

## Transplantation Immunology

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### Posttest

1. A patient with aplastic anemia is given a hematopoietic stem cell transplant from a matched, but unrelated bone marrow donor. At 35 days after the transplant the patient exhibits signs of graft-versus-host disease. One of the ways in which this disease could have been prevented in this patient is by:
  - A. eliminating B lymphocytes from the donor marrow
  - B. eliminating the patient's major histocompatibility complex molecules with intravenous proteolytic enzymes
  - C. treating the patient with interleukin-2 after the transplant
  - D. eliminating T lymphocytes from the donor bone marrow
  - E. eliminating all CD34+ cells from the donor marrow
2. The major drawback of the depletion of T cells from a preparation of allogeneic stem cells to be transplanted to a leukemic patient is:
  - A. elimination of the graft vs. leukemia effect
  - B. higher probability of graft rejection
  - C. no effect on the incidence of graft-versus-host disease
  - D. prolonged post-graft immunosuppression
  - E. technical difficulty
3. Patients who receive hematopoietic stem cell transplants from unrelated donors are frequently treated prophylactically with an immunosuppressive drug such as Cyclosporine. The basis for giving an immunosuppressive drug to a patient whose immune system has been suppressed by chemotherapy and total body irradiation is that Cyclosporine administration:
  - A. minimizes or prevents the development of graft-versus-host disease.
  - B. stimulates the growth of the hematopoietic stem cells in the recipient.
  - C. stimulates the production of stem cell growth factor(s) by the recipient
  - D. suppresses the growth of residual leukemic cells in the patient.
4. An **early** indication that a hematopoietic stem cell transplant has been successful is:
  - A. a normal CD4:CD8 T lymphocyte ratio in the blood of the recipient.
  - B. a rise in the hematocrit in the recipient's blood five days after the transplant.
  - C. an increase in serum antibody levels to a variety of infectious organisms.
  - D. an increase in the number of differentiated leukocytes in the blood of the patient a few weeks after the transplant.
  - E. the absence of a graft-versus-host reaction.
5. Biopsy of a skin rash site and the gut wall epithelium in a patient who has received a hematopoietic stem cell transplant is used to confirm the diagnosis of graft-versus-host disease. The presence of mononuclear cell infiltrates in the skin and in the gut epithelium indicates that graft-versus-host disease is:
  - A. a cell-mediated immune reaction
  - B. an antibody-mediated immune reaction
  - C. both cell-mediated and antibody-mediated
  - D. not an antigen-specific immune reaction
  - E. mediated by natural killer cells

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### Posttest (continued)

6. Which one of the following organ or tissue transplants is least likely to cause a graft-vs.-host reaction?
- A. Bone marrow
  - B. Heart-lungs
  - C. Kidney
  - D. Liver
  - E. Small intestine
7. Which of the following is least likely to be a complication of hematopoietic stem cell transplantation:
- A. autoimmune hemolytic anemia
  - B. graft rejection or failure of the stem cell graft to survive
  - C. graft-versus-host disease
  - D. opportunistic infection
  - E. post transplant immune deficiency
8. Which of the following determinations will give better information about the achievement of **immunological reconstitution** after stem cell or bone marrow transplant?
- A. Development of hypergammaglobulinemia
  - B. Establishment of a state of chimerism
  - C. Normalization of white blood cell counts
  - D. Rise of the CD4<sup>+</sup> T cell count above 400/ $\mu$ L
  - E. Significant antibody response after immunization with tetanus toxoid
9. Athymic nude mice are transplanted with bone marrow from genetically unrelated and immunocompetent BALB/c mice. Identify in the following chart the most likely combination of results seen in the grafted mice.

Nude recipient / BALB/c donor		
	B.M. graft	Systemic effects
A	Rejected	None
B	Rejected	Splenomegaly, diarrhea, wasting
C	Accepted	None
D	Accepted	Splenomegaly, diarrhea, wasting
E	Accepted	Lymphomas, infections

10. Which of the following membrane markers is the basis for the isolation of human stem cells from bone marrow aspirates?
- A. CD10 (CALLA)
  - B. CD19
  - C. CD25
  - D. CD34
  - E. CD40

