Transfusion Camp 2021-2022
Day 2: Seminar 2B, November 19, 2021
"Delayed or Derivative" Transfusion Reactions, developed by Dr. Akash Gupta

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 57-year-old female presents to the ER with worsening fatigue. She was recently admitted for resection of a retroperitoneal mass and discharged home 12 days ago. During that admission she received 2 RBC units. Current CBC shows a hemoglobin of 72 g/L. Upon discharge, her hemoglobin was 87 g/L.

Upon examination it is noticed that she has yellow discolouration of her sclera and further history identifies darkening of her urine since being at home.

1. What additional information would you request?
    a. Blood group and antibody screen
    b. Markers of hemolysis (LDH, haptoglobin, bilirubin)
    c. Direct antiglobulin test
    d. All of the above

Hemolytic transfusion reactions are reactions that cause unwanted destruction of red blood cells (RBCs). As per the transfusion transmitted injuries surveillance system manual, hemolytic transfusion reactions are divided into acute and delayed. The presence of hemolysis can be evidenced by a drop in hemoglobin, an increase in the indirect bilirubin and LDH levels, and a positive hemolytic screen.

Hemolytic markers show an elevated LDH (499 U/L), low haptoglobin (<0.1 g/L), and elevated total bilirubin (36 umol/L). Additional blood bank testing shows a positive antibody screen and a positive DAT. The antibody specificity is identified as an anti-E and the patient is phenotyped as negative for the E antigen.

2. What is the most likely etiology of her findings?
    a. Acute hemolytic transfusion reaction
    b. Delayed hemolytic transfusion reaction
    c. Warm autoimmune hemolytic anemia
    d. Cold autoimmune hemolytic anemia

Acute hemolytic transfusion reactions are fortunately a rare occurrence and are usually due to an ABO-incompatibility secondary to a clerical error or an error in patient identification. The current incidence of ABO-incompatible transfusions is 1 in

38,000. The most common symptoms from an acute hemolytic transfusion reaction are fever, chills, and hemoglobinuria. Other less common symptoms include pain, hypotension, nausea/vomiting, dyspnea, renal failure, and DIC.

Delayed hemolytic transfusion reactions can present between 3 days and 2 weeks after the transfusion event. Patients will typically present with laboratory evidence of hemolysis and a positive antibody screen. Most of these reactions are minimal, however hemolysis leading to severe anemia and renal failure can occur.

Delayed hemolytic transfusions are not uncommon (1 in 6715 transfused units) and are typically due to the formation of antibodies in the patient against antigens expressed on the donor's RBCs. These antibodies are screened for during the antibody screen, but certain antigen groups (E, Jka, c, Fya, and K) have antibody levels that tend to fall below the detectable limit, over time. As a result, if the patient's antibody history is unknown, subsequent antibody screens can be negative and the patient can receive antigen-incompatible RBCs.

Due to the mild nature of most delayed hemolytic transfusion reactions and the delayed timing, many reactions are often missed as patients will have been discharged and at home by the time they present with symptoms. Unfortunately, when these events are not investigated, the blood bank will not be able to identify the offending antibody to prevent any further hemolytic reactions in the future.

Autoimmune hemolytic anemias can present with similar markers of hemolysis, however the antibodies involved should react against the patient's own cells. In this case we have identified the presence of an alloantibody, which, combined with the timing of events, points towards a delayed hemolytic transfusion reaction.

Case 2

You are attending in the critical care unit of at a community hospital and have sought advice from a neurologist at an academic hospital regarding a patient who has presented with progressive flaccid paralysis following a viral infection. The patient is awake and clinically stable but is now completely paralyzed, ventilator-dependent, and only able to communicate through blinking. The neurologist suspects Guillain-Barre Syndrome and recommends a course of high-dose IVIG (2 g/kg administered over 2 days).

3. Who should consent be sought from in this case?
    a. Consent not required in this situation
    b. The patient
    c. The patient's next of kin
    d. The public guardian

- Obtaining informed consent from this patient will be difficult and time-consuming, but is nonetheless still required because the patient retains capacity: despite being unable to move or speak, he is capable of

understanding the information that is relevant to making a decision about the treatment and is able to appreciate the reasonably foreseeable consequences of a decision (or lack of decision).

