Published in final edited form as:

J Intensive Care Med. 2016 December ; 31(10): 627–641. doi:10.1177/0885066615601046.

Management of Acute Respiratory Failure in Hematological Malignancy Patients

Rakesh Vadde, MD¹ and Stephen M. Pastores, MD, FACP, FCCP, FCCM²

¹Critical Care Fellow, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

²Professor of Medicine in Clinical Anesthesiology, Weill Cornell Medical College and Program Director, Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Acute respiratory failure (ARF) is the leading cause of ICU admission in patients with hematologic malignancies and is associated with a high mortality. The main causes of ARF are bacterial and opportunistic pulmonary infections and noninfectious lung disorders. Management consists of a systematic clinical evaluation aimed at identifying the most likely cause, which in turn, determines the best first-line empirical treatments. The need for mechanical ventilation is a major determinant of prognosis. Several studies have demonstrated successful outcomes with early use of noninvasive ventilation in these patients primarily attributed to the reduction of the need for, and complications from, invasive mechanical ventilation.

Introduction

Hematologic malignancies (leukemias, lymphomas, lymphoproliferative disorders, and plasma cell disorders) account for 20% of cancer diagnoses, with approximately 900,000 patients diagnosed annually worldwide¹. Over the past 20 years, substantial diagnostic and therapeutic advances have increased the overall and disease-free survival of these patients^{2–4}. However, these patients remain at risk for life-threatening infectious and noninfectious complications from either the toxicity of intensive cancer treatments including ionizing radiation, cytotoxic and targeted therapies, the more widespread use of allogeneic hematopoietic stem cell transplantation (HSCT), or from decompensation of comorbid conditions. As a result, the number of patients with hematological malignancies including those undergoing HSCT who are admitted to the intensive care unit (ICU) is increasing.

Acute respiratory failure (ARF) is the most common cause of ICU admission and the leading non-relapse cause of mortality in this patient population^{5,6}. The condition occurs in 10–20% of patients with acute leukemia or lymphoma and in nearly 50% of patients with

Address for Correspondence: Stephen M. Pastores, MD, Program Director, Critical Care Medicine, Department of Anesthesiology and Critical Care Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY, 1275 York Avenue C-1179, New York, NY 10065, P: 212-639-6673, F: 212-794-4333, pastores@mskcc.org.

No financial or other potential conflicts of interest exist for the authors.

neutropenia or those undergoing HSCT^{7,8}. The need for mechanical ventilation is a major determinant of prognosis in these patients with ICU mortality exceeding 75% for those who develop the acute respiratory distress syndrome (ARDS)^{7–18}.

In a previous article in this Journal, Mokart and Saillard reviewed the diagnostic approach of ARF in patients with cancer¹⁹. The objective of this article is to review the main causes and contemporary management of ARF in patients with hematological malignancies. For this review article, we conducted a focused PubMed search of the English medical literature over the past 15 years (January 2000–March 2015) of all the articles related to management of ARF in patients with hematologic malignancies. The keywords used were “cancer”, “tumor”, “malignancy”, “hematology patients”, “acute respiratory failure”, “intensive care”, “management”, “noninvasive ventilation”, “mechanical ventilation”, “invasive”, “prognosis” and “outcomes”. Relevant articles were read in full and their reference lists were searched for relevant articles.

Management Principles

General Measures

The management of ARF consists of a systematic clinical evaluation aimed at identifying the most likely cause (Figure 1), which in turn, determines the best first-line empirical treatments^{6,11}. General supportive measures include supplemental oxygen to correct hypoxemia, diuretics to decrease pulmonary congestion, initiation of empiric antimicrobial therapy in patients with suspected pulmonary infection or sepsis, and use of noninvasive or invasive ventilatory support.

Pulmonary infections remain the most common cause of respiratory failure in hematological malignancies and in those receiving chemotherapy. Factors that are responsible for increased risk of pulmonary infection include defects in humoral or cell-mediated immunity, neutropenia, use of corticosteroids, exposure to multiple antibiotics, and prolonged course of hospitalization. Schnell et al. studied the performance of the DIRECT criteria for identifying the most likely causes of ARF in cancer patients (n=424) admitted to the ICU²⁰. The main causes of ARF were bacterial infections (n=201, 47%), opportunistic pulmonary infections (n=131, 31%) and noninfectious lung disorders (n=92, 22%). Bacterial infections were microbiologically documented in 40% and clinically documented in 60%. Bacterial pneumonias (either microbiologically or clinically documented) more often had delays of <3 days since symptom onset and were associated with neutropenia (ANC < 500 cells/mm³), solid tumors, and multiple myeloma. The most common opportunistic pulmonary infections were invasive pulmonary aspergillosis (31%), respiratory viral infections (28%), and *Pneumocystis jiroveci* pneumonia (27.5%). Noninfectious lung disorders included pulmonary edema (49%), lung cancer or metastasis (49%) and pulmonary drug toxicity due to bleomycin and rituximab (2%)²⁰.

Management of Infectious Causes of ARF

Bacterial Pneumonias

Characteristic features of bacterial pneumonia in patients with hematologic malignancies include unilateral radiological changes, unilateral crackles, and presence of shock on ICU admission²⁰. Atypical presentations may also occur. Fever is common seen but cough, sputum production and classic lobar consolidation is often missing in cancer patients. Initial imaging is either normal or shows diffuse interstitial infiltrates. Pulmonary infiltrates are seen in 15%–20% in febrile neutropenia (ANC<500 cells/mm³), and are associated with increased mortality. In patients with impaired humoral (B-cell) immunity such as acute or chronic lymphocytic leukemia and multiple myeloma, bacterial infections with *Streptococcus pneumoniae* and *Hemophilus influenzae* are more frequent. In patients with chemotherapy-induced neutropenia, bacterial infections are primarily caused by *Staphylococcus aureus*, *Streptococcus pneumoniae*, gram-negative enteric bacilli (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*). In patients with impaired cellular (T-cell) immunity, infections can occur from *Legionella pneumophila*, *Nocardia asteroides*, *Rhodococcus equi* and *Mycobacterium tuberculosis*.

Empiric broad-spectrum antibiotic therapy should be started promptly, especially in patients with febrile neutropenia and tailored down according to the culture results obtained using invasive or non-invasive diagnostic techniques. Choice of initial antibiotic for community-acquired, hospital-acquired, ventilator-associated and aspiration bacterial pneumonias (Table 1) should consider the type^{21–23}, frequency of occurrence, and antibiotic susceptibility of the bacterial pathogens isolated (antibiogram) in the hospital. In patients with neutropenic septic shock, survival has improved over time^{24,25}. The recommended duration of antimicrobial therapy for patients with hospital-acquired or ventilator-associated pneumonia is 7–8 days; a longer course (up to 14 days) is required for multidrug resistant pathogens²⁶. For critically ill hospitalized cancer patients with *Legionella* pneumonia, a 21-day course of levofloxacin is recommended.

Viral infections

Community-acquired respiratory viruses are relatively common causes of pneumonia especially among HSCT recipients, patients with acute leukemias, and those with severe neutropenia or lymphopenia²⁷. Influenza, parainfluenza, and respiratory syncytial virus (RSV) account for most cases. Specific management depends on the type of virus infection (Table 2). Among HSCT patients with RSV pneumonia, upper respiratory tract infection (URTI) was noted to be almost twice more frequent than lower RTI (LRTI) at the time of diagnosis²⁸. Upper RTI progressed to lower RTI in 68% of untreated patients suggesting that early treatment might reduce progression. RSV-attributable mortality was 18% and was associated with severe immunodeficiency, lower RTI, and the pre-engraftment period²⁸. Aerosolized ribavirin is the current treatment of choice for RSV pneumonia in HSCT recipients²⁹. Intravenous immunoglobulin (IVIG) has been used in severe cases as adjunctive therapy. Therapy with palivizumab, a monoclonal antibody has shown benefit in children³⁰. A new oral antiviral, GS-5806 (Gilead Sciences), which interferes with virus-cell fusion and intranasal ALN-RSV01 (Alnylam Pharmaceuticals, Inc.) which interferes with

viral replication, have been demonstrated to be efficacious in experimental RSV infections in adults^{31,32}.

