Antonio M. Esquinas · S. Egbert Pravinkumar
Ayman O. Soubani *Editors*

Mechanical Ventilation in Critically Ill Cancer Patients

Rationale and Practical Approach

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To all our patients, to whom we will always owe at least a little hope

Preface

Survival of critically ill cancer patients admitted to intensive care unit (ICU) for management of acute deteriorations related to underlying malignancy, infections, and treatment-related organ dysfunctions is improving worldwide. In particular outcomes of cancer patients receiving mechanical ventilator support have improved given the timely optimal diagnostic and therapeutic management of critically ill cancer patients with respiratory failure. Advances in the care of deteriorating organ functions in cancer patients, early recognition of acute clinical decline and admission to ICU, use of rapid response teams, and clinical practice algorithms play an important role in the positive outcome of these patients. Furthermore, advances in ventilator support devices, aggressive structured and standardized weaning from mechanical ventilation and intravenous sedatives, use of noninvasive mechanical ventilatory support, and education of health care providers have significantly contributed to the improved survival of cancer patients in the ICU.

This book is focused on the care of cancer patients in the ICU given the increased incidence of cancer and related critical illness. Experts from various countries have contributed to the development of this book by sharing their expertise in their specific area of practice. The book provides an in-depth understanding of the rationale and practice of mechanical ventilatory support in critically ill cancer patients. The book is unique in that it has an international panel of experts focused in the clinical care of cancer patients with critical illness.

The lack of a wider international perspective on ventilatory support in cancer patients triggered the need for this textbook. The chapters are structured in such a way that the reader would appreciate the different aspects of ventilator support such as pre-ICU support, types of ventilatory support, and postoperative ventilatory support. Chapters on ICU end-of-life care, withdrawal of mechanical ventilator support, and health care cost/resource utilization have been included to provide the reader a realistic and wider perspective of ventilatory support for cancer patients.

The book will aid in acquiring knowledge and understanding of ventilatory support for critically ill patients with both solid and hematological malignancies. Coordinating the creation of a book with international authors, like this book, is of no easy task; nevertheless, it has resulted in compilation of knowledge from international authors for a broader view in the management of critically ill cancer patients. We hope that the reader would find this book not only interesting but as a resource of practical knowledge.

The editors would like to acknowledge the willingness of these experts in sharing their experience and knowledge in this area. We would also like to thank Ms. Madonna Samuel and Andrea Ridolfi with Springer Publishing Group for their support throughout the process.

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Part I

Background and Therapeutic Procedures in Critically Ill Cancer Patients

Epidemiology of Mechanical Ventilation and Acute Respiratory Failure in Cancer Patients

1

Dulce Apolinário

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
ICU	Intensive care units
NIV	Noninvasive mechanical ventilation
TRALI	Transfusion-related acute lung injury

1.1 Introduction

The number of cancer patients has increased over the last decades, as a result of survival gains achieved by intensive treatments, with an estimated prevalence for 2012 of 32.6 million persons alive who had been diagnosed with cancer in the previous 5 years [1].

With the improved survival of these patients, the complications associated with the oncologic disease and its treatment have also increased, being the lung the organ most frequently involved, resulting in respiratory failure [2].

This chapter reviews the epidemiology and major causes of acute respiratory failure (ARF) in adult patients with malignancies requiring ventilatory support.

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1.2 Discussion and Analysis of the Main Topic

1.2.1 Acute Respiratory Failure in Cancer Patients

Cancer-related complications or treatment-associated side effects can lead to lung damage that can result in respiratory failure [2].

ARF requiring mechanical ventilation is a leading cause of admission to intensive care units (ICU) for patients with malignancies, who are actually more often admitted to the ICU for respiratory complications than the other ICU patients [3]. The frequency of ARF ranges from 5 to 50% in patients with hematologic and solid malignancies and from 42 to 88% among hematopoietic stem cell transplant recipients [2, 4].

This condition has a poor outcome in cancer patients, with high mortality rate, mainly in patients with ARF requiring mechanical ventilation. In patients with hematologic and solid malignancies who require mechanical ventilation, the mortality is 50% and 75%, respectively [2]. Among hematopoietic stem cell transplant recipients requiring mechanical ventilation and ICU admission, the mortality rate is approximately 85% [2]. Notwithstanding, this clinical scenario has changed in the late years, and improved survival rates have been reported: in a Sepsis Occurrence in Acutely Ill Patients substudy, the outcome of patients with solid cancer was similar to ICU patients without cancer, with ICU mortality rates of 20% and 18%, respectively [3]; still, patients with hematological cancer had a worse outcome with the highest hospital mortality rate (58%) [3]. Investigators attribute the increased survival to advances in oncology, hematology, and critical care, in conjunction with more appropriate selection of cancer patients for ICU admission [2, 4].

Various infectious and noninfectious causes, both by complications of the own cancer and by side effects associated with the therapies, can lead to ARF in these patients [2].

1.2.1.1 Infectious Causes

Cancer patients have an increased risk of pulmonary infections due to defects in humoral and/or cell-mediated immunity, neutropenia, use of immunosuppressant drugs, higher risk of aspiration, frequent exposure to antibiotics, and prolonged hospitalizations [2]. The pulmonary infections are the most frequent cause of ARF in patients with cancer, especially in those with severe comorbidities, underlying hematologic malignancies or those undergoing chemotherapy [2, 4].

The majority of pneumonias have bacterial etiology (47%), being the most frequently documented pathogens the gram-positive cocci (40%), like *Streptococcus pneumoniae* (20%), other streptococci (12.5%), and *Staphylococcus aureus* (7.5%); gram-negative bacilli (49%) such as *Escherichia coli* (10%), *Enterobacter cloacae* (10%), Klebsiella pneumonia (4%), *Pseudomonas aeruginosa* (16%), and *Haemophilus influenza* (4%); gram-negative cocci (1%) including *Neisseria sp.* (1%); and intracellular bacteria (10%) like *Legionella pneumophila* (5%), *Mycoplasma pneumonia* (2.5%), *Coxiella burnetii* (1%), and *Chlamydia pneumoniae* (1%) [5].

Opportunistic pulmonary infections are also common in these patients (31%), such as invasive pulmonary aspergillosis (31%), respiratory viral infections (28%), *Pneumocystis jirovecii* pneumonia (27.5%), tuberculosis (5%), mucormycosis (4.5%), *Cytomegalovirus* infection (1.5%), fusariosis (1.5%), *Scedosporium* sp. infection (1%), and *Toxoplasma gondii* infection (1%) [5]. Fungal pneumonia is more frequent in the setting of prolonged neutropenia, corticotherapy, broad-spectrum antibiotherapy, or underlying leukemia or lymphoma [2]. Community respiratory viruses have also been recognized as a cause of pneumonia among hematopoietic stem cell transplantation recipients and patients with hematologic malignancies, more frequently the influenza (33%), respiratory syncytial (31%), and parainfluenza (27%) viruses [6].

The infections are also the major cause of primary acute respiratory distress syndrome (ARDS) in patients with cancer (65.9%), including bacterial infection (58%) and invasive fungal infections (42%), such as invasive pulmonary aspergillosis and *Pneumocystis jirovecii* pneumonia [7]. In patients with septic shock, secondary ARDS can also occur (22.4%) [7].

1.2.1.2 Noninfectious Causes

Although the noninfectious etiology of ARF in cancer patients is less frequent, with values around 22%, and only 7.6% in the subgroup of patients with ARDS, there are numerous causes for it, and the most frequently described findings are pulmonary edema (49%) and pulmonary infiltration by the malignancy (49%) [5, 7].

One of the noninfectious causes is the decompensation of concurrent respiratory and cardiovascular diseases, which may lead to or worsen respiratory failure [2].

Another cause of ARF in these patients is the transfusion-related acute lung injury (TRALI), which usually manifests itself as lung noncardiogenic pulmonary edema in the sequence of blood product transfusion [2].

Antineoplastic agent-induced lung injury is a major problem for cancer patients having a broad spectrum of manifestations (bronchospasm, hypersensitivity reactions, lung fibrosis, diffuse alveolar hemorrhage, acute interstitial pneumonitis, ARDS, capillary leak syndrome, and organizing pneumonia) [2, 4]. In patients who have previously received radiation to the chest, radiation-induced lung injury may occur and is manifested by an early acute phase in the form of pneumonitis (radiation pneumonitis) and a late phase of pulmonary fibrosis [2].

Venous thromboembolism, manifested as either deep venous thrombosis or pulmonary embolism, is a frequent cancer-related medical disorder, present in about 7.8% of patients hospitalized with cancer, especially with advanced malignancies, renal carcinoma, pancreatic, gastric, and brain tumors [8].

In thrombocytopenic patients with acute or chronic leukemia or multiple myeloma, and in recipients of hematopoietic stem cell transplantation, alveolar hemorrhage is also a frequent cause of respiratory failure [2].

The paraneoplastic syndromes, such as myasthenia gravis, Lambert-Eaton myasthenic syndrome, or Guillain-Barré syndrome, can cause respiratory failure due to respiratory muscle weakness, as well as upper airway compromise caused by weakness of the facial, oropharyngeal, and laryngeal muscles [2].

The disease own progression can lead to ARF by direct neoplastic involvement of the respiratory tract, resulting in upper or lower airway obstruction, or even to disseminated parenchymal disease or lymphangitis [4].

In patients undergoing thoracic cancer surgery, ARF may also occur postoperatively due to atelectasis, pneumonia, pulmonary edema, and development of bronchopleural fistula [2].

1.2.2 Mechanical Ventilation in Cancer Patients

Many cancer patients with ARF need mechanical ventilation support, with frequencies of 62.2% in solid tumors and 69.6% in hematological cancers [3]. The identified risk factors for invasive mechanical ventilation in subjects with malignancies admitted for ARF are respiratory disease severity (oxygen flow required and number of quadrants involved on chest x-ray) and hemodynamic dysfunction at ICU admission [9].

Although the prognosis of these critically ill patients is disappointing, especially if they require endotracheal intubation, it is demonstrated that half of the cancer patients with good performance status and nonprogressive disease requiring ventilator support survive, so they should receive full intensive care [10].

In the last years, noninvasive mechanical ventilation (NIV) has been increasingly used as an alternative to invasive ventilation, as it has the benefits to reduce the infectious complications in patients affected by hematologic cancers or those with immunosuppressant drugs, avoid intubation-related trauma, enhance patient comfort, and reduce the need for sedation [2, 4]. Nonetheless, NIV has to be used in appropriate situations because its failure has been associated with increased mortality [4]. NIV may also be a reasonable option in cancer patients with respiratory failure who have refused endotracheal intubation or have a "do not intubate" order [2].

1.3 Conclusion

ARF is frequent in cancer patients due to cancer-related complications and treatment-associated side effects. Various etiologies can lead to ARF in these patients, conducting to diagnosis and management challenges. The pulmonary infections are the most frequent causes, but many noninfectious causes are described, such as decompensation of concurrent respiratory and cardiovascular diseases, pulmonary drug toxicity, radiation-induced lung injury, TRALI, antineoplastic agent-induced lung injury, venous thromboembolism, alveolar hemorrhage, paraneoplastic syndromes, disease progression with airway obstruction, disseminated parenchymal disease or lymphangitis, and complications of thoracic cancer surgery.

Regardless of the cause, ARF is a severe condition and frequently requires ventilatory support and ICU admission. It is still associated with a poor outcome and high mortality, despite the general improved outcome over the last decade.

1.4 Key Major Recommendations

- ARF remains a frequent and severe complication in cancer patients. Despite most of the times being of infectious origin, there are many other possible causes, the knowledge of its epidemiology and main etiologies being essential.
- Many cancer patients with ARF will need mechanical ventilation support and ICU admission.

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Breathlessness in Advanced Cancer Patients: Protocols and Recommendations

2

Manuel Sánchez Cánovas, Juan Gutiérrez Mejía, Alberto Carmona Bayonas, and Paula Jiménez-Fonseca

2.1 Introduction: Definition and Epidemiology

Breathlessness and dyspnea are common terms used to describe a conscious, unpleasant, intense, and frightening experience related to shortness of breath. Patients describe breathlessness as suffocating, choking, or tightness of breath. It can be described along three dimensions: (1) air hunger, a need to breathe while being unable to increase ventilation; (2) effort of breathing, physical tiredness associated with breathing; and (3) chest tightness, feeling of constriction and inability to breathe in and out [1, 2].

This is a frequent and distressing symptom in cancer patients; however, it is often overlooked [3]. In fact, for many people, breathlessness is tolerated and sublimated, and there is evidence of massive underreporting of the symptom [4].

Thus, epidemiological data is unlikely to reflect objectively much information. Although the case series are heterogeneous, depending on the baseline characteristics of patients and tumors, it may be present in around 20–40% of cancer patients at the diagnosis of advanced disease, with symptoms prevalence reaching 70% in the last 6 weeks of life. Therefore, breathlessness is the second most common reason for starting palliative sedation.

