5.1 Introduction

Great progress has been made in stem cell transplantation over the last years. Most of the progress can be ascribed to an understanding of the human leukocyte antigen (HLA) system for donor selection, immunosuppression for prevention and treatment of graft-versus-host disease (GVHD), and significant advances in infectious disease prevention, therapy and supportive care. As a result of this progress, the number of potential candidates to receive a transplant has greatly increased, and the survival figures have been progressively encouraging. In fact, the term “hematopoietic stem cell transplantation” (HSCT) has supplanted the previously employed term “bone marrow transplantation” to reflect the broader range of donor stem cell sources available: bone marrow, fetal cord blood, and growth factor-stimulated peripheral blood [1]. Unfortunately, the use of aggressive chemotherapeutic regimens frequently results in life-threatening complications, requiring transfer to the intensive care unit (ICU). Pulmonary complications, both infectious and noninfectious, occur in up to 60% of HSCT recipients, and a significant percentage of them will require ICU admission [1–3]. Infectious complications are more common in allograft recipients because of the requirement of immunosuppressive agents to prevent and treat GVHD. In addition, GVHD itself causes an immunodeficient state. In contrast, noninfectious acute lung injury syndromes (e.g., idiopathic pneumonia syndrome, diffuse alveolar hemorrhage) occur after
both allogeneic and autologous transplantation with similar frequency [1]. The recognition as well as management of pulmonary complications that result from immunosuppression is a challenging task for clinicians. Although the above-described improvements in patient care have improved the overall survival, once a patient with a hematologic malignancy requires advanced intensive care support, the prognosis worsens significantly with high associated mortality rates, particularly in patients with acute respiratory failure (ARF). Although the survival rate of HSCT recipients admitted to the ICU has been steadily improving, it remains under 50%, with a long-term survival rate under 20% [4].

5.2 Main Indications for ICU Admission

It is estimated that 15–30% of the HSCT recipients are admitted to the medical ICU for the management of different complications, with 20% of them requiring mechanical ventilation (MV). In our experience from data collected within a 10-year period [5], 89 patients with hematological malignancies with pulmonary complications were admitted to a respiratory ICU. Fifty-two of 89 (58%) of these patients were HSCT recipients. Patients were admitted to the ICU because of ARF in 61 instances (68%; including 23 patients with acute respiratory distress syndrome, ARDS), sepsis syndrome (12%), pulmonary hemorrhage (9%), heart failure (8%), and miscellaneous conditions (2%). The most common cause of ARF was a pulmonary infection, which was diagnosed in 60% of the patients for whom a specific diagnosis was obtained. Other authors have also found that infection is the most frequent cause of admission to the ICU, particularly in those with neutropenia where up to 80% have a clinically documented infection [6–8]. Also, among organ failures at ICU admission, acute respiratory failure and severe sepsis or septic shock are present in up to 80% of critically ill cancer patients [2, 9] (Table 5.1).

Clinical management of infections in critically ill immunocompromised patients is complex since virtually any microorganism may be involved at any time in the evolution, mainly depending on the net state of immunosuppression. The high associated mortality requires a rapid and sometimes invasive diagnostic approach to trying to obtain an etiological diagnosis allowing the early introduction of specific treatment.

### Table 5.1 Indications by organ system for ICU admission

| Indication        | HSCT recipients (%) | Hematologic patients (%) |
|-------------------|---------------------|--------------------------|
| Respiratory       | 48%                 |                          |
| Sepsis            | 23%                 |                          |
| Cardiac           | 19%                 |                          |
| Neurologic        | 6%                  |                          |
| Bleeding          | 2%                  |                          |
| Others            | 2%                  |                          |

Modified from ref. [10]