The incidence rates of LRTI from influenza can range from 7% to 35%. Associated risk factors include lymphopenia and recent HSCT. Mortality rates following influenza pneumonia can range from 15% to 28%. A poor predictor of survival in HSCT patients with influenza pneumonia is an absolute lymphocyte count ≤ 200 cells/mL³³. The two main classes of anti-influenza drugs are neuraminidase inhibitors (e.g., oseltamivir and zanamivir) and M2 inhibitors (e.g., amantadine and rimantadine). Prompt initiation of therapy, preferably within 24–48 hours of onset of symptoms is essential. A long-acting neuraminidase inhibitor, laninamivir, had efficacy comparable to that of oseltamivir³⁴. DAS181 and Favipravir (T-705) are new investigational antiviral drugs that are undergoing clinical trials.

Human parainfluenza virus type 3 (HPIV3) is the most commonly detected type in leukemia and HSCT patients (80%–90%) followed by HPIV 1 and 2. Reported risk factors are higher corticosteroid exposure, neutropenia, lymphopenia, infection early after allogeneic HSCT, a higher APACHE II score, and coinfections³⁵. Treatment options are limited by the lack of effective agents and randomized controlled trials (RCTs); some centers consider treating HPIV with ribavirin and/or IVIG³⁶.

Human metapneumovirus (HMPV) is genetically very similar to RSV and is reported to infect about 5–9% of HSCT recipients. The rate of progression to LRTI can range from 21% to 40%, and the mortality rate increases with the onset of LRTI (33–40%). High fatality rates (80%) are noted in HSCT recipients with positive bronchoalveolar lavage for HMPV. A recent study examined the efficacy of ribavirin combined with IVIG in HSCT recipients with HMPV LRTI and found no difference in mortality rates³⁷.

Cytomegalovirus (CMV) pneumonia is common in patients with lymphoma or leukemia. The risk for CMV pneumonia is high with the use of chemotherapeutic agents such as cytarabine and fludarabine; treatment with T-cell suppressor agents such as corticosteroids and methotrexate, and T-cell depleting drugs such as rituximab and alemtuzumab. The diagnosis requires detection of virus in lung tissue either by histopathology or culture. Quantitative polymerase chain reaction (PCR) tests and the CMV pp65 antigenemia test are available for detecting viral replication. The treatment of choice is ganciclovir or foscarnet³⁸. CMV-specific immunoglobulin (CMV-IVIG) has been used for the treatment of CMV pneumonitis in allogeneic transplant recipients, and it may improve outcomes if used in combination with antiviral therapy³⁹. Adenovirus infections⁴⁰ in transplant recipients are increasingly recognized as significant causes of morbidity and mortality.

Fungal Infections

Pneumocystis jiroveci pneumonia (PCP) is more common in hematological cancers (leukemias, lymphomas) than with solid tumors^{41,42}. CMV coinfection is common with PCP. Bronchoalveolar lavage has excellent sensitivity for the diagnosis of PCP. Trimethoprim/sulfamethoxazole (TMP/SMX) is the drug of choice; however its efficacy may be suboptimal in cancer patients. Some centers have used the combination of

TMP/SMX with pentamidine in critically ill intubated patients but no studies have been done to prove efficacy. In patients with PCP who are intolerant of or refractory to high-dose trimethoprim-sulfamethoxazole, a combination of clindamycin plus primaquine is the preferred alternative⁴³. Adjunctive use of glucocorticosteroids is not generally recommended and should only be considered in individual patients. Patients who have been successfully treated for PCP pneumonia should receive secondary oral prophylaxis with intermittent TMP/SMX or monthly pentamidine to prevent recurrence⁴³.

Aspergillosis is seen in 30% of severe neutropenia cases and mainly affects the lungs and sinuses, with mortality rates as high as 60%⁴⁴. The gold standard for diagnosis is detection of hyphae by histopathologic or cytopathologic examination of lung tissue. Voriconazole is now considered the drug of choice for invasive aspergillosis as it has been shown to be more efficacious with fewer side effects than amphotericin B^{45–47}. Posaconazole and caspofungin have been used in refractory cases with partial response. Compared with voriconazole monotherapy, combination therapy with anidulafungin led to higher survival in patients with invasive aspergillosis⁴⁸.

Fusarium species frequently involve the lungs and skin and are associated with an overall mortality of 50–80% in HSCT recipients especially because of their high rate of drug resistance. Diagnosis is difficult to make due to the poor sensitivity of respiratory cultures. Combination therapy of amphotericin B and voriconazole and radical surgical debridement are the recommended treatments⁴⁶. Other fungal infections that are frequently seen include invasive candidiasis and mucormycosis^{49,50}. Treatment and duration of antimicrobial therapy for fungal pneumonias are shown in Table 2.

Management of Non-Infectious causes of ARF

Noninfectious etiologies of ARF in patients with hematologic malignancies include cardiogenic pulmonary edema, pulmonary hemorrhage, aspiration pneumonitis, radiation-induced pneumonitis, venous thromboembolism, transfusion-related acute lung injury (TRALI), retinoic acid syndrome, leukemic pulmonary leukostasis, leukemic pulmonary infiltrates, and pulmonary lysis syndrome^{20,51–53}. Specific management depends on the noninfectious disorder causing the ARF (Table 3).

Cardiogenic pulmonary edema (CPE) is the most common noninfectious complication that results in ARF in these patients. It is a frequent early complication that is attributed to large amounts of intravenous fluids needed to administer antibiotics, blood products, cytotoxic drugs (e.g., anthracycline), and parenteral nutrition. Patients with CPE tend to have rapid improvement of symptoms with diuretics, which is also useful for diagnosis. Cardiac dysfunction and pulmonary edema may be exacerbated by the development of acute renal failure due to the cancer, drug-related tubular toxicity, or malignant cell lysis. Management includes adequate diuresis, judicious use of fluids and blood products, and non-invasive ventilation if needed.

Pulmonary hemorrhage is relatively common in patients with acute leukemia and HSCT and is usually associated with thrombocytopenia, coagulopathy, and infectious disorders.

Management of transfusion-related acute lung injury (TRALI) is primarily supportive with supplemental oxygen and judicious use of diuretics, although in severe cases, intubation and mechanical ventilation may be required. The majority of patients recover within 72 to 96 hours. Retinoic acid syndrome is caused by all-trans retinoic acid (ATRA) and is associated with fever, respiratory distress, and diffuse ground-glass opacities on chest imaging. This syndrome responds well to discontinuation of ATRA and prompt administration of corticosteroids⁵³. Rapid cytorreduction by hydration and chemotherapy and use of corticosteroids (by inducing apoptosis) may be effective in patients with ARF due to leukemic pulmonary leukostasis, leukemic pulmonary infiltrates, and pulmonary lysis syndrome⁵⁴.

Among HSCT recipients, noninfectious pulmonary complications can occur during the pre-engraftment period (hyperacute graft-versus-host disease [GVHD], peri-engraftment respiratory distress syndrome (PERDS), and diffuse alveolar hemorrhage (DAH)), early post-engraftment (idiopathic pneumonia syndrome, sinusoidal obstruction syndrome) and late post-engraftment (pulmonary alveolar proteinosis, pulmonary veno-occlusive disease (PVOD), cryptogenic organizing pneumonia (COP), post-transplant lymphoproliferative disease and bronchiolitis obliterans syndrome [BOS])^{20,51,52}. Management strategies for these disorders are shown in Table 4. Corticosteroids have been shown to benefit HSCT patients with ARF associated with hyperacute GVHD, PERDS, and DAH during the pre-engraftment period as well as IPS, COP and BOS during the post-engraftment period. Defibrotide, a deoxyribonucleic derivative with fibrinolytic activity, has been used successfully to treat pulmonary veno-occlusive disease.