- In this situation, the physician is obliged to utilize whatever communication tools are available, even if that is restricted to having the patient answer a series of yes/no questions by blinks or hand-squeezes.
- In situations where the patient is unable to sign a consent form due to impaired vision, physical impairments, or illiteracy, it is sufficient for the staff to write "patient unable to sign" on the form and document the reasons why. Although having the consent discussion witnessed is not a universal requirement by all institutions, it would be advisable in this case.
- However, it should be remembered that the signature of a witness to a consent discussion attests only to the identity of the patient named on the form and that the person's mental state at the time appeared to allow for an understanding of what was signed: it does not attest to the adequacy of the explanations given by the individual who obtained the consent.
- Treatment without consent can only be initiated if the patient's life is at immediate risk and neither patient nor their substitute decision-maker are able to provide consent; this is not the situation in the current scenario.

Have one resident read out the following consent discussion, then ask the group to provide any comments/criticisms.

Hi, I am the physician on call and I would like to talk about a possible treatment plan regarding your disease. The neurologist has recommend we treat you with intravenous immune globulin.

With this treatment, we should hopefully be seeing improvement in your clinical status within a few days.

The risks of IVIG treatment include headache, fatigue, nausea, chills, back pain, pain, vomiting, pyrexia, cough, diarrhea, and stomach discomfort. Very rarely, transfusion-related acute lung injury, anaphylaxis, and thromboembolic reactions such as myocardial infarction, stroke, pulmonary embolism, and deep vein thromboses have occurred.

The other effective alternative therapy for treatment of your condition is plasma exchange, however we do not have the facilities at this hospital to offer that service.

If you are okay with this plan, I've already placed the order and we are ready to start the infusion right now.

Areas of possible improvement:

- Explain the underlying disease process
- Better description of what IVIG is and how it works to treat Guillain-Barre syndrome

- Length of treatment time (one transfusion vs daily for 5 days)
- What the treatment entails (what the product is/looks like, how long the infusion takes, at the bedside vs treatment room, etc)
- Too many risks mentioned (see question 4 below)
- Does not mention hemolysis
- Does not use layperson terms
- Does not ask if any questions
- Unless urgent, patients should be given time to consider their options

4. Which of the following risks should be disclosed?
    a. Acute renal failure
    b. Anaphylaxis
    c. Hemolysis
    d. Thrombosis

- There are innumerable risks associated with any medical intervention, and it is not necessary or desirable to list them all. Rather, your duty as a physician is to inform your patient of the *material* risks, which are defined as risks a "reasonable person", in your patient's position, would find important when making decisions about their medical treatment. This can generally be interpreted as adverse events that are common or potentially life-threatening (even if those life-threatening reactions are rare).
- When administering high-dose IVIG, common adverse reactions include fever and chills, urticaria and headache. Rare but potentially life-threatening reactions include thrombosis and anaphylaxis. Hemolysis is both a common and potentially severe complication of high-dose IVIG and amongst non-group O patients may occur in as many as 1 in 3 infusions, although only rare cases will be severe enough to require medical intervention.
- Because IVIG is a fractionated plasma product which has been manufactured using pathogen inactivation technologies such as solvent-detergent treatment, the theoretical risk of contamination with bacteria (sepsis) or leukocytes (graft-versus-host-disease) is arguably too small to mention. It must be acknowledged, however, that because fractionated plasma products are manufactured from the plasma donations of tens of thousands of individual blood donors, they have historically carried a very high risk of disease transmission of cell-free pathogens such as hepatitis and HIV. This was particularly true of products such as coagulation factor concentrates that underwent relatively little processing during their manufacture (an international outbreak of hepatitis C from IVIG was documented as recently as 1994.)
- Currently, the manufacturing process of these products is such that a number of pathogen reduction and inactivation steps can be applied that are as of yet not routinely applied to blood components such as red blood cells, platelets and plasma. Pathogen inactivation has been shown to be very effective in preventing transmission of many viral pathogens

- Nonetheless, given the extremely high number of donor exposures per vial of fractionated plasma product and the fact that pathogen reduction and inactivation strategies are not guarantees against the transmission of all known agents (eg., parvovirus, hepatitis A and hepatitis E), a "reasonable person" is still entitled to the knowledge that receipt of a fractionated plasma product may yet result in a chronic infectious disease, even if that risk is very low. Note that a reported case of vCJD transmission from a fractionated plasma product (a FVIII concentrate infused in the UK in 1998, with vCJD diagnosed post-mortem 11 years later) suggests that prion transmission is included as a potential risk of IVIG therapy.

