Massive Transfusion

Case 1

A 62 year old man with atrial fibrillation is brought by land transport to the emergency department after being struck while commuting to work 30 minutes ago. He has a medical bracelet stating he is on warfarin. He is intubated at the scene for a low GCS. He is hypotensive (systolic blood pressure 85 mmHg) and tachycardic (127 bpm). He has received 2 L of saline and 1 gram of tranexamic acid during transport to the trauma room (no RBCs). His abdomen is distended, he has a positive FAST and CT shows a ruptured spleen and an unstable pelvic fracture. Significant traumatic brain injury also suspected but CT shows no acute hemorrhage. The patient is being prepped for urgent laparotomy for splenectomy and pelvic fixation.

1. Which of the following is the first best intervention to support his coagulation?
   A) Administer 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate)
   B) **Administer 2000 IU of PCC**
   C) Initiate viscoelastic monitoring to guide any transfusion therapy
   D) Transfuse 4 units of plasma

   A) Fibrinogen concentrate is an important component in the management of the acute coagulopathy of trauma/shock. It is currently only administered in response to a low fibrinogen level as measured by the A10 FIBTEM on ROTEM (<8-10 mm) or lab based Clauss fibrinogen (<1.5-2.0 g/L). There is a study in the UK that has completed its enrollment (CRYOSTAT2; https://cryostat2.co.uk/) in which trauma patients have been randomized to 15 units of cryoprecipitate (irrespective of baseline fibrinogen level – approximately 6 grams of fibrinogen) vs. best supportive care. The trial is powered for mortality with a target of 1568 patients. Fibrinogen concentrate (FC) and cryoprecipitate can be used interchangeably (approx. 10 U (2 pools) of cryoprecipitate = 4 grams of FC). Early empiric transfusion of fibrinogen concentrate should be rarely applied given the lack of evidence from trials. The only exceptions are extreme post-partum hemorrhages, severe brain injury, post-cardiac arrest in the field, and the severest traumas when a delay in obtaining a baseline fibrinogen level could cause harm and the medical team can assume profound hypofibrinogemia and give a dose while waiting for the lab testing.
   B) Based on medical bracelet it should be assumed that the patient was anticoagulated with warfarin at time of injury, and correcting this immediately is the highest coagulation priority. Do not delay treatment waiting for the INR. Reversal of warfarin for bleeding with unknown INR is recommended by the Canadian National Advisory guidelines (2000 IU) and the British Society for Haematology (25-50 IU/kg; 1750-3500 IU). In this setting, prothrombin complex concentrates (PCCs) have been shown in RCTs to be safer (less congestive heart failure) and more effective/faster in achieving INR correction than plasma. As PCCs are lyophilized concentrates of factors 2, 7, 9, and 10, they cannot be relied upon to correct deficiencies of other factors, although whether these additional factors are required to achieve clinical hemostasis in other settings is the subject of ongoing study (e.g., the FiiRST-2 study of fibrinogen + PCC vs. plasma in severely bleeding trauma patients (n=350); FARES-2 study of plasma vs. PCC in cardiac surgery (n=750)).

C) Compared to traditional coagulation testing (platelet count, PT, aPTT, fibrinogen), viscoelastic test platforms such as TEG® and ROTEM® provide faster-turnaround time and capture of additional hemostatic processes such as a clot lysis. A cluster randomized trial in over 7000 cardiac surgery patients found viscoelastic testing to be superior to conventional clotting assays (TACS). In contrast, the iTACTIC study in trauma randomized 432 patients to TEG/ROTEM vs conventional assays and did not find a difference in patient outcomes (and TEG/ROTEM patients were almost twice as likely to get coagulation factor replacement) – the estimate of the difference in mortality was uncertain and larger trials will be required (absolute Risk Reduction 0·97 (95% CI 0·78 to 1·20).

D) Administering plasma <u>instead</u> of PCC for the reversal of warfarin in this situation would not be advised, for the following reasons: a) the likelihood that the patient has developed trauma-induced coagulopathy is less likely than the patient being therapeutically anticoagulated; b) even if the patient had developed an acute coagulopathy of trauma/shock, the patient still needs the warfarin reversed; and c) plasma takes longer to prepare, is slower to infuse and less reliable than PCCs in reversing warfarin; d) plasma is associated with higher rates of transfusion-associated circulatory overload (TACO). Clinical studies document a rate of 2-4% ATE/VTE event rate for either PCC or plasma reversal in emergency reversal. In this case, plasma may be also be required for the MHP; however reversing warfarin first with PCC is the priority. Once PCC is administered draw a repeat INR and fibrinogen and administer plasma/fibrinogen replacement thereafter for coagulation support.

