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REVIEW

Critically ill allogeneic hematopoietic stem cell transplantation patients in the intensive care unit: reappraisal of actual prognosis

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The outcome of allogeneic hematopoietic stem cell transplantation (allo-HSCT) patients has significantly improved over the past decade. Still, a significant number of patients require intensive care unit (ICU) management because of life-threatening complications. Literature from the 1990s reported extremely poor prognosis for critically ill allo-HSCT patients requiring ICU management. Recent data justify the use of ICU resources in hematologic patients. Yet, allo-HSCT remains an independent variable associated with mortality. However, outcomes in allo-HSCT patients have improved over time and many classic determinants of mortality have become irrelevant. The main actual prognostic factors are the need for mechanical ventilation, the presence of GvHD and the number of organ failures at ICU admission. Recently, the development of reduced-intensity conditioning regimens, early ICU admission and the increased use of noninvasive ventilation, combined with time effect and general advances in hematology, in allo-HSCT procedures and in ICU management have contributed to improve general outcome. A rational policy of ICU admission triage in these patients is very hard to define, as each decision for ICU admission is a case-by-case decision at patient bedside. The collaboration between hematologists and intensivists is crucial in this context.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the standard of care for many hematologic disorders.[1–4] The number of patients who benefit from allo-HSCT is continuously increasing. More than 12 000 allo-HSCT cases have been reported in 2010 in Europe.[5]

Outcome has significantly improved over the past decades.[6] Still, allo-HSCT remains associated with significant mortality and a significant number of patients require intensive care unit (ICU) management because of life-threatening complications.[7] Intensivists will be increasingly asked to manage these patients given the growing incidence of hematological malignancies.

For many years, the prognosis of hematologic patients admitted to ICU has been extremely grim, with >90% mortality rates for patients requiring mechanical ventilation (MV) in the 1990s. Therefore, ICU management was considered as futile and seriously debated.[8,9] Recent data support the use of ICU resources in these patients, with dramatically decreased mortality rates and long-term benefits.[10–12] Whether these trends are confirmed in allo-HSTC patients is more controversial.[13,14] Considering all recent advances in HSCT techniques and ICU management, the reappraisal of actual prognosis became crucial to identify patients who are most likely to benefit from ICU support.[8,11,15]

This article aims to review the most recent literature to summarize the actual prognosis of critically ill adult allo-HSCT recipients admitted to the ICU, to address unresolved issues and keys for ICU admission decision. We performed a systematic PubMed search using the keywords 'ICU', 'allo-HSCT' and 'prognostic factors' to identify recent pertinent publications.

PATIENTS ADMITTED TO THE ICU AND REASONS FOR ICU ADMISSION

Characteristics of patients admitted to the ICU

The likelihood of ICU admission varies from center to center, with published series reporting a wide range of admission rates from 9 to 57%.[13,16–37] Median age varies from 34 to 54 years, with older patients treated in centers that perform a majority of reduced-intensity conditioning (RIC) regimens. Most publications included patients who received allo-HSCT in the 2005–2010 period, but a few publications analyzed patients treated in the late 1990s.[13,18,23,25,34] Time between allo-HSCT and ICU admission greatly differs according to series, ranging from 12 days[13] to 156 days.[23] The main indication for allo-HSCT was AML, representing ~40% of patients, followed by ALL, myelodysplastic syndromes, lymphoma (~20%) and myeloma (~10%). Disease status before allo-HSCT was poorly documented. Malignancies in complete remission represented ~50 and 30% in PR or stable disease, and 20% in a refractory disease.[13,30] Conditioning regimen was mostly myeloablative conditioning, making result interpretation difficult, considering the development of RIC in the past decade. In 3 publications, myeloablative conditioning represented >90% of patients.[13,21,22] Only one publication studied patients who received only RIC allo-HSCT.[30] Stem cell source was mainly represented by peripheral hematopoietic stem cells.[17,18,21,30] Cord

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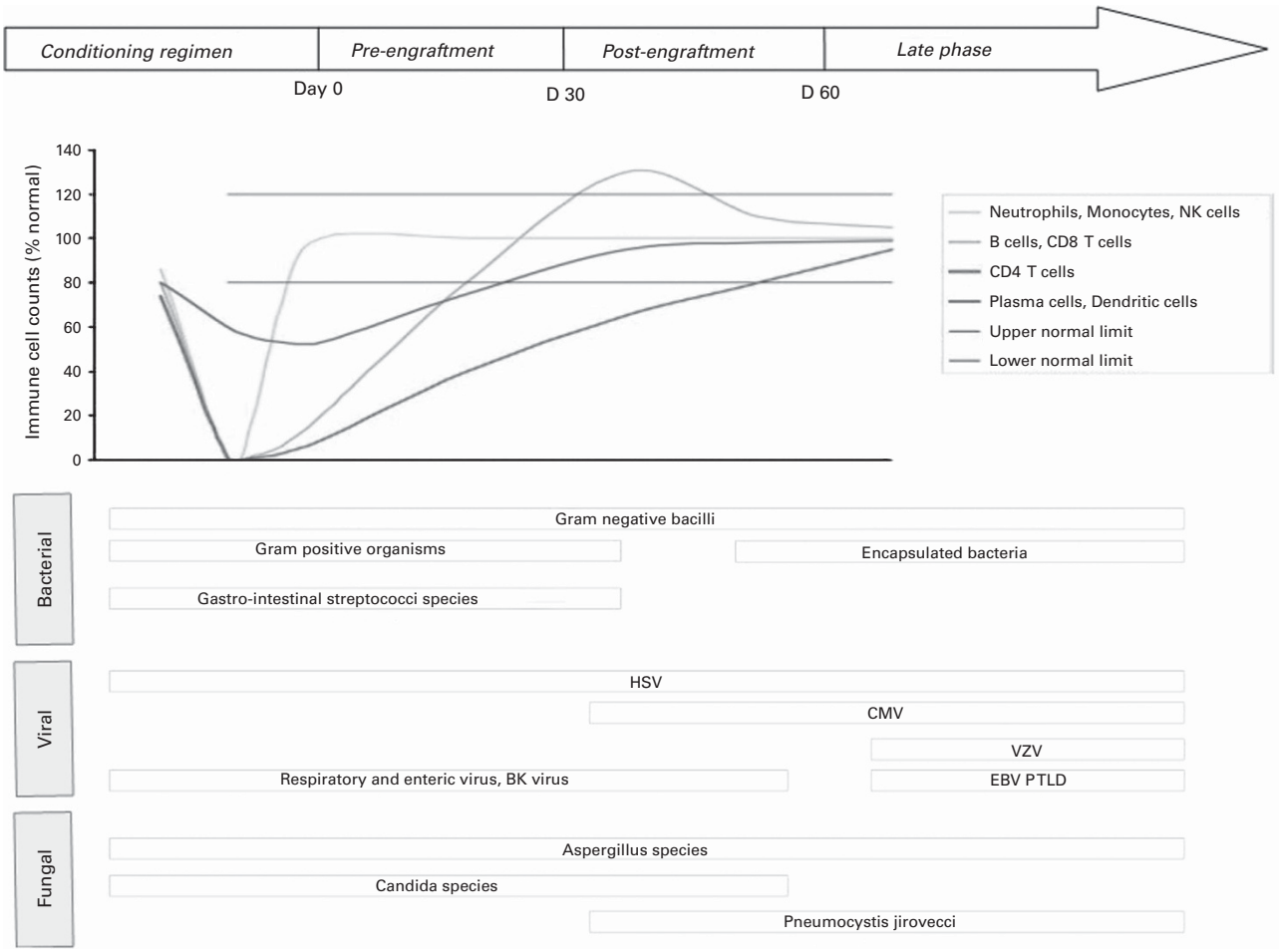

