Critical Care of the Hematopoietic Stem Cell Transplant Recipient

Bekele Afessa, MDa,*, Elie Azoulay, MD, PhDb

KEYWORDS
- Bone marrow transplantation
- Intensive care units
- Mechanical ventilation
- Mortality
- Multiple organ failure
- Prognosis

An estimated 50,000 to 60,000 patients undergo hematopoietic stem cell transplantation (HSCT) worldwide annually. Peripheral blood is the source of more than 95% of autologous transplantation in adults. The most common indications for HSCT are multiple myeloma and lymphoma, accounting for 56%. Multiple myeloma and acute leukemia are the most common indications for autologous and allogeneic transplantation, respectively. Among adults, 44% of allogeneic transplants are from unrelated donors, and bone marrow accounted for 28% of unrelated donor transplants between 2003 and 2006 compared with 66% between 1999 and 2000. Very few adults receive umbilical-cord-blood transplants.

Because their innate and acquired immune systems are impaired, HSCT recipients frequently have infectious and noninfectious complications. The post-transplant recovery of the immune system depends on the underlying disorder, conditioning regimen, stem cell source, and on complications, such as graft-versus-host disease (GVHD). The post-transplant complications follow characteristic time patterns. The pretransplant conditioning regimen virtually eliminates all preexisting innate and acquired immunity. After HSCT, the immune system recovers along predictable patterns depending on the underlying disorder, stem cell source, and complications such as GVHD. Recovery occurs faster in autologous recipients, in those who receive peripheral blood stem cell grafts, and after nonmyeloablative conditioning regimen.

The post-transplant period is divided into 3 phases: pre-engraftment, early post-transplant, and late post-transplant. The pre-engraftment phase (0 to 30 days) is
characterized by neutropenia and breaks in the mucocutaneous barriers. During this phase, the most prevalent pathogens are bacteria and *Candida* species and, if neutropenia persists, *Aspergillus* species. During the period of neutropenia, there is no significant difference in the type of infection between allogeneic and autologous HSCT recipients. The early post-engraftment phase (30 to 100 days) is dominated by impaired cell-mediated immunity. The effect of this cell-mediated defect is determined by the development of GVHD and the immunosuppressant medications used to treat it. *Cytomegalovirus* (CMV), *Pneumocystis jiroveci* and *Aspergillus* species are the predominant pathogens during this phase. The late post-transplant phase (>100 days) is characterized by defects in cell-mediated and humoral immunity and in function of the reticuloendothelial system in allogeneic transplant recipients. During this phase, allogeneic HSCT recipients are at risk of viral infection and infection by encapsulated bacteria such as *Haemophilus influenzae* and *Streptococcus pneumoniae*. In endemic areas of the world, pulmonary tuberculosis occurs during the late post-transplant phase. After neutrophil engraftment, infections occur more frequently in allogeneic HSCT recipients.3

Some of the post-transplant complications may be life-threatening and require treatment in the intensive care unit (ICU). A recent publication has provided an excellent review of the critical care outcome of adult and pediatric HSCT recipients.4 This article reviews the critical care support of adult HSCT recipients.

### RATE AND REASONS OF ICU ADMISSION

The reported numbers of HSCT recipients admitted to the ICU range from less than 5% to more than 55%, with an overall rate of 15.7%.5–15 In the studies of patients treated before 1995,5–7,12,14,16 272 of 1412 HSCT recipients (19.3%) were admitted to the ICU compared with 371 of 3037 patients (12.2%) after 19959,11,15,17,18 (P<.001). In one study that included only autologous HSCT recipients, less than 6% of them were admitted to the ICU.15 In the only study of adult umbilical-cord–blood recipients, 57% of them were admitted to the ICU.11

The most common reason for ICU admission is respiratory (Box 1).5–8,10,11,18,19 Among 844 HSCT recipients admitted to the ICU, the primary reason for admission was respiratory in 492 (58.3%).6–8,12,14,15,17–21 Pneumonia and sepsis-induced acute lung injury (ALI)/ARDS are common causes of hypoxemic respiratory failure in HSCT recipients.22 Airway compromise due to mucositis may also lead to ICU admission during the pre-engraftment period.7,8,21 Several noninfectious pulmonary complications can lead to respiratory failure in HSCT patients leading to ICU admission. Among these complications, pulmonary edema, DAH, and PERDS usually occur during the first 30 days following transplant and IPS can occur at any time following transplant.23–25

