Therapeutic Apheresis in Hematologic Disorders: When and Why?

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Introduction

Therapeutic apheresis refers to a group of related interventions characterized by the use of extracorporeal blood separation in the treatment of disease. The establishment of therapeutic apheresis in modern transfusion practice is due in large part to technological advances such as automation and optimization of equipment and to the formalization of evidence-based guidelines for appropriate use.

Applications of therapeutic apheresis are cross-disciplinary and include renal, neurological, dermatologic, oncologic, and hematologic disorders. Apheresis has also become an important facilitator in the expanding world of hematopoietic progenitor cell (HPC) transplantation and cellular therapies.

The decision to embark on a course of therapeutic apheresis is not always straightforward and depends both on the presence of an appropriate indication and the suitability of the patient to undergo the procedure. Furthermore, because the procedures are complex, requiring specially trained staff and expensive equipment, the logistical arrangement of apheresis procedures requires planning and consideration of multiple factors.

In this chapter, we will discuss clinical vignettes that highlight the issues that must be considered when deciding when and why to employ therapeutic apheresis in hematologic disorders.

Case 1: Hemolysis and Renal Failure After Hematopoietic Progenitor Cell Transplantation

A 25-year-old Hispanic male with myeloid sarcoma in remission after chemotherapy underwent peripheral blood hematopoietic cell transplantation (HCT) with the use of an HLA-identical sibling donor. The recipient's ABO/Rh type is B, RhD positive; his sibling donor is O, RhD positive. He received a preparative regimen of fludarabine, cyclophosphamide, and total body irradiation, with cyclosporine for graft-versus-host disease (GvHD) prophylaxis.

His posttransplant course is complicated by CMV and HHV6 reactivation and subsequent graft failure. He develops worsening anemia and oliguric renal impairment requiring dialysis. On day+25 posttransplant, workup reveals rising LDH and total bilirubin, undetectable haptoglobin, and pancytopenia requiring red cell and platelet transfusions almost daily. There is no

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evidence of bleeding. Peripheral blood smear reveals many schistocytes; coagulation indices are normal. Von Willebrand factor-cleaving protease (ADAM-TS 13) level is 46 %. Direct antiglobulin test (DAT) is negative.

Pertinent laboratory indices:

	Day 0	Day+25 posttransplant	Reference ranges
Hemoglobin (g/dL)	10.4	7.2	13.5–17.5
WBC (K/uL)	0.40	0.03	4.0–10.0
Platelets (K/uL)	51	13	150–400
BUN (mg/dL)	11	139	6–20
Creatinine (mg/dL)	0.74	4.88	0.67–1.17
AST (U/L)	10	84	0–40
Total bilirubin (mg/dL)	0.6	5.9	0.0–1.2
Direct bilirubin (mg/dL)	<0.2	1.7	0.0–0.3
Haptoglobin (mg/dL)	NT	<10	30–200
LDH (U/L)	125	1698	113–226
ADAM-TS 13	NT	46 %	38–162 %

**NT* not tested

Question 1. What is the most likely diagnosis?

A. Passenger lymphocyte syndrome
B. Thrombotic thrombocytopenic purpura
C. Transplant-associated thrombotic microangiopathy
D. Atypical hemolytic uremic syndrome

Expert Clinical Perspective: In this patient, there is laboratory evidence of active hemolysis and renal impairment on a background of graft failure without autologous marrow reconstitution. Passenger lymphocyte syndrome (PLS), caused by donor-derived isohemagglutinins leading to hemolysis of recipient red cells, is a reasonable consideration, as this is a minor ABO-incompatible HCT. However, in PLS the DAT is generally positive and donor-derived antibody (in this case, anti-B) would be eluted from circulating red cells.

The coexistence of schistocytes, thrombocytopenia, and renal impairment suggests a microangiopathic hemolytic anemia rather than immune red cell destruction. Normal ADAM-TS 13 levels speak against TTP. Atypical HUS is usually a chronic disorder due to abnormalities of complement associated with a number of genetic mutations; the disease generally manifests in early childhood and would be unlikely in this case.

This constellation of clinical findings is best attributed to transplant-associated thrombotic microangiopathy (TA-TMA). TA-TMA is more common after allogeneic HCT, but also occurs in the autologous setting; the reported prevalence varies widely, reflecting disparities in awareness as well as diagnostic difficulty.