5.3 Etiology of Pulmonary Infections

#### 5.3.1 Bacterial Infections

Bacteria are the most frequent cause of pulmonary infections in patients with hematological malignances, accounting for 15–20% of all respiratory infections in HSCT recipients [1] with an associated mortality of 22% [10] (Table 5.2). Different series have shown that bacterial pneumonia is also the most common cause of admission to the ICU in HSCT recipients [11]. One of the problems in diagnosing bacterial pneumonia in hematological patients is the inability to identify the organism in the majority of these patients, which may underestimate the incidence of these infections. Factors that generally increase the risk of bacterial pneumonia following HSCT include pre-transplantation immune status, type of conditioning regimen, and degree and duration of neutropenia [12]. In transplant recipients, bacterial infections may occur at any time in the post-

### Table 5.2 Etiologic diagnosis in HSCT recipients and in hematological patients

| Infection Type       | HSCT recipients (%) | Hematologic patients (%) |
|----------------------|---------------------|--------------------------|
| Bacterial            | 11                  | 23                       |
| Fungal               | 13                  | 19                       |
| Polymicrobial        | 20                  | 8                        |
| Other infections     | 2                   | 4                        |
| Pulmonary edema      | 5                   | 4                        |
| DAH                  | 8                   | 4                        |
| NOC                  | 3                   | 4                        |
| Other non-infections etiologies | 7          | 6                        |
| Undetermined         | 23                  | 28                       |

Modified from ref. [7]
transplantation period; however, they seem to be more common in the pre-engraftment phase due to the presence of mucositis and neutropenia. Potential pathogens are myriad. Encapsulated organisms, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*, are particularly prevalent; however, many other bacteria must also be considered, particularly *Staphylococcus aureus* (including methicillin-resistant, MRSA) and multi-resistant gram-negative bacilli, such as *P. aeruginosa* [13]. Some epidemiological studies have shown that *Legionella* sp. pneumonia is more prevalent in the immunocompromised host [14]. It is important to consider that 15–30% of cases diagnosed as bacterial pneumonia are mixed bacterial/opportunistic infections [11–13]. This fact has to be considered, particularly in patients that do not respond to appropriate specific antibiotic treatment.

### 5.3.2 Invasive Fungal Infections

Since neutrophils are the key cells in the defense against *aspergillus* sp. and other molds, the neutropenic patient and particularly HSCT recipients are at highest risk for dissemination. A steady rise in the documented cases of invasive pulmonary aspergillosis (IPA) post-transplantation has been documented. The risk for IPA is much higher following allogeneic HSCT when compared to autologous transplantation (incidence is 2.3–15% and 0.5–4%, respectively) [15]. Mortality rates for HSCT recipients with IPA have historically been as high as 80%; however, during the past 2 decades, the outcome of this infection seems to be changing. Recently, the Prospective Antifungal Therapy Alliance Registry performed a multicenter study to assess the epidemiology and outcomes of invasive fungal infections in HSCT recipients [16]. In this study, a total of 250 proven or probable invasive fungal infections were included. Almost 70% of the patients had received an allogeneic HSCT, and 31% had received an autologous HSCT. In this series, mortality rates of 21% and 35% at 6 and 12 weeks of diagnosing proven or probable IPA were reported, numbers that are consistent with those reported by other authors, confirming the survival gain evidenced after the inclusion of azoles in the therapeutic armamentarium of invasive fungal infections. Interestingly, the absence of MV or/and hemodialysis was significantly associated with improved survival.

With regard to Candida infections, with the expanded use of the new antifungal therapies, a higher incidence of infections caused by *Candida krusei* and *Candida glabrata* has been reported [17, 18]. Also infections due to fusarium, *Penicillium purpurogenum* [19], and *Scedosporium prolificans* [20, 21] are increasingly being reported. In contrast, a marked decrease in the incidence of *P. jiroveci* pneumonia has been observed over the last years, mainly because of prescription of specific prophylaxis in patients at risk [22]. In a recent report, *P. jiroveci* infection was documented in 2.5% of patients undergoing allogeneic HSCT (2.5%). The majority of cases occurred late in the course following HSCT (median 14.5 months) [23] and with a CD4+ count less than 200 cells/mm³.