Ventilatory Management of ARF

The clinician must carefully weigh the benefits and risks of the initial mode of ventilatory support (noninvasive or invasive) in patients with hematologic malignancies (Figure 2). Non-invasive positive pressure ventilation (NIPPV) consists of the delivery of mechanically assisted positive airway pressure breaths using a nasal or facial mask. The use of NIPPV is indicated for patients with respiratory failure who are alert, cooperative, and able to protect their airway and before the onset of severe respiratory acidosis ($\text{pH} < 7.1$). Major contraindications to NIPPV include hemodynamic instability or shock, respiratory or cardiac arrest, cardiac arrhythmias, excessive secretions, altered sensorium or encephalopathy unless due to hypercarbia, recent facial or head and neck surgery, facial deformity and upper airway obstruction secondary to tumor involvement.⁵⁵

NIPPV has two major modes of ventilatory support, namely continuous positive airway pressure (CPAP)⁵⁵ and bilevel positive airway pressure (BiPAP). Inspiratory and expiratory pressures are individualized based on patient tolerance and clinical status. Treatment is generally started with relatively low pressures and gradually titrated up with close bedside monitoring of patient comfort, ventilator synchrony, tidal volumes, and vital signs.

Common complications of NIPPV include pressure ulcers over the nasal bridge, mucosal pain, sinus congestion, and gastric insufflation (particularly with inspiratory pressures > 20

mm Hg). NIPPV should be avoided in patients with a history of diaphragmatic hernia or Morgagni hernia as it can exacerbate the respiratory failure⁵⁶.

The need for arterial blood gas (ABG) analysis will be governed by the patient's clinical progress but should be measured in most patients after 1–2 hours of NIPPV and after 4–6 hours if the earlier ABG sample showed little improvement. If there has been no improvement in PaCO₂ and pH after this 4–6 hour period, despite optimal settings, NIPPV should be discontinued and IMV considered [47]. A Simplified Acute Physiology Score II (SAPS II) of >35 and PaO₂/FiO₂ after 1 hour on NIPPV are independent predictors of NIPPV success⁵⁷.

Several studies have demonstrated successful outcomes with early use of NIPPV in these patients^{58–61} primarily attributed to the reduction of the need for, and complications from, intubation and IMV which is known to be associated with high mortality (Table 5). Adda et al. retrospectively analyzed 99 patients with hematologic malignancies who were admitted to the ICU over a 10-year period (1995–2005) and received NIPPV⁵⁹. Of these, 53 (54%) patients failed NIPPV and required IMV. Hospital mortality in these patients was high when compared to those who succeeded with NIPPV (79% vs. 41%, respectively). Multivariate analysis revealed that a high respiratory rate during NIPPV (32 breaths/min [30–36] vs. 28 [27–30]), longer delay from ICU admission to NIPPV, need for vasopressors or renal replacement therapy, and meeting oxygenation criteria for ARDS (PaO₂/FiO₂ ratio of 175 [101–236] vs. 248 [134–337]) were independent predictors of NIV failure. Patients who failed NIPPV had a significantly longer ICU stay (13 days [8–23] vs. 5 [2–8]) and a significantly higher rate of ICU-acquired infections (32% vs. 7%). ICU mortality in patients who failed NIPPV was greater than the early intubation group (61% vs. 50%, *p* < 0.01). The authors concluded that intubation should be considered early in patients who remain tachypneic during NIPPV and in those with severe hypoxemia⁵⁹.

Depuydt et al similarly analyzed 137 hematological patients admitted to the ICU with ARF (defined as PaO₂/FiO₂ <200) within the first 24 hours [52]. Of these, 24 (17.5%) received NIPPV, 67 (48.9%) required IMV, and 46 (33.6%) received supplemental oxygen only. ICU mortality rates in these 3 subgroups were 71%, 63%, and 32%, respectively (*p* = .001) and in-hospital mortality were 75%, 80%, and 47%, respectively (*p* = .001). The authors found that increasing cancer-specific severity of-illness score on ICU admission and more organ failure after 24 hours of admission, but not the type of initial respiratory support, were associated with ICU or in-hospital mortality⁶⁰.

Gristina et al. retrospectively analyzed 1302 patients with hematological malignancies who were admitted to several Italian ICUs with ARF between 2002 and 2006⁶¹. Of these, 21% initially received NIV; 46% of these patients subsequently required IMV. Outcomes were better among patients who had successful use of NIV (58% survival) compared to both those who required IMV from the onset of ARF (31% survival) and those who required IMV after NIV failure (23% survival), especially in patients with ARDS. Delayed IMV was also associated with slightly higher mortality than immediate IMV but was not statistically significant (65% vs. 58%, *p* = 0.12). After propensity-score adjustment, NIV was associated with significantly lower mortality than IMV⁶¹. The authors concluded that NIV should be

considered the first-line ventilatory strategy for the management of ARF in this patient population.

When to switch from Noninvasive to Invasive Mechanical Ventilation

There are several situations when NIV should be switched to IMV. These include the following: a) increasing respiratory deterioration (as evidenced by a >20% decrease in $\text{PaO}_2/\text{FiO}_2$ or a 20% increase in PaCO_2 , or signs of respiratory muscle fatigue such as paradoxical abdominal movement) despite maximal tolerable NIV settings; b) increasing hemodynamic instability (defined as the use of norepinephrine exceeding >10 mcg/min); c) neurological deterioration (defined as development of agitation or somnolence; Glasgow Coma Scale <13); and d) intolerance/dyssynchrony of NIPPV^{55,62}.

Prophylactic Use of Non-invasive ventilation

A few studies have examined the prophylactic use of NIPPV in hematologic cancer patients with hypoxemic respiratory insufficiency and have shown improved outcomes^{58,63–65}. In one study, periods of NIPPV lasted at least 45 minutes and alternated every 3 hours with periods of spontaneous breathing. Wermke et al. studied the role of prophylactic NIPPV in 526 HSCT recipients (16% with ARF) on the wards at a single center and showed that NIPPV performed in the wards was ineffective⁶³ most likely related to inadequate training and timely management with titration of NIPPV settings. In contrast, in a similar study where nursing and medical teams had greater NIV experience and with strict intensivist supervision of NIV on the wards, Squadrone et al. showed that continuous positive airway pressure (CPAP) use resulted in a significant reduction in ICU admission and need for IMV and was associated with higher survival⁶⁴. The main limitation of NIV use in the wards is the unwarranted delay in intubation and ICU admission which is well known to result in poor outcomes. Overall, prophylactic NIV is a reasonable and safe strategy in a closely monitored setting. However, additional studies are needed to select the ideal candidate who will benefit from prophylactic NIV.

Settings of Prophylactic NIV

At the start of NIPPV, the clinician should set the positive end-expiratory pressure to 7 cm of H_2O and pressure support to 15 cm of H_2O . Later these values can be adjusted according to patient tolerance and ABG analysis. In one study of HSCT patients with ARF, NIPPV was administered intermittently for at least 30 min every 3 hours with response assessed twice daily by monitoring the oxygenation index (OI), arterial oxygen saturation, and respiratory rate. The OI was shown to be an independent risk factor for overall survival in these patients⁶³.

Weaning/Liberation from IMV to NIV

Some investigators have examined the use of NIPPV to facilitate discontinuation of IMV. Vaschetto et al. evaluated the benefit of early extubation followed by NIPPV vs. invasive pressure support (PS, control group) to facilitate weaning and extubation in 20 selected patients with resolving hypoxemic ARF⁶⁶. The number of IMV-free-days at day 28 was 20

± 8 days in the NIPPV group vs. 10 ± 9 days in the control group ($p = .014$). The rate of extubation failure, ICU and hospital mortality, number of tracheotomies, septic complications, days and rates of continuous sedation and ICU length of stay were not significantly different between the two groups. The study however, was limited by the small sample size, heterogeneous patient population which included trauma patients, and the different weaning strategies. A systematic review of 16 trials involving 994 subjects, predominantly with chronic pulmonary obstructive disease, showed that a weaning strategy that includes NPPV reduced the rates of mortality and ventilator-associated pneumonia without increasing the risk of weaning failure or reintubation⁶⁷.

