HEMATOLOGY REVIEW FOR SURGICAL CRITICAL CARE

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I. Blood and Blood Components

A. Red blood cells (RBC) are the primary O2-carrying component of whole blood; 300 mL/unit; typical hematocrit of 29%; usually transfused in 10-15 mL/kg "challenges;" expected increase per unit transfused is one gram (hemoglobin) or 3% (hematocrit); typical shelf-life up to 42 days; group O blood type is considered universal donor (O negative for female recipients)

B. Plasma is the primary source of coagulation factors; makes up 55% of blood volume; 200-250 mL/unit; contains 400-450 mg fibrinogen/unit; other factors in 60-70% range; buffers severe acidosis (via its high citrate content); "jumbo" plasma unit 700-800 mL from single donor (aphaeresis); FFP-plasma frozen within 8 hours of receipt; FP24- plasma frozen within 24 hours or receipt; liquid plasma- never frozen plasma; FFP is to be used within 24 hours, otherwise, relabeled thawed plasma- previously frozen FFP or FP24 with 5 day shelf life; AB plasma is considered universal donor

C. Platelets are derived from megakaryocytes and play an active process in coagulation through clotting factor, fibrin and endothelial interactions; released as 5-6 packs (units) (40-50 mL/unit) from random donors or from single donor (aphaeresis unit, 200-250 mL) with typical count of 80,000 platelets; stored at room temperature and on an agitator;

traditional shelf-life of 5 days; avoid transfusion in patients with TTP (worsens neuro symptoms and renal failure), HIT and DIC; no universal donor required

D. Cryoprecipitate is a concentrated product obtained from plasma; transfused as a pooled units (4-6 unit pools), therefore, typical bag is 80-100 mL; each (10-15 mL) unit typically contains 100 IU of factor VIII, 250 mg of fibrinogen, and adequate stores of von Willebrand factor (vWF) and factor XIII; as with plasma, compatibility testing is not strictly necessary, but AB type is the universal plasma donor; in the emergency setting, typically given to address hypofibrinogenemia

E. Whole blood is utilized in austere settings when (1) blood supplies are stressed or depleted and (2) when donor screening is completed and results are known prior to donation (military setting); usual volume of each unit is 450-500 mL which has a hematocrit of >38%, platelet count >150, 000, 100% clotting factor levels and 1000 mg fibrinogen; must be type-specific product

II. Massive Transfusion (MT) and Hemorrhage

A. Hemorrhage accounts for greatest number of deaths within the first hour of arrival after injury; exsanguination is responsible >80% O.R. deaths and ~50% deaths in the first 24 hours after injury

B. MT traditionally defined as ≥10 units of red blood cells; other definitions include- loss of one blood volume in 24 hours, 50% blood volume loss within a 3 hour period, or loss of blood at 150 mL/min; seen in 8-10% trauma patients in military setting and 1-3% in the civilian setting

C. MT protocols have been developed to address this; composed of a system whereby physician activates the protocol and predetermined blood and blood products are delivered in rapid and sustained manner; ratios and units delivered per cycle are institution-specific; many centers also employ these protocols for non-trauma patients as well

D. MT protocols ratios typically include red blood cells, plasma, platelets and cryoprecipitate. Some use pharmacologic adjuncts as well. Plasma: RBC ratios are typically in the 1:3-1:1 range with platelets and cryoprecipitate use more variable. Well-developed protocols, irrespective of the ratios, have been associated with dramatic reductions in mortality, reduction in multi-organ failure and ARDS, reduction in overall blood and blood component utilization and lower hospital charges

E. Activation of MT protocols may be directed by clinical gestalt, laboratory or physiological triggers or a validated scoring system; use/request of uncross-matched product has been shown to precede recognition of major bleeding and MT scenarios, as such, transfusion of uncross-matched products should activate an institution's MT protocol; the TASH and ABC scores are both validated scoring systems that have been shown to predict the need for MT with AUROC 0.80-0.90; the scores have good PPV and great NPV; these scoring systems

employ a combination of hypotension, tachycardia, (+)FAST, mechanism of injury, and base deficit

