Care of the Critically Ill Pediatric Hematopoietic Cell Transplant Patient

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Learning Objectives

- To understand the various indications for and the types of hematopoietic cell transplants (HCT) at a level that will provide the pediatric intensive care provider an adequate foundation to care for these children when they develop critical illness.
- To recognize the various etiologies of respiratory failure in the pediatric HCT patient with a focus on those conditions most commonly found in this unique patient population.
- To anticipate the cardiac complications that most commonly occur in the pediatric HCT recipient.
- To understand the clinical manifestations of endotheliopathy in these children with a focus on sinusoidal obstruction syndrome (hepatic veno-occlusive disease) and transplant associated thrombotic microangiopathy.
- To appreciate the high risk of infectious disease in this immunocompromised patient population and to identify common pathogens.
- To appreciate the timing, clinical manifestations and potential treatments for conditions relatively unique to the HCT patient including engraftment syndrome and graft versus host disease.
- To recognize common neurologic emergencies in the pediatric HCT recipient.
- To identify the development of post-transplant lymphoproliferative disease (PTLD) in these high-risk children.
- To understand the role of Chimeric Antigen Receptor (CAR)-Immune Effector Cell Therapy and the potential consequences that may result in critical illness including cytokine release syndrome and CAR T-cell related encephalopathy syndrome (CRES)/immune effector cell associated neurotoxicity syndrome (ICANS).

40.1 Introduction

Hematopoietic cell transplantation (HCT) holds the potential to be a curative therapy for a number of life-limiting malignant and nonmalignant diseases. However, the process is fraught with many risks and life-threatening complications that require critical care services. The ability to effectively prevent and treat these serious complications holds the potential to not only improve outcomes for this most vulnerable patient population but also afford the opportunity to extend this life-saving therapy to other at-risk populations.

In order to most effectively care for these children, the pediatric critical care provider must have a thorough and working understanding of the HCT process. This understanding must include an appreciation for the relationship between the timeline of the HCT process and the most common infectious and noninfectious complications of this treatment. The critical care provider must be able to recognize those life-threatening conditions unique to the HCT patient as well as the presentation of more common critical illnesses in this patient population. It is important to understand that these children not only incur an immunosuppressed state at various stages of the HCT process, but also a dysregulated immune system at other points that may foster uncontrolled inflammation.

In this chapter, the common pulmonary, cardiovascular, and neurologic conditions associated with HCT that result in substantial morbidity and mortality will be reviewed. The clinical manifestations of HCT-associated endotheliopathy including the sinusoidal obstruction syndrome/hepatic veno-occlusive disease as well as transplant associated thrombotic microangiopathy will be described. Conditions relatively unique to the HCT patient such as engraftment syndrome and graft versus host disease (GVHD) will also be reviewed. Finally, the novel

chimeric antigen receptor (CAR) autologous T-cell immunotherapy, now being used to treat refractory or relapsed precursor B-cell acute lymphoblastic leukemia with unprecedented success, will be considered with an emphasis on its unique life-threatening toxicities including cytokine release syndrome and CAR T-cell related encephalopathy syndrome (CRES)/immune effector cell associated neurotoxicity syndrome (ICANS).

40.2 Hematopoietic Cell Transplantation Process

40.2.1 Indications and Types of Transplants

Hematopoietic cell transplantation (HCT) is a potentially curative therapy for a variety of malignant and nonmalignant conditions. Autologous HCT refers to the infusion of a patient's own previously collected stem cells following high-dose chemotherapy. To optimize stem cell collection, patients typically undergo stem cell mobilization and apheresis early in their treatment course (prior to heavy cumulative marrow toxic therapy). The cells are then cryopreserved. Later, high-dose consolidation chemotherapy used to treat the primary disease ablates the marrow (myeloablative therapy) and autologous HCT facilitates hematopoietic recovery. As depicted in ◘ Table 40.1, autologous HCT is used in a variety of high-grade solid tumors.

Different graft sources are associated with varying times to achieve post-HCT hematopoietic recovery and may be associated with infections and other morbidities.

Allogeneic HCT refers to the infusion of hematopoietic stem cells (HSCs) from an either related or unrelated donor source. Indications for allogeneic HCT include high-risk leukemias, bone marrow failure syndromes, and nonmalignant genetic diseases (◘ Table 40.1). Allogeneic HCT for solid tumors is currently under investigation. For malignant diseases, new allogeneic donor hematopoietic cells facilitate a graft-versus-tumor (GvT) effect which may enhance long-term cure rates. In nonmalignant diseases, allogeneic donor hematopoietic cells either directly replace the patient's own hematopoietic cells to cure their primary disease (e.g., primary immune deficiencies and hemoglobinopathies) or cross-correct enzyme deficiencies in neighboring cells and thereby attenuate manifestations of genetic diseases. Donor sources may be classified based on histocompatibility (human leukocyte antigen (HLA) match) and relation to the recipient (◘ Table 40.2). Different graft sources are associated with varying times to achieve post-HCT hematopoietic recovery and may be associated with infectious and other morbidities (◘ Table 40.3).

The primary indication for HCT may pose special management considerations that should be recognized. For example, patients with sickle cell anemia (SCA) undergoing HCT require reduction in their hemoglobin S percent prior to initiation of preparative regimens to avoid sickle cell crises and multiorgan dysfunction. Further, patients with SCA require vigilant monitoring for posterior reversible encephalopathy syndrome (PRES) and require ongoing seizure prophylaxis while receiving calcineurin inhibitor graft-versus-host-disease (GVHD) prophylaxis/treatment. Patients with SCA may have lower baseline blood pressure compared to the general population, so it is important that relative hypertension be recognized. Patients with acute lymphoblastic leukemia (ALL) and adrenoleukodystrophy (ALD) should be particularly monitored for adrenal crisis as they may require stress dose corticosteroid administration during illness. Patients with Hurler syndrome may present with cardiomyopathy requiring careful selection of medications when hypertension is present. These patients may also present with difficult airways, have obstructive sleep apnea, and increased intracranial pressure.

Table 40.1 Indications for allogeneic and autologous hematopoietic cell transplant

Allogeneic		Autologous
Nonmalignant diseases	**Malignant diseases High risk/relapsed or refractory disease**	
Hereditary bone marrow failure syndromes Fanconi anemia Blackfan-Diamond anemia Severe aplastic anemia Dyskeratosis congenita Congenital amegakaryocytic thrombocytopenia Severe congenital neutropenia Shwachman Diamond anemia	*Leukemia* AML ALL APML CML MDS JMML	*Solid tumors* Germ cell tumor Ewing sarcoma Neuroblastoma Wilms tumor Medulloblastoma
Immunodeficiencies SCID Wiskott-Aldrich syndrome Severe congenital neutropenia CGD IPEX	*Lymphoma* Burkitt lymphoma Hodgkin lymphoma Anaplastic large cell lymphoma B-cell non-Hodgkin lymphoma T-cell non-Hodgkin lymphoma	*Lymphoma* Burkitt lymphoma Hodgkin lymphoma Anaplastic large cell lymphoma Diffuse large B-cell lymphoma
Hemoglobinopathies Sickle cell disease Thalassemia		
Inherited metabolic conditions Mucopolysaccharidosis Metachromatic leukodystrophy		
Other Osteopetrosis Adrenoleukodystrophy Hemophagocytic disorders	*Other* MDS	

Adapted from: Majhail et al. (2015) and Sureda et al. (2015)
SCID severe combined immunodeficiency, *CGD* chronic granulomatous disease, *IPEX* immunodysregulation polyendocrinopathy enteropathy X-linked, *AML* acute myelocytic leukemia, *ALL* acute lymphocytic leukemia, *APML* acute promyelocytic leukemia, *CML* chronic myelocytic leukemia, *MDS* myelodysplastic syndrome, *JMML* juvenile myelomonocytic leukemia

40.2.2 Conditioning (or Preparative) Regimens

In autologous HCT, marrow toxic high-dose myeloablative conditioning/preparative regimens used to treat the primary malignancy require stem cell rescue to restore normal hematopoiesis. With few exceptions, conditioning/preparative regimens are used prior to allogeneic HCT. The regimen may consist of chemotherapy with or without radiation and/or serotherapy (e.g., alemtuzumab or antithymocyte globulin) and facilitates tumor burden reduction (in malignant conditions) and adequate immunosuppression for engraftment of the donor hematopoietic stem cells.

Preparative regimens may be classed as myeloablative (MAC), nonmyeloablative (NMA), or reduced intensity conditioning (RIC). Myeloablative regimens consist of alkylating agents with or without high dose total body irradiation (TBI) causing irreversible or near irreversible pancytopenia and require stem cell rescue to restore marrow function. Nonmyeloablative regimens are used primarily to achieve adequate immunosuppression because bone marrow ablation is not neces-

Table 40.2 Types of autologous and allogeneic hematopoietic cell transplants and their donor sources

Type of transplant		Donor source
Autologous		Patient's own hematopoietic stem cells
Allogeneic	Syngeneic	Identical twin donor
	HLA identical sibling/ family donor	10/10 or 8/8 HLA match Umbilical cord blood unit (4/6, 5/6, 6/6 HLA match)
	Matched unrelated donor	Unrelated person (via donor registry) 10/10 or 8/8 match Umbilical cord blood unit (4/6, 5/6, 6/6 HLA match)
	Related haploidentical donor	Family member with one HLA haplotype genetically identical with patient
	Mismatched unrelated donor (mMUD)	Unrelated person (via donor registry) where there is mismatch in HLA

Adapted from: Majhail et al. (2015) and Sureda et al. (2015)
HLA human leukocyte antigen

sary to achieve adequate donor engraftment (usually based on the primary transplant indication). Preparative regimens that do not adequately fall into either of these categories are typically classed as reduced intensity (or reduced toxicity) conditioning regimens. More intense preparative regimens may be associated with a higher risk of endothelial damage and varying rates of associated morbidities such as sinusoidal obstruction syndrome (SOS)/hepatic veno-occlusive disease (VOD), transplant associated thrombotic microangiopathy (TA-TMA), interstitial pneumonitis, idiopathic pulmonary fibrosis, reduced pulmonary function, and renal injury. The choice of specific preparative regimen typically depends on the recipient's age (avoid TBI in children <3 years), primary disease, co-morbidities, and risk of graft failure/rejection.

40.2.3 Timeline

All HCT recipients undergo a comprehensive medical clearance prior to the initiation of the preparative regimen. This entails a detailed medical history including a review of prior treatments as well as assessments of the performance score (Lansky/Karnofsky), organ function, and the co-morbid conditions. The infusion of the HSCs follows administration of the preparative regimen. Infectious prophylaxis, isolation precautions, and transfusion support are typically required until the recipient achieves hematopoietic recovery. Neutrophil engraftment is defined as the first of three consecutive days following HCT with an absolute neutrophil count (ANC) of more than 500/μL. This usually occurs 2–4 weeks after HCT dependent upon the stem cell source (Fig. 40.1). Red blood cell and platelet recovery usually follow thereafter. Complete immune reconstitution (in particular humoral immunity) may only occur months to years following HCT.

Table 40.3 Comparison of the currently used graft sources

Graft source	Availability and collection	$CD34^+$ cells/kg typically present	Time to achieve hematopoietic recovery	Incidence of GVHD
Bone marrow	Requires time for donor medical clearance	Intermediate	Intermediate	Intermediate
	Collection may be limited by donor weight in relation to recipient weight			
	Future donor lymphocyte infusion (DLI) possible			
Peripheral blood	Requires time for donor medical clearance	Greatest	Fastest	Greatest
	Requires stem cell mobilization prior to collection			
	Typically, able to achieve higher cell dose collection/kg of recipient weight			
	Future DLI possible			
Umbilical cord blood	Rapidly available (no medical clearance needed)	Lowest	Slowest	Lowest
	Future DLI not standardly available			

Adapted from: Majhail et al. (2015), Sureda et al. (2015), and Gluckman (2011)
GVHD graft versus host disease

40.3 Respiratory Complications Post-HCT

Pulmonary complications post-HCT are very common and are a significant source of nonrelapse mortality. Between 17% and 44% of HCT children will require critical care services, with respiratory failure being the leading cause for pediatric intensive care unit (PICU) admission.