NIPPV in patients with Do Not Intubate (DNI) or intractable dyspnea

NIPPV can be an option in patients with DNI code status but still request for aggressive supportive interventions. This approach was endorsed by an international consensus conference on NIPPV⁶⁸ in selected cancer patients who are likely to have reversible causes of ARF (e.g., acute cardiogenic pulmonary edema, pulmonary infection, or COPD exacerbation). NIPPV may also be an alternate measure to treat intractable dyspnea, as demonstrated by the use of nocturnal NIPPV showing relief of symptoms⁶⁹. However, NIPPV should not be used to prolong life in patients with terminal respiratory failure.

Feasibility of High-Flow Nasal Cannula Oxygen Therapy

High-flow nasal cannula (HFNC) delivers heated humidified oxygen up to 100% at a maximum flow rate of 60 L/min of gas via nasal prongs which match patient flow demands better, reduce anatomic dead space, and provides some amount of positive pressure in the airway⁷⁰. In a retrospective single center study of 45 patients with hematologic malignancies and ARF predominantly due to bacterial pneumonia and PCP pneumonia⁷¹, Lee et al demonstrated that the use of HFNC was feasible, with a failure rate of 67%, similar to that of NIV failure rates reported in previous studies^{58,60}.

General Principles for Invasive Mechanical Ventilation

Patients who immediately or ultimately require IMV for severe respiratory failure or ARDS need to be managed using low tidal volumes (ideally 6 mL/kg of predicted body weight) and targeting inspiratory plateau pressures < 30 cm H₂O⁷², judicious titration of positive end-expiratory pressure (PEEP), conservative fluid management, and close hemodynamic monitoring. Using dexmedetomidine or propofol-based sedation regimen rather than a benzodiazepine-based sedation regimen may reduce ICU length of stay and duration of mechanical ventilation⁷³. In refractory cases, the use of prone positioning⁷⁴, high frequency oscillatory ventilation, recruitment maneuvers, vasodilator therapy and extracorporeal oxygenation (ECMO) may be considered as well as the adjunctive use of neuromuscular blocking agents⁷⁵ and corticosteroids although the routine use latter remains controversial and requires further study. It is important to note that many of the clinical trials in ARDS excluded patients with hematologic malignancies or those undergoing HSCT.

Extracorporeal Membrane Oxygenation (ECMO)

In recent years, there has been increasing use of ECMO as an alternate therapeutic option for ARDS in patients who do not respond to conventional mechanical ventilation strategies. Although ECMO has been shown to be associated with better outcomes in a few select studies^{76,77}, there is limited data available in patients with hematological malignancies. Gow et al. analyzed 25 patients (21 with hematologic malignancies and 4 HSCT recipients) who received ECMO⁷⁷. The median duration of ECMO was 4.1 days. The survival to decannulation and to discharge with hematologic malignancies were 9 (41%) and 7 (32%), respectively. Of the 4 HSCT recipients, two survived and were discharged home. Risk factors for mortality included pulmonary support as reason for ECMO, impaired lung function before ECMO, and development of infection.

Outcomes and Prognosis

Studies in the late 1990s and early 2000s revealed ICU and in-hospital mortality rates ranging from 30–50% and 50–70%, respectively^{5,78}. Similarly, the 3–5 year survival of these patients also remains low, especially when mechanical ventilation is needed. Several risk factors have been shown to affect mortality in patients with hematologic malignancies including those undergoing HSCT who develop ARF. These include race (African-Americans and Hispanics have higher mortality rates)¹⁶, poor performance status⁷⁹, poor Charlson comorbidity index, allogeneic HSCT, higher SAPS II score^{13,61}, high level of C-reactive protein on ICU admission¹⁴, presence of ALI/ARDS on ICU admission⁶¹, presence of shock requiring vasopressors or need for renal replacement therapy (RRT)¹², failure to identify the pathogen causing the pulmonary infiltrate^{6,58}, malignant organ infiltration with leukemia or lymphoma⁵⁴, documented invasive aspergillosis⁴⁴, ARF due to pulmonary toxicity from chemotherapy and >96 h of invasive mechanical ventilation¹⁶.

One study showed better survival of critically ill hematology patients with ARF in ICUs with higher case volume¹². Interestingly, the type of hematological malignancy was not an independent risk factor for ICU mortality^{13,14}. The improved outcomes in recent years^{4,24,25,80} can be explained by use of selection criteria such as good performance status, endotracheal intubation within the first 24 hours of ICU admission⁸¹ and availability of chemotherapy options. Good prognostic factors include requirement of minimal life support intervention and time of admission to ICU <24 hours⁷⁹ as studies have shown poor prognosis if duration to ICU admission was >2 days with or without intubation⁸². Improvement in mortality in patients who are admitted to ICU (with or without need of ventilatory support) can be explained by progress in early use of NIV and lung protective ventilation strategies and major changes in antimicrobial therapy.

Among HSCT recipients who develop ARF, the overall in-hospital mortality rate is around 50%. After adjusting for a multitude of patient- and hospital-level factors, any need for invasive mechanical ventilation in this subgroup of patients with ARF was associated with worse outcomes, with mortality as high as 90%–97% if neutropenia is present. Several studies have established that ICU mortality is no longer linked to the characteristics of the underlying disease but depends instead on the severity and reversibility of the ARF event⁶. In particular, mortality is higher when investigations fail to identify the cause of ARF⁵⁸

Other studies have showed that HSCT recipients who respond well to 4 hours of NIV have a good prognosis. Criteria for response include increase in $\text{PaO}_2/\text{FiO}_2$ by 20%, a decrease in respiratory rate and a low Crawford score. The combination of lung injury with hepatic and renal failure or mechanical ventilation has an extremely high mortality rate. Boyaci et al. reported that baseline APACHE II score and requirement for vasopressors during the ICU stay were the most significant independent risk factors for mortality among HSCT recipients⁸³.

In a multicenter prospective study of 1011 hematologic malignancy patients who were admitted to ICUs in France and Belgium, 25% of whom had undergone HSCT, Azoulay et al. reported a hospital mortality rate of 39.3%⁷⁹. This is certainly encouraging, particularly as most patients had at least two organ dysfunctions with 75% of them requiring mechanical ventilation, vasoactive drugs, or RRT. These patients had no health-related quality of life (HRQOL) alterations after 3 months compared to patients who were not admitted to the ICU and had 80% disease-control rate after 6 months⁸¹.

Conclusions

Acute respiratory failure (ARF) is the most common cause of ICU admission and the leading non-relapse cause of mortality in patients with hematologic malignancies. The need for mechanical ventilation is a major determinant of prognosis in these patients with ICU mortality exceeding 75% for those who develop ARDS. The main causes of ARF are bacterial infections, opportunistic pulmonary infections and noninfectious lung disorders. Empiric broad spectrum antibiotic therapy should be started promptly, especially in patients with febrile neutropenia and ARF. Several studies have demonstrated successful outcomes with early use of NIPPV in these patients primarily attributed to the reduction of the need for, and complications from, intubation and IMV which is known to be associated with high mortality.

References

1. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *International journal of cancer. Journal international du cancer*. Dec 15; 2010 127(12):2893–2917. [PubMed: 21351269]
2. Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. *Lancet*. Oct 12; 2002 360(9340):1131–1135. [PubMed: 12387961]
3. Khassawneh BY, White P Jr, Anaissie EJ, Barlogie B, Hiller FC. Outcome from mechanical ventilation after autologous peripheral blood stem cell transplantation. *Chest*. Jan; 2002 121(1):185–188. [PubMed: 11796449]
4. Peigne V, Rusinova K, Karlin L, et al. Continued survival gains in recent years among critically ill myeloma patients. *Intensive care medicine*. Mar; 2009 35(3):512–518. [PubMed: 18853139]
5. Staudinger T, Stoiser B, Mullner M, et al. Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. *Critical care medicine*. May; 2000 28(5):1322–1328. [PubMed: 10834673]
6. Azoulay E, Schlemmer B. Diagnostic strategy in cancer patients with acute respiratory failure. *Intensive care medicine*. Jun; 2006 32(6):808–822. [PubMed: 16715324]
7. Azoulay E, Thiery G, Chevret S, et al. The prognosis of acute respiratory failure in critically ill cancer patients. *Medicine*. Nov; 2004 83(6):360–370. [PubMed: 15525848]