III. Acute Coagulopathy of Trauma (ACoT)

A. ACoT has been described as an endogenous impairment of hemostasis that occurs early after injury; coagulation abnormalities are common following major trauma and are present on arrival in ≥25% of patients with major trauma; mortality among trauma patients is increased dramatically when ACoT is present (more than 4-fold increase in mortality)

B. Hallmark of ACoT is microvascular-bleeding leading to massive blood loss; purported etiologies include hemodilution, major surgery inducing complex hemostatic changes, consumption of coagulation factors, and excessive fibrinolysis.

C. Major risk factors for ACoT include extensive tissue damage, shock/acidosis (base deficit of ≥10 or sustained SBP<90 mmHg), large amount of prehospital IV fluid (≥3000 mL), and hypothermia (temperature <35□C); ACoT is associated with increased transfusion requirements and organ failure

IV. Damage Control Resuscitation

A. The three tenets include: permissive hypotension, limiting crystalloids and delivering higher ratios of plasma and platelets; to address these, institutions developed and implemented MT protocols; however, the ratios have been the most studied component

B. All published studies to date have been non-randomized and most have been retrospective reviews based on changes in practice; most studies on ratios have demonstrated survival advantage with increasing plasma: RBC and platelet: RBC ratios; at this time, the optimal ratio of plasma: RBC appears to be between 1:1-1:2

C. Survival bias potential has been raised by several authors; survival bias suggests that patients are not surviving because they received higher ratios of products but they are receiving (achieving) higher ratios because they are surviving long enough; this reaffirms those who state that this reflects an availability bias ("you can't give what you don't have") as one of the initial studies pointing out survival bias did not administer plasma within the first 90 minutes of arrival

D. During the acute resuscitation phase, increasing volumes of crystalloid are associated with worse outcomes; these include increased frequency of and longer time to recovery from ALI and ARDS, increased gastrointestinal dysmotility and anastomotic leak rates, more frequent coagulation disturbances and higher mortality; these complications remain significant even when controlling for shock and severity of injury; these complications are more common (and seen with even less fluid administration) in the elderly trauma patient

E. Recent civilian (US and UK) and military guidelines recommend fluid restrictive strategies in the prehospital settings, titrating small fluid boluses (250 mL) for palpable radial pulse palpable and normal mental status; a randomized trial from Dutton et al demonstrated that there was no survival benefit from resuscitating patients with evidence of hemorrhage to a SBP >70 mmHg or >100 mmHg; a recent pilot study from Morrison et al noted that patients with penetrating torso trauma who were randomized to an intra-operative MAP of >50 mmHg had less blood loss, received less total fluids and less blood products than those randomized to MAP>65 mmHg

V. Hemostatic Adjuncts

A. Internal - Pharmacologic

Factor VIIa

Initially developed for use in Hemophilia, subsequently used in life-threatening hemorrhage from trauma, surgery, liver failure. Was also shown to have a role in reducing stroke volume hemorrhage. Exceptionally expensive due to its recombinant nature. Dosing schedule never well elucidated.

Trial in trauma stopped prematurely due to futility. Has been effectively shown to reduce transfusion requirements but NEVER to reduce mortality. Being used less and less due to expense and concern for side-effect profile (thrombotic events)

Prothrombin Complex concentrates

Again, not designed for use in trauma, but have been used successfully in anecdotal cases of patients not responding to hemostatic resuscitation. The correct dosage still needs to elaborated as well as the exact patient population that may benefit from this drug.

B. External

Multiple agents have been used both on and off-label with mixed results. One early failure was Woundstat, which was withdrawn due to a concern regarding thromboses of nearby vessels.

Quikclot – one of the first to market. Initially in granule form, then repackaged into a "teabag". Initial product HIGHLY exothermic, then reformulated. First generation granules very effective, but at price of tissue damage. Makers have moved into third generation dressings now, and are concentrating less on Quikclot but still commercially available.