2. The first gram of tranexamic acid was administered as push during land transport, but the second gram was not administered, as per the CRASH-2 dosing protocol. It is now two hours after the initial trauma occurred and the patient is about to be taken to the OR. The best approach to giving additional tranexamic acid in this situation is:
   A) Bolus the 2nd gram now
   B) Measure the fibrinogen level and if <1.0 g/L administer the 2nd gram of TXA
   C) Order viscoelastic testing and only administer if there is excessive lysis at 30 minutes
   D) Order D-dimers and only administer if the levels are above the normal range.

   A) Although the CRASH-2 protocol for tranexamic acid was a 1 gram bolus over 10 minutes followed immediately by a 2nd gram over 8 hours (ie, injected into 1 L of NS and run at 125 mg/hr), the logistics of starting an infusion are considerable (additional line/pump, delay to administer until pump can be set up) and often means that the 2nd dose is missed. The ROC-TXA (traumatic brain injury), MATTERS (military trauma), WOMAN (postpartum hemorrhage) and STAAMP TXA (pre-hospital TXA) trials all used bolus infusions (indeed the ROC-TXA 2 gram arm received 2 grams as a bolus infusion "wide open". The ROC-TXA trial confirms the 2 gram bolus is as good or better than the 1+1 infusion. The Ontario provincial MHP plan recommends administering tranexamic acid a total dose of 2 g within 3 hours of injury, with the target to administer the dose within 60 minutes of injury/onset of hemorrhage. When TXA was given between 3-8 hours after injury, there was no difference in the overall mortality rate, but there was an increase in the proportion of patients dying from hemorrhagic complications (vs. other kinds of deaths). Similarly, there was no benefit in the WOMAN trial if TXA was given past 3 hours. The reason for these observations is not clear but one hypothesis has to do with tPA vs. uPA effects. tPA peaks in the first 3 hours and is nicely inhibited by tranexamic acid. In contrast, uPA (urokinase PA) peaks at 8 hours and is actually potentiated by tranexamic acid, thereby worsening fibrinolysis and clot breakdown. This

would be especially problematic in patients who are still at risk of bleeding (eg., following a traumatic brain injury). Therefore it is important not to initiate tranexamic acid more than 3 hours after time of injury. There were no increases in ATE/VTE events in TXA trials, with the exception of HALT-IT. Clinical trials in both cardiac and non-cardiac surgery do not document any increased risk of ATE/VTE, even in ASA class III/IV patients with arterial/venous thromboembolic history. In the setting of gastrointestinal hemorrhage (HALT-IT), administration of this medication as a 1 gram bolus followed by a 24-hour, 3 gram infusion did not result in decreased mortality or bleeding, but did increase the risk of thrombosis and seizures. Possible explanations include the higher dose used, and the high prevalence of cirrhosis in the study population, a condition associated with baseline impairment of fibrinolysis. Hence, tranexamic acid should therefore be avoided in the setting of acute gastrointestinal bleeding. Notably, while some physicians withhold tranexamic acid in the setting of ureteral or intracerebral bleeding due to fear of inducing an obstructive clot, available evidence from clinical trials suggests this concern is not justified, particularly in patients experiencing traumatic hemorrhage, for whom this medication has been shown to be life-saving.

B) Exploratory analysis of the CRASH-2 trial showed no difference in outcome for patients regardless of the type of injury suffered or their presenting blood pressure or GCS score: the only variable of significance was the time taken to administer tranexamic acid, with earlier treatment (particularly if given within 1 hour) associated with superior outcomes. Prospective studies of blunt trauma, by contrast, have shown that less than 10% of patients will present with a fibrinogen level less than 1.5 g/L (Hagemo, Crit Care. 2014 Mar 26;18(2):R52). Waiting for a fibrinogen level of < 1.0 g/L before administering tranexamic acid will therefore likely result in both under- and delayed treatment, both of which are known to result in worse clinical outcomes. Therefore, it is much more important to give all trauma patients with bleeding and hemodynamic instability tranexamic immediately rather than delay treatment waiting for laboratory investigations. Some studies have advocated for withholding TXA unless the D-Dimer is positive or there is clot lysis on ROTEM – this strategy is not appropriate based on data from the ROC-TXA study (Dixon AL, et al. Tranexamic acid administration in the field does not affect admission thromboelastography after traumatic brain injury. J Trauma Acute Care Surg. 2020 Nov;89(5):900-907). These tests are insufficiently specific to select a population where TXA can be withheld.

