Transfusion Camp for Nurse Practitioners
Materials based on Transfusion Camp 2018-2022 with permission from the Transfusion Camp Steering Committee
Morning Seminar on Day 3

Bleeding Assessment and Anticoagulants/Antiplatelets

Case 1
You are seeing a 52-year-old woman for elective hip replacement. Past medical history is significant for hypertension. When asked about other comorbidities, the patient casually notes that she had some bleeding in the past, but does not think it was really unusual or severe. Her current medications are hydrochlorothiazide and a daily multivitamin. She has two children.

1) Which one of the following is the appropriate next step in perioperative bleeding risk assessment?
   A. Ask about family history of bleeding disorders
   B. Check labs: INR, aPTT, CBC
   C. No further assessment required, patient is ok to proceed to OR
   D. Take more thorough history of bleeding symptoms

Facilitator guide

- **Option D (Take more thorough history of bleeding symptoms) is correct**
  - Evidence that bleeding history provides as much or more information about bleeding risk
  - It can be difficult for patients to accurately define their own bleeding risk. It is important to take a complete bleeding history which includes quantifying frequency and severity of past bleeding as well as asking about prior bleeding challenges.
  - Guidelines recommend bleeding history prior to laboratory testing (Chee YL et al BJH 2008; 140:496-504)
- Option A:
  - While family history can add to the bleeding history, the patient's personal bleeding history is more influential and is the most appropriate next step.
  - Congenital bleeding disorders can have incomplete penetrance and/or X linked inheritance (discussed in greater detail in subsequent questions).
  - Patients can have both acquired and de-novo bleeding conditions.
- Option B
  - A normal CBC, INR and aPTT does not exclude a bleeding disorder.
    - May miss mild factor deficiencies
    - Will not identify platelet defects, VWD, disorders of fibrinolysis and connective tissue disorders
  - Coagulation tests should not be performed routinely preoperatively
    - Reserved for patients with increased pre-test probability or those undergoing high risk procedures
- Option C
  - See description for option D. A comprehensive bleeding history needs to be completed to assess for a bleeding disorder.

Her comprehensive bleeding history is as follows 1) tonsillectomy age 7: required return to OR at 24 hours for surgical hemostasis and 1 unit transfusion RBCs; 2) G3A1L2: prolonged bleeding following spontaneous pregnancy loss at 13 weeks and required D&C and IV iron; and 2 uncomplicated C sections. Currently post menopause. Previously menstrual cycles were regular and lasted for 7 days with 3 heavy days where she changed pads every 2 hours. She feels that this history is not unusual since her mother and sisters had similar problems. Despite her mother and sisters having similar bleeding symptoms, no one in her family has been assessed for a bleeding disorder.

2) Which one of the following is the appropriate next step in patient management?

A. Book OR, note need for careful surgical hemostasis
B. Check labs: FVIII, FIX
C. Check labs: von Willebrand Factor multimer analysis
D. Refer to a hematologist

Facilitator guide

- **Option D (Refer to a hematologist) is correct**
  - History of perioperative bleeding, menorrhagia, easy bruising and a positive family history is suggestive of a bleeding disorder and investigation is recommended.
  - Guidelines recommend that this investigation be conducted by a hematologist, preferably one specializing in hemostasis.
- Option B
  - FVIII (Hemophilia A) and FIX (Hemophilia B) are both X linked and therefore are unlikely to cause severe manifestations in a woman. While, some carriers can experience abnormal bleeding this is not the next best step. Interpreting factor levels is nuanced and workup should be completed by a clinician with expertise in the area.
- Option C
  - Despite VWD being a consideration for this patient, multimer analysis is not the next best step (initial work up includes FVIII, VWF antigen and VWF activity). Furthermore, as above, this testing should ideally be completed by a clinician with expertise in the area. This also takes into account the multiple laboratory factors that can influence testing. If
  - ordering these tests, it is important to have a good understanding of local laboratory processes. Even issues like a delay in testing the sample because of shipping can impact on the results.

