Educational Case

Educational Case: A perioperative patient blood management

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The following fictional case is intended as a learning tool within the Pathology Competencies for Medical Education (PCME), a set of national standards for teaching pathology. These are divided into three basic competencies: Disease Mechanisms and Processes, Organ System Pathology, and Diagnostic Medicine and Therapeutic Pathology. For additional information, and a full list of learning objectives for all three competencies, see https://www.journals.elsevier.com/academic-pathology/news/pathology-competencies-for-medical-education-pcme.[1]

Primary objective

Objective TM1.1: Blood components. Define the blood components and blood component substitutes available for clinical use; the evidence-based indications and dosing for transfusion of these components; and how the efficacy of transfusion may be monitored.

Competency 3: Diagnostic Medicine and Therapeutic Pathology, Topic: Transfusion Medicine (TM), Learning Goal 1: Concepts of Blood Transfusion.

Patient presentation

A 44-year-old woman presents to the clinic for preoperative clearance prior to bilateral total knee arthroplasty and reports a one-month history of dyspnea on exertion. She first noticed this while playing the third hole of a golf game, and this distressed her because she is an avid golfer. She does not report any symptoms at rest and states that her symptoms are with exertion and typically subside after about 15 min of rest. She does not report any nausea, vomiting, chest pain, or fever/chills.

The past medical history is significant for osteoarthritis of both knees that is refractory to medical therapy as well as uterine fibroids and associated heavy, painful menstrual periods. She takes 325 mg acetaminophen twice daily for pain. The patient is an office worker. She lives with her husband in a single-family home, has 1–2 standard drinks a week, but does not report any history of tobacco or drug use. In addition to being a lifelong golfer, she was also a long-time marathon runner before her knee problems. Her family history is positive only for hypertension in her father.

Diagnostic findings, Part 1

The patient has a blood pressure of 126/68 mmHg, a pulse of 88 beats per minute, a respiratory rate of 16 breaths per minute, and her oxygen saturation is 98% while breathing room air. Mild conjunctival pallor is noted. Both knees show bony enlargement, crepitus, effusion, and decreased range of motion. Physical examination is otherwise normal. Standing X-rays of both knees taken prior to the visit at the orthopedic surgery clinic show significant joint space narrowing, particularly of the medial joint space as well as osteophyte formation.

Questions/discussion points, Part 1

What is the differential diagnosis for this patient's dyspnea?

This 44-year-old woman presenting with exertional dyspnea and conjunctival pallor with a past medical history of heavy menstrual bleeding and uterine fibroids raises concern for a symptomatic anemia that should be optimized prior to surgery. Other diagnoses to consider in the differential include pulmonary disease such as interstitial lung disease and cardiac causes such as congestive heart failure.

Diagnostic findings, Part 2

Further testing is begun for this patient with a posteroanterior chest radiograph and a complete blood count (CBC). The results of the CBC are listed in Table 1. The patient's chest radiograph is normal.

Table 1
Laboratory values at presentation.

	Value	Normal range
Complete blood count		
Hemoglobin	10.7 g/dL	13.3–16.2 g/dL
Hematocrit	32.1%	38.8–46.4%
Red blood cell count	3.12×10^6/mm^3	4.30–5.60×10^6/mm^3
Mean corpuscular volume	75.1 μm^3	79–93.3 μm^3
Mean corpuscular hemoglobin concentration	30 g/dL	33–35 g/dL
Red cell distribution width	20%	12–14%
Mean corpuscular hemoglobin	24 pg/cell	27–33 pg/cell
Reticulocyte count	1.2%	0.8–2.3% Red Cells
Platelets	450×10^3/mm^3	165–415×10^3/mm^3
White blood cell count	5.2×10^3	3.54–9.06×10^3/mm^3

Questions/discussion points, Part 2

Interpret the CBC

Generally, the diagnosis of anemia is confirmed by a low hemoglobin and hematocrit. Therefore, this patient can be diagnosed with an anemia given a hemoglobin of 10.7 g/dL which is below 13.3 g/dL, the lower limit of normal for an adult woman.

