Transfusion Camp 2023-2024
Day 1: Seminar 1B, September 22, 2023
Plasma, PCC & Fibrinogen Cases, Dr. Sheharyar Raza and Dr. Aditi Khandelwal

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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

A 56-year-old individual (78 kg) with atrial fibrillation presents to the emergency department with acute onset of severe shortness of breath and pre-syncope with any exertion. The patient is on warfarin – dose has been stable for 6 months without dose adjustment. The patient had some chest congestion last week and went to a walk-in clinic and received Clarithromycin. Heart rate is 130 bpm and blood pressure is 80/30 mmHg. Heart sounds are faint. JVP is grossly distended. Chest-x-ray reveals marked cardiomegaly. Cardiology has been paged for STAT echo for pericardial tamponade from hemorrhage. INR is 10.5. Patient is to undergo the life-saving procedure immediately.

1. Which one of the following is the most appropriate management strategy at this time?
    A) 1 unit of plasma, vitamin K 10 mg po
    B) 4 units of plasma, vitamin K 10 mg IV
    C) PCC 3000 IU, vitamin K 10 mg IV
    D) PCC 3000 IU, vitamin K 2 mg po

2. How fast should you run the PCCs into the patient?
    A) As fast as you can push in by syringe
    B) Each 1000 units is run over 1 minute
    C) Each 1000 units is run over 5 minutes
    D) Each 1000 units is run over 30 minutes

3. The cardiology team wants to know how quickly the INR will be normalized so that they can do the procedure. Which one of the following is the best course of action for warfarin reversal in this case?
    A) Collect the INR sample immediately after infusion, proceed with the procedure, and give additional doses of PCC if the post-infusion INR>1.5 and the patient has ongoing bleeding
    B) Re-check the INR after PCCs to determine if additional doses are required before starting the procedure
    C) The effect of PCCs will be seen immediately after administration in all patients and there is no need to re-check the INR
    D) The effect of the treatment (PCCs and vitamin K) takes 6 hours to normalize the INR, so delay the procedure for 6 hours

4. Which of the following is an appropriate indication for PCC administration?
    A) Elective reversal of oral anticoagulant therapy before a scheduled invasive procedure.
    B) Rapid reversal of warfarin therapy or vitamin K deficiency in patients exhibiting major bleeding.
    C) Reversal of warfarin therapy or vitamin K deficiency in patients requiring a surgical procedure within 12 to 24 hours.
    D) Treatment of INRs over 8 to 10 without bleeding or need for surgical intervention.

Prothrombin Complex Concentrate (PCC) are lyophilized concentrates of factors 2, 7, 9, and 10 – PCCs are NOT concentrated plasma. They also contain small amounts of heparin, protein C and S, and antithrombin. There are two brands in Canada and the UK (Octaplex and Beriplex) that are used interchangeably. Only 4 factor PCCs are available in Canada. A 3-factor PCC is available in the UK (Cofact) that has lower levels of factor 7.

PCCs are indicated in patients who are anticoagulated with a vitamin K antagonist (warfarin/coumadin) or who have vitamin K deficiency and:

- Have life or limb threatening bleeding (e.g., intracranial hemorrhage, massive gastrointestinal hemorrhage, pericardial tamponade).
- Require emergency operative procedures with moderate to high risk of bleeding that cannot be delayed for medical reasons for more than 6 hours (e.g., perforated bowel, subdural hematoma).

Reversal of anticoagulation with blood products, including PCCs, is not appropriate solely to expedite taking a patient to the operating room or interventional radiology for scheduling reasons (e.g., available operating room for patient needing a non-urgent procedure). It is completely inappropriate to use PCCs for an elective procedure (e.g., colonoscopy) or for reversal of an elevated INR (even if over 10) in the absence of bleeding or a planned procedure. The use of plasma is no longer appropriate for management of vitamin K antagonist reversal due to the widespread access to PCCs. (Exception: anticoagulant associated bleeding in patients with heparin induced thrombocytopenia (HIT) must be treated with frozen plasma, since PCCs contain a small amount of heparin).

Other considerations for PCC use:

- Treatment of bleeding in patients receiving direct Factor Xa inhibitors (rivaroxaban, apixaban, edoxaban).
- PCCs for reversal of direct thrombin inhibitors (e.g., Dabigatran) is not recommended
- Use in a patient with a massive hemorrhage when plasma is unavailable
- Coagulopathy associated with liver dysfunction, or in other settings where the risk/benefit profile of plasma transfusion (fluid overload) is deemed to be unfavorable

PCCs cost about $600 per 1000 IU and approximately 2-4% of recipients experience thromboembolic complications (Dentali et al. Thromb Haemost 2011;106:429-38). PCCs are manufactured from human plasma and carry theoretical risks of disease transmission. Informed consent is required. These risks are less than frozen plasma due to the viral inactivation steps during the manufacturing process. However the risk of disease transmission may still occur from manufacturing failures and from emerging pathogens that are resistant to the pathogen reduction strategies (parvovirus, hepatitis A, prions). The risk of TACO is less with PCC vs. plasma due to the smaller volume required.