TA-TMA is of unclear etiology but is thought to be due to endothelial damage and activation and is frequently seen alongside other HCT complications such as infections and GvHD. It is possible that TA-TMA represents the final pathway of endothelial injury secondary to multiple causes. Furthermore, the diagnosis is often confounded by renal injury from underlying disease or medications.

An autopsy study (Siami et al. 2008) showed that although the renal findings are very similar to those of TTP or HUS, TA-TMA is distinct in that the kidney is often the only affected site. Because renal biopsy may be risky in this population, noninvasive diagnostic criteria were developed by two consensus groups (Ho et al. 2005; Ruutu et al. 2007). Hypertension and proteinuria are important clinical findings; some cases are relatively mild, but in severe cases, patients are critically ill and mortality is high.

Question 2. How would you manage TA-TMA?

A. Therapeutic plasma exchange.
B. Replace cyclosporine with mycophenolate mofetil or corticosteroids.
C. Rituximab infusion 375 mg/m^2 weekly for 4 weeks.
D. Supportive care with transfusion and renal replacement therapy.

Expert Clinical Perspective: There is no established treatment strategy for TA-TMA. Despite

clinical and histologic similarities to TTP, early cases of TA-TMA were distinguished by the lack of response to therapeutic plasma exchange (TPE) (George 2008). Unlike in TTP, there is no known pathogenic antibody or macromolecule that is putatively being removed by plasma exchange. If TPE is attempted, plasma is generally used as the replacement fluid.

TA-TMA is a Category III indication for TPE according to the 2013 American Society for Apheresis (ASFA) guidelines (Schwartz et al. 2013). The success of TPE is highly variable and may be influenced by timing of other clinical interventions. Multiple published series have shown that TPE for TA-TMA is associated with poor response and high mortality (Laskin et al. 2011). The potential complications of apheresis (central venous access difficulties, bleeding, hemodynamic instability due to fluid shifts, and transfusion reactions, particularly TRALI) should be considered.

While a significant proportion (50–63 %) of patients respond to withdrawal of the offending agent (e.g., calcineurin inhibitors such as cyclosporine), many will require additional treatment to better control the disease. A number of pharmacologic agents have been explored for the treatment of TA-TMA including rituximab, vincristine, pravastatin, and eculizumab, with similar overall response rates (69–80 %) but significant differences in cost (Kim et al. 2015).

Case 2: Effect of Therapeutic Plasma Exchange on Warfarin Anticoagulation

A 41-year-old Caucasian male presents with myasthenic crisis and is scheduled to undergo urgent TPE, using 5 % albumin as a replacement fluid. His past medical history is also significant for activated protein C resistance (factor V Leiden defect), for which he takes warfarin; his INR is currently 2.5. Hematology team is consulted to determine whether it is necessary to stop his anticoagulation prior to the procedure.

Question 3. How do you advise the primary clinical team?

A. Correct INR using prothrombin complex concentrates (PCC) before apheresis.
B. Discontinue warfarin and delay the procedure for 3–5 days to normalize INR.
C. Continue with plasma exchange as planned, monitor coagulation indices 24 h after TPE.
D. Plasma exchange is contraindicated in this patient, recommend alternative therapy.

Expert Clinical Perspective: Myasthenic crisis is a life-threatening condition characterized by neuromuscular respiratory failure. Rapid intervention with plasma exchange or IVIG is recommended; but some reports suggest that TPE yields faster clinical improvement (Jani-Acsadi and Lisak 2007). Plasma exchange directly removes acetylcholine receptor antibodies from the circulation, and its clinical efficacy roughly correlates with the reduction in antibody levels. A typical course of treatment consists of five exchanges (1–1.5 plasma volumes each) over 7–14 days, using a mixture of 5 % albumin and saline as the replacement fluid.

Coagulation factors are inadvertently removed during plasma exchange, resulting in transient prolongation of clotting indices in patients on warfarin anticoagulation (Zantek et al. 2014). Immediately post apheresis, the INR rises to roughly double the baseline value, but generally recovers within 24 h post procedure.