Hemodynamic instability in HSCT recipients can be precipitated by hypovolemia and sepsis. Poor oral intake associated with mucositis and gastrointestinal bleeding associated with mucositis and thrombocytopenia can lead to hypovolemic shock with multiple organ dysfunction requiring ICU admission. Autologous and allogeneic HSCT recipients are at increased risk of sepsis during the neutropenic, pre-engraftment period. In allogeneic HSCT recipients, GVHD and its treatment lead to prolonged immunodeficiency with additional risk of sepsis. Hemodynamic compromise secondary to sepsis was the primary reason for ICU admission in 101 of 548 HSCT recipients (18.4%) described in the literature.7,12,14,15,18–21 Some studies have described cardiac dysrhythmias to be the primary reason for admission to the ICU in 8% to 17% of HSCT recipients.18,19,21 Thrombocytopenia and GVHD predispose HSCT recipients to hemorrhagic complications.26 Intracranial bleeding is reported in
2% to 5% of HSCT recipients. In one autopsy study of 180 HSCT recipients, intracranial hemorrhage was found in 32%. Seizure and other central nervous manifestations are reported to be the primary reason for ICU admission in approximately 11% of HSCT recipients. Although hemostatic complications leading to bleeding and thromboembolic events are common in HSCT recipients, gastrointestinal bleeding has been reported to be the reason for ICU admission in only 15 of 326 (4.6%) patients. Neutropenic colitis and acute intestinal GVHD can lead to ICU admission for perforation and bleeding. Although acute renal failure is common in critically ill HSCT recipients, it is reported to be the primary reason for ICU admission in less than 5%.

ICU COURSE AND COMPLICATIONS

The ICU course of HSCT recipients is complicated with multiorgan dysfunction. Some of the organ dysfunctions occur at ICU admission whereas others develop during the ICU course. Single or multiorgan failure has been reported in 64% to 94% and multiorgan failure in 22% to 81% of HSCT recipients admitted to the ICU. However, because of variations in organ failure definitions and incomplete reports, it is difficult to determine specific organ failure rates. Respiratory failure is the most common organ failure and develops in most patients. Afessa and colleagues
reported ARDS in 62% of their patients. ARDS and interstitial pneumonia were the most common cause of death in the study by Jackson and colleagues.7 Naeem and colleagues11 reported acute renal failure in 20 (80%) and hepatic failure in 13 (52%) of their 25 umbilical blood transplant recipients admitted to the ICU. A similarly high rate of acute renal failure, in 43 of 57 HSCT recipients (73.7%), was reported by Letourneau and colleagues.10 However, other studies have reported these rates to be less than 20%.13,21

DIAGNOSTIC INTERVENTIONS

Various diagnostic and therapeutic procedures are performed in HSCT recipients admitted to the ICU. An earlier study had reported pulmonary artery catheterization to be performed in most HSCT recipients admitted to the ICU.5 There are limited randomized clinical trials aimed at defining the role of pulmonary artery catheterization in the critically ill. A review by the Cochrane Collaboration group showed pulmonary artery catheterization to have no effect on patient outcome, including mortality and length of stay.31 Most of the recent studies of critically ill HSCT recipients do not mention pulmonary artery catheterization or report a lower use rate.15 The authors believe that the pulmonary artery catheter use rate in the critically ill HSCT recipient may have declined since the 1996 publication of a retrospective study showing potential harm associated with it.32

The patient’s immune system dysfunction, post-transplant timing, epidemiologic history, noninvasively obtained microbiological and other laboratory values, and the pattern and rapidity of development of chest radiographic findings often help to narrow the differential diagnosis and initiate empiric therapy in the critically ill HSCT recipient presenting with pulmonary infiltrates. However, the atypical presentations of some common diagnoses, the occurrence of unusual diagnoses, the coexistence of multiple conditions responsible for the infiltrates, and the detrimental effect of missed diagnosis often lead to invasive diagnostic interventions, such as bronchoscopy, and rarely, surgical lung biopsy.33–38 Unfortunately, such invasive procedures are not without complications in the critically ill HSCT recipient. In a study by Jackson and colleagues,7 11 patients had invasive mechanical ventilation (MV) initiated following bronchoscopy or open lung biopsy and 9 of them died.

Recently, Azoulay and colleagues39 have described the role of diagnostic bronchoscopy in hematologic and oncology patients, including HSCT recipients with acute respiratory failure. In this observational, prospective, multicenter study, bronchoscopy provided the only conclusive result in 33.7% of the patients who underwent the procedure.39 However, the bronchoscopy was associated with respiratory deterioration in 22 of 45 (49%) patients who were not intubated during the procedure, leading to endotracheal intubation for MV support in 16 of them (36%). The noninvasive diagnostic strategies for evaluation of pulmonary conditions include blood cultures; serology for Aspergillus antigen; examination of spontaneously expectorated sputum for bacteria, Aspergillus, and other fungi; induced sputum for P jiroveci; urine antigen for Legionella pneumophila, and S pneumoniae; CMV circulating antigen; nasopharyngeal aspirations; and echocardiography.39 Azoulay and colleagues39 included 148 patients from 14 medical centers in their prospective, observational study; 141 (95.3%) had at least 1 noninvasive evaluation and 101 (68.2%) underwent bronchoscopy. The noninvasive diagnostic strategy led to 105 diagnoses in 94 (66.7%) patients and the bronchoscopy led to 58 diagnoses in 51 (50.5%) patients. Among the 148 diagnoses established in the study, 88 (60.3%) were made only by noninvasive tests, 41 (28.1%) only by bronchoscopy, and 17 (11.6%) by both types. There were no
statistically significant difference in mortality between the bronchoscopy and noninvasive groups. This study highlights that the diagnosis of pulmonary infiltrates in hematology and oncology patients, including HSCT recipients with acute respiratory failure, can be established by following a noninvasive strategy. However, bronchoscopy plays a complementary role in selected patients.