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### Posttest Answers

1. **(D) is correct.** It is the immunocompetent T cells in the allogeneic donor marrow that mediate the graft-versus-host disease. Because differentiated T cells do not express CD34, stem cell transplantation is associated with a lower risk of GVHD than transplantation of unfractionated bone marrow. Autologous stem cells or cord blood stem cells are even less likely to contain autoreactive T cells able to induce GVHD.
2. **(A) is correct.** T cell depletion of the graft can reduce significantly the incidence of GVHD. The major problem is that the clinical outcome in leukemic patients is worse, with high mortality. In part this is due to the fact that a low grade, controllable GVHD is associated with better outcomes in leukemic patients, perhaps as a result of the elimination of leukemic cells by the grafted lymphocytes (graft-versus-leukemia effect). In addition, the transplantation of T cell depleted bone marrow into immunosuppressed adults may result in a persistent state of severe immunodeficiency. These data suggest that the T cells facilitate the engraftment of the donor stem cells within the host bone marrow, although the mechanism for this is not understood.
3. **(A) is correct.** Prophylaxis with Cyclosporine, an inhibitor of T lymphocyte activation, is used to offset the development of graft-versus-host disease in patients receiving allogeneic hematopoietic stem cell transplants. Cyclosporine is not known to stimulate stem cell growth factor(s) production nor does it suppress the growth of leukemia cells.
4. **(D) is correct.** As in the case discussed in this POPS, an increase in the number of normal appearing white blood cells in the blood of the recipient which occurs at three weeks to one month after transplantation is taken as an indicator of the success of the hematopoietic stem cell transplant. The hematopoietic stem cells populate the recipient's bone marrow cavities differentiating into blood leukocytes, which then appear as mature cells in the peripheral blood. Neither the number of T lymphocytes nor the CD4:CD8 T lymphocyte ratio can be used as an indicator of the success of a hematopoietic stem cell transplant. Generally the antibody titers to commonly encountered infectious agents are lowered by the chemotherapy and radiotherapy performed immediately prior to transplantation. However, the antibody titers do not automatically rebound following a successful transplant. A patient's hematocrit does not rise in the days immediately following transplantation, but requires several weeks to months to return to normal levels. Similarly, the disappearance of graft-versus-host disease mediated by T lymphocytes in the donor marrow could not be taken as an indicator of success of the transplant. The disappearance of graft-versus-host disease may indicate that the immunosuppressive drug has successfully treated this disease.
5. **(A) is correct.** Graft-versus-host disease is largely, if not entirely, mediated by immunocompetent T lymphocytes that are present in the hematopoietic stem cell transplant from the donor. These T lymphocytes become activated by the alloantigens of the transplant recipient, mature into activated, antigen-specific T lymphocytes, and localize to sites such as the skin, gut epithelium, liver, and elsewhere in the body where they initiate destruction of recipient cells. The activated graft cells participating in the reaction release large amounts of cytokines, some of which attract and activate monocytes and macrophages, also abundant in the infiltrates. Residual populations of recipient immune cells, often autoreactive, become activated as well and play a significant pathogenic role in GVHD. Antibodies do not appear to play a major or significant role in graft-versus-host disease; natural killer cells are also not major factors in this disease.

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### Posttest Answers (continued)

6. **(C) is correct.** The likelihood of developing a GVH reaction is minimal when solid organs with minimal endogenous lymphoid tissue, such as the kidney and the heart, are grafted. However, the likelihood increases in a heart-lung transplant due to the lung-associated lymphoid tissues.
  
7. **(A) is correct.** Autoimmune hemolytic anemia in a hematopoietic stem cell transplant recipient may occur during GVHD if autoreactive clones are activated, but the frequency of this event is low. The other answers, such as graft rejection or failure of the graft to take, graft-versus-host disease, immune deficiency after transplant, and opportunistic infection are all observed with considerable higher frequency following hematopoietic stem cell transplantation.
  
8. **(E) is correct.** The induction of an active immune response by immunization is considered as evidence of immunological reconstitution. It is likely that a state of chimerism, in which cells of both donor and recipient origin repopulate the bone marrow without reacting to each other is the best possible outcome for this type of transplant, but by itself does not prove that there has been total reconstitution of the immune system. The same is true for other positive outcomes, such as normalization of the white blood cell count and of the CD4<sup>+</sup> T cell count. On the other hand, polyclonal hypergammaglobulinemia is often seen in cases of GVHD and reflects the indiscriminate activation of B cells, not associated with recovery of the ability to respond to a specific challenge.
  
9. **(D) is correct.** Athymic mice will lack T cells and will not be able to reject the graft, however, the grafted T cells will be able to mount a GVHD. The three major manifestations of GVHD are splenomegaly, diarrhea, and wasting. Lymphomas and infections are more prevalent in immunocompromised animals, but not as a consequence of the bone marrow transplant.
  
10. **(D) is correct.** CD34 is a marker that allows selection of stem cells from the bone marrow, peripheral blood, or cord blood. It can be used for selection of either autologous or allogeneic stem cells. The several varieties of stem cell grafting are becoming the approach of choice for the treatment of hematopoietic malignancies. CD10 is a marker of leukemic cells, which can be used to "purge" them from autologous bone marrow, for example. CD19 is a mature B cell marker. CD25 is a marker associated with the IL-2 receptor which is up-regulated in activated lymphocytes. B cells express CD40, and its interaction with CD154 (CD40 ligand), expressed by activated helper T cells, delivers an important differentiation signal to the B cell.