**Seminar Day 4, March 25, 1430-1600**
**Transfusion Camp**
**Advanced Hemostasis and Testing - Dr. Eric Tseng**

---

**Please start by reviewing any questions that trainees may have from the preceding lectures.**

**Case 1**

A 65 year old male is in the preoperative clinic in preparation for surgery for a radical prostatectomy. He had an idiopathic DVT 1 year ago, requires extended duration anticoagulation and is taking Rivaroxaban 20 mg daily. He has hypertension, mild renal insufficiency (baseline creatinine of 115 umol/L) secondary to hypertension and has hepatic dysfunction secondary to NASH. His weight is 75 kg.

1. Which one of the following is the recommended strategy for pre-operative management of her anticoagulation?

   A. Discontinue Rivaroxaban last dose 5 days pre-op, bridge with heparin
   B. Discontinue Rivaroxaban last dose 4 days pre-op, no bridging needed
   **C. Discontinue Rivaroxaban last dose 3 days pre-op, no bridging needed**
   D. Discontinue Rivaroxaban last dose 2 days pre-op, no bridging needed

   Rivaroxaban is a direct inhibitor of factor Xa. Its peak action is 1 to 3 hours and 33% is renally cleared (Table). Based on the provided age, weight, and creatinine his Cockcroft-Gault creatinine clearance is 60 ml/min.

| Creatinine Clearance (ml/min) | Half-Life (hours) |
|---|---|
| >80 | 8 |
| 50-79 | 9 |
| 30-49 | 9 |
| <30* | 7-11 |

*Rivaraxoban is not recommended for patients with a creatinine clearance < 30 ml/min

   All patients who are receiving an anticoagulant and undergoing surgery should be stratified according to their risk of bleeding-*low risk* e.g. cardiac catheterization, cardiac ablation, colonoscopy without removal of large polyps, and uncomplicated laparoscopic procedures, such as cholecystectomy vs. *high risk* e.g. cardiac surgery, neurosurgery, large hernia surgery, and major cancer/urologic/vascular surgery, neuraxial anesthesia.

   **Prompt:** What if the patient was undergoing low risk surgery? When should the rivaroxaban be stopped?

Because of its short half-life, for patients who are having surgery that is low risk, discontinuation with last dose 2 days before surgery (e.g. skip 1 dose) is adequate assuming creatinine clearance > 30 mL/min. For surgeries with higher risk of bleeding rivaroxaban should be discontinued with last dose 3 days before surgery assuming creatinine clearance > 30 mL/min.

**Prompt:** What if the patient had a decreased creatinine clearance (e.g. ~ 30 mL/min)?

If the creatinine clearance has decreased to < 30 ml/min, rivaroxaban should be discontinued at least 2 days prior to low risk procedures and 4 days prior to high risk procedures. See Thrombosis Canada Guidelines: NOACs/DOACs: Perioperative management.

Because rivaroxaban has a short half-life, bridging with other anticoagulants such as heparin is not required.

2. The patient's surgery is uneventful, with minimal intra-operative blood loss. He has achieved hemostasis. Which one of the following is the recommended strategy for post-operative anticoagulation in this patient?

    A. Give no anticoagulation on day 1 post-op, then resume Rivaroxaban at usual therapeutic dose (20 mg) on day 2 post op if no evidence of bleeding
    B. **Give prophylactic dose Rivaroxaban (10 mg) on on day 1 post-op, then resume Rivaroxaban at usual therapeutic dose (20 mg) on day 2**
    C. Give Rivaroxaban 10 mg daily for 14 days post-op, then resume usual therapeutic dose (20 mg) afterwards
    D. Give IV heparin for 24-48 hours after the surgery and resume therapeutic dose Rivaroxaban after bleeding risk subsides

Postoperatively, the resumption of rivaroxaban depends on the risk of bleeding. Resumption should be delayed until there is no evidence of active bleeding. For major abdominal surgery or urologic surgery where hemostasis has not been completely achieved, rivaroxaban should be delayed until there is no drainage or active bleeding. For procedures with good hemostasis, prophylactic anticoagulation can be restarted 4 to 6 hours after surgery with a reduced dose of 10-mg dose followed by a therapeutic dose on day 2 or 3. Patients unable to take oral medication may require bridging with parenteral anticoagulants until the oral route is available. Thrombosis Canada suggests starting 2 days postoperatively with major surgery.