Figure 1. Infectious causes of ICU admission according to time since allo-HSCT (adapted from Tomblyn *et al.*[53]). PTLD = post-transplant lymphoproliferative disorder. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

blood represented 1 to 10% of transplants.[13,17,18,27,30] HLA-identical sibling remained the main type of allo-HSCT (37–70%). The use of HLA-matched unrelated donor, HLA-mismatched and haploidentical transplant greatly differed according to transplantation center.

Reasons for ICU admission

The most common reason for ICU admission is acute respiratory failure (ARF), followed by severe sepsis and septic shock, neurological failure, acute kidney injury (AKI) and others (bleeding, cardiac and liver dysfunction, representing < 5% of ICU admissions). ARF was the reason for ICU transfer in ~60% of the cases. Etiological frequencies are not clearly reported, but were dominated by pulmonary infections, acute cardiac failure and intra-alveolar hemorrhage. Hemodynamic instability represented 12 to 75% of patients, with a majority of bacterial infections (13 versus 7% of fungal and 4% of viral infections).[22] Infections were documented in 50% of cases, and clinically suspected in 50% of patients.[21] AKI was present in 65% of patients, with an increased incidence throughout time, with almost all patients being exposed to a median of three nephrotoxic drugs, such as aminoglycosides, cyclosporine, vancomycin, acyclovir, contrast agents, renin–angiotensin–aldosteron system inhibitors, liposomal amphotericin B, foscarnet and IV immunoglobulins.[20] The main causes of AKI reported were dominated by sepsis and circulatory shock. Specific causes of AKI are rare and mainly represented by engraftment syndrome (8%), veno-occlusive disease (3%)[38] and thrombotic microangiopathies.[20] Coma was mainly represented by posterior reversible encephalopathy syndrome, drug toxicity such as cyclosporine, betalactams and carbapenems, metabolic disorders, infectious causes and cerebral hemorrhages.[39,40] Life-sustaining therapies consisted of MV in 21–72%, noninvasive ventilation (NIV) in 28–40%, use of vasopressors in 47–68% and renal replacement therapy in 22–41%.[13,20,24,25,30,35]

Diagnostic strategy

Diagnostic strategy is crucial, as the absence of diagnosis is a key prognostic factor, particularly in ARF setting.[41,42] To facilitate diagnostic strategy in ARF in cancer patients, Azoulay and Schlemmer[43] proposed a standardized clinical approach, known as the 'DIRECT strategy'. This strategy is based on six factors: delay since allo-HSCT, pattern of immune deficiency, radiographic appearance, clinical experience, clinical picture and findings by high-resolution computed tomodensitometry, to guide clinicians in selecting the most probable hypothesis. It can be applied to allo-HSCT patients, as ARF represents up to 80% of ICU admission.[29,30] Etiologies can be schematically divided into infectious and noninfectious etiologies. Infectious causes represented ~65% of ICU admissions and noninfectious causes represented 35% of admissions.[21] However, infectious and noninfectious causes frequently occur in combination and multi-organ failure (MOF) is often multifactorial.

Allo-HSCT patients carry a huge immunodepression. The knowledge of the type of immunodeficiency (Figure 1) is crucial to guide diagnosis and quickly initiate antimicrobial empirical treatment if needed, as the speed and appropriateness of

antimicrobials is a major prognostic factor.[44] The degree of immunosuppression greatly depends on comorbidity, malignancy and antitumor treatment. The characteristics of allogeneic HSCT are crucial to evaluate: delay since allo-HSCT, donor type, stem cell source, disease status, conditioning regimen, GvHD prophylaxis, blood count, infectious history, GvHD and immunosuppression. Bacterial infection is the leading cause of organ failure before neutropenia recovery. The main pathogens are Gram-negative bacilli, gastrointestinal streptococci species and Gram-positive cocci. After neutropenic phase, viral infections, invasive aspergillosis and opportunistic infections are likely to occur. The main viruses include herpes viruses (CMV, HSV, VZV, HHV6) and respiratory viruses such as influenza and adenovirus.[45–49] BK virus is particularly problematic in the context of hemorrhagic cystitis, and EBV with risks of post-transplant lymphoproliferative diseases. The fungal risk is major during the neutropenic phase, especially in the setting of GvHD requiring corticosteroids. It includes filamentous fungi (*Aspergillus* species and Mucormycoses)[50,51] and *Pneumocystis Jiroveci*. Late infections are caused by all types of pathogens, but risks are predictable and surmountable with prevention strategies, such as prophylaxis and post-transplant vaccination.[52–54]

Noninfectious causes of organ failure are usually diagnosed after exclusion of infections. They are mainly represented by cardiac edema, treatment toxicity,[39,40,54–63] hemorrhages, GvHD, long-term allo-HSCT complications,[60,64] comorbidity decompensation and relapse. Several post-allograft complications can occur, but they do not all occur at any particular stage of the disease. Delay between HSCT and ICU admission guides diagnostic strategy (Figure 2), with each phase carrying specific complications.

