Transfusion Camp 2021-2022
Day 3: Seminar 3A, January 21, 2022
"Perioperative Bleeding Assessment", Originally developed by Dr. Elianna Saidenberg. Modified by Dr. Zachary

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Please start session by asking trainees if they have any questions from the didactic sessions.

Please remind trainees that although one answer is bolded as the correct answer, there may be more than one reasonable answer to the questions. The purpose of the seminar is to promote discussion and explore why certain answers may be more appropriate in certain situations.

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.

2a) What is the patient's bleeding score using the Condensed MCMDM-1 Bleeding Questionnaire?

Facilitator guide

- At least 8 based on information provided.
- Opportunity for learners to practice applying a bleeding score. Direct them to online resources to assist.
    - Bloody Easy Coagulation Simplified (pg 34)
        - Transfusionontario.org → Bloody Easy E-tools & Publications → Bloody Easy for Health Care Professionals → Bloody Easy Coagulation Simplified, 2nd Edition
    - ASH Pocket Guides – von Willebrand Disease

2b) 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)

3a) 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.

Advanced follow up question 1: Which VWD patients would not be expected to correct during pregnancy?

  - Type 2 VWD would not be expected to fully correct during pregnancy as there is a qualitative/ functional rather than quantitative defect. Type 3 VWD would also not be expected to correct as there is almost a complete absence of VWF.
  - While most Type 1's will correct, some severe Type 1's may not have full correction and as noted above it is important to confirm VWF levels during pregnancy.

- Option A
  - Patients with bleeding disorders are at risk for excessive peri-operative bleeding even with low risk bleeding procedures
- Option B
  - Multiple procoagulant changes occur during pregnancy including increases to

fibrinogen, factors II, VII, VIII, X, XII, XIII, fibrinolysis inhibitors and VWF
    - Factors IX and XI do not change significantly during pregnancy
- Option D
    - DDAVP (synthetic formulation of Vasopressin) not Oxytocin is used to treat mild cases of hemophilia and Type 1 VWD
    - Both Vasopressin and Oxytocin are released by the posterior pituitary. Vasopressin (and DDAVP) can increase uterine contractions but Oxytocin has limited impact on VWF levels.

Advanced follow up question 2: Why is the patient's aPTT normal if her FVIII level is low?
- While a FVIII level of 45% is below the lower limit of the reference range, it is likely sufficient for hemostasis and will not always result in prolongation of clotting times
- Important point is that patients can have bleeding disorders with normal INR, aPTT and CBC. Thus, they are not good screening tools. Remind participants of the following:
    - aPTT initially designed to screen for presence of hemophilia in males presenting with bleeding symptoms even before it was known that there are 2 types of hemophila (A and B). Point is that it works as a screening tool for a specific condition WHEN the pre-test probability is high. However, can still miss mild hemophilia
    - INR indicated for monitoring of vitamin K antagonist therapies. The only congenital bleeding disorder which will give isolated prolongation of PT/ INR is FVII deficiency. Without evidence to suggest presence of a congenital bleeding disorder, the information from PT/INR test will be difficult to interpret
    - OVERALL- INR, aPTT are not sufficiently sensitive nor specific to be useful as widely applied screening tests for congenital hemostatic disorders in the absence of relevant clinical data

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.

Advanced follow up question: Does a normal PTT exclude a lupus anticoagulant?
  - Note a normal aPTT does not exclude a lupus anticoagulant. Most labs use a lupus insensitive reagent for routine coagulation testing to prevent interference from clinically insignificant lupus anticoagulants.

Case 3

A 28 year old G1A0L0 is followed for an uncomplicated pregnancy. A CBC performed at 20 weeks GA shows a platelet count of 109 $x10^9$/L. She has only one previous laboratory test result, done when she was investigated for possible infectious mononucleosis 4 years prior. At that time her platelet count was 297 $x10^9$/L. MCMDM-1 score is 1 based on easy bruising.