3. 72 hours after surgery, you are called as it has been discovered that a medical error has occurred. Your patient has received Rivaroxaban 20 mg BID for two days, instead of the usual 20 mg once daily dose. The PT is 20 seconds (9.7-11.8 s) and APTT is 45 seconds (20-32). Which one of the following is an appropriate management plan?

    A. Assess patient and order CBC, creatinine, determine the creatinine clearance. If no evidence of bleeding no need for any change in management
    **B. Assess patient and order CBC, creatinine, determine the creatinine clearance. If no evidence of bleeding hold rivaroxaban for 24 hours and then resume**
    C. Assess patient and order anti-Xa level. If supratherapeutic anti-Xa level, hold rivaroxaban for 24 hours
    D. Give prothrombin complex concentrate

    All patients who are suspected to have supratherapeutic levels of DOAC or have DOAC associated bleeding should be risk stratified according to the presence and severity of bleeding into ***minor*** (e.g. epistaxis, menorrhagia, mucosal bleeding), ***moderate*** (e.gs gastrointestinal bleeding not associated with hemodynamic instability) and ***severe or life threatening*** bleeding (e.g. life threatening gastrointestinal or intracranial bleeding).

    Thus the first step and most important aspect of management is to assess whether she is actively bleeding (in this case she is not bleeding). A CBC should be sent to determine if the hemoglobin concentration has declined. Creatinine clearance should be determined to ensure that she does not have a creatinine clearance <30ml/min. In the absence of visible bleeding or a reduction in hemoglobin concentration supportive management is sufficient and hemostatic therapy (i.e. PCC) is not required. Hold rivaroxaban for at least the next 24 hours.

    **Prompt:** What if the PT and APTT were normal? How would this change your management?

    The moderator should ask the group whether routine coagulation tests are helpful (PT, aPTT, INR).

    An elevation in PT and APTT is consistent with an anticoagulant effect from rivaroxaban but routine coagulation tests do not reliably reflect the circulating levels of rivaroxaban and are not suitable for quantitative assessment of rivaroxaban. The PT is relatively prolonged with rivaroxaban, shows a linear dose response to rivaroxaban, but its usefulness is limited because of the variability of PT reagents. Therefore, patients may have normal PT and still have therapeutic levels of rivaroxaban.

    The APTT is less sensitive than the PT for rivaroxaban and shows considerable variability based on the reagents used. There is poor correlation between the degree of APTT prolongation and the plasma concentration of Rivaroxaban.

In this case, if the PT and APTT are normal, it would be important to recognize that the patient nevertheless still has therapeutic anticoagulant effect on board and rivaroxaban should still be held.

Anti-Xa assays correlate well with rivaroxaban serum concentrations if calibrated to rivaroxaban, but are not correlated with clinical outcomes (ie. bleeding). However, few centres have anti-Xa assays for rivaroxaban and other anti-Xa agents so this is not the most appropriate plan.

4. Alternate ending: 72 hours after surgery, you are called as it has been discovered that instead 20 mg once daily of rivaroxaban he has been administered 20 mg bid for 2 days. The PT is 20 seconds (9.7-11.8 s) and APTT is 45 seconds (20-32). He begins to have hematemesis and is hypotensive (60/30 mm Hg). You aim to maintain hemoglobin > 70 g/L while bleeding and consult for endoscopic management. The last dose of rivaroxaban was 1 hour ago. Which one of the following is an appropriate management plan?

   **A. Administer prothrombin complex concentrate (PCC) 50 U/kg maximum 3000 U iv or according to hospital policy.**
   B. Andexanet alfa
   C. Fresh frozen plasma
   D. Hemodialysis to remove rivaroxaban

   As the patient is hypotensive, this potentially is a life threatening bleed. Principles of management include the following considerations:

