ICU Complications of Hematopoietic Stem Cell Transplant, Including Graft vs Host Disease

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Case Presentation

A 44 year-old woman with a history of acute myeloid leukemia (AML) underwent a non-myeloablative haploidentical peripheral blood hematopoietic stem cell transplant (HSCT) 10 days ago. She was admitted to the hospital with fevers to 39 °C. On examination, she is anxious-appearing, with a temperature of 38.9 °C, a heart rate of 120 beats/min, a respiratory rate of 28 breaths/min, a blood pressure of 98/64 mmHg, and an oxygen saturation of 94% on 4 L/min oxygen via nasal cannula. A tunneled central venous catheter is in situ in her right internal jugular vein. Her total white blood cell (WBC) count is <0.5 cells/mm³ and platelet count is 8000 cells/mm³. A chest CT scan shows diffuse patchy bilateral infiltrates (Figure). She is started on empiric antibiotic coverage with piperacillin/tazobactam, and 3 L of crystalloid are administered. Several hours later, she is more hypotensive, with nadir systolic pressures of 80–88 mmHg, and is more hypoxic, now saturating 85% on 6 L/min nasal cannula oxygen.

Question

How should this patient be managed?

Answer Broad spectrum antibiotics and lung-protective respiratory support.

All patients after HSCT are immunosuppressed, profoundly so in the early post-transplant period before engraftment has occurred. This patient is likely to have a pneumonia with secondary septic shock, but a central line-associated infection from her tunneled central line is possible, as are

non-infectious complications of HSCT. Respiratory failure is the most frequent cause of intensive care unit (ICU) admission after HSCT, most frequently from an infectious cause. The patient was placed on high-flow nasal cannula (HFNC) for oxygenation support and started on a norepinephrine infusion for hemodynamic support. Antibacterial coverage was changed to meropenem, levofloxacin, and vancomycin, and voriconazole was added for antifungal coverage. Her central line was removed. Her respiratory status continued to decline, and endotracheal intubation and mechanical ventilation were required 24 h after admission. She was placed on volume assist-control with a tidal volume of 6 mL/kg predicted body weight, and bronchoscopy with bronchoalveolar lavage (BAL) was performed. The BAL fluid was initially bloody, but cleared with sequential aliquots. Microbiologic studies of the BAL fluid were positive for respiratory syncytial virus and *Pseudomonas aeruginosa*. She was maintained on low tidal-volume ventilation and vasopressors were weaned off. Her white blood cell count slowly began to recover, and her respiratory status began to improve. She was extubated on hospital day 12 and was discharged from the ICU on hospital day 14.

Principles of Management

Hematopoietic stem cell transplant (HSCT) has become an essential therapeutic modality in the treatment of malignant and non-malignant hematologic disease. In 2016, more than 23,000 HSCTs were performed in the United States, including approximately 15,000 autologous HSCTs and more than 8500 allogeneic transplants [1]. Allogeneic transplants are associated with more morbidity and mortality than autologous transplants, and are further categorized based on conditioning regimen (myeloablative [MA] vs non-myeloablative [NMA]), donor-recipient relation (related vs unrelated), HLA matching (full match vs haploidentical vs mismatched), and stem cell source (bone marrow, peripheral blood,

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umbilical cord blood). In general, NMA regimens are associated with less peri-transplant morbidity and mortality than fully ablative transplants. In both MA and NMA transplants, the cytotoxic conditioning regimen required in HSCT rapidly induces neutropenia by injuring hematopoietic precursor cells within the bone marrow [2, 3]. Neutropenia persists until donor cell engraftment or bone marrow recovery. The period of aplasia and neutropenia places the HSCT patient at high risk for infectious complications. In addition to the lack of immune cells, the mucosal barrier of the intestinal tract is disrupted by chemotherapy, creating portals through which enteric pathogens can enter the bloodstream [4–6]. The respiratory system is also more susceptible to infection, with qualitative and quantitative dysfunction of alveolar macrophages, lymphocytes, and neutrophils [7–9]. Even after the marrow and mucosal surfaces have recovered, the immunological consequences of HSCT can cause further complications requiring critical care. Refinement of transplant techniques over the last 2 decades has dramatically decreased transplant-related mortality, but approximately 15% of HSCT patients require critical care [10] and earlier ICU admission has been associated with improved survival rates [11, 12]. Still, ICU mortality in allogeneic HSCT patients remains approximately 50% [13].