C) See (B)

D) See (B)

3. Which of the following has been shown to increase appropriate plasma utilization during an MHP?

A) Early MHP activation for acute gastrointestinal bleeding

B) Requiring the transfusion of 4 units of red blood cells before a multicomponent MHP cooler is issued

C) Reserving plasma transfusion for patients with a Shock Index (SI) score > 1 or Assessment of Blood Consumption (ABC) score > 2

D) Use of a 1:1:1 ratio-based protocol

A) Coagulopathy is relatively uncommon in GI bleeds; in the TRIGGER trial of liberal vs restrictive transfusion practices, only 4-6% of patients were noted to require plasma, platelets, or cryoprecipitate (UK study). Patients with cirrhosis are more likely to have prolonged laboratory tests of coagulation at baseline, but it is unclear whether this in fact represents impaired hemostasis, and clinical trials in patients with variceal bleeding

have suggested that aggressive fluid administration may in fact worsen hemorrhage. Thus, plasma transfusions are likely unnecessary in the majority of GI bleeds. Until additional clinical trials are performed, plasma should only be transfused to patients with an INR>1.8 from liver disease and active GI bleeding that cannot be controlled through endoscopic therapy (injection/banding).

B) Many cases of MHP represent over-triage, with hemostasis achieved relatively quickly through surgical intervention. Issuing plasma for all traumas therefore results in a high-likelihood that the plasma will be transfused unnecessarily or go unutilized and therefore wasted on return to the blood bank. In one study, leading with 2-4 units of RBCs before activating the MHP results in a lower rate of MHP activation and in a higher likelihood that plasma would be provided to patients who truly needed it (eg., experienced 24 hr blood loss exceeding 10 units of RBCs) and as a result less plasma was returned unused (Boutefnouchet T et al. Injury 2015; 46: 1772). Re-emphasize that you do not need to activate the MHP just to get uncrossmatched RBCs.

C) While elevated SI (HR/BP) or ABC scores are moderately specific for predicting which patients will require massive transfusion support, neither is very sensitive. In one study, an SI ≥ 1 had 68% sensitivity and 81% specificity, while ABC ≥ 2 was 47% sensitive and 90% specific (Schroll R et al, Injury 2018 Jan;49(1):15-19). While these scores may be useful for confirming a trauma patient is likely to require massive transfusion support, they are less reliable to rule out the need for an MHP. Using these scores to determine when to begin thawing plasma is therefore not advisable. Unfortunately, there is no MHP activation tool currently validated to have both high sensitivity and specificity.

D) While issuing blood components in a ratio approximating whole blood (eg., for every 4 units of RBCS, transfusing 4 units of plasma and a therapeutic dose of platelets equivalent to 4 pooled whole blood-derived donors ie., "1:1:1") appeared to result in improved patient outcomes in retrospective studies of trauma patients, the PROPPR RCT showed equivalent patient outcomes when the dose of plasma and platelets is proportionately reduced by half ("2:1:1"). This would suggest that relying upon a 1:1:1 ratio in managing trauma patients (and likely other massively bleeding patient populations) results in unnecessary plasma transfusion, the bulk of which will be rare blood group AB plasma which is in chronic short supply (PROPPR trial, Holcomb, JAMA 2015; 313: 471-482).

4. When managing a massively bleeding patient, the most important laboratory test to collect is:
   A) Activated partial thromboplastin time (aPTT)
   B) **Blood group and antibody screen**
   C) Fibrinogen level
   D) Hemoglobin level

   A) The aPTT is of value in identifying patients with undiagnosed hemophilia or those taking unfractionated heparin or dabigatran; treating these conditions with factor concentrates, protamine and idarucizumab, respectively, would be an important means of achieving hemostasis and thereby decreasing transfusion requirements. However, the likelihood of patients presenting with these conditions without also having any accompanying medical history is rare, and probably less common than the chance of detecting a lupus anticoagulant, which can increase the aPTT without increasing the risk of bleeding (these are therefore often considered nuisance laboratory artefacts). The aPTT is in fact so seldom useful in the management of massively bleeding patients that MHPs no longer recommend drawing it routinely if the initial aPTT is non-informative,

and have uncoupled it from the PT/INR. If the first INR and PTT are concordant (similar level of derangement), then only the INR is needed hourly to assess for the need to transfuse more plasma.