This patient's diagnosis of anemia can also be further refined from the results of the CBC to better establish a more precise differential diagnosis of the anemia's etiology. The first step in the assessment of anemia is determining whether the anemia is microcytic, normocytic, or macrocytic based upon whether the mean corpuscular volume, which is a measure of the average volume of red blood cells (RBCs) in the sample, is low, normal, or high, respectively.

The MCV is low and means this patient has a microcytic anemia. The next step is to determine whether it is a hypoproliferative anemia (i.e., there is an issue with RBC production) or whether it is hyperproliferative (i.e., RBC production is increased but still inadequate because the cells have a decreased lifespan). This can be determined from the reticulocyte count, a measure of the percentage of immature RBCs in the sample.

The reticulocyte count is inappropriately normal for the magnitude of the anemia, which indicates the bone marrow is not responding appropriately to the anemia by increasing the rate of erythropoiesis. Additionally, the platelet count is elevated in this patient, which can be a nonspecific indicator of iron deficiency anemia. From this constellation of values from the CBC, we can conclude this patient has a *hypoproliferative microcytic* anemia.

What is the differential diagnosis of a hypoproliferative microcytic anemia?

Generally, the primary cause of a hypoproliferative microcytic anemia is any process that leads to impaired hemoglobin production. These can be hereditary, such as thalassemia, or acquired due to iron deficiency, exposure to certain toxins such as lead, or as a sequela of chronic disease. A thalassemia is unlikely in this patient given her active athletic history and that she does not report any family history of anemia. Toxin exposure is also unlikely given that the patient does not report any reported occupational exposure to toxins or other risk factors for exposure. Anemia of chronic disease is also possible given her history of osteoarthritis.

In addition, the red cell distribution width (RDW) is elevated. The RDW increases as the degree of RBC size variability increases. The RDW is usually increased in iron deficiency anemia, as this condition is often characterized by a larger variety of RBC sizes. In contrast, the RDW usually remains normal in anemia of chronic disease. Given this differential diagnosis, ferritin is ordered to confirm the diagnosis of iron deficiency anemia.

Table 2
Follow-up ferritin two days after initial presentation.

	Result	Normal values
Ferritin	7 ng/mL	10–150 ng/mL

Diagnostic findings, Part 3

The serum ferritin result is shown in Table 2.

Questions/discussion points, Part 3

What can be concluded from this laboratory result?

In this context, the decreased level of ferritin, the storage form of iron in the human body, confirms the diagnosis of iron-deficiency anemia. This is also consistent with her history of heavy periods as the cause of her chronic blood loss and iron depletion. If this were anemia of chronic disease, then the ferritin level would be normal or elevated.

What are the principal steps in management for this patient prior to her procedure?

In keeping with the principles of patient blood management (PBM), the patient's iron deficiency anemia should be treated to optimize this patient prior to surgery. If this were anemia of chronic disease, then treatment would be focused on treating the underlying chronic disease/inflammatory process.

What is a basic definition of patient blood management?

PBM is the appropriate use of blood transfusion for optimal patient care.[2] This consists of both responsible, conservative use of blood products as well as measures undertaken to prevent the need for transfusion, such as preoperative optimization and minimization of perioperative blood loss.[3] For this patient, this means a combination of preoperative optimization through addressing her anemia as well as a number of potential perioperative measures to minimize blood loss.

While the risks of transfusion are relatively small, they are not zero. Moreover, restrictive threshold strategies are usually associated with better patient outcomes compared to more liberal transfusion strategies even when controlling for demographics, clinical conditions, and disease/injury severity.[2,3]

Why is detecting and treating preoperative anemia important?

Anemia is a significant predictor of requiring transfusion during surgery.[4] Prevalences vary widely among patient populations, but a general estimate is about a third of patients have preoperative anemia.[4]

What are the roles of erythropoietin, B12, iron, and folic acid supplementation for preoperative anemia?