   - Hemodynamic support is essential with aggressive fluid therapy and red cell transfusions.
   - If the last rivaraxoban dose was within 2 hours, oral charcoal can be used to bind rivaroxaban.
   - As rivaroxaban is highly protein bound, rivaroxaban is not dialyzable . Rivaroxaban, apixaban and edoxaban are not dialyzable but hemodialysis can be used to reduce the level of dabigatran.
   - Tranexamic acid is not routinely recommended for the hemostatic management of DOAC-related GI bleeding but may be considered on a case by case basis. Please see commentary below regarding the result of the HALT-IT study
   - PCC (i.e. octaplex, Beriplex) 50 U/kg at a maximum 3000 U iv Some hospitals suggest a fixed dose of 2000 U iv with a repeat dose in an hour if still bleeding. There have been 2 randomized controlled trials in healthy volunteers (Erenberg, Levi) that have shown variable results of the PCCs on the PT but as there appears to be some effect, the use of PCC are used to treat bleeding associated with hemodynamic instability. The variability in results is likely due to sample size, the dose of rivaroxaban used and the duration of anticoagulation in the two trials. A systematic review (Piran Blood Adv 2019) of 10 observational studies (340 patients) showed effective hemostasis in 69% of patients, with a 4% risk of

thromboembolic complications. If thrombotic complications with PCC occur, the blood bank and Health Canada should be notified (Vanessa's Law)

- Surgical consultation should be sought to achieve local hemostasis.
- Andexanet alfa (a recombinant human Xa variant-competes with rivaroxaban to bind Xa) is not yet approved in Canada for reversal of rivaroxaban.
- Fresh frozen plasma will not reverse the anticoagulant effect.
- For advice for DOAC associated bleeding, the hematology service can be contacted however the blood bank at each site will need to be informed regarding the need for PCCs.

**Prompt:** What about tranexamic acid in this case?

Tranexamic acid was not found to be associated with a reduction in mortality in patients with significant upper or lower gastrointestinal bleeding in the multicentre, randomised, placebo-controlled HALT-IT trial (Lancet 2020; 395: 1927–36). In this study, 12,009 adults were randomized to tranexamic acid 1g bolus + 3 g over 24 hours vs placebo. Death occurred in 9·5% in the TXA group and 9·2% in the placebo group. The risk of venous thromboembolic events was higher in the tranexamic group than placebo group in a subgroup of patients with variceal bleeds or liver disease RR 7.3, 95% CI 1.6–31.9). *Patients on anticoagulants made up only 9% of the HALT-IT trial population so it is uncertain what the role of tranexamic acid would be in this case.*

**Additional Questions for Hematology/Hematopathology Residents:**

**A) What would you give this patient if he had a history of heparin-induced thrombocytopenia?**

PCC contains small amounts of heparin, which is added to prevent activation of the coagulation factors. Therefore, patients with a history of HIT cannot receive PCC for anticoagulant reversal, and their reversal strategy would instead rely upon the other measures listed above including consideration of TXA.

**B) 5 days after surgery, the patient is readmitted to hospital with reduced level of consciousness and delirium of unclear etiology. He subsequently develops a fever, headache, and neck stiffness. The admitting team is concerned about meningitis, and would like to perform a lumbar puncture. The team orders a rivaroxaban anti-Xa level and it is 115 ng/ml. Is it safe to perform this procedure?**

The clinical utility of direct oral anticoagulant anti-Xa levels remains unclear, including levels correlated with bleeding, clotting, and procedural safety outcomes. In pharmacokinetic studies of patients taking therapeutic dose rivaroxaban, the median peak and trough concentrations

are 274 ng/ml and 30 ng/ml, respectively (Samuelson Chest 2017). As such, a rivaroxaban anti-Xa concentration of < 30 ng/ml is considered to be undetectable. Therefore, if the random level is 115 ng/ml there is clinically significant rivaroxaban drug concentrations present and the procedure should be deferred until more time has elapsed as per the expected pharmacokinetics of the drug.

## Case 2

An 87 year old man with atrial fibrillation presents to the emergency department with moderate dyspnea and pre-syncope which led to a fall. Heart rate is 110 bpm and blood pressure is 100/70. He was recently prescribed dabigatran 150 mg b.i.d. (switched over from warfarin by his cardiologist 2 weeks ago). His creatinine clearance is 40 ml/min. CT head shows a small intracranial hemorrhage.