The etiologies for respiratory failure in this population are diverse. Unfortunately, all etiologies can result in severe respiratory failure, leading to invasive mechanical ventilation. Although the mortality of intubated pediatric HCT patients has improved over time, currently reported mortality rates still discouragingly range between 40% and 60%. Respiratory complications post-HCT can be categorized into infections and noninfections. The diverse etiologies of pulmonary complications render identification and treatment challenging. The testing for infectious sources is imperfect, and many of the noninfectious complications

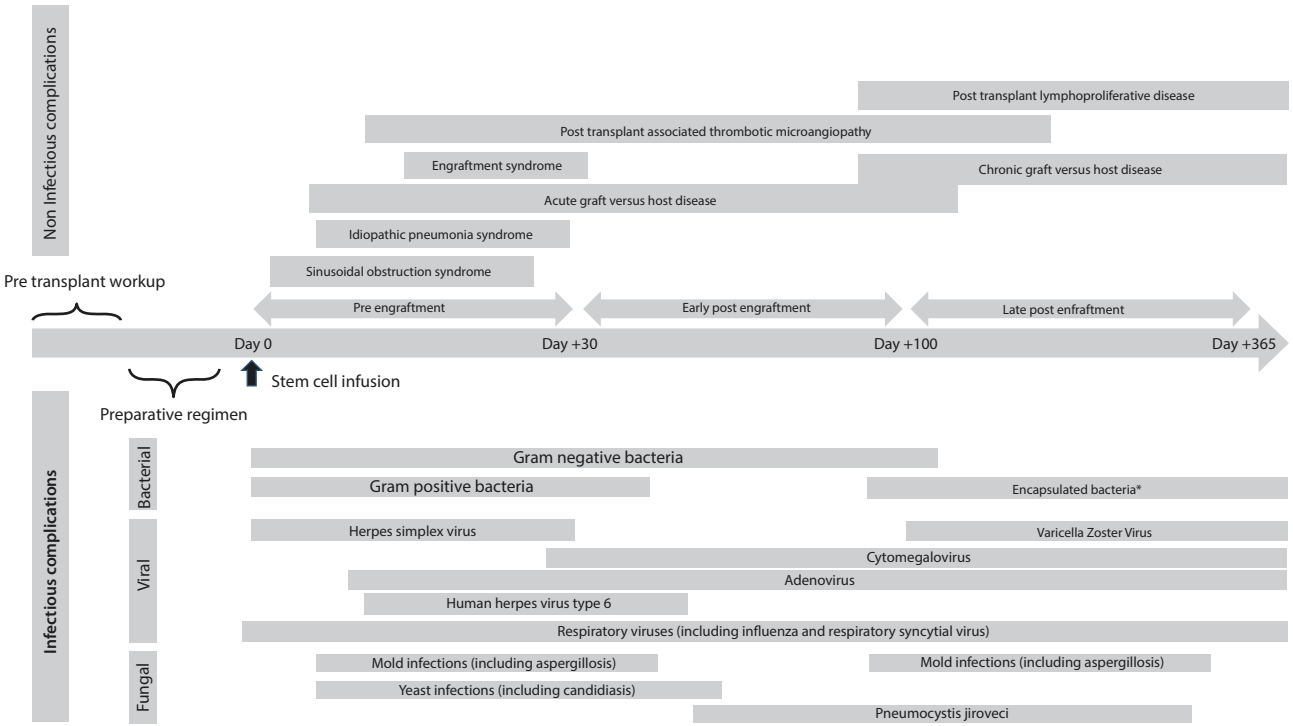

Fig. 40.1 Timeline of common infectious and noninfectious conditions following hematopoietic cell transplant (HCT). The figure depicts the timeline of common infectious and noninfectious conditions following HCT. The periods of HCT are illustrated just above the timeline for a frame of reference. Infectious complications are included below the timeline while noninfectious conditions are illustrated above the timeline. * includes pneumococcus and hemophilus

are based primarily on a constellation of clinical symptoms and/or remain a diagnosis of exclusion.

40.3.1 Infectious Complications

The stage of immune reconstitution affects which pathogens are most likely to cause respiratory infection. The early, preengraftment phase is dominated by common pathogens such as gram-negative and gram-positive bacteria as well as candida. During the periengraftment period, viruses and opportunistic fungi become more prevalent. Encapsulated bacteria and viruses occur most commonly in the postengraftment phase.

The HCT patient is at significantly increased risk for pulmonary infections post-transplant. Lower respiratory tract infections account for up to 50% of all pulmonary complications in children post-HCT. The early, preengraftment phase is dominated by infections secondary to common pathogens including gram-negative and gram-positive bacteria as well as candida. During the periengraftment period, viruses and opportunistic fungi become more prevalent. This is followed by a concern for encapsulated bacteria and viruses in the postengraftment phase (Fig. 40.1).

The diagnostic approach to pulmonary disease in this patient population varies from center to center with the need for bronchoscopy and bronchoalveolar lavage spawning debate. The data surrounding the value of bronchoscopy in the general immunocompromised patient are conflicting with diagnostic yield reports varying between 27% and 85%. However, reports suggest that there is a 20% decrease in mortality if the diagnosis results in a change in therapy. Conversely, the risk of complications with bronchoscopy remains a concern with an incidence as high as 30% in children being reported. Although one study cited less than 1% risk of a new mechanical ventilation requirement following bronchoscopy among the immunocompromised, the risk seems to be higher in HCT recipients. While concerns for complications may result in a

delay, it is important to note that the earlier the bronchoscopy is performed in the disease course, the better the diagnostic yield and the less the risk of complications.

40.3.2 Noninfectious Complications

Noninfectious pulmonary complications following HCT are relatively common, and present a challenge to diagnosis and treatment.

Noninfectious pulmonary complications are challenging and many of them are poorly understood. The diagnosis is often one of exclusion and there are very little treatment options outside of supportive care and corticosteroids. However, progress is being made. There is continued investigation into many of these respiratory problems and new exciting therapies are being assessed and implemented. Collaborative, multicenter studies are needed to further define diagnostic criteria of each specific disease and to optimize possible therapeutic strategies. Several noninfectious complications, organized by general timing of onset, are highlighted in Table 40.4 (Fig. 40.1).

The approach to respiratory support must be considered differently in this patient population than for other critically ill pediatric patients. The risk for both unusual infectious and noninfectious complications in these children often creates a diagnostic challenge. Additionally, there is often a unique opportunity for early intervention as they are frequently hospitalized at the time of respiratory illness development. Moreover, the children post-HCT who develop respiratory illness have a very high risk of developing severe pediatric acute respiratory distress syndrome (PARDS) irrespective of the underlying cause of pulmonary dysfunction. One multicenter study of intubated children post-HCT reported that 92% developed PARDS within the first week of invasive mechanical ventilation. Finally, mortality is exceedingly high among these patients with published mortality rates ranging between 40% and 60%.

The approach to respiratory support for these children is highly variable with little supporting data. Therefore, care is often based on the extrapolation of data from other adult immunocompromised populations and best clinical judgement. One of the most difficult clinical decision points in this population is the timing of intubation. With the exceedingly high mortality rate, clinicians are often hesitant to intubate, opting instead to attempt noninvasive measures. However, emerging data suggest that spending a longer time in respiratory distress prior to intubation results in higher mortality for these children; nonsurvival among this patient population has been reported to be associated with longer lengths of PICU stay prior to intubation, increased use of noninvasive ventilation prior to intubation, and with receiving supplemental oxygen for a week prior to intubation.

In terms of specific forms of respiratory support, there are very little data regarding the use of high flow nasal cannula (HFNC) specific to the pediatric HCT recipient. In a randomized control trial (RCT) of HFNC versus face mask oxygen among 100 immunocompromised adults, there was no difference in the rate of intubation or the work of breathing. In another study of 127 immunocompromised adults, HFNC did not decrease the mortality nor reduce the need for intubation when compared to face mask oxygen. A smaller Japanese study found an 80% failure rate of HFNC among 56 adults with hematological disease. Although there are limited data specific to the pediatric HCT population, HFNC does not seem to be effective in preventing intubation among these patients. Moreover, in utilizing HFNC for this patient population, it is important to remember that data suggest delaying intubation is associated with worse outcomes for these children.

The data for noninvasive ventilation (NIV) are potentially more promising. In an RCT of 40 adults following solid organ transplant, the use of NIV over

Table 40.4 Noninfectious pulmonary complications post-hematopoietic cell transplant (HCT)

Disease process	Definition and incidence	Clinical manifestations and risk factors	Diagnostic findings	Specific treatment
Early complications (within 100 days post-HCT)				
Diffuse alveolar hemorrhage (DAH)	Bleeding in multiple different alveoli creating respiratory distress following HCT	Often occurs with the engraftment of stem cells Respiratory distress Fever Hemoptysis can occur, but is NOT common	Diagnostic criteria: 1. Evidence of widespread alveolar damage 2. Absence of infection 3. Bronchoscopy findings of: Increasing bloody return from three different bronchi > 20% hemosiderin laden macrophages, or Blood in at least 30% of alveolar surface	Supportive care High dose corticosteroids
Periengraftment respiratory distress syndrome (PERDS)	Systemic capillary leak resulting from the graft interacting with the host immune system	Fever Weight gain Diffuse rash Pulmonary edema Hepatic dysfunction Renal dysfunction Encephalopathy	No specific diagnostic criteria, but usually occurs during neutrophil engraftment	Supportive care Controlling fluid balance Corticosteroids
Early or late complications				
Pulmonary cytolytic thrombi (PCT)	Fever and pulmonary nodules that demonstrate necrotic, basophilic thromboemobli on biopsy	Fever Cough Often coincides with GVHD	Pulmonary nodules on chest CT imaging	Corticosteroids Cyclosporine
Idiopathic pneumonia syndrome (IPS)	A wide spectrum of disease processes (many experts believe IPS encompass many of the other noninfectious complications listed on this table).	Cough, tachypnea, dyspnea Negative infectious work up	Evidence of widespread alveolar damage with no identified infection, cardiac dysfunction, acute renal failure, or fluid overload Restrictive PFT findings	Supportive care Corticosteroids Etanercept
Transplant associated thrombotic microangiopathy (TA-TMA)	Systemic endothelial dysfunction that can affect multiple organs including the lungs. Arterioles and capillaries are damaged with thickened walls and lumens obstructed by thrombi. Incidence is highly variable but reported to be as high as 20–30%	It can be mild to severe Pulmonary hypertension Multiorgan involvement particularly in the kidney It can be precipitated by immunosuppressive agents (i.e., calcineurin inhibitors)	Multiple various definitions, but common themes: Elevated LDH New or worsening thrombocytopenia Schistocytes on peripheral smear	Supportive care Discontinuing calcineurin inhibitors Eculizumab for severe cases