OUTCOME AND PROGNOSTIC FACTORS OF CRITICALLY ILL ALLO-HSCT PATIENTS ADMITTED TO THE ICU

Outcome

Prognosis of allo-HSCT patients in the 1990s was extremely grim, especially when MV was needed with mortality rates approaching 100%. Indeed, before 1993, only 3% of patients requiring MV survived, and all patients >40 years of age or intubated within 90 days of HSCT died by day 100 post extubation.[65] In the publication of Rubenfeld and Crawford[14] that studied allo-HSCT patients requiring MV between 1980 and 1992, 6% survived more than 30 days after extubation. None with ARF combined with either hemodynamic instability or hepatic or renal failure survived.[14] In 1998, Price *et al.*[66] reported a 19% survival rate in patients requiring MV compared with 66% among patients not requiring MV. In a prospective multicenter trial, Bach *et al.*[67] reported in 2001 a baseline probability of death of 82–96% in patients requiring MV, and up to 98–100% if combined with hepatic and renal dysfunction. In the publication of Jackson *et al.*,[68] once again, patients requiring both hemodynamic support and MV had a very poor prognosis.

For the past years, greatly improved survival rates have been reported in hematology patients admitted in the ICU. Azoulay *et al.*[10] recently reported outcomes of 1011 critically ill hematologic patients, including 14% of allo-HSCT patients. Hospital mortality, 90-day and 1-year mortality rates of critically ill patients with hematological malignancies were 39%, 48% and 57% respectively.[10] These results are encouraging, particularly as most patients had at least 2 organ dysfunctions, and 75% required MV, vasoactive drugs or renal replacement therapy. These results justify the use of ICU resource in hematologic patients. Yet, allo-HSCT remains an independent variable associated with mortality.[69] Table 1 summarizes the main outcomes recently reported of critically ill allo-HSCT patients.

Prognostic factors

The identification of prognostic factors has been the cornerstone of many previous studies. Several prognostic factors have been tested, such as patient and disease characteristics, transplantation features and severity scores at ICU admission and during ICU stay (Table 1). Table 2 outlines the independent prognostic factors recently identified.

It is now clear that short-term outcome of critically ill patients is mainly determined by the number of organ failures, and not by malignancy characteristics or disease status.[10,24] MOF at ICU admission appears as the main prognostic factor, especially when MV is required with almost a 100% mortality rate,[13] and no progress has been accomplished in the past decade in this situation.[20,24] Severity scores reflecting organ dysfunctions, such as APACHE II, APACHE III, SOFA and SAPSII, can help in severity assessment[19,24,30,31] but have not been validated in allo-HSCT patients.

In ARF setting, the use of MV remains a dreadful event and is the main determinant of short-term survival.[67,70,71] The need for ventilatory support ranges from 28 to 76% in recent studies,[13,16,21,24,25,27–35] and ICU mortality varies from 63 to 85% (Table 3). These results are far worse than the respective 70% and 62% ICU and hospital survival rates reported in a large observational study of unselected ICU patients requiring MV.[72] These results are even worse when MV is needed for more than 10 days, with only 7% of survivors.[32] The presence of GvHD strongly impairs outcome, with 1-year survival of 10%.[67] Patients with active GvHD still carry a dismal outcome and MV provides no benefits in these patients.[29,36,37] However, despite these disappointing results, several points deserve to be underlined. First, beyond the poor short-term outcome, a number of mechanically ventilated survivors had a good long-term prognosis. Pene *et al.*[13] reported hospital survival rates of 16%, with 17 and 12 patients alive after 6 months and 1 year respectively, out of 209 patients with 122 requiring MV. Second, survival has improved in patients requiring MV and, except for patients with GvHD, hospital mortality has dropped from 82 to 66% in the presence or absence of acute GvHD.[29] Patients benefit from MV if they are well selected. Indeed, the survival rate of patients requiring MV within the engraftment period is acceptable and similar to the rates reported in cohorts of cancer patients.[13,70] Third, NIV is increasingly used and frequently successful in 61%.[30] Moreover, NIV failure was not associated with poor prognosis.[58,73,74] The use of high flow oxygen therapy through a nasal cannula (HFNC) associated with NIV recently demonstrated promising results in ARF in cancer patients, with a significant improvement of day-28 mortality and decrease in invasive MV requirement.[75] NIV appears to be highly effective in well-selected situations, such as cardiac edema and capillary leak syndrome, but totally ineffective in lesional pulmonary edema. This strategy deserves to be investigated in allo-HSCT patients.

In patients admitted for septic shock, vasopressor use remains an important prognostic factor.[19,26–28,31] Neurological failure at admission was associated with a better hospital survival, probably because most of the patients presented a reversible cause.[30] Hepatic failure represents a major issue for the next years, with bilirubin level being associated with an adverse prognosis.[13,20] Optimal management of these patients is far from being well codified as literature on hepatic dysfunction in allo-HSCT patients in the ICU is nonexistent. Liver dysfunction is always multifactorial, including sepsis, veno-occlusive disease, treatment toxicities, parental nutrition and hepatic GvHD, making diagnosis very difficult.[56] This dysfunction is poorly documented and transjugular biopsy is rarely performed and rarely helpful. This thematic represents a great investigational field. Acute renal failure at ICU admission is an adverse prognostic factor[20,33,34] as is the use of renal replacement therapy.[24,29,32] Allo-HSCT recipients are known to be at high risk for AKI as they are often exposed to