There is no correlation between objective measurements of dyspnea and the experience of breathlessness perceived by the patient. It is a personal subjective

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experience colored by social and physiological unique characteristics and shaped under cognitive, sensory, behavioral, and emotional components from each patient. This explains why breathlessness can only be correctly interpreted by sufferers.

On the other hand, the experience of caregivers who are looking after a patient with dyspnea is in general negative, exhausting, and abundant in extreme tension that gives place to poor sleep and anxiety. Thus, appropriate care of advanced cancer patients should also take into account carers' needs and well-being. Recently the term "total dyspnea" has being proposed in consideration of the complexity of the symptom and its multiple dimensions affecting all domains of quality of life (e.g., emotional, functional, social, spiritual, etc.) because of their deep consequences [1, 5].

2.2 Etiology and Pathogenesis

Breathing is autonomously regulated at the respiratory centers located in the medulla and pons, triggered by specialized neuron networks under the major influence of the partial pressure of carbon dioxide (PCO_2) concentration and pH at the surrounding cerebrospinal fluid. Higher level of control is found at the motor cortex, which allows for transient voluntary changes of breathing patterns. The motor cortex interacts with the sensory cortex, integrating information of afferent receptors via the glossopharyngeal and the vagus nerve. Normally this information should be complementary and similar.

The origin of breathlessness experience is still matter of research. It is a consequence of a complex integration from multiple receptors along the respiratory and cardiovascular system at different neurologic levels [6]. There are several theories on the origin of dyspnea:

1. According to the corollary discharge theory, a copy of the respiratory commands is sent from the motor to the sensory cortex, informing other regions of the brain of the respiratory pattern and producing conscious awareness of the respiratory effort.
2. Dyspnea may also arise by the existence of mismatch between the output of the respiratory controllers, in the motor cortex and afferent signals arriving from the lungs and chest wall receptors that gauge the response of the effector ventilator pump, which is mediated through the phenomenon called efferent-reafferent dissociation.
3. The experience may also be directly provoked by mechanoreceptors and chemoreceptors, centrally and peripherally, that influence the perception of "chest tightness and air hunger" [3], as follows:
   (a) Peripheral chemoreceptors located in the carotid and aortic bodies respond to the partial pressure of O_2 in arterial blood (PaO_2), PCO_2, and pH serum changes. Carotid chemoreceptors are more sensitive than aortic bodies to variations of these parameters.

(b) Skeletal muscles also have metaboreceptors that respond to increasing levels of tissue metabolites like lactate, produced during anaerobic metabolism. Exercise-induced dyspnea in normal individuals may be explained by this mechanism, independently of the occurrence of hypoxemia or hypercapnia.
(c) Receptors in the oral mucosa, nasal airway, and facial receptors at the sensitive territory of trigeminal nerves can be stimulated with airflow, so that their stimuli decrease breathlessness experiences and improve exercise tolerance in patients with chronic dyspnea.
(d) Other mechanoreceptors and chemical receptors have been detected at the lower airway, some represented by unmyelinated nerve endings (C-fibers) responding to irritant signals and bronchoconstriction, while others as stretch receptors from parenchymal zones sensitive to distention, and finally pressure receptors from the airway walls and alveolar walls (J receptors) combined with pulmonary vascular receptors responding to high vascular pressures have also been related to breathlessness.
(e) Chest wall receptors located in joints, tendons, and intercostal muscles decrease breathlessness when stimulated.

Functional brain image has shown the activation of neurologic areas in the anterior insula and posterior cingulate gyrus induced by breathlessness; these areas have been related with pain perception which may explain why opioids have an effect in the palliative treatment of dyspnea [7–9]. The most frequent cause of dyspnea in cancer patients would be the existence of a primary lung tumors or the existence of pulmonary metastases. However, the origin of this symptom may be varied:

1. Direct effect of cancer; this section encompass several pathogenic mechanisms:
   (a) Obstruction of the airway: it can be the result of a primary tumor, lymph nodes, or metastatic disease. However, breathlessness can also have its origin in the excess of secretions associated to some tumor subtypes or the infiltration of vocal cords.
   (b) Injuries of the lung parenchyma (tumor, infections, radiotherapy, etc.).
   (c) Vascular syndromes, such as symptomatic pulmonary embolism in immobilized patients or thrombogenic tumors, superior vena cava syndrome (especially in small-cell lung cancer or lymphoma), etc.
   (d) Pleural effusions (malignant mesothelioma or metastases from other sites).
   (e) Weakness of the respiratory muscles; secondary to cachexia, electrolytic alterations, or neuromuscular disease or paraneoplastic syndromes (e.g., Guillain-Barre, Eaton-Lambert syndrome, etc.).
   (f) Decrease in the chest wall distensibility, which could be secondary to massive ascites or visceromegaly. This is typical of hepatocellular carcinomas, peritoneal metastases (e.g., gastric tumors), or ovarian cancer.
   (g) Other possible causes that could be included within this group would be systemic alterations such as anemia, acidosis, and neuropsychiatric disorders (depression, anxiety disorders, etc.), which are very common in cancer patients.

2. Effect of antineoplastic therapy (iatrogenic adverse events):

   (a) Cancer therapy constitutes a potential cause for dyspnea; specifically, both radiotherapy and chemotherapy (e.g., bleomycin, gemcitabine, everolimus, anti-PD1, etc.) can provoke pneumonitis, pulmonary fibrosis, cardiopulmonary toxicities, anemia, venous thromboembolic disease, cachexia, etc. Serious adverse events can contribute to the onset of dyspnea or the worsening of the previous health status.
   (b) It is expected that novel, emerging antitumor strategies such as immunotherapy or other targeted therapies may become a sources of respiratory distress in the cancer population. Therefore, it will be a challenge to develop effective management algorithms for these new modalities. Further research in this field is required to unveil the underlying physiopathological mechanisms, in order to prevent and manage these complications efficiently.
   (c) Finally, aggressive surgical approaches for lung primary tumors and metastases (e.g., lobectomy, pneumonectomy, etc.) can be a source of residual breathlessness, particularly in patients with prior vulnerabilities or chronic respiratory comorbidities.

3. Other contributing factors:

Chronic comorbidities (e.g., chronic obstructive pulmonary disease, cardiovascular disorders, bronchial hyperresponsiveness associated with asthma, etc.) are common in oncologic patients due the coexistence of multiple risk etiologic factors and increases in average life expectancy. In certain groups of patients, they may constitute the main causes for the onset or exacerbation of dyspnea.

2.3 Breathlessness Management in Oncological Patient: Diagnosis and Treatment

Concerning the palliative management of dyspnea, two basic fronts should be addressed:

(a) The etiologic approach: dyspnea has many causes involving either the breathing airways and lungs or the cardiocirculatory system. If we can identify them, they could be tackled with a targeted treatment (e.g., anticoagulants for pulmonary embolism, antibiotics, corticoids, etc.).
(b) The symptomatic strategy: dyspnea is per se a very disabling symptom for all patients, calling for an immediate therapeutic attitude regardless of the underlying etiology.

Obviously these dichotomies are two sides of the same coin, so both therapeutics should be resolved and approached at the same time. The key to distinguish which one should constitute our starting focus of attention should be given by the patient, taking into account that a number of severity criteria exist that need to be identified in patients with respiratory distress: tachypnea, altered mental status, tachycardia, hemodynamic

instability, and use of accessory muscles. Patients' prognosis and the potential reversibility of the respiratory syndrome should also be promptly elucidated.

The presence of severity criteria would force us to begin supportive care rapidly and should not lead to a delay in the establishment of palliative care management in these patients. This will not only impact on quality of life and anxiety, but it will also subsequently facilitate the realization of the necessary etiological studies.

In contrast, a patient who is apparently out of danger, and in situation of no severity, will mainly benefit from the identification of a causative factor to better target his treatment, without exempting us from controlling the symptoms that might present.

2.3.1 Etiologic Approach to Management

In general, the idiosyncrasy of cancer should not constitute an obstacle for the correct assessment in dyspneic patients. It is true that the differential diagnosis covers a wider range of possibilities in comparison with the general population, but the algorithm to follow does not include significant differences.

It will be crucial to evaluate the origin of our patient's dyspnea properly, since it will impact the management and outcomes in reversible conditions. Conducting a good anamnesis and thorough clinical examination will be the first step to identify the etiology and guide the subsequent workup. We show some examples in Table 2.1.

Table 2.1 Suggested workup in acute respiratory failure

Clinical findings	Diagnostic suspicion	Workup
Fever	Pneumonia	Chest X-ray
Sudden onset in immobilized subjects	Pulmonary embolism[a]	Computed tomography angiography
Abdomen distension	Ascites	Abdominal ultrasound
Unilateral auscultatory silence	Pleural effusions—pneumothorax	Chest X-ray
Facial and neck swelling	Superior vena cava syndrome	Chest CT scan
Normal oxygen saturation	Anxiety states	Not required
Neurological symptoms	Brain metastases	TC cerebral
Laryngeal stridor	Upper airway obstruction	Laryngoscopy
Wheezing	Bronchospasm	Chest X-ray (to discard associated complications)
Chemotherapy/radiotherapy	Pneumonitis	Chest X-ray
Lower extremity edema	Acute heart failure	Chest X-ray
Cachexia, other gastrointestinal complaints	Anemia, electrolytic alterations	Blood tests

[a]The risk of venus thromboembolism (VTE) is estimated to be fourfold higher in cancer patients compared with noncancer patients. VTE has been found to be an adverse prognosis factor in all stages of cancer [10]. In fact, it has been described as the second cause of death in cancer patients

Once we confirm each one of these diagnoses, management will be the specific for each entity. We would like to conclude this paragraph recalling that regardless the etiology and the requested workup, it could be essential for some patients to carry out an arterial gasometry in order to:

(a) Determine the severity of the event which has prognostic and therapeutic implications.
(b) Support the causative diagnosis of acute respiratory failure.

Of note, criteria for diagnosis of acute respiratory failure are based on laboratory and clinical findings. It is confirmed when the pressure of oxygen in arterial blood (PaO_2) is less than 60 mmHg, which is approximately equivalent to an arterial oxygen saturation of 90%, as measured by pulse oximetry.

Despite this approximate equivalence, pulse oximetry has a lower reliability in certain contexts in which it should not substitute an arterial blood gas analysis (serious anemia, jaundice, peripheral hypoperfusion, hypothermia, etc.) the former do not provide pH values or the partial pressure of carbon dioxide ($PaCO_2$), which is helpful in determining the origin of dyspnea, as displayed in Fig. 2.1.

There are some particular oncological fields whose management is essential to know in order to get better results in our patients:

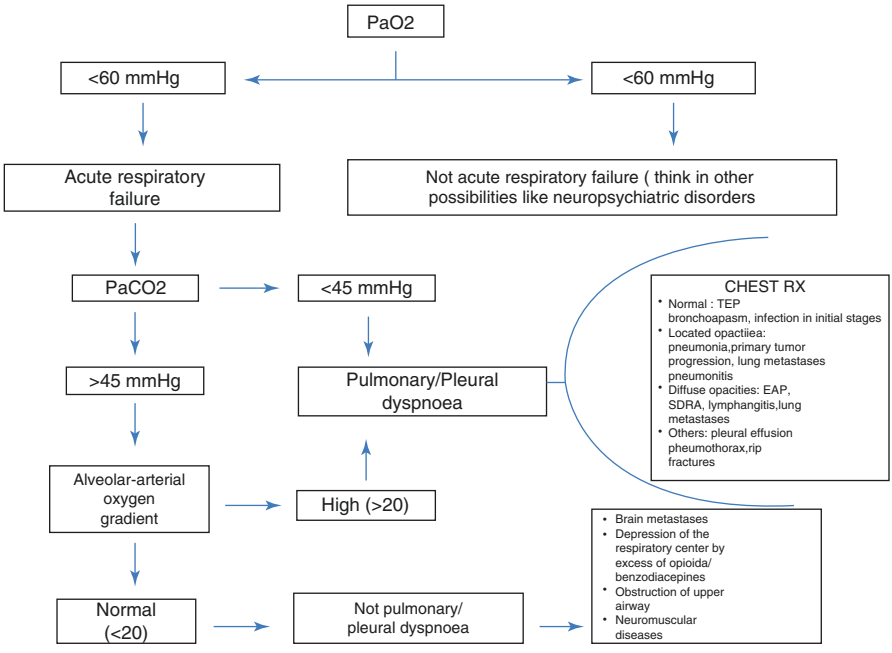

Fig. 2.1 Diagnostic algorithm for acute \ failure in cancer patients

2.3.1.1 Immunological Checkpoint Inhibition Agents (Targeting CTLA-4 and PD-1)

They are new therapeutic strategies whose use is increasing at different malignancies. This new group of medication is associated with immune-related adverse events. Examples related with breathlessness, have been described in sarcoidosis, organizing inflammatory pneumonia, or pneumonitis. The treatment of moderate (grade 2) or severe (grades 3–4) immune-related adverse events requires [11]:

- For patients with grade 2 toxicities, treatment with the checkpoint inhibitor should be withheld and should not be resumed until symptoms or toxicity is grade 1 or less. Corticosteroids (prednisone 0.5 mg/kg/day) should be started if symptoms do not resolve within a week.
- For patients experiencing grade 3–4 immune-mediated toxicities, treatment with the checkpoint inhibitor should be permanently discontinued. High doses of corticosteroids (prednisone 1–2 mg/kg/day) should be given. When symptoms subside to grade 1 or less, steroids can be gradually tapered over at least 1 month.

