**Stem Cell Transplantation**

**Mike Pulsipher**

1. A 14-year-old girl with high-risk relapsed acute myelogenous leukemia is a member of a large family and has five HLA-matched siblings. The patient is blood group O+ and is cytomegalovirus (CMV) seronegative.

Which sibling would be the best donor?

A. 16-year-old sister, CMV negative, blood group O+

B. 12-year-old brother, CMV positive, blood group A+

C. 2-year-old brother, CMV negative, blood group O+

D. 14-year-old identical twin sister, CMV negative, blood group O+

E. 22-year-old pregnant sister, CMV negative, blood group A+

**Explanation**

The correct answer is A. When considering optimal stem cell donors, after HLA matching there are a host of other factors to consider. In general, younger donors are preferred. The thought is that a younger patient has had less antigenic exposure, resulting in lower GVHD. Younger donor stem cells also have greater regenerative capacity. Because there is evidence that receiving stem cells from a female donor who has had children increases the risk of graft-versus-host disease (GVHD) in the recipient, donors with a history of multiple pregnancies are generally avoided. Donation from a pregnant donor is inappropriate because it may put the donor or the donor’s child at unnecessary risk. Blood type is not a major factor, but when all factors are equal, having the same blood type is preferable. A syngeneic donor (identical twin) in acute myelogenous leukemia leads to outcomes similar to an autologous bone marrow transplant and would never be used when matched nonsyngeneic siblings are available. Finally, with regard to CMV infection, patients at highest risk are those who are CMV seropositive or patients who are CMV seronegative and receive stem cells from a donor who is CMV seropositive. Using these criteria, the best donors are answers A and C. However, donor C is only 2 years old, and therefore it would be difficult to harvest enough bone marrow stem cells for this larger recipient. Therefore, answer A, the 16-year-old sister who is CMV negative, is the best choice.

2. An 8-year-old boy with acute myelogenous leukemia (AML) 6 months after transplant comes to the clinic complaining of an erythematous maculopapular rash on his arms and legs; dry, irritated eyes; and a persistent cough. His mother has noticed that he gets winded quickly and he has difficulty climbing the stairs.

Which of the following tests is most essential for choosing optimal therapy?

A. Blood polymerase chain reaction (PCR) for cytomegalovirus

B. Skin biopsy

C. Pulmonary function tests and high-resolution CT

D. Galactomannan and beta-D-glucan tests for fungus

E. Upper GI endoscopy

**Explanation**

The correct answer is C. Chronic graft-versus-host disease (GVHD) typically develops between 3 and 6 months after a hematopoietic stem cell transplant. Rash and dry eyes are highly suggestive of chronic GVHD, and a skin biopsy is only confirmatory; this patient could be treated clinically without the biopsy. The cough, shortness of breath, and exertional dyspnea are very concerning for chronic GVHD of the lungs, specifically bronchiolitis obliterans. It is important to make that diagnosis quickly, because it requires systemic therapy, whereas the eyes and skin could possibly be treated with local therapy alone. Pulmonary function tests and a high-resolution CT can significantly aid in the diagnosis of pulmonary GVHD. Diagnostic investigation and prompt treatment are important. Further pulmonary workup after the CT to rule out infection may be necessary if the patient has symptoms or findings consistent with infection.

3. A 12-year-old child with acute myelogenous leukemia develops conjugated hyperbilirubinemia (6.8 mg/dL) and fluid retention on day 9 after a sibling donor transplant.

Which test would be appropriate to identify the cause of the hyperbilirubinemia?

A. CT scan of the abdomen

B. Abdominal ultrasound with Doppler measurements of portal blood flow

C. Hepatobiliary iminodiacetic acid scan of the gallbladder

D. Upper GI endoscopy

E. Immediate liver biopsy

**Explanation**

The correct answer is B. Veno-occlusive disease (sinusoidal obstructive syndrome) typically occurs within the first 30 days after stem cell transplantation. Clinical signs include conjugated hyperbilirubinemia, weight gain, right upper quadrant abdominal pain, platelet consumption, and renal dysfunction. Reversal of flow in the portal vein is a common finding and is best observed on an abdominal ultrasound with Doppler. Liver biopsy is hazardous because of coagulopathy and is seldom used.

4. When should autologous hematopoietic stem cell transplantation be used, and what are the common cancers it is used for?

A. It should be used when high dose therapy is needed to maximize response. Most common cancers it is used for include lymphoma, late relapse of acute lymphoblastic leukemia, neuroblastoma, and Ewing sarcoma.