B) The most important laboratory test to prevent inappropriate use of group O blood and AB plasma is the blood group and antibody screen; without these results, many patients will needlessly be given multiple units of group O RBCs and AB plasma, and after a certain threshold it may become impossible to accurately determine the patient's blood group, meaning they will be locked into the use of universal donor/difficult to source blood components for their intensive care stay. In addition, they cannot be an organ donor if they do not survive. Moreover, in blood banks without electronic crossmatching, patient plasma is required to perform the crossmatch, and the amount of plasma present in one sample is usually sufficient for only 4-6 crossmatched RBCs. Once this is exhausted, unless a new sample can be obtained, blood banks will revert back to uncrossmatched blood. In hospitals with electronic crossmatching, confirming a patient's blood group with a second sample is advisable because it will speed up the provision of crossmatched RBCs (unless ePPID is used and the first sample can be tested twice). It is for these reasons that the timely collection of a group and screen is widely considered an important quality metric in MHP activations. New standards worldwide require a second blood group confirmation before switching to group specific RBCs. If the RBCs keep coming as group O and the plasma AB, call the blood bank and ask if they need a sample.

C) A fibrinogen level must be ordered for significant trauma, obstetrical and cardiac/vascular surgery related hemorrhages. Fibrinogen should also be measured if the patient's hemorrhage requires the transfusion of more than 4-6 units of RBCs irrespective of the cause of hemorrhage. However, it must also be appreciated that the patient's INR will not climb above the usual transfusion threshold of 1.8 until the fibrinogen is less than 0.75 g/L. Thus, even if the patient's fibrinogen is below the recommended threshold of 1.5 g/L, unless it has fallen all the way to 0.7 g/L or less, an elevated INR may actually reflect a global deficiency in coagulation factors rather than an isolated deficiency of fibrinogen. The current guidelines for trauma recommend against giving plasma as the source for fibrinogen replacement (Spahn et al. Crit Care. 2019 Mar 27;23(1):98).

D) While most MHPs recommend a hemoglobin range (e.g., between 60-110 g/L or 80-120 g/L or >70 g/L) in the presence of active bleeding, it is the rate of bleeding/hemodynamics rather than just the measured hemoglobin level that should be used to determine when an MHP should be activated and when RBCs should be transfused. A trauma paper found both under (<80) and over transfusion (>120) associated with increased mortality and hence the importance for performing hourly hemoglobin levels to keep the hemoglobin in a safe range throughout resuscitation (Zielinski MD, Wilson GA, Johnson PM, et al. Ideal hemoglobin transfusion target for resuscitation of massive-transfusion patients. Surgery 2016;160:1560-7). In contrast in gastrointestinal hemorrhage, a restrictive threshold (70-90 g/L) reduces mortality (Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. N Engl J Med 2013;368:11-21). Frequent hemoglobin measurements provide a gauge as to under and over resuscitation and should be performed at least every hour or every 4 units of RBCs during a MHP. Often a patient is noted to have persistent hypotension and a rising hemoglobin level which is often a clue that the hypotension is not from hypovolemia (e.g., spinal shock, cardiac tamponade).

Case 2

A 37 year old G3P2 is post-vaginal delivery of an uncomplicated pregnancy. Her hemoglobin was 102 g/L and her MCV was 74 pre-delivery. The nurse pages you because her HR has increased to 120 from 85 bpm, sBP dropped from 110 to 85 mmHg, and she has just passed a huge amount of blood per vagina approximately 1 hour post-partum. The patient is disoriented and is difficult to rouse.

5. Which of the following is <u>NOT</u> thought to contribute to post-partum hemorrhage?
   A) Congenital coagulation factor deficiency
   B) **Deficiency of vitamin K-dependent coagulation factors**
   C) Retained placenta
   D) Uterine atony

   A) Post-partum hemorrhages caused by coagulation factor deficiencies occur in 0.3 to 0.6/1000 pregnancies in Canada, or approximately 5% of post-partum hemorrhages (PPH). While not the most common cause, PPH due to coagulation factor deficiencies appears to be increasing in severity, with an increasingly large proportion requiring transfusion support and hysterectomy (Mehrabadi A, J Obstet Gynaecol Can. 2014 Jan;36(1):21-33). Careful history taking to identify at-risk women is therefore advised. Note that von Willebrand's Disease, a common cause of post-partum bleeding in women with congenital coagulation factor deficiency, presents with a normal platelet count, aPTT and PT/INR.