2.3.1.2 Bleomycin [12]

Bleomycin is associated with the four main types of pulmonary toxicities: subacute progressive pulmonary fibrosis, hypersensitivity pneumonitis, organizing pneumonia, and acute chest pain syndrome during rapid infusion. The risk appears to be higher in older patients and those with renal insufficiency.

Thoracic irradiation and concurrent administration of cisplatin at high doses may increase the risk. For patients with symptomatic pulmonary toxicity and evidence of impairment on pulmonary functions tests, the management consists in administration of systemic glucocorticoids (prednisone 0.75–1 mg/kg) and discontinuing bleomycin therapy.

2.3.2 Symptomatic Management

In patients with severe symptomatology or the aforementioned severity criteria, the control of the dyspnea becomes a fundamental objective. Before moving toward any etiologic management, the stabilization of our patient will be the priority. Cancer patients can decompensate for various reasons, similar to subjects with other chronic conditions.

Certain types of advanced cancer are not necessarily a synonymous of imminent death, and novel therapies are rapidly changing the landscape of tumors that were previously considered incurable. It is very easy to fall into the mistake of evaluating patients' health status and prognosis superficially which may consequently entail a definitive sedation or limitation of therapeutical effort.

There is also a debate on whether cancer patients are subsidiary to intensive care unit (ICU) admission or not. For a long time, an ICU admission has been denied to most patients with advanced tumors. Fortunately, this perception is beginning to change, and the label of a cancer diagnosis should not preclude the objective and accurate perception of the disease we are confronting.

It is mandatory to carry out a comprehensive assessment of the oncologic antecedents, including the evolution cancer, prognosis, possibilities of tumor control, etc., which should also entail the necessity of updating medical records with anticipated recommendations in case of acute respiratory failure. These anticipated orders as well as the presence of other chronic comorbidities and the acute baseline situation will help us to estimate medium-term prognosis and therefore to decide, in conjunction with the intensivists, whether an ICU admission is advisable. The basic clinical and laboratory criteria that would require an assessment by the ICU specialists include the following:

1. Shock or arterial blood pressure <90 mmHg
2. Severe dysfunction of two or more systems (including the respiratory)
3. Severe acidosis: pH < 7.25
4. PaO_2/FiO_2 ratio <200
5. Serious hypercapnia encephalopathy (Glasgow < 12)

Within the symptomatic management, we have three branches: the ventilatory support, non-pharmacological management, and pharmacological support.

2.3.2.1 Ventilatory Support

Oxygen therapy is recommended in hypoxemic patients with dyspnea [13]. There is no benefit of adding oxygen for cancer patients if they are not hypoxic. Hypoxemia is in general a weak stimulus for dyspnea. It is possible to obtain relief in symptoms associated with breathlessness by facilitating a flow through nasal prongs using room air, maybe as consequence of sensory stimulation. Because of the burdens in oxygen therapy and impact on patients and carers, initiation of this therapy should be clearly identified [14].

The venous blood gas and the patient's history will determine which type of oxygen therapy technique will be the most appropriate. It will be indicated always that hypoxemia is objectified by arterial blood gases:

(a) Nonspecific technique of oxygen therapy is a contraindication for patients who are not chronic CO_2 retainers (e.g., COPD), despite the existence of $PaCO_2$ elevations due to the acute respiratory disorder.
(b) Chronic CO_2 retainers that maintain high basal $PaCO_2$ must be ventilated with noninvasive mechanical ventilation (NIV), such as bi-level positive airway pressure (BiPAP) or even orotracheal intubation if the patients meet the criteria for ICU admission, because of the high risk of hypercapnic encephalopathy syndrome. Only consider intubation at the assumption of poor tolerance to BiPAP, high-flow nasal cannula oxygen therapy (4 L/min) or venturi masks (Ventimask) at (e.g., fraction of inspired oxygen (FiO_2) set at 35% and 6 L/min)

The increment on the complexity of devices for ventilatory support (nasal prongs, Ventimask, large-reservoir venturi masks, BiPAP, orotracheal intubation, etc.),

increasing the FiO_2, will rely on the SaO_2, as per the pulse oximetry (useful for monitoring and tracking).

High flow nasal cannula is suggested to be used early in patient's refractory to standard oxygen therapy with hypoxemia. Usually it is very well tolerated and allows patient to talk, eat, and avoid tight masks associated with NIV [13]. Noninvasive positive pressure ventilation such as BiPAP is indicated in patients with hypoxemia and hypercapnia, in which a substantial improvement is usually seen in the first hours. The success of this treatment is related with the "early" use and experience of the involved staff [15].

The clinical benefit of the BiPAP has been strongly demonstrated in different situations of dyspnea/acute respiratory failure, such as respiratory acidosis, advanced neuromuscular disease, immunocompromised patients, severe acute cardiogenic pulmonary edema, etc. Actually NIV has also a place in the palliation of patients at the end of life situations, by the following reasons:

(a) It reduces the ventilatory work facilitating breathing movements, by which the dyspneic sensation diminishes.
(b) NIV decreases the needs for opioids, which promotes a higher level of consciousness, which is usually regarded by palliative care teams as prerequisite for a good death, since it allows saying goodbye to loved ones.

2.3.2.2 Non-pharmacological Treatment

Non-pharmacological treatment is focused on cognitive, sensitive, emotional, and behavioral areas. This approach is based on models of symptom perception that establish stages of appraisal, from the interpretation of symptoms through patients' lens to the asignment of meaning according to their values, beliefs, previous experiences, expectations, motivations, and personality.

This type of treatment should be started early, if possible before the pharmacological options, and continued even when that medication has started. It is very important for the patient to have certain control over symptoms. Patient's experience is affected by the social context and behavior of others; this is the reason why relatives and other caregivers should be involved in the same educating process. Several interventions have been suggested, like:

(a) Sitting and using good posture; especially in this last point, patients should always acquire whatever position is more comfortable for them even against of what carers believe is a "better position." Pacing movements in a slower execution and dividing the job in several steps will help in symptoms control.
(b) Learning breathing strategies is very useful; one of the best techniques is pursed lip breathing that allows patients to increase tidal volume and vital capacity, improving the removal of CO_2, decreasing respiratory rate, and reducing hyperinflation, while improving dyspnea as a consequence [3, 16].
(c) Using a fan or opening a window, in order to produce a cold airflow that stimulates facial receptors in trigeminal territories.

2.3.2.3 Pharmacologic Support

Opioids are the main treatment of breathlessness in advanced cancer patients. They are usually used by oral or intravenous routes as the first option. However, studies looking for other possible routes of administration have been conducted. It should be noted the lack of efficacy observed for nebulized opioids. However the sublingual application seems to constitute an efficacious therapeutic option effective with fewer side effects in comparison with other systemic alternatives.

The mechanism of how opioids decrease breathlessness is not well known. Opioid receptors are localized at different levels of the cardiovascular, respiratory and central nervous systems. Opioids are safe when prescribed under a stepped incremental-reassessed dose guideline; their use helps to reduce the unpleasantness of dyspnea. Recommendations should be evaluated in an individual case-by-case approach and adjusted according to patient response; clinical judgment should always precede any treatment decision. Patients with prior chronic opioid treatment for pain may need different doses from that of opioid-naïve patients.

The adverse effects associated with opioid treatment include drowsiness, nausea, vomiting, and constipation compared with the placebo. Morphine is recommended over all other types of opioids, by oral or parenteral administration as the first option for symptom control. It should be used carefully in patients with severe renal insufficiency (Table 2.2).

Benzodiazepines have classically been considered as a therapeutic option for the control of dyspnea at the same level of opioids. Different clinical trials have made clear that this single-drug group is superior to opioid when the cause of dyspnea is neuropsychiatric, for example, in anxiety disorders [18]. Benzodiazepines cause more drowsiness in comparison with placebo, but less than with morphine. These results justify the consideration of benzodiazepines as a second line for refractory

Table 2.2 Opioid doses and administration in cancer patients with dyspnea

Clinical setting		
Naïve patients with mild dyspnea	Naïve patients with severe dyspnea	Patients with severe COPD (start at 50% of the above doses and titrate 25% every 24 h as needed)
Hydrocodone 5 mg orally every 4 h	Morphine sulfate 5 mg orally every 4 h	Increase baseline dose by 25–50% and reassess every 24 h [17]
Codeine 30 mg orally every 4 h	Oxycodone 5 mg orally every 4 h	Morphine regular opioid dose +1/6 of daily opioid intake
Morphine 2.5–5 mg/4 h orally and 1–2.5 mg /4 h subcutaneous	Breakthrough management considers an equivalent dose every 1–2 h	Hydromorphone regular opioid dose +1/6 of the daily opioid intake
Hydromorphone 1.3 mg/4 h orally or 0.2–0.5 mg/4 h subcutaneous	Titrate in increments of 50–100% every 24 h as needed	
Breakthrough management consider an equivalent dose every 1–2 h		

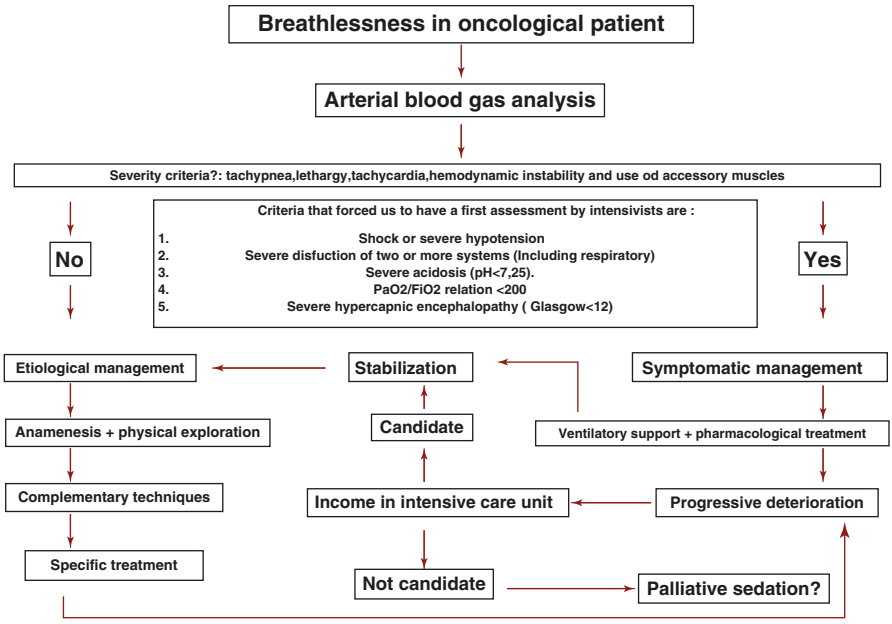

Fig. 2.2 Algorithm of management of dyspnea in oncological patient

symptoms, when opioids or other non-pharmacological measures have failed to control dyspnea. In fact, the combination of morphine with midazolam has shown good results in terminally ill patients.

Occasionally, it is erroneously believed that certain pharmacologic groups, such as bronchodilators, glucocorticoids, and diuretics, can be useful with regard to the control of dyspnea. This is only true in certain clinical scenarios (e.g., diuretics for pulmonary edema, corticoids in bronchospasm, etc.). For patients in the end of life that are not expected to benefit from any of these therapies, the use of palliative sedation provides relief of dyspnea; before considering a sedation, it is fundamental to ensure that the patient has a true indication, since this is an irreversible therapeutic intervention. Finally and to close this chapter, we show an algorithm that tries to summarize the management of dyspnea in this population (Fig. 2.2).

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Acute Respiratory Failure in Patients with Hematologic and Solid Malignancies: Global Approach

3

Sakshi Sethi and Stephen M. Pastores

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
BAL	Bronchoalveolar lavage
BMT	Bone marrow transplant
CMV	Cytomegalovirus
CT	Computerized tomography
DAH	Diffuse alveolar hemorrhage
EMG	Electromyography
FB-BAL	Fiber-optic bronchoscopy with bronchoalveolar lavage
HSCT	Hematopoietic stem cell transplantation
ICU	Intensive care unit
IVIg	Intravenous immunoglobulin
NIPPV	Noninvasive positive pressure ventilation
MV	Mechanical ventilation
PCP	*Pneumocystis jiroveci* pneumonia
PCR	Polymerase chain reaction
PE	Pulmonary embolism

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RSV	Respiratory syncytial virus
TRALI	Transfusion-related acute lung injury
VTE	Venous thromboembolism

3.1 Introduction

The incidence of all types of cancer is predicted to rise from 12.7 million new cases in 2008 to 22.2 million by 2030 [1]. Concomitantly, the last two decades have witnessed notable advances in the diagnosis and management of cancer patients including the use of high-dose chemotherapy, stem cell transplantation, targeted therapies, and immunotherapy. Although these strategies have significantly improved the overall and disease-free survival rates of patients with cancer, they have also resulted in increasing numbers of patients being admitted to the intensive care unit (ICU) for life-threatening toxic and infectious complications which are either cancer related or treatment associated.