ORGAN SUPPORT

Almost all critically ill HSCT recipients develop single or multiorgan failure. Pancytopenia is an expected consequence of the conditioning regimen in HSCT recipients. Neutropenia is a major risk factor for bacterial and fungal infections. Despite prophylaxis, preemptive and therapeutic use of antibiotics, and administration of colony-stimulating factors, infections are common in neutropenic HSCT recipients. The rate of infection depends on the degree and duration of neutropenia. Some recommend that certain minimal criteria be met before the initiation of granulocyte transfusion: an absolute neutrophil count lower than 500/µL and infection unresponsiveness to antibiotic therapy for at least 48 hours.40 However, a retrospective, case-control feasibility study of candidates and recipients of HSCT showed no benefit associated with granulocyte transfusion.41 Similarly, a Cochrane meta-analysis of 8 randomized clinical trials concluded that the available evidence was insufficient to either support or refute the generalized use of granulocyte transfusion therapy in most neutropenic patients, including HSCT recipients.42

Moreover, granulocyte transfusion is associated with multiple complications including fever and chills, respiratory failure due to sequestration of cells in the pulmonary vasculature, transfusion-associated GVHD, human leukocyte antigen (HLA) alloimmunization, and infection. There are limited data to guide clinicians on when to transfuse platelets to HSCT recipients. In a retrospective study of HSCT recipients that excluded patients at high risk of bleeding, an increased risk of bleeding could be established only if the platelet count dropped to less than 13,000/µL.43 The American Society of Clinical Oncology clinical practice guidelines recommend a platelet threshold of 10,000/µL for transfusion.44 However, platelet transfusion at higher levels may be necessary if there is active bleeding, rapid fall in platelet count, or coagulation abnormalities. In the absence of hemodynamic instability, active bleeding, or comorbidities, red blood cell transfusion is rarely needed if the hemoglobin is greater than 7 g/dL.45 To minimize the complications that may arise from leukocyte contamination, leukoreduced red blood cells are used for transfusion. To avoid the occurrence of GVHD, red blood cells must be subjected to irradiation before transfusion. CMV-negative blood components should be administered to CMV seronegative HSCT recipients.

Vasopressor-requiring shock is a common occurrence in critically ill HSCT recipients. Of 499 HSCT recipients included in 6 studies, 236 (47.3%) required vasopressor support.7,8,11,17,19,21 The most common reason for vasopressor administration is septic shock.19 Shock and other factors predispose the critically ill HSCT recipient to acute renal failure.10 Renal replacement therapy was instituted in 118 of 829 HSCT recipients (14.2%) included in 3 studies.7,13,17

MECHANICAL VENTILATION

Most HSCT recipients are admitted to the ICU for respiratory failure and some more develop respiratory failure after ICU admission. Older age, active malignancy at time of transplantation, and donor-recipient marrow HLA mismatch are independent risks for assisted MV after marrow transplantation.46 Among HSCT recipients
admitted to ICU, 42% to 88% receive invasive MV (Table 1). The mortality rate associated with invasive MV exceeded 80% in most of the reported studies, with an overall survival rate of only 13.6% (see Table 1). There are conflicting data regarding the factors that influence the outcome of HSCT recipients receiving MV. Price and colleagues reported peripheral blood stem cell source to be associated with lower mortality. However, this was not confirmed in the study by Afessa and colleagues. The cause of the respiratory failure is likely to influence the prognosis of MV in HSCT recipients. Survival is better for patients intubated for DAH or pulmonary edema. In the study by Huaringa and colleagues, 5 of 26 patients with DAH, 4 of 33 patients with pneumonia, and all 4 patients who experienced congestive heart failure/pulmonary edema survived. However, of the 7 patients with idiopathic pneumonia syndrome, bronchiolitis obliterans organizing pneumonia, multisystem organ failure, or recurrent malignancy, none survived. The mortality rate was 100% in the patients who had CMV pneumonitis (n = 9), aspergillosis (n = 5), and respiratory syncytial virus (n = 4). Two studies had shown MV duration of more than 4 and 7 days to be associated with 100% mortality. However, this was not confirmed by later findings. In the study by Scales and colleagues, 7% of the patients intubated for 10 days or more survived. In the study by Faber-Langendoen and colleagues, 7 of the 16 30-day survivors received MV for 30 days or more and 2 for 3 months or more. Despite the high short-term mortality rate associated with invasive MV, some patients survive