The dose recommended is based on hospital policy. The National Advisory Committee in Canada felt that there was insufficient published evidence to recommend one dosing regimen over another. An example of an acceptable dosing regimen is as follows:

- INR 1.5-3.0 give 1000 IU
- INR 3.1-5.0 give 2000 IU
- INR>5.0 give 3000 IU

In the UK, the dose recommended by the NHSBT is 25 IU/kg and then repeat the INR. The following table can be used (infuse at 2-3 mL per minute):

Body weight (kg)	Total Dose in IU if 25 IU/Kg	No of vials of 500 IU	mls
Less than 60	1500	3	60
60-75	2000	4	80
75-90	2500	5	100
Greater than 90	3000	6	120

A single dose should not exceed 3000 IU. Alternate dosing strategies are available at the National Advisory Committee website.
(https://nacblood.ca/en/resource/recommendations-use-prothrombin-complex-concentrates-canada)

If the INR is unknown and there is life-threatening hemorrhage, a dose of 2000 IU is recommended and immediately repeat the INR. There is no need to wait 10-60 minutes after the infusion to recheck the INR.

The PCC infusion rate is each 1000 IU (40 mL) over 5 to 15 minutes (Beriplex monograph states can be run at ~8mL/min and Octaplex monograph states can be run at 2-3 mL/min), although most institutions run each 1000 units over 5 minutes as reversal is an emergency therapy. There are case reports of thrombosis from rapid infusion of PCCs (e.g., 3000 IU over 1 minute) through a central line and therefore exceeding recommended infusion rate could have adverse consequences (Warren et al. Ann Emerg Med 2009;53:758-61).

The INR should be repeated immediately post-infusion to document correction to an INR of <1.5 (67-100% of patients will have an INR of 1.2-1.3 or less (normal). Also, repeat the INR at 6 hours to ensure no rebound (often due to failure of vitamin K to be administered IV due to an error). For emergency surgery or procedure, surgery should not be delayed waiting for the INR results. The INR should be repeated as soon as possible and additional dosage given intraoperatively if required. There is no maximum daily dose of PCCs, although each infusion should not exceed 3000 IU and additional doses should not be given unless the INR is elevated.

If there is poor immediate correction of the INR post-infusion, asking for the lab to add the PTT and fibrinogen on existing blood samples drawn pre- and post-PCC dosing, plus requesting a hematology consultation is warranted to determine if other factors are driving the coagulopathy (e.g., other anticoagulants, inhibitors, coagulopathy of shock).

Vitamin K should always be given for emergency reversal as the effect of PCCs (and plasma) only last 6 hours. This time-span is dependent on the factor 7 half-life – the shortest of the coagulation factors

within PCCs. Vitamin K is the true reversal agent for vitamin K antagonist, and failure to give vitamin K will result in rebounding of the INR. Vitamin K must be given intravenously (IV) as it works considerably faster than oral. The risk of anaphylaxis or other reaction to IV vitamin K is very small and can be reduced by giving as a slow infusion over 10-15 minutes. The appropriate dose of vitamin K for emergencies is unknown but 5-10 mg IV is commonly recommended by expert opinion. Vitamin K should not be given IM (due to risk of hematoma) or SC (due to decreased effectiveness compared to both IV and PO routes) (Mottice et al. Am J Ther 2016 Mar-Apr;23(2):e345-9). Oral vitamin K is appropriate for patients with INR>8-10 in the absence of bleeding or planned procedure (e.g., outpatient) to correct the INR back to therapeutic range of 2-3 (Lubetsky A, et al. Arch Intern Med 2003;163:2469–2473.).

If you see an INR rebounding after initial correction despite ordering intravenous vitamin K, check the administration record to ensure it was given by the correct route. If IM, SC or PO vitamin K was given in error, administer IV vitamin K immediately (and PCCs if ongoing bleeding).

The important risks of reversal with plasma include: transfusion-associated circulatory overload (TACO), transfusion related acute lung injury (TRALI) and allergic reactions, including anaphylaxis. The risk of thromboembolic (TE) complications has not been well studied. Two RCTs of FFP vs. PCC found no difference in the TE rates, but a major reduction in TACO (Goldstein et al. Lancet 385(9982):2077-2087; Sarode et al. Circulation 128:1234-1243). There have been 4 systematic reviews of PCCs vs. plasma (ICH patients, emergency surgery, bleeding and cardiac surgery) and none found an increase in A/VTE events. The immediate risks of reversal with PCC include allergic reactions (rare; rate unknown). The risk of thrombosis has been estimated at 2-4% for both products and plasma (Dentali et al. Thromb Haemost 2011;106:429-38).

