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Emergent Complications in the Pediatric Hematopoietic Stem Cell Transplant Patient

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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

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

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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, 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 N100), 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, and perirectal mucosa. Complete blood count and blood cultures for bacteria and fungi should be drawn in all febrile patients. In a patient

without a CVC, a peripheral blood culture should be drawn. Urine cultures, skin lesion or wound cultures, viral respiratory cultures, stool cultures, and a chest x-ray and/or computed tomography (CT) should be obtained as clinically indicated. The availability of rapid detection for many viruses, including influenza, respiratory syncytial virus (RSV), and adenovirus, can lead to an early diagnosis and should be considered when symptoms are suggestive of viral disease. Although post-HCT, patients may not be neutropenic, they are still extremely immunocompromised. Patients within 100 days post-HCT and patients at any point posttransplant who have active GVHD and active malignancy or those on immunosuppressive therapy should be treated as significantly immunocompromised with hospital admission highly recommended, although individual institutional practices may vary.

Specific antibiotic choices should be guided by local microbiology, susceptibilities, and individual patient risk factors. The general principle guiding empiric treatment, however, remains the selection of antimicrobial agents with a broad spectrum of activity against gram-negative and gram-positive organisms likely to cause disease in this patient population. It is extremely important to administer antibiotics as quickly as possible. Combination therapy, typically a β -lactam antibiotic (eg, ticarcillin/clavulanate and piperacillin/tazobactam) or a third- or fourth-generation cephalosporin (eg, ceftazidime and cefepime) plus an aminoglycoside (eg, gentamicin and tobramycin) in patients where gram-negative bacteremia is suspected is usually part of the empiric regimen.²⁻⁴ Some studies have shown that monotherapy using broad-spectrum β -lactam antibiotics with antipseudomonal activity have been shown to be as effective as combination therapy. Common monotherapy choices include cephalosporins (eg, ceftazidime and cefepime) or carbapenems (eg, imipenem and meropenem).⁵⁻¹⁰

Vancomycin should be considered for patients with signs of CVC infection, including cellulitis or tenderness at the CVC insertion site, and for patients with a known history of or exposure to methicillin-resistant *Staphylococcus aureus*. When there is clinical suspicion of typhlitis or an intra-abdominal catastrophe, empiric coverage should be broadened to include better anaerobic activity. Triple therapy with metronidazole, a third- or fourth-generation cephalosporin, and vancomycin is commonly used in this setting.

Empiric antifungal therapy is rarely indicated in the ED, unless there is specific evidence of fungal infection on the initial evaluation. Newer liposomal preparations of amphotericin (eg, AmBisome, Abelcet, and Amphotec) can be used as initial empiric therapy or treatment for proven mycoses. In addition, the azole class of antifungals has activity against yeast. Voriconazole is considered the drug of choice for treatment of invasive aspergillosis.¹¹⁻¹⁴ Significant drug interactions and hepatotoxicity are the main limitation of the azoles. The echinocandin class of antifungals (eg, caspofungin, micafungin, and anidulafungin) has activity against azole-resistant *Candida* species and *Aspergillus*. The echinocandins are attractive agents in this population because they are well tolerated and have fewer drug interactions.¹⁴⁻¹⁷

Empiric use of antiviral agents is also not a standard of care in the ED. However, a number of antiviral drugs are available, and the select use of these medications should be considered

in consultation with an oncologist and infectious disease specialist. Stress dose steroids should be considered for patients with adrenal insufficiency from prolonged steroid use, as well as those with pituitary dysfunction.

CASE 2

A 17-year-old girl who underwent matched-unrelated donor (MUD) HCT 4 months ago for acute myeloid leukemia presents to the ED with cough and shortness of breath, which has gotten progressively worse over the last week. On examination, she is awake, alert, and in moderate respiratory distress. She is afebrile, with a heart rate of 102 beats/min, a respiratory rate of 30 breaths/min, and a blood pressure of 117/72 mm Hg. Her oxygen saturation is 87% in room air with improvement to 94% on 2 L of oxygen by nasal cannula. Her examination is remarkable for bilateral crackles in the posterior lung fields and has no murmurs, rubs, or gallops, and her liver edge is palpable at 3 cm below the right costal margin. Her abdomen is soft and nontender. She has bilateral pitting edema to her midcalves.