<table>
<thead>
<tr>
<th>Study</th>
<th>Years</th>
<th>Total</th>
<th>Invasive MV</th>
<th>Mortality of Invasive MV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torrecilla</td>
<td>1981–1987</td>
<td>25</td>
<td>16 (64%)</td>
<td>15 (94%)</td>
</tr>
<tr>
<td>Denardo</td>
<td>1979–1984</td>
<td>50</td>
<td>44 (88%)</td>
<td>40 (91%)</td>
</tr>
<tr>
<td>Faber-Langendoen</td>
<td>1978–1990</td>
<td>191</td>
<td></td>
<td>173 (91%)</td>
</tr>
<tr>
<td>Afessa</td>
<td>1982–1990</td>
<td>35</td>
<td>27 (77%)</td>
<td>25 (93%)</td>
</tr>
<tr>
<td>Crawford</td>
<td>1986–1990</td>
<td>348</td>
<td></td>
<td>333 (96%)</td>
</tr>
<tr>
<td>Paz</td>
<td>1984–1991</td>
<td>36</td>
<td>28 (78%)</td>
<td>27 (96%)</td>
</tr>
<tr>
<td>Epler</td>
<td>1985–1991</td>
<td>71</td>
<td></td>
<td>64 (90%)</td>
</tr>
<tr>
<td>Paz</td>
<td>1984–1993</td>
<td>25</td>
<td></td>
<td>24 (96%)</td>
</tr>
<tr>
<td>Jackson</td>
<td>1988–1993</td>
<td>116</td>
<td>92 (79%)</td>
<td>76 (83%)</td>
</tr>
<tr>
<td>Huaringa</td>
<td>1992–1993</td>
<td>60</td>
<td></td>
<td>55 (92%)</td>
</tr>
<tr>
<td>Kress</td>
<td>1993–1996</td>
<td>20</td>
<td></td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Price</td>
<td>1994–1996</td>
<td>115</td>
<td>48 (42%)</td>
<td>39 (81%)</td>
</tr>
<tr>
<td>Khassawneh</td>
<td>1991–1999</td>
<td>78</td>
<td></td>
<td>58 (74%)</td>
</tr>
<tr>
<td>Afessa</td>
<td>1996–2000</td>
<td>112</td>
<td>62 (55%)</td>
<td>32 (52%)</td>
</tr>
<tr>
<td>Kew</td>
<td>1992–2001</td>
<td>37</td>
<td>25 (68%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Soubani</td>
<td>1998–2001</td>
<td>85</td>
<td>51 (60%)</td>
<td>41 (80%)</td>
</tr>
<tr>
<td>Scales</td>
<td>1992–2002</td>
<td>504</td>
<td>258 (51%)</td>
<td>224 (87%)</td>
</tr>
<tr>
<td>Naeem</td>
<td>1998–2003</td>
<td>25</td>
<td>12 (48%)</td>
<td>10 (83%)</td>
</tr>
<tr>
<td>Pene</td>
<td>1997–2003</td>
<td>209</td>
<td>122 (58%)</td>
<td>103 (84%)</td>
</tr>
<tr>
<td>Trinkaus</td>
<td>2001–2006</td>
<td>34</td>
<td>20 (59%)</td>
<td>11 (55%)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>805/1383 (58.2%)</td>
<td>1381/1598 (86.4%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: MV, mechanical ventilation.
long-term. Two large transplant centers with 539 patients in total, each reported a 6-month survival rate of 3%.46,48 In the study by Jackson and colleagues,7 9 of 92 patients (10%) were alive at a median of 55 months postextubation. In the study by Huaringa and colleagues,49 5% were alive at 6 months. In the study by Khassawneh and colleagues,30 13 of 78 (17%) were alive at 6 months. In the study by Scales and colleagues,13 the 1-year mortality of MV recipients was 87%. In the study by Pene and colleagues,17 6-month and 1-year survival was 14% and 10.6%, respectively.

NONINVASIVE POSITIVE PRESSURE VENTILATION

Despite some improvement, the prognosis of HSCT recipients requiring endotracheal intubation and MV has remained dismal. The use of noninvasive positive pressure ventilation (NPPV) in patients with hematologic malignancy and acute respiratory failure improves gas exchange and reduces tachypnea.52 A randomized clinical trial of 52 immunocompromised patients, including 17 HSCT recipients with pulmonary infiltrates had shown that NPPV reduces endotracheal intubation and serious complication rates, and it reduces mortality.53 The success of NPPV requires its early application and experienced staff with dedicated time. In a study of 237 mechanically ventilated patients with cancer, including 42 HSCT recipients admitted to the ICU, Azoulay and colleagues54 have documented improvement in mortality in recent years. Using multiple logistic regression analysis, they showed that NPPV was partly responsible for the improved survival. Selected HSCT recipients with quickly reversible acute respiratory failure are likely to benefit from NPPV. However, the available data are scarce. Afessa and colleagues19 reported on 71 patients treated with positive-pressure MV: NPPV only in 9 (13%), invasive only in 47 (66%), and combined invasive and NPPV in 15 (21%). In the study by Pene and colleagues,17 66 patients (32%) were initially treated with NPPV for a median of 2 days, of whom 44 (66%) subsequently received invasive MV. The hospital mortality of the 22 patients treated only with NPPV was 55% compared with 82% receiving invasive MV.17

