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Abstract

Hematopoietic stem cell transplantation (SCT) is a therapeutic option for patients with bone marrow failure, certain malignancies and inborn errors of metabolism. Complications requiring intensive care are frequent, and intensivists need to be familiar with the transplantation process and the disorders that are unique to these patients. The transplant process involves the use of high dose chemotherapy or radiation, followed by intravenous infusion of stem cells matched with the recipient at the human leukocyte antigen (HLA) loci. Full recovery of a normal immune system can take a year or more, so following transplantation, patients are exquisitely susceptible to infections. Moreover, complications such as graft versus host disease, idiopathic pneumonia syndrome, sinusoidal obstruction syndrome and transplant associated thrombotic microangiopathy are common in the first hundred days after stem cell infusion. Respiratory failure is a common presentation necessitating intensive care admission and may be due to infectious or non-infectious causes. Mechanical ventilation may be needed along with broad spectrum anti-microbial coverage; corticosteroids are commonly used if graft versus host disease is present. Acute graft versus host disease is most frequent in children receiving grafts from unrelated donors and results in significant morbidity. Increased immunosuppression is the cornerstone of therapy for graft versus host disease, and protection of the children from infection is essential to survival. Sinusoidal obstruction syndrome and transplant associated thrombotic microangiopathy may lead to multiple organ failure with limited therapeutic options, but both disorders can resolve with good supportive care during the period of organ failure. Outcomes for patients who develop multiple organ failure following SCT remain poor despite aggressive supportive care, however, children with failure of a single organ can do well. Integrated multi-disciplinary care between intensivists and transplant physicians, and other specialists such as nephrologists and pulmonologists leads to improved outcomes.

Keywords

Stem cell transplantation • Idiopathic pneumonia syndrome • Respiratory failure • Graft versus host disease • Sinusoidal obstruction syndrome • Transplant associated thrombotic microangiopathy (TMA)

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Introduction

Hematopoietic stem cell transplantation (SCT) is becoming an increasingly common treatment for a variety of malignant and non-malignant disorders in children. Children undergoing SCT may require intensive care for multiple reasons. Life threatening infections, septic shock, respiratory failure, renal failure, seizures, hypertension, bleeding and multiple organ failure are common reasons for these patients to need intensive care services. The number of patients requiring admission to a pediatric intensive care unit (ICU) following SCT is variable, but recent analyses have suggested that up to 40 % of patients undergoing SCT may need ICU admission [1]. Many of the complications following SCT are unique to these patients, such as graft versus host disease (GVHD), sinusoidal obstruction syndrome (SOS), transplant associated thrombotic microangiopathy (TA-TMA), and the idiopathic pneumonia syndrome (IPS), while others such as septic shock and seizures are common to all patients. It is very important that intensivists caring for children following SCT are familiar with the transplantation process and collaborate closely with the transplant physicians. This chapter will focus on complications specific to the SCT population that may necessitate intensive care.

Indications

Indications for SCT have expanded since the first successful allogeneic stem cell transplants in 1968 (see Table 27.1) [2]. The intended therapeutic effect of SCT can be divided into three broad categories. The first category is most intuitive: to correct a defect in blood cell production or function, as used for hemoglobinopathies, bone marrow failure syndromes, immunodeficiencies and disorders of immune regulation. The second category is malignancy, wherein stem cells are used to replace cancerous bone marrow or to “rescue” the bone marrow after marrow ablative doses of chemotherapy and radiation aimed at a solid tumor outside of the bone marrow. Additional control of the malignancy can be obtained

from a graft versus tumor effect in allogeneic transplantation. The third category is transplant as a method of gene therapy for the treatment of inborn errors of metabolism.

Hematopoietic Stem Cell Sources

Hematopoietic stem cell donors are most commonly allogeneic (a related or unrelated person) who is HLA-matched with the recipient. In other cases, the stem cell donor can be the recipient themselves (autologous), or rarely, a genetically identical twin (syngeneic donor). Hematopoietic stem cells can be collected from bone marrow, peripheral blood or cord blood (see Table 27.2) [3].

Table 27.1 Pediatric diseases treated with hematopoietic stem cell transplantation

Malignant diseases	Non malignant diseases
Leukemias/lymphomas	Severe aplastic anemia (acquired)
Solid tumors	Hemoglobinopathies
Neuroblastoma	Thalassemia major
Brain tumors	Sickle cell disease
Sarcomas	Congenital disorders of hematopoiesis
Wilms tumor	Fanconi anemia
Retinoblastoma	Diamond Blackfan syndrome
	Dyskeratosis congenita
	Schwachman diamond syndrome
	Immunodeficiency
	Severe combined immunodeficiency disease
	Chronic granulomatous disease
	Wiskott-Aldrich syndrome
	Hemophagocytic lymphohistiocytosis
	Common variable immune deficiency
	Inborn errors of metabolism
	Hurler syndrome
	Leukodystrophies (e.g., Krabbe disease)
	Osteopetrosis
	Acquired autoimmune disorders ^a

^aExperimental therapy for disorders such as scleroderma

Table 27.2 Comparison of hematopoietic cell sources

Characteristic	Bone marrow	Peripheral blood stem cells (PBSC)	Cord blood
HLA matching	Close match required	Close match required	Less matching required for equivalent outcome
Neutrophil engraftment	Faster than cord blood	Fastest	Slowest
Stem cell dose	Usually adequate; can be challenging if donor is significantly smaller than recipient	High dose easily obtained; survival inferior in pediatrics due to increased chronic GVHD	May be inadequate; limited by unit size; immature cells proliferate very effectively
GVHD risk	Higher than cord blood	Highest ^a	Lowest
Second donation ^b	Possible	Possible	Not possible ^c

^aPBSC not preferred in pediatrics given the GVHD risk

^bIf additional cells are needed from same donor

^cMay use second unit from another donor

Autologous cells and umbilical cord blood cells are collected prior to the transplant and frozen, using dimethyl sulfoxide (DMSO) as a preservative. The infusion of DMSO with the thawed product can cause hypertension and bradycardia, which are usually self-resolving. Late renal injury can also occur, so aggressive hydration is usually given with the infusion. Allogeneic cells are usually collected on the day of transplant and infused fresh, but may require processing, including red blood cell depletion if the donor is ABO incompatible with the recipient. In vivo (using antibodies given to the recipient) or ex vivo (performed using a selection column in the cell processing laboratory) T-cell depletion can also be performed to reduce the risk of GVHD [4, 5].

Donor Selection

Selection of an allogeneic donor is based on human leukocyte antigen (HLA) matching between the donor and the recipient. The HLA genes reside in the major histocompatibility complex, and are located in close proximity on chromosome 6. Therefore, they are generally transmitted as a single haplotype with Mendelian inheritance. The genes are co-dominant, such that proteins inherited from the mother and father are equally expressed. These highly polymorphic genes code for many immune related functions, most importantly, antigen processing and presentation. HLA class I (A, B, C) and II (DR, DQ, DP) molecules are important in T-cell recognition, and are considered major transplant antigens. Initially, loci A, B and DRB1 were recognized to be of key importance for matching, and in the earlier years of transplantation, donor and recipients were matched for six antigens. However, the locus HLA-C is now recognized as having equal importance and typically donor and recipient are matched at 8 loci (A,B,C and DRB1). Early data, not well supported in more recent studies, suggested that DQB1 was an important locus, and some literature refers to 10 of 10 allele matching by including DQB1 in the matching algorithm [6]. The use of molecular techniques for HLA-typing and the availability of larger registries of unrelated donors to select from have had significant impact on improving transplant outcomes [6, 7]. The ideal donor, a sibling with genetically identical alleles at all 4 loci (8/8 match) is available to only 15–30 % of recipients (as HLA is transmitted in a Mendelian fashion 25 % of siblings will be genotypically matched to each other). The majority of recipients need to find a match from an unrelated donor, and large registries of volunteer adult donors, and banks of frozen cord blood have been developed for this purpose. The largest registry is the Be The Match Registry® operated by the National Marrow Donor Program (NMDP) in the United States. Recipients who receive fully matched unrelated donor transplants have higher rates of graft failure and GVHD than with a matched

related donor. However, outcomes of unrelated donor transplants have improved significantly in the last 10 years, particularly in children. Higher resolution DNA typing, larger donor pools and improved supportive care, including aggressive intensive care support during organ failure have resulted in outcomes of unrelated donor transplants that now approach those of matched related transplants [8–12].

Transplant Conditioning Regimens

Recipients generally require pre-transplant conditioning in the form of chemotherapy and/or radiation prior to SCT. Conditioning is used to “make space” in the marrow (myeloablation) and destroy cancerous marrow in malignancies. Additionally, it provides immunosuppression to prevent residual recipient lymphocytes from rejecting the donor stem cells. Myeloablative conditioning regimens are mainly utilized for malignancies where complete elimination of the native bone marrow is necessary. Myeloablative regimens use high dose chemotherapy and sometimes total body radiation, and may be associated with significant transplant-related morbidity and mortality related to tissue injury. Reduced intensity conditioning regimens (RIC) employ medications with significant immunosuppressive properties, but less myeloablative effects. Such regimens are becoming increasingly common in the treatment of immunologic and metabolic disorders where full donor chimerism may not be required to achieve desired effects in reconstituting missing bone marrow function [13]. RIC causes less immediate organ toxicity, but is associated with a higher incidence of mixed donor chimerism and early and late viral infections. Patient undergoing autologous stem cell transplantation for solid tumors such as neuroblastoma or high-risk brain tumors may receive single or multiple high dose myeloablative chemotherapy courses targeted at their primary tumor. Permanent, or at least very prolonged bone marrow ablation occurs as a side effect of this high dose chemotherapy, and therefore, autologous stem transplant (infusion of previously frozen stem cells) is necessary after each high dose chemotherapy cycle to reconstitute the blood-forming capacity of the bone marrow [14, 15].