Early Complications of Hematopoietic Stem Cell Transplant

The early complications of HSCT (day 30–100) are predominantly infectious in nature, and patients typically present to the ICU with septic shock or respiratory failure. The latter is the most common reason for ICU admission after HSCT [10]. Non-infectious complications also occur, and can involve nearly any organ system.

Neutropenic Fever and Neutropenic Sepsis

Neutropenic fever, defined as any fever higher than 38.3 °C or a sustained fever greater than 38.0 °C for more than 1 h with an absolute neutrophil count (ANC) less than 1500 cells/mm³, occurs in more than 80% of patients undergoing HSCT [14, 15]. No organism is identified in about 50% of neutropenic fevers [14, 15]. Bacteremia is documented in up to 25% of patients. Gram-positive bacteria are most commonly isolated [14, 16] (Table 80.1), while Gram-negative infections confer a higher mortality risk [17]. Fungal infections, particularly *Candida* and *Aspergillus* species, are frequent, especially in prolonged or profound neutropenia [15]. Approximately 10% of allogeneic HSCT patients will develop severe sepsis during the engraftment period [18], and mortality is approximately 50% in those who go on to develop septic shock [11,

Table 80.1 Typical pathogens and origins during bacterial sepsis in neutropenic patients [Adapted from [21] (Springer)]

Origin	Frequent pathogens
Unknown	<i>Coagulase-negative Staphylococci</i> , <i>Escherichia coli</i> , <i>Enterococcus</i> species
Lung	<i>Pseudomonas aeruginosa</i> , <i>Streptococcus pneumoniae</i> , <i>Viridans streptococci</i> , <i>Acinetobacter</i> species
Abdomen	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Clostridium</i> species, <i>Enterococcus</i> species, <i>Klebsiella</i> species
Urogenital	<i>Escherichia coli</i> , <i>Pseudomonas aeruginosa</i> , <i>Klebsiella</i> species
Soft tissue	<i>Staphylococcus aureus</i> , alpha-hemolytic <i>streptococci</i>
Central venous catheter	<i>Coagulase-negative Staphylococci</i> , <i>Corynebacteria</i> , <i>propionibacterium</i> species, <i>Candida albicans</i> , <i>Candida tropicalis</i> , <i>Candida parapsilosis</i> , <i>Stenotrophomonas maltophilia</i>

19, 20]. Mortality predictors include concomitant graft-vs-host disease (GVHD), respiratory failure, positive blood cultures, and multi-organ failure [18, 20].

Neutropenic fever and sepsis are medical emergencies, and appropriate empiric antibiotics must be started without delay: ideally within 60 min of presentation [14, 15, 21] and potentially within 30 min [22]. Empiric antibiotics must cover common organisms and should be tailored to patient-specific culture data and institutional epidemiology [14, 15]. Appropriate empiric antibiotics include an anti-pseudomonal penicillin or cephalosporin (e.g. piperacillin/tazobactam or cefepime, respectively), or a carbapenem [14, 15]. Vancomycin is not routinely indicated but should be added in the presence of a suspected catheter-related infection, soft tissue infection, oral mucositis, pneumonia, known colonization with resistant gram-positive organisms, or hemodynamic instability [14, 15, 21]. Aminoglycosides should not be added to an anti-pseudomonal beta-lactam unless required by allergies, resistant organisms, or refractory hemodynamic instability [14, 21, 23–25]. Fluoroquinolones, which are frequently used as prophylaxis in HSCT patients, should not be used as empiric monotherapy due to the likelihood of resistance.

In hemodynamically unstable patients, anti-pseudomonal beta-lactams should be escalated to a carbapenem and consideration should be given to the addition of an aminoglycoside or aztreonam [14, 15, 21, 23]. Vancomycin should be added if not already part of the regimen, and anti-fungals with activity against yeasts and molds (e.g. liposomal amphotericin, caspofungin, or voriconazole) should be strongly considered in all unstable patients [14, 15, 26, 27].

Identification of infectious organisms and control of infectious sources are essential to optimize outcomes but the infectious workup should not delay antibiotic administration. Blood cultures and respiratory cultures should be obtained and sinus, head, chest, and abdominal imaging performed as indicated [14, 15]. Abdominal pain or diarrhea

associated with fever suggests neutropenic enterocolitis (typhlitis) which can lead to intestinal necrosis [28, 29]. In the hemodynamically unstable patient with a central venous catheter, early catheter removal is associated with improved survival [19]; infected or potentially infected catheters should be removed without delay.

