Questions for American College of Surgeons critical care course

Q1. In which of the following patient scenarios, would the use of a prothrombin complex concentrate be MORE appropriate than the use of FFP?

A2.
1. Reversal of an INR of 6.0 in a 74-year-old female with a history of atrial fibrillation and congestive heart failure.
2. A 26-year-old male with a traumatic brain injury and an INR 1.5 (from acute traumatic coagulopathy) who requires placement of an intracranial pressure monitor.
3. A 36-year-old female with a severe pelvic fracture and an INR of 2.1 from acute traumatic coagulopathy with continued hemorrhage despite blood transfusions.
4. A 54-year-old female with septic shock from perforated diverticulitis and an INR of 2.2

Explanation:

In this case, reversal of the anticoagulant effect from the use of Warfarin would be best performed with Prothrombin Complex Concentrate (PCC) in case A above.

The patient with the traumatic brain injury does not require further transfusion of EITHER PCC or FFP to reduce the INR, as they will be ineffective in reducing the risk of complications from this procedure.

The patient is scenario 3 has ongoing blood loss that needs to be dealt with either surgically or angiographically to resolve the coagulopathy. Only AFTER this ongoing blood loss has been resolved will the FFP be effective in controlling his coagulopathy.

The female with septic shock does not require correction of her coagulopathy unless she requires an invasive procedure, in which case FFP would provide both reversal of the coagulopathy as well as volume, and so would be preferable in any case.

Prothrombin Complex Concentrates

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

Administration and monitoring

It should be given IV push at a rate not to exceed 10 ml/min
Rapid infusion may induce fever, chills, headaches, nausea and vomiting
Must be given in a dedicated line and not mixed with any other drugs or fluids.

Flush line with normal saline before and after infusion.
Reversal of INR typically occurs within 10 minutes of infusion. The INR may be checked at 30 minutes and dose repeated if needed.

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

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
Use 100 kg maximum weight if patient is >100 kg

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.

Safety

Use of this product has been associated with thrombosis and disseminated intravascular coagulation especially in patients undergoing surgery and in patients with known liver disease. Patients initiated on this product should be monitored for these complications

Cost considerations (Approx.)

FFP 4-8 units = $220-$440
Profilnine® SD (80 kg patient given 25 units/kg) = 2000 units = $1020
Recombinant factor VIIa (80 kg patient given 90 mcg/kg) = 7.2 mg = $7560

Q2. A 65 year old male who takes Pradaxa (Dabigatran) for his intermittent atrial fibrillation presents to your hospital with a large flank hematoma following a fall. A CT scan demonstrates extension of this hematoma into the retroperitoneum with evidence of active extravasation. How would you BEST reverse his anticoagulation?

A2.
1. Administration of weight-based dosed Prothrombin Complex Concentrate
2. Administration of Fresh Frozen Plasma
3. Administration of Activated Factor VIIa
4. Hemodialysis

Explanation:

Unfortunately, to date there are no known simple and effective ways to reverse the anticoagulant effects of the direct thrombin inhibitor, Dabigatran. Given that this new drug is being recommended as the agent of choice for nonvalvular atrial fibrillation, it is likely that surgeons are going to increasing come across patients who are taking this drug.

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. As best, FFP may replace some of the coagulation factors lost from the hemorrhage, but may not have any effects on reversing the anticoagulation associated with this medication.

Factor VIIa was shown in an animal (murine) model of anticoagulation to dramatically reduce the activated partial thromboplastin time (APTT). However, at this time, there is no human clinical data to support the use of recombinant factor VIIa to reverse Dabigatran in bleeding patients. Given its extremely high cost and questionable side-effect profile, it is difficult to recommend it until further study has been performed.

The manufacturers themselves in their package insert 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, and in the urgent but non-emergent scenario described above, would be the preferred option.

Q3. Which of the following is NOT a diagnostic criteria for heparin induced thrombocytopenia (HIT)?

A3.
1. History of exposure to low molecular weight heparin in the past week
2. A platelet drop of 60% within 2 days of starting heparin without prior exposure
3. A drop in the platelet count that starts 6 days after starting heparin
4. An acute thrombosis following heparin exposure with no previous history

Explanation:

There are many causes of thrombocytopenia in hospitalized patients, and it has been estimated that 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 sequalae is heparin induced thrombocytopenia. HIT is divided into 2 types: a benign, nonimmune mediated form (type I) and an immune-mediated form (type II).

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.