### 5.3.3 Cytomegalovirus (CMV)

Traditionally, CMV pneumonia has affected 20–35% of HSCT recipients [24], being a common cause of ICU admission. However, the application of antiviral prophylaxis and the systematic use of preemptive therapy have changed the epidemiology of CMV pneumonia in HSCT recipients. Currently, in allogeneic HSCT recipients, the incidence of CMV pneumonia is 10–30% [25]. Also mortality is revised downwards between 30% and 50%. In the pre-prophylaxis era, onset of CMV pneumonia almost invariably occurred between engraftment and day 100. The use of prophylaxis has also shifted the onset of CMV pneumonia in allogeneic HSCT to after the first 100 days, especially in patients with non-myeloablative HSCT and during the treatment of chronic GVHD [26].

Despite improvements in specific treatment, survival of patients with established respiratory failure requiring mechanical ventilation is very poor.

### 5.3.4 Respiratory Viruses

Recent developments in molecular-based diagnostic tools have shown that conventional respiratory viruses [influenza, parainfluenza, respiratory syncitial viruses (RSV), adenoviruses, enteroviruses, and rhinoviruses] may commonly cause respiratory illnesses with significant morbidity and mortality among HSCT recipients. The incidence of these
viral infections following HSCT ranges between 11–65% [27]. Upper respiratory tract infections in HSCT recipients are usually self-limiting. However, the progression to pneumonia carries a significant associated mortality. In one study of community respiratory viral infections following HSCT, the main viruses were RSV (35%), parainfluenza (30%), rhinovirus (25%), and influenza virus (11%). Of these, pneumonia occurred in 49% of patients with RSV infection, 22% of those with parainfluenza virus, and 3% of rhinovirus infection [28]. In another recent review of 343 cases of community respiratory viral infections in 306 adults with hematological malignancies (mostly HSCT recipients), parainfluenza (mainly type 3) accounted for 27% of infections, influenza (mainly type A) for 33% of infections, and RSV for 31% of infections. Community respiratory viral infections progressed to pneumonia in 35% of patients with equal frequency among the three viruses [27]. Interestingly, community respiratory viruses are often co-pathogens with other organisms, including bacteria, fungi (aspergillus), or other viruses (CMV). Herpes simplex virus 1 reactivates in 80% of HSCT recipients and occasionally may be associated with pneumonia. However, universal prophylaxis with acyclovir and gancyclovir has significantly reduced the incidence [27, 29]. Human herpes virus (HHV-6) may act as a co-pathogen with CMV or act as an isolated cause of pneumonia [30].

5.4 Survival in the ICU

In this book, Groeger and colleagues report updated data on outcomes in patients with hematological malignancies admitted to the ICU. Suffering from hematologic malignancies is one of the most powerful predictors of mortality due to ARF in the ICU, and this is particularly true when patients with HSCT are considered and when MV is required. For many years, survival was considered dismal, with physicians supporting either denial of ICU admission or considering early treatment limitation decisions. Shuster and Marion [31] found a mortality of 80% in 77 patients treated in the ICU. Our study, evaluating prognostic factors of non-HIV-positive immunocompromised patients with pulmonary complications, showed that the mortality rate among HSCT recipients was almost twofold higher than that of patients with hematological malignances or of those who had received solid organ transplants. The requirement of mechanical ventilation was a critical predictor of poor outcome with mortality rates approaching 95% [7]. Long-term survival rates after MV are also dismal in recipients of allogeneic HSCT with active GVHD, with approximately 5% of patients surviving 6 months. Consequently, some clinicians have questioned the utilization of mechanical ventilatory support for these patients.

