits epoxide reductase and vitamin K reductase and prevents carboxylation of gamma glutamic acid residues on F II, VII, IX, and X, and protein C and S, thus making these factors nonfunctional [9–11]. The activity of FII, VII, and X is reduced to 30–15%, which corresponds to an INR of 2–3. Warfarin has a variable pharmacokinetic and pharmacodynamics profile, which is dependent on the patient's race, genetic make-up, diet, and concomitant use of other drugs. Thus, bleeding is a major complication of warfarin therapy with an incidence of 15–20% per year [12–14]. Supratherapeutic INR (ST-INR) is one of the most important risk factors for hemorrhage. Almost one-third of patients on chronic warfarin therapy ($>$5 years) will have an INR $>$6.0 [14]. The risk of intracranial hemorrhage (ICH) increases significantly if the INR is $>$4, although most patients with ICH have an INR in the therapeutic range [14,15]. The ICH occurs in up to 2% of patients, and mortality can be as high as 79% [16,17]. Importantly, the mortality almost doubles for each one-point increase in the INR $>$2.5 [15].

ST-INR is commonly encountered due to the use of sensitive recombinant tissue thromboplastin reagents for PT [9]. However, the management of ST-INR remains challenging. Current ACCP guidelines recommend a step-by-step approach based on the extent of ST-INR [7,8]. Our data showed that patients with an INR $>$6 have poor correlation between INR and the extent of VKDF deficiencies [9]. This is due to loss of linearity of PT measurement (hence INR) beyond 50 s (and INR of 5) on most instruments. Thus, a patient with an INR of 6.0 is potentially at the same risk of bleeding as someone with an INR of 15!

Vitamin K administration is essential for treating ST-INR. The dose and route of administration had to be based on the extent of INR prolongation, urgency of reversal, and the need for re-coumadinization (Table I) [7,8,15]. It should not be given subcutaneously due to poor and erratic absorption, especially in obese patients [18]. Current preparation of vitamin K (phytonadione) is much safer when administered as slow infusion (e.g., 5 mg in 25 mL normal saline over 15–30 min) when compared with older preparations (containing castor oil) that were associated with anaphylaxis when given intravenously [19]. In the last 11 years, at our institution there has not been a single reported case of anaphylaxis due to intravenous Vitamin K.

British and Australasian guidelines recommend prothrombin complex concentrate (PCC) for urgent warfarin reversal. However, FFP continues to be standard of care in the United States despite lack of evidence of its efficacy. FFP transfusion requires ABO blood typing, thawing plasma in most centers, and infusions lasting several hours. This can lead to transfusion-associated circulatory overload (TACO), especially in elderly patients with compromised cardiac and renal function. In addition, the dose of FFP required to reverse warfarin is 30 mL/kg, which is rarely administered [20].

PCC contains concentrated FII, VII, IX, and X. There are two types of PCCs: activated PCC (e.g., FEIBA), which is licensed to treat hemophiliacs with inhibitors, and nonactivated PCC, which was used to treat hemophilia B due to FIX content. Importantly, only nonactivated PCCs can be used safely for warfarin reversal. There are two types of nonactivated PCCs (Table II): four factor PCCs, available in Europe (BERIPLEX®, CSL Behring and OCTAPLEX®, Octapharma AG), that contain sufficient amounts of all VKDF (including protein C and S) and 3-factor PCCs, avail-