B. It should be used any time this approach can provide a meaningful survival benefit over chemotherapy. Most common cancers it is used for include neuroblastoma, responsive brain tumors in young children to avoid/minimize early radiation therapy, and relapsed lymphoma.

C. It should be used for tumors in which a graft-versus-tumor effect does not occur. Most common cancers include neuroblastoma, lymphoma, selected brain tumors, rhabdomyosarcoma, and Ewing sarcoma with lung metastases.

D. It should be used to avoid extensive treatment with chemotherapy and to shorten treatment. Most common cancers include neuroblastoma, relapsed Wilms’ tumor, and selected brain tumors.

E. It should be used to avoid complications of graft-versus-host disease. Most common cancers include neuroblastoma, selected brain tumors, and relapsed lymphoma.

**Explanation**

Autologous transplantation, often called high-dose chemotherapy with stem cell rescue, is an approach that is limited to tumors with a dose-response curve that allows cure to be achieved after receiving one or more rounds of intensive therapy. It should not be limited to tumors in which a graft-versus-tumor effect (GVT) from an allogeneic donor does not occur, but for any disease for which it can be shown to have a beneficial effect on survival above standard chemotherapy. There are rare situations in which a patient with a disease like acute myeloid leukemia (AML), which has a great GVT effect and usually requires an allogeneic hematopoietic stem cell transplant (HSCT), can benefit from autologous bone marrow transplant (BMT) (eg, lower risk disease that relapses late, has a molecular marker, and patients achieve a very deep remission—acute promyelocytic leukemia and t(8:21) AML). Some tumors have a great response to high-dose chemotherapy but can be cured equally well with intensive chemotherapy (eg, relapsed Wilms’ tumor). Whether autologous HSCT should be used in this setting for Wilms’ tumor is controversial, and patient/center preference is used. Use of this approach to avoid graft-versus-host disease is highly desirable; however, in many cancer types, GVT is vital and needed for success (high risk acute lymphoblastic leukemia and AML). The most common tumor types benefitting from autologous HSCT include neuroblastoma, responsive brain tumors (several tumor types in children younger than 3 years to avoid, postpone, or minimize radiation therapy, relapsed responsive medulloblastoma), and relapsed lymphoma that is responsive to chemotherapy. There has been benefit shown in other diseases, as well (eg, relapsed germ cell tumors, disseminated retinoblastoma). With this explanation in mind, option B is the correct answer.

5. A 6-year-old child with a history of acute myelogenous leukemia comes to your clinic for routine follow-up 60 days after a matched unrelated stem cell transplant. The child is being treated with tacrolimus for graft-versus-host disease (GVHD) prophylaxis. The child is hypertensive and has proteinuria. She is on a high dosage of steroids for treatment of GVHD, and she has had a good response but has a mildly elevated unconjugated bilirubin, her creatinine is up, and her platelets have fallen.

Which test(s) is/are most likely to yield a diagnosis?

A. Kidney biopsy

B. Skin biopsy

C. LDH, haptoglobin, and examination of smear for schistocytes

D. Renal ultrasound

E. CT examination of the abdomen

**Explanation**

The correct answer is C. Transplant-associated thrombotic microangiopathy (TA-TMA) is a significant complication of hematopoietic stem cell transplantation (HSCT). TA-TMA belongs to the family of thrombotic microangiopathies including hemolytic uremic syndrome and thrombotic thrombocytopenic purpura. TA-TMA occurs when endothelial damage resulting from HSCT causes microangiopathic hemolytic anemia and platelet consumption, resulting in thrombosis and fibrin deposition in the microcirculation. The kidney is most commonly affected. Patients present with anemia, thrombocytopenia, schistocytes on blood smear, elevated LDH, and decreased haptoglobin. Calcineurin inhibitors, sirolimus, total body irradiation, high-dose busulfan, and infections may be potential risk factors for the development of TA-TMA. Further testing of complement (CH50 and sC5b-9) can help discern whether patients have this disorder and could potentially benefit from eculizumab (works by blocking completment C5).

6. Which of the following statements about myeloablative, myeloablative but reduced toxicity, reduced intensity, and non-myeloablative approaches is not correct?

A. Myeloblative approaches are needed for high-risk malignancies to maximize depth of remission and decrease the likelihood of relapse.

B. Reduced intensity regimens can be successfully used for most nonmalignant disorders to minimize risk of late effects.

C. Reduced intensity regimens can markedly decrease the risk of transplant-related mortality in patients who have underlying significant comorbidities but at the cost of more relapse and possibly more graft-versus-host disease.