Case 3

An 80 year-old woman presents to her local ER with hemopericardium 3 days following insertion of a pacemaker for sick sinus syndrome. Physical examination reveals a heart rate of 130 BPM, blood pressure of 90/50 mmHg with a 15 mmHg pulsus paradoxus, quiet heart sounds and distended neck veins. Laboratory investigations reveal a Hgb of 100 g/L, a WBC of 9 x 10^9/L and a platelet count of 90 x 10^9/L. Her INR is elevated at 2.9, aPTT and fibrinogen are normal at 40 seconds and 3.0 g/L, respectively, and the patient's family informs you she is on long-term warfarin. A bedside echocardiogram reveals a large pericardial effusion with signs of tamponade.

ICU is consulted and, after consulting with their staff, the fellow proposes that a pericardiocentesis be performed by cardiology – but only after the patient's anticoagulation has been reversed. The emergency medicine physician then consults with hematology on the available options to achieve this, and is told that the fastest option is prothrombin complex concentrate (PCC). The ER physician writes an order for 2000 units, to be administered by nursing via mini-bag infusion.

*Ask one resident to enact how they would explain the **alternatives** of this treatment to the patient, and then pose the following questions to the group:*

5. Which of the following individuals is responsible for obtaining informed consent for PCC?
    a. The ICU fellow
    b. The hematologist
    c. The ER physician
    d. The ER nurse

- The physician who is proposing the treatment is the most appropriate individual to obtain informed consent to perform it. While this discussion can be delegated to individuals on that physician's team, those individuals must be able to fully explain the risks, benefits and alternatives to the patient, and responsibility still ultimately resides with the staff.

- The individual proposing the treatment may wish to consult other services for assistance in understanding the risks, benefits and alternatives to the treatment they are proposing, but as the patient's most responsible physician, it is still their decision as to what treatment to pursue. In this case the most responsible physician is still the ER physician; nursing will only carry out an order for PCC that they have written or co-signed, even if the treatment has been proposed by hematologist, and even if the PCC has been proposed in response to a request for anticoagulant reversal by the ICU fellow. While nursing may be of assistance in communicating this decision to the patient, and has an important role in advocating on their behalf (eg. ensuring that an informed consent discussion has occurred), the physician who writes the order for PCC is ultimately responsible for the obtaining informed consent.

6. Which of the following should <u>not</u> be offered as an alternative to PCC infusion to this patient?
    e. Plasma
    f. IV vitamin K
    g. Platelets
    h. Pericardiocentesis while fully anticoagulated

- While the ordering physician would be justified in preferring PCC in this patient due to its proven efficacy, ease of administration and low risk profile, there is an obligation to offer alternative treatments, particularly if the patient expresses concerns regarding the specific risks associated with PCC (eg., history of heparin-induced thrombocytopenia).
- Plasma has a number of disadvantages to PCC (particularly a higher rate of adverse transfusion reactions including TACO and slower rate of infusions), but in an open-label randomized controlled trial of PCC vs plasma for treatment of major bleeding in patients taking vitamin K antagonists, both treatments resulted in equivalent hemostatic efficacy.
- Vitamin K has a slower onset of action but will result in a complete and more durable reversal of warfarin effect than either PCC or plasma (typically within 6 hours if given intravenously) and should therefore also be offered as an alternative, although as with plasma the delay in care may place the patient at increased risk from ongoing bleeding.
- Although performing an emergency pericardiocentesis in a fully anticoagulated patient is likely the highest-risk alternative to offer, this potentially life-saving option should not be withheld in a patient who declines to receive blood products; indeed, withholding a pericardiocentesis in this patient unless they agree to a transfusion would arguably be coercive. According to the CMPA, "Consent obtained under any suggestion of compulsion either by the actions or words of the doctor or others may be no consent at all and therefore may be successfully repudiated."
- When discussing alternatives to the proposed treatment, the risks of each should also be disclosed and contrasted, and the physician may make plain

what their preferences are and why. Once the patient has been fully informed, their choice should then be honoured. However, there is no obligation by the physician to offer an alternative treatment that they do not believe will have any therapeutic benefit simply because the patient requests it or because it would be "better than nothing".

- In this situation, there is no reason to believe, from either clinical experience or theoretical reasoning, that a platelet transfusion would decrease bleeding risk in this patient, given their platelet count and absence of apparent platelet dysfunction. It would therefore be inappropriate to suggest otherwise to the patient by proposing it as a treatment option, particularly given the associated risks of this product.
- Similarly, offering a Jehovah's Witness a blood product simply because they express a willingness to receive it (eg, albumin or a recombinant coagulation factor concentrate) would be inappropriate if those products were not felt to have any actual therapeutic benefit.