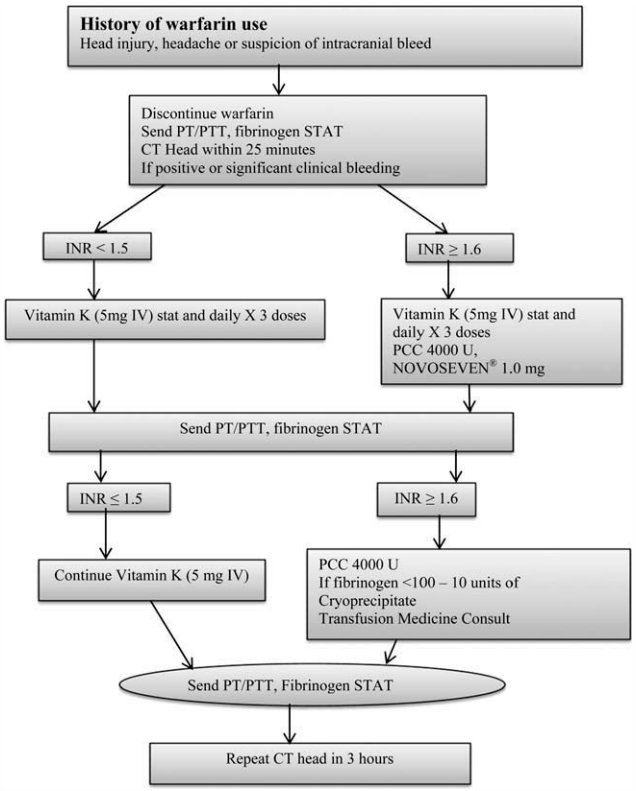

Figure 1. Trauma/intracranial hemorrhage coumadin protocol (TCP) for Parkland Health & Hospital System (PHHS).

able in the US (PROFLNINE® SD, Grifols and BEBULIN®, Baxter), that contain insufficient amounts of FVII [1]. In the US, 3-factor PCC alone may not completely correct ST-INR; it is, therefore, essential to administer IV vitamin K (either low dose or standard dose) for the liver to synthesize FVII within 3–6 h. Additionally, a small amount of plasma (10 mL/kg) may be required to correct INR [1]. The extent of INR correction does not, however, reflect hemostatic effect. Our current warfarin reversal protocol is given in Table I.

In cases of ICH it is essential to rapidly correct INR to prevent hematoma expansion [21]; furthermore, FFP is not effective in achieving this goal. As a result, the authors have developed a trauma coumadin protocol to rapidly correct coagulopathy (Fig. 1); treatment uses a fixed dose of PCC (4,000 units at 50 U/kg, based on average patient weight of 80 kg) and a low dose (1 mg) of recombinant FVIIa [15].

Reversal of Unfractionated Heparin

Bleeding remains a common complication of UFH therapy. FFP is occasionally requested to treat heparin-associated bleeding and prolonged PTT. These patients have a relative antithrombin deficiency due to presence of a high amount of UFH in circulation. Administration of FFP provides antithrombin which interacts with UFH and may worsen bleeding. Protamine sulfate had to be given to neutralize up to 80% of anticipated circulating UFH because excess protamine acts as an anticoagulant and may worsen bleeding [22]. Thus, assuming 5,000 U of heparin in circulation, 4,000 units (80%) should be neutralized by administering 40 mg protamine (1 mg neutralizes 100 units). There is no specific antidote for LMWH-related bleeding; use of protamine sulfate may partially reverse its effect [23].

Reversal of new oral anticoagulants

Dabigatran etexilate (PRADAXA®, Boehringer Ingelheim Pharma) is an oral direct thrombin inhibitor (DTI) recently FDA approved for primary stroke prevention in patients with atrial fibrillation [24]. Dabigatran was superior to warfarin in stroke prevention and intracranial hemorrhage; however, gastrointestinal bleeding complications were significantly higher than warfarin [25]. Dabigatran etexilate is a prodrug, which is converted to its active form dabigatran by esterase present in the gut, liver, and plasma, and is cleared by kidneys [26]. The advantage of this DTI is that there is no need to monitor the drug. However, disadvantages include twice daily therapy, absence of a laboratory test to monitor its effect or therapeutic drug levels if needed, and no known antidote. Patients who present with bleeding on DTI generally have prolonged PT, PTT, and very long thrombin time [27]. Fibrinogen may be spuriously undetectable because the fibrinogen assay is based on thrombin clotting time. Variations in these tests are reagent dependent.