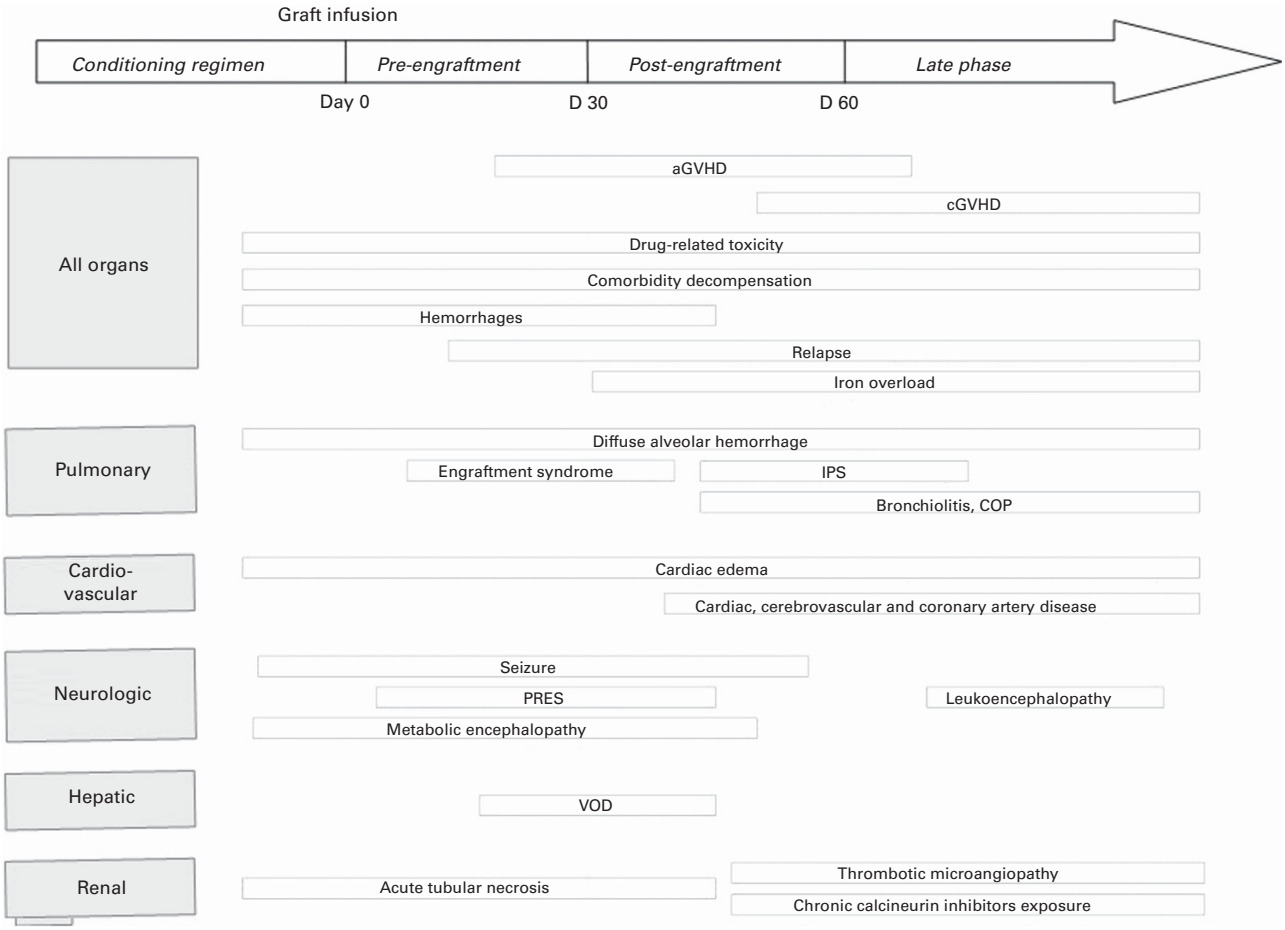

Figure 2. Noninfectious causes of ICU admission according to time since allo-HSCT. aGvHD = acute GvHD; cGvHD = chronic GvHD; COP = cryptogenic organized pneumonia; IPS = idiopathic pulmonary syndrome; PRES = posterior reversible encephalopathy syndrome; VOD = veno-occlusive disease.

combinations of various aggressions. AKI adversely affects survival, gradually with the severity, with stage 3 being associated with only 19% of patients being alive at hospital discharge.[20]

Time effect is a major factor in recent improvements. Lengline *et al.*[29] analyzed two cohorts of allo-HSCT patients admitted to the ICU between 1997–2003 and 2004–2011. Significant survival improvement over time was observed, with ICU, day-90 and 1-year mortality of 30%, 51% and 48% in the 2004–2011 cohort versus 52%, 69% and 67% in the 1997–2003 period.[29]

Patients and underlying malignancy are not relevant prognostic factors. Age does not appear to affect outcome, but should be interpreted carefully, as the older patients received preferentially RIC regimens. Comorbidity, assessed by the hematopoietic cell transplantation comorbidity index, appears to be relevant in predicting outcome.[17,76] Disease response status before the graft could affect ICU outcome.[30] Transplant characteristics do not appear as prognostic factors, with published cohorts being very heterogeneous in terms of conditioning regimen, donor type, stem cell source and indication. Only one study investigated the impact of RIC on ICU outcome in a homogeneous cohort, with ICU and hospital mortality rates of 39% and 60%, respectively.[30] This suggests that improvements in outcome of allo-HSCT recipients after RIC can be transposed into the ICU.

IMPROVEMENTS OVER TIME

Over the past decades, HSCT has seen a rapid expansion in use and a constant evolution in its technology. Major advances have been made, contributing to improve general outcome. Of striking feature, decreased mortality was in parallel with decreased liver disease, renal injury, pulmonary complications, infections and acute GvHD.[6] Reduced incidence of organ failures and infection rates seem to be associated with a multimodal management.