THE IMPORTANCE OF RECENT CLINICAL TRIALS IN CRITICAL CARE

After decades of failure and negative results, recent clinical trials in critical care have revealed that some interventions improve the outcome of the critically ill. In a randomized clinical trial, Van de Berghe and colleagues55 showed intensive insulin therapy aimed at achieving blood glucose levels between 80 and 110 mg/dL reduces the mortality rate of critically ill surgical patients, a significant number of them receiving parenteral nutrition. However, the result could not be confirmed in other groups of patients.56,57 Moreover, intensive insulin therapy may predispose critically ill septic patients to hypoglycemia-related adverse effects.58

The ARDS Network group has shown that tidal volume of 6 (vs 12) mL/kg of predicted weight is associated with reduced mortality and duration of MV in patients with ALI and ARDS.59

In a randomized clinical trial of patients with septic shock refractory to vasopressors, Annane and colleagues60 showed that a 7-day treatment with low-dose hydrocortisone and fludrocortisone reduces mortality in a subgroup of patients with relative adrenal insufficiency. However, the finding was not confirmed by a later trial that used different inclusion criteria and treatment.61 In a randomized clinical trial of 1690 patients with severe sepsis and septic shock, treatment with recombinant human activated protein C reduced mortality.62 However, the potentially life-threatening complication of recombinant human activated protein C and the premature termination of subsequent studies have led to controversies and its limited use in
clinical practice.\textsuperscript{63} In the randomized clinical trial by Rivers and colleagues,\textsuperscript{64} early goal-directed therapy reduced the mortality rate of patients with severe sepsis and septic shock from 46.5\% to 30.5\%. Although there may not be clarity about which component of the therapy is responsible for the mortality reduction, its application in clinical practice has led to significant reduction of sepsis-associated mortality worldwide.\textsuperscript{65}

The International Surviving Sepsis Campaign Guidelines make several recommendations for the management of the critically ill, based on the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system to rate the available evidence and the strength of recommendation.\textsuperscript{66} We have listed some of these recommendations in Table 2. However, we advise caution when applying these recommendations to the critically ill HSCT recipient. Although the Surviving Sepsis Campaign recommendations were based on the available clinical trials, HSCT recipients were inadequately represented or actively excluded from most of these trials. The authors believe that early goal-directed therapy for severe sepsis and septic shock and a lung protective strategy with low tidal volume for ALI/ARDS are likely to benefit critically ill HSCT recipients. It is advisable to avoid hypoglycemia and hyperglycemia. However, the available conflicting data do not provide strong support to make specific recommendations about the target glucose level for critically ill HSCT recipients. Although the role of short-term, low-dose corticosteroid for septic shock has not been specifically studied in HSCT recipients, the authors believe it is unlikely to have significant adverse effect. HSCT recipients were actively excluded from the original clinical trial evaluating the role of recombinant human activated protein C.\textsuperscript{62} An open-label, multicenter, single-arm clinical trial to investigate the safety and efficacy of recombinant human activated protein C in HSCT recipients with severe sepsis was prematurely terminated due to low enrollment: 7 patients at 3 of the 15 sites.\textsuperscript{67} Among 6 of the 7 patients who completed the

<table>
<thead>
<tr>
<th>Table 2</th>
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<tbody>
<tr>
<td><strong>Recommendations for the management of severe sepsis based on the 2008 International Surviving Sepsis Campaign Guidelines</strong>\textsuperscript{66}</td>
</tr>
<tr>
<td>Recommendation</td>
</tr>
<tr>
<td>Fluid resuscitation targeting central venous pressure of 8 (12 if positive-pressure ventilation) mm Hg</td>
</tr>
<tr>
<td>Vasopressors to maintain mean arterial pressure of 65 mm Hg</td>
</tr>
<tr>
<td>If central venous oxygen saturation &lt;70% or mixed venous oxygen saturation &lt;65% despite fluid, and hematocrit &lt;30%, consider red blood cell transfusion</td>
</tr>
<tr>
<td>If central venous oxygen saturation &lt;70% or mixed venous oxygen saturation &lt;65% despite fluid and hematocrit $\geq$ 30%, consider dobutamine</td>
</tr>
<tr>
<td>Consider low dose intravenous hydrocortisone for septic shock poorly responsive to fluid and vasopressors</td>
</tr>
<tr>
<td>Consider recombinant human activated protein C for sepsis induced organ dysfunction with APACHE II score $\geq$ 25</td>
</tr>
<tr>
<td>Target a tidal volume of 6 mL/kilogram of predicted weight when ventilating patients with ALI/ARDS</td>
</tr>
<tr>
<td>Use intravenous insulin to control hyperglycemia in patients with severe sepsis</td>
</tr>
</tbody>
</table>

*Abbreviation: APACHE, Acute Physiology And Chronic Health Evaluation.*
drug infusion, 2 experienced serious bleeding, a nonfatal DAH, and a fatal intracranial hemorrhage. The available evidence does not justify the use of recombinant human activated protein C in HSCT recipients.