Over the last years, the pessimistic vision of the dismal outcome of hematological patients admitted to the ICU seems to be changing. First, the number of hematological patients requiring further ICU admission or MV has been decreasing [9]. Second, recent series support the notion that the prognosis for hematological patients admitted to the ICU has improved compared to that reported in the 1980s and early 1990s [32, 33]. Benoit et al. [32], evaluating a cohort of 124 patients with a hematologic malignancy admitted to the ICU for a life-threatening complication, observed an ICU and in-hospital mortality of 42% and 54%, respectively. Soubani et al. [2] evaluated 85 patients admitted to the medical ICU, representing 11.4% of patients who had undergone HSCT during the study period. Fifty-two patients (61%) survived their ICU stay, and 35 patients (41%) were discharged alive from the hospital. The long-term survival rate (>6 months) in this cohort was 28%. Moreover, 19 patients receiving MV (37%) survived their ICU stay, and 33 (97%) patients who did not require MV survived. The study showed short-term and long-term survival rates among adult HSCT recipients who had been admitted to the ICU that were higher than those previously reported. Azoulay et al. [34], in a study evaluating a large group of cancer patients with ARF due to a variety of causes, reported a mortality rate of less than 50%, reaffirming the survival gains achieved in critically ill cancer patients in recent years.

Although the above-mentioned results are promising, some factors should lead us to temper this optimistic picture. A recent meta-analysis by Van Gestel et al. [35] in a population of children did not show survival improvement over time when the variable MV was considered. When the specific studies included in this meta-analysis were individually evaluated, it was shown that some of them showed improved survival in
ventilated, post-HSCT patients, while others did not show such improvement. Even in those studies that reported improved survival, the need for MV was a strong indicator of worse prognosis. These controversial results may be due to many different variables accounting for survival in hematological patients requiring ICU admission.

In the following, we report some of the most determining variables that have been related to survival in HSCT recipients.

### 5.4.1 Selection of Patients

The number of HSCT recipients requiring ICU admission is decreasing [2]. This lower ratio of admissions is unlikely to be due to the underutilization of ICU resources. Rather, it is probably related to a shorter neutropenic phase, better antimicrobial prophylaxis and treatment, and improved experience in the management of these patients before their condition deteriorates. Also, the improved survival may partially be explained by the implantation of restrictive policies for selecting patients to ICU admission. Although the selection of the best candidates for ICU care is difficult and there are no objective data to support the decision [36], it is possible that selection of patients who are most likely to benefit from ICU admission might explain part of the survival gains. Also, it is possible that the decrease in mortality was, in fact, accompanied by a decrease in the number of patients requiring MV, a known risk factor for poor outcome. Reasons for a decrease in the number of HSCT patients who require MV may be related to a decrease in pulmonary complications in these patients or because hematologists and intensivists are better at the early management of pulmonary complications, thereby minimizing the number of patients who ultimately require MV [3, 37].

### 5.4.2 Transplant Specific Factors

HSCT recipients have “per se” an adverse prognostic factor in many studies. However the prognosis of both autologous and allogeneic HCT seems to be different. In allogeneic HSCT recipients, infectious complications are more common because they require the administration of immunosuppressive agents after transplantation to prevent or treat GVHD. In addition, GVHD itself causes an immunodeficient state by involving mucosal surfaces, the reticuloendothelial system, and bone marrow. Because of all this, the mortality of recipients of allogeneic HSCT, requiring life-sustaining measures, is extremely high [3, 9]. In contrast, autologous HSCT recipients, who receive a less intense conditioning regimen, have a similar prognosis to other critically ill cancer patients in that their short-term risk of death depends only on the number and type of organ dysfunctions. Few studies have emphasized the radically different outcomes between allogeneic and autologous HSCT recipients in the ICU. Shorr et al. [38] collected data focusing only on autologous HSCT, with the aim of determining the frequency of and risk factors for the use of MV in this population. These authors concluded that MV is infrequently needed following autotransplants. Of 159 patients included, only 17 required MV (10.7%), with 3 of them surviving the episode (17.6%). It is possible that the large proportion of autologous transplantation recipients included in the recently published cohorts might be a confounding factor and led to an underestimation of the mortality rate of allogeneic graft recipients. In particular, the recent series by Soubani et al. [2], which showed a significant improvement in survival in HSCT recipients, included a cohort with almost half of the patients (47%) having received an autologous HSC transplant.