Graft Versus Host Disease (GVHD) Prophylaxis

GVHD mainly occurs after allogeneic SCT, but it is occasionally reported in patients with autologous SCT. Multiple factors including stem cell source, degree of HLA match, conditioning regimen, donor and recipient age and associated co-morbidities influence the risk and severity of GVHD. The highest risk of GVHD occurs in mismatched unrelated donor transplants, and the least incidence of GVHD is

observed in fully matched, related transplants. Stem cells from cord blood are less likely to trigger GVHD than other stem cell sources, while transplants using peripheral blood stem cells (PBSC) are associated with higher risk of chronic GVHD [16, 17]. GVHD prophylaxis with immunosuppressive agents is standard practice for SCT recipients. The most common prophylactic regimens are calcineurin inhibitors (cyclosporine (CSA) or tacrolimus), commonly in combination with a second agent such as methotrexate, mycophenolate mofetil (MMF, Cellcept®) or corticosteroids. Calcineurin inhibitors are usually started several days prior to the stem cell infusion to achieve therapeutic levels by the time the new graft is infused. Medications such as antithymocyte globulin (ATG) or alemtuzumab (Campath-1H) that remove T-cells and antigen-presenting cells from the recipient are also used for GVHD prophylaxis in certain transplant regimens. These medications not only remove antigen presenting cells from the recipient, but may also remove some mature lymphocytes from the infused stem cell product. T-cell depletion of the donor graft is used for certain disorders (e.g., Fanconi anemia) that are at higher risk of severe GVHD-related complications, or as standard of care in some transplant centers [15]. The length of GVHD prophylaxis varies based on underlying condition and the risk for GVHD. This prophylaxis may last from 100 days to 6–9 months post transplantation. In contrast to solid organ transplants, where recipients take immunosuppressive medications to prevent graft rejection for their lifetime, recipients of hematopoietic stem cell transplants are expected to be free of immunosuppressive therapy at some point due to the ability of the new graft to adapt and learn to live in the recipient body (tolerize). It is important to note that any GVHD prophylaxis by immunomodulatory agents for T-cell depletion or immune suppression increases the risk of opportunistic infection [18]. It should be recognized that uncontrolled GVHD is profoundly immune suppressive and aggressive effective treatment of GVHD is essential for recovery from infections and recovery of immune competence.

Infection Prophylaxis

Routine infection prophylactic measures have been established that significantly reduce transplant-related mortality. Transplant patients are typically kept in HEPA (High-Efficiency Particulate Air)-filtered and positive pressure rooms, with appropriate isolation restrictions based on the degree of immunosuppression. Good hand hygiene plays a very important role in horizontal infection transmission, especially with enteric pathogens such as *Clostridium difficile* and norovirus (the official genus name for the group of viruses previously described as Norwalk-like viruses). Good skin, oral and dental hygiene is also very important. Mucosal

integrity is disrupted by the conditioning regimen, with oral and gastrointestinal mucositis, and plays a significant role in post-transplant infectious complications. Patients with mucositis (mucosal integrity breakdown due to chemotherapy or radiation) are at a very high risk of seeding oral and enteric pathogens into the blood stream, and therefore, regular mouth care is needed. Mouth and gut prophylaxis varies based on institutional guidelines and transplant-associated risk factors [19]. Rectal instrumentation (e.g., thermometers, enemas, digital exams) is contraindicated in SCT patients [20, 21]. All SCT patients receive antiviral prophylaxis based on their prior viral exposure. Patients who are seropositive for herpes simplex virus (HSV) or cytomegalovirus (CMV), or who receive stem cells from HSV or CMV seropositive donors, are screened by blood polymerase chain reaction (PCR) once or twice weekly for viral reactivation, and treated pre-emptively with antiviral agents for any rise in PCR copies. Improved technology now allows screening for an increased number of viruses, and screening and pre-emptive treatment of adenovirus infection and Epstein Barr virus (EBV) reactivation is common. Intravenous immunoglobulin supplementation is often used to maintain immunoglobulin G levels within normal limits for age [21, 22]. All transplant patients should receive CMV-safe blood products, commonly depleted of leukocytes at the point of collection. *Pneumocystis jiroveci* (formerly *Pneumocystis carinii*) prophylaxis is provided for approximately 1 year post transplantation using pentamidine or trimethoprim/sulfamethoxazole. Trimethoprim/sulfamethoxazole is commonly started after stem cell engraftment due to its myelosuppressive properties [21]. Antifungal prophylaxis is vital after SCT and should be directed against yeast (e.g., *Candida* species) and molds (e.g., *Aspergillus*). The most common antifungal medications used are amphotericin B, voriconazole, caspofungin, or micafungin [23]. Environmental measures such as using face masks as well as avoiding gardening, construction and moldy areas after discharge from the hospital also helps avoid inhaling fungal spores.

Complications Following Hematopoietic Stem Cell Transplantation

Infections

SCT recipients are at increased risk for infections given their state of immune deficiency: the susceptibility to particular infections differs based on the phase of immune recovery after transplant [24]. Most of the infecting organisms arise from the patient's endogenous flora or reactivation of a latent infection. The first phase, the *pre-engraftment period* (day 0 to day approximately +30 following transplant) is remarkable for both neutropenia and breakdown of mucosal barriers

Table 27.3 Prominent infectious agents following HSCT

Pre-engraftment	Early engraftment	Late engraftment
Bacterial <i>Staphylococcus epidermis, Staphylococcus aureus, Viridians streptococci</i> <i>Escherichia coli, Klebsiella spp., Pseudomonas</i>	Viral Cytomegalovirus (CMV) Adenovirus	Bacterial <i>Streptococcus pneumoniae</i>
Viral Herpes simplex virus (HSV) Respiratory viruses respiratory syncytial virus, parainfluenza, influenza, human metapneumovirus Adenovirus Enteric viruses – rotavirus, enterovirus	Respiratory viruses– respiratory syncytial virus, parainfluenza, influenza, human metapneumovirus Adenovirus Epstein-Barr virus (EBV) Human herpes virus 6 (HHV 6) Polyoma viruses (BK virus and JC virus)	Viral Varicella-zoster virus Cytomegalovirus (CMV)
Fungal <i>Candida spp.</i> <i>Aspergillus spp.</i> <i>Mucor spp.</i>	Fungal <i>Pneumocystis jiroveci</i> Parasitic <i>Toxoplasma gondii</i>	

from conditioning regimens. In this phase, recipients are particularly susceptible to bacterial and fungal infections. Common bacterial infections include catheter associated bloodstream infections (CA-BSI) and bloodstream infections (BSI) secondary to bacterial translocation from damaged mucosal surfaces commonly in the gastrointestinal tract. Viral infections that affect mucosal surfaces are also prevalent in this phase [24–26]. The next phase, *early engraftment* (approximately day +30 to +100) is remarkable for granulocyte recovery, but significantly impaired cell mediated immunity [24, 25]. During *late engraftment* (after 100 days), there is continued immune reconstitution, but patients still have significant impairment in cell-mediated and humoral immunity, and may have defects in reticuloendothelial function especially in conjunction with GVHD. Hypogammaglobulinemia can be a finding during this period [24, 25]. Prominent infections following SCT are presented in Table 27.3.

Management of bacterial infections includes supportive care and broad spectrum, empiric antibiotic therapy that is tailored to culture results. Administration of broad spectrum antibiotics, selected by careful study of the flora prominent in each institution, at the onset of fever is essential. It is not acceptable to delay the use of antibiotics until a positive culture is obtained. In patients that are persistently febrile despite negative bacterial cultures, imaging such as CT scans looking for invasive fungal infections may be indicated. Additionally, broad spectrum fungal coverage (e.g., amphotericin B) should be added. Azoles and caspofungin are appropriate treatment for invasive aspergillosis infections and candidal infections [27]. Treatment for viruses, if available, is variably effective (see Table 27.4) [24, 28].

Table 27.4 Viral infections and therapy

Viral pathogen	Therapy
Cytomegalovirus (CMV)	Ganciclovir ^a , foscarnet, cidofovir CMV immune globulin (CMVIG) ^b
Adenovirus	Cidofovir
Herpes simplex virus (HSV)	Acyclovir, valacyclovir, famciclovir Foscarnet (acyclovir resistant HSV) Cidofovir (acyclovir/foscarnet resistant HSV)
Polyoma virus (BK)	Cidofovir, leflunomide
Epstein-Barr virus (EBV)	Rituximab
Human Herpes Virus Type 6 (HHV6)	Ganciclovir, foscarnet, cidofovir
Varicella-Zoster virus infection (VZV)	Acyclovir, valacyclovir (low risk patients) Famciclovir (low risk patients)
Respiratory Syncytial virus (RSV)	Ribavirin ^c , RSV immunoglobulin
Parvovirus B19	Intravenous immunoglobulin

^aMyelosuppressive, needs to be used with caution in the early phase post SCT, especially prior to engraftment

^bAlong with anti-viral medication

^cAerosolized, data mixed on efficacy

Respiratory Failure Following Hematopoietic Stem Cell Transplantation

Respiratory failure following SCT is among the most common reasons for these patients to require intensive care. The proportion of children undergoing SCT that require mechanical ventilation is variable with studies reporting up to 30 % needing mechanical ventilation [1]. It is important for clinicians to ascertain the presence of pre-transplant pulmonary