DISCUSSION CASE 2

The differential diagnosis for this patient includes both infectious and noninfectious post-HCT cardiac and pulmonary complications, as well as veno-occlusive disease. In consultation with the transplant physicians, an evaluation that includes a workup for infection, echocardiogram, electrocardiogram (ECG), chest x-ray, and chest CT should be promptly considered in patients post-HCT presenting to the ED with cardiopulmonary symptoms.

Many antineoplastic drugs have known cardiac side effects, with anthracyclines (eg, doxorubicin, daunorubicin, and mitoxantrone) being the most notable example. Anthracyclines are used to treat a wide variety of pediatric hematologic and solid tumor malignancies. Although not used as part of the preparative regimen for transplantation, many pediatric patients undergoing HCT will have had prior exposure to anthracyclines, and therefore, will be at lifelong risk of developing anthracycline-induced cardiomyopathy and congestive heart failure (CHF). Anthracycline-induced CHF can present during therapy and up to decades after the initial exposure but most often occurs within the first 2 years. Studies have consistently shown that cumulative lifetime exposure of 300 mg/m² or greater is the most important risk factor for developing acute CHF. Other risk factors shown to have variable significance are female sex, trisomy 21, younger age at diagnosis, history of cyclophosphamide or ifosfamide exposure, and history of spinal, mediastinal, or total body irradiation.¹⁸⁻²¹

Alkylating agents (eg, cyclophosphamide and ifosfamide) are another class of chemotherapeutic agents known to have cardiotoxic side effects. Cyclophosphamide is commonly used in the HCT preparative regimen. Cyclophosphamide has been shown to cause arrhythmias, CHF, hemorrhagic myopericarditis, and cardiac tamponade.^{22,23} Up to 90% of pediatric patients receiving cyclophosphamide as part of the conditioning regimen will have minor ECG changes. The most common ECG changes consist of a reduction in summed ECG voltages reflecting some degree of left ventricular dysfunction.²²⁻²⁴

Typically, the cardiac side effects of cyclophosphamide occur acutely within the first 2 weeks after administration of the drug.^{22,23} Unlike anthracyclines where the risk of cardiotoxicity is dependent on lifetime exposure, the risk of cyclophosphamide cardiotoxicity seems to be dependent on exposure to a single dose.²²⁻²⁴

Patients presenting with respiratory distress after HCT must also be evaluated for pulmonary etiologies. Potential HCT-related pulmonary complications can be divided into infectious and noninfectious causes. As discussed previously, bacterial, fungal, and viral infections such as HSV and CMV more commonly occur in the first 3 months posttransplant. However, viral infections, encapsulated bacteria, and *P jiroveci*, in particular, can occur months later.²⁵ Noninfectious pulmonary complications include diffuse alveolar hemorrhage (DAH), idiopathic pneumonia syndrome (IPS), bronchiolitis obliterans (BO), and BO with organizing pneumonia (BOOP), a manifestation of cGVHD.²⁶⁻²⁹ Table 3 describes the presenting symptoms and diagnostic features of noninfectious pulmonary complications after HCT.

Diffuse alveolar hemorrhage is a rare, noninfectious pulmonary complication after HCT, with an incidence of 4% to 5% in the pediatric population. It is associated with a high mortality rate.^{30,31} It typically occurs around the time of engraftment or shortly thereafter. The pathogenesis is unclear. Complete blood count and coagulation studies should be obtained and corrected if abnormal. In addition to supportive care measures, patients are often treated with high-dose steroids based on adult studies of DAH and evidence of corticosteroid efficacy in other noninfectious pulmonary complications after HCT as discussed below.^{30,32}

Idiopathic pneumonia syndrome, BO, and BOOP are collectively referred to as late-onset noninfectious pulmonary complications (LONIPCs). They generally start to appear around 90 days after transplant, although IPS can be seen significantly earlier.^{25,27,28,33} Small retrospective studies have shown that the incidence of LONIPCs is 10% to 15% in pediatric patients who have undergone HCT.^{25,27,33} Patients at the greatest risk of developing these complications are those who have undergone allogeneic HCT or have severe cGVHD. Bronchiolitis obliterans, especially, is thought to be a form of cGVHD of the lungs and may be seen with other manifestations of cGVHD.³⁴