Acute respiratory failure (ARF) is the leading cause for ICU admission in cancer patients and usually associated with high mortality rates especially in those requiring mechanical ventilation [2–4]. The incidence of ARF is about 5% in patients with solid tumors and up to 50% in those with hematological malignancies. Among hematopoietic stem cell transplant (HSCT) recipients requiring MV and ICU admission, the incidence of ARF ranges from 42 to 88% with an overall survival rate of approximately only 15% in those receiving MV [5].

The various causes of ARF in critically ill cancer patients are shown in Fig. 3.1. The most common causes include infections, cardiogenic and non-cardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), antineoplastic therapy (chemotherapy, radiation therapy)-induced lung injury, malignancy-related medical disorders, and progression of underlying cancer.

3.2 Pulmonary Infections

Pulmonary infections are the leading cause of ARF, and the spectrum of possible responsible organisms depends on the underlying comorbidities (such as chronic lung disease, smoking history, cardiac failure, prolonged corticosteroid therapy), type of underlying malignancy, type of antineoplastic therapy, presence of neutropenia or defects in both cell-mediated and humoral immunity, frequent antibiotic exposure, and prophylactic treatments (Table 3.1).

3.2.1 Bacterial Pneumonia

Cancer patients with bacterial pneumonia tend to have atypical clinical features where fever is common but cough and sputum production are not. The chest radiograph may be normal or demonstrate diffuse interstitial infiltrates; the classic lobar

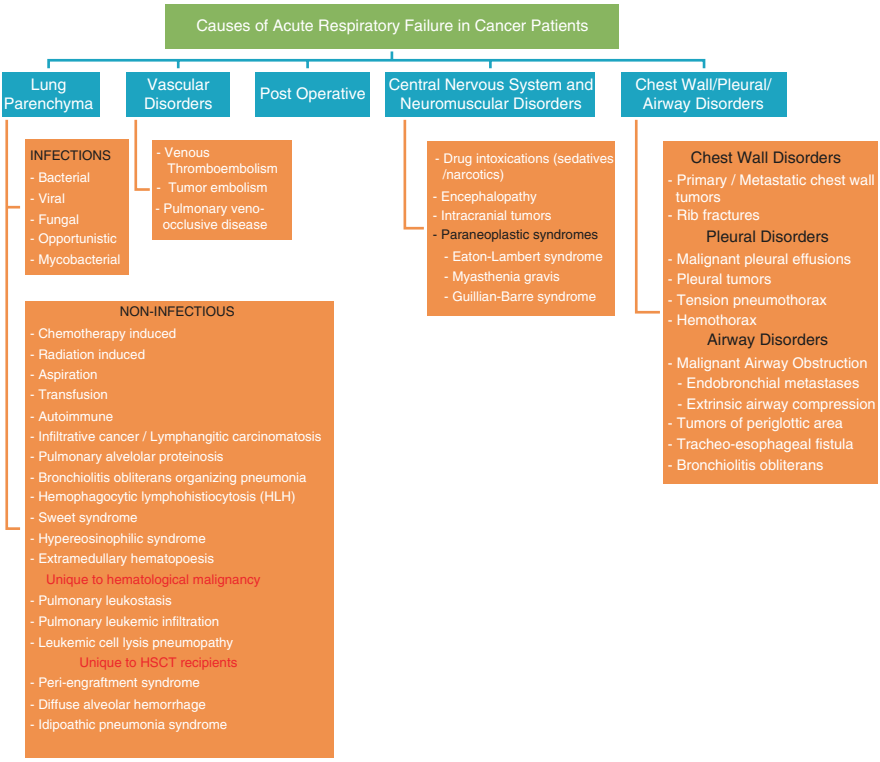

Fig. 3.1 Causes of acute respiratory failure in cancer patients

Table 3.1 Causative organisms depending upon the underlying immune deficiency

Immune deficiency	Cancers/conditions	Common organisms
Impaired humoral (B cell) immunity	CLL, multiple myeloma, BMT	Encapsulated bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*)
Impaired cell mediated (T cell) immunity	Lymphomas, AML, ALL, high-dose corticosteroids, BMT	*Pneumocystis jiroveci* pneumonia, mycobacteria, *Cryptococcus* and other pathogenic fungi, *Legionella pneumophila*, *Nocardia asteroides*, *Rhodococcus equi* and other bacteria, herpes virus (esp. cytomegalovirus)
Chemotherapy-induced neutropenia		*Staphylococcus aureus*, *Streptococcus pneumoniae*, gram-negative enteric bacilli (*Pseudomonas aeruginosa*, *Klebsiella pneumoniae*), opportunistic fungi (especially *Aspergillus*)
Compression, obstruction, ulceration	Solid cancers	*Bacteria*, *Stenotrophomonas maltophilia* (frequent antibiotic exposure, prolonged mechanical ventilation)

CLL chronic lymphocytic leukemia, *BMT* bone marrow transplantation, *AML* acute myelogenous leukemia, *ALL* acute lymphoblastic leukemia

consolidation however is usually absent. Aspiration pneumonia is common in patients who have head and neck or esophageal cancers, poor cough and difficulty clearing secretions, upper airway dysfunction due to laryngeal nerve involvement, and cancer patients who require a tracheostomy. Cancer patients who are debilitated and received enteral feedings in the supine position, those who received high-dose narcotics, and those who have central nervous system metastases are also high risk for aspiration.

3.2.2 Fungal Pneumonia

Aspergillus pneumonia can be a life-threatening lung infection associated with dyspnea, chest pain, and hemoptysis. The chest radiograph may show patchy bronchopneumonia or multiple nodular lesions. Computerized tomography (CT) scans may reveal peripheral wedge-shaped infarcts or a characteristic halo or air crescent sign. Recovering *Aspergillus* spp. from a respiratory culture (sputum or bronchoalveolar lavage [BAL]) in the appropriate clinical setting suggests a high probability of invasive pulmonary aspergillosis necessitating antifungal therapy. Voriconazole is the antifungal agent of choice.

3.2.3 *Pneumocystis jiroveci* Pneumonia (PCP)

Patients usually have a subacute presentation with fevers, dyspnea, and hypoxia and bilateral ground-glass opacities on chest imaging. Detection of *P. jiroveci* by conventional staining methods or polymerase chain reaction (PCR) in samples of induced sputum, BAL fluid, or lung biopsies is diagnostic. Trimethoprim-sulfamethoxazole or pentamidine with adjunctive corticosteroid therapy remains the preferred treatment for severe cases.

3.2.4 Viral Pneumonia

The most common viruses responsible for pneumonia in cancer patients include cytomegalovirus (CMV), respiratory syncytial virus (RSV), influenza viruses A and B, parainfluenza virus, human adenoviruses, human parainfluenza viruses 1–3, human enteroviruses, human rhinoviruses, and human metapneumoviruses. CMV pneumonia clinically presents with fever, nonproductive cough, and dyspnea. Radiographically, it can present as lobar consolidation, focal parenchymal infiltrates, ground-glass opacities, or bilateral reticulonodular infiltrates. Viral shell vial culture and conventional culture of BAL samples, fluoroscopic antibody testing, and PCR testing of respiratory secretions are used for diagnosis of CMV. Therapeutic options include ganciclovir or foscarnet for CMV pneumonia and aerosolized ribavirin for RSV pneumonia either used alone or in combination with IV immunoglobulin (IVIg).

3.3 Noninfectious Causes

3.3.1 Antineoplastic Agent-Induced Lung Injury

Various chemotherapeutic agents can cause pulmonary toxicity resulting in ARF in cancer patients. A myriad of clinical syndromes may be associated with antineoplastic-induced lung injury including interstitial pneumonitis/fibrosis, ARDS, capillary leak syndrome, hypersensitivity pneumonitis, diffuse alveolar hemorrhage (DAH), organizing pneumonia, and bronchospasm. Diagnosis should be considered in any patient who develops cough, exertional dyspnea, and low-grade fever during or several months after chemotherapy. Pulmonary function tests usually reveal a restrictive defect with reduced diffusing capacity. Chest imaging shows patchy or diffuse ground-glass opacities or consolidations. Radiation recall pneumonitis can occur in patients with history of prior radiation to the chest. Chest imaging reveals pulmonary infiltrates in the same field as in the previous radiation therapy. Drugs commonly associated with radiation recall pneumonitis include doxorubicin, etoposide, paclitaxel, gemcitabine, and trastuzumab [6]. Diagnostic procedures are performed to exclude other likely etiologies especially infections or recurrence or progression of tumor. Definitive diagnosis usually requires transbronchial or open lung biopsy in conjunction with appropriate history. Management includes cessation of the implicated chemotherapeutic drug and use of systemic corticosteroids.

3.3.2 Radiation-Induced Lung Injury

Radiation-induced lung injury can occur in patients who receive chest radiotherapy for intrathoracic or chest wall malignancies. Factors influencing the severity of injury include the volume of lung irradiated, the total dose, dose per fraction used, concomitant chemotherapy, and steroid withdrawal. Pathogenesis involves production of local inflammatory and fibrotic cytokines and activation of cell adhesion molecules. The lung injury can manifest either as early acute phase (radiation pneumonitis) or a late phase (pulmonary fibrosis). Radiation pneumonitis occurs 1–3 months after radiotherapy and commonly presents with insidious onset of dyspnea, cough, and fever. Interstitial or alveolar infiltrates within the irradiated field are found on chest radiograph. It is mostly self-limiting, but severe respiratory failure requiring systemic corticosteroids can also occur. Radiation fibrosis occurs 6–12 months after irradiation and is irreversible, and use of corticosteroids is not recommended.

3.3.3 Transfusion-Related Acute Lung Injury (TRALI)

Cancer patients who require frequent transfusions of blood and its products (including granulocyte transfusion in neutropenic patients) are most susceptible to TRALI. This syndrome presents as ARF in association with fever, hypotension, and non-cardiogenic pulmonary edema with bilateral infiltrates on chest x-ray. Pathogenesis is

multifactorial and includes the passive transfer of donor antibodies directed against histocompatibility antigens or granulocyte-specific antigens in the recipient resulting in complement activation, blood products from alloimmunized female donors, and transfusion of donor serum with normal serum IgA concentrations to a recipient with anti-IgA antibodies. Diagnosis is supported by the presence of granulocyte, leukoagglutinating, or lymphocytotoxic antibodies from either donor or recipient serum. Treatment is mainly supportive and most cases resolve within a few days.

3.3.4 Diffuse Alveolar Hemorrhage (DAH)

DAH is a life-threatening cause of respiratory failure in patients with thrombocytopenia, patients with hematologic malignancies, and those undergoing hematopoietic stem cell transplantation (HSCT). Common risk factors for HSCT recipients include pretransplant intensive chemotherapy, total body irradiation, thoracic irradiation, and old age. Signs and symptoms include dyspnea, cough, fever, and hemoptysis (present in one-third of cases). Chest radiograph shows diffuse interstitial and alveolar infiltrates, predominantly in the middle and lower lung zones. The diagnosis is confirmed by demonstration of progressively bloodier BAL fluid and the presence of greater than 20% hemosiderin-laden macrophages in BAL fluid. Management includes supportive measures with corticosteroids, platelet transfusions, epsilon-aminocaproic acid or recombinant factor VIIa (rFVIIa), and mechanical ventilatory support. Prognosis is usually guarded with mortality exceeding 50% in most studies.

3.3.5 Pulmonary Leukostasis

Pulmonary leukostasis is an uncommon cause of severe hypoxemic respiratory failure in patients with acute leukemia who present with extremely high leukocyte or blast counts (>100,000/μL) and is associated with high mortality rates. In this syndrome, the leukocytes aggregate and form thrombi in the pulmonary vasculature. Another syndrome, *leukemic cell lysis pneumopathy*, can present within 48 hours of initiating chemotherapy. It manifests with severe hypoxemia and diffuse infiltrates secondary to leukostasis in the pulmonary vasculature and is associated with perivascular hemorrhage and interstitial edema. Management includes leukapheresis, hydroxyurea, adequate hydration, supplemental oxygen, and ventilator support in severe cases.

3.3.6 Venous Thromboembolism (VTE)

Thrombotic events are most commonly associated with malignancies of the pancreas, ovary, and brain. Cancer patients are more susceptible to deep venous thrombosis and pulmonary embolism (PE) due to various factors including intrinsic tumor procoagulant activity, antineoplastic drugs, hormonal therapies, surgery, immobilization, and indwelling central venous catheters. Clinical features include sudden-onset dyspnea,

pleuritic chest pain, hemoptysis, and hypoxemia. CT scan remains the gold standard imaging modality for the diagnosis of PE.

Anticoagulation and thrombolytic therapy are more challenging in cancer patients, because they have a higher risk of recurrent VTE than noncancer patients on one hand and a larger risk for bleeding complication on the other, especially in those with brain tumors or metastatic disease. Thus, treatment has to be individualized and based on overall goals of care. Low-molecular-weight heparins are preferred over unfractionated heparin for treating cancer patients with PE. Inferior vena cava filters are recommended to prevent or treat PE in high-risk patients with contraindications or failure of anticoagulation therapy.