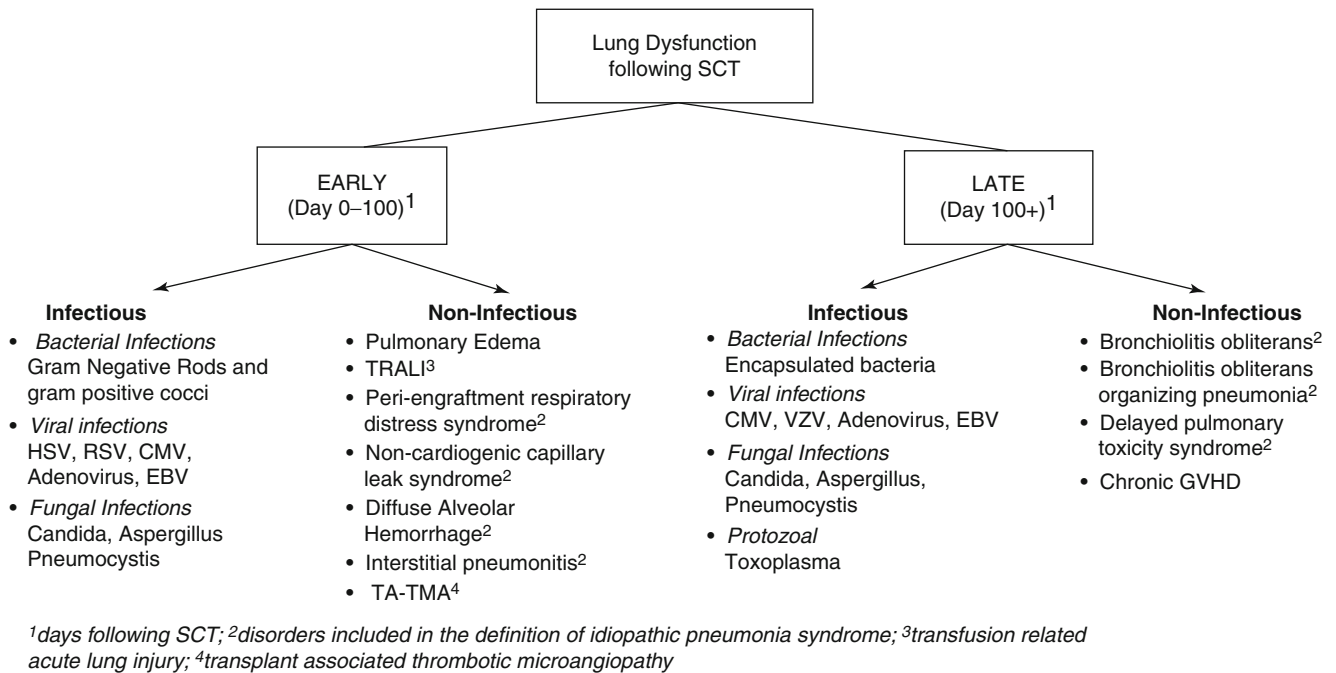


Fig. 27.1 Causes of lung dysfunction following hematopoietic stem cell transplant

morbidity such as lung damage from chemotherapy (bleomycin, busulfan and cyclophosphamide), a history of respiratory infections, any prior surgical procedures involving the lung and the use of radiotherapy. The presence of these conditions may impact the course of respiratory illness following transplant. A wide variety of processes may involve the lung following SCT leading to the development of respiratory failure. Some processes may be intrinsic to the lung such as pneumonitis or may be extrinsic such as fluid overload. Generally, respiratory failure in the post-transplant setting is divided into infectious and non-infectious categories, and like other processes following SCT, follows a temporal profile paralleling immune recovery (see Fig. 27.1). Clinically, it is important to note that this distinction may be difficult to discern as multiple processes may contribute to lung dysfunction resulting in respiratory failure.

Non-Infectious Causes of Lung Injury

This is becoming a proportionately larger contributor to post-transplant pulmonary-related morbidity and mortality, as prompt use of anti-microbials is now standard of care for febrile patients, and some potentially severe infections may be aborted. Non-infectious lung injury post-transplant can occur early (within 100 days of SCT) or late (after 100 days of SCT). A variety of non-infectious lung processes that occur following SCT constitute the idiopathic pneumonia syndrome (IPS). IPS is a distinct constellation of lung diseases characterized by non-infectious widespread lung injury after SCT that may affect the pulmonary parenchyma, the

vascular endothelium or the airway epithelium. By definition, this injury cannot be attributable to active infection, cardiogenic causes, or renal failure/fluid overload [29]. The reported incidence of acute IPS ranges from 5 to 23 % after allogeneic stem cell transplantation with onset occurring within a 100 days of transplant [29–37]. Two separate pediatric studies reported the incidence to be 11 and 23 % respectively [33, 34]. The risk factors for the development of IPS underscore the potential mechanisms of injury: direct injury (myeloablative conditioning, including total body irradiation) and immune-mediated injury (allogeneic transplant, presence of GVHD, HLA disparity of donor and recipient). Although IPS can occur in autologous transplants, this is rare, and outcomes are better. Other risk factors for IPS include older recipient age and worse pre-transplant lung function [29–34, 36–38]. The mechanisms leading to the development of the disease processes that make up this syndrome remain unclear. However, the clinical spectrum of IPS has been replicated in animal models by varying combinations of antigen mismatching, high dose chemotherapy, and injection of lipopolysaccharide (LPS) in murine models of GVHD [39–46]. The triggers of the inflammatory cascade and lung injury are still unknown. Much recent attention has been focused on a proposed “gut-lung-liver” axis of inflammation. This model is supported by the association of GVHD and hepatic injury with IPS. The model proposes that LPS translocation across damaged mucosa in the gut plays an important role in triggering a systemic inflammatory cascade, inducing lung injury [46]. Tumor necrosis factor

(TNF)- α may have an important role in the pathogenesis of IPS, as blocking TNF- α decreases severity of IPS in animal models, and potentially in patients [36, 45, 47]. Although GVHD is not classically described in the lungs, the interactions between donor alloreactive T-cells, recipient antigen presenting cells, donor accessory cells and pulmonary parenchymal cells in the development of IPS is of great interest [48]. In experimental models, the importance of these interactions in development of lung injury following hematopoietic SCT has been demonstrated. In all likelihood the pathogenesis of IPS likely involves complex interactions of all of these factors [29].

Peri-engraftment respiratory distress syndrome (PERDS) occurs around the time of stem cell recovery, typically 2–3 weeks after the transplant infusion. As the name suggests, symptoms (fever, shortness of breath, hypoxemia, weight gain, pulmonary edema) begin within 5 days of neutrophil engraftment [29]. Although reported in recipients of both allogeneic and autologous transplants, response to steroids and survival is better in the autologous group [29, 49, 50]. Patients who undergo non-myeloablative conditioning regimens also have better outcomes [29, 51]. PERDS refers to the pulmonary manifestations of a broader engraftment syndrome, characterized by fever, rash, non-cardiogenic pulmonary edema, and weight gain. The symptoms of engraftment syndrome may also include hepatic dysfunction, renal insufficiency and encephalopathy. The engraftment syndrome itself may not portend a poor outcome: many patients with engraftment syndrome do not require pulmonary support [50, 52–54]. A similar entity, *noncardiogenic capillary leak syndrome* is also characterized by respiratory symptoms, weight gain, and edema, and typically occurs within the first 30 days post-transplant [55, 56]. The chest radiographs are remarkable for bilateral pulmonary infiltrates, pleural effusions and pulmonary edema in both categories, and it is unclear if these are distinct entities [29].

Diffuse alveolar hemorrhage (DAH) is another distinct entity that occurs soon after transplant. Allogeneic transplant is associated with a higher incidence, and unlike some forms of IPS, reduced intensity conditioning does not appear to be protective. The reported time to onset for early onset DAH is up to 50 days post-transplant, although there are reports of late alveolar hemorrhage. DAH is characterized by progressive shortness of breath, cough, and hypoxemia, and rarely, frank hemoptysis. Bronchoalveolar lavage reveals progressively bloodier returns of fluid with repeated lavages. Hemosiderin laden macrophages may be present, but this finding is non-specific. Chest radiographs are remarkable for bilateral, initially central infiltrates. Treatment is typically high dose steroids and supportive care in the form of mechanical ventilation with high mean airway pressures. One retrospective study did demonstrate a lower mortality in a cohort of their patients receiving aminocaproic acid, although this

has not been demonstrated prospectively [57]. Despite therapy, the mortality for DAH is high and is reported to range between 48 and 100 % [29, 54, 57–65].

Thrombotic microangiopathy is another distinct pathology being increasingly noted to affect the pulmonary vasculature of a subset of SCT recipients. This disorder can present as hypoxemic respiratory failure with or without pulmonary hypertension. In a patient with unexplained hypoxemia, the presence of pulmonary hypertension is suggestive of the diagnosis; however, it is difficult to make the diagnosis in the absence of a lung biopsy, and it may only be apparent on autopsy [66].

IPS can also present as a non-infectious *acute interstitial pneumonitis*. This condition presents with fever, cough, dyspnea, and hypoxemia and usually occurs 2–6 months after transplant. As the name suggests, the chest radiograph is remarkable for bilateral interstitial infiltrates [29]. One form of IPS that appears to result as direct injury from radiation and chemotherapy is the *delayed pulmonary toxicity syndrome (DPTS)*. DPTS, while traditionally grouped with IPS, is infrequent, and is characterized by lung dysfunction that is associated with chemotherapeutic agents, particularly 1,2-bis(2-chloroethyl)-1-nitrosurea (BCNU), cyclophosphamide and cisplatin. Unlike other forms of IPS, it is quite responsive to corticosteroid treatment [29]. DPTS was first described with autologous transplant recipients for the treatment of breast cancer, and is remarkable for its late onset (months to years after the transplant) [67].

Late onset non-infectious pulmonary complications have a reported incidence of 8–26 % among recipients who survive more than 3 months [35, 68–72]. Some degree of pulmonary dysfunction (especially impaired diffusion capacity and restrictive lung disease) has been reported in 25–85 % of children who survive hematopoietic stem cell transplantation, although not all are symptomatic and many experience improvement [73]. Chronic restrictive lung disease may result from radiation, chemotherapy, or infection; the etiology is not clearly understood, and may be multi-factorial.

Bronchiolitis obliterans organizing pneumonia (BOOP), is a distinct category of chronic restrictive lung disease, and is rare, perhaps because the diagnosis is difficult to secure, or one of exclusion, in the absence of a lung biopsy. Risk factors for BOOP include chronic and acute GVHD, and it occurs almost exclusively after allogeneic transplant suggesting that immune dysregulation is the mechanism of pulmonary injury [74, 75]. Clinical symptoms include dry cough, dyspnea, fever, and a restrictive pattern on spirometry. The onset has been reported to range from 1 month to 2 years after transplant. The chest radiograph demonstrates patchy airspace disease and nodular opacities, and may have a “ground glass” appearance. Response to increased immunosuppression, typically steroids, is good. Some reports have successfully used lower dose of steroids in conjunction with macrolides [29, 35, 69, 72, 76–80].