Late complications (after 100 days post-HCT)				
Bronchiolitis obliterans syndrome (BOS) and chronic GVHD of the lungs	Progressive airway obstruction that results from fibrosis of the terminal airways and bronchioles; a 2005 NIH consensus reported this is chronic GVHD. It is reported to be one of the most common late pulmonary complications with an incidence ranging from 2% to 26%.	Insidious onset of respiratory symptoms including cough, wheeze, and dyspnea Hyperinflation Often afebrile History of recurrent respiratory infections GVHD in other organs Occurs most commonly in allogeneic HCT	Exclusion of infection and consistent lung biopsy OR Obstructive findings on PFT (FEV_1/FVC < 0.7 and FEV_1 < 75% predicted) and CT findings of air trapping with small airway thickening and bronchiectasis	Corticosteroids first-line therapy; burst followed by a long taper over a year Cyclosporine or tacrolimus Azithromycin Etanercept FAM therapy: Fluticasone, azithromycin, and montelukast
Cryptogenic organizing pneumonia (COP); historically known as bronchiolitis obliterans organizing pneumonia (BOOP)	Involves the bronchioles and distal air spaces. Progressive filling of the alveoli and lumens of the terminal bronchioles with granulation tissue. There is extensive inflammation of the lungs, but no fibrosis.	Fever Cough Dyspnea	Exclusion of infection CT findings of diffuse airspace disease Biopsy with patchy distribution (often peribronchiolar) of fibroblasts/myofibroblasts that involve both alveoli and alveolar ducts, intraluminal fibrosis in distal airspaces Restrictive PFT findings	Corticosteroids, burst followed by long taper
Pulmonary veno-occlusive disease (PVOD)	Rare form of pulmonary hypertension likely a result of endothelial damage	Initially asymptomatic Progressive dyspnea Hypoxia Signs of right heart failure (i.e., peripheral edema, hepatomegaly, and pleural effusions)	Echocardiographic findings consistent with pulmonary hypertension CT findings of ground glass opacities, septal thickening, and mediastinal lymphadenopathy	Supportive care Caution and increased monitoring with pulmonary vasodilators due to a high risk of significant, fatal, pulmonary edema Defibrotide and N-acetylcysteine have unclear benefit

GVHD graft versus host disease, *CT* computed tomography, *PFT* pulmonary function testing, *LDH* lactate dehydrogenase

supplemental oxygen alone was associated with an improvement in oxygenation, a decreased intubation rate (20% vs. 70%) and improved mortality (20% vs. 50%). Similar findings were demonstrated in another RCT of 52 immunocompromised adults. Additionally, a small study of 40 adults with hematologic malignancies found that those randomized to early continuous positive airway pressure (CPAP) had a decrease in the need for intubation and intensive care unit transfer. However, the most recent and largest study had less encouraging results. In that multicenter RCT of NIV versus supplemental oxygen in 374 immunocompromised adults, there was no difference in the rate of intubation, the duration of mechanical ventilation, and the length of stay or survival. In children, a retrospective review of pediatric oncology patients found a 26% failure rate of NIV with hemodynamic instability being a significant risk factor for failure. In a recent multicenter review of intubated pediatric HCT patients, 41% received NIV prior to intubation and those that did had an increased risk of PICU mortality (OR, 2.1; 95% Confidence Interval (CI), 1.2-3.6; $p = 0.01$). Overall, the usefulness of NIV in the pediatric HCT patient remains to be established. Although there may be a potential benefit, NIV would not appear to be indicated in the hemodynamically unstable patient. Additionally, and similar to HFNC, NIV must be implemented within the context of data suggesting delayed intubation is associated with worse outcomes for these children.

Given the significant risk of developing PARDS in the HCT recipient, invasive mechanical ventilation should be implemented with a considerable focus on lung protective strategies. Among these children, data demonstrate an association with increasing peak inspiratory pressures (particularly >31 cmH_2O) and higher mortality, suggesting a need to limit peak pressures below this level. Additionally, there is evidence suggesting these patients may benefit by limiting the fraction of inspired oxygen (FiO_2) and employing a high peak end expiratory pressure (PEEP)/low FiO_2 strategy. In a cohort of 222 pediatric HCT patients receiving mechanical ventilation, those who were treated in a manner compliant with the ARDSnet high PEEP/low FiO_2 strategy at 24 hours of ventilation had improved survival. Further, data suggest that the oxygenation index (OI) is useful for identifying patients at increased risk of mortality in this population.

The value of high frequency oscillatory ventilation (HFOV) in this population is also unestablished. One single center study of immunocompromised children found that those who had improved oxygenation at 24 hours of HFOV were more likely to survive. In another retrospective, twelve center study that included 85 pediatric HCT patients, an earlier transition to HFOV from conventional ventilation was associated with improved survival with survivors being transitioned at a lower OI and earlier in the course of conventional ventilation. In that study, no one survived after being transitioned to HFOV after 1 week of conventional ventilation. In addition, overall survival was poor among the cohort transitioned to HFOV at only 23.5%.

40.4 Cardiovascular Complications Post-HCT

The two most common acute cardiac complications observed in the pediatric HCT population are arrhythmias and cardiomyopathy/cardiac dysfunction.

Cardiac complications can occur in children following HCT. The two most common acute complications observed in this population are arrhythmias and cardiomyopathy/cardiac dysfunction. Hypertension is also a significant cardiovascular concern, and may be associated with the PRES, which is discussed in the neurologic complication section.

Arrhythmias have been reported to occur in 8–11% of children following HCT. It is an early transplant complication with the majority of arrhythmias occurring within the first 100 days post-HCT. The data describing the occur-

rence, types, and specific therapies for arrhythmias in children post-HCT are scarce, and thus, most knowledge is extrapolated from the adult literature. Although pediatric data are sparse, children with arrhythmias post-HCT are more likely to be admitted to the ICU and have a higher mortality. Therefore, it is important for the pediatric intensive care practitioner to have a sound knowledge of this complication. In adults, arrhythmias such as atrial fibrillation, atrial flutter, and supraventricular tachycardia are the most common to affect this population. In a small, single center study of children undergoing HCT, three of the 40 patients experienced nonsustained ventricular tachycardia; all of these patients were asymptomatic. Risk factors for arrhythmias include exposure to anthracycline-based chemotherapeutic regimens and having received thoracic or total body irradiation. In the acute setting, treatment for these symptomatic or hemodynamically compromising arrhythmias is no different than the standard approach for any patient.

Cardiac dysfunction, particularly left ventricular dysfunction, is a well-known, but rare complication found in children undergoing HCT. The dysfunction can occur both at the time surrounding transplantation and as a long-term sequela following HCT. A large study noted that less than 1% of adult HCT patients had a significant, life-threatening cardiac complication within the first 100 days. In a smaller pediatric study of 40 patients, four (10%) developed heart failure. All four children improved. Risk factors for adults have been established and include age and general cardiovascular health. As with arrhythmias, major risk factors for cardiomyopathy and heart failure include anthracycline treatment and radiation therapy. Cyclophosphamide is also known to cause heart failure, particularly at higher doses, secondary to necrosis of myocardial cells. GVHD involving the heart has also been described as a source of cardiac toxicity. Critical care of the HCT patient with heart failure is generally the same as that of any patient with heart failure. Specific care for the HCT patient requires careful monitoring and follow up for long-term cardiac complications.

40.5 Endotheliopathies Post-HCT

40.5.1 Sinusoidal Obstruction Syndrome (SOS)

Sinusoidal obstruction syndrome (SOS), previously known as hepatic veno-occlusive disease (VOD), is a potentially life-threatening complication that can occur in up to 30% of pediatric patients undergoing HCT.

The underlying pathophysiology is likely due to toxins generated by the conditioning regimen, which cause cytokine-mediated inflammation and a procoagulable state, that ultimately result in damage to the sinusoidal endothelial cells and hepatocytes of zone 3 of the hepatic acini. Clinically, this results in decreased hepatic outflow which can lead to portal hypertension, fluid retention, polyserositis due to capillary leak syndrome, tender hepatomegaly, coagulopathy, multiorgan failure, sepsis, and death.

Risk factors for the development of SOS can be divided into preexisting, pre- and post-HCT factors (Table 40.5). It most commonly occurs within 30 days post-transplant (although late onset SOS has been reported). Historically, VOD was characterized by the clinical triad of right upper quadrant pain, weight gain, and an elevated serum bilirubin level as outlined in the Seattle, Modified Seattle and Baltimore criteria. However, given that up to 30% of pediatric patients remain anicteric, the pediatric SOS criteria were updated by the European Group for Blood and Marrow Transplantation (EBMT) and published in 2017 (Table 40.6).

Sinusoidal obstruction syndrome (SOS), previously known as hepatic veno-occlusive disease (VOD), is a potentially life-threatening complication that can occur in up to 30% of pediatric patients undergoing HCT.

Table 40.5 Risk factors for developing sinusoidal obstruction syndrome

Preexisting risk factors	Pre-transplant factors	Post-transplant factors
Age: < 1 year	Total body irradiation	Type of transplant: Allogeneic transplant Matched unrelated donor Multiple sequential autologous transplant Non T-cell depleted transplant
Poor performance status	Treatment with these medications: Cyclophosphamide Busulfan Melphalan Gemtuzumab Ozogamicin	Use of concomitant drugs that cause cholestasis: Cephalosporins Progestogens Azole antifungals Calcineurin inhibitors Methotrexate
Preexisting hepatic dysfunction: Hepatitis Iron overload Prior TPN use		Use of sirolimus with concurrent use of calcineurin inhibitors
Prior myeloablative HCT		
Osteopetrosis		
Underlying disease: Familial HLH JMML		

TPN total parenteral nutrition, *HCT* hematopoietic cell transplant, *HLH* hemophagocytic lymphohistiocytosis, *JMML* juvenile myelomonocytic leukemia

The diagnosis of SOS remains a clinical one and there are no specific or sensitive biomarkers or imaging criteria that are pathognomonic. Keen clinical suspicion is critical as early diagnosis and specific intervention may improve outcomes.

The findings of reversal of blood flow in the hepatic veins, a hepatic artery resistance index greater than 0.75 and/or an abnormal portal vein waveform on doppler ultrasonography of the liver are all supportive of a diagnosis of SOS; however, none are confirmatory, and when found, are typically late findings. Trans-jugular liver biopsy with a pressure gradient of 10 mmHg is highly specific (91%) for SOS in adults. However, due to the high risk of complications and lack of pediatric correlative evidence, this procedure is generally avoided in children, with consideration primarily given when late-onset SOS is suspected to assist with the more elusive diagnosis.

SOS can vary widely in severity from mild to severe with 25% of patients having severe disease. The mortality also varies ranging from 9% in mild cases up to 75–98% in severe disease (Table 40.7). Severe VOD requires PICU care and is associated with renal failure (54%), pulmonary failure (23%), cardiac failure (63%), changes in mental status (78%), multiorgan failure (30–60%), sepsis, and death.