Combat Gauze – Kaolin impregnated gauze roll. For external use only, but can be packed into large hemorrhaging wounds, or into the nasal cavity for example. True efficacy unclear in controlling bleeding in trauma patients with ACoT. Now carried extensively by army – made by same manufacturers as quikclot.

C. Internal – OR adjuncts

Thrombin/Fibrin glues

Use mostly restricted to the operating room. More effective in slowly oozing broad surfaces than large volume or injured vessels. Certainly have a role, but one product has not been shown to have significant superiority over another.

Collagen gauzes, granules

Surgicel/Nugauze – oxidized cellulose. Effective for minor surface bleeding. Cheap and non-toxic. Can even be left inside the patient, and will reabsorb. Bacteriostatic.

Other granules, powders available. None effective for major bleeding.

VI. Coagulation Testing

A. Rapid identification of clotting abnormalities appears critical to improving survival; unfortunately, the majority of tests focus on single part of clotting cascade; prothrombin time (PT) and INR reflect defects or integrity of the intrinsic pathway while partial thromboplastin time (PTT) reflects the extrinsic pathway; in the rapidly bleeding and unstable patient, these tests are often rendered worthless due to long intervals inherent in drawing blood, processing specimen, and obtaining results

B. PT, INR, and PTT reflects only status of plasma proteins; these studies neglect the contribution of the other components of whole blood; PT, INR, and PTT may indicate a certain degree of coagulopathy and, when markedly elevated, correlate with worse outcomes; however, these tests were never developed or intended for following patients with acute coagulopathy from trauma; these tests were developed and validated in patients being treated with oral (warfarin- PT and INR) or intravenous (heparin-PTT) anticoagulants; while PTT may occasionally be prolonged with newer anticoagulants (dabigatran, rivaroxaban), PT and INR are normal; other coagulation tests (platelet and fibrinogen count) are limited by their pure quantitative values and lack of testing of function or qualitative assessment

C. Multiple point-of-care coagulation devices have been developed; unfortunately, these have only been formally evaluated with patients on oral anti-coagulants; in addition, these PT/INR point-of-care devices demonstrate good correlation at lower values (INR<2.0) but show considerable variability (and poor correlation) at values higher than 2.0

D. Whole blood-based, viscoelastic testing has recently gained popularity, though the technology has been around for >50 years; both thrombelastography (TEG) and rotational thromboelastometry (ROTEM) are available in the US for evaluating the ACoT; in both, a small sample of blood is added to a cuvette and the clotting process is initiated by the addition of one or a combination of activators (kaolin, tissue factor, calcium chloride); these tests have been shown to correlate not only with poor outcomes, but, more importantly, with plasma, platelet and cryoprecipitate/fibrinogen transfusions; TEG has also been

shown to predict hypercoagulability, specifically in-hospital venous thromboembolism, myocardial infarction, and stroke

E. The TEG values generated include: ACT and r-value (representing the time between start of the assay and initial clot formation), k-time (time to reach specified clot strength), alpha-angle (slope of tracing that represents rate of clot formation), maximal amplitude (greatest amplitude of tracing, reflects absolute clot strength), and the LY30 (which represents clot stability and the % amplitude reduction 30 min after maximal amplitude achieved); ROTEM values include: in-TEM (represents intrinsic pathway activation), hep-TEM (assesses the intrinsic pathway's integrity with heparin influence removed), ex-TEM (represents extrinsic pathway activity), fib-TEM (inhibition of platelets), and ap-TEM (representing the amount of fibrinolysis)

F. Prolongation of the TEG's ACT and r-value and the ROTEM's in-TEM and ex-TEM factor reflect factor deficiency or severe hemodilution (usually treated with plasma or factor concentrates); prolonged k-time or decreased alpha-angle correlate with states of hypofibrinogenemia (usually treated with cryoprecipitate or fibrinogen concentrates); decreased maximal amplitude by TEG and fib-TEM by ROTEM correspond with platelet defects or decreased activity (usually treated with platelet transfusion); increased LY30 or ap-TEM are seen in cases of hyperfibrinolysis (treated with amino-caproic acid or tranexamic acid)