8. Soares M, Salluh JJ, Spector N, Rocco JR. Characteristics and outcomes of cancer patients requiring mechanical ventilatory support for >24 hrs. *Critical care medicine*. Mar; 2005 33(3):520–526. [PubMed: 15753742]
9. Soares M, Salluh JJ, Azoulay E. Noninvasive ventilation in patients with malignancies and hypoxemic acute respiratory failure: a still pending question. *Journal of critical care*. Mar; 2010 25(1):37–38. [PubMed: 19577417]
10. Chaoui D, Legrand O, Roche N, et al. Incidence and prognostic value of respiratory events in acute leukemia. *Leukemia*. Apr; 2004 18(4):670–675. [PubMed: 14762443]
11. Azoulay E, Mokart D, Rabbat A, et al. Diagnostic bronchoscopy in hematology and oncology patients with acute respiratory failure: prospective multicenter data. *Critical care medicine*. Jan; 2008 36(1):100–107. [PubMed: 18090351]
12. Lecuyer L, Chevret S, Guidet B, et al. Case volume and mortality in haematological patients with acute respiratory failure. *The European respiratory journal*. Sep; 2008 32(3):748–754. [PubMed: 18448491]
13. Owczuk R, Wujtewicz MA, Sawicka W, Wadzyk A, Wujtewicz M. Patients with haematological malignancies requiring invasive mechanical ventilation: differences between survivors and non-survivors in intensive care unit. *Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer*. May; 2005 13(5):332–338. [PubMed: 15864663]
14. Massion PB, Dive AM, Doyen C, et al. Prognosis of hematologic malignancies does not predict intensive care unit mortality. *Critical care medicine*. Oct; 2002 30(10):2260–2270. [PubMed: 12394954]
15. Bach PB, Schrag D, Nierman DM, et al. Identification of poor prognostic features among patients requiring mechanical ventilation after hematopoietic stem cell transplantation. *Blood*. Dec 1; 2001 98(12):3234–3240. [PubMed: 11719359]
16. Allareddy V, Roy A, Rampa S, et al. Outcomes of stem cell transplant patients with acute respiratory failure requiring mechanical ventilation in the United States. *Bone marrow transplantation*. Oct; 2014 49(10):1278–1286. [PubMed: 25111514]
17. Savani BN, Montero A, Wu C, et al. Prediction and prevention of transplant-related mortality from pulmonary causes after total body irradiation and allogeneic stem cell transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. Mar; 2005 11(3):223–230.
18. Ho VT, Weller E, Lee SJ, Alyea EP, Antin JH, Soiffer RJ. Prognostic factors for early severe pulmonary complications after hematopoietic stem cell transplantation. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2001; 7(4):223–229.
19. Saillard C, Mokart D. Diagnostic strategy for acute respiratory failure in onco-hematology patients. *Intensive Care Med*. 2015; xx:xx–xx.
20. Schnell D, Mayaux J, Lambert J, et al. Clinical assessment for identifying causes of acute respiratory failure in cancer patients. *The European respiratory journal*. Aug; 2013 42(2):435–443. [PubMed: 23143549]
21. Postma DF, van Werkhoven CH, van Elden LJ, et al. Antibiotic treatment strategies for community-acquired pneumonia in adults. *The New England journal of medicine*. Apr 2; 2015 372(14):1312–1323. [PubMed: 25830421]
22. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Mar 1; 2007 44(Suppl 2):S27–72. [PubMed: 17278083]
23. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children: executive summary. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb 1; 2011 52(3):285–292. [PubMed: 21217178]
24. Legrand M, Max A, Peigne V, et al. Survival in neutropenic patients with severe sepsis or septic shock. *Critical care medicine*. Jan; 2012 40(1):43–49. [PubMed: 21926615]

25. Zuber B, Tran TC, Aegerter P, et al. Impact of case volume on survival of septic shock in patients with malignancies. *Critical care medicine*. Jan; 2012 40(1):55–62. [PubMed: 21926606]
26. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. Feb 15; 2005 171(4):388–416. [PubMed: 15699079]
27. Chemaly RF, Ghosh S, Bodey GP, et al. Respiratory viral infections in adults with hematologic malignancies and human stem cell transplantation recipients: a retrospective study at a major cancer center. *Medicine*. Sep; 2006 85(5):278–287. [PubMed: 16974212]
28. Khanna N, Widmer AF, Decker M, et al. Respiratory syncytial virus infection in patients with hematological diseases: single-center study and review of the literature. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Feb 1; 2008 46(3): 402–412. [PubMed: 18181739]
29. Shah DP, Ghantaji SS, Shah JN, et al. Impact of aerosolized ribavirin on mortality in 280 allogeneic haematopoietic stem cell transplant recipients with respiratory syncytial virus infections. *The Journal of antimicrobial chemotherapy*. Aug; 2013 68(8):1872–1880. [PubMed: 23572228]
30. Gutfraind A, Galvani AP, Meyers LA. Efficacy and Optimization of Palivizumab Injection Regimens Against Respiratory Syncytial Virus Infection. *JAMA pediatrics*. Feb 23.2015
31. De Clercq E. Chemotherapy of respiratory syncytial virus infections: the final breakthrough. *International journal of antimicrobial agents*. Mar; 2015 45(3):234–237. [PubMed: 25684638]
32. DeVincenzo J, Lambkin-Williams R, Wilkinson T, et al. A randomized, double-blind, placebo-controlled study of an RNAi-based therapy directed against respiratory syncytial virus. *Proceedings of the National Academy of Sciences of the United States of America*. May 11; 2010 107(19):8800–8805. [PubMed: 20421463]
33. Nichols WG, Guthrie KA, Corey L, Boeckh M. Influenza infections after hematopoietic stem cell transplantation: risk factors, mortality, and the effect of antiviral therapy. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Nov 1; 2004 39(9): 1300–1306. [PubMed: 15494906]
34. Watanabe A, Chang SC, Kim MJ, Chu DW, Ohashi Y. Long-acting neuraminidase inhibitor laninamivir octanoate versus oseltamivir for treatment of influenza: A double-blind, randomized, noninferiority clinical trial. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Nov 15; 2010 51(10):1167–1175. [PubMed: 20936975]
35. Chemaly RF, Hanmod SS, Rathod DB, et al. The characteristics and outcomes of parainfluenza virus infections in 200 patients with leukemia or recipients of hematopoietic stem cell transplantation. *Blood*. Mar 22; 2012 119(12):2738–2745. quiz 2969. [PubMed: 22246027]
36. Shima T, Yoshimoto G, Nonami A, et al. Successful treatment of parainfluenza virus 3 pneumonia with oral ribavirin and methylprednisolone in a bone marrow transplant recipient. *International journal of hematology*. Oct; 2008 88(3):336–340. [PubMed: 18712461]
37. Renaud C, Xie H, Seo S, et al. Mortality rates of human metapneumovirus and respiratory syncytial virus lower respiratory tract infections in hematopoietic cell transplantation recipients. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. Aug; 2013 19(8):1220–1226.
38. Le Page AK, Jager MM, Iwasenko JM, Scott GM, Alain S, Rawlinson WD. Clinical aspects of cytomegalovirus antiviral resistance in solid organ transplant recipients. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. Apr; 2013 56(7): 1018–1029. [PubMed: 23243176]
39. Alexander BT, Hladnik LM, Augustin KM, et al. Use of cytomegalovirus intravenous immune globulin for the adjunctive treatment of cytomegalovirus in hematopoietic stem cell transplant recipients. *Pharmacotherapy*. Jun; 2010 30(6):554–561. [PubMed: 20500045]
40. Acute respiratory disease associated with adenovirus serotype 14—four states, 2006–2007. *MMWR. Morbidity and mortality weekly report*. Nov 16; 2007 56(45):1181–1184. [PubMed: 18004235]
41. Bollee G, Sarfati C, Thiery G, et al. Clinical picture of *Pneumocystis jirovecii* pneumonia in cancer patients. *Chest*. Oct; 2007 132(4):1305–1310. [PubMed: 17934116]