Table 40.6 Diagnostic criteria for sinusoidal obstruction syndrome

Seattle criteria	Modified Seattle criteria	Baltimore criteria	EBMT criteria
Two or more of the following within 30 days post-HCT: – Bilirubin ≥2 mg/dL – Hepatomegaly, RUQ pain – Ascites with/without unexplained weight gain >2% over baseline	Two or more of the following within 20 days post-HCT: – Bilirubin >2 mg/dL – Hepatomegaly or RUQ pain – Unexplained weight gain > 2% over baseline	Bilirubin ≥2 mg/dL and two or more of the following within 21 days post-HCT: Hepatomegaly (usually painful) Ascites Weight gain >5% over baseline	Two or more of the following (no limitation for time of onset): – Rising bilirubin above baseline on three consecutive days or bilirubin ≥2 mg/dL – Hepatomegaly above baseline – Ascites above baseline – Weight gain >5% above baseline or otherwise unexplained weight gain on three consecutive days despite the use of diuretics – Unexplained consumptive and transfusion refractory thrombocytopenia

HCT hematopoietic cell transplant, *RUQ* right upper quadrant, *EBMT* European Group for Blood and Marrow Transplantation

Table 40.7 Grades of severity of sinusoidal obstruction syndrome

	Mild	Moderate	Severe
Persistent, refractory thrombocytopenia	<3 days	3–7 days	>7 days
Elevated transaminases (ALT, AST)	≤2 × ULN	>2 and ≤5 × ULN	>5 × ULN
Bilirubin (mg/dL)	<2	<2	≥2 Rate of rise: Doubles in 48 hours
Ascites	Minimal	Moderate	Parecentesis needed
Coagulation	Normal	Normal	Impaired
Glomerular filtration rate mL/min	60–89	30–59	≤29
Oxygen requirement	≤2 L/min	>2 L/min	Invasive pulmonary ventilation

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *ULN* upper limit of normal

Early initiation of specific therapy with defibrotide in severe SOS may positively impact outcomes. This drug is a polydeoxyribonucleotide that acts locally in the hepatic region (with minimal systemic anticoagulation effect) and has anti-ischemic, antithrombotic, and anti-inflammatory properties. The recommended pediatric dose is 25 mg/kg/day intravenously divided every 6 hours. Treatment duration is 21 days or until there is resolution of multiorgan dysfunction and SOS whichever is longer.

The Bearman model suggests that rapid weight gain is associated with poorer outcomes among patients with SOS. Goldstein et al. reported universal mortality among pediatric HCT recipients with acute renal failure and acute fluid overload who were unable to restore euvolemia. Fluid restriction, inclusive of blood products and medications, and controlled diuresis (potentially with albumin infusion if the serum albumin level is <3 g/dL) as needed to maintain euvolemia is recommended for patients with SOS. Renal replacement therapy is indicated in patients with worsening fluid overload despite conservative measures and for patients with electrolyte abnormalities. Paracentesis may be considered if there is failure to respond to conservative management, intra-abdominal hypertension/compartment syndrome, or cardiopulmonary compromise secondary to tense ascites. Care must be taken with paracentesis to avoid hypotension which will precipitate worsening of intravascular volume depletion and multiorgan dysfunction. Therefore, volume controlled drainage at an initial rate not to exceed 5 mL/kg/hour is advised.

Similarly, thoracentesis is advised for patients with SOS and pleural effusions in the presence of pulmonary dysfunction (recommended 10 mL/kg in children (with a 1.5 L maximum) within the first hour). Pleural drains can be clamped for 24 hours once the drainage is <3 mL/kg/day and removed if there is no re-accumulation after 24 hours.

Ursodeoxycholic acid may be used as prophylaxis in patients at risk for developing SOS. Other medications that may provide some benefit in the treatment of SOS include high dose methylprednisolone which inhibits proinflammatory cytokine production and N-acetylcysteine which is a precursor to the free radical scavenger and anti-oxidant: glutathione. Both cytokine production and low levels of glutathione have been linked to the development of SOS. Additionally, vitamin K and fresh frozen plasma can be used as supportive measures to help correct concurrent coagulopathy secondary to hepatic dysfunction.

40.5.2 Transplant Associated Thrombotic Microangiopathy (TA-TMA)

Transplant associated thrombotic microangiopathy (TA-TMA) is clinically characterized by *de novo* Coombs negative anemia, thrombocytopenia, elevated lactate dehydrogenase (LDH) levels, proteinuria of ≥30 mg/dL, hypertension, and the presence of schistocytes on peripheral smear. It is a potentially fatal complication with a high rate of long-term morbidity and mortality.

Although the pathogenesis is unclear, it involves the dysregulation of either the classical or alternate complement pathways. This leads to endothelial damage that results in small vessel thrombosis and tissue injury. It most frequently affects the kidneys, but can also result in pulmonary hypertension, polyserositis, ischemic bowel changes, PRES, and multiorgan dysfunction syndrome. Risk factors for TA-TMA include high dose chemotherapy and conditioning

regimens that include etoposide, melphalan and platinum-based drugs, busulfan, fludarabine, total body irradiation, infections (most commonly *Aspergillus*, cytomegalo-, adeno-, and BK virus), calcineurin inhibitors, and/or acute GVHD.

The initial treatment of TA-TMA is supportive and includes the management of hypertension, drainage of pleural, pericardial or ascitic fluid, and the treatment of any concurrent infections and acute GVHD. The use of calcineurin inhibitors should be limited, taking care to balance the risk of worsening GVHD. If indicated, alternative GVHD prophylaxis should be initiated. Second-line therapies for TA-TMA include rituximab and therapeutic plasma exchange, but response is often variable. In cases that progress despite supportive measures and have severe multiorgan failure or significant microangiopathic hemolysis, eculizumab, a C5 monoclonal antibody inhibitor provides targeted therapy. Treatment should be continued until symptoms resolve and then continued for approximately 8 weeks as maintenance therapy. Further multicenter study of the role of eculizumab in the treatment of TA-TMA is ongoing.

40.6 Infectious Complications Post-HCT

Infections are a common complication in HCT patients and are associated with high morbidity and mortality.

Given the disruptions to the immune system caused by HCT, it is not surprising that infectious complications are common in HCT recipients. Infections are one of the most common reasons for transfer to the PICU, with a multicenter analysis demonstrating that 46% of HCT patients transferred to PICU have at least one infection. The most common types of infections causing transfer to the PICU are sepsis (including severe sepsis and septic shock) and respiratory infections. In a variety of studies, 12–25% of patients transferred to the PICU were transferred due to sepsis, severe sepsis, or septic shock. Moreover, infection is one of the most frequent causes of death for HCT patients. A study using the VPS (Virtual Pediatric Systems) database demonstrated a mortality rate of 22% in HCT patients with at least one infection. Additionally, the Sepsis Prevalence and Outcomes (SPROUT) study reported a mortality rate of 68% in HCT patients with severe sepsis; the mortality of HCT patients was four-fold higher than non-HCT patients and three-fold higher than other immunocompromised patients without a history of HCT.

When evaluating a potential infection in an HCT recipient, it is important to understand where that patient is in the HCT process, as deficits in both immune defense mechanisms and physical barriers (such as mucosa) evolve over time after HCT. ◘ Figure 40.1 provides an overview of the effects of HCT on the immune system and susceptibility to pathogens. In the initial post-HCT, preengraftment period, the patient has profound neutropenia as well as injuries to mucosal barriers. As a result, the HCT patient at this point is particularly vulnerable to bacterial and fungal infections, which are often derived from the patient's own skin and gastrointestinal (GI) tract microbiota. Among viral infections, herpes simplex virus (HSV) reactivation is common and may contribute to worsening of mucositis. Once engraftment has occurred, adequate neutrophil counts and mucosal healing help control bacterial and fungal infections. However, adaptive immune function, particularly that of T-cells, remains poor and patients are subject to increased risk of viral and fungal infection. After approximately 100 days post-HCT, immune cell populations continue to recover and regain function. At this point, high-risk infections include encapsulated bacteria (particularly in chronic GVHD), varicella-zoster virus (VZV), and fungal infections including *Aspergillus* and *Pneumocystis jiroveci*.

Other factors affecting susceptibility to infections in HCT patients include the type of conditioning regimen, the source of transplanted cells, the underly-

ing disease, and the presence of acute and/or chronic GVHD. For example, nonmyeloablative conditioning may result in less severe and less prolonged neutropenia, although still causing deficits in adaptive immunity, particularly T-cell function. The use of T-cell depleted grafts tends to increase susceptibility to viral and fungal infections. The increased use of antimicrobial prophylaxis in HCT patients has helped to reduce the incidence of infection and related mortality. Specific details of screening and prophylaxis for post-HCT infections may vary somewhat between transplant centers based on local pathogen prevalence and antimicrobial resistance; it is important to understand local practices.

Immunosuppression after HCT may decrease or erase the typical signs and symptoms of infection.

Given the disruption to the immune system after HCT, these children may not present with the typical inflammation-related signs and symptoms, so a high degree of suspicion is important in evaluating these patients. Neutropenic patients will obviously not mount an increased white blood cell count, but may also be impaired in developing other signs related to neutrophil migration such as purulence at a wound site or an infiltrate on chest x-ray. High dose steroids might inhibit the ability to mount a fever.

40.6.1 Bacterial Infections

Bacterial infections are mostly derived from the patient's own flora preengraftment. After >100 days, encapsulated bacteria are more common causes of infection.

Bacterial infections are particularly common in the preengraftment phase (Fig. 40.1). The most common organisms include gram-positive bacteria from the skin or GI tract (coagulase-negative *Staphylococcus*, *Staphylococcus aureus, and Streptococcus* spp.) or gram-negative bacteria from the GI tract (*Escherichia coli*, *Enterobacter* spp., *Klebsiella* spp., and *Pseudomonas* spp.). These infections arise from translocation through compromised physical barriers (i.e., mucosal injury from mucositis and indwelling central venous catheters providing a portal of entry in the skin). Bacterial cultures are the gold standard for diagnosis, but are often negative in these patients given the frequency of pretreatment with antibiotics. Empiric antibiotic coverage will vary depending on local pathogens and antimicrobial resistance profiles, but should provide good gram-positive and gram-negative coverage including activity against pseudomonas. International guidelines have recommended adult HCT patients receive prophylaxis with a fluoroquinolone starting at transplant if they are anticipated to have 7 days or more of neutropenia. Some pediatric transplant centers are extending these recommendations to adolescents.

Overall bacterial infections become less common postengraftment, but there is an increased risk of infection with encapsulated bacteria (particularly *Streptococcus pneumoniae*) after 100 days post-HCT, particularly in patients with chronic GVHD which is associated with splenic dysfunction. Antibiotic prophylaxis for *Streptococcus pneumoniae* is recommended for adults and children with chronic GVHD along with pneumococcal immunizations. Patients with hypogammaglobulinemia (serum IgG level < 400 mg/dL) may be indicated to receive intravenous immunoglobulin (IVIG) in the setting of bacterial infection or as prophylaxis. However, routine IVIG administration for bacterial infection is not recommended.

40.6.2 Fungal Infections

Candida and *Aspergillus* are the most common causes of invasive fungal disease in HCT patients.

Invasive fungal infections are associated with substantial mortality in HCT patients. The most common invasive fungal infections are caused by *Candida* and *Aspergillus* species, generally in the first 100 days post-HCT.

The diagnosis of fungal infections can be challenging given the slow growth on cultures and infections in difficult to sample areas such as the lungs. Histological studies of tissue from infected areas may be required for diagnosis. Useful diagnostic adjuncts for fungal infections include testing for fungal cell wall components, including β-D-glucan (Fungitell®), which is found in all fungi except *Cryptococcus* spp., *Zygomycetes* (including *Mucor* and *Rhizopus*), and *Blastomyces dermatidis*. In addition, *Aspergillus* galactomannan can be measured in serum. Current recommendations are to provide prophylaxis for fungal infections for allogeneic and autologous HCT patients expected to have prolonged neutropenia and/or mucosal damage from the start of conditioning at least until engraftment is achieved. In some patients, lymphocyte recovery, especially in the setting of prolonged immunosuppression as a treatment for GVHD, may be delayed for months or years; these patients may require antifungal prophylaxis postengraftment. The recommended prophylaxis regimen may vary by center depending on local epidemiology of fungal infections and patterns of resistance to antifungal drugs. For patients with prolonged neutropenia or requiring GVHD treatment, who are at higher risk for infection from molds such as *Aspergillus* or fluconazole-resistant *Candida* spp., recommended prophylactic agents include micafungin, posaconazole, or voriconazole. Posaconazole and voriconazole require monitoring of drug levels to avoid toxicity and to assure adequate levels for prophylaxis or treatment of the infection.