Treatment of LONIPCs typically includes high-dose steroids with or without increasing immunosuppression.^{25,27-29,33,34} Patients with IPS have also been shown to respond to etanercept, a tumor necrosis factor- α blocker.^{35,36} Despite treatment, patients with pulmonary complications tend to do significantly worse, with mortality rates approaching 60%, especially in those patients in whom treatment is not started early. Efforts to rule out infectious causes as well as to obtain radiographic evaluation with CT should be made. Hospital admission for further evaluation including pulmonary function testing and comprehensive infectious disease workup including bronchoscopy and/or biopsy is warranted.

Lastly, the differential diagnosis of the patient described above should include veno-occlusive disease of the liver (VOD). Veno-occlusive disease of the liver most commonly

occurs within the first 35 days after HCT, but it can occur later.³⁷ The pathogenesis of VOD is believed to be initiated by damage to the hepatic sinusoidal endothelium resulting in deposition of fibrin, factor VIII, and large von Willebrand multimers. This can ultimately lead to sinusoidal obstruction, hepatocyte necrosis, and fibrosis.^{38,39-41} Criteria for the diagnosis of VOD have been established independently in 2 studies.^{42,43} Criteria developed by McDonald et al⁴² require the presence of 2 of 3 clinical manifestations of hepatomegaly or right upper quadrant pain, weight gain, and hyperbilirubinemia, whereas the criteria of Jones et al⁴³ are stricter and require the presence of all 3 clinical symptoms. Risk factors for the development of VOD are the use of busulfan, cyclophosphamide, melphalan, or total body radiation in the conditioning regimen; prior abdominal radiation; elevated ferritin prior to transplant; recent exposure to gemtuzumab ozogamicin (anti-CD33 antibody used, particularly in patients with acute myeloid leukemia); and history of previous HCT.⁴⁴⁻⁴⁸ Treatment of mild and moderate VOD is supportive with fluid and sodium restriction, as well as minimization of hepatotoxic medications. There is increasing evidence that defibrotide is an efficacious treatment even in cases of severe VOD involving multiorgan failure.^{49,50}

CASE 3

An 8-year-old boy underwent a MUD HCT for acute lymphoblastic lymphoma 75 days ago. He is brought by emergency medical services (EMS) to the ED after having a generalized seizure lasting 2 minutes at home. When EMS arrived, he was postictal. He has no history of seizures. He has acute GVHD (aGVHD) of the skin. His current medications include Bactrim for *P jiroveci* prophylaxis, cyclosporin A and prednisone for GVHD treatment, and amlodipine for hypertension. Emergency medical services reports that his serum glucose was 88 mg/dL and that his vital signs upon EMS arrival to the house were as follows: temperature, 37°C; heart rate, 125 beats/min; respiratory rate, 24 breaths/min; blood pressure, 165/92 mm Hg; and oxygen saturation, 98% on room air. In the ED, he has remained afebrile. His current vital signs are as follows: heart rate, 110 beats/min; respiratory rate, 22 breaths/min; and blood pressure, 122/83 mm Hg. He is still postictal, but the remainder of his physical examination is unremarkable.

CASE 3 DISCUSSION

Transplant-associated neurotoxicity is not uncommon. The differential diagnosis includes posterior reversible encephalopathy, hypertensive urgency or emergency, hemorrhagic event, central nervous system (CNS) relapse, metabolic disturbances, transplant-associated thrombotic microangiopathy (TA-TAM), intrathecal chemotherapy side effects, and infection. There are 3 periods of vulnerability to neurotoxicity.^{51,52} The first is during or immediately after the conditioning regimen as a direct result of neurotoxic drugs, such as busulfan, or total body irradiation.⁵¹⁻⁵³ The second period of vulnerability is when patients are thrombocytopenic, awaiting full count recovery, which can increase the risk for intracranial bleeding.^{51,52} Intracranial bleeds can also occur later after HCT secondary to infection, intracranial relapse, hygromas, or other unidentified causes.⁵⁴ The third period of vulnerability is while patients are on immunosuppressive agents for GVHD prophylaxis or treatment, especially calcineurin inhibitors.^{51-53,55,56}