42. Torres HA, Chemaly RF, Storey R, et al. Influence of type of cancer and hematopoietic stem cell transplantation on clinical presentation of *Pneumocystis jirovecii* pneumonia in cancer patients. *European journal of clinical microbiology & infectious diseases* : official publication of the European Society of Clinical Microbiology. Jun; 2006 25(6):382–388.
43. Maschmeyer G, Carratala J, Buchheidt D, et al. Diagnosis and antimicrobial therapy of lung infiltrates in febrile neutropenic patients (allogeneic SCT excluded): updated guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Medical Oncology (DGHO). *Annals of oncology* : official journal of the European Society for Medical Oncology/ESMO. Jan; 2015 26(1):21–33.
44. Burghi G, Lemiale V, Seguin A, et al. Outcomes of mechanically ventilated hematology patients with invasive pulmonary aspergillosis. *Intensive care medicine*. Oct; 2011 37(10):1605–1612. [PubMed: 21866367]
45. Herbrecht R, Patterson TF, Slavin MA, et al. Application of the 2008 Definitions for Invasive Fungal Diseases to the Trial Comparing Voriconazole Versus Amphotericin B for Therapy of Invasive Aspergillosis: A Collaborative Study of the Mycoses Study Group (MSG 05) and the European Organization for Research and Treatment of Cancer Infectious Diseases Group. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. Mar 1; 2015 60(5):713–720. [PubMed: 25414266]
46. Vento S, Cainelli F, Temesgen Z. Lung infections after cancer chemotherapy. *The Lancet. Oncology*. Oct; 2008 9(10):982–992. [PubMed: 19071255]
47. Park WB, Kim NH, Kim KH, et al. The effect of therapeutic drug monitoring on safety and efficacy of voriconazole in invasive fungal infections: a randomized controlled trial. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. Oct; 2012 55(8):1080–1087. [PubMed: 22761409]
48. Marr KA, Schlamm HT, Herbrecht R, et al. Combination antifungal therapy for invasive aspergillosis: a randomized trial. *Annals of internal medicine*. Jan 20; 2015 162(2):81–89. [PubMed: 25599346]
49. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 Update by the Infectious Diseases Society of America. *Clinical infectious diseases* : an official publication of the Infectious Diseases Society of America. Feb 15; 2011 52(4):427–431. [PubMed: 21205990]
50. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. *The New England journal of medicine*. Jun 14; 2007 356(24):2472–2482. [PubMed: 17568028]
51. Afessa B, Peters SG. Noninfectious pneumonitis after blood and marrow transplant. *Current opinion in oncology*. Mar; 2008 20(2):227–233. [PubMed: 18300774]
52. Shorr AF, Susla GM, O'Grady NP. Pulmonary infiltrates in the non-HIV-infected immunocompromised patient: etiologies, diagnostic strategies, and outcomes. *Chest*. Jan; 2004 125(1):260–271. [PubMed: 14718449]
53. Larson RS, Tallman MS. Retinoic acid syndrome: manifestations, pathogenesis, and treatment. *Best practice & research. Clinical haematology*. Sep; 2003 16(3):453–461. [PubMed: 12935962]
54. Azoulay E, Canet E, Raffoux E, et al. Dexamethasone in patients with acute lung injury from acute monocytic leukaemia. *The European respiratory journal*. Mar; 2012 39(3):648–653. [PubMed: 21828031]
55. Non-invasive ventilation in acute respiratory failure. *Thorax*. Mar; 2002 57(3):192–211. [PubMed: 11867822]
56. Tone K, Kiryu I, Yoshida M, Tsuboi K, Takagi M, Kuwano K. Morgagni hernia with respiratory failure aggravated by noninvasive positive pressure ventilation: a case report and overview of the literature. *Respiratory investigation*. May; 2014 52(3):203–208. [PubMed: 24853023]
57. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive care medicine*. Nov; 2001 27(11):1718–1728. [PubMed: 11810114]

58. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *The New England journal of medicine*. Feb 15; 2001 344(7):481–487. [PubMed: 11172189]
59. Adda M, Coquet I, Darmon M, Thiery G, Schlemmer B, Azoulay E. Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Critical care medicine*. Oct; 2008 36(10):2766–2772. [PubMed: 18766110]
60. Depuydt PO, Benoit DD, Roosens CD, Offner FC, Noens LA, Decruyenaere JM. The impact of the initial ventilatory strategy on survival in hematological patients with acute hypoxemic respiratory failure. *Journal of critical care*. Mar; 2010 25(1):30–36. [PubMed: 19682849]
61. Gristina GR, Antonelli M, Conti G, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. *Critical care medicine*. Oct; 2011 39(10):2232–2239. [PubMed: 21666446]
62. Nava S, Hill N. Non-invasive ventilation in acute respiratory failure. *Lancet*. Jul 18; 2009 374(9685):250–259. [PubMed: 19616722]
63. Wermke M, Schiemanck S, Hoffken G, Ehninger G, Bornhauser M, Illmer T. Respiratory failure in patients undergoing allogeneic hematopoietic SCT—a randomized trial on early non-invasive ventilation based on standard care hematology wards. *Bone marrow transplantation*. Apr; 2012 47(4):574–580. [PubMed: 21927036]
64. Squadrone V, Massaia M, Bruno B, et al. Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive care medicine*. Oct; 2010 36(10):1666–1674. [PubMed: 20533022]
65. Principi T, Pantanetti S, Catani F, et al. Noninvasive continuous positive airway pressure delivered by helmet in hematological malignancy patients with hypoxemic acute respiratory failure. *Intensive care medicine*. Jan; 2004 30(1):147–150. [PubMed: 14593457]
66. Vaschetto R, Turucz E, Dellapiazza F, et al. Noninvasive ventilation after early extubation in patients recovering from hypoxemic acute respiratory failure: a single-centre feasibility study. *Intensive care medicine*. Oct; 2012 38(10):1599–1606. [PubMed: 22825283]
67. Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*. Feb 18; 2014 186(3):E112–122.
68. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute Respiratory failure. *Am J Respir Crit Care Med*. Jan; 2001 163(1):283–291. [PubMed: 11208659]
69. Hilbert G, Gruson D, Vargas F, et al. Noninvasive continuous positive airway pressure in neutropenic patients with acute respiratory failure requiring intensive care unit admission. *Critical care medicine*. Sep; 2000 28(9):3185–3190. [PubMed: 11008980]
70. Sotello D, Rivas M, Mulkey Z, Nugent K. High-flow nasal cannula oxygen in adult patients: a narrative review. *The American journal of the medical sciences*. Feb; 2015 349(2):179–185. [PubMed: 25285514]
71. Lee HY, Rhee CK, Lee JW. Feasibility of high-flow nasal cannula oxygen therapy for acute respiratory failure in patients with hematologic malignancies: A retrospective single-center study. *Journal of critical care*. Mar 20; 2015
72. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *The New England journal of medicine*. May 4; 2000 342(18):1301–1308. [PubMed: 10793162]
73. Fraser GL, Devlin JW, Worby CP, et al. Benzodiazepine versus nonbenzodiazepine-based sedation for mechanically ventilated, critically ill adults: a systematic review and meta-analysis of randomized trials. *Critical care medicine*. Sep; 2013 41(9 Suppl 1):S30–38. [PubMed: 23989093]
74. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *The New England journal of medicine*. Jun 6; 2013 368(23):2159–2168. [PubMed: 23688302]