General improvements in hematology

Prognosis of hematological malignancies has improved thanks to the emergence of innovative therapeutic strategies, the use of new drugs, monoclonal antibodies and targeted therapies, combined with the development of biologic tools, such as minimal residual disease monitoring.[77] It results in a better disease control before allo-HSCT, a prognostic factor for ICU admission.[30] Moreover, the development of supportive care, including new antimicrobial and antifungal treatments, hematopoietic growth factors and better transfusion policies have contributed to a global reduction of toxicity. The control of infectious complications has improved since the development of molecular methods for viral and fungal detection, the use of preemptive treatments and prevention of nosocomial infections.[78–81]

HSCT improvements

Several changes in transplantation practice appeared to have contributed to improve outcomes. Better donor selection, as well as a more accurate HLA matching for unrelated donors, probably

Table 1. Prognostic factors of adult allogeneic HSCT recipients admitted to the ICU

Reference	*Main patient characteristics*	*Main outcomes*	*ICU admission rate*	*Independent prognostic factors*
Kew *et al.*[28]	Study period: 1992–2001 $n = 37$ HSCT recipients (76% allogeneic)	Day-30 mortality: 62% 1-Year mortality: 78%	9%	1-Year survival: Vasopressors use
Naeem *et al.*[31]	Study period: 1998–2003 $n = 44$ Allogeneic HSCT, cord blood only	ICU mortality: 72%	57%	ICU transfer:[a] MAC regimen ICU mortality:[a] APACHE III score Vasopressors use Platelet count
Pene *et al.*[13]	Study period: 1997–2003 $n = 209$ Allogeneic HSCT recipients	ICU mortality: 52% Hospital mortality: 68% 6-Month mortality: 73% 1-Year mortality: 79%	20%	Hospital mortality: Time between HSCT and ICU admission MV Increased bilirubin level Corticosteroid treatment for GvHD
Yang *et al.*[35]	Study period: 1994–2005 $n = 41$ HSCT recipients (85% allogeneic) requiring MV	ICU mortality: 80% Hospital mortality: 83% 2-Year mortality: 93%	27%	ICU mortality:[a] Age APACHE II Shock Acute renal failure Respiratory rate Heart rate
Scales *et al.*[32]	Study period: 1992–2002 $n = 504$ HSCT recipients (52% allogeneic)	1-Year mortality: 87%	19%	1-Year mortality:[a] MV RRT
Huynh *et al.*[27]	Study period: 2001–2006 $n = 154$ HSCT recipients (62% allogeneic)	ICU mortality: 53% Hospital mortality: 64% 6-Month mortality: 81%	25%	6-Month mortality: Allogeneic HSCT MV Vasopressor use
Gilli *et al.*[25]	Study period: 1995–2005 $n = 91$ Allogeneic HSCT recipients	ICU mortality: 56% Day-100 mortality: 78% 1-Year mortality: 84%	14%	ICU mortality: SOFA score
Hayani *et al.*[26]	Study period: 2000–2007 $n = 106$ HSCT recipients (57% allogeneic), before and after introduction of RACE teams (Rapid Assessment of Critical Events)	2000-2004 cohort: ICU mortality: 34% Hospital mortality: 45% Day-100 NRM: 48% 2005–2007 cohort: ICU mortality: 38% Hospital mortality: 48% Day-100 NRM: 50%	2000–2004: 12% 2005–2007: 14%	ICU mortality: Admission diagnosis (sepsis versus others) Vasoactive drugs
Depuydt *et al.*[21]	Study period: 2000–2007 $n = 44$ Allogeneic HSCT recipients	ICU mortality: 61% Hospital mortality: 75% 6-Month mortality: 80%		Hospital mortality: Bacterial infections
Solh *et al.*[33]	Study period: 1998–2009 $n = 179$ Allogeneic HSCT recipients requiring MV before day 100	Day-100 mortality: 83%	20%	Overall survival: Creatinine level Platelet count
Bayraktar *et al.*[17]	Study period: 2001–2010 $n = 377$ Allogeneic HSCT recipients	Hospital mortality: 64% 1-Year mortality: 85%	13%	Hospital mortality: HCT-CI $\geqslant 2$ RIC ICU admission during conditioning regimen Acute GvHD
Townsend *et al.*[34]	Study period: 1996–2007 $n = 164$ Allogeneic HSCT recipients	ICU mortality: 68% 1-Year OS: 19% 5-Year OS: 17%	30%	ICU survival: RIC MV Urea
Gilbert *et al.*[24]	Study period: 2006–2010 $n = 164$ HSCT recipients (93% allogeneic) with ARF requiring MV	Day-100 mortality: 56% Hospital mortality: 63% Overall mortality: 87%	21%	100% mortality rate: Renal failure and concomitant respiratory or liver dysfunction at the time of intubation
Benz *et al.*[18]	Study period: 1998–2007 $n = 250$ Allogeneic HSCT recipients	ICU mortality: 64% 6-Month mortality: 85% 1-year survival: 28%	13%	ICU admission: Acute GvHD $\geqslant 2$ HLA mismatch
Allareddy *et al.*[16]	Study period: 2004–2010 $n = 6074$ SCT patients with ARF requiring MV (allogeneic 68%)	Hospital mortality: 51%	/	Hospital mortality: Continuous MV $\geqslant 96$ h

Table 1. (Continued)

Reference	*Main patient characteristics*	*Main outcomes*	*ICU admission rate*	*Independent prognostic factors*
Boyaci *et al.*[19]	Study period: 2007–2010 *n* = 48 HSCT recipients (85% allogeneic)	ICU mortality: 69%	/	ICU mortality: APACHE II Vasopressors
Canet *et al.*[20]	Study period: 2007–2011 *n* = 75 Allogeneic HSCT recipients	ICU mortality: 19% Hospital mortality: 46%	11.6%	Hospital mortality: Acute kidney injury Acute kidney injury associated with liver dysfunction
Moreau *et al.*[36]	Study period: 1998–2008 *n* = 53 Allogeneic HSCT recipients	ICU mortality: 57% Day-100 mortality: 60% 6-Month mortality: 66%	10%	Day-100 mortality: Active GvHD MV
Galindo-Becerra *et al.*[23]	Study period: 1993–2014 *n* = 68 HSCT recipients (75% allogeneic)	ICU mortality: 90%	20%	ICU mortality: MV
Escobar *et al.*[22]	Study period: 2007–2011 *n* = 97 HSCT recipients (66% allogeneic)	ICU mortality: 64% 1-Year mortality: 84%	30%	ICU mortality: Acute GvHD
Lengline *et al.*[29]	Study period: 1997–2011 *n* = 497 Allogeneic HSCT recipients	1997–2003 cohort: ICU mortality: 52% Day-90 mortality: 69% Hospital mortality: 67% 2004–2011 cohort: ICU mortality: 30% Day-90 mortality: 51% Hospital mortality: 48%	1997–2003: 20.4% 2004–2011: 22.8%	Day-90 mortality: GVHD grade 3–4 RRT MV HSCT > 2003
Mokart *et al.*[30]	Study period: 2003–2011 *n* = 102 Allogeneic HSCT, RIC only	ICU mortality: 39% Hospital mortality: 60% 6-Month mortality: 78% 1-Year mortality: 83%	17%	ICU admission: Age > 60 years Absence of complete remission before HSCT Hospital mortality: ICU admission for neurological dysfunction MV SAPS II at ICU admission Time between diagnosis and HSCT
Platon *et al.*[37]	Study period: 2009–2013 *n* = 73 Allogeneic HSCT recipients	ICU mortality: 40% Hospital mortality: 63% 1-Year mortality: 84%	23%	ICU mortality: Active GvHD MV Worsening SOFA score from day 1 to 3