In contrast, 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-depen- dent antibodies that trigger platelet aggregation by binding to molecular complexes formed by platelet factor 4 (PF4) and heparin

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).

In the scenario given above, all are diagnostic of possible HIT except for a severe drop in the platelet count within such an early timeframe. This may be more related to DIC or sepsis. HIT can be screened for using the following scoring system below, and is confirmed by the presence of anti-PF4 antibodies, which are detected by an ELISA blood test.

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.

4Ts Category	2 Points	1 Point	0 Point
Thrombocytopenia	Platelet count falls >50% from baseline OR platelet nadir ≥10-19 x 10^9/L.	Platelet count falls 30-50% from baseline OR platelet nadir 10-19 x 10^9/L.	Platelet count falls < 30% from baseline OR platelet nadir < 10 x 10^9/L.
Timing of platelet count fall.	Clear onset between days 5 and 10 OR platelet count falls ≤1 day (Heparin exposure within 30 prior days)	Fall in platelet counts consistent with onset between days 5 and 10, but timing is not clear OR onset after day 10 of heparin exposure OR fall in platelet counts ≤1 day with prior heparin exposure between 30 and 100 days prior	Platelet count falls < 4 d without recent heparin exposure.
Thrombosis or other sequelae	New thrombosis, skin necrosis, or acute systemic reaction after unfractionated heparin exposure.	Progressive/recurrent thrombosis or unconfirmed but clinically suspected thrombosis.	No thrombosis or thrombosis preceding heparin exposure.
Other causes of thrombocytopenia	None apparent.	Possible other causes present.	Probable other causes present.

Adapted from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. J Thromb Haemost 2006;4:759 – 65.

The 4Ts score is assigned by summing the values for each of the 4 categories.

A score of 1, 2, or 3 is considered low clinical suspicion
4 or 5 is considered intermediate clinical suspicion; and

6,7, or 8 is considered high clinical suspicion.

Q4. A 64 year old female with a history of coronary artery disease and cardiac stents presents for consideration of an elective sigmoid colectomy for recurrent diverticulitis. She is also on anti-platelet therapy. Which of the following circumstances does NOT describe current recommendations regarding the appropriate interval before is it safe to operate on this patient?

A4.
1. 5 days following cessation of Clopidogrel (Plavix)
2. 7 days after cessation of ticlodipine therapy
3. 4 days after her last dose of full strength aspirin (i.e. 325mgs)
4. Immediately after reversal with platelets in any patient on Plavix or aspirin (if the patient described presents with acute perforation before her elective case was performed)

Explanation:

There is some controversy about the safety of operating on patients who have recently being receiving anti-platelet therapy. This is partly because of the anecdotal experience of surgeons operating on patients when the drug is supposed to have been metabolized, and experiencing excessive bleeding during surgery. According to the manufacturers, Clopidogrel has a half-life in the circulation of approximately 6 hours. It is metabolized by the liver and excreted in the urine and in feces. Leaving aside the issue of whether it is safe to stop this medication therapy, the current recommendations by the manufacturers (Sanofi-Aventis) are to hold Plavix for five days prior to elective surgery.

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.

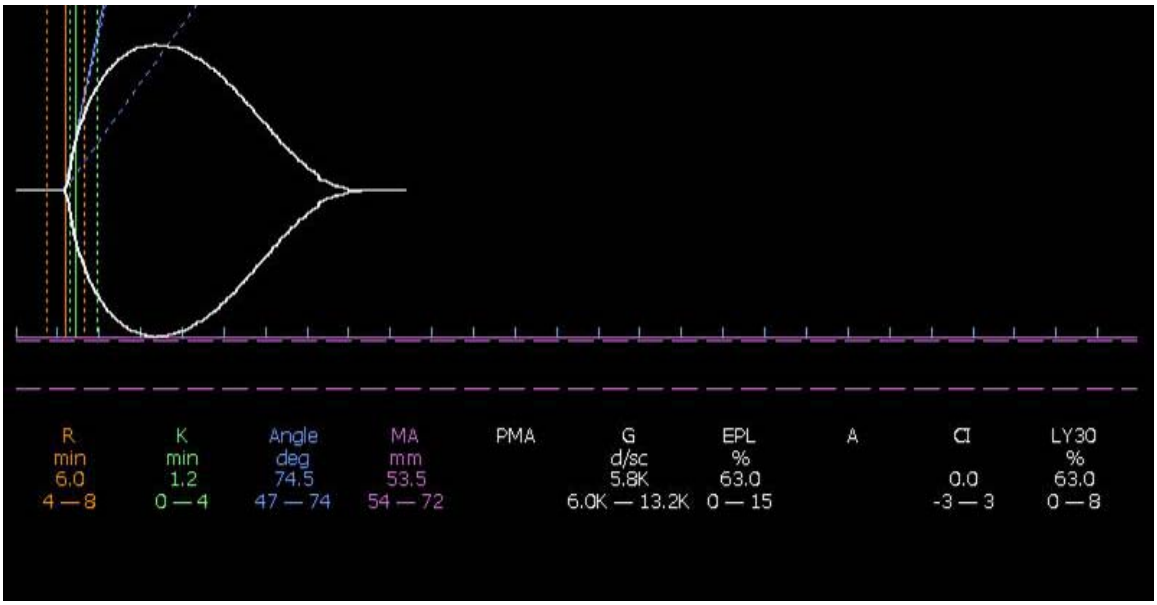
Current recommendations for Aspirin are less clear, but most authorities recommend that full strength aspirin should be held for a minimum of seven days prior to major abdominal surgery. The American College of Chest Physicians recommends 7 to 10 days in the latest version of its guidelines published in 2012. They also have similar recommendations for all the named antiplatelet drugs above.