The patient is assessed by a hematologist. Initial laboratory investigations reveal the following:

- CBC within normal limits
- INR, aPTT within normal limits
- von Willebrand Factor antigen 0.28 u/mL (N=0.45-1.80)
- von Willebrand Factor activity 0.30 u/mL (N=0.45-1.80)
- FVIII 0.45 u/mL (N=0.5-1.49)

3) The patient's history and lab findings are consistent with von Willebrand's disease type 1 (VWD). Why did she not experience bleeding with her two Ceasarean sections?

A. Cesarean sections are low risk for bleeding and excessive hemorrhage would not be

expected in a patient with a non-severe bleeding disorder

B. During pregnancy there is a compensatory increase in factors IX and XI which help mitigate bleeding at delivery
C. Von Willebrand Factor levels are hormone-responsive and increase with pregnancy and use of hormone-containing medications
D. The patient received oxytocin which is known to increase levels of von Willebrand factor

Facilitator guide

- **Option C (Von Willebrand Factor levels are hormone-responsive and increase with pregnancy and use of hormone-containing medications) is correct**
    - Remind participants that not all women's levels correct in pregnancy. Thus, pregnant women with vWD need to be followed by a hematologist during pregnancy to determine if levels have corrected. If levels have not corrected, peri-partum hemostatic therapies may be needed.

4) Following consultation with a hematologist, the patient still wishes to proceed with hip replacement. Which one of the following is **false** about peri-operative management of this patient?
    A. According to international guidelines, her surgery should be done early in the day and early in the week at a hemophilia treatment centre
    B. As her von Willebrand factor levels and FVIII levels are both decreased, she will require factor replacement with two different products
    C. She will need factor concentrate infused before surgery and again in the post-operative period
    D. She should receive DVT prophylaxis

Facilitator guide

- **Option B (As her von Willebrand factor levels and FVIII levels are both decreased, she will require factor replacement with two different products) is false**
    - Both von Willebrand factor containing concentrates available in Canada (HumateP and Wilate) contain both vWF and FVIII.
- Option A is true
    - It is recommended that surgery be done in a hemophilia treatment centre as the requisite coagulation laboratory and transfusion service support are available as well as consulting hematologists. It is recommended that procedures are done early in the day and in the week to ensure there is adequate laboratory support for the patient. For example, specialized coagulation testing is less often available on the weekends.
- Option C is true
    - Patients with factor deficiencies are at risk for both immediate and delayed surgical bleeding and it is recommended that factor levels be kept up for several days following surgery.
- Option D is true
    - In general, factor deficiencies are not protective against VTE. In the absence of bleeding, patients should be given pharmacological VTE prophylaxis (if otherwise indicated for the general patient population) while they are receiving factor replacement. If there is

bleeding or the patient does not receive adequate factor replacement, the patient should be assessed for non-pharmacological DVT prophylaxis.
    - The duration of factor replacement/ VTE prophylaxis should be determined by a multi-disciplinary team.

Case 2

A 24-year-old male is scheduled for aortic valve replacement. Past medical history is significant for bicuspid aortic valve and only medication is Enoxaparin 40 mg daily for DVT prophylaxis (started on admission). Pre-operative testing shows APTT is 45 seconds (N= 26 to 35 seconds). A repeat test confirms the same PTT.

The resident on call remembers transfusion camp and completes a comprehensive bleeding assessment. MCMDM-1 Bleeding Questionnaire score is 0 (including no bleeding following wisdom teeth removal). They consult hematology for additional recommendations.

5) You are rotating through general hematology. Which one of the following represents the best next step?
    A. Stop Enoxaparin and repeat testing in 1 day
    B. Administer vitamin K 10 mg and repeat testing in 1 day
    C. Order 50:50 mixing study
    D. No further testing is required as the bleeding score is 0

Facilitator guide

- **Option C (Order 50:50 mixing study) is correct**
    - Mixing studies can assist in working up prolonged coagulation tests and differentiating between factor deficiencies and inhibitors.
    - Note that while a 50:50 mixing study is generally considered the first step in evaluating prolonged coagulation times (including on residency exams) some experts may move directly to more specific tests.