Abbreviations: APACHE III = Acute Physiology And Chronic Health Evaluation III; HCT-CI = hematopoietic cell transplantation comorbidity index; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit; MAC = myeloablative conditioning; MV = mechanical ventilation; NRM = nonrelapse mortality; OS = overall survival; RIC = reduced-intensity conditioning; RRT = renal replacement therapy; SAPS II = Simplified Acute Physiology Score II; SOFA = Sepsis Related Organ Failure Assessment. [a]Results of univariate analysis (no multivariate analysis available).

improved survival. The accessibility of allo-HSCT has been greatly increased by the development of alternative donor sources, such as cord blood and haploidentical transplantation.[82,83] Allo-HSCT has been expanded to older patients and to those with comorbidity[76] with the development of RIC and reduced toxicity conditioning regimens,[84,85] translating into reducing the incidence of severe GvHD and nonrelapse mortality. The use of peripheral blood hematopoietic stem cells rather than bone marrow is a major therapeutic advance, resulting in faster hematopoietic and immunologic reconstitution and decreasing infectious complications.[86] Improved GvHD prevention, diagnostic approach and treatment have decreased its severity.[6,87] The use of Defibrotide, as well as the increasing use of RIC, could play a role in decreasing veno-occlusive disease incidence.[38,88]

Moreover, progress in selecting patients has been made, particularly in refining risk strategies and evaluating comorbidity.[5,76] Interestingly, patients who actually undergo transplantation are older, carrying more comorbid conditions and with more advanced disease than 10 years ago.[29] However, outcome keeps improving.

ICU management improvements

In parallel, several improvements in ICU management can be noted. The finding that patients with multiple organ dysfunction and high organ failure scores at ICU admission have higher mortality rates has generated several hypotheses regarding the possible link between delayed ICU admission and mortality.[89] High acute illness severity at ICU admission can be explained by different factors, mainly represented by diagnostic difficulties and suboptimal evaluation in wards, resulting in underestimation of disease severity followed by an unexpected clinical deterioration. An early ICU management may translate into better survival, allowing the use of noninvasive diagnostic strategies,[90,91] reducing the number of patients admitted with MOF and initiating early organ failure support. Five recent studies demonstrated the benefit of early ICU admission in the context of cancer patients with ARF,[89] newly diagnosed AML,[92] septic shock of pulmonary origin,[93] cancer patients admitted to the ICU[94] and for patients with hematologic malignancies admitted to the ICU.[10] Yet, it has never been clearly demonstrated in allo-HSCT patients. It implies a close cooperation between hematologists and intensivists

Table 2. Prognostic factors of outcome of critically ill allogeneic HSCT patients

Pretransplant characteristics	HCT-CI [21]
	Age >60 years[34]
	Absence of CR before HSCT[34]
	Time between diagnosis and HSCT[34]
Transplant-related characteristics	MAC[35]
	RIC[21,38]
	HLA mismatch[22]
	GvHD[13,21,22,26,33,40,41]
ICU-related characteristics	MV[13,20,27,28,31,33,34,36,38,40,41]
	Vasopressors[23,30,31,32,35]
	RRT[28,33,36]
	APACHE II[23,35]
	SOFA[29,41]
	SAPS II[34]
	Platelet count[35,37]
	Bilirubin level[13,24]
	Urea or creatinine level[24,37,38]
	Time between HSCT and ICU admission[13]
	Bacterial infections[25]
	ICU admission for neurological dysfunction[34]

Abbreviations: APACHE II = Acute Physiology And Chronic Health Evaluation II; HCT-CI = hematopoietic cell transplantation comorbidity index; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit; MAC = myeloablative conditioning; MV = mechanical ventilation; RIC = reduced-intensity conditioning; RRT = renal replacement therapy; SAPS II = Simplified Acute Physiology Score II; SOFA = Sepsis Related Organ Failure Assessment.

upstream to evaluate the best moment for ICU transfer,[94] and improved recognition of impending clinical deterioration in the ward. The implementation of dedicated 'rapid sepsis teams' may help to develop this strategy. Hayani *et al.*[26] evaluated the impact of critical care outreach on allo-HSCT recipients, introducing Rapid Assessment of Critical Events (RACE) teams and reducing the number of failed organs at ICU admission. Along this line, the development of HSCT-specialized ICU could improve outcome, as has been demonstrated in cancer-specialized ICU.[95]

The development of new ICU admission policy and a better patient selection contributed to improved ICU survival.[96] Management of organ failure has also improved with the use of early goal-directed therapy in septic shock,[97] the use of lower tidal volume in acute respiratory distress syndrome,[98] the increasing use of NIV[73,74] and the recent utilization of HFNC.[99] Several recent publications investigated the place of NIV and HFNC. Lemiale *et al.*[100] compared NIV with standard oxygen therapy in immunocompromised patients with hypoxemic ARF in a multicenter randomized trial (INVICTUS study), and did not find any mortality difference between the two arms. In another study focusing in ARF in hematology patients, once more, NIV did not decrease hospital mortality compared with standard oxygen.[101] These results contradict older data, showing that early initiation of NIV was associated with significant reduction of intubation rate and improvement in hospital survival.[102] However, it has to be kept in mind that mortality rates of patients requiring MV in the 2000s were much higher, probably explaining this dissonance. HNFC has been compared with standard oxygen and NIV in the recent FLORALI study in unselected ARF hypoxemic patients, with no difference in terms of intubation rate.[103] However, HFNC was associated with higher day-90 survival, but we cannot conclude that HFNC increased mortality, as it was not the primary outcome, and ventilation settings were controversial. In the setting of cancer patients with hypoxemic ARF, HFNC associated with NIV was independently associated with improved survival and lower ventilation-free days.[75] The optimal oxygen delivery system is currently under examination, and a recent publication focused on Venturi mask versus HFNC in ARF immunocompromised patients, with no difference highlighted.[104]