The cost difference between plasma and PCC is minimal and therefore using plasma instead of PCC for cost containment is not appropriate. Some physicians order plasma when the reversal is not urgent (ie. They want to reverse the INR by the following day) – this doesn't make sense as the appropriate treatment in this clinical scenario is vitamin K 10 mg IV.

Case 2

A 15-year-old adolescent (45 kg) presents to the emergency department feeling unwell for 2 weeks with fever, myalgias, malaise and anorexia. The patient was seen earlier today by the pediatrician who noted jaundice and referred the patient to a tertiary care pediatric emergency. On physical exam, the patient has mild abdominal distention (query ascites) and splenomegaly. There is no bruising except at intravenous puncture sites. The laboratory investigations show markedly elevated liver enzymes (ALT 234 IU, N<40 IU), a bilirubin of 76 umol/L (N<20), albumin 24 g/L (N>35 g/L), INR of 1.8 (N<1.2), fibrinogen of 1.2 g/L (N>2 g/L). The platelet count is 65 x 10^9/L (N>150 x 10^9/L). The hepatologist has recommended an urgent liver biopsy to determine the cause and severity of the liver disease. The transjugular liver biopsy is scheduled in 4 hours.

5. Which one of the following is the most appropriate transfusion strategy for this patient in preparation for the liver biopsy?
    A) No need for transfusion at this time
    B) Transfuse 1000 IU of PCC and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate in the UK)
    C) Transfuse 1 adult dose of platelets
    D) Transfuse 3 units (15 ml/kg) of plasma to ensure INR is <1.5 before the procedure

6. The radiologist has requested that the INR be corrected to 1.2 or less. What should you do?
    A) Call your staff physician and get direction on how to proceed
    B) Delay the procedure for 1 day and see if the next radiologist with do it without INR correction
    C) Discuss with the radiologist performing the procedure, the risks of plasma, explain why plasma is unlikely to lower the INR, and alert them to the 2019 Society for Interventional Radiology Guidelines
    D) Transfuse 3 units plasma in an effort to lower the INR and get the liver biopsy completed

Retrospective large case series of patients with liver disease undergoing common procedures find no increase in bleeding with elevated INRs, compared to patients with normal INRs (van de Weerdt EK, et al. Transfusion. 2017;57(10):2512-25). No large randomized trials have been completed, and these trials are not feasible due to the very low complication rate (numbers needed for the trial would be extremely high to determine if plasma increases or decreases adverse event rates).

Patients with liver disease have widespread derangements (elevated vWF, elevated factor 8, decreased ADAMTS-13, decreased protein C/S, decreased antithrombin, decreased plasminogen, reduced fibrinolysis) (Northup PG, et al. Clin Gastroenterol Hepatol. 2013 Sep;11(9):1064-74; Tripodi A, et al. N Engl J Med. 2011 Jul 14;365(2):147-56). It is possible that this patient is actually balanced in terms of her hemostasis at an INR of 1.8, or even hypercoagulable. Many centres are able to do major surgical procedures on patients with cirrhosis/liver failure, including liver transplantation, without any plasma despite INR>3.0. Therefore, the use of plasma should be restricted to patients undergoing high risk procedures (neurosurgical procedures, high risk interventional radiology procedures) or be reserved for the management of bleeding complications post procedure.

It is unknown what the appropriate INR cut-off should be (if any) for a liver biopsy – there is no relationship between the INR and the risk of bleeding but the recent guidelines from the Society for interventional radiology 2019 guidelines recommend reasonable thresholds for low and high risk of bleeding procedures with liver disease (see detailed powerpoint slides from plasma lecture and charts below; Patel et al. J Vasc Interv Radiol 2019).

SUMMARY OF THE SIR 2019 GUIDELINES:

Decision-making regarding patients on anticoagulants, with underlying coagulopathy, and/or thrombocytopenia prior to invasive procedures in Diagnostic Imaging

(The following is extracted from the **Society of Interventional Radiology Consensus Guidelines for the Periprocedural Management of Thrombotic and Bleeding Risk in Patients Undergoing Percutaneous Image-Guided Interventions**—Part II: Recommendations. Davidson JC, et al. J Vasc Interv Radiol 2019; 30: 1155-67)

The guidelines divide patients into two procedures categories for decision making (low risk and high risk procedures). **The guidelines also divide patients into 3 general categories for types of coagulopathy** (anticoagulants, coagulopathy from liver disease, and coagulopathy for all other causes).