3.3.7 Postoperative Respiratory Failure

The incidence of postoperative respiratory complications resulting in ARF in cancer patients can range from 6 to 76%, depending upon the type of surgery and underlying comorbidities. It is most commonly seen after thoracic and upper abdominal surgeries such as intrapericardial or extrapleural pneumonectomy and esophagectomy. Common etiologies include atelectasis, pneumonia, pulmonary edema, and bronchopleural fistula, and mortality rates are generally high.

3.4 Paraneoplastic Syndromes

3.4.1 Myasthenia Gravis

Myasthenia gravis is commonly associated with thymomas and can result in respiratory failure requiring prolonged mechanical ventilation. Diagnostic tests include edrophonium (Tensilon) test showing improvement in muscle strength after administration of the drug and electromyogram (EMG) studies showing decremental response of the muscle action potential to repetitive stimuli. Management includes cholinesterase inhibitors, thymectomy, plasmapheresis, corticosteroids, immunosuppressive therapy, and IVIg.

3.4.2 Lambert-Eaton Myasthenic Syndrome

This is a rare syndrome strongly associated with small cell lung cancer that presents with slowly progressive muscle weakness and late respiratory failure due to impaired neuromuscular junction transmission from decreased acetylcholine release. Confirmatory tests include the presence of antibodies directed against voltage-gated calcium channels and EMG showing increase in muscle action potential amplitude of at least 100% compared with pre-exercise baseline value. Therapeutic options include treatment of the underlying malignancy, drugs to increase the available acetylcholine at the postsynaptic membrane, cholinesterase inhibitors, plasma exchange, IVIg, corticosteroids, and immunosuppressive therapy.

3.4.3 Guillain-Barré Syndrome

This syndrome is a form of acute sensorimotor neuropathy that is associated with malignancies like Hodgkin's lymphoma and chemotherapeutic agents such as vincristine, oxaliplatin, and sunitinib. Lumbar puncture reveals albuminocytologic dissociation. Management involves plasma exchange and IVIg. ARF results from progressive upper airway and respiratory muscle weakness. Close monitoring of vital capacity and inspiratory/expiratory pressures is required to prevent emergency intubation and cardiopulmonary arrest.

3.5 Airway Obstruction

Upper airway obstruction can result from tumors of hypopharynx, larynx, thyroid, esophagus, and lung causing ARF. Signs and symptoms include dyspnea, wheezing, hoarseness, and stridor. These patients usually require emergent airway management including cricothyroidotomy or tracheostomy. Central airway obstruction can be endoluminal, extraluminal, or a combination of both. Endoluminal lesions can be treated with laser, electrocautery, or brachytherapy, whereas extraluminal compression requires airway stent placement.

3.6 Diagnostic Strategy and Management of ARF in Cancer Patients

A detailed clinical history and thorough physical examination are the first step to identify the cause of ARF in cancer patients. Azoulay and colleagues suggested six criteria to help identify the etiology of ARF which can be listed using the mnemonic DIRECT: *d*elay since malignancy onset or BMT, pattern of *i*mmune deficiency, *r*adiographic appearance, clinical *e*xperience and knowledge of the literature, *c*linical picture, and findings by HRCT. This strategy provides guidance for selecting empirical antimicrobial drugs and life-supporting interventions as well as other treatments and diagnostic investigations [7]. Rapid investigations and early identification of the cause of ARF have been shown to improve patient survival.

Fiber-optic bronchoscopy with bronchoalveolar lavage (FB-BAL) is the diagnostic strategy of choice for cancer patients whose respiratory symptoms are not severe enough to warrant ICU admission. However, the procedure can be associated with many complications with decline in respiratory status requiring mechanical ventilation being the most dreaded. Moreover, the diagnostic yield with FB-BAL is only about 50% prompting interest in noninvasive strategies for identifying the cause of ARF [8]. The recent expansion of new noninvasive diagnostic tools as listed in Table 3.2 requires reconsideration of the role of semi-invasive or invasive tests such as FB-BAL and lung biopsy.

Finally, the diagnosis of noninfectious causes of ARF also requires a careful approach as most of these patients require a significant change in their management,

Table 3.2 Noninvasive diagnostic testing for cancer patients with ARF

Radiography Chest radiography Thin-section high-resolution computed tomography Echocardiography or pleural ultrasonography
Sputum Bacteria, mycobacteria, and fungi (*Aspergillus*)
Tests for *Pneumocystis jiroveci* (MGG staining and immunofluorescence)
PCR for *Pneumocystis jiroveci*
Blood cultures
Serum tests Serology: *Chlamydia*, *Mycoplasma*, *Legionella* Herpes consensus PCR test Circulating *Aspergillus* antigen, beta-D-glucans, *Aspergillus galactomannan* Circulating cytomegalovirus antigen
Nasopharyngeal aspiration Tests for viruses (PCR and immunofluorescence)
Urine tests Cytology, bacteriology *Legionella*, *Streptococcus*, and *Histoplasma* antigens
Biological markers B-type natriuretic peptide (BNP) or pro-BNP C-reactive protein Procalcitonin

such as initiation of corticosteroid therapy, addition or change in chemotherapy, or discontinuation of a seemingly toxic chemotherapeutic agent. Noninfectious causes of ARF mostly fall into one of the following three categories: (a) acute or subacute nonspecific pulmonary infiltrates with severe hypoxemia in the initial phase of malignancies, especially hematological. Chest CT and other noninvasive tests can be helpful, but management entails rapid initiation of chemotherapy and broad-spectrum antibiotics against community-acquired organisms. FB-BAL is necessary only if initial treatment fails. (b) Progressive, subacute, lung infiltrates in patients with recurrence of underlying cancer. Radiographic findings can reveal peribronchial and perivascular nodules suggestive of specific lesions or interlobular septal thickening resulting in prominent secondary pulmonary lobules manifesting as tessellating polygons suggestive of carcinomatosis. Transbronchial biopsy is really helpful in this situation. (c) Acute respiratory failure in patients receiving consolidation therapy for hematological malignancies. Chest imaging reveals diffuse interstitial infiltrates characterized by a diffuse ground-glass appearance. FB-BAL is essential to rule out opportunistic infections before chemotherapy-associated lung toxicity is considered. Lung biopsy has a role to play in this group of patients.

Basic management principles include supplemental oxygen to correct hypoxemia, early initiation of appropriate empiric antimicrobial therapy in patients with suspected pneumonia, diuretics to decrease pulmonary congestion, and ventilator support including early use of noninvasive positive pressure ventilation (NIPPV) as well as invasive mechanical ventilation (MV), if necessary [9].

3.7 Prognosis and Outcome

ARF in cancer patients portends dismal outcomes despite aggressive management. Various studies report survival rates close to 50% for cancer patients admitted to the ICU with ARF, which further declines to about 20% for those requiring MV. Factors associated with higher mortality include, but not limited to, documented invasive aspergillosis, lack of definitive diagnosis, use of vasopressors, first-line conventional MV, conventional MV after NIPPV failure, and late NIPPV.

Physicians should assist all cancer patients and their families to make informed decisions regarding the use of MV and other life-sustaining treatments in the ICU and to complete advance directives. End-of-life discussions have been shown to be associated with increased family satisfaction, less aggressive medical care near death, and earlier hospice referrals. In contrast, aggressive care is associated with worse patient quality of life and worse bereavement adjustment. Ethics and palliative care consultations also greatly benefit end-of-life discussions with family members of cancer patients dying in the ICU [10].

3.8 Key Major Recommendations

1. The most common causes of ARF in cancer patients include infections, cardiogenic and non-cardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), antineoplastic therapy (chemotherapy, radiation therapy)-induced lung injury, malignancy-related medical disorders, and progression of underlying cancer.
2. A detailed clinical history and thorough physical examination are the first step to identify the cause of ARF in cancer patients.
3. Fiber-optic bronchoscopy with bronchoalveolar lavage has a diagnostic yield of only about 50% in cancer patients with ARF. Noninvasive strategies such as respiratory virus PCR testing, sputum and blood cultures, urine and serum tests, echocardiography, and chest imaging are often useful.
4. Corticosteroids are often used for patients with chemotherapy-induced lung injury and radiation pneumonitis.
5. Management of ARF includes supplemental oxygen to correct hypoxemia, early initiation of appropriate empiric antimicrobial therapy for pneumonia, diuretics to decrease pulmonary congestion, early use of noninvasive positive pressure ventilation (NIPPV) in selected cases, and lung-protective ventilatory support for ARDS.

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Radiation Therapy: Impact on Lung Function and Acute Respiratory Failure

4

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4.1 Introduction

Chest wall radiotherapy (RT) is a well-established part of early breast cancer management, as well as of lung and neck cancer [1, 2]. Currently, ACCP Lung Cancer Guidelines published in 2013 suggest the use of postoperative radiotherapy (PORT) for patients with stages I and II non-small cell lung cancer (NSCLC) and a positive bronchial margin. In patients with NSCLC, who cannot tolerate a lobectomy or segmentectomy, stereotactic body radiation therapy (SBRT) and surgical wedge resection are suggested over no therapy. Also, SBRT is favored in compromised patients and in those for whom an adequate margin is unlikely with a surgical wedge resection. The RT should involve once-daily therapy and a total dose of 60–66 Gy. In patients with infiltrative stage III (N2,3), NSCLC radiotherapy is recommended, either as palliative care or as complementary to chemotherapy. In patients with extensive-stage small cell lung cancer (ES-SCLC) who have completed chemotherapy, a course of consolidative thoracic radiotherapy (TRT) is suggested [3].

The use of SBRT is increasing over time, both due to the increasing cancer burden worldwide and the efficacy, low toxicity profile, cost-effectiveness, and ease of compliance with SBRT. An average incidence of 9–28% of radiation pneumonitis (RP) after SBRT is estimated, while 5–15% of patients irradiated for breast cancer may develop a form of lung toxicity [4–9].

The lung is a radiosensitive organ, and the reaction to radiation is a complex process. In humans, a lethal dose (LD50) of 10 Gy (single fraction) has been described [10]. The absorption of ionizing radiation causes immediate chemical,

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subcellular, and cellular interactions, while its morphological expression regarding gross tissue injury and organ dysfunction is often considerably delayed. The latent period between the exposure and the manifestation of damage is critically dependent on how efficiently the normal cells can repopulate the tissue [11].

Numerous factors are altering the risk of developing pulmonary radiation damage. These include radiation treatment factors, prior irradiation, use of chemotherapy, and coexisting lung disease, mainly the presence of interstitial lung disease and chronic obstructive lung disorders. Thus, the extent of lung damage arises as a result of physical and biological factors. The size of the radiation dose, its quality, and whether the exposure is single, fractionated, or protracted are the main physiological factors influencing subsequent tissue changes. Meantime, the presence or absence of repair and repopulation processes of the different tissue cells, their radiosensitivity and population kinetics, their state of oxygenation, and the differential sensitivity of the mitotic cycle phases play a crucial biological role in the extension of radiation damage [12].

The most important of the factors determining the extent of injury in a tissue is its ability to repopulate after radiation damage. The diving stem cells begin to die when they attempt their first or second postirradiation divisions, while the nondividing, differentiated cells, relatively unaffected by radiation, will continue to function. The injury will not become apparent until the number of functional cells falls below a critical level. The time of damage onset is more dependent on the cell kinetics of the tissue and less reliant on the size of the dose [13].

The lung's response to radiation therapy is clinically expressed into two syndromes that are not necessarily related: the so-called radiation pneumonitis (RP) that develops within 6 months after exposure and radiation pulmonary fibrosis (RPF), which is a delayed or late reaction, that develops from about 6 months to years after exposure.

4.2 Radiation Pneumonitis

RP consists of acute lung toxicity during or between 1 and 6 months after completion of a thoracic irradiation course. There is typically a latent period between radiation exposure and the development of acute pulmonary reactions, due to the low mitotic index of the pulmonary parenchymal cells.

The risk of radiation-induced injury is related to several factors. There is a direct relation to the incidence of RP and the volume of the lung irradiated within the tangential fields, as well as the use of additional supraclavicular (SC) fields [14]. Other factors that may increase the incidence and severity of radiation-induced lung disease are prior exposure to chemotherapy, mainly paclitaxel-based regimens, high-dose chemotherapy, and hormone replacement therapy in breast cancer patients [15, 16].

Symptoms may develop before radiographs changes. The most common manifestations are dyspnea, which can vary from mild to severe, and nonproductive cough, typically prominent. Fever occasionally occurs, either high spiking or low

grade but, nonetheless, transient. Hemoptysis is rare, though in the late phase of the disease, pink (blood-colored) sputum may be expectorated [17, 18].

Routine chest examination may reveal moist rales, a pleural friction rub, or evidence of consolidation over the area of irradiation. Skin changes secondary to radiation exposure can be present, but do not correlate well with the extent of pulmonary radiation damage. A polymorphonuclear leukocytosis and elevated erythrocyte sedimentation rate are neither common nor specific laboratory findings.