Respiratory Failure

Acute respiratory failure and acute respiratory distress syndrome (ARDS) are major problems after HSCT [30, 31]. Data from the 1990s indicated that 40–60% of patients undergoing HSCT experience a respiratory complication [32]. More recent data suggest that more than 15% of patients undergoing allogeneic transplant develop ARDS with a mortality rate of 50–70% [33, 34]. Most cases of respiratory failure and ARDS after HSCT are related to infection, either a primary pulmonary infection or sepsis [35]. Common pulmonary infections and associated risk factors are shown in Table 80.2. Respiratory viral infection is common after

HSCT [36, 37], and is associated with significant mortality, especially with progression to lower respiratory tract infection [38–40]. In some cases, antiviral therapy with agents such as oseltamivir (influenza) or ribavirin (respiratory syncytial virus) is indicated [41]. Bacterial pneumonias are also common and may occur as a co-infection or secondary infection with a respiratory virus. Fungal and other opportunistic infections such as *Pneumocystis jirovecii* must also be considered [42]. As in immunocompetent patients, treatment of ARDS centers on treatment of the underlying cause while providing supportive care with low tidal volume mechanical ventilation. Neuromuscular blockade and prone positioning should be considered in patients with an arterial PO_2 : $FiO_2 \leq 150$ mmHg [43–45].

Non-invasive ventilation (NIV) is frequently used as first-line respiratory support in HSCT patients [46]. However, early studies which showed a mortality benefit in immunosuppressed patients with using NIV compared to invasive mechanical ventilation were limited by relatively few numbers of HSCT patients and extremely high mortality in the control groups [47, 48]. It is nearly impossible to control delivered tidal volume with NIV and high delivered non-invasive tidal volumes are linked to higher rates of NIV failure [49]. More recent data suggest that NIV may not be beneficial in HSCT patients and heated humidified high-flow oxygen may be a better option [30, 49–53].

Chest computed tomography (CT) scanning should be performed in all patients with respiratory symptoms [15]. The presence of respiratory failure, respiratory symptoms, or abnormalities on chest imaging should prompt evaluation for a respiratory infection. In many cases a non-invasive evaluation is appropriate, but bronchoscopy may be indicated in some patients [48, 54, 55], and bronchoscopic findings that lead to a change in management are associated with improved outcomes [55].

Two specific forms of respiratory failure after HSCT warrant special mention: diffuse alveolar hemorrhage and idiopathic pneumonia syndrome. Diffuse alveolar hemorrhage (DAH) occurs in up to 12% of patients and is associated with poor outcomes [56, 57]. Diagnosis is most commonly made by observation of progressively bloody aliquots of bronchoalveolar lavage. Steroids are the mainstay of treatment of DAH, with some evidence that efficacy is greatest at doses <250 mg/day of methylprednisolone equivalent [57]. Idiopathic pneumonia syndrome (IPS) is a form of non-infectious lung injury after HSCT and is clinically defined by diffuse alveolar injury when infection, cardiac dysfunction, renal failure, and volume overload have been excluded [58]. IPS can have many manifestations, including ARDS, pulmonary capillary leak, DAH, or cryptogenic organizing pneumonia. IPS is thought to affect up to 15% of patients after myeloablative allogeneic HSCT, and only ~2% of patients after non-myeloablative HSCT. Median time of onset of IPS

Table 80.2 Common pulmonary infections after HSCT

Infection	Common pathogens	Risk factors for occurrence and severity	Reference
Bacterial	<i>Streptococcus pneumoniae</i> <i>Streptococcus viridans</i> <i>Staphylococcus aureus</i> <i>Pseudomonas aeruginosa</i> <i>Acinetobacter</i> <i>Stenotrophomonas maltophilia</i> <i>Nocardia asteroides</i>	Neutropenia Oral mucositis Aspiration Antecedent viral pneumonia	[35]
Viral	Influenza Adenovirus Respiratory syncytial virus Parainfluenza Human metapneumovirus Cytomegalovirus	Neutropenia Lymphopenia Allogeneic transplant Bone marrow graft source Steroid therapy Infection pre-engraftment Presence of co-pathogens Older age GVHD	[35, 37–39]
Fungal	<i>Aspergillus</i> species <i>Pneumocystis jirovecii</i> Mucorales (e.g. <i>Rhizopus</i> , <i>Mucor</i>) <i>Fusarium</i> species <i>Histoplasma capsulatum</i> <i>Coccidioides immitis</i> <i>Blastomyces dermatitidis</i>	Prolonged neutropenia Lymphopenia Steroids GVHD Geographic exposure Residential exposure	[35, 42]