Erythropoietin (EPO) is an endogenous hormone that is produced by renal peritubular interstitial cells in response to hypoxia that stimulates erythropoiesis in the bone marrow.[5] A recombinant form of this hormone can be administered to stimulate a rapid increase in RBC production a few days to a few weeks prior to her surgery.[5] EPO is not indicated for this patient, as there is no evidence of impaired kidney function. Intravenous iron was given to address the patient's iron deficiency.[5] Intravenous iron was preferred over oral iron as oral iron supplementation is limited by GI side effects and poor absorption.[6] Folate and B12 can be given if the patient is deficient, as they are sometimes relatively easily treatable etiologies of macrocytic anemia.[5] In sum, this patient has microcytic anemia, demonstrable iron deficiency, and no suspicion or evidence of folate or B12 deficiency.

Diagnostic findings, Part 4

The patient is treated with intravenous iron, and her hemoglobin normalizes to 15.1 g/dL on a subsequent measurement. Following pre-operative treatment, the patient's hemoglobin normalizes to 15.1 g/dL. The patient is scheduled for a bilateral total knee arthroplasty. She asks if she should donate blood for herself in advance, as her older brother contracted hepatitis C from a blood transfusion in the early 1980s. Her physician educates her about the safety of the blood supply and reassures her that donating for herself is not routinely necessary unless the patient has a very rare RBC phenotype.

At the time of surgery, the surgical team elects to use many measures to decrease the need for blood transfusion, including anti-hemorrhagic agents, intraoperative cell salvage, normovolemic hemodilution, and reinfusion of the blood removed during the salvage and hemodilution process.

Questions/discussion points, Part 4

What are some common indications for transfusion of various blood products?

A summary of some common indications for these blood products is shown in Table 3.[7],[8]

The most common blood products are RBCs, platelets, plasma, and cryoprecipitate. RBCs provide oxygen-carrying capacity. For example, RBCs are commonly transfused when a patient has signs or symptoms of anemia along with a hemoglobin of less than 7 g/dL in most patient populations. Another common indication is acute blood loss or in a massive transfusion.

Platelets provide primary hemostasis and are often transfused when a patient has bleeding due to severe thrombocytopenia. For example, platelets are commonly transfused when a patient is bleeding or under-going surgery, and the platelet count is less than 50 k/uL. Another common indication is to prevent spontaneous bleeding in a patient with a platelet count less than 10 k/uL.

Plasma provides coagulation factors for secondary hemostasis. For example, plasma is commonly transfused when a patient has coagulo-pathic bleeding or oozing due to multiple coagulation factor deficiencies. An INR of greater than 1.5–2.5 is sometimes used, but the optimal INR-based threshold is not known. Another common indication for plasma is massive transfusion. Instead of plasma transfusion, an infusion with prothrombin complex concentrate (PCC; consisting of factors II, VII, IX, and X) is currently preferred for the rapid reversal of warfarin due to the decreased risks of transfusion reactions from PCC compared to plasma.

Cryoprecipitate is essentially the fibrinogen that is isolated from a unit of plasma. It is usually transfused as an adjunct to plasma in the setting of massive transfusion or for patients with coagulopathic bleeding due to hypofibrinogenemia.

What is an INR?

INR stands for international normalized ratio and is a standardized measure for assessing the extrinsic and common coagulation pathways. It is calculated from the patient's prothrombin time, which is a measure of the speed of coagulation when tissue factor and calcium are added to a sample of the patient's plasma.

What pharmacologic agents can be used to minimize perioperative blood loss and subsequently avoid blood transfusion?

Antifibrinolytics such as tranexamic acid (TXA) and aminocaproic acid have been found to reduce blood loss and the subsequent need for allogeneic RBC transfusion intraoperatively.[9] These medications are lysine analogs that can be given intraoperatively to inhibit plasminogen activation and subsequent breakdown of clots. These merely prevent clot breakdown and do not induce clotting. As such, no significant risk of thrombosis has been demonstrated.[9]

What is intraoperative cell salvage?

There are devices available that are able to collect bloodshed into the operative field, mix it with an anticoagulant, and store it for reinfusion later in the procedure.[5] Using this method, approximately 50% of the blood lost during certain procedures can be recovered and reinfused.[5] These devices typically also wash the blood to remove constituents that are not conducive to transfusion, such as free hemoglobin, contaminants, and activated clotting or immunologic factors.