    Advanced follow up question: What must be done during a 50:50 mixing study if concerned for acquired Hemophilia A (Factor 8 inhibitor)?
    - Compared to other types of inhibitors (e.g. lupus anticoagulant), factor 8 inhibitors have slower kinetics and may be missed on the initial measurement (e.g. mix may initially show correction). Performing a second measurement after allowing 1-2 hours for incubation will prevent this and bring out slower acting factor 8 inhibitors.
    - The test is also done at 37 degrees

- Option A
    - While heparin can increase the APTT this does not occur to a significant degree with prophylactic dosing.
    - A normal thrombin time and/or anti-Xa level will exclude heparin contamination and accidental heparin overdose.
- Option B
    - Vitamin K deficiency does not cause isolated APTT elevation.
- Option D

- Despite not having a significant bleeding history, as the patient is undergoing a high risk surgery that will require intraoperative anticoagulation, pre-operative coagulation testing may be considered (utility is area of ongoing study).
    - Next slide shows Choosing Wisely Canada anesthesia recommendations against routine pre-operative blood work in non cardiac surgery. (this is cardiac surgery)
- The cause of the prolonged PTT should be determined.
    - A negative bleeding history does not exclude FXII deficiency, antiphospholipid antibodies, and mild factor deficiencies.
        - Mild factor deficiencies may result in increased bleeding during high risk procedures.
        - FXII deficiency and APLA will impact peri-operative use and monitoring of anticoagulation

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Five Things Physicians and Patients Should Question

1 **Don't order baseline laboratory studies (complete blood count, coagulation testing, or serum biochemistry) for asymptomatic patients undergoing low-risk non-cardiac surgery.**

Conducting baseline laboratory investigations before low-risk non-cardiac surgery contributes little value to perioperative care. A focused clinical history and physical examination may reliably identify relevant abnormalities sought by routine laboratory testing before low-risk surgery. In addition, evidence suggests that abnormal results in this setting only rarely influence management and do not improve clinical outcomes. Preoperative testing may add value in the setting of a symptomatic patient or higher-risk surgery, but should not be performed routinely before low-risk surgery on asymptomatic patients.

A 50:50 mixing study is done and does not correct.

6) Which one of the following is most likely to confirm a diagnosis?
   A. Fibrinogen level
   B. Factors VIII and IX
   C. Lupus anticoagulant (non-specific inhibitor) testing
   D. Factor VIII inhibitor test

Facilitator guide

- **Option C (lupus anticoagulant (non-specific inhibitor) testing) is correct**
  - Lupus anticoagulants can cause prolongation of the aPTT that will not correct with a 50:50 mixing study.
  - Outside of the peri-operative period some experts may recommend against ordering lupus anticoagulant testing in a patient with no history of thrombosis or pregnancy complications as testing is unlikely to change clinical management.

- Option A
  - Fibrinogen deficiency does not cause isolated PTT elevation.
- Option B
  - Both factor VIII and IX deficiency would be expected to correct with a mixing study. These are also unlikely to be present in a patient with no bleeding history.
  - Note that a non-correcting 50:50 mixing study does not definitely exclude factor deficiencies in high probability patients (e.g. significant bleeding history).
- Option D
  - Specific inhibitors can cause prolongation of the aPTT that will not correct with a 50:50 mixing study.
  - However, unlike non-specific inhibitors (lupus anticoagulant), specific inhibitors are associated with bleeding manifestations.
  - In a non-bleeding patient, non-specific inhibitors (lupus anticoagulant) should be assessed first.

Case 3

A 65 year old female is in the preoperative clinic in preparation for surgery for a left knee arthroplasty. She had an idiopathic DVT 1 year ago, requires indefinite anticoagulation and is taking Rivaroxaban 20 mg daily. She has hypertension and is taking ASA daily for primary prophylaxis of cardiovascular events, mild renal insufficiency (creatinine clearance 60 ml/min) secondary to hypertension and has mild hepatic dysfunction secondary to NASH (PT, APTT are normal). BMI is 30 kg/m^2.