Since it is known that the effect is temporary for a single-plasma volume TPE, a conservative approach is appropriate, with no change to warfarin dosing or other treatment plans unless the pre-procedure INR is >6. The patient may be monitored carefully to ensure that he is in the therapeutic range (INR 2.0–3.0), and not higher, before apheresis.

The use of PCC is not recommended in this case due to the risk of thrombotic events, especially in a patient with underlying thrombophilia. Plasma may be used as a third or more of the volume of the replacement fluid if warranted, since the patient has a planned surgical procedure within 24 h of TPE.

Case 3: Management of Severe Cold Agglutinin Disease

A 62-year-old Caucasian female presents with a history of worsening shortness of breath and fatigue over the past 3 days. On examination, she is pale and icteric. Workup reveals profound anemia, elevated LDH, hyperbilirubinemia, and hemoglobinuria; peripheral smear shows polychromasia, spherocytosis, and large red cell agglutinates. She receives multiple red cell transfusions, but experiences continued severe hemolysis.

Pertinent laboratory indices:

	Day 0	Reference ranges
Hemoglobin (g/dL)	4.7	13.5–17.5
Hematocrit (%)	14	40–51
WBC (K/uL)	13.25	4–10
Platelets (K/uL)	68	150–400
Total bilirubin (mg/dL)	6.5	0.0–1.2
Direct bilirubin (mg/dL)	2.5	0.0–0.3
Haptoglobin (mg/dL)	<10	30–200
LDH (U/L)	796	113–226

ABO/Rh type: O positive
Red cell antibody screen (indirect antiglobulin test): positive
Direct antiglobulin test (DAT): polyspecific 3+, C3d 3+
Eluate: positive, panagglutinin
Red cell cold autoantibody titer: 526

Question 4. The clinical team requests TPE. What is your recommendation?

A. Red cell exchange transfusion
B. Therapeutic plasma exchange
C. Prednisone 1 mg/kg daily
D. Rituximab 375 mg/m^2 weekly

Expert Clinical Perspective: This patient has cold agglutinin disease (CAD), characterized by autoimmune hemolytic anemia with intravascular red cell destruction. Autoantibodies in CAD are IgM, primarily intravascular, and bind poorly to red cells at body temperature. Initial therapy primarily involves avoiding exposure to cold; transfusions should be carried out in warm rooms, the patient should be kept warm, and blood warmers should be used when possible.

In cases with severe hemolytic anemia, rituximab is the most effective and best-evaluated treatment (Berentsen et al. 2004; Schollkopf et al. 2006). Prednisone and splenectomy are generally ineffective, because the liver is the dominant site of destruction of C3b-sensitized red cells.

TPE may be useful in acute hemolytic crisis (severe CAD is an American Society of Apheresis (ASFA) Category II indication for TPE (Schwartz et al. 2013)), but due to continued production of the autoantibody, the effect is modest and transient. If TPE is used, it should be combined with concomitant immunosuppressive therapy. There is also the risk that TPE may worsen hemolysis in CAD, due to the physical cooling of the patient's blood in the extracorporeal circuit of the apheresis device.

Importantly, serum protein electrophoresis, immunoglobulin quantification, bone marrow biopsy, and flow cytometry of bone marrow aspirate may be needed to rule out underlying hematologic malignancy.

Case 4: Therapeutic Plasma Exchange in Hyperviscosity Syndrome

A 75-year-old black male presents with confusion, lethargy, and rapid mental status deterioration. Laboratory testing reveals anemia; elevated total and ionized calcium, uric acid, and total serum protein; decreased IgG and IgM; and elevated IgA levels. Peripheral blood smear shows macrocytosis with rouleaux formation. Skeletal survey is remarkable for multiple lytic lesions. He is diagnosed with IgA multiple myeloma (MM). Results of serum viscosity assessment are pending.

Pertinent laboratory results:

	Results	Reference ranges
Hemoglobin (g/dL)	6.8	13.5–17.5
Hematocrit (%)	22.8	40–51
WBC (K/uL)	6.34	4.0–10.0
Platelets (K/uL)	171	150–400
Total protein (g/dL)	10.4	6.4–8.3

	Results	Reference ranges
Albumin (g/dL)	3.6	3.5–5.2
IgA (mg/dL)	5530	70–400
IgG (mg/dL)	110	700–1600
IgM (mg/dL)	10	40–230
Total Ca (mmol/L)	3.59	2.15–2.55
Ionized Ca (mmol/L)	1.60	1.12–1.32

Question 5. What is the next best step?