Case 4

A 30 year-old woman, referred for elective thoracolumbar spinal fusion with instrumentation and bone grafting for severe scoliosis, is noted on the day before surgery to have a hemoglobin of 80 g/L and an MCV of 60 fL. She reports a history of chronic anemia and menorrhagia but is otherwise well and is keen to have the surgery performed as soon as possible. The attending surgeon anticipates that there will be significant bleeding during the procedure and, given the patient's current hemoglobin is fairly certain that transfusion support will be required. In fact, he suggests that 2 units of RBCs be transfused before even taking the patient to the OR, but defers to your opinion as the anesthetist regarding the best course of action.

*Ask one resident to enact how they would explain the **long-term risks** of transfusion to the patient (ie., risks that typically manifest more than one month after the transfusion)*

Ask another resident to enact how they would present possible alternatives to transfusion in this situation

Then pose the following questions to the group

7. Which of the following is the greatest long-term risk posed to this patient from a red blood cell transfusion?
    a. Chronic hepatitis B
    b. Iron overload
    c. **Pregnancy complications**
    d. Transplant complications

- While infection with hepatitis B should be considered a material risk of transfusion (a case occurred in Ireland from a RBC transfusion just recently),

the risk remains extremely low, estimated to occur at a rate of 1 in 7.5 million transfusions in Canada.

- Iron overload is a significant hazard to patients who are started on long-term transfusion therapy, but only occurs after 20 or more units of RBCs are transfused outside the setting of hemorrhage or apheresis therapy. Thus, while this risk should be disclosed to any patient in whom chronic transfusion therapy is being proposed (or who has already developed iron overload), it is not a relevant concern in this patient.
- Sensitization to antigens contained within a blood product is a relatively common complication of transfusion and should be disclosed if the resulting antibodies are likely to pose a clinical hazard to the patient. In this case, inducing the formation of an anti-RBC antibody (a consequence of approximately 5% of RBC transfusion episodes) in a woman of child-bearing age will result at a minimum in the need for more aggressive monitoring during future pregnancies and possibly for interventions aimed at decreasing the incidence and severity of hemolytic disease of the newborn (such as IVIG therapy and intrauterine transfusion support).
- Similarly, a patient who is awaiting an organ transplant should be informed that transfusion of cellular blood products increases the risk of HLA sensitization, which in turn decreases the likelihood of finding a compatible donor. As there is nothing in this patient's history to suggest they may require an organ transplant however, this should not be considered a high risk in her particular case.

8. Which of the following is the best course of action in this situation?
    a. Administer IV iron and erythropoietin today for tomorrow's surgery
    b. Postpone the surgery and refer for anemia management
    c. Maximize blood sparing interventions intra-operatively, including systemic tranexamic acid and careful use of electrocautery
    d. Seek consent from the patient to transfuse 2 units of RBCs prior to taking her to the OR

- A key component of an informed consent discussion is that whenever possible it be performed early enough to allow the patient to avail themselves of alternative interventions. In this case, the patient most likely has iron deficiency and would benefit from intravenous iron, although other etiologies for her microcytic anemia would need to be considered as well (for example, a hemoglobinopathy or anemia of chronic disease). Administering IV iron the day before surgery, however, even if accompanied by erythropoietin, will have very little effect on the patient's hemoglobin intra-operatively and will thus be of little benefit as a transfusion-sparing alternative.
- Similarly, while tranexamic acid is a valuable hemostatic adjunct in orthopedic and other surgical procedures, it is unlikely that this alone will decrease the need for transfusion in a patient who will undergoing a major surgical procedure starting with such a severe degree of anemia. Thus, while IV iron

and tranexamic should be offered to this patient, it is not realistic to frame these as alternatives to transfusion in the current context.

- Given the established adverse effects of perioperative transfusion (including post-operative infections, a transfusion risk which the patient should also be informed of), and the likelihood that blood exposure could be avoided with proper investigation and management of the patient, the preferred course of action in this situation would be to re-book the procedure for a later date. However, the patient would need to consent to this approach if the surgical team is indeed offering immediate surgery with transfusion support as an alternative course of action.