MORTALITY

Several studies have reported the short-term mortality rate of HSCT recipients admitted to the ICU (Table 3). Overall, 772 of 1193 (65%) patients died in the hospital or within 30 days of ICU discharge (see Table 3). Limited data are available with regard to long-term mortality rate. The 6- to 12-month mortality rates range between 67% and 96%, with overall rate 74% (see Table 3). The outcome of HSCT recipients admitted to the ICU has improved over the years. Of 267 patients treated in the ICU before 1995, 212 (79.4%) died compared with 327 of 502 patients (62.9%) treated after 1995 (P < .001). This improvement of survival over time may be due to selection bias. The earlier literature reported a very high mortality rate. This may have led health care providers to refuse admission of selected critically ill HSCT recipients to the ICU and also caused reluctance among HSCT recipients to be admitted there. Other possible explanations for the improved outcome include wider use of colony-stimulating factors for neutropenia, more frequent use of autologous transplant, use of peripheral blood stem cell transplantation, use of corticosteroids for respiratory failure due to DAH and PERDS, earlier application of noninvasive ventilation, lung protective strategies for acute lung injury, and early goal-directed therapy for severe sepsis.

Table 3
The mortality of HSCT recipients admitted to the ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Total</th>
<th>Hospital and 30-Day Death (%)</th>
<th>6-Month to 1-Year Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Denardo</td>
<td>1979–1984</td>
<td>52</td>
<td>43 (83)</td>
<td>50 (96)</td>
</tr>
<tr>
<td>Torrecilla</td>
<td>1981–1987</td>
<td>23</td>
<td>22 (96)</td>
<td></td>
</tr>
<tr>
<td>Afessa</td>
<td>1982–1990</td>
<td>35</td>
<td>27 (77)</td>
<td></td>
</tr>
<tr>
<td>Paz 216</td>
<td>1991–1993</td>
<td>10</td>
<td>7 (70)</td>
<td></td>
</tr>
<tr>
<td>Jackson</td>
<td>1988–1993</td>
<td>111</td>
<td>89 (80)</td>
<td></td>
</tr>
<tr>
<td>Price</td>
<td>1994–1996</td>
<td>115</td>
<td>62 (54)</td>
<td></td>
</tr>
<tr>
<td>Groeger</td>
<td>1994</td>
<td>253</td>
<td>141 (56)</td>
<td></td>
</tr>
<tr>
<td>Staudinger</td>
<td>1996–2000</td>
<td>112</td>
<td>58 (52)</td>
<td></td>
</tr>
<tr>
<td>Kim</td>
<td>1999–2001</td>
<td>18</td>
<td>17 (94)</td>
<td></td>
</tr>
<tr>
<td>Kew</td>
<td>1992–2001</td>
<td>37</td>
<td>23 (62)</td>
<td>29 (84)</td>
</tr>
<tr>
<td>Soubani</td>
<td>1998–2001</td>
<td>85</td>
<td>50 (59)</td>
<td>55/76 (72)</td>
</tr>
<tr>
<td>Naeem</td>
<td>1998–2003</td>
<td>25</td>
<td>18 (72)</td>
<td></td>
</tr>
<tr>
<td>Pene</td>
<td>1997–2003</td>
<td>209</td>
<td>141 (67)</td>
<td>165 (79)</td>
</tr>
<tr>
<td>Trinkaus</td>
<td>2001–2006</td>
<td>34</td>
<td>20 (59)</td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>772/1193 (65)</td>
<td>675/916 (74)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PROGNOSTIC FACTORS

There are several prognostic factors that may influence the outcome of HSCT recipients admitted to the ICU (Box 2). Advanced age, coexisting comorbidities, and lower functional status have an adverse effect on survival. Allogeneic HSCT has higher 100-day mortality than autologous HSCT. The 100-day post-transplant mortality of autologous HSCT recipients with multiple myeloma is less than 5%, whereas it exceeds 10% in acute leukemia not in remission. In allogeneic transplant recipients with leukemia not in remission, the 100-day mortality exceeds 20%. In autologous HSCT recipients, the most common cause of death is underlying disease relapse (70%), followed by infection (8%) and organ toxicity (6%). In allogeneic HSCT recipients from HLA-identical sibling donors, the most common cause of death is underlying disease relapse (41%), followed by infection (17%), GVHD (13%), and organ toxicity (10%). In allogeneic HSCT recipients from unrelated donors, the most common cause of death is underlying disease relapse (34%), followed by infection (20%), GVHD (14%), and organ toxicity (10%). Except in patients with active disease, patients receiving allogeneic transplants after reduced-intensity conditioning have lower early mortality.