Table 1. Low risk and high-risk procedure categorization (if a procedure is not listed estimate risk from similar procedures in procedure list below).

Low risk (common examples)	High risk (common examples)
• Catheter exchanges (gastrostomy, biliary, nephrostomy, abscess, including gastrostomy/gastrojejunostomy conversions) • Diagnostic arteriography and arterial interventions: peripheral, sheath < 6 F, embolotherapy • Diagnostic venography and select venous interventions: pelvis and extremities • Dialysis access interventions • Facet joint injections and medial branch nerve blocks (thoracic and lumbar spine) • IVC filter placement and removal • Lumbar puncture • Non-tunneled chest tube placement for pleural effusion • Non-tunneled venous access and removal (including PICC placement) • Paracentesis • Peripheral nerve blocks, joint, and musculoskeletal injections • Sacroiliac joint injection and sacral lateral branch blocks • Superficial abscess drainage or biopsy (palpable lesion, lymph node, soft tissue, breast, thyroid, superficial bone (eg, extremities and bone marrow aspiration)) • Thoracentesis • Transjugular liver biopsy • Trigger point injections including piriformis • Tunneled drainage catheter placement • Tunneled venous catheter placement/removal (including ports)	• Ablations: solid organs, bone, soft tissue, lung • Arterial interventions: > 7-F sheath, aortic, pelvic, mesenteric, CNS • Biliary interventions (including cholecystostomy tube placement) • Catheter directed thrombolysis (DVT, PE, portal vein) • Deep abscess drainage (eg, lung parenchyma, abdominal, pelvic, retroperitoneal) • Deep non-organ biopsies (eg, spine, soft tissue in intraabdominal, retroperitoneal, pelvic compartments) • Gastrostomy/gastrojejunostomy placement • IVC filter removal complex • Portal vein interventions • Solid organ biopsies • Spine procedures with risk of spinal or epidural hematoma (eg, kyphoplasty, vertebroplasty, epidural injections, facet blocks cervical spine) • Transjugular intrahepatic portosystemic shunt • Urinary tract interventions (including nephrostomy tube placement, ureteral dilation, stone removal) • Venous interventions: intrathoracic and CNS interventions

Figure 1. Algorithm for deciding on appropriate management for patients on anticoagulants.

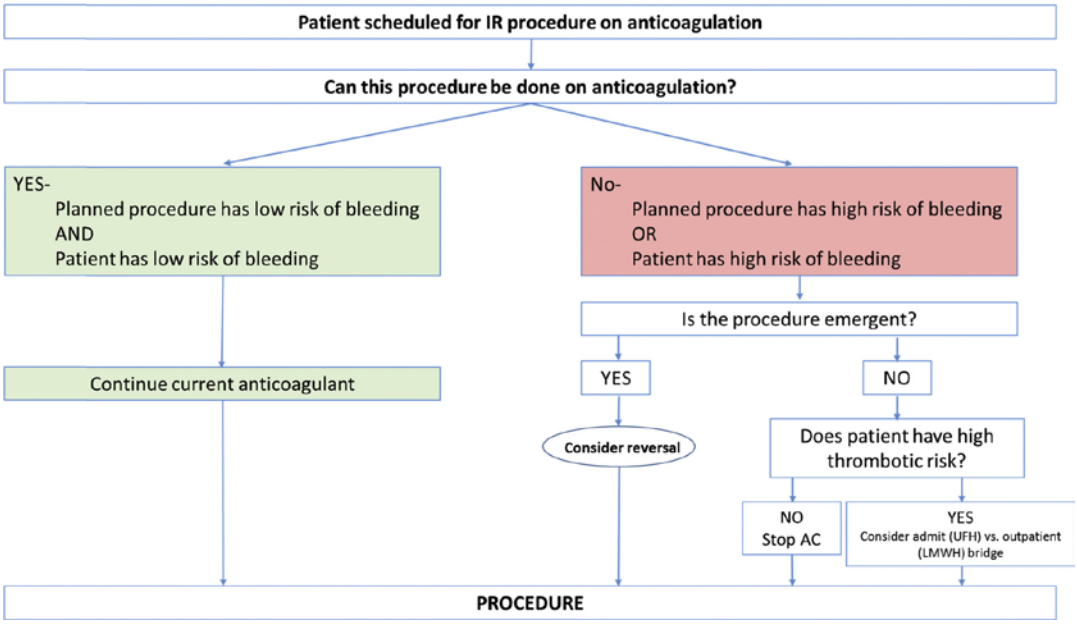

Table 2. Decision making guide for patients with coagulopathy NOT related to an anticoagulant or liver disease (cirrhosis). Low risk and high risk procedure list see Table 1.