A. Initiate therapeutic plasma exchange immediately.
B. Transfuse 2U RBC to optimize patient for TPE.
C. Wait for the serum viscosity result before starting TPE.
D. Treatment of hypercalcemia with zoledronic acid/steroids before apheresis.

Expert Clinical Perspective: Symptomatic hyperviscosity may complicate Waldenström's macroglobulinemia or MM and may occasionally be the presenting clinical feature. Hyperviscosity in monoclonal gammopathies is an ASFA Category I indication for therapeutic plasma exchange (TPE) (Schwartz et al. 2013). It is appropriate to begin hydration with intravenous fluid and treatment with bisphosphonates while arranging for plasma exchange, but it is imperative to start TPE as soon as possible to prevent further neurologic deterioration. There is no need to wait for serum viscosity results; the patient is symptomatic and therefore TPE is required. Pre-procedure red cell transfusion should be avoided as this can increase viscosity and worsen neurologic symptoms.

Apheresis may be carried out in such a way as to result in a positive fluid balance. Note that the paraprotein contributes significantly to oncotic pressure, and significant fluid shifts may result after its removal by TPE.

A single-plasma volume exchange using a mixture of 5% albumin and saline as replacement fluid is recommended. Due to the highly efficient removal of IgA paraprotein by TPE, the patient is likely to experience significant improvement in mental status and lowering of blood viscosity after a single TPE procedure. Only one or perhaps two daily TPE procedures are generally needed to relieve neurologic symptoms in hyperviscosity syndrome, by which time more definitive therapy has generally been initiated.

Case 5: ABO-Incompatible Kidney Transplantation

A 46-year-old female with a long history of focal segmental glomerulosclerosis now has dialysis-dependent renal failure. She is scheduled to undergo kidney transplantation from a living unrelated donor. Her ABO/Rh type is O+ and the donor has A+ blood group. The recipient has an anti-A titer of 256.

Question 6. What are her treatment options?

A. Initiate a course of pre-transplantation plasma exchange and immunosuppression.
B. Defer transplantation, continue dialysis, and wait for another kidney to become available.
C. Splenectomy
D. Proceed with kidney transplantation; no other specific interventions are necessary.

Expert Clinical Perspective: Blood group incompatibility remains a significant barrier to kidney transplantation. Major ABO incompatibility exists in approximately one-third of random donor-recipient pairs. Pre-transplant conditioning with TPE and immunosuppressive therapy reduce ABO antibody titers, permitting engraftment of ABO-incompatible kidney transplants (Tobian et al. 2009). ABO-incompatible kidney transplantation is an ASFA Category II indication for TPE (Schwartz et al. 2013). ABO-incompatible liver transplantation has also been performed with a similar TPE-containing preparative regimen (Maitta et al. 2012).

The process requires coordination on the part of the apheresis team as well as the transplant team. Pre-transplant TPE generally consists of exchange of one plasma volume every other day, with the use of 5% human albumin and saline as

replacement fluid. The total number of procedures performed generally correlates with the ABO antibody titer in the indirect antiglobulin phase of serologic testing; gel microcolumn agglutination is considered more reliable than tube testing for ABO antibody titer (Shirey et al. 2010). In some protocols, pre-transplant TPE is followed immediately by administration of cytomegalovirus hyperimmune globulin (Tobian et al. 2008) or IVIG.

ABO antibody titers are closely monitored before and after transplantation. After transplantation, TPE therapy may be performed to prevent rebound of anti-A and anti-B titers until tolerance or accommodation occurs. TPE is then discontinued and reinstituted as needed based on creatinine levels, biopsy results, and ABO titer. Some protocols have been developed in which patients do not require posttransplant TPE (Yabu and Fontaine 2015). Overall, the results are positive, with excellent allograft performance and no episodes of hyperacute rejection.

Case 6: Red Cell Exchange Transfusion in Acute Complications of Sickle Cell Disease

A 16-year-old female with sickle cell anemia presents to the emergency room with new onset of left-sided weakness. She has a history of frequent vaso-occlusive crises and multiple episodes of acute chest syndrome. Magnetic resonance imaging of the brain reveals new cortical infarcts.