In the studies that reported the type of transplant, the mortality rate of allogeneic HSCT recipients admitted to ICU was 70.0% (604 of 867) compared with 58.3% (319 of 558) of autologous HSCT recipients (P<.001). GVHD is also a poor prognostic factor in the critically ill HSCT recipient. The available data do not show clear association between ICU mortality and source of stem cell. In the study by Price and colleagues, there was no significant difference in overall mortality between peripheral blood stem cell and bone marrow transplant recipients. However, in patients receiving MV, the mortality rate was lower in peripheral blood stem cell recipients. Subsequent studies have not found an association between stem cell source and ICU mortality. There are limited data with regard to umbilical

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<td><strong>Prognostic factors influencing the outcome of the critically ill HSCT recipient</strong></td>
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- **Pretransplant**
  - Age
  - Functional status
  - Underlying diagnosis

- **Transplant-related**
  - Disease status at transplant
  - Conditioning regimen
  - Transplant type
  - Source of stem cell

- **ICU-related**
  - Reason for ICU admission
  - Organ failure
  - Severity of critical illness
cord blood transplantation and ICU outcome. In one study that included only umbilical cord blood stem cell recipients, the short-term mortality rate was 72%, which is comparable to other sources. Among the 209 allogeneic HSCT recipients reported by Pene and colleagues, the stem cell source was bone marrow in 67%, peripheral blood in 28%, and umbilical cord blood in 5%. The stem cell source had no effect on mortality.

The reason for ICU admission and the timing of the admission may influence outcome. Some studies have shown the presence of pneumonia, gram-negative infection, and infection or gastrointestinal bleeding at ICU admission to be associated with increased mortality. There are conflicting data addressing the effect of the timing of ICU admission after transplant on mortality. Some studies have shown that ICU admission during an earlier period following HSCT is associated with higher mortality rate, whereas others have found to the contrary. Several other studies have not found statistically significant association between timing of ICU admission and mortality.

The authors have described earlier the dismal prognosis of respiratory failure requiring invasive MV. The development of nonrespiratory organ failure also correlates with increased mortality. Jackson and colleagues reported 100% mortality for patients admitted to ICU with multiorgan failure. In the study by Scales and colleagues, the 1-year mortality rate of HSCT recipients who received hemodialysis in the ICU was 94%. In a study by Soubani and colleagues, no patient with serum lactate of more than 6 survived.

ARDS and severe sepsis are frequent complications of critically ill HSCT recipients. In a study by Afessa and colleagues, the 30-day mortality rate of patients with ARDS was 74% compared with 35% of those without ARDS, and the mortality rate of patients with sepsis was 70% compared with 23% of those without sepsis.

**Mortality Prediction**

The clinical decision-making process regarding the critically ill often requires the active participation of health care providers and patients and surrogates. This process is facilitated by knowledge of the patient’s prognosis. Although they have no role in individual patient decision-making, there are several adult ICU prognostic models developed and validated to predict the probability of hospital death. The adult ICU prognostic models are derived from age, comorbidities, lead time bias, ICU admission diagnosis and admission source, and physiologic variables. The latest versions of the adult ICU prognostic models are Simplified Acute Physiology Score (SAPS) 3, Acute Physiology and Chronic Health Evaluation (APACHE) IV, and Mortality Prediction Model (MPM) III. The pertinent comorbidities included in these models are immunosuppression/hematologic malignancy in APACHE IV, hematological malignancies in SAPS 3, and metastatic neoplasm in MPM III. There are no data evaluating the performance of these new models in predicting the prognosis of the critically ill HSCT recipient. Although these models were based on data from tens and hundreds of thousands of patients, critically ill HSCT patients were not adequately represented. Among the older generation adult ICU prognostic models, APACHE II and III, SAPS II, and MPM II have been studied in the critically ill HSCT recipient. Several studies have shown nonsurvivors to have higher APACHE II and III scores, and MPM II predicted probability of death compared with survivors. APACHE II, SAPS II, and MPM II models underestimate the mortality rate of the HSCT patient admitted to the ICU. In the study by Jackson and colleagues, mortality was 100% when APACHE II score exceeded 45. In a study of
414 patients with cancer, including 38 HSCT recipients admitted to the ICU, all patients with APACHE III score exceeding 80 died in the ICU. Most of the studies addressing the role of the adult ICU prognostic models in HSCT recipients did not describe the discrimination and calibration of the models. In the study by Afessa and colleagues, the observed and APACHE III-predicted hospital mortality rates were 46% and 42%, respectively, and the area under the receiver operating characteristic curve was 0.704 with good calibration (Hosmer-Lemeshow statistic 6.563, \( P = .564 \)).