   B) Warfarin, like all oral anticoagulants, is contraindicated in pregnancy and is therefore very unlikely to be a factor in post-partum hemorrhage. While vitamin K deficiency is a significant concern in newborns (with supplementation therefore advised to decrease the risk of intracranial hemorrhage), this is thought to represent inadequate absorption from maternal stores during pregnancy or breast feeding; vitamin K deficiency in the mothers themselves is very rare. Vitamin K is often administered in acute hemorrhage and/or trauma to "correct" an INR – this is not indicated – vitamin K deficiency from being NPO after trauma takes days to present with an elevated INR.

   C) A retained placenta is a significant cause of post-partum hemorrhage during the third stage of labour. While a careful attempt at manual delivery may be made, great care should be taken in the setting of placental anomalies. In these cases, attempts at manual placenta removal should be abandoned if a cleavage plane cannot be obtained; in the setting of massive bleeding, it may be preferable to perform an urgent hysterectomy. A significant cause of PPH mortality is the ill-advised attempts to salvage the uterus at the expense of the patient. If after 4-6 units of RBCs have been transfused, there is continued bleeding, hemodynamic instability, and no sign of hemorrhage control with uterine sparing interventions, a hysterectomy is advised. Do not wait for 10-20 units to be transfused to consider hysterectomy – the patient may develop a life-threatening coagulopathy that may become difficult to reverse.

   D) Uterine atony refers to inadequate contraction of the uterus following delivery and typically presents as a post-partum hemorrhage within the first 24 hour. A higher incidence has been noted in in patients with prolonged labor, overdistention of the uterus (eg., macrosomia, twin pregnancy, multiple previous pregnancies, polyhydramnios), and age > 35 for first pregnancy (aka elderly primigravida). Induced or general anesthetic during labour may also increase risk. PPH is becoming more frequent over time and the reason is unclear. Uterine atony is the most common cause of post-partum hemorrhage, and the incidence is increasing worldwide. Other risk factors for PPH include prolonged labour, multiple pregnancy, higher parity, uterine atony, uterine

rupture, vaginal tear, congenital bleeding disorders, antidepressant therapy (specifically SSRIs, which can induce platelet dysfunction), iron deficiency, obesity, older age, C-section, and prior PPH. While oxytocin is an important treatment for PPH (and is advised prophylactically during the induction of anterior shoulder presentations) it may lose its efficacy if administered for prolonged periods during induction.

6. Recent small clinical trials have suggested that replacing clotting factors with a combination of a coagulation factor concentrates may be an alternative strategy. If a decision was made to use prothrombin complex concentrates instead of plasma (e.g., due to unavailability at the local hospital due to smaller hospital size) for the management of post-partum hemorrhage, which of the following would be the most important additional factor concentrate to add?
   A) Factor XIII
   B) Fibrinogen
   C) Recombinant activated factor VII
   D) Von Willebrand Factor

   A) Factor XIII is an important co-factor for clot stabilization, but both acquired and congenital deficiencies are very rare and usually manifest as delayed onset bleeding following surgical intervention. In the absence of clinical trials showing benefit of achieving superphysiologic FXIII levels there is no justification for empiric treatment. A large randomized clinical trial in cardiac surgery found no benefit to administering FXIII to bleeding patients with adequate factor XIII levels.
   B) Fibrinogen levels have been shown to correlate with the incidence and severity of PPH. Although small and methodologically challenged clinical trials (required written informed consent from PPH patients) have not shown benefit of pre-emptive fibrinogen in patients with PPH and normal fibrinogen levels at baseline, the susceptibility of PPH patients to develop severe hypofibrinogenemia during the course of PPH (both through dilution and increased consumption via amniotic fluid embolism) justifies its early empiric use, particularly if a decision is made to replace plasma with PCC. If the patient is hemorrhaging and the fibrinogen is below 1.5-2.0 g/L fibrinogen replacement is advised.
   C) Recombinant activated factor VII has not been shown to improve outcomes in the management of PPH, and given the cost and risk of thrombosis associated with this product there is no justification for administering it in all but the most exceptional cases (eg., patients with congenital factor VII deficiency or factor VIII deficiency with an inhibitor).
   D) While deficiency in vWF is an important consideration when investigating the cause of PPH, the prevalence is not high enough to justify empirical replacement in all patients. However, patients with PPH and a high score on a validated bleeding assessment tool should be brought back at 3-6 months postpartum for screening for vWD.