5. The patient's INR is 1.1 (0.9-1.1), aPTT is 60 (20-32) seconds, TT is >60 (14-21) seconds. Which one of the following is likely true about his anticoagulation therapy?
   **A. There is evidence of presence of dabigatran effect**
   B. There is evidence of presence of warfarin effect
   C. Levels suggest that the patient has not been taking either warfarin or dabigatran
   D. Levels suggest that the patient is taking both warfarin and dabigatran

An elevated APTT and a thrombin time (TT) are helpful in determining if there is dabigatran on board, but it must be remembered that a patient can have a normal APTT even in the presence of dabigatran since the APTT may be normal approximately 25% of the time.

- An APTT that is greater than 1.5-2 x normal may predict excess dabigatran. A normal TT however, does rule out the presence of dabigatran.
- Some laboratories may have a dedicated assay that provides a dabigatran concentration in µg/ml (based on the thrombin time principle) however, the clinical correlates of these cut-offs (safe ranges for intervention or surgery) have not been established.

  Dabigatran is renally cleared and renal impairment may cause dabigatran accumulation. Frail and elderly patients who may not have renal impairment at the outset of dabigatran therapy can easily develop it with minor physiological insults. Determining the time since his last dose and his serum creatinine and calculated creatinine clearance (by Cockcroft-Gault equation) would be important in deciding if this patient is at risk of being over anticoagulated with dabigatran.

  The half-life of warfarin is 36-42 hours. As such one would expect by 2 weeks after warfarin cessation that its anticoagulant effects (on INR) would no longer be present.

  **Prompt:** What are the disadvantages of using dabigatran in this patient?

Patients aged 80 years and older should be treated with a dose of 110 mg b.i.d. and not 150 mg b.i.d. Dabigatran is contraindicated with creatinine clearance < 30 ml/min and should be used with caution in patients with creatinine clearance between 30 and 50 mls/min. The creatinine clearance should be considered while prescribing dabigatran and should also be monitored in elderly patients on dabigatran. The frequency is not established but once every 6 months is recommended based on expert opinion. Monitoring should also include careful review of medication lists to ensure no drug-drug interactions (particularly drugs that induce or inhibit p-glycoprotein).

6. Which one of the following represents an appropriate management strategy for this patient?

A. Hold dabigatran
B. Hold dabigatran, give activated PCC (FEIBA) 50 U/kg
**C. Hold dabigatran, give idarucizumab 5 grams IV**
D. Hold dabigatran, give plasma and cryoprecipitate/fibrinogen concentrate

The antidote for dabigatran is idarucizumab. Idarucizumab is a humanized monoclonal antibody fragment that binds dabigatran with a higher affinity than dabigatran for thrombin. Idarucizumab has been shown in the REVERSE-AD cohort study of patients undergoing urgent procedures or who had uncontrolled bleeding to rapidly neutralize Dabigatran effects (based on normalization of dilute thrombin time or ecarin clotting time). 93% of patients undergoing procedures had normal hemostasis, and in the bleeding patients the median time to hemostasis was 2.5 hours. The indications for idarucizumab have been suggested as follows and are reserved for patients with life threatening bleeding

- Life-threatening bleeding: Intracranial hemorrhage, symptomatic or expanding, extradural hemorrhage, or uncontrollable hemorrhage
- Bleeding in a closed space or critical organ: Intraspinal, intraocular, pericardial, pulmonary, retroperitoneal, or intramuscular with compartment syndrome
- Persistent major bleeding despite local hemostatic measures, or risk of recurrent bleeding because of delayed DOAC clearance or DOAC overdose
- Need for urgent intervention that is associated with a high risk of bleeding and that cannot be delayed to allow for drug clearance
- Emergency surgery or intervention in patients at high risk for procedural bleeding: Neurosurgery (intracranial, extradural, or spinal), lumbar puncture, cardiac or vascular surgery (aortic dissection/aneurysm repair), hepatic or other major organ surgery

Idarucizumab is administered as 5 g in two divided doses of 2.5 g IV bolus over 5-10 min, 15 min apart. The half-life is prolonged in patients with renal insufficiency. The estimated cost is $2500/5 g.

The same risk stratification (minor, moderate, life threatening bleed) that was discussed for rivaroxaban is also used for the other DOACs. The management of bleeding in a patient at risk of thrombosis balances the risk of bleeding with the risk of thrombosis.

A **moderate** bleed is GI bleeding without hemodynamically instability. If he were hemodynamically stable had a GI bleed instead of an intracranial bleed, fluids and PRBCs, endoscopic management and holding dabigatran are adequate.