Rivaroxaban (XARELTO®, Janssen Pharmaceuticals) is a direct FXa inhibitor also recently FDA approved for DVT prophylaxis following hip and knee surgeries and stroke prevention in a patient with nonvalvular atrial fibrillation. It is metabolized by the liver cytochrome P450 and mainly excreted by the kidneys [28]. Although Rivaroxaban also requires no laboratory monitoring, its presence could be detected by an existing anti-Xa assay using low molecular weight heparin curve (author's personal experience); importantly, its therapeutic levels are unknown. Furthermore, there is no known antidote. One randomized clinical trial for primary stroke prevention in atrial fibrillation showed that rivaroxaban was superior to warfarin. Although, ICH was significantly less with rivaroxaban, there was a significantly higher associated-incidence of gastrointestinal bleeding and requirement of blood transfusions [29].

Management of bleeding in patients on these new oral anticoagulants is challenging. The anti-IIa assay (Hemoclot Thrombin Inhibitors, Biophen Research Use Only) can be used to assess therapeutic level of dabigatran. In our laboratory, thrombin time was found to be too sensitive to even the lowest concentration (0.1 μg/mL) of dabigatran, whereas PTT proved better in detecting the drug in therapeutic range (0.1–0.3 μg/mL. Dialysis (62–68% dialyzable) may be useful in removing dabigatran in a bleeding patient especially in a patient with renal failure, since it is mostly free in plasma [30,31]. Because Rivaroxaban is mostly protein bound, plasma exchange may be potentially beneficial [32], however, there is no published clinical experience. Placement of a central line for these procedures will be challenging due to grossly abnormal coagulation tests. In animal models, PCC has been shown to be hemostatically more efficacious than recombinant FVIIa [33]; this is possibly due to significant increases in prothrombin levels, which provide more substrate for thrombin generation (akin to prothrombin gene mutation) and, thus, neutralize the DTI. PCC was similarly found to better correct laboratory abnormalities in healthy volunteers receiving rivaroxaban as compared to dabigatran [27]. Because increased prothrombin levels cannot be obtained by FFP, FFP would likely not be effective but quite possibly harmful to elderly patients with compromised cardiac status and underlying renal insufficiency (resulting in TACO). Our protocol for DTI management is given in Table III.

Antiplatelet agents

Antiplatelet agents (APAs) are used for primary and secondary prevention of arterial thrombotic events and after revascularization procedure. The characteristics of commonly used APAs are given in Table IV. Bleeding is a common

complication of APA especially following surgical procedures. Due to lack of randomized clinical trials, the management of patients on APA, who are bleeding or need emergent reversal of antiplatelet drugs, is very challenging. Platelet transfusion is the best option. Reversal of APA was recently reviewed by one of the authors (Ravindra Sarode) [34].

ASA is absorbed from the gastrointestinal tract and during its passage through the portal circulation to the liver, ASA irreversibly binds to platelets. Once metabolized in the liver, the ASA metabolite is ineffective. Thus, newly released platelets from the bone marrow are unaffected. Since 10% of platelets are renewed daily, in a patient with a platelet count of 250×10^9/L, there are 50×10^9/L functional platelets 2 days after discontinuing ASA. Although ASA is a very effective antiplatelet agent, it does not increase the risk of perioperative bleeding [35]. In fact, in patients with high risk for coronary artery disease or cerebrovascular accident, preoperative discontinuation of ASA may lead to increased postoperative thrombotic complications [36]. Therefore, it appears that platelet transfusion to negate antiplatelet effect of ASA may not be necessary unless the patient has an ICH or requires neurosurgical procedure or eye surgery. In such a scenario, one dose of platelets (one apheresis or four to six pooled platelets from whole blood donations) may be given [34]. The PFA-100, VerifyNow ASA (Accumetrics, San Diego, CA) and platelet aggregometry may be useful in detecting ASA effect in nonurgent situations, if platelet transfusion is clinically deemed necessary [34].