Pertinent laboratory results:

	Results	Reference ranges
Hemoglobin (g/dL)	8.1	13.5–17.5
Hematocrit (%)	23.5	40–51
WBC (K/uL)	7.6	4.0–10.0
Platelets (K/uL)	171	150–400
Hemoglobin electrophoresis		
HbF %	2.8	0.0–2.0
HbA_2 %	4.3	2.2–3.2
HbA %	6.4	94.8–97.8
HbS %	86.5	–

Question 7. What treatment plan do you recommend?

A. Simple transfusion of two red cell units
B. Red cell exchange transfusion
C. Immediate administration of tissue plasminogen activator
D. Immediate administration of warfarin plus aspirin

Expert Clinical Perspective: Children and adults with sickle cell anemia have a high prevalence (4.01 %) and incidence (0.61 per 100 patient years) of cerebrovascular accidents (Ohene-Frempong et al. 1998). In the absence of primary stroke prevention, approximately 10 % of children with HbS will have overt stroke and an additional 20–35 % will have silent cerebral infarction, which can cause cognitive decline and predispose them to additional silent infarcts and overt strokes (Miller et al. 2001).

Initial management of a focal neurologic deficit includes evaluation by a multidisciplinary team, including a hematologist, neurologist, neuroradiologist, and transfusion medicine specialist. Prompt neuroimaging and red cell exchange transfusion are recommended if the hemoglobin is >4 and <10 g/dL (Kassim et al. 2015). Oxygen therapy should be initiated to maintain >95 % oxygen saturation.

Acute stroke in sickle cell disease is an ASFA Category II indication for red cell exchange, using HbS-negative red cell units as the replacement fluid (Schwartz et al. 2013). Red cell units should ideally be antigen matched with at least the C, E, and K antigens on the red cells of the patient. The goal of exchange transfusion is to decrease HbS to less than 30 %, with a target hematocrit of less than 30 ± 3 % to avoid hyperviscosity. Limited data exist regarding the use of thrombolysis, anti-platelet agents, or other anticoagulants in adults with sickle cell disease presenting with an acute stroke.

Case continues: Three years later, the above patient requires shoulder surgery due to avascular

necrosis of the humeral head. Her hemoglobin is 8.5 g/dL and HbS is 45 %.

Question 8. What is the next best step?

A. Preoperative iron supplements and administration of erythropoietin to boost red cell production.
B. Prophylactic preoperative red cell exchange transfusion.
C. Simple prophylactic red cell transfusion.
D. Prophylactic transfusion is not necessary if close attention is paid to intraoperative hydration and oxygenation.

Expert Clinical Perspective: Chronic red cell exchange is indicated for secondary stroke prophylaxis in patients with sickle cell disease and is preferable to chronic simple red cell transfusions due to the avoidance of iron overload. Maintenance of HbS levels at less than 30 % prior to the next transfusion is the recommended target of long-term transfusion therapy (Yawn et al. 2014). In patients undergoing major surgical procedures, preoperative simple transfusion to increase hemoglobin levels to 10 g/dL and decrease HbS levels to less than 30 % is generally recommended. In patients undergoing surgery who have a hemoglobin level higher than 8.5 g/dL without transfusion, are on chronic hydroxyurea therapy, or who require particularly high-risk surgery (neurosurgery, prolonged anesthesia, cardiac bypass), expert guidance may be helpful to determine the appropriate transfusion method (red cell exchange vs simple transfusion).

Case 7: Red Cell Exchange in Falciparum Malaria

A 45-year-old male Peace Corps volunteer returned to the United States from Liberia. He presents at the emergency room with fever (39 °C), headache, neck stiffness, arthralgia, and fatigue. Blood cultures were drawn and lumbar puncture was performed: cerebrospinal fluid (CSF) was unremarkable.