7. Which one of the following is known to increase this patient's risk of peri-operative bleeding?

   A. She is taking ASA 81 mg daily for primary prophylaxis
   B. She has mild renal insufficiency secondary to hypertension

C. She has mild hepatic dysfunction secondary to NASH
D. She has a BMI of 30 kg/m^2

With any anticoagulant, concomitant use of antiplatelet agents increases bleeding risk. However, discontinuation of antiplatelet agents is dependent on the risk of cardiovascular events when anti-platelet agents are discontinued. ASA is discontinued 7-10 days before non cardiac surgery if the risk of cardiovascular events is low. If the risk is moderate to high, ASA is continued. (ASA is continued for cardiac surgery). If ASA is required, inform patients of the increased risk of bleeding and optimize perioperative management. Baseline renal function tests (rivaraxoban is not recommended for patients with a creatinine clearance < 30 ml/min) and liver enzymes (to exclude hepatic dysfunction), coagulation parameters (i.e. PT, APTT to exclude a coagulopathy) as well as platelet number need to be determined prior to surgery. Optimizing the hemoglobin concentration (i.e. ensuring patient is not anemic or iron deficient and treating iron deficiency) prior to surgery decreases the need for blood transfusion.

Rivaraxoban does not have as many drug interactions as the vitamin K antagonists however rivaroxaban is metabolised via cytochrome P450 3A4 (CYP3A4) mainly and inhibitors of CYP3A4 that increase the plasma concentration should be discontinued such as clarithromycin and amiodarone.

Although she has mild hepatic dysfunction, her coagulation parameters are normal. Her BMI is not markedly elevated.

8. 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 Xa. It's peak action is 1 to 3 hours and 33% is renally cleared (Table).

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, neuroaxial anesthesia.

Because of its short half-life, for patients who 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. 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.

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

A. Resume Rivaroxaban at usual dose on day 2 post op if no evidence of bleeding
B. Resume Rivaroxaban at usual dose when there is no evidence of bleeding
C. Resume Rivaroxaban at prophylactic dose on day 1 post operatively
D. Resume Rivaroxaban at prophylactic dose when there is no evidence of bleeding

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, rivaroxaban can be restarted 4 to 6 hours after surgery with a reduced dose of 10-mg dose followed by a therapeutic dose. 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.

10. 72 hours after surgery, you are called as it has been discovered that instead of the 20 mg of rivaroxaban she has been administered 20 mg bid for 2 days. The PT is 20 seconds (9.7-11.8)

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. Use another anticoagulant

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 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. Hold rivaroxaban for at least the next 24 hours.

The elevation in PT and APTT is consistent with an anticoagulant effect from rivaroxaban but routine coagulation tests do not 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. However, 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 the reagents used. There is poor correlation between the degree of APTT prolongation and the plasma concentration of Rivaroxaban.

Anti-Xa assays correlate well with rivaroxaban if calibrated to rivaroxaban. Few centres have anti-Xa assays for rivaroxaban and other anti-Xa agents.

11. Alternate ending: 72 hours after surgery, you are called as it has been discovered that instead 20 mg of rivaroxaban she 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). She 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. Which one of the following is an appropriate management plan?

A. **If rivaroxaban given within last 2 hours consider charcoal to remove the drug, administer tranexamic acid 1 g iv then 1 g iv over 8 hours, administer prothrombin complex concentrate (PCC) 25 U/kg maximum 3000 U iv or according to hospital policy.**
B. If rivaroxaban given within last 2 hours consider dialysis to remove drug, administer tranexamic acid 1 g iv administer PCC 25 U/kg maximum 3000 U iv or according to hospital policy.
C. If rivaroxaban given within 7 hours, administer andexanet alfa.
D. If rivaroxaban given within 6 hours, give frozen plasma to reverse anti-coagulant effect.

As the patient is hypotensive, this potentially is a life threatening bleed. 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. Tranexamic acid (10 mg/kg iv followed by 1 gram iv every 8 hours is recommended by Thrombosis Canada) and can be administered (there have been no studies to show the effectiveness of tranexamic acid in this scenario but its use is extrapolated from other trials with bleeding such as trauma) as well as 4 factor PCC (i.e. octaplex, Beriplex) 50 U/kg at a maximum 3000 U iv as recommended by Thrombosis Canada. 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 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.

Surgical consultation should be sought to achieve local hemostasis.

Andexanet alpha (a recombinant human Xa variant-competes with rivaroxaban to bind Xa) is not yet approved for reversal of rivaroxaban.

Fresh frozen plasma will not reverse the anticoagulant effect.