Low risk procedure	PT/INR: not routinely recommended • If INR performed: correct to within range of 2.0–3.0 Platelet count: not routinely recommended • Transfuse 1 pool of platelets if platelet count < $20x10^9$/L
High risk procedure	PT/INR: routinely recommended • If INR performed: correct to less than 1.8 Platelet count: routinely recommended • Transfuse 1 pool of platelets if platelet count < $50x10^9$/L

Table 3. Decision making guide for patients with coagulopathy related to liver disease (cirrhosis). Low risk and high risk procedure list see Table 1.

Low risk procedure	PT/INR: not routinely recommended • Procedure can be performed at any elevation of the INR Platelet count: routinely recommended • Transfuse 1 pool of platelets if platelet count < $20x10^9$/L Fibrinogen: routinely recommended • Transfuse 4 grams of Fibrinogen concentrate if fibrinogen <1.0 g/L
High risk procedure	PT/INR: routinely recommended • If INR performed: correct to less than 2.5 Platelet count: routinely recommended • Transfuse 1 pool of platelets if platelet count < $30x10^9$/L Fibrinogen: routinely recommended • Transfuse 4 grams of Fibrinogen concentrate if fibrinogen <1.0 g/L

Plasma transfusion prior to procedures in the setting of liver disease is discouraged by the AASLD Guidelines, which state the INR should not be used to guide decisions prior to procedures due to its inutility (Northup et al. Hepatology 2021), and the BCSH guideline for plasma (Green et al. British Journal of Haematology, 2018, 181, 54–67). The CSTM Choosing wisely have stated "DON'T transfuse plasma if <1.8" = therefore do not use plasma below this level in the setting of liver disease. It is inappropriate to EVER give plasma for either a thoracentesis or a paracentesis, no matter how elevated the INR is. The platelet count is a much better predictor of bleeding at the time of a procedure, especially if the platelet count is less than 20 x 10^9/L.

Note: The cut offs for INR for liver disease vs. other conditions (e.g., warfarin reversal) are different. Do not use the same cut offs for all decisions regarding plasma and PCCs.

Three large retrospective reports have evaluated the change in INR after plasma infusion in patients with mildly elevated INRs (1.3-2.0). The infusion of plasma did not reduce the INR post-infusion. This is likely due to the fact that the effect of plasma does not last very long (4-6 hours) and the INR of frozen plasma is not 1.0 and can be as high as 1.3-1.5 (coagulation factors drop due to the effect of freezing/thawing and then storage at room temperature for up to 5 days).

The major risks include: TACO (1 in 50 to 1 in 100), TRALI (1 in 5000), allergic reactions (1 in 100), anaphylaxis (1 in 20,000), and viral risks. Informed consent is required. In a euvolemic patient be very careful to monitor the patient volume status before and during the infusion to mitigate the risk of TACO, especially in non-bleeding patients where the volume may be problematic.

7. The patient subsequently develops a variceal bleed with hypotensive shock. Her INR is now 3.4 (N<1.2) and fibrinogen is 1.6 g/L (N>2). You should:
    A. Transfuse 1 unit of plasma and repeat INR
    B. Transfuse 5-10 mL/kg of plasma (2 units or 500 mL)
    C. Transfuse 15 ml/kg of plasma (3 units or 750 mL)
    D. Transfuse 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate in the UK)

The correct dose of plasma for an adult patient is 15 mL/kg (adult dose 3 to 5 units, depending on the patient's weight); (Green et al. British Journal of Haematology, 2018, 181, 54–67). The dose of 2 units or less is inappropriate for adults and is likely a "carry-over" from the old practice of giving 2 RBCs at a time (and now "1 unit at a time"). The expected rise in coagulation factors from 15 mL/kg (3-5 units) is 20% in clotting factor levels. This patient is 45 kg and thus 675 mL would be required and for adults, this patient should receive 3 units FP.

If the patient has an in-date group and screen, the preparation time of plasma is a minimum of 25-30 minutes, as the product has to be thawed in a water bath. If the patient has no in-date group and screen, an additional 15 minutes is required to determine the patient ABO blood group. In emergencies, AB plasma will be issued if there is no time to complete the patient blood group (AB plasma lacks anti-A and anti-B and is the "universal" blood donor group for plasma). AB plasma is in chronic short supply and should only be used in emergencies. No matching for Rh-group is required for plasma. Of note, there are some jurisdictions that do use A plasma instead of AB plasma in emergency massive hemorrhage protocols.