VII. Coagulation Disorders

A. Hemophilia A is a sex-linked recessive, factor VIII deficiency associated with prolonged PTT and normal PT (treated with factor VIII or cryoprecipitate); hemophilia B is also a sex-linked recessive factor IX deficiency associated with prolonged PTT and normal PT (treatment with factor IX or cryoprecipitate)

B. von Willebrand's disease is the most common congenital bleeding disorder; several types, ranging from minimal bleeding to overt hemorrhage; while type I and II are autosomal dominant, type III is recessive; both the PT/PTT can be normal, check bleeding time (ristocetin test); type I and II are treated with cryoprecipitate and DDAVP, while type III is treated with cryoprecipitate or VIII:vWF concentrate; in semi-elective settings, key to treatment is the administration of cryoprecipitate (six units) approximately six hours prior to intervention

VIII. Anemia in the ICU

A. 85% of patients who are in the ICU for longer than a week will end up receiving a blood transfusion. However, the TRICC trial in 1999 showed that a restrictive transfusion strategy of keeping patient's hemoglobins between 7-9 g/dL was as effective as 10-12 g/dL and in some patients was advantageous. There was improved survival in less injured and younger (<55 years) cohorts.

B. Transfusion in the non-bleeding ICU patient should consist of a single unit of PRBC at a time, followed by laboratory testing to assess whether transfusion of further units is truly necessary.

C. There is a dose-dependent relationship between the transfusion of blood products and the development of complications, particularly nosocomial infections. The immunosuppressive effect of blood transfusion has been well studied and is likely the cause of this increased incidence. Therefore in the stable ICU patient, each transfusion should be carefully weighed as to its potential benefit and risks.

D. The caveat of course is that patients who are actively bleeding from whatever source e.g. GI hemorrhage, trauma, etc. should be aggressively resuscitated, preferably using the principles of damage control resuscitation as already detailed.

E. Ethryopoetin and other similar medications should be limited only to patients with chronic kidney diseases and anemia from cancer or blood dyscrasias. Their efficacy in raising the hemoglobin of the average ICU patient is limited (10% in one study), and their expense does not justify their use. Concern regarding thrombotic events has also led the FDA to attach a black box warning to these drugs.

IX. Thrombocytopenia and HIT

A. As many as 33% of patient admitted to the intensive care unit will develop some degree of thrombocytopenia during their hospitalization. However, the most feared cause due to the associated serious thrombotic sequelae is heparin-induced thrombocytopenia. HIT is divided into 2 types: a benign, nonimmune mediated form (type I) and an immune-mediated form (type II).

B. Type I thrombocytopenia may be observed in up to 25% of patients 1 to 4 days after the initiation of heparin therapy, particularly in the postoperative setting. This nonimmune thrombocytopenia (generally associated with a platelet count of 100/L to 130/Lx10^9/L) is transient, asymptomatic, and appears to be caused by a direct platelet agglutinating effect of heparin. This form is self- limiting and generally self-resolving without any therapeutic adjustment.

C. type II HIT, or "true" HIT, is an antibody- mediated syndrome that most commonly appears within 5 days to 14 days from the initial heparin administration. HIT is a serious prothrombotic disease caused by heparin-dependent antibodies that trigger platelet aggregation by binding to molecular complexes formed by platelet factor 4 (PF4) and heparin

D. The risk of developing Heparin-induced Thrombocytopenia (HIT) is affected by type of heparin used (with highest risk associated with bovine UFH, followed by porcine UFH, and lower risk for LMWH), the duration of heparin exposure (maximal risk for treatments lasting 4 days to 14 days), a history of recent heparin exposure (within the past 100 days), the patient setting (postoperative vs. medical vs. pregnancy), and the patient's sex

(estimated 1.5 to 2 times higher relative risk in women compared with men, possibly because of increased immune responses).