A **mild** bleed includes ecchymosis, menorrhagia, epistaxis etc. with no hemodynamic instability.

Plasma and cryoprecipitate/fibrinogen have not been shown to be effective in reversal of factor II inhibitors or Xa inhibitors.

**Prompt:** How would you treat this patient if idarucizumab was not available?

Option B refers to management if idarucizumab is not available.

- Activated charcoal may be helpful but must be given within 1-2 hours of ingestion and is used with bleeding that is associated with hemodynamic instability i.e. life threatening bleeding.
- Adequate fluids and hydration (adequate perfusion to the kidneys) as well RBC transfusion in a bleeding patient are standard for patients who are bleeding.
- In cases of severe/ life threatening bleeding activated PCCs (FEIBA) has been recommended by some with variable effects. There may be a delay in obtaining FEIBA as many hospital blood banks would not stock it readily. The blood bank needs to be aware of the emergent need for FEIBA.
- At sites where FEIBA is not available, and the patient has a severe/life threatening bleed, the use of PCCs could also be considered (although there is no strong evidence to support this).
- Tranexamic acid can be used to reduce fibrinolysis for life threatening bleeding.
- Hemodialysis theoretically removes ~65% of dabigatran so could be attempted after careful consideration in life threatening bleeding.
- Consultation with hematology subspecialists (TM, Coagulation) is appropriate.

## Case 3

A 17 year old female is referred to a hematologist for a slightly elevated APTT. This has been confirmed on more than one occasion. Her bleeding history reveals epistaxis as a child that was recurrent and required several visits to the emergency department. She has had no procedures or operations. She has a history of menorrhagia. Both her mother and only sister have menorrhagia. Her younger brother had recurrent epistaxis as a child.

| **Initial Laboratory Tests** | | |
|---|---|---|
| Hemoglobin | 122 g/L | RI: 115-165 g/L |
| Platelet count | 256 | RI: 150-400 X $10^9$/L |
| PT/INR: | 1.0 | RI: 0.8 - 1.2 INR |
| APTT: | 45 s | RI: 22 - 35 s |
| 1:1 immediate APTT mix: | 29 s | RI: 22 - 35 s |
| Thrombin Time: | 22 s | RI: 20 - 30 s |
| Fibrinogen (Clauss): | 3.1 g/L | RI: 1.6 - 4.2 g/L |

7. Which one of the following represents an appropriate initial laboratory testing strategy for this patient?

A. Check factors VIII, IX, XI, XII and vWF
B. Check factors X, IX, VII and II
**C. Check vWF: Ag, vWF: Activity, FVIII levels**
D. Check factors VIII and XIII

This patient's bleeding history is notable for mild to moderate mucocutaneous bleeding and menorrhagia. She also has a family history suggesting an inherited disorder, albeit mild but with autosomal dominant inheritance. The absence of surgical challenges in both her and her family members renders it difficult to assess their response to hemostatic stressors. Menorrhagia may be subjective. The results of the correction of the 50:50 mix and the normal thrombin time taken together suggest that we are dealing with a factor deficiency. The next step would be to check factor levels of the intrinsic pathway and for vWD.

In summary, given the patient's age (young), gender (female), type of bleeding (mucocutaneous), family history (both genders are affected suggesting autosomal dominant pattern) and results of coagulation screen, TT and 50:50 mix the most likely **diagnosis is congenital von Willebrand's disease, Type I.**

Factor XI deficiency is a less likely possibility. Factor XII deficiency is not associated with bleeding. In this case, it may be reasonable to check Factor XII as part of the differential diagnosis for an elevated PTT but given the history is that the patient is bleeding, Factor XII may not be clinically relevant in this case.