is 19 days after HSCT and mortality ranges from 60–80% in all patients, with nearly 100% mortality if mechanical ventilation is required [58]. Though the pathophysiology of IPS is incompletely understood, research indicating a pathogenic role for TNF- α has led to the use of the anti-TNF- α antibody etanercept to treat IPS, with mixed clinical results [59–62]. The single randomized placebo-controlled trial in adults included only 34 patients and showed no benefit to etanercept when added to steroids (methylprednisolone 2 mg/kg/day) [63].

Neurologic Complications

Neurologic complications are frequently encountered after HSCT [64]. Intracerebral hemorrhages are a constant threat in thrombocytopenic patients. Infections of the central nervous system (CNS), including viral, bacterial, and fungal, can occur, and may require modification of antibiotic regimens to ensure CNS penetration. Seizures and generalized encephalopathy can occur, often with cryptic causes. Posterior reversible encephalopathy syndrome (PRES) is increasingly recognized, especially in patients receiving tacrolimus-based GVHD prophylaxis. Any of these complications may be life-threatening, and close collaboration with neurology and neurocritical care specialists may be required.

Acute Kidney Injury

Acute kidney injury (AKI) is common after HSCT and affects up to 40% of patients, with higher incidence after allogeneic transplant than autologous transplant [65, 66]. In addition to the usual ICU causes of AKI such as septic shock, there are many specific contributors to the risk of AKI in HSCT, including preparative chemotherapeutic regimens, nephrotoxins (e.g. tacrolimus, cyclosporine, antimicrobials), elevated cytokine levels, GVHD, and hepatic sinusoidal obstruction [65]. Hemorrhagic cystitis arising from chemotherapy toxicity or viral infection can cause significant blood loss and obstructive nephropathy due to blood clots. Management of AKI primarily consists of limiting exposure to nephrotoxins (if able) and maintaining adequate hemodynamics. If hemorrhagic cystitis is present, continuous bladder irrigation with a three-way catheter should be considered. The requirement for renal replacement therapy is ominous and portends a high mortality rate [65].

Hepatic Veno-Occlusive Disease

Hepatic veno-occlusive disease (VOD), also known as sinusoidal obstruction syndrome, primarily occurs after

myeloablative HSCT, but can occur after a non-myeloablative transplant [67]. VOD is thought to be caused by damage to the hepatic endothelium and leads to obliteration of hepatic sinusoids and hepatocyte necrosis. Incidence of VOD is thought to be approximately 14%, though estimates vary. Diagnosis is based on clinical findings (table) including hepatomegaly, elevated bilirubin ascites, and weight gain [68]. There are limited therapeutic options for VOD, and the prognosis is poor.

Acute Graft-Versus-Host Disease

A major complication of allogeneic HSCT is graft-versus-host disease (GVHD), which is divided into acute and chronic forms. Acute GVHD is a major contributor to peri-transplant morbidity and mortality, and is caused by donor-origin T-cells recognizing recipient tissues as foreign and instigating an immune response against the transplant recipient [69]. Acute GVHD generally occurs within the first 100 days after transplant and can affect the skin, mucosa, intestinal tract, and liver. Grading is based on severity of clinical manifestations, which include skin erythema or maculopapular rash; nausea, emesis, or diarrhea, and elevated bilirubin levels (Fig. 80.1, Table 80.3) [69–72]. Acute GVHD can progress to frank epidermal desquamation, massive diarrhea and hematochezia, and fulminant liver failure, respectively. Severe skin acute GVHD behaves much like a burn injury, and the expertise of a burn center may be required. Corticosteroids are the mainstay of treatment for acute GVHD, and the prognosis of steroid-refractory disease is poor [69, 73]. Prophylaxis against GVHD is an essential part of allogeneic transplant regimens and includes a variety of modalities, including calcineurin inhibitors, anti-metabolites, and post-transplant cyclophosphamide [74]. As GVHD prophylaxis has improved, more patients are presenting with Grade II or Grade III acute GVHD (and fewer are presenting with Grade IV acute GVHD), the incidence of hepatic acute GVHD is decreasing, and overall mortality from acute GVHD is decreasing in patients treated with tacrolimus-based GVHD prophylaxis [73].