Finally, other reasons related to the transplantation technique that can indicate an improved survival are the reduced toxicity of conditioning regimens, the use of alternative hematopoietic precursor sources, such as mobilized peripheral blood stem cells, and cytokines, such as hematopoietic cell colony-stimulating factors, which significantly shorten the time to engraftment, thus decreasing the incidence of infectious pulmonary complications.

### 5.4.3 Ventilatory Support

The outcome of alo-HSCT recipients requiring MV has not improved for 2 decades, with consistent survival rates of less than 20% [37, 39, 40]. Patients requiring MV have a worse prognosis than similar patients matched for general severity-of-illness...
scoring systems such as APACHE II, because MV may be directly injurious through increasing the risk for nosocomial pneumonia [41, 42]. Moreover, the association of ARF requiring MV with other organ failures has been reported to be almost uniformly fatal (Fig. 5.1). The avoidance of intubation using ventilatory strategies aimed at minimizing further lung injury may change the dismal prognosis associated with MV in HSCT recipients. Different studies have shown that early implementation of noninvasive ventilation (NIV) is indicated in an early stage of hypoxic ARF in immunocompromised patients, since it decreases both the requirement of intubation and the incidence of nosocomial pneumonia, and consequently this ventilatory support might improve survival [43–45]. However, caution should be used concerning the unselective use of NIV in immunocompromised patients. Azulay et al. [34] conducted a prospective study to identify factors associated with death in critically ill cancer patients admitted for ARF. These authors observed that mortality in patients treated with NIV who subsequently did not require conventional MV was only 15%, confirming the critical goal that this technique can add to the management of critically ill cancer patients. However, mortality in patients that required conventional MV after 72 h of NIV was very high. The absence of benefit from NIV in patients with severe lung involvement is in agreement with previous reports, suggesting that in selected cases NIV might have a deleterious impact by delaying conventional MV in patients who have ARDS and are managed with nonoptimal diagnostic and treatment strategies. Depuydt et al. [46], in a retrospective revision of 26 patients with hematologic malignancies treated with NIV for ARF, could not demonstrate a survival benefit for the use of NIV in comparison with control patients receiving MV and matched for SAPS II. In this study, NIV was mainly used for the treatment of patients with acute severe hypoxic failure, and 60% of them required immediate endotracheal intubation as well as vasopressor therapy because of circulatory shock [45]. They hypothesized that the protective effect of NIV might be exerted only if applied immediately in an early, more compensated phase of their critical illness.

In summary, based on the extremely poor prognosis of patients requiring MV and the promising results obtained with NIV, it seems logical to recommend the application of this type of ventilatory support to HSCT recipients with pulmonary infiltrates once significant respiratory failure has ensued. Further studies are needed to confirm these results and to determine the optimal duration of NIV in hematological patients.

### 5.4.4 Importance of Establishing a Specific Diagnosis

HSCT recipients with pulmonary infiltrates need to be managed aggressively, and the underlying etiology must be identified as early as possible. The possibility
of non-infectious complications and the difficulty of making an antibiotic selection in light of growing resistance and the wide spectrum of potential etiologic factors emphasize the importance of designing strategies aimed at obtaining an early diagnosis. This is particularly true if we consider that inadequacy of the empirical treatment in the ICU setting increases the risk of death significantly [47]. In this sense, it has been shown that early diagnosis of both viral and fungal infections decreases mortality [48]. The use of both non-invasive and bronchoscopic techniques may facilitate the diagnosis in the majority of cases [49]. Some authors advocate the use of non-invasive diagnostic techniques as the cornerstone of the diagnostic workup of these patients, leaving bronchoscopic techniques for those selected patients with no evident risk of deterioration [50]. However, various studies in non-hypoxemic patients outside the ICU have shown that fiberoptic bronchoscopy is a low-risk procedure that can be performed in most patients and may add to the prompt identification of the specific etiologic agent, facilitating an etiology-guided treatment and avoiding unnecessary and potentially harmful additional treatment [51].