D. Non-myeloablative regimens are used for the very highest risk patients to minimize toxicity and for certain diseases such as aplastic anemia.

E. Myeloablative reduced toxicity approaches are often needed to decrease graft rejection and maximize chimerism in certain non-malignant disorders.

**Explanation**

Myeloablative regimens are used to both maximize depth of remission and to minimize the risk of rejection. This has been shown to reduce relapse in disorders such as high-risk acute myeloid leukemia and acute lymphoblastic leukemia, where these approaches are standard; hence, answer A is true. Although reduced intensity regimens can be successfully used in some nonmalignant disorders, many disorders cannot be treated as effectively with these approaches because of higher risks of partial chimerism or rejection. In these disorders, reduced-toxicity approaches are best. With this in mind, answer B is the correct answer (the only statement that is incorrect) and answer E is true. A very important use of reduced intensity conditioning (RI or RIC) regimens is in patients who have major comorbidities, such as decreased lung or heart function, or partially controlled fungal infections. Although transplant-related mortality (TRM) decreases with these approaches, relapse increases, and the need to use peripheral blood stem cells for the success of these approaches results in more graft-versus-host disease. The trade-off of sacrificing intensity for graft-versus-leukemia effect can cure many patients who do not have good alternatives; however, they need to be in a good remission (minimal residual disease–negative, preferably) to have a reasonable chance of success. For the sickest patients, non-myeloablative approaches offer an alternative and can cure a number of patients with little toxicity (although with higher relapse). Severe aplastic anemia treatment regimens are non-myeloablative and generally result in few if any late effects and normal fertility. With this in mind, C and D are true.

7. A 12-year-old girl is doing well 21 days after a hematopoietic stem cell transplant (HSCT). She is on tacrolimus and mycophenolate for graft-versus-host disease prophylaxis. Over 2 days she develops high blood pressure that is refractory to medication. On the third day she has a 2-minute tonic-clonic seizure.

What is the most useful investigation at this time?

A. MRI of the head

B. CT of the head

C. Lumbar puncture

D. Renal ultrasound

E. EEG

**Explanation**

The correct answer is A. Posterior reversible encephalopathy syndrome (PRES) is a syndrome characterized by headache, confusion, seizures, and visual loss and is most often caused by malignant hypertension. For patients with HSCT, intractable hypertension and the associated PRES have been linked to the use of calcineurin inhibitors (tacrolimus or cyclosporine). The diagnosis of PRES typically is made with MRI imaging of the brain, which reveals a characteristic pattern of enhancement, commonly in the posterior circulation. The findings of PRES may be seen on CT but are better visualized with MRI.

8. You are treating a 12-year-old boy with relapsed acute myeloid leukemia with a haploidentical T-cell-depleted allogeneic hematopoietic stem cell transplant (HSCT) from his father. At day +55 you note painless cervical adenopathy.

What should your workup and treatment plan include?

A. Blood culture, a throat swab, and antibiotics covering oral flora

B. Serum Epstein-Barr virus (EBV) titers, a PET scan, and therapy with rituximab if EBV titers are elevated

C. A biopsy of the mass followed by withdrawal of immune suppression to stimulate a graft-versus-leukemia effect

D. Serum CMV titers followed by ganciclovir therapy if elevated

E. Serum galactomannan and beta glucan testing followed by broad-spectrum antifungal therapy

**Explanation**

The correct answer is B. Although the scenario of throat infection causing cervical adenopathy is possible, no throat pain or painful adenopathy is noted. Given the risk of post-transplant lymphoproliferative disease (PTLD) in a patient receiving haploidentical HSCT, EBV-lymphoproliferative disorder (EBV-LPD) should be considered; therefore, assessment for EBV titers is vital. Further staging for post-transplant EBV-LPD includes a PET scan. Treatment in the setting of post-transplant rising EBV titers can be initiated before any visible disease is noted and would be initiated if positive in this case. A biopsy is sometimes performed if there is a question about relapsed disease or if more definitive confirmation of LPD is needed. Therapy for EBV-LPD involves the use of rituximab and decreasing immune suppression if possible. More intense therapy with cyclophosphamide or other agents is sometimes necessary, and cytotoxic T-lymphocytes against EBV are also useful therapy when available. It is unlikely that fungal or CMV infections would present with cervical adenopathy.