7. Which of the following statements regarding the management of post-partum hemorrhage is true?
   A. Fibrinogen concentrates increase the risk of thromboembolic complications compared to cryoprecipitate
   B. Once it occurs, initiation of rapid transfusion support is more important than attempting source control
   C. The main risk of using recombinant factor VIIa is thromboembolic events
   D. Tranexamic acid is still of benefit when given more than three hours after onset of bleeding

A) A large randomized trial comparing cryoprecipitate to fibrinogen concentrates in cardiac surgery (FIBRES; n=827) found a trend towards more thrombotic events in patients administered cryoprecipitate that did not reach statistical significance. A smaller RCT in patients undergoing abdominal surgery for cancer in the UK found a statistically higher rate of thrombosis with cryoprecipitate when compared to fibrinogen concentrate. In a retrospective analysis of the patients in the PROPPR trial, patients administered cryoprecipitate (in adjusted analysis) were more likely to experience thrombotic events. The CRYOSTAT-2 trial is complete and may shed further light on the risk of thrombosis with cryoprecipitate (Cryo 15 units vs. standard of care in trauma).

B) While post-partum hemorrhage is a significant contributor to maternal mortality (1:150 cases result in death), the great majority can be managed without blood transfusion. While the incidence of PPH is high (estimated at 5% of deliveries and growing), only 0.6% of vaginal deliveries require transfusion support, and only 1:1000 deliveries require 4 or more units of RBCs. Therefore, not every post-partum hemorrhage requires activation of a MHP, and attempts at source control (eg., uterotonic drugs such as hemabate, ergot, miso, or oxytocin) should always be the first-line treatment. Even when RBC transfusion is necessary, it is often not necessary to transfuse hemostatic blood components such as plasma, platelets and fibrinogen concentrate (or cryoprecipitate) – while having these products prepared is a reasonable precaution in patients with major obstetrical bleeds, they do not necessarily need to be transfused just because they are available. Communication with the blood bank (so that 4 units of RBCs are available at all times, uncrossmatched if necessary) and the coagulation lab (so that samples are processed quickly) are very important in maintaining a state of readiness should bleeding worsen. Even in cases of more significant bleeding requiring hemostatic blood components, attempting source control through the use of balloon tamponade, arterial embolization or hysterectomy should not be delayed. The uterus has a huge arterial blood supply and a woman can lose her entire blood volume through the placental bed in 7 minutes: never let a patient bleed to death in an attempt to salvage her uterus. A bleeding protocol for the prevention, early identification and treatment should be implemented at every hospital with obstetrical patients (e.g., California hemorrhage protocol: Improving Health Care Response to Obstetric Hemorrhage Toolkit, Version 3.0 | California Maternal Quality Care Collaborative (cmqcc.org))

C) Recombinant factor VIIa is unproven in the management of refractory postpartum bleeding. A recent, small, unblinded study found a reduction in need for hysterectomy (7 vs. 19%) with an increased risk of thromboembolic complications (5 vs 0%). Minimal differences in bleeding outcomes were observed. The authors recommended blinded trials before use outside of a clinical trial because of the limitations of the study and the significant thrombotic risk. The dose in this report was 60 ug/kg or about 3-5 mg per dose for an average sized woman. Note that in Phase III RCT of rVIIa in severe trauma, $28 000 worth of the drug did not result in any mortality or morbidity benefit aside from decrease in blood products use (esp plasma), likely secondary to the misleading effect of rVIIa on the INR. The trial was stopped early following futility analysis. Multiple systematic reviews have failed to confirm a mortality benefit for treatment and prevention of bleeding, and clear risk of thrombotic events, albeit, the increased risk was noted to be statistically significant in the group age ≥ 65.

D) Tranexamic acid (1 gram and then 1 gram in 0.5-1 hour if still bleeding or starts to re-bleed in first 24 hours) has been shown to be effective in reducing hemorrhagic deaths in women with post-partum hemorrhage, but the effect in the WOMAN trial was relatively small (NNT = 250) and while safe there was no effect observed on overall mortality rate or need for hysterectomy (primarily because the majority of women enrolled in the trial were in low and medium HDI countries where hysterectomy is the first line treatment of bleeding as transfusion of blood is often not available). There was no apparent benefit when the drug

was administered more than 3 hours after onset of bleeding. Thus, while tranexamic acid should be considered standard of care in any woman losing more than 500 mL of RBCs following vaginal delivery (or 1000 mL following C-section), there is no point in giving it more than 3 hours after onset of bleeding.