Chronic Graft vs Host Disease

Chronic GVHD is the major cause of non-relapse-related mortality after HSCT [75]. Despite its name, chronic GVHD is defined clinically, rather than by time after transplant, and can present at any time during the transplant course. By 2 years after transplant, up to 30–70% of patients will have some manifestation of chronic GVHD [76–78]. Though the biology of chronic GVHD is complex and incompletely understood, clinically it mimics

Fig. 80.1 Cutaneous Manifestations of Acute Graft-Versus-Host Disease. From [72], with permission. (a) Palmar erythema with microvesicles. (b) Morbilliform lesions on thighs. (c) Confluent ery-

thema with scale mimicking staphylococcal scalded skin syndrome. (d) Erythema with sheet-like desquamation mimicking toxic epidermal necrolysis

autoimmune disease [75]. While diagnostic criteria include effects on the skin, oral mucosa, eyes, liver, GI tract, joints, genitals, and lungs, chronic GVHD can affect almost any organ system and is staged according to severity of organ involvement [78]. Selected manifestations and diagnostic criteria are in Table 80.4. Of the manifestations of chronic GVHD, the most relevant to the ICU physician is pulmonary chronic GVHD.

Pulmonary Chronic GVHD

The only recognized manifestation of chronic pulmonary GVHD is bronchiolitis obliterans syndrome (BOS), which is diagnosed by documentation of the new onset of an obstructive ventilator defect (FEV_1 : $FVC < 0.7$ and $FEV_1 < 75\%$ predicted) and air trapping (documented by expiratory CT scan or pulmonary function tests) in the absence of an explanatory pulmonary infection [78]. BOS results from

Table 80.3 Manifestations and grading of acute graft-vs-host disease

Organ site	Manifestation	Grading
Skin	Erythema	Stage 0: No rash
	Maculopapular rash	Stage 1: Maculopapular rash, < 25% BSA
	Blisters/ulceration	Stage 2: Maculopapular rash, 25–50% BSA
	Desquamation	Stage 3: Maculopapular rash, >50% BSA Stage 4: Erythroedema (>50%) + bullae and Desquamation >5% BSA
Gastrointestinal tract	Anorexia	Stage 0: No nausea, vomiting, anorexia;
	Nausea, vomiting	Diarrhea <500 mL/day
	Diarrhea	Stage 1: Persistent nausea, vomiting, anorexia;
	Abdominal pain	Diarrhea 500–999 mL/day
	Ileus	Stage 2: Diarrhea 1000–1500 mL/day
	Bloody diarrhea	Stage 3: Diarrhea >1500 mL/day
		Stage 4: Severe pain or grossly bloody stool
Liver	Elevated bilirubin	Stage 0: Bilirubin <2 mg/dL
	Cholestasis	Stage 1: Bilirubin 2–3 mg/dL
		Stage 2: Bilirubin 3.1–6 mg/dL
		Stage 3: Bilirubin 6.1–15 mg/dL Stage 4: Bilirubin >15 mg/dL

BSA body surface area; Refs: [69–71]

peribronchiolar fibrosis and obliteration of small airways resulting in the characteristic obstructive physiology [75]. Interstitial and subpleural fibrosis may also occur, resulting in concomitant restrictive physiology. BOS occurs in approximately 3–5% of all patients after allogeneic HSCT, and 14% of those with chronic GVHD, but is likely underdiagnosed [76, 79, 80]. Inhaled corticosteroids appear efficacious in improving FEV₁ in established BOS [81]. Systemic steroids are also commonly used to treat BOS and most patients are maintained on anti-GVHD immunosuppression with tacrolimus, sirolimus, or a calcineurin inhibitor [76]. The combination of inhaled fluticasone, azithromycin, and montelukast (FAM) appears to slow the decline in lung function with BOS [82] but has not yet been proven in a randomized controlled trial. While FAM is standard therapy for established BOS, recent data argue strongly against using azithromycin as prophylaxis against BOS due to decreased survival due to a higher rate of hematologic relapse [83]. Though FAM has been shown to decrease the progression of BOS, mortality due to progressive lung disease remains high, and patients typically present to the ICU with respiratory failure. Unfortunately, with end-stage BOS, there are no effective therapeutic options. A select few patients may be eligible for consideration for lung transplantation, but this is unusual,