75. Alhazzani W, Alshahrani M, Jaeschke R, et al. Neuromuscular blocking agents in acute respiratory distress syndrome: a systematic review and meta-analysis of randomized controlled trials. *Critical care* (London, England). 2013; 17(2):R43.
76. Hemmila MR, Rowe SA, Boules TN, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Annals of surgery*. Oct; 2004 240(4):595–605. discussion 605-597. [PubMed: 15383787]
77. Gow KW, Lao OB, Leong T, Fortenberry JD. Extracorporeal life support for adults with malignancy and respiratory or cardiac failure: The Extracorporeal Life Support experience. *American journal of surgery*. May; 2010 199(5):669–675. [PubMed: 20466114]
78. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA. Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. *Critical care medicine*. Jan; 2003 31(1):104–112. [PubMed: 12545002]
79. Azoulay E, Mokart D, Pene F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium—a groupe de recherche respiratoire en reanimation onco-hematologique study. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. Aug 1; 2013 31(22):2810–2818. [PubMed: 23752112]
80. Lecuyer L, Chevret S, Thiery G, Darmon M, Schlemmer B, Azoulay E. The ICU trial: a new admission policy for cancer patients requiring mechanical ventilation. *Critical care medicine*. Mar; 2007 35(3):808–814. [PubMed: 17235261]
81. Price KJ, Cardenas-Turanas M, Lin H, Roden L, Nigam R, Nates JL. Prognostic indicators of mortality of mechanically ventilated patients with acute leukemia in a comprehensive cancer center. *Minerva anesthesiologica*. Feb; 2013 79(2):147–155. [PubMed: 23032926]
82. Mokart D, Lambert J, Schnell D, et al. Delayed intensive care unit admission is associated with increased mortality in patients with cancer with acute respiratory failure. *Leukemia & lymphoma*. Aug; 2013 54(8):1724–1729. [PubMed: 23185988]
83. Boyaci N, Aygencel G, Turkoglu M, Yegin ZA, Acar K, Sucak GT. The intensive care management process in patients with hematopoietic stem cell transplantation and factors affecting their prognosis. *Hematology* (Amsterdam, Netherlands). Sep; 2014 19(6):338–345.

Figure 1.
Causes of Respiratory Failure in Hematological Malignancy Patients

Figure 2. Management of Respiratory Failure in Hematologic Malignancy Patients

PaO₂= arterial oxygen tension; FiO₂= fraction of inspired oxygen; RR= respiratory rate; IMV= invasive mechanical ventilation; NIV= noninvasive ventilation; ABG= arterial blood gas

Table 1**Antimicrobial Recommendations for Bacterial Pneumonia (21–23)**

Clinical Diagnosis	Likely Pathogen(s)	Choice of Antibiotics and Duration
Community-acquired pneumonia non-ICU	<i>S. pneumoniae</i> <i>H. influenzae</i> <i>M. catarrhalis</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i> <i>Legionella</i> spp.	Ceftriaxone 1 gm IV daily for 5–7 days Plus/OR ⁽²¹⁾ Azithromycin 500 mg IV/PO daily for 3 days OR Levofloxacin 750 mg IV/PO daily for 5 days
Community-acquired pneumonia ICU	As above (plus) <i>Staphylococcus aureus</i> (rarely) <i>Pseudomonas aeruginosa</i> aerobic gram-negatives (severe cases)	Piperacillin/tazobactam 4.5 gm IV q6 hrs or Cefepime 1 2 gm IV q8–12 hrs for 5–7 days plus Azithromycin 500 mg IV/PO daily for 3 days plus/minus Vancomycin 1 gm IV q12 hrs for 5–7 days (stop if MRSA surveillance is negative)
Aspiration pneumonia +/- lung abscess	<i>Streptococci</i> <i>Enterobacteriaceae</i> <i>Klebsiella pneumoniae</i> Anaerobes	Ampicillin/Sulbactam 3 gm IV q6 hrs OR Ceftriaxone 1–2 gm IV daily plus Metronidazole 500 mg IV/PO q8 hrs (Duration for Aspiration Pneumonia is 7 days and Lung abscess is variable, until clinical and radiographic resolution)
Hospital-acquired (HAP) or ventilator-associated (VAP) pneumonia If pleural effusion is present: Diagnostic Pleural tap R/O complicating empyema or para pneumonic effusion	<i>Enterobacteriaceae</i> <i>Pseudomonas aeruginosa</i> <i>Acinetobacter</i> sp. <i>S. aureus</i> , including MRSA ⁽²³⁾	Piperacillin/tazobactam 4.5 gm IV q6 hrs or Cefepime 2 gm IV q8–12 hrs plus/minus Vancomycin 1 gm IV q12 hrs (stop if MRSA surveillance is negative) Duration of HAP/VAP is 7–8 days. Extended infusions of certain agents may be considered to optimize pharmacokinetics and pharmacodynamics when multidrug resistant pathogens are suspected.
Legionnaires' disease Hospitalized with pneumonia and/or immunocompromised		Levofloxacin PO/IV 750 mg once daily for 7–10 days A 21-day course is often recommended for immunosuppressed patients or for patients who are severely ill at the onset of antibiotic therapy.

Table 2**Antimicrobial Recommendations for Viral and Fungal Pneumonias**

Clinical Diagnosis	Recommended Treatments	Unique Considerations
Influenza	Oseltamivir 75 mg oral q12h for 5 days Alternative treatment: Laninamivir ⁽³⁴⁾ DAS181, IV Zanamivir and Favipravir (T-705) are undergoing clinical trials.	Higher dose (150 mg q12h): no additional benefit Zanamivir retains activity against most Oseltamivir resistant H5N1 laninamivir had efficacy comparable to that of Oseltamivir
Adenovirus ⁽⁴⁰⁾	Cidofovir 5mg/kg once a week for 2 doses and then once in 2 weeks <i>Plus</i> Probenecid 1.25gm/m2 three hours before and 3&9 hours after each Cidofovir infusion	Predictor of response: decrease in viral load Ribavirin – mixed response results New drug: Bronciclofovir (CMX001-Chmierz) oral Cidofovir prodrug in Phase III trial
Human metapneumovirus	No proven therapy Intravenous Ribavirin from anecdotal reports with mixed results	
Respiratory syncytial virus	Aerosolized ribavirin can be administered, as 2 g for duration of 2 h q8h or as 6 g over 18 h/d for 7–10 d Consider RSV immune globulin for severe infections	Appropriate precautions: Teratogenic effects in pregnant healthcare workers and visitors A new oral antiviral, GS-5806 (Gilead Sciences), and ALN-RSV01 (Alnylam Pharmaceuticals, Inc.) are being investigated (36, 37) Palivizumab (RSV monoclonal antibody) has been used as prophylaxis in high risk children
Cytomegalovirus	Ganciclovir 5 mg/kg IV q12h or Valganciclovir 900 mg oral q12h CytoGam (CMV immunoglobulin)- limited data ⁽³⁹⁾ ¹ If Ganciclovir resistant: Foscarnet 60 mg/kg q8h IV	Suspect resistant CMV if treatment failure or relapse: Do genotype resistance testing ⁽³⁸⁾
Invasive pulmonary aspergillosis (IPA)	Voriconazole 6 mg/kg IV on day 1; then 4 mg/kg IV q12h; Goal trough (Day 4): 1.0–5.5 mg/L is associated with improved response rates and reduced adverse effects ⁽⁴⁷⁾ Combination therapy with Voriconazole and Anidulafungin led to higher survival Alternative therapies: Liposomal Amphotericin B, Amphotericin B lipid complex, Caspofungin, Micafungin, Posaconazole, Itraconazole	Voriconazole better than Amphotericin B Vori: check for drug interactions If CrCl < 50ml/min: Switch Voriconazole IV to oral route (IV vehicle – nephrotoxic)
Mucormycosis	Liposomal Amphotericin B 5–10 mg/kg/day Alternative: Posaconazole 400 mg oral q12h (if NPO, 200 mg oral q6h)	Duration of treatment based on: 1 Resolution of clinical features of infection 2 Resolution or stabilization of radiographic abnormalities 3 Resolution of underlying immunosuppression
Pneumocystis jiroveci pneumonia	Trimethoprim-sulfamethoxazole 15mg/kg per day divided in q6–8 hrs Duration: 21 days Alternative: In milder cases- Clindamycin +Primaquine or Atovaquone In severe cases- Pentamidine or caspofungin(experimental)	If Pao2 < 70 mm Hg or A-a gradient >30: consider adding steroids
Candidemia	Caspofungin 70 mg IV loading dose, then 50 mg IV daily or micafungin 100 mg IV daily ⁽⁴⁹⁾ Duration: 14 days after last positive blood culture Alternative: Anidulafungin 200 mg IV loading dose then 100 mg IV daily	Echinocandins have higher microbiological clearance rates than azoles ⁽⁵⁰⁾ Fundoscopic examination within 1 week to exclude endophthalmitis