Case 5

You are asked to assess a 16 year-old boy for a lung transplant for bleomycin-induced lung toxicity. The patient demonstrates an understanding of the procedure but reports that he has recently become a Jehovah's Witness and therefore does not wish to be transfused. His parents, realizing that refusal of transfusion support may delay his eligibility for surgery, wish to over-rule his wishes on the argument that he has not reached the age of majority and therefore cannot fully understand the implications of his decisions. They also recall being told that he requires "special blood" due to his history of Hodgkin's disease, but are unsure exactly what that refers to

Ask one resident to enact how they would explain the <u>benefits</u> of transfusion to the patient and his family

Questions for the group:

9. In adjudicating between the conflicting wishes of the patient and his family, which of the following is the best course of action?
    a. Ask the Jehovah's Witness hospital liaison and Hospital legal affairs to meet with the patient and his family in order to achieve consensus
    b. Defer surgery until the patient is 18 years of age
    c. Respect the parent's wishes, even if that means waiting until the patient is under anesthesia before transfusing
    d. Respect the patient's wishes, even if that means cancelling the surgery

- According to the CMPA, "The legal age of majority has become progressively irrelevant in determining when a young person may consent to his or her medical treatment. As a result of consideration and recommendations by law reform groups as well as the evolution of the law on consent, the concept of maturity has replaced chronological age.
- The determinant of capacity in a minor has become the extent to which the young person's physical, mental, and emotional development will allow for a

full appreciation of the nature and consequences of the proposed treatment, including the refusal of such treatments." This position has been codified by all provincial colleges with the exception of Quebec, which maintains a fixed age of 14 as the threshold below which consent of the parent, guardian or court is required. The only exception to this approach is consent to medical assistance in dying, where current legislation still upholds 18 as the minimum age for which such a decision can be made; below this threshold a patient's parents or guardian still cannot decide on the minor's behalf

- Thus, in the current situation, in which the patient does appear capable of making informed decisions, their wishes must be respected and it is not necessary to defer the surgery until they are 18 to allow these wishes to override those of the parents.
- While seeking input from the patient's religious institute and hospital administrators would be wise in this situation (particularly to determine whether a surgeon is locally available who is willing to perform the surgery without transfusion support), deferring to these two groups to convince the patient and the family to adopt the same position regarding the acceptability of transfusion is probably not realistic; even after they have provided important contextual information it is likely a conflict of opinion will remain which the treating physician will still need to adjudicate.

Additional information regarding medical decision making from the Canadian Pediatric Society: https://cps.ca/documents/position/medical-decision-making-in-paediatrics-infancy-to-adolescence

10. Which of the following special blood does this patient require?
    a. CMV-negative
    b. HLA-matched
    c. HPA-matched
    d. Irradiated

- Although Canadian guidelines for the prevention of transfusion-associated graft-versus-host-disease have recently become more stringent, a history of Hodgkin's lymphoma, at any stage of disease, is still considered an indication for lifelong irradiation of cellular blood products; in one prospective study, 2 out of 53 patients with Hodgkins lymphoma developed Ta-GVHD (generally a fatal condition) after the transfusion of non-irradiated blood products, and case reports have shown this risk continues even in patients who have achieved complete remission.
- While RBC transfusions can induce the formation of anti-HLA and HPA antibodies, there are no established indications for the transfusion of HLA- or HPA- matched RBCs. HLA-matched platelets, however, may be of benefit in patients with a history of refractory thrombocytopenia due to anti-HLA antibodies, while HPA-matched platelets may be considered in patients who have developed either neonatal alloimmune thrombocytopenia or post-

transfusion purpura due to the development of anti-HPA antibodies. In the absence of these conditions (as is apparently the case here), platelet transfusions from random donors are acceptable

11. If this patient didn't have a history of Hodgkin's lymphoma, and instead required a lung transplant due to complications of an HIV infection, would that change your recommendation regarding the type of special blood they require?

a. Yes
b. No

- Without the history of Hodgkin's lymphoma, there would be no indication for irradiation of their blood products, even with a history of HIV or with a future need for immunosuppression for the lung transplantation
- In general, Ta-GVHD develops in patients who cannot defend themselves against T-cells present in blood product, and which proliferate in the recipient post-transfusion: either the patients do not recognize these donor T cells as foreign due to shared HLA haplotypes, or they cannot effectively clear them from circulation due to a weakened immune system
- The types of recipient immunodeficiency that predispose patients to Ta-GVHD are complex and not entirely well-defined, but it is patients who lack their own T-cells that appear to be at greatest risk. This selective T-cell deficiency can be congenital; acquiring it requires either myeloablative doses of chemotherapy (eg., when given for stem cell transplantation, rather than for treatment of cancer or to prevent rejection of a transplanted organ), or the administration of medications that are particularly toxic to T-cells (eg.,purine analogues)
- The lack of Ta-GVHD in patients with HIV is difficult to explain, as these patients are also T-cell deficient. One explanation is that they are primarily deficient in CD4 T-cells, and these cells are required for the proliferation the donor CD8 T-cells. For this reason, the selection of irradiated RBCs and platelets is generally not required for HIV-positive patients, and thus for this patient, would no longer be necessary