LIMITATIONS OF THE PUBLISHED EXPERIENCES AND UNRESOLVED ISSUES

The outcome in critically ill allo-HSCT patients has been assessed in several studies. The results are difficult to interpret as the majority of them are single center, retrospective and based on small sample size, making them underpowered, and they use different criteria and threshold variables for ICU admission and to define organ failures. Moreover, they are usually designed by intensivists and several major disease characteristics such as disease response and cytogenetics are poorly documented.

Patient heterogeneity remains one of the limiting factors. Most of the studies mixed allogeneic and autologous HSCT recipients who have radically different outcomes. In addition, most of the studies included patients with data up to 15 years back and did not reflect recent improvements. The majority of the results were drawn from data combining different stem cell sources, conditioning regimens, GvHD prophylaxis, donor sources, malignancies and response status. Therefore, the predictive power of prognostic factors has to be carefully interpreted according to transplantation features.

In addition, the criteria for ICU admission greatly differ. ICU admission criteria are very heterogeneous and not clearly evaluated. Most trials did not address the issues of patient selection bias. Steroid sensitivity over time and remission status of GvHD at ICU admission are crucial factors but rarely assessed. Nevertheless, these data reflect an overall trend toward improved outcome.

Many questions remain unresolved.[11] First, traditional prognostic scoring systems have been criticized for having limited value in predicting mortality of allo-HSCT patients. Second, the prognosis of critically ill allo-HSCT patients benefiting from haploidentical transplantation or from a second allo-HSCT[105] is currently unknown and deserves to be investigated. Another important challenge is whether earlier involvement of multi-specialist management may translate into an earlier ICU transfer, before MOF onset. Furthermore, it has not been established whether transplantation units equipped to provide critical care management attain superior outcomes. Recent evidence supports the use of prophylactic NIV performed in the ICU in hematology patients.[73,74] This strategy needs to be evaluated in allo-HSCT patients. Moreover, biological data are lacking to explain the detrimental interaction between GvHD and >90% mortality after life-sustaining interventions. Finally, new strategies have to be developed in the three subgroups of patients carrying the poorest prognosis: patients requiring MV, GvHD and MOF.

A promising, but underinvestigated, issue is the nutritional status of allo-HSCT patients. They cumulate various risk factors for malnutrition, including chemotherapy-induced nauseas, mucositis, diarrhea, digestive GvHD, infections, inflammation and prolonged hospitalization. Nutritional support is recommended during HSCT.[106] Enteral nutrition has recently demonstrated its protective effect on early overall survival, infectious mortality and incidence of grade 3–4 GvHD[107–109] and could play a role in immunomodulation.[110]

Finally, no data are available for evaluating long-term outcome and quality of life after ICU stay. Relative to healthy controls, HSCT survivors reported poorer physical, psychological and social functioning that persists many years after HSCT.[111] Moreover, allo-HSCT patients are exposed to late complications, including infections, chronic GvHD, second cancers, iron overload and liver, endocrine, ocular, musculoskeletal, vascular, renal and neurologic disorders responsible for substantial morbidity.[112] The psychosocial aspect and quality of life is a major issue for these patients, with depression, anxiety, fatigue and sexual dysfunction being

Table 3. Outcomes of adult HSCT recipients admitted to the ICU requiring mechanical ventilation

Reference	*MV rate*	*Main outcomes*
Kew *et al.*[28]	68%	Overall mortality: 80%
Naeem *et al.*[31]	50%	ICU mortality: 83% Versus 62% in non-MV patients
Pene *et al.*[13]	58% (32% NIV, whom 66% needed IMV)	ICU mortality: 82% Hospital mortality: 84% 6-Month mortality: 86% 1-Year mortality: 89%
Yang *et al.*[35]	100%	ICU mortality: 80% Hospital mortality: 83%
Scales *et al.*[32]	51%	Overall mortality of patients with MV $\geqslant$ 10 days: 93%
Huynh *et al.*[27]	71%	ICU mortality: 70% Hospital mortality: 78% 6-Month mortality: 87%
Gilli *et al.*[25]	76% (28% NIV, 48% IMV)	Overall mortality: 80% Versus 32% if no respiratory support
Depuydt *et al.*[21]	73% (9% NIV, all were intubated)	Hospital mortality: 84% 6-Month mortality: 88%
Solh *et al.*[33]	100%	Day-100 mortality: 83%
Townsend *et al.*[34]	62% (35% NIV, 50% MV)	Successful NIV 19%
Gilbert *et al.*[24]	100% MV	All patients requiring MV: Day-100 mortality: 56% Hospital mortality: 63% Overall mortality: 87% Patients requiring MV and RRT: Day-100 mortality: 60% Hospital mortality: 90% Overall mortality: 100%
Allareddy *et al.*[16]	17% IMV $<$ 96 h 41% IMV $\geqslant$ 96 h 6.4% NIV	Hospital mortality if continuous IMV $<$ 96 h: 61% Hospital mortality if continuous IMV $\geqslant$ 96 h: 67% Hospital mortality if NIV: 55% Hospital mortality if no continuous IMV: 31%
Lengline *et al.*[29]	1997–2003 cohort: NIV: 31% IMV: 58% 2004–2011 cohort: NIV: 28% IMV: 44%	1997–2003 cohort: Successful NIV: 33% Hospital mortality if IMV with aGvHD: 85% Hospital mortality if IMV without aGVHD: 84% 2004–2011 cohort: Successful NIV: 51% Hospital mortality if IMV with aGVHD: 82% Hospital mortality if IMV without aGvHD: 66%
Mokart *et al.*[30]	39% IMV, NIV 41%	Successful NIV: 61% ICU mortality: 39% Hospital mortality: 60% Factors independently associated with: NIV success: neutropenia at ICU admission NIV failure: hemodynamic instability at ICU admission Hospital mortality of patients treated with IMV: serum bilirubin level