Table 3**Treatment of Non-Infectious Causes of Respiratory Failure in Patients with Hematologic Malignancies**

Clinical Diagnosis	Treatment Considerations
Cardiogenic Pulmonary Edema	Excellent response to diuretics; measurement of serum pro-BNP levels and echocardiography are useful in assessment.
Aspiration Pneumonia/Pneumonitis	Antibiotics with activity against gram-negative bacteria for first 48 hours and decision to continue is based on clinical condition; No benefit with steroids.
Radiation-induced Pneumonitis	Methylprednisolone 1 mg/kg/day for 2–4 weeks and tapered over 6–12 months (No trials done to evaluate adequate dose and duration); few case reports of benefit with cyclosporine A, azathioprine and inhaled steroids. Prevention: Amifostine is effective, along with chemoradiation. No benefit of pentoxifylline and captopril.
Venous Thromboembolism	Low molecular weight heparin (LMWH) is superior to unfractionated heparin. Fondaparinux is an acceptable alternative to LMWH for initial anticoagulation; Duration is usually life-long for cancer patients. Inferior vena cava filter placement is considered when anticoagulation is contraindicated but its role is controversial. Prophylaxis in surgical patients: LMWH and intermittent pneumatic compression devices during hospital stay and treatment with LMWH should be continued for up to 1 month post-discharge
Transfusion-related acute lung injury (TRALI)	Supportive; resolution of symptoms occur within 72–96 h. Corticosteroids and diuretics are useful but neither has been studied in a prospective trial.
Leukemic pulmonary leukostasis	No specific therapy is available (supportive therapy with isotonic saline, rasburicase recommended); hydroxyurea 50–60 mg/kg/day until the leukocyte count falls below 10,000–20,000/dL; imatinib mesylate with or without hydroxyurea in CML with myeloid blast crisis; leukapheresis in acutely ill patients with severe thrombocytopenia and coagulopathy (except in AML-M3)
Leukemic pulmonary Infiltrates	Chemotherapy Supportive care
Pulmonary lysis syndrome	Supportive Therapy: interruption of chemotherapy is helpful. High risk for diffuse alveolar damage: aggressive blood transfusion strategy (hemoglobin level >10 g/L and platelet count >50,000/dL) in patients who require mechanical ventilation Unclear role of corticosteroids, other anti-inflammatory agents, or inhibitors of cytokines or leukotrienes

Table 4**Treatment of Non-Infectious Causes of Respiratory Failure after HSCT**

Pre-Engraftment (<30 days)	Time from HSCT	Treatment Considerations
-Hyperacute GVHD	< 14 days	Steroids within 7 days have better outcomes; Increased risk of acute and chronic GVHD; higher risk of non-relapse mortality
1. Peri-engraftment respiratory distress syndrome	4–25 days	Discontinue G-CSF Mild cases: Supportive care Moderate-to-severe cases: Steroids 1mg/kg q12h for 3 days and taper over 1 week
(1) Diffuse Alveolar Hemorrhage	<30 days but can occur later	Methylprednisolone 1 gm daily divided in 4 doses for 5 days, followed by 1mg/kg for 3 days, tapering off over 2–4 weeks Aminocaproic acid, 1 gm q 6h along with corticosteroids has better survival Recombinant factor VIIa, 90 mcg/kg q 2–3 h has shown good response; however, dosing and schedule is unclear
Early Post-Engraftment (30–100 days)		
(2) Idiopathic Pneumonia syndrome	14–90	No proven treatment Steroids showed early response but no survival benefit Etanercept (TNF-binding protein) has high response rates and improved survival Combination of steroids and etanercept have better survival Role of lipopolysaccharide – under investigation
1. Sinusoidal obstruction syndrome	30–100 days	Largely supportive; fluid management, adequate oxygenation and transfusional support to minimize ischemic liver injury and avoidance of hepato/nephrotoxins. Defibrotide (polydeoxyribonucleotide) 25 mg/kg/day q6h for 14 days or until complete response; High dose methylprednisolone can be considered TPA and heparin can be used, but associated with significant risk of hemorrhage TIPS has been shown to worsen the process and no survival benefit In selected cases, liver transplantation is considered. Prophylaxis: ursodiol; use of non-myeloablative regimens; fludarabine instead of cyclophosphamide
Late Post-Engraftment (>100 days)		
1. Protein alveolar proteinosis		Treatment: Whole lung lavage using double-lumen endotracheal tube Limited evidence: Hyperbaric chamber or extracorporeal membrane oxygenation (ECMO) has been used to perform whole-lung lavages in cases of severe hypoxemia.
1. Pulmonary veno occlusive disease		Defibrotide has shown favorable results but needs further evidence Lung transplantation- for severe refractory cases Epoprostenol may serve as a beneficial vasodilator “bridge” to lung transplantation
1. Cryptogenic organizing pneumonia		No standard therapy; however, treatment of choice is systemic corticosteroids 1mg/kg per day for prolonged duration (high rate of recurrence upon taper)
1. Post transplant lymphoproliferative disease		Rituximab/monoclonal antibody therapy (375 mg/m ² once weekly for 4 doses) Reduction of immunosuppressive agents
1. Bronchiolitis obliterans syndrome		Challenging with no standard therapy. Treatment options include: Systemic and inhaled steroids, Etanercept, mTOR inhibitors, Extracorporeal photopheresis, Imatinib, Azithromycin 12-week course, Montelukast, combination of corticosteroids and bronchodilators

GVHD-Graft versus host disease; G-CSF-granulocyte colony stimulating factor; TIPS-transjugular intrahepatic portosystemic shunt

Table 5
Summary of Studies Comparing Use of NIPPV vs. IMV in Patients with Hematological Malignancies and ARF

Authors, year	Study design	Patients	IMV/NIV	HM/HSCT	Hospital Mortality	Independent prognostic factors for increased mortality
Soares et al. 2005 ⁽⁸⁾	Cohort, prospective, single center	463	444/19	104	64%	Older age, poor performance status, cancer recurrence/progression, PaO ₂ /FiO ₂ <150, SOFA score and airway/pulmonary invasion or compression of tumor
Azoulay et al. 2008 ⁽¹¹⁾	Cohort, prospective, multicenter	110	110/0	110/45	55%	History of BMT, need of vasopressors or dialysis, intubation during ICU stay
Lecuyer et al. 2008 ⁽¹²⁾	Cohort, retrospective multicenter	1753	967/265	1753/157	40%	SAPS II score, need of IMV, renal replacement therapy and vasopressors, ARDS, shock
Adda et al. 2008 ⁽⁵⁹⁾	Cohort, Retrospective, single center	99	53/46	99/NA	79% vs 41% (IMV/NIV)	NIV failure and increased number of hours on NIV, delay with ICU admission
Depuydt et al. 2010 ^[56]	Cohort, retrospective, single center	137	67/24	137	80% vs 75% (IMV/NIV)	Higher SOFA and cancer specific scores
K.J Price et al. 2013 ^[73]	Cohort, retrospective, single center	167	161/NA	NA	83 %	Advanced disease status and elevated SOFA score at the time of intubation
Mokart et al. 2013 ^[76]	Randomized, prospective, multicenter	219	32/88	293	31% (28-day mortality)	Older age, the number of chemotherapy lines and delay in ICU admission
Azoulay et al. 2013 ^[27]	Cohort, prospective, multicenter	1011	484/318	1011/252	60% vs 46% (IMV/NIV)	Poor performance status, Charlson comorbidity index, allogeneic HSCT, organ dysfunction score, malignant organ infiltration and invasive aspergillosis
Allareddy et al. 2014 ^[26]	Cohort, retrospective, multicenter in HSCT	6074	1811/387	6074/6074	64% vs 55% (IMV/NIV)	Duration of IMV (>96 h)
Boyaci et al. 2014 ^[70]	Cohort, retrospective, single center in HSCT	48	18/23	48/48	69% (ICU mortality)	Baseline APACHE II score and requirement of vasopressors during ICU stay

Abbreviations: IMV-invasive mechanical ventilation; NIV – non-invasive mechanical ventilation; HM – Hematological malignancies; BMT – Bone marrow transplant; SOFA – Sequential Organ Dysfunction Score