9. A 3-year-old boy with X-linked chronic granulomatosis disease is day +25 after haploidentical bone marrow transplant (father donor) using posttransplant cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis. He engrafted on day +16 and was preparing for discharge when cytomegalovirus (CMV) was noted to be positive on PCR, and he developed a fever and mild rash. His counts have fallen to a WBC of 0.1 and he remains transfusion dependent. What diagnostic evaluations/treatments should you pursue?

A. Rule out infection by sending blood cultures, start broad spectrum antibiotics, and obtain other diagnostic workup as appropriate. Consider skin biopsy and treat with steroids for likely acute GVHD (aGHVD).

B. Initiate an infectious workup and treat with broad-spectrum antibiotics. Consult with the PICU team because the low blood counts are likely a preseptic presentation.

C. Test for possible rejection with rapid FISH chimerism and consider withdrawal of immune suppression if donor chimerism is low.

D. Send blood cultures, start antibiotics, and treat his CMV with foscarnet. Send rapid chimerism by STR to assess for possible rejection. If donor chimerism is low or absent, work on obtaining an alternative donor for a second procedure.

E. Start steroids to treat aGVHD and give supportive care with granulocyte colony stimulating factor.

**Explanation**

This patient is at high risk for rejection because he is undergoing bone marrow transplantation (BMT) for a nonmalignant condition that is often associated with excessive inflammation, and he has received a haploidentical procedure. Suspicion for rejection should be high. This patient also initially showed count recovery but later developed a fever, rash, and low counts, a classic presentation of acute rejection. Of note, however, infection or graft-versus-host disease (GVHD) could also cause a picture similar to this, so this must be approached carefully. Option A includes many things that should be done, but with counts falling to nearly 0, GVHD is less likely, and there is no mention of assessing for graft failure. Option B focuses on infection and possible sepsis. Although overwhelming sepsis could present like this, other signs such as hypotension would likely be present. Option C is not correct because this boy received a transplant from his father, so FISH chimerism, which relies on sex differences between donor and recipient, cannot be performed. Option D is correct—a rule-out for bacteria must be performed with initiation of antibiotics even though all of these symptoms (fever, rash, low counts) can be explained by acute rejection. The fever could also be associated with the cytomegalovirus (CMV) reactivation, and if this proves to be acute rejection, the rejection was likely triggered by the CMV reactivation. When rejection is proven by noting absent donor chimerism, full control of the infection followed by a salvage hematopoietic stem cell transplant (HSCT) procedure to restore engraftment should be done as soon as possible. Option E focuses only on acute GVHD, which is not likely, and growth factors such as granulocyte colony stimulating factor (G-CSF) do not improve counts in the face of acute rejection.

10. All of the following conditions in a patient should prompt consideration of cancelation of transplantation or use of a minimal or reduced-intensity regimen *except* which of the following?

A. Direct bilirubin of 3.0

B. Karnofsky/Lansky score of 50%

C. Corrected DLCO of 52%

D. GFR of 70%

E. Cardiac ejection fraction of 45%

**Explanation**

The correct answer is D. For answer A, the risk of veno-occlusive disease/sinusoidal obstruction syndrome is markedly increased when bilirubin is elevated above 2, and total body irradiation/busulfan approaches need to be modified. For answer B, a Karnofsky score less than 80% should prompt consideration and less than 60 definitely result in modification of myeloablative approaches. For answer C, FEV1, FVC, and DLCO corrected less than 60 markedly increase risk of complications with myeloablative approaches. For answer D, most transplant centers allow patients with GFR above 60 to undergo full-intensity approaches. For answer E, cardiac ejection fraction less than 50% is associated with significant risk.

11. An 11-year-old with B-cell acute lymphoblastic leukemia (B-ALL) who is 8 months from a total body irradiation–based matched unrelated donor transplant and off immune suppression has an elevated WBC of 20,000/μL along with circulating peripheral blasts.

What treatment options offer the best chance of long-term remission?