**Please give the seminar group that the likely diagnosis is von Willebrand's disease, type I.**

8. How would you advise this patient?

A. Avoid trauma such as IM injection, arterial punctures, contact sports and regular use of antiplatelet agents (e.g. aspirin, clopidogrel)
B. Assess the response to DDAVP electively
C. Use tranexamic acid for menorrhagia
**D. All of the above**

- A wallet card and / or medic-alert bracelet is important for medical emergencies and should be carried by all patients. Most patients do not require prophylactic therapy on a regular basis. Avoiding trauma such as IM injections, arterial punctures, and contact sports will reduce the bleeding risk. Avoid regular antiplatelet agents (e.g. aspirin, clopidogrel, NSAIDs).
- Electively assess the response to DDAVP 0.3 µg / kg IV or SC (Canadian product monograph: max 20 µg / dose; other countries have removed the maximum dose) to determine whether DDAVP can be used to reduce the risk of bleeding. DDAVP can also be given intranasally. If a responder to this strategy, DDAVP may be used for minor procedures and / or minor surgery and / or minor bleeding episodes. She has type I von Willebrand's disease which is a reduction in von Willebrand antigen. Type I von Willebrand's disease is the most common type, it is autosomal dominant and responds to DDAVP.
- Tranexamic acid (Cyclokapron) 25 mg / kg po q8h may be used for mucosal bleeding and menorrhagia and along with DDAVP for minor procedures and / or minor surgery and / or minor bleeding episodes.
- VWF / Factor VIII concentrate (Humate-P or Wilate) may be indicated for severe bleeding or major surgery – dose according to monograph. VWF/Factor VIII concentrate should be requested in advance of surgery to ensure that the blood bank will carry it in scenarios where there is a high risk of bleeding. In Canada, cryoprecipitate should not be used prior or for surgical procedures.

9. She is now 25 years old and is 30 weeks gestation. She should have a CBC and iron indices to ensure she is iron replete. Which of the following applies to her vWF: Ag, vWF: Activity, FVIII levels?

**A. If levels are more than 0.50-80 IU/mL you advise that she can proceed with regional anesthesia and vaginal delivery or Cesarean section.**
B. If levels are 1.00 IU/mL or more you advise that she can proceed with regional anesthesia and vaginal delivery or Cesarean section.
C. If levels are 0.5-0.8 IU/mL you advise to avoid regional anesthesia but she can have vaginal delivery or Cesarean section.

D. If levels are 0.50-80 IU/mL you would advise to avoid regional anesthesia and vaginal delivery.

Von Willebrand factor antigen and factor VIII levels will increase during pregnancy for patients with Type I vWD so that antepartum hemorrhage does not appear to be higher than the general population. Thus routine prophylaxis is not required. If faced with hemostastic challenges during pregnancy e.g. placental abruption, the risk of excessive bleeding is higher.

The period of highest risk of bleeding is at delivery so that ensuring the hemoglobin concentration is normal and that the individual is iron replete reduces the risk of needing a transfusion should there be any bleeding at the time of delivery. Increasing the hemoglobin concentration by treating iron deficiency has been shown to reduce anemia at delivery.

Women with mild type 1 VWD with normal levels of von Willebrand factor antigen and factor VIII levels
do not require prophylactic treatment with hemostatic agents for delivery. The mode of delivery is directed by obstetric considerations, as vaginal delivery and cesarean section appear to be equally safe for mother and fetus. Delivery should occur by the least traumatic method and should occur in hospital. Invasive fetal scalp monitoring and forceps and vacuum extraction should be avoided in a potentially affected fetus (vWD type I has an autosomal dominant inheritance pattern) to minimize the risk for scalp hematoma and intracranial hemorrhage. Intracranial hemorrhage in neonates with VWD is rare though. A neonate would not require an NICU admission following delivery however a pediatric referral prior to delivery is warranted with pediatric hematology referral after delivery.

vWD is not a contraindication to administering neuraxial/regional anesthesia as in patients with mild type I disease, factor levels will be high enough i.e. > 0.5-0.8 IU/ml required for neuraxial anesthesia and delivery.

Von Willebrand factor antigen levels will return to pre-pregnancy levels within one week of delivery. Some women experience a precipitous drop in antigen levels following delivery. The risk of postpartum hemorrhage is thought to be 2-3 fold higher than in the general population. Tranexamic acid can be used if bleeding exceeds normal blood loss for vaginal delivery or Cesarean section.