P2Y12 inhibitors are considered to be more potent APAs than ASA with higher bleeding complications [37]. Clopidogrel (PLAVIX®) [38] and prasugrel (EFFIENT®) [39] are prodrugs requiring metabolism in the liver whereas ticagrelor (BRILINTA™) [40,41] is a direct P2Y12 inhibitor. In general, their effect lasts for 3–5 days and are associated with higher bleeding risk especially perioperatively [42,43]. In the laboratory, platelet aggregometry and VerifyNow P2Y12 have been used to detect inhibition of P2Y12 receptor function, however, PFA-100 is not useful [34]. One dose of platelets may be transfused to a patient, who is undergoing emergent surgery and two doses for ICH, neurosurgical procedure, or eye surgery [34]. If platelet transfusion is not desirable in some patients for various reasons, pharmacologic alternatives such as desmopressin (1-deamino-8-D-arinine vasopressin [DDAVP] 0.3 μg/kg) and recombinant Factor VIIa (NOVOSEVEN®, 15–20 μg/kg) may be used [34]. However, risk for potential thromboembolic complication from recombinant Factor VIIa (to a lesser extent for desmopressin) had to be weighed against the benefit.

TABLE III. Management of Patient on New Oral Anticoagulants at University Hospital, University of Texas Southwestern Medical Center

- Discontinue the drug
- Check PTT and thrombin time for Dabigatran
- PT/INR for Rivaroxabain
  - if normal then probably no drug in circulation
- Use topical agent or surgical approach to control bleeding
- Ongoing bleeding − 50 U/kg of PCC (BEBULIN or PROFILNINE)

Re-balanced hemostasis in chronic liver disease

With the exception of Factor VIII and von Willebrand factor (VWF), the liver synthesizes all procoagulant factors, natural anticoagulants, thrombopoietin [44], ADAMTS13 (A Disintegrin and Metalloproteinase with a ThromboSpondin type 1 motif, member 13) that regulates VWF multimer sizes and elements of the fibrinolytic system [44,45]. Although INR is primarily used to monitor warfarin therapy, it is also used as a prognostic index to calculate a patient model for end-stage liver disease scores, e.g., for prioritizing candidates for liver transplantation [46]. In warfarinized patient, INR reflects selective VKDF deficiency, whereas in liver disease, there is more than just VKDF deficiency; thus, INRs are not comparable between the two conditions. Moreover, decreased natural anticoagulants, altered fibrinolytic pathway as well as elements of dysfibrinogenemia are not evaluated by PT/INR. Recent published reports on the complex coagulopathy of liver disease suggests that there is a re-balanced hemostasis in chronic liver disease (CLD; Table V), and that thrombin generation in CLD is either similar to normal plasma [47] or even increased [48]. Thus, mild-to-moderate prolongation of PT/INR does not correlate with bleeding outcome even during invasive procedures [49]. In addition, in patients presenting with variceal bleeding (structural bleeding), any amount of FFP or platelets preprocedure to correct laboratory values is likely to delay the procedure by several hours (i.e., time to obtain ABO typing, thawing FFP and slow transfusion due to compromised circulatory, and renal function). FFP may worsen bleeding because it further increases portal pressure due to high oncotic contents. Therefore, the recent guidelines of the American Association for the Study of Liver Diseases

TABLE IV. Antiplatelet Agents (APA), Mechanism of Action and Guideline for Reversal

	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Dipyridamole
MOA	COX-1 inhibitor	P2Y12 inhibitor	P2Y12 inhibitor	P2Y12 inhibitor	Phosphodiester ase inhibitor
Onset of action following loading dose	Minutes	2 hr	2 hr	1 hr	Slow
Half-life	0.5 hr	7–8 hr	7 hr	7–9 hr	13.5 hr
Steady state of inhibition	Hours	3–7 days	3–5 days	3–5 days	Hours
Reversible	3–5 days	5 days	5–9 days	5 days	Unknown
Bleeding risk	+	+++	++++	++++	+
Platelet transfusion for urgent surgery	No	One dose	One dose	One dose	No
Neurosurgery, eye surgery, ICH	One dose	Two doses	Two doses	Two doses	One dose
Elective surgery	No waiting required	5 days	7 days	5 days	No waiting required

MOA, mechanism of action; ICH, intracranial hemorrhage.