There is impaired pulmonary lung function, with a predominantly restrictive pattern. The measurement of carbon monoxide diffusion capacity (DLCO) is the most accurate predictive component for pulmonary radiation damage. The DLCO falls by 20–60% during the first 3–5 months after irradiation and then usually returns to its previous level 12 months later. The change in DLCO correlates with the volume loss of tissue for gas transfer, reflecting the alveolar-capillary block in affected tissues. Peak oxygen consumption significantly decreases in some patients, mainly affecting patients with coexisting lung diseases [18].

The CT severity score of RP ranges from grades 1 to 5, according to the National Cancer Institute Common Toxicity Criteria version 3.0 (CTCAE version 3) [19] (Table 4.1). Grade 2 severity is defined when diffuse consolidation or patchy consolidations with ground-glass opacities are present in the irradiated field. The extensive RP beyond the irradiated field, including the contralateral lung, upgrades the severity index from grade 3 to grade 5.

The onset and course of the disease can be either fulminant with severe respiratory insufficiency and cyanosis progressing to acute cor pulmonale in a matter of days, or subtle if the affected area of the lung is small. Overall, the early onset of symptoms implies a more severe and more extensive clinical course [17]. Radiation pneumonitis is considered as a form of acute or subacute lung injury corresponding to the site that is irradiated. It occurs more often when the dose exceeds 20 Gy and always leads to lung fibrosis [20].

4.2.1 Pathogenesis of Radiation Pneumonitis

The initiating arranger of RP is the inflammatory cascade. The main cells involved are the endothelial cells interacting with inflammatory leukocytes, the macrophages, and, at the late fibrosis phase, the fibroblasts [21]. Specific T-lymphocyte

Table 4.1 CT severity score of radiation pneumonitis

Grade 1	Minimal radiographic findings (or patchy or bibasal changes) with estimated radiographic proportion of total lung volume that is fibrotic of <25%
Grade 2	Patchy or bibasal changes with estimated radiographic proportion of total lung volume that is fibrotic of 25–50%
Grade 3	Dense or widespread infiltrates/consolidation with estimated radiographic proportion of total lung volume that is fibrotic of 50–75%
Grade 4	Estimated radiographic proportion of total lung volume that is fibrotic of >75%
Grade 5	Death

subsets are activated and participate in the repair process acting protectively against radiation-induced lung fibrosis. T helper type 1 (Th1) and T helper type 2 (Th2) lymphocyte polarization in the context of the immune response plays a crucial role. Th1 lymphocytes facilitate generation of IL-2 and IFN-γ resulting in enhanced cellular immune responses, while Th2 lymphocytes are associated with the production of IL-4 and IL-10, thus facilitating immunoglobulin production. Th2 responses prevail in progressive lung inflammation, with further development of pulmonary fibrosis, while Th1 response resolve without a disabling outcome [22–24].

There is a vicious cycle of inflammation, angiogenesis-hypoxia, cell death-proliferation, maintained by cytokines, growth factors, and fibroblasts that promote collagen accumulation [22, 25].

The key cytokine involved in the early stages of RP is TNF-a with pro-inflammatory and immunoregulatory effects, while TGF-β cytokine holds a mandatory role in the later stage of fibrosis. TNF-a expression is impaired under the action of anti-inflammatory interleukins, such as IL-4, IL-10, and IL-13. Also, macrophage colony-stimulating factor (M-CSF) and macrophage chemoattractant protein-1 (MCP-1) may promote the attraction of macrophages into the irradiated lungs [10, 26].

Recent studies based on the development of the human genome project and pharmacogenomics suggest that single-nucleotide polymorphisms (SNPs) in inflammation-related, DNA repair-related, stress response-related, and angiogenesis-related genes may be used as biomarkers to predict the development of RP. The implication of TGF-β, lineage protein 28 (Lin28), and numerous DNA repair-related genes is demonstrated by preliminary reports, though accurate evaluation and risk stratification for the occurrence of RP are not completely elucidated yet [27].

4.2.2 Treatment of Radiation Pneumonitis

The treatment of RP remains challenging, though symptomatic. Several agents have been experimentally tested for the prevention or treatment of RP and RPF. However, corticosteroids remain the mainstay for radiation pneumonitis. Antibiotics can be used, especially in the case that atypical chest infection cannot be ruled out. Previous trials with inhibitors of TNF-a, such as infliximab, and TGF-β inhibitors, such as naringenin, pentoxifylline, and relaxin that block, downregulate, and inhibit TGF-β, respectively, have shown some promising results, but none of them have been established in the clinical practice [22, 28]. Serious pulmonary toxicity (grades 3 and 4) always requires hospitalization with oxygen supplementation or mechanical ventilation if needed, fluids, empirical antibiotics, and intravenous steroids [29, 30]. The recommended dose of steroids is for oral prednisone 0.75–1 mg/kg/day and for intravenous methylprednisolone 2–5 mg/kg/day for at least 3 days or dexamethasone 8 mg twice per day [29, 31].

4.3 Radiation Fibrosis

Radiation fibrosis applies to the clinical syndrome resulting from chronic pulmonary lung damage. Typically it occurs 6–12 months after radiation therapy completion but usually remains stable after 2 years. Occasionally patients may present radiation fibrosis without a history of acute radiation pneumonitis. Symptoms range from minimal to varying degrees of dyspnea and radiographic signs of pneumonia with pulmonary infiltrates ipsilateral to the radiated site [29]. In some cases, chronic pulmonary insufficiency may develop and progress to chronic cor pulmonale from the resultant pulmonary hypertension, with associated cyanosis, hepatomegaly, or liver tenderness [18].

Radiation fibrosis is a more difficult radiographic diagnosis to make since the fibrosis distorts the outline of the radiotherapy ports. The delayed changes of fibrosis usually appear 6–9 months after the end of an RT course and become stable after 2 years. If the fibrosis is mild, subtle changes are present, such as the elevation of the hemidiaphragm, apical thickening, widening of the mediastinum, and paramediastinal fibrosis. The fibrosis can be severe enough to shift the trachea and cause stenosis. The fibrotic lung is prone to infection, affecting overall the survival of these patients. Late in the course of RF, the diaphragm can scar and become immobile [18].

From pathophysiological aspect, the gas-exchange interface is reduced by fibrosis, with thickening of alveolar-capillary barriers, resulting in impaired gas transfer. Both static and dynamic lung compliance are impaired and may be accompanied by a reduction in vital capacity [32].

4.3.1 Pathogenesis of Radiation Fibrosis

The exact mechanism of RF is not yet elucidated completely. Different pathophysiological mechanisms of lung fibrosis have been proposed. One suggests the presence of a tolerance threshold for the normal lung tissue that is not reached by the delivery of RT alone. Thus, any adjuvant treatment with a systemic anticancer agent may overpass the host's lung tolerance threshold. Another theory suggests that the repair capacity of the pneumocytes has been impaired by previous RT and any subsequent therapy will promote further lung injury and permanent fibrotic changes. The most commonly reported antineoplastic drugs that have been implicated in the development of RF are anthracyclines, gemcitabine, paclitaxel, trastuzumab, and everolimus [29, 33–36].

4.3.2 Treatment of Radiation Fibrosis

The treatment of both radiation fibrosis and radiation pneumonitis remains empiric and mainly supportive and is escalated depending on the severity of the symptoms. Although evidence exists for effective treatment, there is no therapeutic strategy of

proven benefit for the treatment of radiation pulmonary fibrosis. The supportive strategy includes supplementary O_2, bronchodilators, and antibiotics if needed. New anti-fibrotic drugs targeting connective tissue growth factor (CTGF) are in the initial stages of development and may be implicated as therapeutic agents for radiation fibrosis [37].

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Radiation Pneumonitis and Noninvasive Ventilation

5

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Radiation therapy is a major treatment modality for cancer as an intent to cure as well as palliative therapy. While its efficacy has been well proven, the complications of therapy can limit its effectiveness which ultimately affects morbidity and mortality posttreatment. Radiation exposure to the lung, in particular, can have acute and chronic toxicities manifested as radiation pneumonitis and pulmonary fibrosis, respectively.

Radiation is a form of energy that inhibits cell growth and division. After multiple exposures to radiation, the cells that make up a tumor shrink in size. Radiation targets cells that are actively dividing in specific areas of the cell cycle (Table 5.1); those in phase G0 are less responsive to radiation therapy. Since cancer cells are known for rapid cellular division and growth, they are most susceptible to radiation. The exact mechanism of cell death is unknown, but most evidence dictates that double-stranded DNA breaks are the main contributors, though single-stranded breaks, base damage, and cross-link damage between DNA-DNA and DNA protein are factors as well [1, 2]. The double-stranded DNA breaks lead to irreparable damage and cell death [2]. While tumor destruction is the ultimate goal, normal tissue cells can also be affected. Those that grow quickly will be acutely affected, while tissue that is slow growing may not show signs of toxicity until years after treatment have completed [1].

Thoracic radiotherapy is a common treatment modality for breast cancer, pleuropulmonary cancer, and mediastinal lymphomas. The most common structures at risk are the lungs, heart, esophagus, brachial plexus, and mammary glands [3]. Radiation pneumopathy is the direct lung-induced injury due to radiation therapy. The severity of toxicity depends on a variety of factors including the dose, length of

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Table 5.1 Cell Cycle Phase

Cell cycle phase	Description
G0	Cell rest, carry out day-to-day body functions
G1	RNA and protein synthesis made for cell division
S	Synthesis of DNA made for new cells as the chromosomes are copied
G2	Apparatus for mitosis is built
M	Mitosis

Adapted from [1]

treatment, and volume of body exposed to radiation as well as patient-specific factors, such as genetic predisposition, pretreatment functional status, underlying lung injury, and smoking [4]. The two main radiation-induced pulmonary toxicities as stated previously include acute radiation pneumonitis and radiation fibrosis.

Acute radiation pneumonitis occurs 6–12 weeks after completion of thoracic radiotherapy [3], but the damage begins immediately. Within the first few hours of radiation, type I and type II pneumocytes are affected. Type I pneumocytes, found on 90% of the alveolar epithelium surface, are deleted. The type II pneumocytes, the cells that synthesize and secrete surfactant and regulate surface tension, rapidly proliferate leading to hyperplasia and increased surfactant production [4]. The next site of damage is the basement membrane; in normal physiology, the basement membrane fuses the capillaries to alveoli providing a thin membrane for gas exchange from intra-alveolar air into the vasculature. After exposure to radiation, there is separation of the basement membrane and proliferation of fibroblasts in the extracellular membrane (ECM). In addition to poor gas exchange, the change in ECM causes an increased vascular permeability and ultimately perivascular congestion [4]. Macrophages become activated to release cytokines and chemokines within in the interstitium leading to the activation of fibroblasts and collagen buildup, an effect which is worsened by radiation interference of gene expression causing an overabundance of cytokine and growth factor [4]. Lastly, there is thrombosis of the capillaries and degeneration of the small arterioles with areas of necrosis in the regions targeted by radiation therapy [3], and these acute changes are usually reversible after 3–4 weeks [1].

The workup of acute pneumonitis involves a combination of history of thoracic radiation exposure, clinical picture, imaging studies, and PFTs. Clinically, the acute phase is usually asymptomatic with the earliest evidence of damage seen on imaging. The most common presenting symptoms are dyspnea and nonproductive cough [3]. Patients tend to develop nonspecific symptoms, such as low-grade fever or cough, more commonly after receiving higher doses (>50 Gy) of radiation [4], and those who receive radiation therapy to more than 75% of lung tissue have the highest risk of developing severe pneumonitis [3]. Laboratory workup does not contribute much to diagnosis as it is nonspecific, mainly with an elevation of inflammatory markers [3]. Chest x-ray and chest CT may show diffuse interstitial infiltrates that can coalesce and be associated with effusions—both pleural and interlobular [1]. Acute radiation pneumonitis can cause a restrictive disease, evident by changes in

the pulmonary function tests with mainly a decreased DLCO, decreased compliance, and decreased lung volumes due to alveolar degeneration and interstitial fibrosis [1]. An obstructive pattern can exist if the patient has underlying obstructive lung disease [4].

Treatment of acute radiation pneumonitis focuses mainly on symptomatic improvement. Corticosteroids have shown the quickest and effective improvement; however, prior to administering corticosteroids, the clinician must rule out all infectious etiology first. The prognosis of acute radiation pneumonitis varies. The majority of patients recover with no lasting effects. Rarely, patients can develop bronchiolitis obliterans with organizing pneumonia (BOOP) which manifests as what clinically appears to be an infectious pneumonia immediately following radiation therapy [3]. There is an association between the development of BOOP and patients receiving radiation therapy for breast cancer with tamoxifen therapy, and this condition also responds to steroids [3]. ARDS, while a significant and severe complication, is extremely rare. If the acute pneumonitis does not regress, patients may ultimately develop pulmonary fibrosis [4].