Candida infections are the most common cause of invasive fungal disease in the preengraftment period, and can be widely disseminated through the body. Mortality due to invasive Candida infections has been reported to be 10–25%, with higher rates in patients requiring PICU care. Antifungal susceptibilities should be tested on cultured specimens to help guide antifungal treatment. Current consensus recommendations from the European Council on Infections in Leukemia (ECIL-6) are to use one of the echinocandins (caspofungin, micafungin, or anidulafungin) as the first-line therapy. Second-line agents include amphotericin B, fluconazole, and voriconazole. It is important to note that candidemia requires removal of central venous catheters for clearance of infection. In addition, Candida can cause chorioretinitis so ophthalmological evaluation is indicated in invasive Candida infection. Risk factors for invasive Candida infection include previous Candida infection, ongoing immunosuppression (i.e., for GVHD), and receipt of T-cell depleted grafts.

Aspergillus is another common cause of invasive fungal disease associated with mortality rates reported to be as high as 80%. This fungus most commonly causes lung infection, and also has a tendency to cause central nervous system (CNS) disease (about 30% of cases). Of note, it is not susceptible to fluconazole. The first line of recommended anti-fungal agents includes voriconazole, isovuconazole, amphotericin B, or caspofungin. *Aspergillus* is noted for its tendency to be angio-invasive, which can result in devastating hemorrhage particularly in the lungs or the brain. As with candida, fungemia with *Aspergillus* requires removal of central venous catheters for clearance of infection. Risk factors for *Aspergillus* infection are similar to those associated with Candida infection.

Infections with the Zygomycetes (*Rhizopus* and *Mucor*) are less common (less than 35% of fungal infections), but are associated with grim outcomes and 80–90% mortality. These infections particularly favor the sinonasal tract with a propensity to spread locally into the brain. Treatment requires aggressive and early debridement of necrotic tissue and treatment with amphotericin B and/or posaconazole.

Pneumocystis infections generally occur more than 100 days post-HCT. Most HCT recipients receive prophylaxis.

Pneumocystis jiroveci (PJP) is an organism classified as a fungus although previously described as a protozoan. *P. jiroveci* infections typically occur later in the transplant course, greater than 100 days post-HCT, and manifest primarily in the lungs. Prophylaxis is recommended for at least 6 months starting at engraftment for allogeneic HCT recipients as well as autologous HCT patients with underlying malignant disease or who received intensive conditioning regimens. PJP prophylaxis may be extended beyond 6 months for patients who are receiving ongoing immunosuppressive therapy or who have chronic GVHD. The first choice for prophylaxis is trimethoprim-sulfamethoxazole (TMP-SMX) which is not given prior to engraftment due to its myelosuppressive effects. Other options include pentamidine, dapsone, or atovaquone.

40.6.3 Viral Infections

Viral infections after HCT are either reactivation of latent infection or de novo infections. HCT patients with latent infection commonly receive prophylaxis against reactivation.

Viral infections in HCT are frequently caused by reactivation of previously acquired infections, particularly by the herpesviruses (cytomegalovirus, herpes-simplex virus (HSV), Epstein-Barr virus, varicella-zoster virus, etc.), which may also be transmitted in donor cells. HSV tends to reactivate in the preengraftment phase, but other viruses tend to cause infections postengraftment during a period of persistent dysfunction in adaptive immunity. Transplant patients are also vulnerable to new infections including respiratory viruses circulating in the community.

Cytomegalovirus (CMV) is a common latent viral infection that causes active infection in 16–28% of HCT recipients. CMV pneumonia is the most common type of disease, although CMV can affect all organ systems. All HCT recipients should be screened for CMV IgG, and all seropositive patients, or patients receiving a transplant from seropositive donors, will require some degree of antiviral prophylaxis and/or treatment. All allogeneic transplant recipients receive prophylaxis from the time of engraftment to Day 100 and continuing after that if there is a history of CMV disease or the patient is receiving steroids for GVHD. HCT recipients also require ongoing screening, typically on a weekly basis, for evidence of active disease with serum CMV polymerase chain reaction (PCR) assessment or other measurement of viral replication. Any evidence of active CMV infection requires treatment. The first line of therapy is ganciclovir, although it is myelosuppressive and might not be tolerated preengraftment. Other therapeutic options include foscarnet, cidofovir., IVIG, or CMV-specific IgG (Cytogam®).

The herpesviruses CMV, HSV, and VZV are common latent infections that can reactivate post-HCT. Antiviral drugs such as ganciclovir or acyclovir can provide prophylaxis and treatment.

As described above, reactivation with HSV commonly occurs in the preengraftment phase. The most common presentation is the development of mucocutaneous lesions, but disease can be disseminated throughout the body. All HCT recipients should be tested for HSV IgG and seropositive recipients should receive prophylaxis starting at the beginning of conditioning therapy and continuing until engraftment and/or resolution of mucositis. Patients with a history of recurrent HSV reactivations may continue the prophylaxis longer. Acyclovir is the first-line therapy. Ganciclovir will provide sufficient HSV coverage for those patients receiving ganciclovir prophylaxis/treatment for CMV. Oral valacyclovir may be used for patients tolerating oral medications.

Varicella-zoster virus (VZV) reactivation generally occurs later (>100 days) following HCT. Current recommendations are to provide prophylaxis to seropositive HCT recipients with acyclovir or valacyclovir for 1 year after transplant. Any HCT recipient less than 2 years post-transplant who is exposed to a patient with either varicella or zoster infection, or a person who received the VZV vaccine and developed a rash, requires prophylaxis with VZV-specific immunoglobulin (VZIG), or treatment with acyclovir or valacyclovir if VZIG is not available.

Among the other herpesviruses, Epstein-Barr virus (EBV) is most notable in HCT patients for its association with post-transplant lymphoproliferative disorder (PTLD). Antiviral prophylaxis is not currently recommended. Increased viremia with EBV can be treated with reduced immunosuppression or rituximab to avoid PTLD development. Human herpesvirus 6 (HHV-6) has been associated with limbic encephalitis as well as hepatitis, rash, and the idiopathic pneumonia syndrome. Ganciclovir, cidofovir, and foscarnet have *in vitro* activity against HHV-6 and have been reported to be used for treatment.

Adenovirus infection in HCT recipients can represent reactivation or *de novo* infection and can be associated with high mortality rates. Cidofovir and brincidofovir are first-line treatments.

Adenovirus is a common pathogen in pediatric allogeneic HCT recipients, with evidence of viremia in 6–42% of children with allogeneic HCT (versus 3–15% in adults). Adenovirus infection can represent a reactivation or a *de novo* infection. Adenovirus can cause a wide range of diseases, including upper and lower respiratory tract infections, hemorrhagic cystitis, enteritis, myocarditis, hepatitis, nephritis, and disseminated disease involving multiorgan failure. Mortality rates are reported to be as high as 60–80% with disseminated disease. HCT recipients at the highest risk of adenoviral infection are those who received T-cell depleted, haploidentical, or umbilical cord grafts; who have GVHD of grade 2 or higher; or were treated with anti-T-cell antibodies. Weekly viral PCR screening is recommended for these patients. Cidofovir has the most evidence for effectiveness against adenovirus, but it is associated with dose-limiting nephrotoxicity. The more recently developed brincidofovir has demonstrated effectiveness with less nephrotoxicity; however, this is an oral drug and may not be absorbed or tolerated with GI tract pathology. Immune suppression may also be tapered in the presence of significant adenoviral disease.

Respiratory viral infections are common in the community, often following a seasonal pattern, and can result in significant morbidity and mortality in HCT patients. These infections are typically diagnosed by antigen- or PCR-based assays on samples from the respiratory tract (usually nasopharyngeal). Influenza has been associated with increased mortality in HCT patients, and is treated with neuraminidase inhibitors such as oseltamivir or zanamivir depending on local resistance patterns. In addition to isolation protocols in health care settings, patients less than 6 months post-HCT may receive prophylaxis with neuraminidase inhibitors during local influenza season. Inactivated influenza virus vaccination is recommended for parents and other family members and for HCT recipients more than 4 months post-HCT. Another common seasonal pediatric respiratory virus, respiratory syncytial virus (RSV), has been historically reported to be associated with increased morbidity and mortality in HCT patients. More recent studies in pediatric HCT patients have found a low burden of RSV infection among these patients and with minimal mortality, perhaps reflecting the effectiveness of cohorting and isolation of infected patients. Severe RSV disease has been treated with ribavirin, and in some cases, prophylaxis with palivizumab may be appropriate. Other respiratory viruses such as rhinovirus, human metapneumovirus, and parainfluenza virus are also reported with lower frequencies in HCT patients, but can be associated with progression to lower respiratory tract disease and mortality. Ribavirin has been reported as a treatment for human metapneumovirus and parainfluenza virus.

The human polyomaviruses (BK virus and JC virus) are latent viruses that can develop into active infection in the setting of immunosuppression. BK virus is most well known for its association with hemorrhagic cystitis, which is reported to occur in 5–15% of HCT patients, typically at 3–6 weeks post-transplant. Hemorrhagic cystitis can also be associated with adenovirus or CMV infection, or with urotoxic conditioning regimens. Brincidofovir, cidofovir, leflunomide, and fluoroquinolones have been used for the treatment of BK virus hemorrhagic cystitis. JC virus has been associated with late CNS disease, usually progressive multifocal leukoencephalopathy.

New modalities in treating viral infection include multivirus-specific banked T-cells.

Antiviral drugs are often limited by various toxicities. A new modality of treatment for viral infections uses banked, partially HLA matched T-cells that target specific viruses. Single-culture, virus-specific T-cells have been developed that target up to five viruses simultaneously (EBV, adenovirus, CMV, BK virus, and HHV-6). These new treatments may significantly change the treatment of viral infections in HCT patients.

40.6.4 Protozoal Infections

HCT patients may be vulnerable to protozoal infections depending on regional, occupational, or travel exposures. Thus, careful attention to travel history and occupational or recreational exposures is important. Toxoplasmosis is relatively rare in the United States, but more common in parts of Europe. In regions of high prevalence, screening for toxoplasma sero-reactivity may be indicated. HCT patients typically have reactivations of toxoplasma, particularly chorioretinitis or cerebral abscesses. Prophylaxis with TMP-SMX for PCP also provides good coverage for toxoplasma. Other parasitic diseases that may be found depending on the region served are *Strongyloides*, *Plasmodium*, or *Cryptosporidum*.

40.7 Engraftment Syndrome

Engraftment syndrome is characterized by noninfectious fever, systemic vascular leak, dyspnea, hypoxia, pulmonary infiltrates, organ dysfunction, skin rash, and diarrhea. It typically occurs within 4 days of granulocyte recovery.

Engraftment syndrome (ES) is characterized by a constellation of signs and symptoms that include noninfectious fever, systemic vascular leak (hypotension, edema, pleural effusion, ascites, and weight gain), dyspnea, hypoxia, pulmonary infiltrates, organ dysfunction, skin rash, and diarrhea. There is no set universal criteria for the diagnosis of ES, and as a result, its reported incidence varies widely from 17% to 48%. Regardless of the criteria used to diagnose ES, care must be taken to distinguish ES from other post-transplant complications such as acute GVHD, SOS, or sepsis due to their overlapping clinical similarities.

The pathophysiology of ES is hypothesized to be the result of a proinflammatory state due to an increase in leukocyte activation and proinflammatory cytokines as a result of endothelial cell damage that occurs in the pretransplant conditioning regimen. While ES occurs on average 10–28 days post-HCT, it typically occurs within 4 days of granulocyte recovery. Preengraftment syndrome (PES) is a similar condition that can occur after umbilical cord transplant as early as 3–7 days post-transplant (◘ Table 40.8).