7) Which one of the following is the most appropriate next step in investigation of this patient's laboratory abnormality?
   A. Platelet antibody studies to investigate for possible immune thrombocytopenia
   B. Repeat CBC in 2 weeks to determine platelet count trend

C. Test family members to determine if patient has a hereditary platelet disorder
D. Assess for Type 2b VWD as cause of thrombocytopenia

Facilitator guide

- **Option B (Repeat CBC in 2 weeks to determine platelet count trend) is the correct answer.**
  - Gestational thrombocytopenia is the most common cause of low platelet counts in pregnancy. It usually presents in the second trimester and the resultant thrombocytopenia is usually mild (nadir above 70) and not progressive. Thus, monitoring the platelet count to see if the counts remain stable or worsens is the appropriate course of action at this time.
  - This patient does not have major bleeding manifestations. Spontaneous bleeding secondary to thrombocytopenia is generally not encountered until platelet counts drop below 30 and usually below 10. Therefore, the patient is well within a safe range and observation is most appropriate.
- Option A
  - Platelet antibody studies are not indicated for routine clinical investigation of thrombocytopenia as they are difficult to perform and have limited sensitivity and specificity. FNAIT is outside the scope of this presentation. However, if you have OB or pediatrics trainees in your group you may suggest that they read about role of these investigations in neonates with thrombocytopenia and women with previously affected pregnancies
- Option C
  - Congenital thrombocytopenia can worsen during pregnancy, but typically, such patients will not have had normal platelet counts in the past as this patient did.
- Option D
  - Type 2b VWD can lead to thrombocytopenia through increased affinity of VWF for platelets, however this is rare and unlikely in someone without bleeding manifestations. Therefore, this is not the most appropriate test.

The patient has CBC done every 2 weeks. When she is at 24 weeks GA her platelet count has decreased to $79x10^9$/L. She has no bleeding symptoms and ultrasound shows no fetal or placental abnormalities. The patient is referred to a hematologist. Serologic investigations for infectious and autoimmune conditions associated with thrombocytopenia are done and are all negative.

A diagnosis of ITP is made. She continues to have CBC done every 2 weeks with a plan to increase frequency of monitoring to weekly at 34 weeks.

At 32 weeks GA the patient's platelet count has dropped to $48x10^9$/L

8) What should the patient be counselled about delivery at this time?
   A. Vaginal delivery is unsafe for the mother at a platelet count less than $50x10^9$/L
   B. Vaginal delivery is unsafe for the fetus due to the risk of neonatal ITP
   C. Patient should have labour induced within 2 weeks given the risk of further deterioration of platelet counts
   D. Neuraxial anesthetic is relatively contraindicated at a platelet count below $50x10^9$/L

Facilitator guide

- **Option D (Neuraxial anesthetic is relatively contraindicated at a platelet count below $50x10^9$/L) is correct**
- Option A
  - In women with ITP, it is recommended that mode of delivery be recommended based on obstetrical indications only
- Option B
  - Vaginal delivery is safe for thrombocytopenic infants. However, instrumented delivery (vacuum, foreceps) and scalp vein monitoring are not recommended. Thus, there is a greater possibility of the need for operative delivery
- Option C
  - Unless there is evidence of fetal distress, there is no indication for early delivery. Rather, efforts should be focused on increasing maternal platelet count prior to term.

9) The patient indicates that she wishes to have the option of epidural or spinal anesthetic. Which one of the following is the best management plan.
   A. Advise the patient that an epidural or spinal anesthetic will not be possible.
   B. Rituximab 375 mg/m^2 IV x 4 doses
   C. Prednisone 1 mg/ kg po daily x 14-21 days
   D. IVIG 0.4 g/kg x 1

Facilitator guide

- **Option C (Prednisone 1 mg/kg po daily x 14-21 days) is correct**
  - Corticosteroids are considered first line treatment for ITP in both pregnant and non-pregnant patients.

- Option A
  - While not all patients will ultimately be able to receive an epidural or spinal anesthetic in almost all cases an attempt should be made to raise the platelet count to allow for epidural or spinal anesthetic if in keeping with patient preferences.
- Option B
  - Rituximab is not a first line treatment for ITP in either pregnant or non-pregnant patients.
- Option D
  - In general, corticosteroids are preferred over IVIG for initial treatment of ITP in both pregnant and non-pregnant patients.
  - IVIG may be considered as initial treatment based on patient specific factors
    - Concern re. corticosteroid exacerbation of mood disorders, diabetes, hypertension
  - If IVIG is to be administered standard dosing is 1 g/ kg with a second dose administered the following day if required. In some cases, the dose can be split over 5 days if there is significant concern for IVIG associated hemolysis.