Pertinent laboratory results:

	Results on presentation	Reference ranges
Hemoglobin (g/dL)	8.2	13.5–17.5
Hematocrit (%)	24	40–51
WBC (K/uL)	10.3	4.0–10.0
Platelets (K/uL)	42	150–400
Absolute reticulocyte count (K/uL)	147	26–95
LDH (U/L)	536	113–226
Total bilirubin (mg/dL)	1.0	0.0–1.2
Haptoglobin (mg/dL)	<10 (undetectable)	30–200

A peripheral blood smear contains intraerythrocytic ring-shaped trophozoites; the level of parasitemia is 15 %. Rapid immunoassay is strongly positive for *P. falciparum*. The patient becomes increasingly lethargic and confused, with deep breathing. Additional labs reveal hypoglycemia (42 mg/dL) and acidosis (plasma bicarbonate level <12 mmol/L).

Question 9. What do you recommend?

A. Artemether-lumefantrine
B. Atovaquone-proguanil
C. Parenteral quinidine gluconate
D. Urgent red cell exchange transfusion

Expert Clinical Perspective: Severe malaria is characterized by hyperparasitemia (>5 % in non-endemic areas) with or without signs of major organ dysfunction, including profound anemia (hemoglobin <5 g/dL), acidosis, hypoglycemia, impaired consciousness, seizures, pulmonary edema, renal failure, shock, and disseminated intravascular coagulation. The mortality rate of severe falciparum malaria ranges from 5 to 20 %. Death due to severe malaria can occur within hours of presentation; therefore, prompt initiation of antimalarial therapy and supportive care are crucial.

Oral agents are not recommended for initial treatment of severe malaria; therefore in this case, intravenous quinidine gluconate is the best available therapy in the United States.

Red cell exchange transfusion has been used to treat severe malaria since 1974, but its use is controversial. A single two-volume RBC exchange can reduce the fraction of remaining patient red cells to roughly 10–15%. However, malaria parasite levels may rebound after red cell exchange transfusion (Watanaboonyongcharoen et al. 2011). Furthermore, the procedure is not without risks, including circulatory overload, transfusion-transmitted infection, hypocalcemia, and possible need for central venous access. Case reports and short case series show benefit, but this may be due to reporting bias.

According to the 2013 ASFA guidelines, severe parasitemia (>10%) and cerebral malaria are considered Category II indications for red cell exchange transfusion. Based on analysis of the literature, the CDC no longer recommends the use of exchange transfusion as an adjunct to antimalarial drugs for the treatment of severe malaria, since a survival benefit was not demonstrated (Tan et al. 2013).

Case 8: Hereditary Hemochromatosis

A 52-year-old Caucasian male of Irish ancestry, with no known medical illnesses, presented to his primary care physician with fatigue and polyarticular arthritis. Routine laboratory workup revealed normal blood glucose, slight hyperlipidemia, and elevated serum ferritin and transferrin saturation (see below). He denies a history of blood transfusion or taking iron supplements. He admits to social alcohol use on weekends and denies thyroid or sexual dysfunction.

He is 5′11″ (180 cm) tall and weighs 178 lbs (81 kg); physical examination is otherwise unremarkable. HFE genotyping revealed two copies of the p.Cys282Tyr mutation.

Pertinent laboratory results:

	Results on presentation	Reference ranges
Hemoglobin (g/dL)	15.5	13.5–17.5
Hematocrit (%)	44.8	40–51
MCV (fL)	96	79–92
WBC (K/uL)	6.1	4.0–10.0
Platelets (K/uL)	215	150–400
Serum ferritin (ng/mL)	2242	30–300
Serum iron (mcg/dL)	279	59–158
Transferrin (mcg/dL)	292	200–360
Transferrin saturation (%)	100	20–50
ALT (U/L)	48	6–41

Question 10. He is referred to your practice for further management. What do you recommend?

A. Iron chelation with deferoxamine
B. Therapeutic phlebotomy of 500 mL whole blood (220 mL of packed red cells) every 2 weeks
C. Erythrocytapheresis with removal of 400 mL of packed red cells every 4 weeks
D. Referral to a gastroenterologist for liver biopsy

Expert Clinical Perspective: This patient has classic HFE hereditary hemochromatosis, the most common inherited disorder in persons of Northern European descent (Merryweather-Clarke et al. 1997). Therapeutic phlebotomy, either by removal of 500 mL of whole blood per visit or by double red cell unit removal by apheresis (DRCA), is the only effective therapy for this disorder. The target of phlebotomy is a ferritin level of about 50–75 ng/dL. Advantages of erythrocytapheresis versus simple whole blood phlebotomy include removal of nearly twice the volume of packed red cells per procedure, and thus nearly twice the amount of iron per visit, and replacement of lost volume with an equal volume of saline. Although there is a moderate increase in cost associated with the use of the double red cell apheresis device, the procedures are well tolerated and the number of outpatient visits required to achieve the targeted level of iron removal is halved.