Canadian Blood Services now offers Solvent Detergent Plasma (SDP) under the brand name "Octaplasma". Pathogen inactivated products like solvent detergent treated plasma are expected to

replace Frozen Plasma (FP) by 2025. SDP's manufacturing process offers many advantages over FP. SDP is created using pools of up to 1500 donor units. Treatment by solvent detergent inactivates lipid membranes of enveloped pathogens and neutralizes non-enveloped viruses (e.g. Parvovirus B19, Hepatitis A virus). Filtration removes white blood cells, contaminants, pathogens. Adsorption removes prions. SDP is considered a pathogen-inactivated plasma product. In the clinical setting, compared to FP, SDP carries a lower risk of infections, allergic reactions, TRALI, and febrile reactions. SDP also has more consistent factor levels and is considered a better replacement for clotting factors where other factor concentrates (purified protein products) or recombinant products are not available. For treatment of a bleed or prophylactic use, FP and SDP have comparable efficacy. SDP dose is the same as FP (15 ml/kg). SDP bags are smaller in size (200mL) compared to FP (250 – 300mL). In clinical use, rapid thawing has resulted in presence of strands within the product which can be avoided by slower thawing – and this has contributed to challenges in SDP being adopted at Trauma centres. Contraindications to SDP plasma include severe Protein S deficiency, IgA deficiency, and hypersensitivity to ingredients.

Case 3a

A 35-year-old patient (65 kg) is admitted to the ICU from the ER with endocarditis within 4 hours of presenting to the hospital. The patient is not bleeding, is intubated for airway protection and on two inotropes. The patient's temperature is 39° C. Blood work is as follows: Hemoglobin 108 g/L, platelet count 18 x 10^9/L(N>150x10^9/L), INR 1.6 (N<1.2), aPTT 42 s (N<36 s), and fibrinogen 1.3 g/L (N>2.0 g/L). The peripheral blood smear shows occasional fragments (schistocytes). Blood cultures are positive for gram-positive organism in 2/2 bottles; final culture results are pending. You make the correct diagnosis of sepsis related DIC. The patient is not bleeding and no procedures are planned in the next 6 hours.

8. Which one of the following is the most appropriate transfusion strategy for this patient?
   A) No transfusion indicated at this time
   B) Transfuse 1 adult dose of platelets
   C) Transfuse 1 adult dose of platelets and 4 units of plasma
   D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate in the UK)

In the absence of bleeding or a planned surgical procedure, blood product transfusion is almost never necessary. Plasma has a high rate of adverse reactions and is a large volume (750-1250 mL for an average adult). Its effect starts to diminish after 6 hours and therefore repeated infusions would be required to normalize the INR continuously. Infusions for patients with INRs between 1.3 and 2.0 fail to show an improvement in the INR.

There is no evidence available that suggests fibrinogen replacement is required and guidelines recommend against replacement in patients with DIC (Hunt et al. N Engl J Med 2014;370:847-59; Levi et al N Engl J Med 1999; 341:586-592). The only indication for prophylactic fibrinogen replacement is in patients with Acute Promyelocytic Leukemia (APL) during the acute presentation until coagulopathy resolves and the high-risk period for intracranial hemorrhage has passed (this is based on expert opinion only Breen et al. BJH 2012;156:24-36).

Platelet transfusion is not recommended in the case of consumptive thrombocytopenia without active bleeding or pending surgical procedure.

Case 3b

A 17 year old patient is seen in the ER with profuse vaginal bleeding and hemorrhagic shock 6 hours after a pregnancy termination. The patient's BP is 90/50, HR 112, temperature is 38.1° C. Blood work is as follows: Hemoglobin 65 g/L, platelet count 28 x 10^9/L(N>150x10^9/L), INR 1.4 (N<1.2), aPTT 40s (N<36s), and fibrinogen 1.1 g/L (N>2.0). Ultrasound shows retained products of conception. She is hemodynamically unstable and you have ordered 2 units of uncrossmatched (you decide it would be imprudent to wait 60 minutes for crossmatched blood) O D-negative and K-negative red cells.