Initial evaluation of the patient presenting with altered mental status should include a complete blood count, prothrombin time, partial thromboplastin time to look for evidence of thrombocytopenia, or coagulopathy that could increase the risk of intracranial hemorrhage. A chemistry panel should be sent, as several chemotherapeutic and immunosuppressive agents are known to cause reversible metabolic disturbances that may present as altered mental status or seizure. For example, cyclosporine A and cisplatin are known to cause hypomagnesemia, whereas vincristine and cyclophosphamide can cause hyponatremia secondary to a syndrome of inappropriate antidiuretic hormone secretion–like syndrome.⁵⁷ Lactate dehydrogenase, haptoglobin, indirect bilirubin, and peripheral smear should be done to look for evidence of intravascular hemolysis to rule out TA-TAM. Imaging studies including head CT and magnetic resonance imaging, if indicated, should be performed. An infectious disease work-up should be considered, particularly if there is no obvious etiology on physical exam, laboratory, or imaging studies. The most common causes of CNS infections after HCT are Epstein-Barr virus, adenovirus, CMV, human herpes virus-6, toxoplasmosis, and aspergillosis.⁵² Cerebral spinal fluid should be sent for viral titers or polymerase chain reaction assays in addition to bacterial and fungal culture. Cytology can also be sent to look for malignant cells if there is concern for CNS relapse.

The most common cause of neurotoxicity after HCT is secondary to calcineurin inhibitors (CI) such as cyclosporin A and tacrolimus, which are frequently used for GVHD prophylaxis.^{52,53,55,56} In addition to electrolyte imbalances, CIs can cause hypertensive urgency or emergency and posterior reversible encephalopathy. Posterior reversible encephalopathy most commonly presents with hypertension, seizures, visual disturbances, delirium, mental status changes, or focal neurologic deficits.^{52,55,58,59} Although the diagnosis may be suggested by CT,^{52,59} magnetic resonance imaging is most sensitive, showing bilateral, symmetric enhancement of the parieto-occipital white matter on T2-weighted images.^{52,56,58,59} Additional risk factors for developing CI neurotoxicity include concomitant corticosteroid use, hypomagnesemia, or history of a hemoglobinopathy.^{51-53,56,58,59} Serum CI levels do not necessarily correlate with neurotoxicity, and patients are often in the therapeutic range when they present with neurologic complaints.^{56,59} Fortunately, discontinuation of the CI usually results in complete resolution of symptoms over time.

Patients receiving post-HCT intrathecal chemotherapy, such as intrathecal methotrexate or cytarabine, to prevent relapse of their malignancy can also experience neurologic side effects. Transplant-associated thrombotic microangiopathy is also a potential cause of altered mental status and will be discussed in greater detail within case 4.

Treatment of neurologic complications after transplant is primarily supportive, including antiepileptics when indicated, empiric antimicrobial therapy, correction of underlying metabolic disturbance, and transfusion of platelets, fresh-frozen plasma, and/or cryoprecipitate in cases of coagulopathy. When evidence suggests CI toxicity, the CI should be stopped, as symptoms are usually quickly reversible after discontinuing the drug.^{52,56,58,59}

CASE 4

A 13-year-old boy who underwent haploidentical HCT for acute myeloid leukemia 50 days ago presents to the ED with gross hematuria, lower abdominal pain, dysuria, frequency, and urgency. His current medications include Bactrim and voriconazole for antimicrobial prophylaxis and tacrolimus for GVHD prophylaxis. On examination, he is hemodynamically stable but in obvious discomfort. He has tenderness to palpation over the suprapubic area. His examination is otherwise unremarkable. His urine has bright red blood and small clots.