DRCA results in faster initial drop in ferritin, but same time to normalization of ferritin, and higher cost of the DRCA procedure itself. In

another study, the use of DRCA actually saved costs by limiting loss of productivity (patients spent less time coming to phlebotomy appointments).

Apheresis devices for collection of double red cell units are generally available only in transfusion services of blood centers. However, referral to a blood center optimizes care of the hemochromatosis patient and is a cost-effective approach to therapy (Leitman et al. 2003). More than 70 % of patients with hemochromatosis meet eligibility criteria for blood donation. Making hemochromatosis-donor blood available for transfusion minimizes costs (no charge for the procedure), reduces wastage, and also provides a benefit to the community. The height and weight requirements for double red cell donation by apheresis may be waived by the blood center if the procedure is performed with therapeutic intent.

Liver biopsy is no longer required as a diagnostic procedure; the HFE genotype combined with the complete blood count, ferritin, transferrin saturation, and ALT provide all information necessary to make the diagnosis. The elevated ALT should normalize within the first months of phlebotomy therapy; if it remains elevated despite steady decreases in ferritin, another process such as steatohepatitis should be suspected.

Case 9: Extracorporeal Photopheresis for Treatment of Acute Graft-Versus-Host Disease

A 27-year-old woman with acute myeloid leukemia received a peripheral blood-derived hematopoietic cell transplant (HCT) from a matched unrelated donor. By day+28 posttransplant, her clinical course is complicated by thrombocytopenia, upper gastrointestinal bleeding, and biopsy-proven acute graft-versus-host disease (GvHD) of the skin and gastrointestinal system including the liver. For management of acute GvHD, she is currently on methylprednisolone and cyclosporine; she completed a course of infliximab and basiliximab without improvement. On day 56 posttransplant, the team requests extracorporeal photopheresis (ECP) to treat her acute GvHD.

Pertinent laboratory results:

	Results	Reference ranges
Hemoglobin (g/dL)	8.9	13.5–17.5
Hematocrit (%)	23.0	40–51
MCV (fL)	78.5	79–92
WBC (K/uL)	5.58	4.0–10.0
Platelets (K/uL)	21	150–400
PT (s)	17.8	11.6–16.2
PTT (s)	58.7	25.3–37.3
ALT (U/L)	129 U/L	6–41
AST (U/L)	103 U/L	9–34
Total bilirubin (mg/dL)	31.4	0.0–1.2
Direct bilirubin (mg/dL)	27.0	0.0–0.3

Question 11. What is your recommendation?

Expert Clinical Perspective: This critically ill patient has severe grade IV steroid-refractory acute GvHD of the skin and gastrointestinal system including the liver, further complicated by coagulopathy and active intestinal bleeding. While ECP is approved for use in chronic GvHD of the skin, evidence for efficacy in acute GvHD is less robust. While overall published response rates in steroid-refractory acute GvHD range from 66 to 100 % in skin to 27–71 % in liver, ECP usually fails to benefit patients with grade IV acute GvHD (Couriel et al. 2006). Nevertheless, a trial of ECP may be suggested for a specified time period in this patient. A typical course consists of two treatments per week for approximately 4 weeks and less frequently thereafter.

Complex technical planning is necessary to initiate a course of ECP. This patient will likely need placement of a fresh indwelling central venous access catheter. A hematocrit of greater than 28 % must be maintained to achieve a safe extracorporeal volume while undergoing the procedure. In view of the thrombocytopenia and the prolonged clotting times, the use of citrate rather than heparin to anticoagulate the extracorporeal circuit should be recommended.

Case 10: Hematopoietic Cell Collection in Allogeneic Healthy Donors

A 17-year-old African-American girl presents to a hematology clinic with a diagnosis of severe aplastic anemia (SAA). Hematopoietic cell transplantation (HCT) is advised, and her siblings are investigated as potential hematopoietic progenitor cell (HPC) donors. Her 26-year-old healthy sister is a 10/10 HLA match. She has ten potential donors in NMDP registry.