9. Which one of the following is the most appropriate transfusion strategy for this patient in addition to transfusing red blood cells?
    A) No transfusion indicated at this time
    B) Transfuse 1 adult dose of platelets
    C) Transfuse 1 adult dose of platelets and 4 units of plasma
    D) Transfuse 1 pool of platelets and 4 grams of fibrinogen concentrate (or 10 units of cryoprecipitate)

Platelets are indicated in an actively bleeding patient to slow the rate of bleeding until definitive surgical procedure to address the underlying cause of bleeding. Usually, the target is ≥50x10^9/L. Give 1 adult dose of platelets to increase the platelet count (ideally by at least 25 x 10^9/L). Fibrinogen replacement should be given as a source of fibrinogen, and is more effective at raising the fibrinogen level than plasma. Cryoprecipitate and FC have a smaller volume than plasma, and both are rarely reported to be associated with adverse reactions. The European Bleeding guidelines recommend AGAINST using plasma solely for fibrinogen replacement (Spahn et al. Crit Care. 2019 Mar 27;23(1):98). A mildly elevated INR should correct, at least partially, with fibrinogen replacement as well. The standard adult dose of cryoprecipitate is 10 Units (which contains approx. 3-4 grams of fibrinogen) or fibrinogen concentrate 4 g. The target fibrinogen level is unknown, but with severe ongoing bleeding experts recommend raising the fibrinogen level to over 1.5-2 g/L in most settings (Rossaint et al. Critical Care 2016; **20**:100) and above 2 g/L for postpartum hemorrhage. Repeat the CBC, INR and fibrinogen immediately after the platelet and fibrinogen replacement has been administered. A randomized, controlled trial of fibrinogen concentrate vs. cryoprecipitate for hemorrhage after cardiac surgery found the latter strategy non-inferior for bleeding control (Callum J et al. JAMA 2019) and its use has superseded cryoprecipitate across Canada due to the reduced risk of pathogen transmission, cryoprecipitate production impacts on platelet production, and concerns regarding inferior outcomes with whole blood filtered RBCs (Heddle N, et al. Lancet Haematology 2016).

Case 3c

A 35-year-old patient is admitted to the hematology service following a diagnosis of acute promyelocytic leukemia (APL). APL is associated with a high rate of early hemorrhagic deaths from ICH. The patient is afebrile with stable vital signs and the patient's only complaints are fatigue and a petechial rash on their legs. Blood work is as follows: Hemoglobin 74 g/L, platelet count 18, WBC 63, INR 1.4, aPTT 39 s, and fibrinogen 0.9 g/L. The patient is to start emergency induction chemotherapy tonight, and is not bleeding.

10. Which one of the following is the most appropriate transfusion strategy for this patient?
    A) No transfusion indicated at this time
    B) Transfuse 1 unit RBC and 1 adult dose of platelets
    C) Transfuse 1 unit RBC and 4 grams of fibrinogen (or 10 units of cryoprecipitate)
    D) Transfuse 1 adult dose of platelets and 4 grams of fibrinogen (or 10 units of cryoprecipitate)

In general, acute leukemia patients do not need plasma or cryoprecipitate for acute leukemia related DIC. A large study compared 2 academic hospitals: hospital A routinely used cryoprecipitate and plasma for patients with coagulopathy/thrombocytopenia; hospital B never used any cryoprecipitate or plasma. There was no difference in the bleeding rates (or thrombosis rates) between the two institutions despite caring for identical patients.

There is one exception, however: patients with APL. Approximately 20-30% of deaths in APL result from hemorrhagic complications (with 7-14% early death rate in large case series). Since APL is highly curable many "expert opinion" reviews recommend keeping PLT>50 and fibrinogen >1.5 g/L. No recommendations regarding use of FP appear in recent reviews. It is reasonable at this time to transfuse platelets and fibrinogen in the absence of active bleeding to hit the above listed targets of 1.5 g/L for fibrinogen and >50 x 10^9/L for platelets in the initial presentation of APL. These recommendations are not based on clinical studies. It is unknown how long into APL treatment fibrinogen replacement is required. Individual patient assessment required – use response to chemo, lab test results over time, and bleeding symptoms in decision to switch from prophylactic to therapeutic treatment strategy.

Cryoprecipitate dosage: 1 unit per 5-10 kg of body weight (most adult centres use a standard pool size of 10 units for all adults; most countries (UK, USA) it comes pre-pooled in groups of 5 units). In a bleeding patient, 1 pool (10 units of cryoprecipitate (Canada); or "2 pools" of 5 units in the UK/USA) would result in a 0.7-0.9g/L rise in fibrinogen. Each cryoprecipitate unit is 5-15 mL of volume. To pool the cryoprecipitate, 10-50 mL of saline is added to reconstitute the fibrinogen. Hence, total volume for 10 units is 150-200 mL. Each unit has a minimum of 0.15 g of fibrinogen (minimum per 10 unit pool = 1.5 grams; although the average measured fibrinogen content is 3-4 grams per pool).