What is acute normovolemic hemodilution?

Acute normovolemic hemodilution (ANH) is a strategy for the conservation of blood products, wherein blood is removed from the patient shortly after the beginning of the intraoperative period and replaced with a large volume of crystalloid or colloid. This technique decreases the effective loss of blood by decreasing the patient's hemoglobin and RBC concentration during the period where the most blood loss occurs.[5],[9] Following this period, the patient can then be reinfused with their own fresh whole blood. ANH may reduce transfusions, but the evidence is mixed.[5],[9]

What is autologous blood transfusion and why is it avoided?

Autologous blood transfusion is a blood transfusion using a patient's own blood products that were donated preoperatively in advance of the perioperative period.[10] By using the patient's own blood products, this can theoretically decrease the risk for transfusion-related reactions and the risk of transfusion-transmitted infection. However, the preoperative donation has become much less common in the USA, as it is likely to create an anemia prior to the procedure and requires significant preop-erative planning and resources despite rarely being transfused back to the patient.[10] More importantly, the safety of the donor blood supply is dramatically better than it was in the 1980s.[11–14] However, autologous donation often plays an important role in the procurement of blood with rare RBC phenotypes.[15]

Diagnostic findings, Part 5

Using these PBM strategies, the surgical team is able to avoid blood transfusion for this patient over the course of her hospitalization. The patient does well and is discharged with the resolution of her presenting symptoms. About one year after the surgery, she continues to do well and celebrates her 45th birthday by playing 18 holes of golf at The Old Course at St Andrews in Fife, Scotland.

Questions/discussion points, Part 5

What are some other examples of PBM?

Specific practices vary among institutions and can change frequently with new data, but some common current strategies are listed in Tables 4

Table 3
Blood products and some common indications for transfusion.

Blood product	Common indications
Red blood cells (RBCs)	Signs and symptoms of anemia & Hgb <7.0 g/dL
Platelets	Prevention of spontaneous bleeding & platelet count <10 k/uL
	Bleeding or surgery & platelet count <50 k/uL
Plasma	Coagulopathic bleeding
	Massive transfusion
Cryoprecipitate	Hypofibrinogenemia

Table 4
Three pillars of patient blood management.

	Pillar 1: Detection and management of anemia	Pillar 2: Minimization of bleeding and blood loss	Pillar 3: Improve tolerance to anemia
Preoperative	Identify anemia 4–6 weeks before surgery Treat iron deficiency Consider erythropoietin (EPO)	Identify and manage bleeding risk Review medications Minimize iatrogenic blood loss	Compare estimated blood loss with patient-specific tolerable blood loss Formulate patient-specific plan using blood conservation modalities
Intraoperative	Schedule surgery with optimization of red cell mass	Meticulous hemostasis and surgical techniques Balanced physiology to aid optimal coagulation Antifibrinolytics and cell salvage	Optimize cardiac output, oxygenation, and ventilation Evidence-based transfusion thresholds
Postoperative	Manage anemia	Prevent and/or manage bleeding Minimize iatrogenic blood sampling	Evidence-based transfusion thresholds

Table 5
Some common patient blood management strategies.

RBCs	Consider single-unit red blood cell transfusions for adults who do not have active bleeding
Platelets	Do not routinely transfuse more than a single dose of platelets
Plasma	Only consider plasma if clinically significant *coagulopathic* bleeding or oozing and not due to warfarin
Prothrombin complex concentrate (PCC)	Offer immediate PCC for the emergency reversal of warfarin anticoagulation instead of plasma

and 5.[16] Table 4 lists the three basic pillars of PBM: the detection and management of anemia, the minimization of bleeding and blood loss, and the improvement of tolerance to anemia. The first pillar includes the strategy of identifying anemia far enough in advance of the surgery so that the anemia can be corrected (e.g., with iron and/or EPO). Another principle is to assess the patient for bleeding risk via a bleeding history and, if necessary, refer the patient to a hematologist if the patient has a history of bleeding spontaneously or bleeding excessively when challenged. Included in this assessment is a review of medications that can cause a bleeding tendency such as anticoagulants.

