Abstract:
Hematopoietic cell transplantation is the only potentially curative option for a variety of pediatric malignant and nonmalignant disorders. Despite advances in transplantation biology and immunology as well as in posttransplant management that have contributed to improved survival and decreased transplant-related mortality, hematopoietic cell transplantation does not come without significant risk of complications. When patients who have undergone hematopoietic cell transplantation present to the emergency department, it is important to consider a variety of therapy-related complications to optimize management and outcome. In this article, we use clinical cases to highlight some of the more common emergent complications after hematopoietic cell transplantation.

Keywords:
hematopoietic cell transplantation; immunosuppression; congestive heart failure; diffuse alveolar hemorrhage; idiopathic pulmonary syndrome; bronchiolitis obliterans; posterior reversible encephalopathy; thrombotic microangiopathy; graft-versus-host disease; infection; hemorrhagic cystitis; calcineurin inhibitor

*Pediatric Hematology/Oncology, The Johns Hopkins Hospital, Baltimore, MD; †Pediatric Oncology Branch at the National Institutes of Health, Bethesda, MD; ‡Division of Oncology, Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins Hospital, Baltimore, MD; §Division of Pediatrics, Sidney Kimmel Comprehensive Cancer Center at The Johns Hopkins Hospital, Baltimore, MD. Reprint requests and correspondence: Heather Symons, MD, MHS, Divisions of Oncology and Pediatrics, Sidney Kimmel

Emergent Complications in the Pediatric Hematopoietic Stem Cell Transplant Patient

Ashley Munchel, MD*†, Allen Chen, MD, PhD‡§, Heather Symons, MD, MHS‡§

More than 40 000 hematopoietic cell transplants (HCTs) are performed worldwide each year. Hematopoietic cell transplants are indicated for a variety of pediatric disorders including both hematologic and solid tumor malignancies as well as nonmalignant conditions such as hemoglobinopathies, immune deficiencies, metabolic storage diseases, and bone marrow failure syndromes. With improvements in transplant technology, more HCT recipients now survive free of the disease for which they were transplanted; however, there are a variety of transplant-related complications that can cause substantial morbidity and mortality. Knowledge of potential complications, as well as current diagnostic and management strategies, is critical for optimizing outcome for the transplant recipient.

In general, there are a variety of risk factors associated with higher incidence of treatment-related complications after HCT (Table 1). These risk factors include donor/host incompatibility,

Comprehensive Cancer Center at The Johns Hopkins Hospital, 1650 Orleans St, CRB 1 Room 2M52, Baltimore, MD 21237.
amunche1@jhmi.edu (A. Munchel),
chenal@jhmi.edu (A. Chen),
Hsymons2@jhmi.edu (H. Symons)

1522-8401/$ - see front matter

disease status, graft type, graft contents, conditioning intensity, posttransplant immunosuppressive regimen, time from transplantation, neutrophil engraftment, and the presence of graft-versus-host disease (GVHD). In this article, we use clinical cases to highlight some of the more common emergent complications after HCT.

CASE 1

An 8-year-old girl with a cord blood transplant for acute lymphoblastic leukemia 35 days ago presents to the emergency department (ED) after having a fever at home to 103°F. Review of systems revealed clear rhinorrhea for the past 2 days, but no sore throat, otalgia, cough, dyspnea, chest pain, abdominal pain, altered mental status, or rash. Vital signs included the following: temperature (oral), 38.9°C; pulse rate, 118 beats/min; respiratory rate, 20 breaths/min; blood pressure, 118/68 mm Hg; and oxygen saturation, 99% on room air. Generally, the patient is well appearing and in no distress. Her physical examination is otherwise unremarkable. She has no signs of mucositis, clear lungs, nontender abdomen, good perfusion, no fissures or anal mucosal inflammation, and no rash.

DISCUSSION OF CASE 1

Fever is the most common reason for ED visits after HCT, and infection is a major cause of morbidity and mortality. Table 2 shows the risk of certain infections based on predicted posttransplantation immune reconstitution. In 2000, the Centers for Disease Control and Prevention published guidelines that outlined the prevention and treatment of opportunistic infections after HCT, and in 2006, the Center for International Blood and Marrow Transplant Research published recommended screening and preventative practices after HCT, which are summarized below.[1,2]

In the early post-HCT period, days 0 to 30, patients are at high risk of developing serious bacterial infections, particularly from gram-negative bacilli, coagulase-negative *Staphylococcus*, and *Streptococcus* species. Patients are also at risk for fungal infections, particularly from *Candida* and *Aspergillus*, as well as from viral infections such as herpes simplex viruses (HSVs). In days 30 to 90 post-HCT, patients are at greater risk of developing cytomegalovirus (CMV), fungal, and *Pneumocystis jiroveci* infections. In the later post-HCT period (day >100), patients are at risk for encapsulated bacterial infections (particularly in patients with chronic GVHD (cGVHD), which affects splenic function), viral infections such as CMV, varicella zoster (VZV), and *P jiroveci*.

The evaluation of a febrile patient post-HCT requires a careful history and physical examination. Particular attention must be paid to common sites of infection in patients who are immunocompromised, including the skin, indwelling central venous catheters (CVCs), and entrance sites such as lungs, oral,

TABLE 1. Risk factors associated with higher incidence of treatment-related complications after hematopoietic stem cell transplantation.

Factor	Risks
Type of transplant	Higher risk with allogeneic, lower risk with autologous or syngeneic
Pretransplant factors	Higher risk with extensive pre-HCT immunosuppressive therapy, prolonged pre-HCT neutropenia, or pre-HCT infection
Time from transplant	Lower risk with more time elapsed from HCT
GVHD	Higher risk with grade III-IV aGVHD or extensive cGVHD
HLA match	Higher risk with HLA-mismatched donors
Disease status	Higher risk with more advanced disease at the time of transplant
Donor type	Higher risk with alternative donors (matched unrelated, haploidentical, cord) than with a fully matching sibling donor
Graft type	Higher risk with T cell–depleted grafts (depending on the method used)
Immunosuppression after transplant	Higher with immunosuppressive drugs, in particular with corticosteroids, antithymocyte globulin, and alemtuzumab
Conditioning intensity	Lower risk with reduced intensity chemotherapy/radiotherapy
Neutrophil engraftment	Higher risk with delayed engraftment/ nonengraftment

HLA indicates human leucocyte antigen; aGVHD indicates acute graft versus host disease; cGVHD indicates chronic graft versus host disease.