**Additional Questions for Hematology/Hematopathology Residents:**

**What if this 17 year old patient instead was presenting to a peripheral hospital 4 weeks postpartum, with 3 weeks of profuse vaginal bleeding and extensive bruising?**

**She was found to have the following labs:**

- **Hb 68, PLT 256**
- **INR 1.0, aPTT 75 sec (22-35 sec)**
- **1:1 immediate aPTT mix 48 sec (22-35 sec).**

**A) What is the differential diagnosis and what additional investigations would you send?**

This patient has partial correction of a prolonged aPTT on 1:1 mix, which is suggestive of a specific or non-specific inhibitor. Given the provided history, this scenario is most concerning for an inhibitor to factor VIII (acquired hemophilia A). While this condition is most common in elderly individuals it can also occur in younger patients who are postpartum or secondary to autoimmune disease.

Note that while an initial aPTT 1:1 mix may initially fully correct the aPTT prolongation, it will again fail to fully correct to within the normal range when incubated (2 hours at 37 degrees) because of the time and temperature dependence of anti-FVIII antibodies (Kruse-Jarres, Am J Haematol 2017).

The next investigations should therefore include factor VIII, IX, XI, XII activity, lupus anticoagulant (should be negative) along with a Bethesda assay (inhibitor assay) to confirm if there is an inhibitor present.

Please provide the following laboratory results to the group and ask for their interpretation (they should say that the diagnosis is acquired hemophilia A, ie. acquired Factor VIII inhibitor):

- FVIII 1%, FIX 90%, FXI 120%, FXII 115%
- Inhibitor assay: positive (5 Bethesda Units)

**B) What is the immediate and long-term management for this patient?**

The immediate therapy consists of hemostatic therapy. At a peripheral hospital the treatment of choice would be bypassing therapy with either rVIIa (120 mcg/kg q2-4H) or FEIBA 50-100 units/kg q8-12H). Patients may also be given recombinant porcine FVIII (Obizur) if this therapy is available although this is primarily given as specialized care centres.

The long-term plan consists of immune suppression for inhibitor eradication. This typically includes corticosteroids and cyclophosphamide as front-line immune suppressants. However, cyclophosphamide is not safe during pregnancy/lactation, so the mainstay of therapy would be corticosteroids and consideration of second-line options such as rituximab.

## Case 4

75 year old male with diabetes, dyslipidemia and hypertension was seen in ER for a left cerebral hemorrhagic stroke with no intraventricular extension. He had been taking insulin, a statin, metoprolol and ASA 81 mg daily. The ICH was not preceded by a traumatic event and he is awake, alert to person, place and time and 2+ power in his right arm and leg.

10. Which of the following should you do next?

A. Administer tranexamic acid 30 mg/kg intravenously
**B. Check CBC, coagulation parameters**
C. Check CBC, coagulation parameters and while waiting results administer 4 units of plasma
D. Reverse the anti-platelet effect of ASA with platelet transfusion

A is incorrect because the TXA dose is too high. The tranexamic acid for hyperacute primary intracerebral hemorrhage (TICH-2) trial (Sprigg N et al. Lancet, 2018), randomized 2325 patients with ICH and Glasgow Coma Scale > 5 within 8 hours of symptoms to TXA 1 g iv followed by 1 g over 8 hours vs. placebo. There was no difference in the primary outcome of functional status at 90 days (adjusted OR 0·88, 95% CI 0.76–1.03, p=0·11). There was a difference however in death by 7 days (9% with TXA vs 11% with placebo, p=0.04), proportion with hematoma expansion (25% vs 29%) but not death at 90 days (22 vs.21%). This was a negative study because the primary outcome was not improved by TXA. The answer is incorrect because the dose is high.

C is incorrect as he is not taking an anticoagulant, has no liver dysfunction, and the volume of plasma can result in fluid overload

D is incorrect as the PATCH trial showed no benefit to platelet transfusion (Bharoglu MI et al Lancet 2016). In this study, 190 patients that had been taking an antiplatelet agent with a nontraumatic supratentorial ICH with a Glasgow Coma Scale score of 8–15 were randomized to platelet transfusion (within 6 hours of symptoms or within 90 minutes of imaging) or standard care. The study found that the odds of death or dependence at 3 months were higher in the platelet transfusion group than with standard care (adjusted OR 2. 05, 95% CI 1.18–3. 56; p=0.0114.) The trend towards increased risk is likely because there were more patients in the platelet transfusion group that were using two anti-platelet drugs and also had larger bleed volumes. Overall, platelet transfusion seems to be inferior to standard care for patients taking antiplatelet therapy before intracerebral hemorrhage and as such, is not routinely recommended.