E. HIT can be confirmed by the presence of anti-PF4 antibodies, which are detected by an ELISA blood test.

F. When HIT is strongly suspected or confirmed, all heparins should be stopped. This includes the removal of heparin-coated intravascular catheters and the suspension of heparin flushes. If the patient requires anticoagulation for whatever reason, Fondaparinux can be used for DVT prophylaxis and Argatroban for full anticoagulation instead.

X. Management and Reversal of Anti-coagulants and Anti-platelet agents

A. Warfarin can be effectively reversed by the use of either Fresh Frozen Plasma (FFP) or a Prothrombin Complex Concentrate (PCC). The degree of normalization of the INR by each unit of FFP is difficult to predict and will depend on circulating blood volume

This is one of the reasons that it is the author's preference to reverse Warfarin with a PCC< unless there are pressing needs to give the patient volume in addition.

B. Indications for PCC transfusion include:

a) Any patient with serious or life-threatening bleeding (intracranial, gastrointestinal, retroperitoneal, etc.) due to warfarin may be considered for therapy after meeting any one of the criteria below.
b) Patient is unable to tolerate the volume of fresh frozen plasma (FFP) needed for INR reversal (e.g. CHF). Patients typically require 2-4 L of FFP for adequate reversal
c) Critical patients that cannot tolerate the time required for reversal with FFP. Note that infusion of FFP may take 3-6 hours depending on the rate of infusion and the volume required for reversal. Complete INR reversal may be delayed in some circumstances
d) INR is refractory to standard doses of FFP

C. Dosing

There are only two commercially available PCCs for use in the USA – Profilnine, Bebulin

Reversal of INR typically occurs within 10 minutes of infusion. The INR may be checked at 30 minutes and dose repeated if needed.

Dosing for Profilnine shown below (dependent on INR)

Initial **INR <5:** Dose = 25 units per kg

Recheck INR 10 to 20 minutes after drug administration. May re-dose 25 units per kg to achieve a goal INR ≤1.5. If INR >1.5 after 2 doses, give FFP to achieve goal INR

Initial **INR ≥5:** Dose = 50 units per kg

Recheck INR 10 to 20 minutes after drug administration. If INR >1.5, give FFP to achieve goal INR

All patients who receive PCC must be given Vitamin K 10 mg IV as an infusion. Failure to administer Vitamin K may result in a rebound increase in INR after 6 hours.

C. Antiplatelet drugs

Aspirin, Clopidogrel, Ticlodipine and Prasugrel all irreversibly inhibit platelet function therefore their half-live is less important than the fact that for each day after interruption of any of these agents, ~10% to 14% of normal platelet function is restored.

Most authorities recommend that full strength aspirin should be held for a minimum of seven days prior to major abdominal surgery. The American College of Chest Physicians recommends 7 to 10 days in the latest version of its guidelines published in 2012.

Current recommendations by the manufacturers of Plavis (Clopidogrel) are to discontinue the drug for five days prior to elective surgery.

There is anecdotal data to support the use of platelet transfusion to support the irreversible effects of platelet inhibition by Plavix or Aspirin, but no randomized controlled trials. In the circumstance described above, it would be reasonable to transfuse platelets during the operative case to reduce the risk of intra-operative blood loss. Other rescue strategies have included administration of DDAVP, cryoprecipitate, and even Methylprednisolone.

D. Dabigatran and Rivaroxaban

Unfortunately, to date there are no known simple and effective ways to reverse the anticoagulant effects of the direct thrombin inhibitor, Dabigatran. Research has so far shown that the available PCCs in the US have not been able to reliably reverse the anticoagulant effect. They are NOT recommended as first line therapy in these patients.

Currently, 2011 ACCF/AHA guidelines recommend that patients with severe dabigatran-associated hemorrhage be transfused with fresh frozen plasma (FFP) and/or packed red blood cells (pRBC) as necessary. However, this is without any clinical or laboratory evidence that FFP transfusion is effective in these patients.