TABLE V. Rebalanced Hemostatic Changes in Chronic Liver Disease

Hemostatic changes favoring bleeding	Hemostatic changes favoring thrombosis
1. Thrombocytopenia: splenomegaly and decreased thrombopoietin 2. Platelet dysfunction	1. Increased VWF 2. Decreased ADAMTS13 level
1. Decreased procoagulant factors: II, V, VII, IX, X, and XI 2. Vitamin K deficiency	1. Decreased natural anticoagulants: Protein C, Protein S, and antithrombin 2. Increased FVIII
1. Increased levels of t-PA, Low TAFI, decreased alpha 2 antiplasmin	1. Decreased levels of plasminogen, Increased plasminogen activator inhibitor

advise against FFP transfusion to correct INR before liver biopsy; the decision had to be based on patient characteristics [45,50]. Randomized controlled studies have failed to demonstrate the significant benefit from recombinant activated factor VII (rVIIa) in acute upper gastrointestinal bleeding in patients with cirrhosis [51–53] Thus, mild-to-moderate prolongation of PT/INR and platelet count of $>50 \times 10^9$/L do not require preprocedure correction by FFP or platelet transfusion [50,54]. Patients who have grossly abnormal PT/INR and PTT may be transfused FFP at 10–15 ml/kg with the expectation that the coagulation parameters will not correct completely [55,56].

In a normal-sized spleen about one-third of circulating platelets are sequestered (banked platelets), whereas the majority of platelets are in circulating (cash platelets). In a patient with moderate-to-marked splenomegaly, the majority are sequestered in the spleen resulting in peripheral thrombocytopenia. Platelet transfusion in such a severely thrombocytopenic patient may not show adequate increment due to further sequestration. In an elegant in vivo study with labeled platelets, it was shown that transfused platelets were rapidly sequestered in large spleens and upon challenge with epinephrine; these sequestered platelets were released in the peripheral circulation [57]. Based upon this in vivo study, it is likely that in a bleeding patient, a stressful condition with endogenous epinephrine release, these sequestered platelets (banked platelets) will be released in the peripheral circulation (cash platelets). Thus, preprocedure platelet transfusion for patients with splenomegaly had to be restricted to platelets $<50 \times 10^9$/L with the understanding that the platelet count increment may not be as expected [54]. Risk of volume overload and TRALI had to be weighed against trying to correct laboratory number in such patients.

Hypofibrinogenemia (fibrinogen <100 mg/dL) due to decreased synthesis and dysfibrinogenemia due to increased amount of sialic acid on fibrinogen are common findings in patients with CLD [58,59]. Dysfibrinogenemia (fibrinogen level may be >150 mg/dL with prolonged thrombin and reptilase times) is seen in about 76–86% patients with CLD [60]. At our institution, we recommend one dose of cryoprecipitate for hypofibrinogenemia in a bleeding patient [61–64]. Similarly, in a bleeding patient whose coagulopathy does not respond to adequate plasma infusion, the authors suspect dysfibrinogenemia and empirically recommend a dose of cryoprecipitate because, generally there is no time to perform testing for dysfibrinogenemia. In patients with grossly abnormal coagulation parameters and compromised volume status, the authors may recommend PCC (50 U/kg) and cryoprecipitate before surgery.

Disseminated intravascular coagulation

DIC is a clinical syndrome characterized by pathologic activation of the coagulation cascade causing microthrombotic angiopathy and subsequent consumptive coagulopathy. Common laboratory abnormalities include thrombocytopenia ($<100 \times 10^9$/L), prolonged PT and PTT, increased D-dimers and decreased fibrinogen [65,66]. Severe DIC leads to significant consumption of coagulation factors and may result in bleeding. However, most mild-to-moderate DICs are diagnosed by mild-to-moderate abnormalities of coagulation parameters and are not associated with clinical bleeding. Therefore, management of DIC includes treating the underlying etiology. Correction of abnormal coagulation tests by FFP, platelets, and cryoprecipitate had to be reserved only for those who are either bleeding or require major invasive procedures. Transfusion of these components may "add fuel to the fire" leading to exacerbation of microthrombosis and worsening of organ(s) dysfunction. At our institution, for a bleeding patient with DIC, we recommend transfusion therapy to maintain fibrinogen >100 mg/dL (with cryoprecipitate), platelet counts >20 K and PT/PTT $1.5\times$ normal (with FFP at 10–15 mL/kg).