Accurate estimation of the risk of death is important in clinical trials, epidemiologic studies, and most importantly, in clinical practice. Because of the high human and financial costs, the accurate estimation of risk is most important in ICU patients. Because prediction models, including the adult ICU ones based on data from the general population, are unlikely to give us accurate estimation for the risk of HSCT recipient death, some have tried to develop disease-specific models. Parimon and colleagues had reported a model for predicting the 2-year risk of death following allogeneic HSCT. However, this model is not specific for HSCT patients admitted to the ICU. Groeger and colleagues developed and validated a model for predicting mortality of patients with cancer, including 253 HSCT recipients admitted to the ICU. The study included 1713 patients from 4 large cancer centers. The model included 16 predictor variables: \( \text{PaO}_2/\text{FiO}_2 \) ratio, platelet count, respiratory rate, systolic blood pressure, pre-ICU hospital days, intracranial mass effect, allogeneic bone marrow transplantation, recurrent or progressive cancer, albumin less than 2.5 g/dL, bilirubin 2 mg/dL or more, Glasgow Coma Scale score less than 6, prothrombin time more than 15 seconds, blood urea nitrogen more than 50 mg/dL, endotracheal intubation, performance status before hospitalization, and cardiopulmonary resuscitation. The calibration was good for the development and validation models. The areas under the receiver operating characteristic curves were 0.812 and 0.802 for the development and validation models, respectively. Although other studies have also reported multiple logistic regression models based on variables obtained in HSCT recipients admitted to the ICU, they are not as well described and validated as the model by Groeger and colleagues.

**TRIAGE FOR ICU ADMISSION**

Intensivists and hematologists/oncologists often face the question of whether or not to transfer a clinically deteriorating HSCT recipient to the ICU. Because most of the intensivists do not participate in the pre- and post- ICU care of HSCT recipients, they are familiar only with the tip of the iceberg. Thiery and colleagues reported that intensivists and hematologists/oncologists disagree 15% of the time on ICU admission triage decisions for patients with cancer. Appropriate triage for ICU admission is extremely important, especially in institutions with limited critical care resources, and it requires the active participation of intensivists, hematologists/oncologists, and patients and their surrogates for health care. There is a consensus in principle that patients too well or too sick to benefit from ICU support should be denied ICU admission. However, the intensivists’ judgement in determining who is sick enough to benefit from ICU admission is far from perfect. In a prospective study of 206 patients with cancer considered for ICU admission, the intensivists considered 47 patients (22.8%) too well and 54 patients (26.2%) too sick to benefit from ICU admission. Of the 47 patients considered too well, 13 (28%) were subsequently admitted to ICU. The 30-day mortality rate of the 54 patients considered too sick was 74%. One of the authors’ institutions has implemented a triage policy for ICU admission of patients with cancer. According
to the policy, patients with cancer who have previously untreated malignancy, acute tumor lysis syndrome, or a bulky or infiltrating tumor at the earliest phase of treatment, and patients in complete remission are admitted to the ICU for full, unlimited support. Bedridden patients and patients with palliative care as the only treatment option and those who refuse ICU admission are not admitted. All other groups of patients are admitted to ICU on a trial basis, with full ICU support for 4 days and reevaluation on day 5 for the appropriate level of care. In a prospective study, called the ICU Trial, Le-cuyer and colleagues reported their experience with such a policy. Among 188 patients (including 24 autologous HSCT recipients) admitted for ICU Trial, 85 (45.2%) died within the first 4 ICU days. Among the 103 5-day survivors, 14 had received and 31 were scheduled to receive autologous HSCT; all those who received MV, vasopres-sors, or dialysis beyond the third ICU day died. With improving critical care support, there are several reports of HSCT recipients who survive 3 days of MV and other ICU organ support. Based on the available data, the authors recommend saying “yes” more often than “no” in considering HSCT recipients for ICU admission (Fig. 1). Lowering the level of care after ICU trial is not an uncommon practice. In the study by DeNardo and colleagues, do-not-resuscitate (DNR) orders were written in 26 of 50 HSCT recipients (52%) at a mean of 10 days after ICU admission. Similarly, in 2 studies from Mayo Clinic, DNR orders were written in 24 of 35 (68%) and 40 of 112 (36%) HSCT recipients. In the study by Soubani and colleagues, 22 of 33 ICU deaths followed life support withdrawal.

**SUMMARY**

HSCT recipients often develop life-threatening complications following transplant for lethal conditions. Although the mortality rate of HSCT recipients admitted to the ICU has declined over the last 2 decades, it still exceeds 80% in those receiving MV. With improvement in transplantation and critical care, we expect the prognosis of the critically ill to get better. Researchers need to continue their efforts to find better treatment modalities and describe the effect of the modalities on patient outcome. For appropriate use of limited ICU resources, reliable prognostication models need to be developed. When triaging HSCT recipients for ICU admission, the status of the patients’ underlying disease, short- and long-term prognostic factors, and the patients’ wishes should be incorporated into the decision-making process.
REFERENCES