CASE 4 DISCUSSION

The differential diagnosis for this patient includes hemorrhagic cystitis, TA-TAM, or other coagulopathic disorder. Hemorrhagic cystitis (HC) occurs in up to 20% of pediatric patients who have undergone HCT.⁶⁰⁻⁶⁵ A grading system has been developed to describe severity of symptoms: grade 1, microscopic hematuria; grade 2, macroscopic hematuria; grade 3 macroscopic hematuria with clots; and grade 4, macroscopic hematuria with clots and impaired renal function secondary to urinary tract obstruction. Hemorrhagic cystitis is divided into early-onset, occurring within 1 week of transplantation, and late-onset, occurring more than 1 week after transplantation. Early-onset HC is most often due to direct uroepithelial insult from cyclophosphamide, or other alkylating agents, in the conditioning regimen.^{60,62-64,66-69} It has been shown that the accumulation of cyclophosphamide metabolites in the bladder directly damages the bladder wall.⁶⁹ With hyperhydration and the introduction of Mesna prophylaxis in the late 1970s, the incidence of cyclophosphamide-induced HC has drastically decreased.⁶⁸

Currently, the most common cause of HC is viral reactivation, which occurs at a median onset of 30 to 60 days after transplantation, only rarely occurring more than 100 days after transplantation.^{60,62-64} Adenovirus, CMV, and polyomaviruses have all been implicated. The most common causative organism is BK virus (polyomavirus).^{60,62-64,70} Patients at greatest risk of developing HC include those who were older at transplantation, those who received a matched-unrelated HCT, and those who received antithymocyte globulin or cyclophosphamide in the conditioning regimen.^{60,67}

The most serious consequence of HC is the development of renal failure. Patients have required dialysis due to HC-induced renal failure.⁶⁴ The best way to prevent the progression to renal failure is by preventing clot formation and obstruction. In cases of mild HC, hydration, forced diuresis, platelet transfusions to keep a platelet count of greater than 50 000/mm³, pain management, and antispasmodics such as oxybutynin may be sufficient.^{60,62,64-66} Renal ultrasound should be used to look for clots in the bladder and/or kidneys. When patients are passing clots, they typically require Foley catheter insertion with continuous bladder irrigation until the bleeding can be controlled.^{60,63-65} In patients who continue to have obstruction, suprapubic catheter placement, ureteral stent placement, or nephrostomy tubes may be indicated. The effort to relieve the obstruction needs to be initiated quickly; therefore, prompt urologic evaluation is often advisable. In patients who have refractory bleeding, several other treatments have been tried with variable success, including intravesicular hyaluronic acid,⁶⁶ intravesicular alum,⁷¹ intravesicular formalin,⁶³

intravesicular prostaglandins,^{72,73} and hyperbaric oxygen.^{65,74-76} For BK and adenovirus viruria, the antiviral agent cidofovir has shown promising results.^{62,70}

Transplant-associated thrombotic microangiopathy is a rare cause of late-onset HC. In addition to HC, it can present in many different ways, including altered mental status, acute renal failure/insufficiency, gastrointestinal bleeding, multiorgan failure, or simply as a sudden drop in hemoglobin and platelets in a patient who is otherwise doing well.⁷⁷⁻⁸¹ Despite efforts by the Bone Marrow Transplant Clinical Trials Network and The International Working Group, there is still wide variability in reported incidence of TA-TAM due to the lack of standard diagnostic criteria.⁷⁹ Despite the differences in diagnostic criteria, TA-TAM must be considered in patients with thrombocytopenia and evidence of Coombs negative hemolytic anemia indicated by schistocytes or red cell fragmentation on peripheral smear, elevated lactate dehydrogenase, decreased haptoglobin, drop in hemoglobin, or increased need for red blood cell transfusions.⁷⁷⁻⁸¹ The median time of onset is about 40 days after allogeneic transplantation; however, it can be seen at any time after HCT.^{77,80-82} Although there has been a lot of variability in defining risk factors, different studies have shown increased risk in the following patient groups: female patients, patients who received unrelated or mismatched grafts, patients who received total body radiation or busulfan in the conditioning regimen, patients who have GVHD, patients who are taking cyclosporine A or tacrolimus especially when given concurrently with sirolimus, or those who have a concomitant infection, especially CMV, human herpes virus, or *Aspergillus*.^{77,80,81,83,84}