Pulmonary fibrosis occurs approximately 6 months after completion of radiation therapy and stabilizes over the next 1–2 years [3]. The pathophysiology of pulmonary fibrosis is similar to that of acute pneumonitis, dominated by fibroblast and collagen accumulation and disruption of capillaries leading to focal necrosis which becomes chronic and irreversible. However, these changes persist and the constant release of cytokines leads to fibrosis [3].

The clinical picture is highly dependent on the amount of lung affected by fibrosis development (Fig. 5.1). Patients again may be asymptomatic as it depends on the volume of lung affected by radiation toxicity. Small volumes of lung irradiation usually do not produce clinically active symptomatology [3]. With the destruction of pulmonary vasculature comes intrapulmonary shunting of unoxygenated blood into the systemic system. The larger the area of shunting, the greater the amount of unoxygenated blood and hypoxia [4], leading to increased dyspnea on exertion, cyanosis, cor pulmonale, and

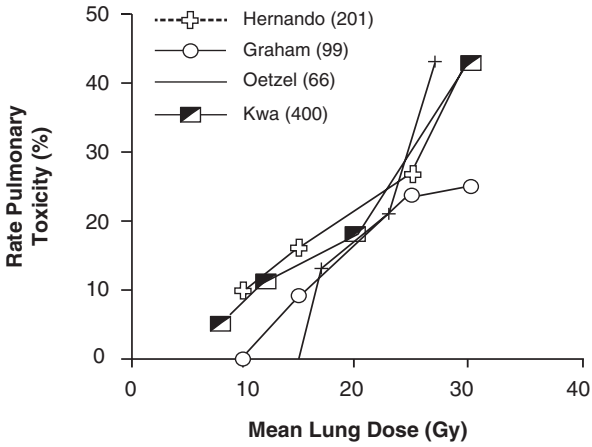

Fig. 5.1 Rate of pulmonary toxicity compared to mean lung dose of radiation therapy [1]

ultimately restrictive respiratory failure. Imaging modalities are similar to acute pneumonitis with high-resolution CT used as the image of choice. A ventilation perfusion scan, while nonspecific, can support the diagnosis by showing areas of decreased perfusion [4]. PFTs again demonstrate a restrictive pattern, and the severity of pneumonitis is determined by the degree of diffusion capacity impairment [4]. PFTs have been shown to continuously decline even 1 year after cessation of radiation [4].

Multiple grading systems have been developed to determine the severity of radiation-induced lung injury. The two most commonly used are the NCI CTC for acute pneumonitis and RTOG for pulmonary fibrosis [5], illustrated in Tables 5.2 and 5.3. Treatment with corticosteroids depends on the severity of symptoms and is usually prescribed as 40–60 mg daily with a very slow taper [6]. Oxygen therapy can be guided by the grade of pneumonitis, and ventilatory support may ultimately be required. As chronic radiation-induced lung injury presents as pulmonary fibrosis, one can make the assumption that ventilation support guidelines should follow those of the more well-known pulmonary fibrosis spectrum.

There is limited data to guide physicians on optimal oxygen therapy during radiation pneumonitis. Some patients may not require oxygen therapy, some require low-flow oxygen modalities, and others may require high-flow modalities depending on the severity of the pneumonitis. The use of noninvasive ventilation (NIV) specifically in radiation pneumonitis is limited. One small study included 19 patients receiving NIV for acute radiation pneumonitis. Seventy-nine percent of the patients had significant improvements in their respiratory parameters and gas exchange with decrease in heart rate, and respiratory rate, with improvement in SpO_2, and PaO_2 allowing for adequate oxygenation and ventilation to be maintained without the need for invasive mechanical ventilation [8]. Acute radiation pneumonitis is similar in physiology and treatment to lupus pneumonitis which manifests as ALI/

Table 5.2 NCI/CTC grading system for acute radiation pneumonitis [3]

Grade	0	1	2	3	4	5
Description	No change from baseline	Asymptomatic, radiographic findings only	Symptomatic but not interfering with ADL	Symptomatic and interfering with ADL with O_2 indicated	Life threatening requiring ventilatory support	Death

Table 5.3 RTOG late radiation morbidity scoring schema for lung tissue [7]

Grade	Description
0	No change from baseline
1	Asymptomatic or mild symptoms (i.e., dry cough) with slight radiographic appearances
2	Moderate symptomatic fibrosis or pneumonitis (severe cough) with low-grade fever, patchy radiographic appearances
3	Severe symptomatic fibrosis or pneumonitis with dense radiographic changes
4	Severe respiratory insufficiency requiring continuous O_2 or assisted ventilation
5	Death directly related to radiation late effects

ARDS. NIV has become more widely used for many causes of acute respiratory failure. In one multicenter survey found when NIV was applied as first-line intervention in ARDS, intubation was avoided in 54% of patients. They also noted patients who had severe disease defined as a Simplified Acute Physiology Score (SAPS) II of >34, and an inability to improve PaO_2/FiO_2 after an hour of NIV use was a marker of NIV failure [9]. This suggests that NIV can be applied successfully in patients with acute radiation pneumonitis with improvement in oxygenation and ventilation and in reducing the need for mechanical ventilation. NIV is also safe to use without impairing lung function. It also suggests that NIV should be trialed before proceeding to intubation and mechanical ventilation as one can predict failure of success after an hour of treatment as long as the settings are titrated appropriately for the patient needs as long as managed by well-trained professionals. The role of NIV would be to provide respiratory support until the anti-inflammatory properties of steroids take effect which is the primary treatment modality for the underlying pneumonitis.

Given the lack of guidelines for ventilatory support in patients with radiation pneumonitis, understanding the pathophysiology is paramount to develop a treatment plan. The development of restrictive lung disease patterns and pulmonary fibrosis can provide insight on how to manage a patient in respiratory distress secondary to radiation pneumonitis. Idiopathic pulmonary fibrosis (IPF) is also a progressive interstitial lung disease with a restrictive ventilatory defect and has been studied with the use of NIV. Most patients with IPF who present with acute respiratory failure (ARF) are hypoxic and hypercapnic with poor prognosis even with ventilatory support and medical management [10], but NIV is still used as a treatment modality with some benefit. In a study of 35 patients admitted to the ICU with a primary diagnosis of IPF, 18 patients were given a trial of NIV, and it was successful in preventing intubation in 8 of the patients. The success of NIV was directly related to the severity of ARF. All of the ten patients who ultimately required intubation had significantly higher respiratory rates, elevated BNP, and CRP on admission, which may represent clinical markers for poor outcomes when deciding if a patient is an appropriate candidate for NIV [11]. The indications for NIV were a respiratory rate greater than 30 breaths/min, use of accessory muscles, or PaO_2/FiO_2 ratio less than 250. Patients were titrated to a tidal volume of 6–8 mL/kg and an oxygen saturation of 92%; changes were made based on arterial blood gas results, and NIV was mostly continuous for 24–48 h and titrated off if the patient was improving. Those who tolerated NIV had reduced mortality rates than those who required intubation either at admission or after failure of NIV [11]. Another small study assessing 11 patients with ARF due to IPF mainly used a continuous positive airway pressure mode at 12 cm H_2O without pressure support in order to avoid ventilatory-associated injury and overinflation, unless patients had a high respiratory rate or respiratory acidosis [10]. Six of the patients failed NIV, and all six died within 3 months; the five patients who tolerated NIV avoided intubation and the duration of survival was significantly longer, but larger controlled studies would be beneficial in order to assess the use of NIV [10].

The incidence of radiation pneumonitis differs depending on the type of cancer, amount of radiation, and presence of underlying lung disease. Despite the wide

variation of clinical illness from a mild restrictive lung disease to ARDS, it is important to consider the sequelae of thoracic radiation therapy. If a patient develops acute respiratory failure due to radiation pneumonitis, noninvasive ventilation should be trialed and may prevent the need for invasive mechanical ventilatory support.

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Blood Marrow Transplantation

6

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Abbreviations

ATG	Anti-thymocyte globulin
BM	Bone marrow
BMDW	Bone marrow donors worldwide
BMT	Blood marrow transplantation
CB	(Umbilical) cord blood
CD34	Cluster of differentiation 34
DLI	Donor lymphocytes infusion
G-CSF	Granulocytes-colony stimulating factor
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukaemia
GVT	Graft-versus-tumour
HLA	Human leukocytes antigens
IL-1	Interleukin-1
KIR	Killer immunoglobulin-like receptors
MAC	Myeloablative conditioning
MHC	Major histocompatibility complex
MUD	Matched unrelated donor
NK	Natural killer
NRM	Non-relapsed mortality
PBSC	Peripheral blood stem cells
PCR	Polymerase chain reaction

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RIC	Reduced intensity conditioning
STR	Short tandem repeat
TBI	Total body irradiation
TNFα	Tumour necrosis factor-alpha
TRM	Transplant-related mortality

6.1 Introduction

Blood marrow transplantation (BMT) is a widespread and validated procedure for the treatment of several haematological diseases. Over the years, the indication for BMT has also been extended to include some non-haematological conditions, such as immune disorders, inborn errors of the metabolism and some types of solid malignancies [1].

The biological basis of BMT was laid between the 50s and the 60s, when it was discovered the major histocompatibility system and the stem cells, and first attempts of transplantation on animals and humans have been performed. In early 70s the identification of cyclosporine as an immunosuppressant agent represents another milestone in the history of transplantation. In 1975 Thomas E. D. et al. published results of the first 110 transplants, providing the basis for the worldwide clinical application of BMT [2].

There are two main classes of BMT: the autologous stem cell transplantation and the allogeneic stem cell transplantation. These two kinds of BMT share the infusion of haematopoietic stem cells after a chemotherapy, called conditioning regimen, but the aim and the role of the use of stem cells between the two procedures is different: in the autologous BMT they have the task to re-establish haematopoiesis after a high dose anticancer chemotherapy, while in the allogeneic BMT stem cells also serve as the main therapeutic weapon. The antitumour role of the allogeneic stem cells is known as "*graft*-versus-*tumour*" (*GVT*, commonly called *graft*-versus-*leukaemia, GVL*) effect.

A person who receives a transplantation is called *recipient*. The source of the allogeneic graft can be a healthy subject who donate his/her organ, the *donor*. In the case of the BMT, haematopoietic stem cells can be drawn from bone marrow, from peripheral blood or from umbilical cord blood.

Progresses in the supportive care, in the choice of less toxic conditioning regimens and in the diagnosis and treatment of graft-versus-host disease (GVHD), the major complication of allogeneic stem cells transplantation, have led to an improved outcome of BMT in the past two decades.

In this chapter the discussion will focus on allogeneic BMT. Actual major indications for allogeneic BMT are summarized in Table 6.1.

6.2 Immunogenetics Basis

For successful transplanting stem cells from a donor to a recipient it is necessary a histocompatibility between the two subjects. The histocompatibility is genetically determined. The antigens of the *major histocompatibility complex (MHC)—Human*

Table 6.1 Allogeneic stem cell transplantation: indications

Haematological neoplasms	AML, ALL, CML (AP/BC), PFM, MDS, MM, NHL, HL
Hemoglobinopathyes	Major β-Thalassemia
	Sickle Cell Anaemia
Congenital platelet disorders	Glanzmann's Thrombasthenia
	Bernard–Soulier Syndrome
Bone marrow failure	Sever Aplastic Anaemia
	Fanconi Anemia
	Blackfan-Diamond Anemia
	Dyskeratosis Congenita
Primary immunodeficiencies	SCID, CVID, Wiskott-Aldrich,
	Syndrome, Bloom's Syndrome,
	Reticular Dysgenesis, Omenn
	Syndrome, Hyper IgM Syndrome,
	BLS, ADA-SCID
Others	CGD, Chediak-Higashi Syndrome,
	Kostmann Syndrome, LAD

AML acute myeloid leukemia, *ALL* acute lymphoblastic leukemia, *CML* chronic myeloid leukemia, *AP* Accelerate phase, *BC* blast crises, *PFM* primary myelofibrosis, *MDS* myelodysplastic syndromes, *MM* multiple myeloma, *NHL* non-Hodgkin lymphoma, *HL* Hodgkin lymphoma, *SCID* severe combined immunodeficiency, *CVID* common variable immunodeficiency, *BLS* bared lymphocytes syndrome, *ADA-SCID* SCID with adenosine deaminase deficiency, *CGD* chronic granulomatous disease, *LAD* leukocyte adhesion deficiency

Leukocytes Antigens (HLA) in our specie—are proteins expressed on the surface of the immune system cells, acting as one of the first steps for the acknowledgement of the Self. HLA are encoded by genes present in a specific region of chromosome 6. This region works as a "super" gene which codes for three loci of class I histocompatibility, called A, B and C, and for those of II class: DP, DR and DQ. The complex of these antigens is strongly "linked" and it constitutes a haplotype [3]. The ideal donor is a HLA-identical sibling. The two haplotypes are inherited from parents, so there is one chance in four (25%) that two siblings are compatible for transplantation of haematopoietic cells (Fig. 6.1). However, it can also be used haematopoietic stem cells only partially compatible. The risk of immunological complications following the transplant increases in proportion to the degree of disparity. In addition to the HLA system, there are minor histocompatibility loci encoded by genes on other chromosomes, both on autosomal and sexual ones. Therefore, the inheritance of minor histocompatibility loci occurs independently of the major histocompatibility system and the genotypic diversity of the minor loci can strongly influence the immunological conflict between donor and recipient. The disparity for minor histocompatibility antigens expressed only on haematopoietic cells give rise to a good immunological effect against the haematological neoplastic disorder that affects the patient (graft-versus-leukaemia, GVL) while the disparities between the ubiquitous antigens increases both GVL, powering so the transplant antileukaemic effect, but at the same time the donor cells aggression to the recipient (graft-versus-host disease, GVHD) is increased too.