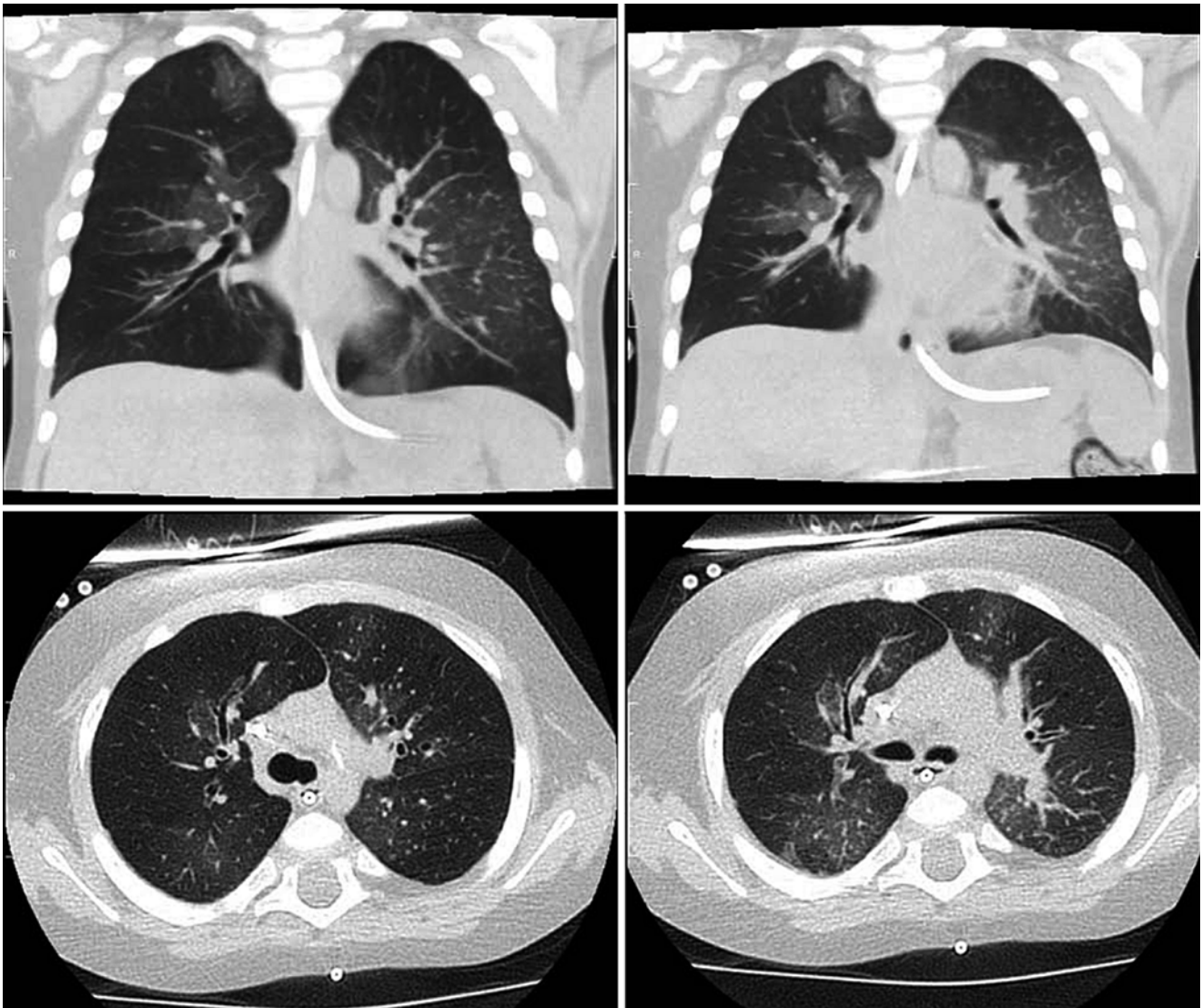


Fig. 27.2 Lung High Resolution Computed tomography (HRCT) in a stem cell transplant recipient demonstrating bronchiolitis obliterans. Inspiratory (*left*) and expiratory (*right*) images in coronal (*top*) and axial (*bottom*) planes demonstrating mosaic attenuation pattern with

patchy ground glass appearance of lung, air trapping and bronchiectasis consistent with bronchiolitis obliterans (Courtesy of Dr. Daniel J Podberesky, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)

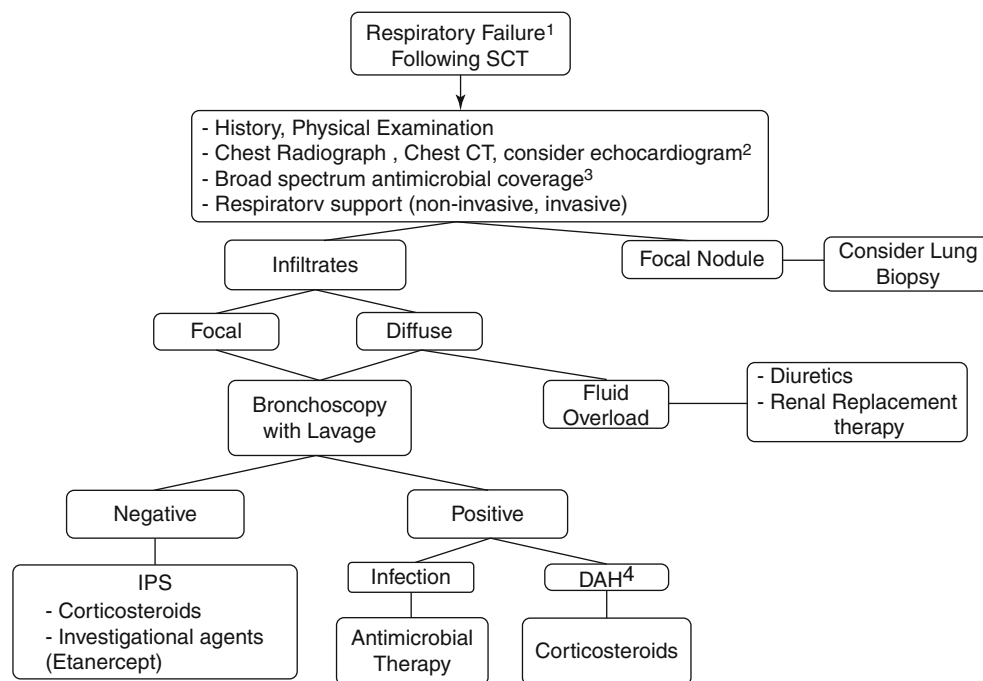
Bronchiolitis obliterans (BO), which is distinct from BOOP, is a manifestation of chronic GVHD of the lung and is likely an immune-mediated process. Risk factors include the presence of GVHD in another organ, previous viral respiratory infections and poor pre-transplant lung function [81–88]. The incidence is lower with T-cell depletion of donor cells, and with reduced intensity conditioning [75, 89]. BO has a more severe clinical course than restrictive lung disease, and is associated with 60 % mortality. BO can occur years after SCT, but the typical onset is 7–15 months post-transplant. BO is characterized by respiratory symptoms, including wheezing, in the absence of fever [29, 90]. Radiographs demonstrate hyperinflation of the lungs, as this is an obstructive process, with CT scans demonstrating bronchiectasis, septal lines and a ground

glass appearance (see Fig. 27.2) [91]. The treatment is immunosuppression with systemic and inhaled steroids, calcineurin inhibitors, and antithymocyte globulin (ATG) [88, 92, 93]. Newer therapies, including azithromycin, infliximab, etanercept, statins, and extracorporeal photopheresis have all shown some efficacy in small trials and case reports [28, 29, 87, 94–99]. Although very rare, successful lung transplantation has been reported [100, 101].

Infectious Causes of Lung Injury

Lung injury and respiratory failure from infectious agents is a significant cause of post-transplant related morbidity and mortality. As described above, the pattern of susceptibility to particular infectious agents/organisms changes with immune

Fig. 27.3 Clinical approach to respiratory failure following hematopoietic stem cell transplant



¹Include patients with respiratory distress and/or hypoxemia; ²Echocardiogram to assess ventricular function and presence of pulmonary hypertension; ³Includes appropriate antiviral and antifungal coverage; ⁴diffuse alveolar hemorrhage

recovery and the common causes of infectious pneumonitis are listed (see Fig. 27.1).

Management

SCT patients requiring intensive care for respiratory failure need a thoughtful and detailed workup to delineate the proximate cause of their lung dysfunction. Our suggested approach to a patient with respiratory failure requiring intensive care is presented in Fig. 27.3. All SCT patients admitted to the ICU for respiratory distress should be assessed clinically for signs and symptoms of infection and fluid overload. The latter may occur in the setting of renal dysfunction and/or heart failure. Bacterial and fungal cultures as well as viral PCR testing should be performed to identify infectious agents. Importantly, a bronchoscopy with a lavage should be considered early. In addition to a routine chest radiograph, further imaging in the form of a CT scan and echocardiography should be performed. A lung biopsy may be considered especially in patients who have focal processes. In the absence of positive microbiologic studies, a diagnosis of IPS may be considered.