The manufacturers themselves in recommend emergency dialysis as the most effective treatment for reversal of this agent, with 60% of the drug supposedly being removed in 2-3 hours. However, this obviously may not always be feasible in the emergency setting, and will likely involve placing a central venous catheter for dialysis access in a fully anticoagulated patient. This nevertheless remains the most reliable option for reversal of this anticoagulant.

Rivaroxaban has been shown in some research to be at least partially reversed by administration of PCC and may therefore achieve some favor in the future because of this theoretical advantage.

XI. Transfusion-associated complications

These can run the gamut of any of the following conditions:

A. Hemolytic transfusion reaction
B. Febrile non-hemolytic transfusion reaction
C. Allergic reactions
D. Bacterial / Viral / Prion contamination
E. Fluid overload
F. TRALI

A. This can be acute or immediate, when it usually occurs within 24 hours of transfusion, and the effects are generally intravascular. Or it may present in a delayed fashion after 1-10 days, when the effects are mostly extravascular. Symptoms commonly include fever and chills in both forms, but DIC, hemodynamic instability and renal failure is much more common with intravascular hemolysis

Overall incidence is 1:12,000 - 25,000, with a mortality of 1:650,000.

B. Febrile reactions are common, approx. 1:100-1:200, and are thought to be due to non-toxic immune complexes. The effects are usually remediated with treatment using Benadryl /Tylenol

C. Allergic reactions (urticarial) are also fairly common, with an incidence of approximately 1:200. They should be treated as above and the transfusion should be stopped.

Both of these complications should always be reported to blood bank in case they represent the more serious but less likely concern for bacterial contamination.

D. Infectious risks are now very low, the exact risk depending on the contaminant being considered. For example HIV is as low as 1 in 2.6 million, while Hepatitis C is also in the same ballpark of 1 in 2.6 million. Hepatitis B is somewhat higher risk at 1 in 600,000, while exact figures for Bacterial contamination are difficult to come by, as it is very rare. West Nile virus could theoretically be transmitted but the risk is not yet known, as in also the case with Rabies. Despite the policy of the US blood banks to defer donors from the UK, there have as yet been no described reports of transmission of new variant Creutzfield-Jakob Disease by blood product administration

E. Circulatory overload is probably clinically under-recognized, and may have an incidence as high as 1:700. Symptoms usually develop within hours, and the population most at risk is the elderly with poor cardiopulmonary status. For unknown reasons, it is more likely with autologous transfusion. The risk can be minimized by slowing the transfusion down to run over 4 hours, and the addition of pre or post diuresis.

F. TRALI or Transfusion-Related acute lung injury has become a serious problem, with an incidence of 1 in 1700-5000. It can be life threatening, and probably now represents the No. 1 cause of transfusion related deaths, as well as being a leading cause of morbidity. It is related to Plasma-containing blood product transfusions, with FFP > Platelets > Red Cells > CRYO > IVIG.

Criteria for its diagnosis include:

i) An acute onset - during or within 6 hrs. of Transfusion
ii) Hypoxemia; an O_2 sat <90% at room air, or a PaO_2/FiO_2 ratio of <300 mm Hg
iii) Bilateral infiltrates on Chest X-ray
iv) No evidence of Left Atrial Hypertension
v) No preexisting Acute Lung Injury before Transfusion
vi) No temporal relationship to alternative risk for ALI

Treatment is support, with intubation as necessary for hypoxemia, diuresis as tolerated to add with the pulmonary edema. Some authorities have advocated the use of steroids, but there is little data to support their use in TRALI. 80% of patients will recover with normal lung function, and future transfusions are not necessarily an issue.

It is important in cases of TRALI to report this to the bloodbank so that the donor plasma can be identified, and both donor and recipient tested for the presence of antibodies. This may lead to the donor being deferred. Plasma from multiparous females has a much higher risk for causing TRALI, such that the United Kingdom for example has moved to collecting plasma from males only. Studies have shown that this approach can significantly reduce the incidence of TRALI when adopted by a blood bank.