Case 3

A 24 year old woman is on route to the trauma room direct from the scene by helicopter transport. She was a passenger on a motorcycle involved in a motor vehicle collision. The driver was pronounced dead at the scene. She is expected to arrive in under 15 minutes. You are told she has head, thoracic and orthopedic injuries. She was thrown approximately 25 metres. You are told she is tachycardic and hypotensive despite 2L balanced crystalloid administered by air ambulance.

8. Which of the following normal practices can be waived in the setting of massive blood loss?
   A) Attachment of patient wristband with unique identifiers
   B) Careful inversion of laboratory specimen test-tubes prior to delivery to the lab
   C) Advanced directives prohibiting the use of blood transfusion (eg., Jehovah's Witnesses)
   D) Matching for patient antibodies against non-ABO/RhD blood group antigens

   A) Attachment of patient identifiers linking the patient with the blood product they are issued must never be skipped, even in the setting of massive blood loss – maintaining product traceability in the event of transfusion-transmitted injury such as an infection or a case of acute lung injury will be very important both for the protection of the patient and the management of other patients potentially exposed to the same blood donor. In the setting of polytrauma, maintaining airtight positive patient identification is even more important so as to avoid accidental ABO-incompatible blood transfusion. If the patient's name is unknown or there is no time to register them and assign them a unique hospital identifier, it is still important to attach a wristband with an anonymous unique identifier; hospitals are advised to have these prepared in advance along with matching specimen labels, and they should not be removed, nor should the name be changed, until the patient has stabilized, even if the patient's actual identity is determined before then. Name changes during massive resuscitation will result in delays in processing samples in the lab and providing blood from the blood bank.
   B) Careful inversion of laboratory specimen tubes (so as to ensure adequate mixing with the tube anticoagulant) is often skipped in the chaos of resuscitating a massively bleeding patient but failure to do so increases the risk of specimen clotting, which means the intended test cannot be performed and a specimen re-draw will therefore be necessary: ultimately, this means more delay in patient care than taking the time to collect the specimen properly in the first place.
   C) Disregarding advanced directives prohibiting the transfusion of blood products is never permissible in adults. Failure to abide by these instructions, even if the alternative is likely death, may be considered assault and subject to prosecution as such. Instead, all attempts should be made to support the adult patient without transfusions, to the extent this is feasible and allowed as per the patient's particular beliefs. Options include the use of coagulation factor concentrates (e.g. fibrinogen concentrate and PCCs if patient consents) rather than plasma, intra-operative cell-salvage, antifibrinolytics, and more aggressive attempts at surgical hemostasis (eg., amputation) than might otherwise be pursued. The use of erythropoietin and IV iron is unlikely to have any immediate benefit but may decrease downstream transfusion requirements if the patient survives into the critical care unit.

D) Provision of antigen negative blood to patients with antibodies should always be attempted but can be abandoned in patients with massive blood loss if it will result in a delay in the provision of blood products and/or patient harm. This is due to the fact that much of blood transfused will be bled out anyway, and even when retained will likely only trigger a more mild hemolytic transfusion reaction than is seen with ABO-incompatible transfusion, usually with delayed onset. Close communication between the clinical team and the blood bank is critically important when managing a massively hemorrhaging patient

The patient survives initial damage control resuscitation efforts and is brought to the OR, where she becomes progressively more stable after her spleen is removed and the pelvis packed. She has been transfused a total of 8 units of RBCs, 4 units of plasma, 2 platelet pools and 4 grams of fibrinogen concentrate. Her most recent labs show: hemoglobin 82 g/L, INR 1.9, platelet count 65, and fibrinogen 2.1.

9. What secondary complications should you watch for in a massively transfused patient?
    A. Hypercalcemia
    B. Hypokalemia
    C. Hypothermia
    D. Seizures

A) Citrate anticoagulant added to blood components may result in *hypo*calcemia and hypomagnesemia, both of which may result in hypotension due to impaired myocardial contractility, cardiac arrhythmias, and vasodilation. Risk of citrate toxicity increases if > 30 mL/kg of blood products (eg., 4u FFP) infused per hour. Even slower infusion rates may still be dangerous if inadequate hepatocellular function or perfusion. Measuring ionized calcium hourly with the MHP bloodwork is critical. Administer 1 g of CaCl IV if ionized calcium <1.15 mmol/L. Similar dose of MgS04 should also be considered, esp if increased QTc. *Hyper*calcemia is not a recognized transfusion complication.