Table 80.4 Typical manifestations and grading of chronic graft-vs-host disease [78]

Organ site	Manifestations	Grading
Skin	Poikiloderma ^a	Score 0: No skin involvement
	Lichen planus-like changes ^a	Score 1: 1–18% BSA
	Dermatosclerosis ^a	Score 2: 19–50% BSA; superficial sclerosis
	Erythema	Score 3: > 50% BSA; deep sclerosis, ulceration, impaired mobility
	Maculopapular rash	
	Depigmentation	
	Papulosquamous lesions	
	Hair loss	
Oral mucosa	Lichen planus-like changes ^a	Score 0: No oral symptoms
	Gingivitis	Score 1: No limitation on oral intake
	Mucositis	Score 2: Partial limitation on oral intake
	Erythema	Score 3: Major limitation on oral intake
	Pain	
	Oral ulcers	
	Xerostomia	
	Pseudomembranes	
Eyes	Keratoconjunctivitis sicca	Score 0: No symptoms
		Score 1: No effect on ADL
		Score 2: Moderate effect on ADL, no vision impairment
		Score 3: Significant effect on ADL, or loss of vision
GI tract	Esophageal web ^a	Score 0: No symptoms, normal bilirubin, normal ALT, normal Alk Phos
	Esophageal strictures ^a	Score 1: No weight loss, normal bilirubin, ALT 3–5x ULN, Alk Phos >3x ULN
	Anorexia	Score 2: Weight loss (5–15%), moderate diarrhea, bilirubin <3 mg/dL, ALT >5x ULN
	Nausea/vomiting	Score 3: Weight loss >15% or need for esophageal dilation or severe diarrhea or bilirubin >3 mg/dL
	Diarrhea	
Lungs	Elevated bilirubin/ALT/Alk Phos	
	Bronchiolitis obliterans (BOS) ^a	Score 0: No symptoms, FEV ₁ ≥ 80%
	Cryptogenic organizing pneumonia (COP)	Score 1: Mild symptoms; FEV ₁ 60–79%
	Restrictive lung disease	Score 2: Moderate symptoms; FEV ₁ 40–59%
	Bronchiectasis	Score 3: Short of breath at rest, O ₂ requirement, FEV ₁ ≤ 39%

Table 80.4 (continued)

Organ site	Manifestations	Grading
Connective tissue	Fasciitis ^a Joint stiffness/contractures ^a Myositis Arthralgias Muscle cramps	Score 0: No symptoms Score 1: Mild tightness/decreased ROM Score 2: Moderate decrease ROM, moderate limitation of ADL Score 3: Significantly decreased ROM; significant limitation of ADL
Hematopoietic	Cytopenias Eosinophilia Autoantibodies Immunoglobulin deficiency	N/A
Miscellaneous	Reynaud's phenomenon Pericardial/pleural effusions Ascites Peripheral neuropathy Nephrotic syndrome Cardiac conduction disturbance	N/A

^aDiagnostic of chronic GVHD; *BSA* body surface area, *ADL* activities of daily living, *ALT* alanine aminotransferase, *Alk Phos* alkaline phosphatase, *ULN* upper limit of normal, *ROM* range of motion

and in most cases goals of care should be addressed prior to aggressive ICU interventions.

Evidence Contour

HSCT is increasing in volume and importance as a therapeutic modality, and the volumes of HSCT patients requiring critical care is accordingly continuing to increase. There is good reason to think that the pathogenesis of critical illness is substantially different in the immunosuppressed HSCT patient. Yet our understanding of critical illness in this population is limited, and many practices are extrapolated from the general critical care population without direct evidence in the HSCT population. In response to this, research agendas for critically ill hematology and oncology patients have been proposed [48].