Fibrinogen concentrates is administered as a single dose of 4 grams (pathogen inactivated). Each vial of fibrinogen concentrate is 1 gram reconstituted in 50 mL sterile water. At present, fibrinogen concentrate use for acquired hypofibrinogenemia is considered to be off-label. In the product monograph, where fibrinogen concentrate use is defined for preoperative replacement in patients with congenital hypofibrinogenemia, the recommended rate of infusion is 4 grams over 40 minutes. However, in the setting of bleeding, clinical studies use rapid injection at a rate of 1 gram over 1 minute without complications (Winearls et al. Trials 2017; 18:241; Nascimento et al. Br J Anaesth. 2016 Dec;117(6):775-782).

Case 4.

You are providing the anesthetic for an 11-year-old undergoing scoliosis surgery with a pre-op weight of 39 kg. Pre-op blood work: hemoglobin 118 g/L, MCV 78, Platelet count 288. No INR was done pre-op as the bleeding assessment tool (bleeding questionnaire eg. MCMDM1) was negative for a bleeding history. At the 2 hour mark of the surgery, approximately 2500 mL of blood loss is recorded and you have transfused 3 units of red blood cells. STAT blood work reveals: hemoglobin 78 g/L, PLT count 134

(N>150), INR 2.1 (<1.2), PTT 45 (N<36) and fibrinogen 1.3 (N>2). The surgeon expects to lose another 1000 mL over the next hour. You have not administered any plasma, platelets or fibrinogen yet.

11. Which one of the following is the most appropriate component strategy for this patient?
    A) Transfuse 1 dose platelets (10-15 mL/kg)
    B) Transfuse 2000 IU of PCC
    C) Transfuse 3 units (15 mL/kg) of plasma and 2 grams of fibrinogen (50 mg/kg) or 5 units of cryoprecipitate
    D) Transfuse or 2 grams of fibrinogen or 5 units of cryoprecipitate

There are no "dose" finding studies that guide when to give plasma during active bleeding. In the setting of major hemorrhage that cannot be controlled with surgical hemostasis, administering plasma if the INR is >1.5-1.8 is reasonable, although the medically sound cut-off is thought to be higher by experts in hemostasis.

There are no definitive studies of "dose finding" for fibrinogen replacement. Some guidelines recommend a trigger of 1.0 g/L (BCSH; Green et al. British Journal of Haematology, 2018, 181, 54–67) and newer studies have questioned this trigger in postpartum hemorrhage, trauma, and cardiac surgery and have recommended a higher trigger 1.5-2.0 g/L. The truth is we don't know what the right threshold or target for fibrinogen is! It is reasonable in the setting of mild-moderate hemorrhage to keep fibrinogen >1.0 and in more extreme bleeding situations target a higher level >1.5-2.0 g/L. Repeat the INR and fibrinogen level after infusion. Formula use (1:1 or 2:1) of plasma is not used unless the rate of hemorrhage is extreme (e.g., PPH or gunshot wounds), rate at least 4 RBC units per hour (or expected transfusion volume of 40 ml/kg for pediatric patients over 24 hours), unable to wait for lab results, and no immediate surgical correction is possible.

Case 5

A 67-year-old is admitted to the ICU with septic shock. They receive aggressive fluid resuscitation with normal saline, vasopressor support, and empiric antibiotic therapy. A total of 2-3 L of IV fluids has been administered.

12. What do you suggest for ongoing fluid resuscitation:

    A) Switch from IV normal saline to 5% albumin
    B) Switch from IV normal saline to 25% albumin
    C) Continue IV normal saline (or another crystalloid)
    D) Switch from crystalloid to colloid

There is randomized trial evidence (SAFE, CRISTAL, ALBIOS) to suggest that albumin has no benefit over crystalloids for patients requiring fluid resuscitation. A 2013 Cochrane systematic showed the lack of benefit in critically ill (trauma, burns and postoperative) patients. This review found that that one type of colloid, hydroxyethyl starch (HES), may contribute to an increased risk of death (RR 1.10; 95% CI 1.02–1.19). In patients with liver dysfunction, meta-analysis has shown a benefit for albumin following large-volume paracentesis; albumin treatment reduced postparacentesis circulatory dysfunction, hyponatremia, and mortality relative to treatment with other colloids. Smaller prospective studies have also suggested the potential benefit of albumin in cirrhotic patients with spontaneous bacterial

peritonitis, as well as in patients with hepatorenal syndrome in conjunction with terlipressin (Clarke et al. Prof Education albumin)

Albumin use is generally recommended for the following indications:

5% albumin preparations:

- Therapeutic plasma exchange
- Thermal injury involving >50% total body surface area, if unresponsive to crystalloid

25% albumin preparations:

- Patients with liver disease and bacterial peritonitis;
- Large volume (>5 litre) paracentesis in cirrhotic patients;
- Hepatorenal syndrome type 1

Albumin is contraindicated in: patients who would not tolerate a rapid increase in circulating blood volume, and patients with a history of an allergic reaction to albumin.