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 DDAVOP, cryoprecipitate, and even Methylprednisolone.

In general the data for antiplatelet therapy is lacking and there is a difficult balance between decreasing the risk for surgical bleeding and increasing the risk of coronary

events. A full discussion should be had with the patient regarding the risks and benefits of each approach.

Q5. A 24 year old male motorcyclist is brought in after collision with a large truck. His primary survey is remarkable for absent pulses on the left lower extremity and a large open wound along the left thigh. The patient's systolic is 95 mmHg and his heart rate is 140. His CXR shows multiple right-sided rib fractures and a hemothorax, while his FAST is positive for fluid in the RUQ. A chest tube is placed and he is taken to the operating room for exploratory laparotomy and left lower angiography and exploration. The massive transfusion protocol is activated. Intra-operatively, diffuse oozing is noted despite anatomic control of hemorrhage. His TEG tracing is as follows:



The primary coagulation defect above should be treated immediately with:

A5.
1. Plasma transfusion
2. Cryoprecipitate transfusion
3. Aphaeresis platelet transfusion
4. Anti-fibrinolytic (tranexamic acid or aminocaproic acid)

Explanation:

The above tracing represents a hyperfibrinolytic state and should be treated immediately with an anti-fibrinolytic agent such as 1.0 g tranexamic acid or 5 g aminocaproic acid. Each of these boluses should be followed by a continuous infusion.

Values generated by TEG 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). Similar values are produced by another viscoelastic whole blood assay, rotational thromboelastometry (ROTEM).

Prolongation of the TEG's ACT and r-value reflect factor deficiency or severe hemodilution and are usually treated with plasma or factor concentrates). A prolonged k-time or a decreased alpha-angle has been shown to correlate with hypofibrinogenemia. This is usually addressed with cryoprecipitate or fibrinogen concentrates. Decreased maximal amplitude corresponds with platelet defects or decreased activity and may be treated with platelet transfusion. An increased LY30 is seen in cases of hyperfibrinolysis. This should be treated with amino-caproic acid or tranexamic acid.

Q6. Which of the following is true regarding the concept and literature of Damage Control Resuscitation (DCR):

A6.
1. There are several randomized trials to support the use of 1:1:1 (plasma:platelets:RBC) over lower ratios of products (1:1:2)
2. Survival bias is a theory that states that patients in hemorrhagic shock will live longer when they receive higher ratios of products
3. The three tenets of DCR are limited crystalloid-based resuscitation, higher plasma: RBC ratios, and earlier use of vasopressor support
4. Both civilian 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

Explanation:

The three tenets of DCR include permissive hypotension, limiting crystalloids and delivering higher ratios of plasma and platelets. To rapidly and effectively address these, institutions developed and implemented MT protocols. Unfortunately, all published studies to date have been non-randomized and most have been retrospective reviews based on changes in practice. While 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

Several authors have raised the argument that these results represent survival bias. 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. However, 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

Recent guidelines from both civilian and military groups recommend fluid restrictive strategies in the prehospital settings. These consensus panels advocate for the titration of small fluid boluses (250 mL) to achieve a palpable radial pulse palpable and normal mental status.