The second pillar includes the strategy of minimizing iatrogenic blood loss. One aspect of this is the minimization of phlebotomy blood draws from unnecessary laboratory tests and the related Choosing Wisely campaigns to educate physicians with evidence-based recommendations for the ordering of laboratory tests.[17,18] This strategy also involves intraoperative techniques, such as the use of meticulous surgical techniques to maximize hemostasis, the maintenance of balanced physiology to aid optimal coagulation, and the use of antifibrinolytics and cell salvage when indicated.

The third pillar is more indirect and involves maximizing the patient's ability to tolerate some degree of anemia. Some aspects of this are to formulate a patient-specific plan that estimates the patient's tolerable blood loss, optimize cardiac output, oxygenation, and ventilation, and utilize evidence-based transfusion thresholds. The latter is the result of decades of strong evidence that demonstrates that most patient populations tend to have better outcomes if they are not transfused to the normal range of the relevant laboratory parameter.[19] Unlike many analytes in the blood, it is not routinely necessary to transfuse a patient's

hemoglobin, platelet count, INR, or fibrinogen level to the normal range. In fact, repeated studies have demonstrated that patients who were transfused liberally tended to have worse outcomes in randomized controlled trials compared to patient who were transfused more conservatively.[20] This is a non-intuitive and critical point, as most analytes in the blood are typically maintained relatively strictly in the normal range (e.g., sodium, potassium, and glucose).

To accomplish this appropriate degree of transfusion, Table 5 lists some concrete strategies that are often recommended for transfusion indications. The context of these recommendations is that many of the evidence-based guidelines contradict popular practices from the past. For example, a common recommendation is to transfuse one unit of RBCs at a time with a post-transfusion reassessment for most patients who are not actively bleeding. The popular practice from the past that this is trying to dispel is the non-evidence-based motto of, "If you're going to give one, then you might as well give two." The new motto is, "Why give two when one will do?" The main concept is to view transfusions just like any other treatment and to apply the principles of evidence-based medicine and lifelong learning to transfusion decisions.[20]

Teaching points

- The four most common blood products are RBCs, platelets, plasma, and cryoprecipitate.
- RBCs are often given for symptomatic anemia with a hemoglobin less than 7 g/dL.
- Platelets are often given for bleeding with a platelet count less than 50 k/uL.
- Plasma is often given for coagulopathic bleeding or oozing due to multiple coagulation factor deficiency and often with an INR over 1.5–2.5. The optimal INR cutoff for plasma transfusion or the prediction of bleeding has not been established.
- Prothrombin complex concentrate is preferred for rapid warfarin reversal instead of plasma transfusion in order to minimize the risk of a transfusion reaction.
- Cryoprecipitate is often given as an adjunct to plasma to provide additional fibrinogen.
- The diagnosis of anemia and its subtypes is based upon careful assessment of complete blood count results and complementary laboratory studies.
- Patient blood management is a multi-faceted approach to optimize the responsible use of blood products.
- The overall goal of PBM is the appropriate use of blood transfusion for optimal patient care. This consists of the conservative use of blood products. Transfusion safety is at an all-time high, but the risks are not zero. Abundant evidence shows that restrictive transfusion strategies are generally associated with better outcomes than liberal strategies as an independent factor.
- Diagnosing and treating preoperative anemia is an important part of PBM, as preoperative anemia is a strong predictor of requiring transfusion during surgery.
- Common treatments of preoperative anemia include EPO, iron, folate, and B12.
- Antifibrinolytics, such as tranexamic acid and aminocaproic acid, can be used intraoperatively to decrease blood loss and the subsequent need for blood products by inhibiting plasminogen.
- Cell salvage involves the collection of bloodshed into the operative field and reinfusing later in the procedure. About 50% of the blood lost during many procedures can be saved and reinfused.
- Acute normovolemic hemodilution involves the removal of blood shortly after the beginning of the surgery and replacing it with a large volume of crystalloid or colloid. The evidence for its efficacy is mixed.
- Autologous blood transfusion uses the patient's own blood products that were donated preoperatively. It has become much less common in the USA as the safety of the blood supply has markedly improved.

Funding

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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