Biology of Neutropenic Sepsis and Respiratory Failure

Neutropenic sepsis is typically thought of as an uncontrolled variant of non-neutropenic sepsis. However, the real picture is likely much more complicated, and neutropenic sepsis and respiratory failure may be very different from their non-neutropenic counterparts. Even the phrase “neutropenic sepsis” is a misnomer, as the HSCT myeloablative regimens also result in pancytopenia. Leukopenia, including neutropenia, lymphopenia, and monocytopenia, dramatically changes not only the acute response to infection, but the regulation of the adaptive immune response and the resolution and repair of injury [3, 7, 8, 84–90]. Platelets are increasingly recognized to play a vital role in the defense against bacterial, viral, and fungal infections, and like leukocytes, are integral

to the development and resolution of organ failure [91–95]. Not surprisingly, thrombocytopenia is associated with poor outcomes in critical illness [96]. Taken together, these data strongly support the notion that common critical care conditions, such as sepsis and respiratory failure, may differ dramatically in HSCT patients compared to “normal” patients. Encouragingly, survival in neutropenic sepsis appears to be improving, but still lags that of non-neutropenic patients [12, 19, 48], and more research is needed.

Resistant and Multi-Drug Resistant Organisms

Drug-resistant and multi-drug resistant (MDR) organisms are an increasing problem in HSCT patients, and the situation shows no sign of improving [16, 97, 98]. Vancomycin-resistant enterococcus (VRE) bacteremia affects up to 35% of patients after HSCT and is associated with poor outcomes [99–101]. Similarly, MDR gram negative infections, particularly carbapenem-resistant Enterobacteriaceae (CRE), are associated with high mortality rates in allogeneic HSCT patients [102]. Successful treatment CRE infections is challenging, and requires early use of multi-drug antibiotic regimens, typically including aminoglycosides, carbapenems, and polymyxins. However, none of the available regimens are particularly effective, and new antimicrobials are desperately needed.

Thrombotic Microangiopathy

An increasingly recognized complication of HSCT is HSCT-associated thrombotic microangiopathy (HSCT-TMA) [103], which has some features in common with better-known microangiopathic processes such as thrombotic

thrombocytopenic purpura and atypical hemolytic uremic syndrome. HSCT-TMA occurs in a large number of patients post allogeneic HSCT (up to 20–40%) and appears to be the result of endothelial injury and complement activation. Most occurrences are within the first 100 days after transplant. Patients can present to the ICU with acute kidney injury and neurologic changes in addition to hemolytic anemia and thrombocytopenia [65, 104]. Management is predominantly supportive, with blood pressure control, cessation of any possible pharmacologic instigators (tacrolimus or cyclosporine), and renal replacement therapy playing major roles. Recent case reports have suggested a possible role in some patients for the anti-CD20 antibody rituximab or the anti-complement antibody eculizumab, though neither of these agents has been definitively proven effective [104].

Cytokine Release Syndrome and Emerging Toxicities of Transplant

As noted above, advances in transplant techniques have allowed the increased use of alternative donors, including related haploidentical donors [105–107]. Similarly, peripheral blood stem cells (PBSC) are increasingly used for transplant instead of bone marrow stem cells [108]. However, the use of peripheral blood results in a larger number of donor T-cells included in the transplanted stem cells. This higher T-cell dose can result in a profound syndrome of fevers, vascular permeability, hemodynamic instability, acute kidney injury, and respiratory failure. This constellation of findings is associated with elevated levels of inflammatory cytokines and has accordingly been labeled as cytokine release syndrome (CRS). While most associated with chimeric antigen receptor (CAR) T-cell therapy [109], CRS is increasing recognized after PBSC transplant and is associated with poor outcomes [110]. Emerging data suggest that anti-IL-6 therapy with tocilizumab may improve outcomes, but more research is needed [110].

Organization of Critical Care: Need for Specialty Hematopoietic Stem Cell Transplant ICUs?

HSCT continues to grow as a therapeutic modality and the pool of both potential donors and recipients continues to increase. As HSCT volumes increase and the complexity and potential toxicity of HSCT regimens expands, the number of critically ill HSCT patients will increase [48]. In response to this growing ICU volume, some centers continue to admit HSCT patients to general ICUs, but many high-volume transplant centers have developed specialty HSCT ICUs. While specialty HSCT ICUs have a number of potential

benefits, there are few data to support (or dissuade) their development. Development of best practices for the provision of critical care to HSCT patients, including the optimum ICU organization is an important area for study [48]. Great progress in the critical care of HSCT patients has been made, but with continued basic and clinical research and further development of the sub-specialty of oncologic critical care, outcomes for critically ill HSCT patients should continue to improve.

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