Risk factors for ES include HLA mismatched transplants, patients less than 8 years of age, the number of infused CD34+ cells, and total body irradiation. Engraftment syndrome can self-resolve in 30% of cases without treatment; however, if it persists, it may lead to increased nonrelapse mortality. Treatment is indicated in the presence of persistent noninfectious fever or severe manifestations of capillary leak such as pulmonary edema. Management involves supportive care with antipyretics, oxygen supplementation, diuretics, and if needed, systemic corticosteroids using methylprednisolone (1 mg/kg/day). ES is typically very corticosteroid responsive and symptoms usually resolve in less than 7 days.

40.8 Graft Versus Host Disease

Graft versus host disease (GVHD) is a potentially debilitating complication of allogenic HCT that occurs due to a dysregulated immune response by activated donor T-cells (and sometimes B-cells) against host cells resulting in inflammation and apoptosis. Historically divided into acute GVHD, occurring within

Table 40.8 Comparison of differential diagnoses of engraftment syndrome

	Clinical features	Onset of symptoms
Engraftment syndrome	Noninfectious fever Signs of vascular leak Weight gain Organ dysfunction	10–28 days post-HCT (usually within 4 days of neutrophil engraftment)
Preengraftment syndrome	Noninfectious fever Signs of vascular leak Weight gain Organ dysfunction	3–7 days post-HCT
SOS	Weight gain Hepatomegaly Ascites Hyperbilirubinemia Unexplained consumptive and transfusion- refractory thrombocytopenia	Usually within 30 days post-HCT (delayed onset SOS has been reported)
Acute GVHD	Noninfectious fever Signs of vascular leak Rash with histological features of GVHD Hyperbilirubinemia	Commonly within the first 100 days post-HCT
Sepsis	Infectious cause of fever Systemic inflammatory response	Any point in time

SOS sinusoidal obstruction syndrome, *GVHD* graft versus host defense, *HCT* hematopoietic cell transplan

100 days of transplant, and chronic GVHD occurring thereafter, this distinction is no longer based on time. Instead, it is now based on clinical symptoms, with overlap syndrome displaying features of both acute and chronic GVHD.

The incidence and severity of GVHD can vary widely and is dependent on multiple factors. Factors that increase the risk of GVHD include: an older age of the donor, female donors, HLA disparity, the use of peripheral blood stem cells as the donor source, concurrent CMV infection, infusion of donor lymphocytes post-HCT for the treatment of recurrent malignancy, inadequate GVHD prophylaxis, and T-cell replete grafts.

The major target organs of acute GVHD are the skin, liver, and intestinal tract, all of which contain high numbers of antigen presenting cells.

Management of acute GVHD is based on severity (Tables 40.9 and 40.10) and involves prevention, treatment, and symptomatic management. Pretransplant prophylaxis may include *in vivo* T-cell depletion with anti-thymocyte globulin and *ex vivo* donor T-cell depletion. Post-transplant immune modulation is achieved through the use of calcineurin inhibitors (e.g., tacrolimus) with strict drug level monitoring to maintain therapeutic levels and to avoid toxic supra-therapeutic effects. Methotrexate, corticosteroids, and mycophenolate mofetil are also used for prophylaxis.

Management of acute GVHD is based on severity and involves prevention, treatment, and symptomatic management.

The mainstay of treatment for acute GVHD is corticosteroids which are effective in up to 60% of cases. Steroid refractory or unresponsive acute GVHD requires second-line agents with either monoclonal antibodies such as infliximab (tumor necrosis factor-alpha blocker) and basiliximab (IL-2 receptor blocker) or extracorporeal photopheresis (ECP) which causes the functional inactivation of allo-reactive T-cells.

Chronic GVHD is one of the leading causes of late nonrelapse morbidity and mortality after HCT, negatively impacting the quality of life of long-term

Table 40.9 Stages of acute graft versus host disease (GVHD)

Stage	Skin	Liver (bilirubin mg/dL)	Gastrointestinal	
			Lower GI stool/day (mL/kg/day)	Upper GI symptoms
O	No rash	≤2.0	<10	–
I	Maculopapular rash <25% BSA	2.1–3.0	10–19.9	Persistent nausea and vomiting
II	Maculopapular rash 25–50% BSA	3.1–6.0	20–30	Persistent nausea and vomiting
III	>50% generalized erythroderma	6.1–15.0	>30	Persistent nausea and vomiting
IV	Generalized erythroderma with bullae and desquamation	>15.0	Severe abdominal pain with or without ileus; lower GI bleeding	Persistent nausea and vomiting

BSA body surface area, *GI* gastrointestinal

Table 40.10 Grades of acute graft versus host disease (GVHD)

Overall grade	Stage based on organ involvement			First-line treatment
	Skin	Liver	Lower GI	
I	1–2	None	None	Topical corticosteroids
II	3	1	1	Methylprednisolone (2 mg/kg/day) Nonabsorbable steroids can be considered for GI GVHD
III	–	2–3	2–4	Methylprednisolone (2 mg/kg/day) Nonabsorbable steroids can be considered for GI GVHD
IV	4	4	–	Methylprednisolone (2 mg/kg/day)

GI gastrointestinal

survivors and prolonging their need for immunosuppression. It occurs in up to 25% of pediatric patients and its clinical and molecular manifestations are similar to those found in some autoimmune conditions. Clinical features include scleroderma-like skin manifestations, fasciitis leading to contractures and decreased range of motion across joints, bronchiolitis obliterans (BO), bronchiolitis obliterans organizing pneumonia (BOOP), polyserositis, and intestinal fibrosis resulting in malabsorption, hepatic dysfunction, and frequent infections due to lymphoid hypocellularity. Corticosteroids are recommended as the first-line treatment for chronic GVHD, with calcineurin inhibitors and early use of ECP as steroid sparing strategies. Rapamycin (mTOR inhibitor) and pentostatin are recommended for refractory chronic GVHD. Rituximab is suggested as a second-line treatment option in refractory cutaneous or musculoskeletal chronic

GVHD and imatinib is suggested as a second-line treatment option in refractory pulmonary or sclerodermatous chronic GVHD. Stringent infection prophylaxis is essential as infection is the leading cause of death among these patients. Prophylaxis against *Pneumocystis jiroveci* should be administered for at least 6 months after the discontinuation of immunosuppressive medications. Prophylactic acyclovir should be used for the prevention of VZV reactivation during the first year after transplantation, and later if systemic immunosuppression is still needed to control chronic GVHD. Prophylaxis against encapsulated bacterial pathogens and invasive fungal infections are also important. Immune reconstitution testing helps guide clinicians regarding the duration needed for anti-microbial prophylaxis. IVIG can also be given to patients with hypogammaglobulinemia to maintain serum IgG levels above 400 mg/dL.

40.9 Neurologic Complications Post-HCT

Neurological complications are common in HCT patients and are associated with significant morbidity and mortality.

Neurological disorders are cited as the cause for PICU transfer in 10–33% of HCT patients. These complications can be the result of CNS infection, metabolic derangements (due to medication or organ dysfunction), anatomical or metabolic abnormalities associated with the underlying diagnosis, or cerebrovascular events. Neurologic complications account for 10–15% of HCT-related mortality. Presenting symptoms may include seizure, encephalopathy, altered mental status, headache, or focal neurological signs. A history of a neurological event prior to HCT (whether due to the underlying disease or medication toxicity) increases the risk of neurological complications post-HCT.

Posterior reversible encephalopathy syndrome (PRES) is a common complication in the first 100 days post-transplant, characterized by headache, seizures, mental status changes, visual changes, and hypertension.

The posterior reversible encephalopathy syndrome (PRES), also known as reversible posterior leukoencephalopathy syndrome (RPLS), is one of the most common neurological complications in HCT patients, occurring in 6–9% of HCT recipients, and frequently prompting transfer to the PICU. PRES is typically observed in the first 100 days post-transplant. Presenting symptoms are headache, acute mental status changes, visual changes including cortical blindness, and seizures, generally in association with an acute rise in blood pressure.

Magnetic resonance imaging (MRI) is the recommended imaging modality and classically reveals signal abnormalities on FLAIR imaging in the posterior regions of the brain, reflective of vasogenic edema (◘ Fig. 40.2). It is theorized that cerebral vascular dysregulation, in response to elevated blood pressure or to endothelial activation, is responsible for causing vasogenic edema. The edema most commonly occurs in the parieto-occipital regions, but may be found elsewhere. PRES has most commonly been associated with the administration of calcineurin inhibitors (cyclosporine and tacrolimus), but also with sirolimus and dexamethasone.

PRES is treated by stopping or reducing the offending medication (usually calcineurin inhibitors) and controlling seizures and hypertension.

Treatment of PRES includes seizure control with benzodiazepines or other anti-epileptic drugs as well as treatment of hypertension. Intravenous continuous administration of anti-hypertensives such as nicardipine or esmolol allows rapid titration of the effect. If a patient is chronically hypertensive, it is important to not reduce the blood pressure below the normal baseline of the patient due to changes in cerebral autoregulation to adapt to higher blood pressures. As calcineurin inhibitors are the usual culprit in PRES, even at nontoxic serum levels, holding, reducing the dose, or changing to another medication for GVHD prophylaxis is indicated.

As suggested by the name, PRES is usually reversible. However, it has been associated with severe morbidity and mortality including status epilepticus, intracranial hemorrhage, and brain herniation. The potential for these complications must be considered if a patient's status does not improve or deteriorates. In addition, some patients with PRES continue to have seizures in the