The treatment of respiratory failure from the ICU standpoint is supportive, until the underlying disease process can be addressed. Fluid overload may play a significant role in lung dysfunction, and aggressive fluid management is often helpful in these patients. Ventilatory support in the form non-invasive ventilation (CPAP, BiPAP and high flow nasal cannula) may be helpful in the early stages; however, body

habitus, skin breakdown and the presence of mucositis may make the interface for non-invasive support tenuous. Invasive mechanical ventilation should be initiated as needed using a lung protective strategy with the utilization of a low tidal volume and an open lung strategy. Being cognizant of ventilator-induced lung injury is extremely important and it is not uncommon in the sickest patients to tolerate oxygen saturations of >80–85 % and allow for moderate respiratory acidosis (pH >7.2–7.25), irrespective of PCO₂. Sometimes, it is preferable to switch early to high frequency oscillatory ventilation, especially in patients needing high mean airway pressures to attain oxygenation and ventilation goals. Other supportive strategies that may be beneficial in individual patients include prone positioning, inhaled nitric oxide and surfactant. The value of these therapies in this patient population remains largely unproven. For example, the largest prone positioning trial in children with acute lung injury excluded SCT patients [102]. However, in certain patients, the selective use of these therapies may be helpful. For instance, patients transplanted for malignant infantile osteopetrosis appear to have a particular predilection for pulmonary hypertension that may be responsive to inhaled nitric oxide [102, 103]. Moreover, the largest pediatric trial of calfactant did include SCT patients, and although those children accounted for the less 20 % of the total study population, SCT patients treated with calfactant (n=10) experienced an 11 % absolute reduction in mortality when compared to SCT patients who received air control (n=17) [104, 105]. Moreover, 60 % of the

SCT patients who received calfactant experienced a 25 % or greater decrease in their oxygenation index [105]. The ultimate supportive therapy for respiratory failure, extracorporeal support, may be considered for this patient population. Extracorporeal membrane oxygenation (ECMO) may be considered for specific patients including those who have engrafted and have normal platelet counts. Isolated reports of the use of ECMO in this patient population have been published [106, 107]. However, most centers exclude SCT patients on the basis of several factors including the reversibility of the lung disease. Early renal replacement therapy, especially in individuals with kidney injury, may be helpful, particularly in children with fluid overload. Small studies in children have suggested both short term oxygenation and survival benefits, however, the mechanisms by which renal replacement therapy may alter the course of respiratory failure in following SCT remain unclear [108, 109].

The mainstay of therapy to address the lung disease in these patients focuses on the etiology. Aggressive and immediate broad spectrum antimicrobial coverage, including antiviral coverage is important. Therapy can be later tailored on the basis of microbiologic testing. In the absence of an infective etiology, corticosteroids are the drugs most commonly utilized to blunt the inflammatory response. The dose is variable (often 2–5 mg/kg/day), and in certain conditions such as DAH patients may require higher pulse doses (e.g., 10 mg/kg) [29, 31, 59, 60]. The risks and benefits for starting corticosteroids must be weighed on a case to case basis, especially in the presence of active infections. Once initiated, corticosteroids are tapered slowly. Another potential therapy for IPS is etanercept, a dimeric fusion protein consisting of two soluble TNF receptors that binds TNF- α (alpha) thereby serving as a TNF- α (alpha) inhibitor. In a small study involving 15 patients with IPS, the addition of etanercept to corticosteroids resulted in improved response rates as defined by the ability to discontinue supplemental oxygen within 28 days of the initiation of therapy [47]. Further trials of etanercept in the treatment of IPS are currently ongoing [110]. Early renal replacement therapy may be helpful, however the mechanisms and the ideal timing of initiation remain unclear [108, 109]. In summary, the management of respiratory failure following SCT is supportive with diligent fluid management and respiratory support, while broad spectrum antimicrobials and corticosteroids can be used to address the underlying cause of disease.

Outcomes

Outcomes following respiratory failure in SCT patients who require mechanical ventilation appear to have improved over time; however, they remain very poor when compared to other populations. In a recent meta-regression analysis, ICU mortality for mechanically ventilated children following SCT was highly variable ranging between 25 and 91 %. More recent

studies appear to show a more promising trend [1, 111–113]. In patients with IPS, mortality is reported between 56 and 94 %.

Graft Versus Host Disease

Graft versus host disease (GVHD) is a significant cause of transplant-related morbidity and mortality. The incidence of acute GVHD in children has been reported to be between 19 and 85 % and varies according to degree of HLA matching and type of donor [114]. GVHD can present as acute or chronic. Chronic GVHD is a distinct entity from acute GVHD. Historically, acute and chronic GVHD have been differentiated by the time of onset (chronic >100 days), but it is now recognized that there may be overlap in the time of onset of the disease. Clinical features, pathophysiology and histology of acute and chronic GVHD are distinctly different [115]. The median time of onset for acute GVHD in one large multicenter study was reported to be 3 weeks after the stem cell infusion [116]. The risk of acute GVHD is increased in unrelated transplants (although as matching improves, risk is reducing) and transplants with more HLA disparity [117]. Other risk factors reported in some, but not all studies, include older donor and recipient age, female (especially multiparous) donors for male recipients, a history of infections (including CMV), the intensity of the conditioning regimen (especially radiation, which increases risk), and the type of GVHD prophylaxis received [114].

Mechanism of Disease

Acute GVHD can develop when an allogeneic graft contains immunologically competent cells with differing antigens between the graft and host and the immune system of the host is unable to reject the graft [118]. Mechanistically, acute GVHD is thought to develop as a consequence of 3 interrelated phases. In phase 1, there is damage to the mucosal surfaces of the host from the chemotherapy and radiation preparative regimen, especially the gastrointestinal tract. The disruption of the mucosal barrier allows translocation of LPS produced by endogenous bacteria, leading to stimulation of inflammatory cytokines in the host, characterized by activation of the host antigen presenting cells [119, 120]. Phase 2 involves the presentation of these allo-antigens to donor T-cells. Subsequently, activation of the donor T-cells leads to further proliferation, and a resulting inflammatory cascade and recruitment of further immune response by donor effector cells. Phase 3 is characterized by damage to host tissues caused by effector cells (including donor mononuclear cells, including cytotoxic T cells, phagocytes, and neutrophils among others). Soluble mediators believed to be particularly important include IL-2, LPS, IL-12, interferon- γ , and TNF [119]. The pathophysiology of chronic GVHD is less well understood, and is thought to involve dysregulation of both the T and B cell systems as well as an autoimmune component

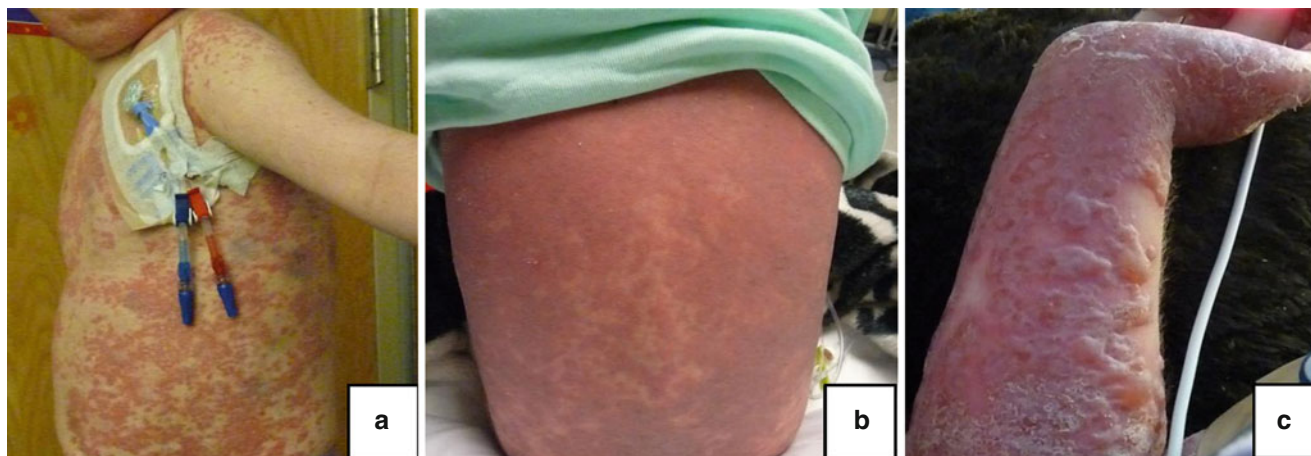


Fig. 27.4 Skin manifestations of acute graft versus host disease. (a) Erythematous morbilliform maculopapular rash involving the trunk suggestive of Stage 1 and 2 skin involvement. (b) Generalized erythroderma suggestive of Stage 3 skin involvement. (c) Bullae involving the extremities suggestive of Stage 4 skin involvement

Table 27.5 Consensus grading of acute graft versus host disease

Organ/extent of involvement			
	Skin	Liver	Intestinal tract
Stage			
1	Rash <25 % of skin ^a	Bilirubin 2–3 mg/dL ^b	Diarrhea >500 mL/day ^c or persistent nausea ^d
2	Rash 25–50 % of skin	Bilirubin 3–6 mg/dL	Diarrhea >1,000 mL/day
3	Rash >50 % of skin	Bilirubin 6–15 mg/dL	Diarrhea >1,500 mL/day
4	Generalized erythroderma with bulla formation	Bilirubin >15 mg/dL	Severe abdominal pain with or without ileus
Grade			
0	None	None	None
I	Stage 1–2	None	None
II	Stage 3	or Stage 1	or Stage 1
III	–	Stage 2–3	or Stage 2–4
IV ^e	Stage 4	or Stage 4	–

Adapted from Przepiorka et al. [124]. With permission from Nature Publishing Group

^aUse of rule of nines to determine body surface area involvement

^bTotal bilirubin, downgrade one stage if an additional cause of elevated bilirubin is documented

^cThe volume of diarrhea applies to adults. For pediatric patients, volume of diarrhea should be based on body surface area

^dPersistent nausea with histologic evidence of GVHD in the stomach or duodenum

^eGrade IV may also include lesser organ involvement, but with extreme decrease in performance status

[121]. Hereafter, we will focus on acute GVHD as it is responsible for the majority of ICU admissions from GVHD.

Clinical Features

Acute GVHD primarily involves three organ systems: the skin, the liver and the gastrointestinal tract. The skin is the most common site of disease. Typically, skin involvement starts as a morbilliform, maculopapular eruption, usually involving the sun-exposed areas (face, arms, behind the ears, shoulders) and the palms and soles (see Fig. 27.4a). Depending on the severity, it may progress to generalized erythroderma with bullae formation (see Fig. 27.4b, c). In addition to problems secondary to loss of mucosal integrity (electrolyte abnormalities, fluid loss, and risk of infection), these patients

can experience severe pain [18]. Hepatic GVHD is marked by cholestasis, hepatitis, and, depending on the severity, progressive hepatic insufficiency and failure [122]. Gastrointestinal GVHD is remarkable for secretory, sometimes bloody diarrhea, abdominal pain, nausea, vomiting and anorexia. Patients may have severe fluid losses, electrolyte abnormalities, anemia and protein losing enteropathy. Other organ systems may also be involved including the eyes [18, 114, 123].