Advanced follow up question: Describe the pros and cons of prednisone versus dexamethasone for this patient?

- Prednisone if often preferred in pregnancy over dexamethasone because of decreased placental transfer to the fetus.
- Potential fetal adverse effects of corticosteroids during pregnancy:
  - Oral clefts and low birth weight (first trimester use)
  - Hypoadrenalism
- Prednisone and dexamethasone have similar adverse effects overall. Dexamethasone is typically given at a high dose for a 4 day treatment course for ITP, while prednisone treatment uses a relatively lower dose but can last for several weeks. Accordingly dexamethasone may increase the risk of short term adverse effects but have less medium/ long term adverse effects.
- Dexamethasone may lead to faster platelet responses.
- Potential maternal adverse effects of corticosteroids during pregnancy:
  - Exacerbation of gestational hypertension/ diabetes
  - Exacerbation of mood disorders

The patient is started on prednisone with good effect. At 36 weeks GA she presents to hospital in early labour, her platelet count is 88 $x10^9$/L.

10) Which one of the following is the best management with regards to epidural/ spinal anesthetic?
   A. Provide IVIG to increase her platelet count to at least $100x10^9$/L ensuring that she can have an epidural anesthetic within 2-4 hours.
   B. Provide a platelet transfusion before insertion and removal of epidural catheter/ spinal anesthetic.
   C. Strongly advise against an epidural or spinal anesthetic since her platelet count is below $150x10^9$/L.
   D. Proceed with epidural/ spinal anesthetic.

Facilitator guide

- **Option D (proceed with epidural/ spinal anesthetic) is the best answer**
  - There is limited evidence and considerable variability in expert opinion regarding a safe platelet count for epidural/ spinal anesthetic.
  - A platelet count above 70-80 $x10^9$/L is generally considered safe, however some anesthetists may require a platelet count above 100 $x10^9$/L.
- Option A
  - While most patients with ITP do respond to IVIG, platelet response can take 1-3 days and there is no guarantee the platelet count will rise above 100.
  - As above, it is unclear that a platelet count above 100 is safer than the patient's current platelet count for epidural insertion. This must be balanced against the resource utilization and potential adverse effects of IVIG.
- Option B
  - The outcome of platelet transfusion in the context of immune-mediated thrombocytopenia is highly uncertain. The risks of platelet transfusion likely outweigh potential benefits patients without life threatening bleeding and thus,

should not be recommended

Advanced follow up question: How does a diagnosis of ITP impact decisions around DVT prophylaxis?

- Like factor deficiencies, ITP is not protective against VTE/ATE and in fact patients with ITP maybe at increased risk of thrombosis compared to the general population. If the platelet count is above 50 $x10^9$/L, ITP patients should receive post-partum prophylaxis if otherwise indicated based on institutional policies. Higher risk patients may still receive DVT prophylaxis for platelet counts < 50 x 10 $x10^9$/L on a case by case basis in consultation with experts in thrombosis.

Advanced follow up question 2: How would management change if the patient presented with placental abruption with fetal distress requiring urgent delivery and platelet count was 15 $x10^9$/L.

- This is a medical emergency and immediate hemostatic treatment is required to stop bleeding and facilitate delivery. If possible, the steroid dose should be optimized to help achieve a more durable response (i.e. return to 1mg/ kg if dose has been reduced or consider pulse dosing), however due to the severity and time sensitivity, additional treatments are also required. The patient should be given TXA, IVIG (usual dose 1 g/kg daily x 2) as well as a platelet transfusion. For life threatening refractory bleeding, additional adjuncts can also be considered on a case by case basis, these may include emergency splenectomy, TPO agonists and/or Rituximab. These treatments are all associated with increased risk in pregnant women and there is limited evidence to guide decision making. Accordingly, a patient centered, multi-disciplinary approach is recommended with involvement from obstetrics, hematology and pediatrics to guide decision making.

Mithoowani S, et al. Management of major bleeds in patients with immune thrombocytopenia. Journal of thrombosis and haemostasis : JTH 2020