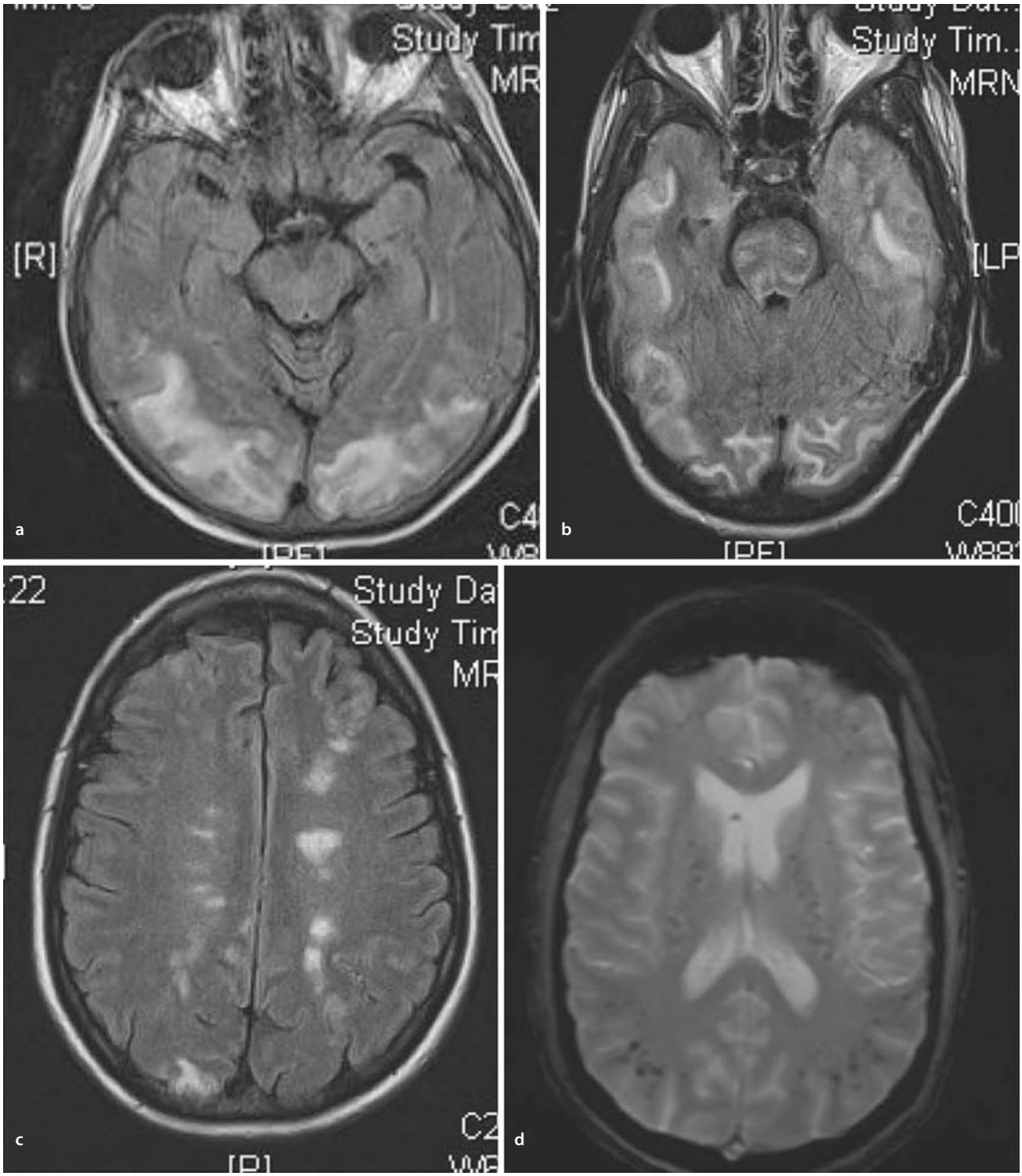

Fig. 40.2 Posterior reversible encephalopathy syndrome (PRES) variants. **a** Classic PRES with bilateral posterior signal abnormality on FLAIR MRI. **b** Bilateral predominantly, but not exclusively posterior signal abnormality on FLAIR MRI reflects vasogenic edema. **c** Multiple areas of FLAIR abnormality in periventricular region on FLAIR MRI in patients with thrombocytopenia on tacrolimus after HCT for AML. **d** Same patient as in **b** with gradient echo MRI (**c**) showing evidence of small hemorrhages in affected areas. *FLAIR* indicates fluid-attenuated inversion recovery, *MRI* magnetic resonance imaging, *HCT* hematopoietic cell transplantation, *AML* acute myeloid leukemia. Pruitt et al. (2013)

short- to long-term. Treatment with anti-epileptic medications may be required beyond the initial presentation with PRES.

CNS infections may have subtle findings in HCT patients, requiring a high index of suspicion.

CNS infections in HCT patients are relatively rare, but are associated with high rates of morbidity and mortality. These patients present with a wide range of symptoms including fever, seizures, headache, encephalopathy, and focal neurological signs. HCT recipients, particularly in the preengraftment period, will have limited ability to mount an inflammatory response which may decrease the severity of symptoms of a CNS infection. In this setting, one should have a low threshold of suspicion for obtaining CNS imaging and sampling cerebrospinal fluid.

The viruses most commonly associated with acute encephalitis are HHV-6, CMV, adenovirus, HSV, and VZV. MRI may be useful. For example, HHV-6 is associated with a pattern of bilateral limbic involvement. Additionally, viruses can be detected in the cerebrospinal fluid by PCR or culture. Fungal CNS disease is most commonly caused by *Aspergillus*, resulting in mass lesions that are at high risk for hemorrhagic conversion given the angio-invasive proclivity of *Aspergillus*. *Candida* is the most common cause of fungal meningitis in HCT patients. Zygomycetes (e.g., *Mucor* and *Rhizopus*) invades the brain from local infection in the sinuses or nasal passages, and is associated with very high mortality rates despite aggressive debridement and antifungal treatment. Bacterial meningitis and cerebral abscesses can be caused by gram-positive and gram-negative bacteria including anaerobes from the patient's own microbial flora. Toxoplasma reactivation can produce cerebral abscesses that might not have the classic ring-enhancing appearance on imaging in the setting of neutropenia. In situations where there is an abscess causing a mass effect, neurosurgical intervention and drainage might be indicated. All acute CNS infections require aggressive and *prolonged* treatment with parenteral antimicrobial agents. Progressive multifocal leukoencephalopathy is a demyelinating disease due to JC virus infection that is found late (months to years) post-HCT; the only treatment is decreasing immunosuppression.

Medications and metabolic derangements can cause seizures, encephalopathy, and other neurological symptoms.

Medications can have neurological effects beyond PRES. Seizures are known to be associated with a number of medications commonly administered to HCT patients in conditioning regimens and/or post-HCT. Chemotherapeutic agents associated with seizures include busulfan, cyclophosphamide, cytarabine, fludarabine, and melphalan. Prophylaxis with anti-epileptic medications is common with busulfan administration. In addition, several anti-infective agents may also be associated with encephalopathy as well as seizures. Radiation and methotrexate can be associated with a more delayed encephalopathy (>100 days post-HCT). Treatment of drug-related neurologic symptoms includes treating seizures and metabolic derangements and discontinuing the offending medication if possible.

Neurological symptoms including seizures and encephalopathy can also be associated with metabolic derangements. These may be secondary to medication effects such as the syndrome of inappropriate antidiuretic hormone (SIADH) associated with cyclophosphamide. Metabolic derangements may also be secondary to organ dysfunction such as uremia in renal failure or hyperammonemia in liver failure.

GVHD primarily causes neurologic problems secondary to treatment with calcineurin inhibitors, resulting in PRES and other disorders. However, chronic GVHD can be associated with immune dysregulation that results in a variety of demyelinating and vasculitic CNS disorders.

Cerebrovascular events are relatively rare, but cause potentially devastating complications of HCT. Intracranial bleeding, whether intraparenchymal, subarachnoid, or subdural, can be associated with thrombocytopenia, coagulopathy (as may occur in liver dysfunction in SOS), and hypertension. Certain

infections can also increase the risk of intracranial bleeding due to invasion of blood vessels by the infectious organism (e.g., *Aspergillus*) or due to vasculitis (e.g., with VZV encephalitis). When intracranial hemorrhage is suspected, CT imaging is the fastest imaging modality to confirm the diagnosis. Patient management includes transfusion of platelets, correction of coagulopathy, and cautious reduction of blood pressure, along with standard supportive care of patients with an intracranial mass and elevated intracranial pressure (ICP). A neurosurgical consult should be obtained and operative intervention may be indicated. Ischemic strokes may also occur, especially in conjunction with infection-associated vasculitis or endothelial injury as it occurs in TA-TMA. Patients undergoing HCT for sickle cell disease are particularly at risk for ischemic stroke. The treatment of an ischemic stroke will vary depending on the severity and underlying cause; with extensive lesions, intensive ICP management and neurosurgical intervention may be needed.

Always consider CNS recurrence of malignant disease in a HCT patient with neurological symptoms.

The underlying disease may also result in specific neurological complications. As mentioned above, sickle cell disease patients undergo HCT with abnormal cerebral blood vessels that predispose to ischemic stroke. Patients with CNS malignancy may be at risk for obstructive hydrocephalus given residual tumor or previous surgery, or may already have a ventriculoperitoneal shunt. Patients with Hurler syndrome also have a high rate of obstructive hydrocephalus and shunt placement. With these patients, shunt malfunction or worsening hydrocephalus should always be considered in the setting of neurological symptoms. Finally, for patients with malignant disease, CNS recurrence or relapse must be a consideration in the differential diagnosis for any neurological changes.

40.10 Post-transplant Lymphoproliferative Disease

The principal treatment for post-transplant lymphoproliferative disease (PTLD) has consisted of cytotoxic chemotherapy using regimens developed for non-Hodgkin lymphoma, and more recently, the B-cell monoclonal antibody rituximab. Additionally, the use of Epstein-Barr virus (EBV) cytotoxic T-lymphocytes has provided promising results for the management of EBV + PTLD.

Post-transplant lymphoproliferative disease (PTLD) is the most common post-HCT malignancy in children. It is commonly associated with EBV infection, although EBV negative disease also occurs. According to the World Health Organization 2008 classification, PTLD can be classified into early lesions, polymorphic PTLD, monomorphic PTLD, and Hodgkin-like PTLD. The course of the disease varies from indolent, localized lymphadenopathy, to rapidly progressive fulminant disease (usually associated with post-HCT PTLD). The degree of immunosuppression appears to be a major determinant for the development of PTLD due to the consequent impairment of EBV-specific T-cell-mediated immunity, which in turn allows EBV-induced B-cell proliferation. While EBV+ PTLD occurring in the setting of solid organ transplantation is sometimes polyclonal and may respond to reduction in immunosuppression, EBV+ PTLD post-HCT is typically monoclonal and rarely responds solely to immunosuppression reduction. In fact, reduction of immunosuppression may be contraindicated following HCT because of the risk of inciting or exacerbating acute or chronic GVHD. The principal treatment for PTLD has consisted of cytotoxic chemotherapy using regimens developed for non-Hodgkin lymphoma, and more recently, the B-cell monoclonal antibody rituximab. EBV+ PTLD is an aggressive malignancy, which in the pre-rituximab era had a median overall survival of 31 days; patients with EBV+ PTLD that have an incomplete response or fail to respond to rituximab have a median overall survival of 33–56 days. Recently, the use of EBV cytotoxic T-lymphocytes has provided promising results for the management of EBV + PTLD. Tumor flare (or pseudo-progression) has been reported in response to this T-cell directed therapy and is an important consideration when tumors are in the proximity of vital structures.

40.11 Chimeric Antigen Receptor (CAR)-Immune Effector Cell Therapy

A chimeric antigen receptor (CAR) is a genetically modified receptor that has three major components, an extracellular antigen recognition domain, a transmembrane domain, and an intracellular signaling domain. The extracellular component allows the recognition of a specific antigen on the target cell (e.g., CD19 in acute lymphoblastic leukemia and non-Hodgkin lymphomas) and the intracellular signaling domain will stimulate cellular proliferation, cytokine release, and elimination of the target cell. Manufacturing the CAR can be performed using viral (e.g., lentivirus or retrovirus vectors transduction) or nonviral (electroporation) gene modification of the immune effector cells (T-lymphocytes or natural killer cells). Tisagenlecleucel is the first chimeric antigen receptor autologous T-cell immunotherapy approved by the Food and Drug Administration (FDA) for the treatment of patients up to 25 years of age with B-cell precursor acute lymphoblastic leukemia that is refractory or in second or later relapse.

This adoptive cellular therapy has been reported to be associated with strikingly high sustainable remission rates, but is also associated with unique toxicities, namely, cytokine release syndrome (CRS) and neurotoxicity (previously known as CAR T-cell Related Encephalopathy Syndrome (CRES); recently referred to as Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)).