Question 12. What is the ideal source of hematopoietic CD34+ cells for her transplant?

A. Matched related bone marrow
B. Matched unrelated cord blood
C. Matched related-donor peripheral blood cells
D. Matched unrelated-donor peripheral blood cells

Expert Clinical Perspective: Human leukocyte antigen (HLA)-matched sibling-donor HCT is the treatment of choice for a young patient (<40 years) with SAA (Marsh et al. 2009). Immunosuppressive therapy using horse antithymocyte globulin (ATG) plus cyclosporine is first-line therapy for patients with SAA who are older than 40 years and as second-line therapy in younger patients if an HLA–matched sibling donor is not available. Unrelated-donor HCT is currently justified only if the donor is a full HLA match and if immunosuppressive therapy or treatment as part of a clinical trial fails.

Evidence from several large studies now uniformly favors the use of bone marrow as the stem cell source for patients with SAA undergoing allogeneic HSCT (Schrezenmeier et al. 2007). There are a few clinical indications for using mobilized peripheral blood grafts in SAA, such as repeat transplantation of patients following rejection of the first graft. Otherwise, specific donor health risks may preclude the use of general anesthesia, which is required for a bone marrow harvest procedure.

Case continues: Her HLA-matched sibling donor has a history of significant adverse reactions to general anesthesia, precluding marrow donation. She presents to donate peripheral blood HPC after 5 days of stimulation with G-CSF. The procedure is complicated by circumoral tingling and cramping sensation in arms and legs. Her symptoms are partially relieved by increasing the rate of the prophylactic intravenous calcium chloride infusion and decreasing the apheresis device inlet blood flow rate, but then worsen. The procedure is terminated after 17 L of blood are processed, due to donor discomfort. The transplant team is concerned that the collection will not yield enough CD34+ cells for successful engraftment.

Question 13. What factors are associated with better mobilization of peripheral blood cells in adult donors?

A. Race
B. Age
C. Baseline WBC count
D. Weight

Expert Clinical Perspective: In adults, multivariate analysis of factors associated with more robust CD34+ mobilization reveals that donors who are Caucasian, female, and lighter in weight have poor HPC mobilization after stimulation with G-CSF. In contrast, robust HPC mobilization was associated with being African-American, male, and heavier in weight (Panch et al. 2013). Plerixafor 240 mcg/kg may be added on the day prior to apheresis to improve CD34+ cell mobilization in donors predicted to have a poor mobilization response to G-CSF alone. In addition to predictions based on donor demographic factors, rapid quantitation of the pre-apheresis circulating CD34+ cell count is critically important in predicting the CD34+ cell yield of apheresis and determining the optimal volume to be processed.

Citrate is the standard anticoagulant used to prevent clotting in the extracorporeal circuit of the apheresis device. However, citrate acts by chelating calcium, and sustained administration of citrate during long leukapheresis procedures in which

12–25 L of blood are processed can lead to marked, symptomatic, and even life-threatening decreases in ionized calcium levels (Bolan et al. 2002). Donors with smaller bone mass may be particularly at risk since they are less able to mobilize calcium in response to the parathyroid hormone surge that results from acute hypocalcemia. Prophylactic intravenous calcium administration is one of several effective strategies used to mitigate hypocalcemia during HPC collection by apheresis.

Controversies in Therapeutic Apheresis

- There are many disorders for which therapeutic apheresis procedures are unlikely to provide clinical benefit, yet rare responses are seen. Therapeutic apheresis continues to be performed in these disorders despite the low quality of evidence for benefit. Therapies which fall into this category include:
  - TPE in transplant-associated microangiopathy
  - TPE for cold agglutinin disease
  - ECP in non-skin acute GvHD
- It should be appreciated that apheresis procedures are not without risk and should be reserved for those disorders in which the likelihood of benefit is clearly demonstrated and outweighs the risks involved.

Answers

Question 1. C
Question 2. B, C, and D
Question 3. C
Question 4. D
Question 5. A and D
Question 6. A
Question 7. B
Question 8. B or C
Question 9. C
Question 10. B or C
Question 12. A
Question 13. A, C, and D

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