Intravenous vitamin K had to be administered because most of these patients are on antibiotics and have poor nutritional status leading to VKDF deficiency [67,68]. Septic patients with florid DIC and multiorgan system failure (three or more) generally cannot tolerate additional plasma volume and may benefit from therapeutic plasma exchange; this removes activated coagulation factors and proinflammatory cytokines, restores the activated protein C pathway, simultaneously replaces antithrombin, ADAMTS13, and complements by FFP to restore hemostasis [69,70]. If DIC is complicated by arterial or venous thromboembolism then systemic anticoagulation with unfractionated heparin (UFH) is preferred due to its short half-life. UFH had to be adjusted by heparin assay (anti-Xa assay; 0.3–0.7 U/mL) rather than PTT, which may be prolonged at baseline in DIC [66]. Critically ill patients with DIC and no clinical sign of bleeding are usually placed on venous thromboembolism prophylaxis with UF heparin or LMW heparin [71]. Replacement therapy with recombinant activated protein C caused increased bleeding tendency; it has been withdrawn from the market [72,73].

Trauma coagulopathy and massive transfusion

Trauma remains the number one cause of death between ages 1 and 44 in the United States [74]. Massive trauma with severe tissue injury induces acute coagulopathy of trauma (ACT) and varied physiologic response, including activation of the sympatho-adrenaline system and immune-complement system, resulting in systemic inflammatory response syndrome [75]. Endothelial injury, release of tissue factor, and early activation of Protein C results in hyperfibrinolysis, further worsening ACT [76]. Based on coagulation tests (prolonged PTT, PT/INR, and decreased fibrinogen), nearly a quarter of all trauma patients developed ACT before resuscitation or on arriving at the hospital [77]. The coagulopathy can worsen with fluid resuscitation and red cell transfusions, thus leading to dilutional coagulopathy. Survival from trauma depends upon careful management of a lethal triad of hypothermia, acidosis, and coagulopathy. Early recognition of trauma-related coagulopathy, prompt, and effective blood component transfusion support as well as correction of anatomic defect by the trauma surgeon has improved mortality.

A massive transfusion protocol (MTP) designed to give red blood cells and coagulation factors (i.e., plasma and platelets) in a prespecified ratio have improved outcomes [78]. Military data obtained retrospectively showed improved survival benefit with a ratio of 1:1:1 (1 pRBCs: 1 plasma: 1 platelets [79]; however, due to lack of a randomized trial and further follow-up study, there is limited applicability in civilian trauma. In civilian trauma, a ratio of 2:1 (pRBC to plasma) with appropriate platelet transfusion has demonstrated improved mortality [80,81]. Recently, in a randomized clinical trial, early administration for tranexamic acid, (1 g over 10 min followed by 1 g infused over 8 h) reduced mortality in bleeding trauma patients [82,83]. Recombinant factor VII, which has been shown to reduce blood component use [78], had to be used judiciously because of risk of thromboembolic complications [84,85]. Viscoelastic whole blood tests, such as thromboelastography and rotational thromboelastometry are still being evaluated for their utility in the management of coagulopathy [86]. Importantly, in an exsanguinating patient, turnaround times for these tests and blood component supply based

on these results may be unacceptable. Similarly, transfusion therapy based on conventional coagulation tests is likely to result in "trying to catch up" on coagulopathy. Therefore, each trauma center had to have a MTP for exsanguinating patients [78].

Conclusion

Although blood component transfusion therapy is quite safe in regard to transmission of known viral infections, the risk of unknown pathogen still exists. Similarly, noninfectious complications of blood component therapy (TACO and TRALI) are increasingly recognized with significant morbidity and mortality; therefore, transfusion therapy should be used judiciously.

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