40.11.1 Cytokine Release Syndrome (CRS)

Cytokine release syndrome (CRS) is a systemic inflammatory response caused by the activation and expansion of immune effector cells including lymphocytes and/or myeloid cells (B-cells, T-cells, NK-cells, macrophages, and monocytes) and the release of very high levels of cytokines. CRS has been reported with other immunotherapy strategies including monoclonal antibodies such as anti-CD52 (alemtuzumab), T-cell engaging monoclonal antibodies (blinatumomab), and haploidentical hematopoietic cell transplantation. High levels of gamma interferon, tumor necrosis factor-alpha, and interleukin-6 (IL6) are the main cytokines associated with CRS. Further, CRS has been reported in 77% of pediatric and young adult patients who were treated with CD19 CAR T-cells; half of them (47%) required critical care support due to severe CRS (≥ grade III) with a median ICU stay of 7 days (range 1–34). Almost half of the patients (44%) developed hypoxia and required oxygen supplementation, 13% required invasive mechanical ventilation, 25% were treated with high dose vasopressors, and 9% underwent renal replacement therapy. The median time to CRS onset and resolution was 3 days (range 1–22) and 8 days (range 1–36), respectively. Patients with CRS usually present with fever, tachycardia, hypoxia (arterial oxygen saturation < 90% on room air), hypotension and, in severe cases, multiorgan failure (hepatic, renal, cardiac dysfunction, and coagulopathy). Risk factors associated with severe CRS include early onset fever (<3 days post CAR T-cell infusion), large tumor burden, and co-existing morbidities. The clinical presentation of CRS can range from very mild grade I (low grade fever and tachycardia) to very severe grade IV CRS (respiratory failure requiring mechanical ventilation, shock, multiorgan failure, and death). Grade I CRS can be managed with supportive measures only (antipyretics) and anti-IL6 therapy (tocilizumab) can be considered for persistent symptoms. Grade II CRS usually presents with hypotension that responds to intravenous fluid and/or low dose vasopressor treatment, and hypoxia that requires oxygen supple-

mentation <40% FiO_2. Anti-IL6 therapy and corticosteroids should be considered in patients not responding to supportive measures and fluid resuscitation. Grade III CRS is characterized by severe hypotension requiring multiple vasopressors (including vasopressin) and/or severe hypoxia requiring >40% FiO_2 supplementation and/or noninvasive respiratory pressure support. Grade IV CRS is defined as persistent hypotension despite fluid resuscitation and multiple vasopressors, and a requirement for mechanical ventilation. In the pivotal ELIANA trial, 50% of the patients received one dose of tocilizumab, 13% received 2 doses, and 6% received 3 doses. One fourth (26%) of the patients required the addition of corticosteroids. The use of anti-IL6 therapy and steroids for patients with CRS did not appear to affect CAR T-cell therapy outcomes. As new immune effector cells are introduced, some have an added "safety switch" designed to eliminate transduced cells, such as anti-CD19 CAR T-cells also expressing inactive, truncated EGFR, which enables the cells to be targeted through administration of the anti-EGFR antibody cetuximab. A natural killer cell product under study has included a "suicide" gene – inducible caspase-9 – that may be pharmacologically activated to eliminate the transduced cells. Functional co-expression of RQR8, a construct combining epitopes from CD34 and CD20, renders CAR T-cells sensitive to the monoclonal anti-CD20 antibody rituximab. Immune effector cell therapies are rapidly emerging. Prompt recognition and management of CRS are essential to optimize outcomes. Specific management decisions are best made in collaboration with immune effector cell clinical teams and should be based on institutional procedures, protocol-specific guidelines, and/or product label specifications.

40.11.2 CAR T-Cell Related Encephalopathy Syndrome (CRES) or Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)

Neurologic toxicities associated with CAR T-cell therapy may include confusion, encephalopathy, tremor, delirium, agitation, somnolence, seizures (convulsive or nonconvulsive), cerebral edema, coma, and death. These may occur simultaneously with CRS, following resolution of CRS or with no antecedent CRS. Grade I CRES usually presents with mild confusion, headache, or tremor. Grade II can be associated with a brief seizure, while grade III is associated with multiple generalized seizures. Grade IV presents as obtundation, deep coma requiring airway protection, and mechanical ventilation. Maude reported neurologic events in 40% of pediatric patients with acute lymphoblastic leukemia who received tisagenlecleucel within 8 weeks post CAR T-cell infusion; 13% developed grade III and none experienced grade IV. Neurotoxicity was more frequent in patients with higher grade CRS. In half of the patients, the neurotoxicity resolved within 10 days and 75% resolved within 18 days of onset. Detailed neurologic assessment tools include the CARTOX-10 point neurologic assessment scoring for patients ≥12 years and the Cornell Assessment of Pediatric Delirium (CAPD) for patients <12 years and/or based on the developmental level. Grade IV neurotoxicity can present as cerebral edema and death. It is recommended that patients with CNS disease and/or a history of seizure disorders receive antiseizure prophylaxis starting at least as early as the day of infusion and continuing for at least 30 days post CAR T-cell therapy. Patients with severe CAR T-cell related neurotoxicity require prompt transfer to the intensive care unit, and neurology consultation and CNS imaging should be strongly considered. It is important that thrombocytopenia and coagulopathy be corrected/avoided to reduce the risk of catastrophic cerebral hemorrhages. In general, steroids are first-line

agents for CRES/ICANS and anti-IL6 therapy may be used concomitantly among patients with concurrent CRS. As with CRS, specific management decisions are best made in collaboration with immune effector cell clinical teams and should be based on institutional procedures, protocol-specific guidelines, and/or product label specifications.

40.12 Summary

Children undergoing HCT represent a high-risk group of patients who frequently require critical care services for a wide variety of infectious and noninfectious pathologic conditions. A sound understanding of the HCT process, its unique and common complications and the potential treatment of these conditions will afford the pediatric critical care provider the best opportunity to intervene effectively and improve outcomes for this most vulnerable patient population. A collegial and collaborative approach by the many disciplines involved in the care of these children would appear essential in optimizing their outcomes. Although outcomes appear to have improved over time, much work remains to impact the substantial morbidity and mortality incurred by children undergoing HCT.

Review Questions

1. A 12 month old male who is Day +7 from a HCT for Hurler disease is transferred to the PICU for fever and hypotension that has persisted despite three boluses of 20 mL/kg normal saline and the initiation of a dopamine infusion at 5 mcg/kg/min. On physical exam, the patient is irritable with severe mucositis, cool extremities with 4 second capillary refill, and coarse breath sounds bilaterally. The heart rate is 150 beats per minute, the blood pressure is 70/40 mmHg, the respiratory rate is 40 breaths per minute, and his oxygen saturation on pulse oximetry is 92% while receiving 40% oxygen via aerosolized face mask. Which of the following is the most likely organism to be the source of the septic shock in this patient?
   A. Aspergillus
   B. Herpes Simplex Virus
   C. *Pseudomonas aeruginosa*
   D. *Streptococcus viridans*

2. A rapid response team is called for a 12 year old girl on the HCT unit with generalized tonic-clonic seizure activity. She is Day +46 from an allogeneic HCT for relapsed acute lymphoblastic leukemia. Her mother reports that the patient had been complaining of a headache and blurry vision for a couple of hours prior to the onset of the seizures. She has been diagnosed with acute GVHD. Medications include fluconazole, ganciclovir, cefepime, and tacrolimus. Vital signs reveal the following: temperature – 37.2°, heart rate – 110 beats per minute, blood pressure – 150/100 mmHg, respiratory rate – 20 breaths per minute. The patient is transferred to the PICU. Which of the following would NOT be an indicated treatment for this patient?
   A. Increase tacrolimus dose to treat GVHD
   B. Lorazepam (0.1 mg/kg) for seizure treatment
   C. Obtain stat head CT scan to rule out intracranial bleeding
   D. Start a nicardipine infusion for controlled reduction in blood pressure to 130/80 mmHg

3. A 14 year old male with acute myelocytic leukemia, Day +17 s/p allogeneic HCT is being transferred to the PICU for the acute onset of respiratory distress. His vital signs reveal a temperature of 39.2°, heart rate – 125 beats per minute, blood pressure – 145/92 mmHg, and respiratory rate – 38 breaths per minute. His oxygen saturation is 93% on pulse oximetry while receiving 60% oxygen via face mask. On clinical exam, he is dyspneic with intercostal retractions and diffuse rales heard on auscultatory exam. He has a cough, but no evidence of hemoptysis. His peripheral pulses are strong and his capillary refill is 2 seconds. His laboratory analysis reveals an absolute neutrophil count >500 cells/μL for the second day in row. His chest radiograph reveals bilateral parenchymal opacifications. Results of bronchoscopic alveolar lavage performed earlier in the day revealed no evidence of infection and 35% hemosiderin laden macrophages. Which of the following best describes his pulmonary condition?
   A. Engraftment syndrome is the most likely cause of his respiratory distress, but he has not satisfied pediatric acute respiratory distress syndrome criteria.
   B. He has diffuse alveolar hemorrhage as the cause of his respiratory distress, but he has not satisfied pediatric acute respiratory distress syndrome criteria.
   C. He has pediatric acute respiratory distress syndrome secondary to diffuse alveolar hemorrhage.
   D. He has pediatric acute respiratory distress syndrome secondary to engraftment syndrome.

4. A 12 year old, 33 kg female with acute myelocytic leukemia, Day +24 s/p allogeneic HCT is admitted to the PICU with the acute onset of respiratory distress and abdominal distention. On clinical exam, she is tachypneic and with end expiratory grunting, She is tachycardic with a regular rhythm and adequate peripheral pulses. Her abdomen is markedly distended with hepatomegaly and right upper quadrant tenderness. She has generalized edema and her weight is up 3 kg since she received her stem cell transplant. On laboratory analysis, her bilirubin has steadily increased and is now 3.7 mg/dL; her prothrombin time is 22.5 seconds with an international normalized ratio (INR) of 2.2. A doppler hepatic ultrasound demonstrated reversal of blood flow in the hepatic veins and a hepatic artery resistance index of 0.95. Which of the following medications is most likely to be of benefit in treating her acute condition?
   A. Defibrotide
   B. N-acetylcysteine
   C. Solumedrol
   D. Ursodeoxycholic acid

5. A 7 year old male, Day +67 s/p allogeneic HCT for refractory leukemia has developed multiple organ dysfunction syndrome characterized by acute renal failure and echocardiographic evidence of pulmonary hypertension. He is being treated with tacrolimus for acute graft versus host disease. His blood chemistries are notable for a blood urea nitrogen (BUN) concentration of 73 mg/dL, a creatinine of 2.1 mg/dL and a lactate dehydrogenase level of 1749 mg/dL. His complete blood count reveals a Coombs negative anemia, a new and progressive thrombocytopenia, and schistocytes on the peripheral smear. His coagulation profile is unremarkable. A tentative diagnosis of transplant associated thrombotic microangiopathy is made. All of the following should be considered in the treatment of this condition EXCEPT:

A. Assurance of appropriate antimicrobial therapies
B. Discontinuation of the tacrolimus and transition to other acute GVHD therapies
C. Initiation of complement blocking antibodies such as eculizumab
D. Initiation of corticosteroid therapy

6. Cytokine release syndrome (CRS) has been associated with a recently approved pre B-cell directed CAR T-cell therapy. Which of the following agents is used in the management of mild to moderate CRS?
   A. Anti-C5 antibody (eculizumab)
   B. Anti-CD19 antibody (blinatumomab)
   C. Anti-CD20 antibody (rituximab)
   D. Anti-IL6 antibody (tocilizumab)

7. Which of the following is NOT a characteristic feature of engraftment syndrome in a child receiving a matched unrelated hematopoietic cell transplant?
   A. Absolute neutrophil count >500 cells/μL
   B. Fever
   C. Post-transplant Day +2
   D. Pulmonary edema

8. Which of the following is a late pulmonary complication after hematopoietic cell transplant?
   A. Bronchiolitis obliterans syndrome
   B. Diffuse alveolar hemorrhage
   C. Idiopathic pneumonia syndrome
   D. Transplant associated thrombotic microangiopathy

9. A 5 year old child with pre B-cell ALL with match sibling hematopoietic cell transplant Day +30 presents with fever, worsening body edema, pallor and dark colored urine. On laboratory assessment, his creatinine level is 2.1 mg/dL and his platelet count is 37,000/μL. Which of following is the most likely cause for these clinical features?
   A. Acute graft versus host disease
   B. Idiopathic pneumonia syndrome
   C. Sinusoidal obstruction syndrome
   D. Transplant associated thrombotic microangiopathy

Answers

1. D
2. A
3. C
4. A
5. D
6. D
7. C
8. A
9. D

Suggested Readings

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