B) As 1 unit of RBCs contains 1 mEq of K+ per day of storage, transfusion-associated *hyper*kalemia may occur in the setting of massive transfusion and may result in life-threatening cardiac arrhythmias. This is a particular concern in pediatric patients and those with renal impairment. While *hypo*kalemia is seen not infrequently in massive blood loss, it is thought to represent the effects of the metabolic alkalosis and epinephrine surges that accompany intravascular volume contraction rather than an actual complication of massive transfusion per se.

C) Most enzymes (including coagulation factors) lose 10% activity with every 1ºC decrease in temperature; platelet function also impaired by hypothermia. Surgical core temperature of even just 34-36ºC has been associated with 16% increase in blood loss, and core temperature may not reflect temperature at bleeding surfaces. Effect of hypothermia is not detectable in standard coagulation tests as samples are warmed in the laboratory to 37ºC prior to testing. In addition to hypothermia from prolonged exposure and immobility, transfused blood products can also lower temperature: 5 units of unwarmed RBCs (4ºC) will reduce the temperature of a 70 kg patient by 1ºC. Plasma thawed immediately prior to issue will have temp close to 37ºC but previously thawed plasma must be stored at 4ºC to mitigate coagulation factor loss and may therefore also lower patient temperature. Infusion of fluids through blood warmer is therefore advised, as well as active rewarming techniques (resistive warming blankets, increase ambient temp to 28C, and in severe cases, bladder irrigation with warm fluids, even ECLS circuit) if temp falls below 36ºC.

D) Other adverse transfusion reactions include: TRALI, ALI, allergic reactions, bradykinin mediated hypotension, TACO and abdominal compartment syndrome; TRIM during ICU phase (infections). Seizures are a known side effect of higher doses of tranexamic acid rather than transfusion, and even then is only observed with the very high doses commonly used in cardiac surgery (eg., boluses of 50 mg/kg or higher) or gastrointestinal bleeding (4 grams within a 24 hour period). The increased risk of seizures is thought to be due to 1) disruption of the blood brain barrier with cardiac surgery; and 2) TXA being structurally similar to the inhibitory neurotransmitter glycine. Since reduced glycine lowers the seizure threshold, it is thought this is the pathway causing this complication.

The patient survives to the ICU phase of care. She is still requiring boluses and inotropes for fluid resuscitation. Her most concerning ongoing issue is her traumatic brain injury. There is no obvious ongoing blood loss. Blood work shows all metrics are within target range, including hemoglobin at 98 g/L. Her lactate is still high at 8, although this is down from 12. Her pH has also improved from 7.10 to 7.33.

10. Given her ongoing need for fluid boluses and inotropes, what is the role of intravenous albumin for her resuscitation?
    A. Albumin increases the mortality rate, compared to saline, in trauma patients and therefore is contraindicated.
    B. Albumin should be administered for critical hypoalbuminemia (<20)
    C. Resuscitation with albumin should be started after 2 L of crystalloid
    D. **There is no role for albumin in the resuscitation of hypovolemic trauma patients**

A) The SAFE study clearly showed there was no difference in mortality from using albumin instead of normal saline in the volume resuscitation of critically ill patients, and this included subgroup analyses of patients with trauma-related injuries or hypoalbuminemia. In fact, albumin use in this study was associated with slightly higher RBC transfusion requirements. Additional sub-studies of the SAFE study in TBI show a concern for higher mortality rates with intravenous albumin (hypothesized to be from increasing intracranial pressure).

B) Intravenous albumin for hypoalbuminemia has been studied in children in the intensive care unit, cirrhotic patients admitted with decompensated cirrhosis, and patients undergoing liver resection. There is no evidence for improvement in patient important outcomes, and the studies in cirrhotic patients show increased rates of congestive heart failure.

C) This is a common "teaching pearl" that one must restrict the volume of crystalloid infused and switch to albumin infusions. This is a common practice but is not based in any evidence base. The large RCTs (SAFE, ALBIOS, FEAST, etc) inform us that we should be "leading" our resuscitation with crystalloids (2021 Surviving Sepsis Campaign Guideline) and using albumin restrictively for patients failing crystalloids and inotropic support.

D) Subgroup analyses from SAFE suggest possible higher mortality rates and higher ICP measures when albumin is transfused. Albumin use should be avoided as much as possible in the setting of trauma.