Abbreviations: aGvHD = acute GvHD; cGvHD = chronic GvHD; HSCT = hematopoietic stem cell transplantation; ICU = intensive care unit; IMV = invasive mechanical ventilation; NIV = noninvasive ventilation; MV = mechanical ventilation.

very common. The increasing use of RIC may have improved long-term outcome with a preserved long-term quality of life.[113] In the ICU setting, few data are available for patients with hematological malignancies.[10,114,115] Studies are warranted to evaluate long-term outcome in allo-HSCT long-term ICU survivors. The place of patient and family wishes and implication in the shared decision-making process also needs to be clearly evaluated.[116,117]

AT THE BEDSIDE, THE CHOICE OF ICU ADMISSION OR NOT?

The decision-making process of ICU admission of allo-HSCT patients is incredibly hard, and no guidelines are available to help us. Critically ill allo-HSCT recipients frequently require high use of ICU resources, with major investment from hematology and ICU teams. However, ethical and cost concerns may make the indications for aggressive life support questionable. A rational policy of ICU admission triage in these patients is very hard to define, as each decision for ICU admission is a case-by-case decision at the patient's bedside, involving intensivists, hematologists and patients, to identify those who may potentially benefit from life-sustaining therapies.[96,118]

In light of recent data, the main question is to determine patients who are likely to benefit from ICU management. Schematically, policy of broad ICU admission and extensive unlimited intensive care support, including MV, is justified for allogeneic HSCT patients admitted early in the ICU, with one isolated organ dysfunction, regardless of disease and transplant characteristics. In these situations, the decision of undelayed ICU admission appears safe, appropriate and consensual.[13,29]

On the other side, some clinical situations are known to be associated with nearly 100% mortality despite optimal care,[11] suggesting that some patients are unlikely to benefit from ICU management. Patients concerned are bedridden patients,[17] patients with uncontrolled or refractory disease,[30] uncontrolled GvHD requiring MV[13,17,18,22,29] and patients with MOF with delayed ICU admission.[24] In these particular situations, ICU transfer

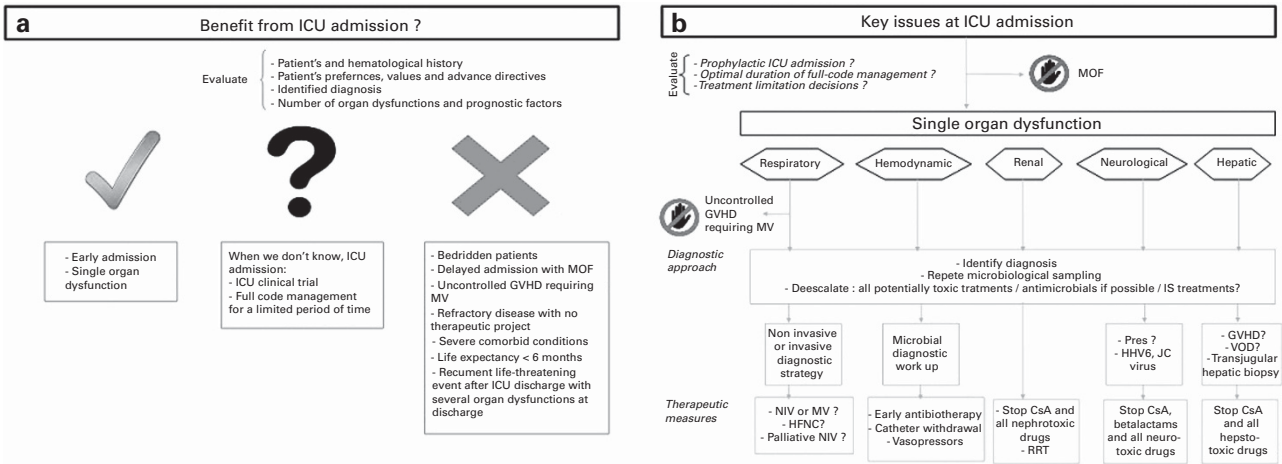

Figure 3. Decision-making process for ICU admission: ICU benefit according to clinical situations (**a**) and ICU management and unresolved questions according to reason for ICU admission (**b**). CsA = cyclosporine A; PRES = posterior reversible encephalopathy syndrome; RRT = renal replacement therapy; VOD = veno-occlusive disease. A full color version of this figure is available at the *Bone Marrow Transplantation* journal online.

does not appear to be a reasonable option. However, systematically denying access to these unfavorable patients is not the answer, as we need to keep improving in these tough situations. Considering ICU trials in these situations could appear to be an interesting option.

Between these two opposite clinical situations, there is a large gray zone, where ICU admission must be a case-by-case and multidisciplinary decision. When we do not know, patients should be transferred to the ICU, in the setting of an ICU trial or benefit from a full-code ICU management without intensity limitation, for a limited time period, with a daily reassessment of organ dysfunctions and factors associated with mortality. Treatment-limitation decisions are then discussed according to evolution, with organ failure between admission and days 5–7 being a major prognostic factor.[8,37,95,119] In patients with no improvements, treatments should not be escalated and high-quality palliative care should be initiated.[120] Nevertheless, palliative ICU management can be offered to highly selected patients,[121] although this approach is only very rarely warranted. In Figure 3, we propose several keys for the decision-making process.

Once again, the goal is to admit patients with one isolated organ dysfunction that is only possible with early ICU admission.

CONCLUSION

Outcomes have improved over time and many classic determinants of mortality have become irrelevant. Except for patients with uncontrolled GvHD requiring MV, improvements in outcome of allo-HSCT patients can be transposed into the ICU. Recent data support the usefulness of ICU admission of selected critically ill allo-HSCT patients, as mortality rates have declined significantly over the past decade. The collaboration between hematologists and intensivists, permitting early ICU admission, is crucial. Future research could be facilitated by the development of prospective multicenter trials.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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