A. Reinduction with an intensive relapse regimen followed by second bone marrow transplant from a different donor if minimal residual disease (MRD)-negative remission can be obtained

B. Treatment with blinatumomab

C. Treatment with chemotherapy followed by donor lymphocyte infusions

D. Collection of T cells from the patient followed by bridging chemotherapy and infusion of tisagenlecleucel after lymphodepleting chemotherapy

E. Treatment with inotuzumab

**Explanation**

The correct answer is D. Relapse of B-ALL after transplant is challenging to treat, and traditional intensive reinduction regimens lead to remission only 40% to 50% of the time. Second hematopoietic stem cell transplant (HSCT) is not likely to be successful unless patients achieve an MRD-negative remission, but with chemotherapy alone they are not likely to be able to get to HSCT. In addition, relapse after second HSCT is very high. Treatment with blinatumomab when patients are in a full relapse results in remission only 40% of the time and may not be sustained long term for patients who relapse after transplant. Similarly, treatment with inotuzumab results in remission in up to 80% of patients, but remissions are not sustained without a second HSCT. Tisagenlecleucel, a 4-1BB-based chimeric antigen receptor T-cell product, puts 80% to 90% of patients into remission, with sustained remissions at 1 year noted in half of the patients without further therapy. Tisagenlecleucel is approved by the Food and Drug Administration for the treatment of multiply relapsed or refractory CD19+ B-ALL in patients up to age 25.

12. A 6-year-old girl with relapsed T-cell acute lymphoblastic leukemia has received two rounds of intensive reinduction chemotherapy and has a 10/10 HLA-matched unrelated donor available for hematopoietic stem cell transplantation (HSCT). The two reinduction chemotherapy rounds were very challenging, with delayed recovery and significant side effects. Pretransplant workup shows good organ function, no evidence of infection, and a minimal residual disease (MRD) level of 0.01% by flow cytometry. Which of the following is the most appropriate course of action?

A. Give a third round of chemotherapy in order for her to achieve an MRD-negative remission prior to HSCT.

B. Move forward with HSCT using a non–total body irradiation (TBI) based myeloablative regimen to decrease the risk of late effects.

C. Move forward with a TBI-based myeloablative regimen and follow closely after HSCT for the presence of MRD, planning for early weaning of immune suppression as tolerated.

D. Move forward with a reduced intensity conditioning regimen because of the significant toxicity she experienced during her reinduction chemotherapy.

E. Move forward with a busulfan-based regimen because this has been shown to be equivalent to TBI and follow closely for MRD posttransplant with a planned early weaning of immune suppression.

**Explanation**

A recent large randomized trial has reaffirmed a significant survival benefit with the use total body irradiation (TBI)–based myeloablative preparative regimens in all but the youngest children with acute lymphoblastic leukemia requiring hematopoietic stem cell transplantation (HSCT). In this case, the low-level positive minimal residual disease (MRD) just prior to bone marrow transplant (BMT) puts the child at higher risk of relapse, more firmly highlighting the need for a TBI-based preparative regimen. Option A is reasonable and could be considered a correct answer, but it is not ideal because this child had very significant toxicity with her first two rounds of chemotherapy. In general, a third round of pretransplant chemotherapy may not be needed in cases where there is only very low-level MRD positivity (< 0.1%), even though it will increase the risk of relapse (mainly because of decreasing likelihood of getting a deeper remission and increasing likelihood of toxicity). A third cycle could offer benefit if there are new agents used that are likely to induce a deeper remission and there is a good chance that the patient will not have major toxicity. Options B and E are both incorrect because the data supporting TBI-based approaches showed superior outcomes compared to intense, non-TBI myeloablative regimens based on either busulfan or treosulfan. Option D is not correct because this patient qualifies for an intense regimen in spite of the toxicity that occurred with the reinduction treatments, and a reduced intensity conditioning approach would likely result in relapse. Finally, option C is the correct approach. When patients have low-level MRD positivity at the time of BMT, they should be checked posttransplant at about day +30 to ensure marrow clearance of MRD. If they have not developed acute graft-versus-host disease, early weaning of immune suppression may be considered to decrease the risk of relapse and should be tailored based upon donor type and HLA match.

13. What is the best infusion product for a 10-year-old Hispanic girl undergoing hematopoietic stem cell transplant for relapsed T-cell acute lymphoblastic leukemia (T-ALL) in second complete remission?

A. Two cord blood units, the first unit a 5/6 match with a total nucleated cell (TNC) count of 5 × 107/kg recipient weight (CD34+ count 0.2 × 106/kg) and the second unit a 4/6 match with a TNC of 2.5 × 107/kg (CD34+ count 0.23 × 106/kg)

B. A haploidentical family T-cell–depleted donor with a CD34+ count of 2 × 106/kg and a CD3+ count of 1 × 106/kg

C. A single cord unit 5/6 match with a count of 4 × 107/kg (CD34+ count 0.2 × 106/kg)

D. A 7/8 allele (8/10 including HLA DQB1, 9/12 including HLA DQB1 and DPB1) unrelated donor with a bone marrow cell dose of 4 × 106 CD 34+ cells/kg and 2 × 107 CD3+/kg