Diagnosis

The diagnosis of acute GVHD is a clinical one and the severity is graded according to the degree of involvement of the skin, liver and gastrointestinal tract (see Table 27.5) [124]. The skin is staged by character and percent body

surface area involved. The liver involvement is staged by the total bilirubin level, and the gastrointestinal tract is staged by the volume of diarrhea. The grading depends on the combined severity of involvement of the skin, liver and gastrointestinal tract (see Table 27.5). A biopsy of the skin and gastrointestinal tract may be performed to establish a pathological diagnosis of GVHD [114]. The differential diagnosis for acute GVHD is broad, and includes skin reactions, conditioning toxicity to the skin, liver or gut, sinusoidal obstruction syndrome and infection. It is important to appreciate that most of the mortality associated with acute GVHD is due to infection as a consequence of the profound immune incompetence associated with active GVHD including its treatment, and not to the clinical features described above.

Treatment

Therapy for acute GVHD is immune suppression to interrupt the cycle of cell proliferation, the generation of pro-inflammatory proteins and tissue injury. Therefore, first line therapy is the initiation of steroids. The reported response rates to steroids vary from 35 to 80 %, depending on the grade and degree of response assessed [125–128]. Once a response is achieved, steroids are slowly weaned. Some patients will have steroid resistant GVHD, typically defined as any worsening after 3 days of therapy, or the lack of improvement in 5 days of therapy. Steroid refractory GVHD is difficult to treat, and morbidity and mortality are high. Additional immune suppressive agents are used, and while response can be seen to any of these, all are generally unsatisfactory [129]. The most common agents used are monoclonal and polyclonal antibodies such as alemtuzumab (Campath-1H) and ATG, IL-2 receptor antagonists (e.g., basiliximab), and anti-TNF- α agents (e.g. infliximab, etanercept). Immunosuppressants including MMF, calcineurin inhibitors, and sirolimus may also be used [114, 129]. Other strategies attempted include pentostatin, infusion of mesenchymal stem cells and extracorporeal photopheresis [130–132]. Of note, all of these strategies are immune suppressive, and increase the risk of infection, but are necessary for control of disease and ultimate return to immune competence. Aggressive supportive care is also necessary for successful treatment and may require an intensive effort. Antibacterial, antiviral and antifungal surveillance and prophylaxis are required, and essential for success, with appropriate escalation of agents with documented or suspected infection [114, 129, 133]. Meticulous skin care with topical emollient therapy and wound care is required to prevent against infection. Ophthalmological examination for evaluation, and subsequent lubrication, is indicated as well as antimicrobial protection of the eyes. Gut rest and hyperalimentation are needed for gastrointestinal GVHD. Gastrointestinal bleeding may require transfusion support, and octreotide

may be effective in controlling secretory diarrhea and gastrointestinal bleeding. Pain control is important and can be challenging; rarely, patients may require mechanical ventilation for adequate doses of pain medication.

Outcome

Long term survival rates correlate with the grade of severity of the GVHD. In a recent, large, multicenter study of adults and children, 5 year survival for those with Grade I-II GVHD was between 80 and 85 %, while those with Grade III GVHD had a 5 year survival of 25 %, and those with Grade IV GVHD had a survival of only 5 % [116].

Sinusoidal Obstruction Syndrome (Veno-Occlusive Disease of the Liver)

Previously termed veno-occlusive disease of the liver, sinusoidal obstruction syndrome (SOS) is a complication of SCT secondary to chemotherapy and radiation toxicity. The term veno-occlusive disease is a misnomer, as the site of initial injury is the sinusoids of the liver. SOS is characterized by liver injury and manifests as a triad of tender hepatomegaly, elevated serum bilirubin with fluid retention and weight gain (see Table 27.5) [134]. The incidence of SOS in children has been reported to be between 11 and 31 % [135–141]. Typically, SOS occurs within 20 days after transplant and generally does not occur beyond 30 days post stem cell infusion although cases have been reported later. Risk factors for the development of SOS include conditioning with certain chemotherapeutic drugs, including busulfan, cyclophosphamide, and melphalan, among others. The availability of an intravenous formulation of busulfan, and reliable, individualized, dosing guided by pharmacokinetics has been helpful in reducing the incidence of SOS secondary to busulfan exposure [142]. Additional risk factors for SOS include high doses of radiation, pre-existing liver disease, younger age, unrelated donor, positive CMV serology in the recipient, and receipt of total parenteral nutrition (TPN) within the 30 days before transplant [135, 137, 138].

Mechanism of Disease

SOS is characterized by injury to the sinusoidal endothelium in the liver followed by subendothelial edema with extravasation of red blood cells and fibrin deposition, with ensuing hepatocyte damage and deposition of collagen. This sequence of events leads to sinusoidal obstruction, the development of portal hypertension, and in advanced cases, to hepatocyte necrosis and liver failure [143]. More recently, disruption in the coagulation cascade related to endothelial activation and injury leading to thrombosis has been thought to play a role in the pathogenesis of SOS [144, 145].

Table 27.6 Diagnostic criteria for sinusoidal obstruction syndrome

Baltimore criteria	Seattle criteria ^a
Prior to day 21 post-SCT,	Prior to day 30 post-SCT,
1. Serum bilirubin level ≥ 2 mg/dL and	1. Two or more of the following:
2. Two or more of the following:	Serum bilirubin level ≥ 2 mg/dL
Ascites	Hepatomegaly and right upper quadrant pain
Hepatomegaly (usually painful)	Ascites and/or unexplained weight gain $>2\%$ over baseline
Weight gain $>5\%$ over baseline	

^aModified Seattle criteria require clinical presentation prior to day 20 post-SCT

Clinical Features

The clinical presentation of SOS begins with the onset of tender hepatomegaly and weight gain, with hyperbilirubinemia following shortly thereafter. Sodium retention is common and ascites is often present. Other clinical findings may include peripheral edema including anasarca, pleural effusions, jaundice, thrombocytopenia, liver and renal failure. SOS severity is classified on the basis of clinical outcome. Mild disease resolves spontaneously while moderate disease resolves with treatment. The majority (70–85 %) of patients have mild or moderate disease. Severe disease is characterized by rapid progression to multiorgan failure (MOF) and death or symptoms that continue beyond day +100 [135]. The risk of development of severe disease can be estimated utilizing percent weight gain and total bilirubin in conjunction with the number of days post-transplant. As might be anticipated, severe disease is associated with higher bilirubin values occurring early after transplant [146].

Diagnosis

The diagnosis of SOS is based on the presence of the clinical criteria, however, these findings can be quite non-specific (see Table 27.6) [147–149]. Common laboratory findings include an increased serum bilirubin level and elevations of liver enzyme levels (which may occur later). Thrombocytopenia is common, as are decreased levels of protein C and antithrombin III [144]. Abdominal ultrasound is a commonly used tool to identify findings that will assist in securing the diagnosis. In addition to excluding other liver lesions that may result in similar symptoms, ultrasound may demonstrate hepatomegaly, ascites and gallbladder wall edema. Doppler evaluation may reveal attenuation of hepatic vein flow, slowing or reversal (late finding) of portal vein flow, and an increased resistive index in the hepatic artery (see Fig. 27.5). Ultrasound, however, may not provide reliable markers for early diagnosis, and should be repeated when the diagnosis is unclear [150–152]. Liver biopsy is diagnostic, but is rarely performed given the significant risk of bleeding, especially in the setting of thrombocytopenia. Transvenous liver biopsy has been suggested as an alternative to percutaneous biopsy, and allows for the measurement of a hepatic venous pressure gradient (elevation >10 mmHg is highly specific for SOS) [145]. However, this strategy may yield small,

non-diagnostic samples for histology. In addition, infrequent use of the technique may lead to limited operator expertise. Consequently, the use of this approach has not gained widespread acceptance.

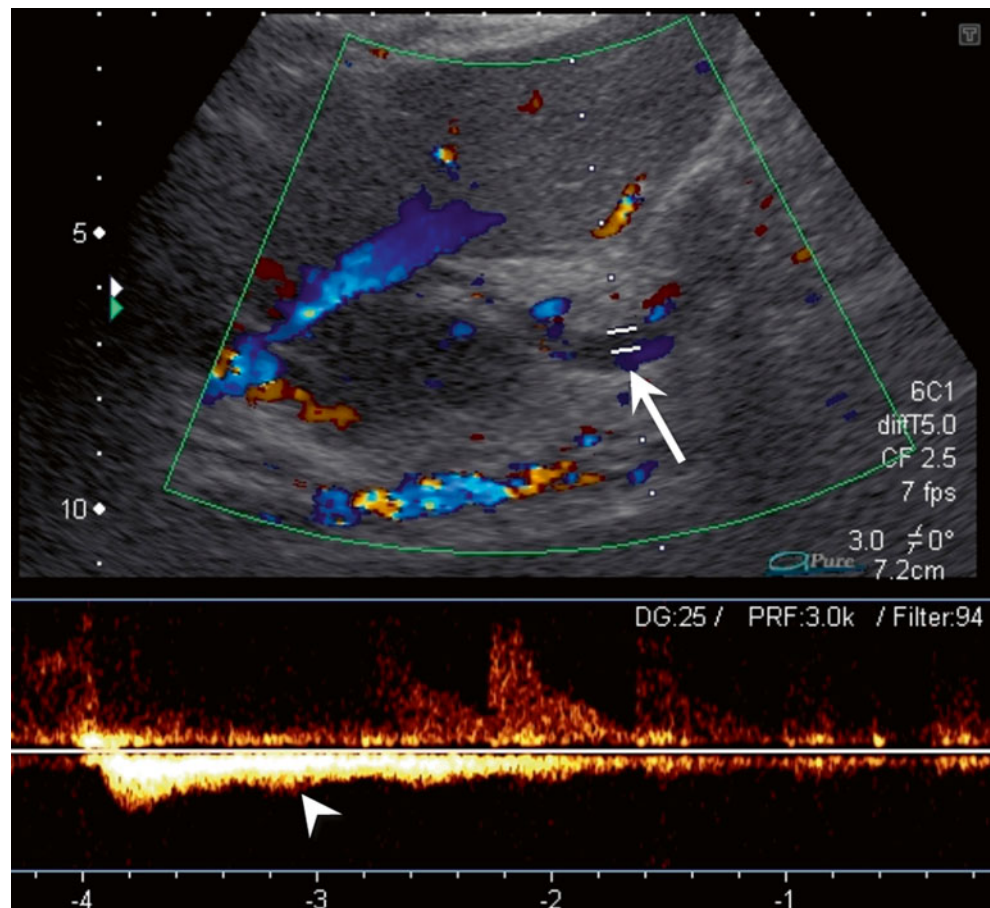
The differential diagnosis for SOS is broad, and includes sepsis with renal insufficiency and cholestasis, TPN-related cholestatic liver disease, and hyperacute GVHD. These disorders may co-exist with SOS and may complicate establishing the diagnosis [145].