The pathophysiology of TA-TAM is not well understood. Current evidence suggests that it could be secondary to abnormalities of the vascular endothelium that promote platelet adhesion and arteriolar microthrombi.^{85,86} Because of its clinical similarity to thrombotic thrombocytopenic purpura, patients are often treated with plasma transfusion or plasma exchange. However, this is often not successful likely due to differences in the underlying pathophysiology. Primary thrombotic thrombocytopenic purpura is the result of a mutation in ADAMTS13 gene or due to an autoantibody that inhibits ADAMTS13 activity, the enzyme responsible for cleaving von Willebrand factor.^{87,88} The uncleaved von Willebrand multimer promotes platelet aggregation and thrombosis formation. Plasma exchange rids the body of the antibody while replenishing the supply of ADAMTS13. In patients with TA-TAM, ADAMTS13 activity is often normal or only slightly decreased. Furthermore, studies have shown that plasma exchange does not replenish ADAMTS13 and does not alter the clinical course in transplant patients with TA-TAM.^{83,89-91} Therefore, given the risk of severe complications of plasma exchange, most do not perform empiric plasma exchange for the treatment of TA-TAM. Alternative therapies have been tried with variable success, including defibrotide,⁸² daclizumab,⁹² and rituximab.⁹³

CASE 5

A 7-year-old girl underwent a MUD HCT for relapsed acute myeloid leukemia 45 days ago. Her chief complaint is a red, itchy rash that she said started on her palms and soles and is now covering her face and trunk. Her ED vital signs are significant for a temperature of

38.3°C, and she appears itchy and uncomfortable. There is a maculopapular erythematous rash as described. There are no other significant physical findings.

CASE 5 DISCUSSION

This patient is most likely presenting with aGVHD, although the differential diagnosis certainly includes infection. Graft-versus-host disease is a consequence of T lymphocytes in the donor graft attacking tissue in the recipient due to antigenic differences between donor and host major and minor histocompatibility complex.⁹⁴⁻⁹⁶ It can be divided into aGVHD or chronic GVHD (cGVHD).

Acute GVHD typically occurs within the first 100 days after transplantation. The greatest risk factor for developing aGVHD is the degree of human leucocyte antigen mismatch between donor and host.⁹⁷⁻⁹⁹ Therefore, patients receiving matched sibling HCT typically experience less GVHD than those who receive matched-unrelated or mismatched-related HCT.⁹⁹ Severity of aGVHD can range from mild to life threatening. A summary of clinical findings and management of aGVHD is shown in Table 4. In brief, the most common tissues involved are the skin, intestines, liver, and immune system.^{98,100} Skin involvement includes a pruritic erythematous maculopapular rash typically originating on the palms and soles. Intestinal symptoms include nausea, anorexia, diarrhea, ileus, and abdominal pain. Typical liver symptoms include transaminitis and hyperbilirubinemia, which can progress to coagulopathy and other signs of liver failure.

Chronic GVHD used to be defined by onset of symptoms greater than 100 days after transplantation. However, the current definition as determined by the National Institutes of Health cGVHD Consensus Project is not based on time of onset but, rather, is dependent on signs and symptoms.¹⁰¹ Chronic GVHD can affect almost any organ of the body including the skin, eyes, oral cavity, gastrointestinal system, liver, and the immune system as described in Table 4.^{98,100-103} The symptoms of cGVHD often resemble autoimmune disorders such as scleroderma, Sjögren syndrome, and vitiligo.

The primary goal with GVHD is prevention. Therefore, patients who undergo allogeneic transplantation are placed on immunosuppressive drugs aimed at preventing severe GVHD. Common prophylactic drugs include calcineurin inhibitors (eg, tacrolimus and cyclosporin), mammalian target of rapamycin (mTOR) inhibitors (eg, rapamycin) and mycophenolic acid.^{98,100,104,105} If a patient develops signs of aGVHD, the first-line therapy is often corticosteroids. Topical steroids may be sufficient for isolated, mild-skin aGVHD. For more advanced disease, the most common treatment is methylpred-nisone 2 mg/kg per day, given in combination with a CI, mTOR inhibitor, or mycophenolic acid.^{98,100,106}

Treatment of cGVHD is often lengthier and requires long-term close follow-up in a transplantation center. Treatment often includes local therapy to the involved organ (ie, steroid eye drops, steroid swish and spit for oral GVHD, etc) or systemic therapies with corticosteroids and additional immunosuppressive agents, as with aGVHD.¹⁰¹⁻¹⁰³

It is always important to remember that GVHD and its therapies greatly impact the immune system. As a result, patients with aGVHD or cGVHD should be considered highly immunosuppressed and treated accordingly.^{98,100,101}