E. A partially mismatched sibling donor with a C/DRB1 crossover (5/6 or 6/8 match) with a CD34+ dose of 6 × 106 CD34+ cells/kg and a CD3+ dose of 4 × 107/kg

**Explanation**

The correct answer is C. Answer A has an excellent cell dose with the combination of 2 cord units, although one of the single units had a cell count greater than 4 × 107/kg and would be adequate, with no advantage to giving the second unit. Answer B shows a haplo T-cell–depleted donor who should have a much higher CD34+ count (doses closer to 10 × 106 CD34+ cells/kg are preferred, and the T-cell dose is too high [maximum 1 × 105/kg]). Answer C is a single cord unit with an appropriate dose and thus is the correct answer. Answer D is an unrelated donor, and although they are a 7/8 match, they have DQ and DP mismatches. When 7/8 donors have additional mismatches at DP or DQ, the risk of transplant-related mortality and graft-versus-host disease is increased. Finally, answer E is a crossover sibling donor with a C and DR mismatch. This donor would be appropriate only if treated like a haplo donor. Sibling donors with a single HLA crossover (A or DRB1) can be considered for use in bone marrow transplant and have outcomes similar to fully matched unrelated donors.

14. You are collecting autologous peripheral blood stem cells from a teenaged patient with a relapsed brain tumor. You are treating the patient with daily G-CSF at 10 µg/kg and testing the peripheral blood CD34+ count daily as the patient recovers from salvage chemotherapy. The absolute neutrophil count is now 5,000/µL and the circulating CD34+ count in the blood is 5/µL.

How should you proceed?

A. Proceed with collection because counts have recovered.

B. Double G-CSF, add GM-CSF, and wait for a rise in CD34+ count before beginning collection.

C. Continue the G-CSF dosage as is, add plerixafor in the evening, and collect the next morning.

D. Do not attempt to collect. Stop the G-CSF and after a period of time do a collection with plerixafor alone.

E. Allow the patient to recover from chemotherapy and then do a mobilization with G-CSF without chemotherapy.

**Explanation**

The correct answer is C. Answer A is not appropriate--with precollection numbers less than 20 CD34+ cells/μL it is unlikely that sufficient cell numbers will be collected with the procedure. Doubling the G-CSF and adding GM-CSF (answer B) may improve CD34+ numbers, but adding plerixafor in the evening (answer C) is better and it generally markedly improves collection numbers, generally making it so that the next day there will be sufficient numbers for collection. Answer D is not a good idea, because collecting with plerixafor alone does not yield CD34+ numbers as high as G-CSF/plerixafor combinations, and E is not correct because although G-CSF alone mobilization can work, but when someone fails to mobilize with chemotherapy, using G-CSF alone is less effective than a combination of G-CSF and plerixafor.

15. Your patient presents with a diffuse rash on the trunk and extremities, including palms and soles on day +16 after cord blood transplant. Liver function tests are normal; weight is stable; oxygen saturation is normal; the patient is not eating; and stool output includes 2 small, loose stools per day.

How should you proceed?

A. Treat with 2 mg/kg prednisolone and wean after 3 days for engraftment syndrome.

B. Obtain a skin biopsy, because this is probably a drug rash or viral exanthem.

C. Treat with topical steroids alone.

D. Treat with both IV and topical steroids and follow closely for response, increasing therapy if the rash worsens or does not resolve within a week.

E. Push the patient’s trough level of cyclosporine to the high end of the therapeutic range for graft-versus-host disease (GVHD).

**Explanation**

The correct answer is D. Engraftment syndrome can mimic acute GVHD and happens more often with cord blood transplant. It generally happens early after transplant (days 8 to 14 after infusion) and usually is accompanied by fever, hypoxia, and weight gain. Given that this patient does not have those characteristics and has involvement of palms and soles, this is probably acute skin GVHD. Because it covers the trunk and extremities, it involves more than 50% of the skin area and therefore is skin stage 3. Stage 3 skin GVHD is often difficult to treat by topical therapy or increasing calcineurin inhibitors alone. Systemic therapy with prednisolone is probably necessary, so this therapy should be started along with topical therapy to help with pruritus and speed response. A skin biopsy to rule out a drug rash or viral exanthem is not often helpful but may be performed. Judgment about possible viral or drug reactions should be made in the context of the addition of new medications or other signs and symptoms. In this case, the patient is at a classic time for acute GVHD, so treatment with or without a skin biopsy is appropriate.