Management

The management of SOS is mainly supportive and is dependent on disease severity. The close monitoring of fluid balance and electrolyte levels, in conjunction with sodium restriction and the use of diuretics, is important to avoid the need for ventilation secondary to fluid overload [135, 145, 153]. The early institution of renal replacement therapy may be helpful for patients with associated renal insufficiency and fluid overload or electrolyte abnormalities. Many therapies have been attempted for severe SOS with organ failure, including thrombolytic therapy and transhepatic shunts [144, 154–158]. Perhaps the most promising new therapy is defibrotide, a polydisperse oligonucleotide with antithrombotic and profibrinolytic effects, that is currently undergoing clinical trials. The response to defibrotide is encouraging and patients receiving this therapy have been found to have up to a 76 % response rate in reversal of disease [159]. The drug is not licensed by the FDA pending efficacy studies, but is available for compassionate use in the United States. Additionally, high dose corticosteroids may be effective for patients with earlier stages of disease, especially in those that do not meet the criteria for defibrotide [160]. Finally, in patients with hepatic failure liver, transplantation may be considered an option for a very small number of patients with end stage liver disease, but no irreversible dysfunction in other organs.

Prevention of SOS is important since therapeutic options are limited. Various prophylactic agents have been explored, especially in patients with previous hepatic injury, but with equivocal results. Antithrombin III demonstrated no protective effect in a large pediatric study [161]. Heparin may have some benefit, but has an increased risk of hemorrhage; low molecular weight heparin appears to be safer and may have some preventative

Fig. 27.5 Liver ultrasound with Doppler at the level of the main portal vein (*arrow*) in a stem cell transplant patient with sinusoidal obstruction syndrome demonstrating doppler waveform (*arrowhead*) below the baseline consistent with reversal of flow (Image courtesy of Dr. Alexander J Towbin, MD, Department of Radiology and Medical Imaging, Cincinnati Children's Hospital Medical Center, Cincinnati OH)



effect [162–166]. Prostaglandin E1 therapy has yielded mixed results with clear risk for toxicity [167, 168]. Ursodiol, is commonly used as supportive therapy and is generally safe, but has provided mixed results for the prevention of SOS [169]. Defibrotide has also been studied as a prophylactic therapy in high-risk children with promising results [170–173].

Outcomes

Mortality from SOS typically does not occur from fulminant liver failure, but rather, from respiratory and renal failure in the setting of fluid overload [153]. Outcomes appear related to the severity of the disease. Mild and moderate disease generally resolves with good outcomes; 100 day mortality rates for moderate disease are considered to be 20 %. However, individuals with severe disease and multiple organ failure have a dismal prognosis with a 100 day mortality approaching 98 %.

Transplant-Associated Thrombotic Microangiopathy

Transplant-associated thrombotic microangiopathy (TA-TMA) is a significant and relatively common complication of the SCT process. Most large retrospective studies report a TA-TMA

prevalence of 20–25 % [174]. TA-TMA belongs to the family of thrombotic microangiopathies (TMAs) including hemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Mechanism of Disease

TA-TMA occurs when endothelial injury, in the context of SCT, causes microangiopathic hemolytic anemia and platelet consumption resulting in thrombosis and fibrin deposition in the microcirculation [175, 176]. High dose chemotherapy, radiation, calcineurin inhibitors (e.g., cyclosporine), graft versus host disease (GVHD) and infections such as adenoviremia and BK viremia have been implicated as causative factors for TA-TMA [174, 177–179]. TA-TMA usually occurs in allogeneic transplant recipients within the first 100 days post HSCT, but can also occur in patients after autologous transplant [174, 180]. While endothelial injury represents the final common pathway of disease, the exact pathophysiology of TA-TMA remains unclear, limiting the development and evaluation of targeted therapies. The kidney is the most commonly affected organ, although injury has been reported in the lungs and the gastrointestinal tract [178, 181, 182]. The histological features of TA-TMA in the kidney include thickened capillary walls, fragmented erythrocytes, occluded

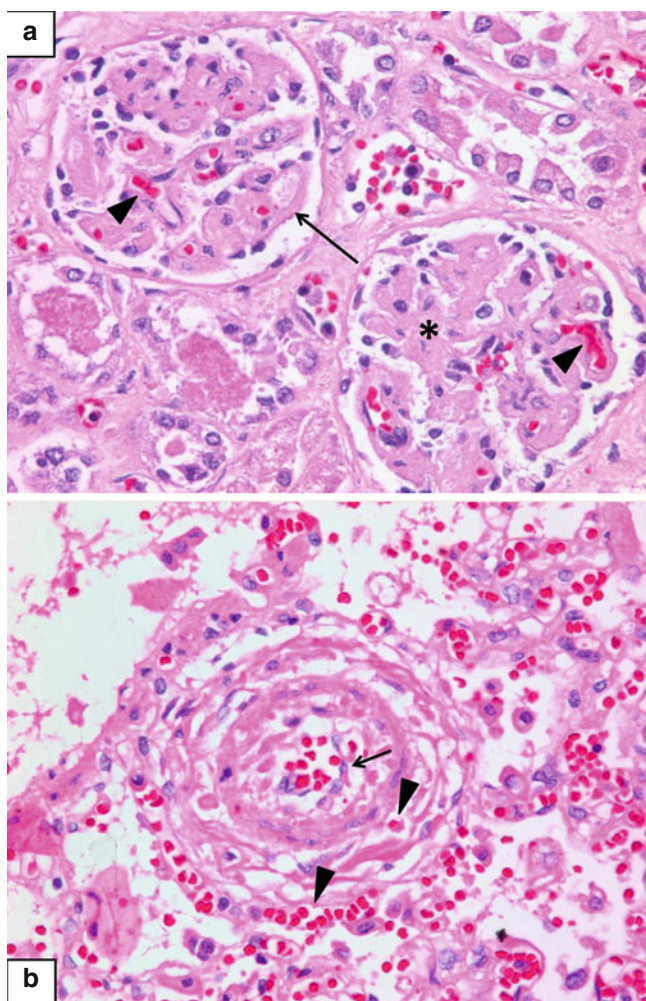


Fig. 27.6 Histologic changes of transplant-associated thrombotic microangiopathy (TA-TMA) in the kidney and lung. (a) Renal glomeruli demonstrating thickened capillary walls (arrows) with vessel occlusion. Red blood cell fragments can be seen (arrow heads) with mesangial expansion (asterisk) (H&E stain; magnification $\times 200$). (b) Pulmonary arterioles demonstrating endothelial separation from underlying basement membrane (arrow) with red blood cell extravasation (arrow heads) into the intima and into the lung tissue with red cell fragments (H&E stain; magnification $\times 200$)

vascular lumens, and endothelial separation with swelling, fibrin deposition, and necrosis (see Fig. 27.6a). Similar changes may also be seen in the pulmonary and mesenteric vascular beds (see Fig. 27.6b).

Clinical Features and Diagnosis

The diagnosis of TA-TMA remains challenging and requires a high index of suspicion. The acute presentation of TA-TMA may mimic acute multiorgan failure, sepsis, and/or polyserositis, and therefore, the diagnosis is easily overlooked or attributed to another process [175, 183]. Current clinical consensus diagnostic criteria for TA-TMA include hematologic and renal markers such as *de novo* anemia and

thrombocytopenia, elevation of lactate dehydrogenase levels (LDH) levels, low haptoglobin levels, the presence of schistocytes on blood smear, and the doubling of serum creatinine level [184, 185]. These criteria are inadequate for the early diagnosis of TA-TMA, and pose significant challenges in SCT patients, who have multiple potential reasons for these laboratory abnormalities, and in whom anemia and thrombocytopenia are almost universal [174, 186]. Serum creatinine is a poor marker of renal function in chronically ill SCT patients as it is strongly depends on muscle mass, and can remain relatively normal even with significant renal dysfunction [175, 180, 187]. Several autopsy studies have demonstrated that these criteria significantly under diagnose TA-TMA [175]. Current guidelines do not include other kidney injury markers such as elevation of blood pressure or proteinuria; more recently, a “renal-centric” approach to diagnosing TA-TMA has been suggested [174]. Renal biopsy, while very useful for the diagnosis of TA-TMA, remains a challenging procedure in SCT patients at risk for bleeding. Since the pulmonary vasculature maybe involved in TA-TMA, clinicians caring for these patients need to be aware of pulmonary TMA as a diagnosis in the setting of SCT patients presenting with respiratory failure and pulmonary hypertension [188, 189]. In summary, TA-TMA has to be included in the differential diagnosis of acutely ill SCT patients treated in the PICU. A high index of suspicion for TA-TMA is needed in patients with other endothelial disorders such as SOS, especially in patients with multiorgan failure, severe hypertension, posterior reversible encephalopathy syndrome (PRES), acute hemolysis and thrombocytopenia, pulmonary hypertension and polyserositis [183, 188, 190].