More controversial is whether or not the achievement of an early and specific diagnosis improves survival in HSCT recipients admitted to the ICU. Some investigators have reported that obtaining a specific diagnosis does not alter mortality in these patients [52–54]. Other researchers have reached different conclusions [51, 52]. The impact of diagnostic delay on mortality is an important emerging general theme in the care of seriously ill patients, particularly as it affects the adequacy of initial therapy [55]. Recommendations should focus on which is the best diagnostic strategy. In this sense, non-invasive techniques are increasingly used with success in these patients [52]. Bronchoscopy has, no doubt, an important role in the diagnosis, but a diligent analysis of its risk must be performed in each particular patient [52].

5.4.5 Other Factors Influencing Survival

Interestingly, in patients who are selected for ICU admission, the characteristics of the underlying malignancy are not associated with survival. Thus, the response to chemotherapy, stage of the malignancy, and other characteristics of the cancer have little or no impact on short-term survival [9]. The importance of leucopenia as a risk factor for mortality in critically ill patients with a hematologic malignancy is controversial. Different studies have reported a higher mortality in patients with prolonged neutropenia; however, this has not been confirmed by other authors [33]. The infectious etiology of the pulmonary complication has been classically considered as the most important cause of mortality in patients with a hematologic malignancy admitted to the ICU [7, 56], however, a recent study by Benoit et al. [8] reported a better prognosis in patients with documented bacterial infection than in those with non-bacterial pulmonary infections. Even in the absence of an identifiable bacterial microorganism, severely ill hematological patients admitted to the ICU with a clinical suspicion of bacterial infection had a better prognosis.

Other factors that have been considered as early predictors of poor outcome are the use of vasopressors, high urea levels [33], the number and severity of organ failures [9], liver failure, use of glucocorticoids for treating GVHD, and interval time between transplantation and ICU admission.

Although various retrospective analyses in immunocompromised patients indicate that higher APACHE II scores predict mortality [7], extrapolating a specific mortality rate to a particular patient is fraught with difficulty [55]. The information provided by general severity scores should only be considered in light of other clinical and more relevant variables.

Finally, some specific complications have been identified as predictors of favorable outcome, such as the engraftment syndrome, congestive heart failure, and diffuse pulmonary hemorrhage [57].

5.5 Conclusions

Over the last years, important advances in the management of hematological patients requiring ICU admission have taken place. As a result, survival in these patients has improved over the last decade. Thus, the general reluctance to admit patients with a hematologic malignancy to the ICU, even those with severe critical illness, is currently no longer justified. Not all transplanted patients with ARF can be expected to succumb. In the select, low-risk population of patients with autologous SCT with ARF, survival rates fall
within a range that we see for many other diseases that are routinely managed in ICU, such as sepsis-related ARDS [42]. In these patients, dedicated and aggressive support in the early phases of respiratory failure to attempt to establish an etiology seems warranted, allowing the early introduction of specific treatment. Early diagnosis is advantageous, and bronchoscopy, when carefully indicated, substantially increases the diagnostic yield, causing changes in the empirical treatment in the majority of patients [7]. The appropriate timing for withholding or withdrawal of support is probably the most contentious issue surrounding the care of these patients [42]. In patients in whom potential benefits of ICU admission are in doubt, a trial of full intensive ICU management should be given for a limited time period, during which daily evaluation of organ dysfunction may provide a more accurate prediction of survival than at admission [9].

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