SUMMARY

Hematopoietic cell transplant carries with it risk of significant morbidity and mortality. Although this review is by no means a complete list of potential emergencies after HCT, it covers some of the more common or most dangerous complications that require quick intervention upon presentation to the ED. Getting a thorough history including current medications, time since transplantation, treatment history including type of HCT, chemotherapeutic agents, and/or radiation therapy received and performing a thorough physical examination are extremely important in assessing the potential short- and long-term complications after HCT. Soliciting the assistance of consultants such as a pediatric oncologist, pulmonologist, gastroenterologist, urologist, and/or infectious disease specialist is often warranted. Rapid recognition, diagnosis, and treatment of post-HCT conditions that may present to the ED will continue to help improve long-term survival and quality of life for HCT recipients.

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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.

TABLE 2Risk of infection based on posttransplantation immune reconstitution.^{1,2}

Time After Transplantation (mo)	Common Risk Factors for Infection	Common Infections
0-1	Regimen-related toxicity Graft failure Neutropenia	Bacterial (<i>Staphylococcus</i> , <i>Streptococci</i> , gram-negative bacilli) Fungal (<i>Candida</i> , <i>Aspergillus</i>) Viral (HSV, respiratory and enteric viruses)
1-3	aGVHD	Fungal (<i>Candida</i> , <i>Aspergillus</i> , other fungi) <i>P jiroveci</i> Viral (CMV, respiratory and enteric viruses) Bacterial (<i>Staphylococcus</i>)
3-12	cGVHD Relapse	<i>P jiroveci</i> Viral (VZV, CMV, respiratory and enteric viruses) Encapsulated bacteria
>12	cGVHD Relapse	<i>P jiroveci</i> Viral (VZV, CMV, respiratory and enteric viruses) Encapsulated bacteria

TABLE 3Differential diagnosis of noninfectious pulmonary complications.^{25,27-29,33,34}

Diagnosis	Signs/Symptoms	Radiologic Findings	Other Diagnostic Findings
DAH	Acute-onset respiratory distress $\pm$ hemoptysis	Diffuse bilateral infiltrates	No infectious etiology BAL with progressively bloodier fluid and hemosiderin laden macrophages
BO	Dyspnea, nonproductive cough, and/or exercise intolerance	Air trapping or bronchiectasis	No infectious etiology PFT with FEV ₁ <75% predicted and FEV ₁ /FVC <0.7
BOOP	Fever, dyspnea, productive cough, and/or exercise intolerance	Peripherally distributed patchy air space consolidation and nodular opacities	No infectious etiology
IPS	Dyspnea, cough, and/or exercise intolerance	Bilateral diffuse parenchymal interstitial/alveolar infiltrate	No infectious etiology

PFT indicates pulmonary function test; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; BAL indicates bronchial alveolar lavage.

TABLE 4

Acute and chronic GVHD.^{101,104}

Site	Clinical Findings	Management ^a
aGVHD		
Skin	Rash (can be erythematous, maculopapular, bullous, or desquamating); classic involvement of palms and soles Often pruritic	Replace extra insensible losses if severe GVHD
Liver	Hepatomegaly; right upper quadrant tenderness; elevated bilirubin, alkaline phosphatase, and transaminases	Caution using drugs metabolized in the liver
Gut	Diarrhea, sometimes bloody; abdominal pain	Hydration as needed for dehydration, packed red cell transfusions for significant blood loss
cGVHD		
Skin	Sclerodermatous or lichenoid changes; contractures may be present	May lose ability to sweat so manage potential electrolyte abnormalities
Liver	As with aGVHD	Caution using drugs metabolized in the liver
Gut	Weight loss, nausea, abdominal pain, failure to thrive	Slow caloric replacement with parenteral nutrition and/or enteral feeds with elemental formula
Pulmonary	Shortness of breath, hypoxia	Consider trial of bronchodilators and a leukotriene inhibitor
Eyes	Dryness	Artificial tears, steroid and/or cyclosporine eye drops may be necessary; potential for corneal abrasions
Mouth	Dryness, ulcerative or lichenoid lesions	Steroid swish and spit

^aGeneral management of GVHD includes consideration of additional immunosuppressive medications in consultation with a pediatric oncologist and aggressive management of fevers and infections given immunosuppression intrinsic to GVHD.