Management

In large part due to the lack of understanding of the TA-TMA pathogenesis, therapeutic options are limited. Patients treated for “probable-TMA” or prior to irreversible organ damage have a better response to clinical interventions [191]. The discontinuation of calcineurin inhibitors (e.g. cyclosporine) is the most accepted intervention in the management of TA-TMA. However, the discontinuation of this therapy must be supervised by a skilled transplant physician in order to minimize the risk of provoking or exacerbating GVHD. Several case reports demonstrate the benefit of using rituximab and defibrotide as single agents or in combination with therapeutic plasma exchange (TPE) [183, 192–194]. The effectiveness of TPE in the treatment of TA-TMA remains uncertain due to variable outcome measurements and an incomplete understanding of its exact therapeutic mechanism. The success of TPE may be influenced by the timing of the clinical interventions. TPE has been found to be most effective when initiated early after the TA-TMA presentation [183, 195]. The successful treatment of the underlying triggers of TA-TMA such as infections and GVHD is also important for success.

Outcomes

In its most severe form, mortality rates for TA-TMA are very high (60–90 %), while milder cases have an increased risk of later chronic kidney disease (CKD) [175, 196]. Patients surviving acute TA-TMA are left with severely affected renal function, and many later progress to CKD [187]. SCT patients diagnosed with TA-TMA are four times more likely to develop CKD, and nine times more likely to have long term hypertension than SCT patients without TA-TMA. TA-TMA-associated renal complications such as hypertension result in significant subsequent heart disease, a major cause of morbidity and mortality in childhood SCT survivors [197, 198].

Kidney Injury Following Hematopoietic Stem Cell Transplantation

Both acute and chronic kidney disease are common complications in SCT recipients. The reported incidence of acute kidney injury ranges from 20 to 50 % and 5 to 28 % for chronic kidney disease. Up to 10 % of patients who have acute kidney injury require renal replacement therapy [199–209]. The cause of renal injury in this patient population is often multifactorial; etiologies include drug and radiation toxicity, infusion reactions, septic shock, SOS, TA-TMA, and renal infection secondary to immunosuppression (e.g. BK nephropathy). Risk factors for renal insufficiency include allogeneic transplant, drug toxicity (particularly cyclosporine, amphotericin B, and cyclophosphamide), total body irradiation, sepsis, hepatic impairment (including hyperbilirubinemia, weight gain, and SOS), and pre-transplant renal impairment. Interestingly, the incidence of pre-transplant renal impairment is relatively low. The clinical consequences of renal impairment are often fluid overload, as SCT recipients require substantial volume of fluid for blood product replacement, medications, and nutritional support. Mortality in transplant recipients with renal failure is usually secondary to other organ system dysfunction, including respiratory failure, hepatic disease, septic shock and multiorgan failure [201–205, 207].

Diagnosis

The diagnosis of acute kidney injury has typically relied on changes in serum creatinine levels and urine output. However, criteria such as pRIFLE (pediatric risk, injury, failure, loss and end-stage renal disease) may afford greater sensitivity in diagnosing acute kidney injury, while markers like cystatin C that are unaffected by age, muscle mass and weight may be superior to creatinine clearance in estimating glomerular filtration rate (GFR) [210–215]. Though not validated in SCT recipients, studies have demonstrated that cystatin C is a better estimator of GFR than creatinine clearance in pediatric oncology and SCT patients [216–218].

Management

The treatment of kidney injury is largely supportive and includes aggressive monitoring of renal function, overall fluid status, and urine output, as well as the prevention of further injury by avoidance of nephrotoxic drugs if possible (e.g., using liposomal amphotericin B). Increasingly, there has been an emphasis on prevention of fluid overload in critically ill children in the critical care literature, and this extends to the SCT recipient where fluid restriction may be even more challenging given the need for blood products and medications. Several studies have demonstrated increased morbidity and mortality in children who had greater fluid overload at the initiation of renal replacement therapy [219–224]. In a study of SCT recipients with renal failure who received renal replacement therapy, patients who either started at, or attained less than 10 % fluid overload survived, while all those who remained fluid overloaded beyond this degree died [209]. Thus, the aggressive use of diuretics and renal replacement therapy are warranted in these patients to treat fluid overload. Diuretics remain the first choice of therapy to address fluid overload. It is not uncommon for SCT patients to need higher than usual doses of diuretics given their underlying kidney injury. The indications for the initiation of renal replacement therapy in SCT patients are similar to other patients in the ICU and modalities include continuous renal replacement therapy (CRRT) and intermittent hemodialysis. Peritoneal dialysis, given the risk of infection, is rarely used. In addition to removing fluid, CRRT may offer immune benefit as demonstrated in a small study in children [109]. However, the optimal timing of the initiation and the dose of renal replacement therapy for these patients remains unclear.

Outcomes

The outcome for SCT patients developing kidney injury and requiring renal replacement therapy is poor. Data from the pediatric renal replacement therapy registry suggested a 45 % survival rate to intensive care discharge for these children; however, survival was markedly lower for patients requiring mechanical ventilation and those with multiple organ failure [208]. In another recent report, the need for continuous renal replacement therapy was associated with a poor long-term survival as only a single patient survived more than 6 months [225].

Neurologic Complications Following Hematopoietic Stem Cell Transplantation

Neurologic complications following SCT occur in up to 15 % of children [226–228]. Clinically, patients may present with seizures, altered mental status, visual abnormalities, ataxia, cranial nerve palsies, parasthesias, and paresis. A thorough approach including a detailed history and physical exam

assessing the state of immune reconstitution (for both bleeding and infection risk), the history of the primary disease including the risk of central nervous system (CNS) relapse, and the use of neurotoxic medications is necessary when evaluating these patients. The common causes of neurologic complications are toxicity from medications to prevent graft versus host disease (specifically calcineurin inhibitors), metabolic toxicity (including electrolyte abnormalities such as hypomagnesemia), irradiation and chemotherapy toxicity, CNS infections, cerebrovascular accidents (especially hemorrhage related to coagulation abnormalities including thrombocytopenia), hypertension, and rarely, immune-mediated encephalopathy. Risk factors for neurotoxicity include total body irradiation, GVHD >Grade 2, and GVHD prophylaxis with cyclosporine [226]. The most common complication reported with allogeneic transplantation is drug toxicity especially related to cyclosporine, although other drugs including tacrolimus have been implicated [226, 227, 229–234]. Of note, patients with CNS toxicity from calcineurin inhibitors may not have drug levels in the toxic range [231].

In addition to the appropriate laboratory evaluation and discontinuation of neurotoxic medications, CNS imaging in the form of a computerized tomogram is indicated. Magnetic resonance imaging (MRI) may be preferred; however, it may not always be available in a timely manner. While imaging may reveal a focal finding such as a CNS hemorrhage, imaging findings may be completely normal in the setting of metabolic and drug toxicity. However, in a substantial percentage of patients with drug toxicity, especially secondary to cyclosporine, imaging findings are consistent with posterior reversible encephalopathy syndrome (PRES). PRES is a clinical syndrome characterized by headache, seizures, visual abnormalities, encephalopathy, and less frequently, focal neurologic deficits. As the name suggests, this disorder is most often reversible with discontinuation of the offending drug; however, this recovery may take weeks. Classic findings on MRI include hyperintensity of the subcortical and cortical regions in the parieto-occipital regions on T2-weighted and FLAIR images (see Fig. 27.7) [235]. Paramount in the treatment of PRES is the discontinuation of the offending agent; an alternate agent may be used including a different calcineurin inhibitor. Although hypertension is not present in all patients, calcineurin inhibitors themselves can cause hypertension, and aggressive blood pressure control is indicated in the supportive care of PRES [235–237].

Conclusion

The field of hematopoietic stem cell transplantation continues to move forward with expanding indications, utilization of better matching techniques and newer drug therapies to treat complications associated with SCT. Despite this, a proportion of SCT patients develop complications and need critical care. Notably, organ failure in

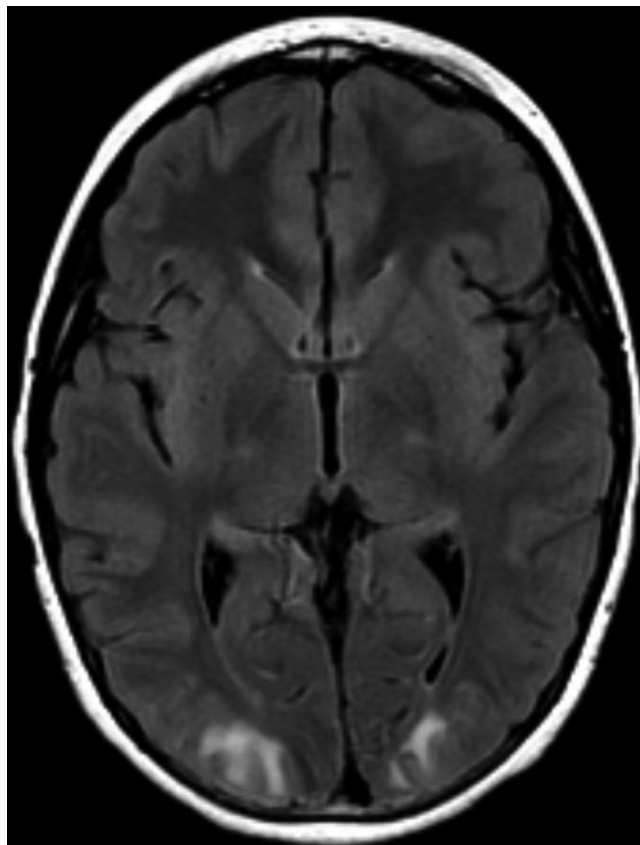


Fig. 27.7 Brain MRI from stem cell transplant recipient with posterior reversible encephalopathy syndrome (PRES). Axial FLAIR image with bilateral symmetric abnormal signal in the occipital subcortical white matter and cortex demonstrating characteristic changes for PRES (Courtesy of Dr. Marcia K Kukreja, MD, Department of Radiology and Medical Imaging, Cincinnati Children’s Hospital Medical Center, Cincinnati OH)

these patients is associated with an immune system that is dysfunctional, making the clinical course of an otherwise uncomplicated disease processes tenuous. Although critical care outcomes for these patients are improving, this cohort of patients continues to have an unacceptably high morbidity and mortality. Hence, it is important for critical care physicians to familiarize themselves with the unique complications and care needs of these patients and manage them closely in conjunction with the transplant service. Given the complexity of the disease processes and the ever increasing arsenal of therapeutic strategies, a multidisciplinary approach to their care is essential.

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