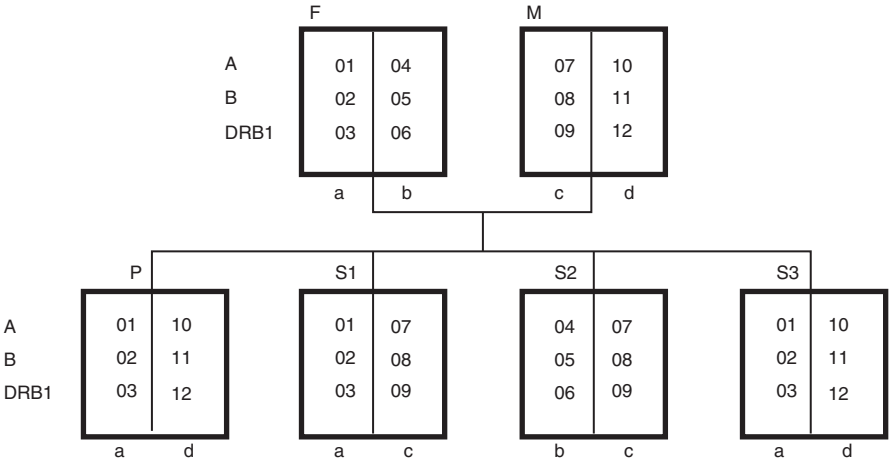

Fig. 6.1 HLA typing of a hypothetical family. Low resolution. HLA typing of a hypothetical family. Patient (*P*) has inherited "*a*" haplotype from the father and "*d*" from the mother. Sibling 3 (*S3*) is the HLA-matched (6/6) donor. Sibling 1 (*S1*) is the haploidentical (3/6) donor, sharing "*a*" haplotype with the patient. *A, B, DRB1* HLA loci, *a, b, c, d* haplotypes, *F* father, *M* mother, *P* patient, *S1* sibling 1, *S2* sibling 2, *S3* sibling 3

As already mentioned, for those who don't have an HLA-identical sibling it can be used non-HLA-identical stem cells. The donor who is not HLA-identical sibling to the patient is the so-called *alternative donor*. The first alternative donor to be used is the volunteer donor (*matched unrelated donor, MUD*). The availability of this category of donors was made possible by the establishment of registers for the collection of HLA typing. Every industrialized country has its own national register, which actively communicates with the other countries registries. In 1988 it's been formed the *Bone Marrow Donors Worldwide* (*BMDW*, www.bmdw.org), headquartered in Leiden in the Netherlands. BMDW is a global project for the collection of HLA phenotypes of potential bone marrow donors and cryopreserved cord blood units. At now, it collects over 27 million of HLA typing from 75 participating registers, located in 53 countries, and of 53 cord blood banks in 36 nations. In the BMDW's file, the potential donors are all typed for the first class of histocompatibility, but the majority have also the second-class, and of some there is the molecular typing too.

The HLA typing technique has changed over time going from a serological method for identifying the various antigens to a molecular technique that helps to identify compatibility allelic level. In addition to improving typing technique, the HLA loci panel used to evaluate compatibility is been extended. Indeed, if in the past it was studied six HLA loci, A and B for first class and DR for the second class, today the compatibility study extends the C locus and is expanded, with molecular biology, to DRB1 and DQB. The possibility to identify an alternative donor studying at the molecular level a greater number of loci has significantly improved the outcome of this type of transplant, so that results obtained from a

donor compatible 10/10 loci are comparable to those obtained by an HLA-identical sibling.

The probability for a patient to identify a histocompatibility donor for transplantation is variable as a function of ethnicity. Caucasian subjects have the maximum probability, estimated around 70% to identify a donor and about 60% to find a cord blood unit with adequate compatibility and cellularity. In the case of patients who can't find a donor (or a cord blood unit) is now possible to perform transplants using as source of stem cells HLA-haploidentical donors. For years haploidentical transplants have had limited spread for the very significant overall toxicity: no engraftment, too slow immune reconstitution and various organs and systems toxicity. These issues have been, at least partially, overcome by the completion of new transplant methods represented by:

- *Haploidentical transplantation with megadose of purified haematopoietic cells*; it is based on using a highly effective antileukaemic conditioning regimen, on the administration of a megadose of stem cells and on a more intense immunosuppression to allow engraftment and establishment of a complete chimerism.
- *T cell replete haploidentical transplant of bone marrow or peripheral haematopoietic stem cells*.
- *Haploidentical transplantation with tolerance induction*; tolerance is induced by administration of cyclophosphamide in the period immediately after the reinfusion of stem cells.

Interestingly, especially in the context of acute myeloid leukaemia, haploidentical BMT uses the powerful immune-modulatory effect of donor NK cells, which are able to promote the engraftment, to avoid graft-versus-host disease and to prevent, sometimes, leukemic relapse. Basically in 3/6 incompatible transplant it is crucial the alloreactivity of *killer immunoglobulin-like receptors (KIR)* expressed by NK cells. This effect can be predicted by the diversity of class I HLA antigens between donor and recipient [4].

6.3 Haematopoietic Stem Cells Sources

Until the early 90s, the only source of stem cells was bone marrow (BM); subsequently the peripheral blood (peripheral blood stem cells, PBSC) and the placental blood (CB) have proven to be viable alternative sources of haematopoietic progenitor cells, capable of reconstituting the bone marrow environment after a high doses chemo-radiotherapy treatment.

The bone marrow donation is done by multiple stings through bilateral posterior iliac crests to a donor who received an epidural anaesthesia. During the operation of donation, one or two units of pre-deposited autologous blood can be reinfused, in order to minimize donor's transfusion risks.

The collection and the use of peripheral blood stem cells was made possible by the relatively recent availability of rapid techniques for the identification of

haematopoietic progenitors (CD34 antigen discovery) and by the availability of recombinant human growth factors (granulocyte colony-stimulating factor, G-CSF). The donation of peripheral blood stem cells occurs after G-CSF stimulation, which lasts for about 5 days, and it is generally performed by an accredited Transfusion Center that performs automated isolation and apheresis collection of CD34 positive cells from volumes of peripheral blood. Peripheral blood stem cells are the almost exclusive source for autologous transplant, while their use for the allogeneic transplantation is still debated. Biological and functional studies have shown that stem cells mobilized to peripheral blood with G-CSF have different characteristics from those directed drawn from bone marrow, and those differences can affect the results of transplantation. Not all authors agree, but in principle it can be argued that the peripheral stem cells expose the recipient to a higher incidence of chronic GVHD, impacting negatively on quality of life, but at the same time they ensure a more rapid immunological recovery and a more marked GVL effect [5]. These observations led to an almost exclusive use of peripheral blood stem cells in the adult population and in the later stages of disease, as in the cases of relapse/refractory leukaemia.

The umbilical cord blood can be donated by women who have passed the selection through specific donation requirements. Cord blood transplants have the advantage that, at the moment of transplant choice, stem cell units are readily available, being already stored cryopreserved at the Cord Blood Banks. Another advantage of cord blood transplants is the use only partially compatible (5/6 and 4/6 histocompatibility), allowed by the lower incidence and severity of GVHD linked to this stem cell source. The disadvantages of this type of alternative donor are represented by the greater slowness in terms of engraftment, due to the low cellularity of the cord blood, and the slower immune reconstitution; both of these reflects negatively in terms of overall results. Furthermore it is a rather expensive procedure.

6.4 Conditioning Regimens, Chimerism and Transplant Immunology

BMT consists of four basic moments: conditioning regimen, infusion of haematopoietic stem cells, engraftment and immune reconstitution.

Conditioning regimens are the treatments used to prepare a patient for stem cell transplantation, to suppress the immune response for avoiding the immunological rejection and to eradicate the neoplastic disease. It can also be defined as the anticancer chemotherapy protocol, sometimes accompanied by total body radiation therapy (TBI) or by monoclonal antibodies, which creates in recipient's bone marrow the condition necessary for the establishment of the stem cells. The other necessary condition to avoid allogeneic graft rejection is the immunosuppression, which is given by administrating immunosuppressive drugs, mainly represented by *calcineurin inhibitors*, like cyclosporine and tacrolimus, and by anticancer chemotherapeutics, mainly methotrexate and, in the haploidentical setting, cyclophosphamide. Anyway, the same conditioning regimen anticancer chemotherapy has a potent

immunosuppressant effect which significantly concurs to induce immune tolerance to the allogeneic graft. Once stem cells are injected and there isn't been immunological rejection, they reach recipient's haematopoietic niches by an innate homing mechanism; occupying the spaces created by the conditioning regimen, donor's cells repopulate the bone marrow to then reconstitute the peripheral blood. The coexistence of the donor and recipient tissue is defined "chimera", from the name of the Greek mythic creature. In the field of stem cell transplantation, the term *chimerism* refers to the replacement of patient haematopoiesis with the one of the donor. Chimerism is currently evaluated by the use of a polymerase chain reaction (PCR) for the amplification of highly polymorphic *short tandem repeat* (*STR*) sequences. Its clinical application is an important tool for assessing transplanted patient's minimal residual disease: a loss of the complete chimerism is a warning sign of impending relapse [6]. In the case of a mixed chimerism, it can be tried to restore back a complete by immunosuppressant suspension, by *infusion of donor lymphocytes* (*DLI*) or, more recently, by combined use of DLI and *azacitidine* [7], an analogue of the cytosine nucleoside which inhibits DNA methylation.

As already mentioned, another goal of the high doses of chemotherapy is to eradicate the neoplastic disease of the recipient. The conditioning regimens were originally designed to be myeloablative (*MAC, Myeloablative Conditioning*); the rationale was to kill the maximum number of bone marrow and cancerous cells to achieve a complete chimerism. Furthermore a more intensive anticancer chemotherapy was considered more effective in preventing the relapse. So the most common conditioning regimen till early 90s was the association of total body irradiation (TBI), at least 1200 cGy total dose, with high doses of cyclophosphamide (120 mg/kg). As an alternative to radiotherapy has been used busulfan at the total dose of 1 mg/kg four times a day for 4 days. Of course, these types of conditioning regimens are burdened by a high degree of organ toxicity, and for this they can be taken into account only in young patients with low risk factors for transplant mortality, suffering from high-risk diseases.

Over the years it has tried to intensify chemotherapy protocols in an effort to reduce the risk of relapse; however, intensifying the conditioning the number of relapses is not progressively reduced as hoped but there was a progressive increase in transplant toxicity, which has resulted in increased mortality. Then it has been understood that the "curative" action of the BMT depends only in part on the direct action of the conditioning regimen but it is mostly due to the graft-versus-leukaemia effect (GVL); this phenomenon gives to allogeneic stem cells injection a immunotherapeutic role. Target antigens of the immune response of the graft are still not known. The GVL appears to be due to the disparities between the histocompatibility antigens of donor and recipient. These mismatches are also the basis of the major complication of transplantation, the graft-versus-host disease (GVHD). In a proinflammatory environment, such as that due to the damage to the mucosa induced by conditioning regimen, activation of alloreactive T lymphocytes of the donor is promoted. The immune attack, in the case of GVL, is against leukaemia cells of the recipient, while, in the case of GVHD, targets are the healthy tissues. This common aetiology explains why the two phenomena, GVL

and GVHD, often occur overlapped and it also explains the observations that relapse is less common, but still possible, in patients with chronic GVHD. Another proof of the effect GVL and its intimate connection with GVHD is the use of donor lymphocytes in relapses, which can restore the complete chimerism and remission, as well as to initiate a GVHD [8].

The evidence that antileukaemic effect of the transplant is only partly due to chemotherapy conditioning regimen, but rather is driven mainly by GVL, have led to the creation of *reduced intensity conditioning (RIC)* regimens, also called "non-myeloablative" [9]. Some of these RIC protocols can retain a partial myelotoxicity, while some others have only an immunosuppressive action. The main limitations of RIC regimens are the low effectiveness on the malignant disease and, in some cases, the inability to induce a complete chimerism. Having to give up the powerful anticancer action of a highly cytotoxic regimen, RIC schemes should be reserved exclusively for those patients where it is not possible to carry out a conventional transplant. So transplants with reduced intensity conditioning allow to offer the possibility of a BMT to those patients who for general conditions, comorbidities, and age might not otherwise be transplanted.

6.5 Complications

The transplant mortality still represents a major obstacle to the success of allogeneic transplantation. *Transplant-related mortality (TRM* or *NRM—non-relapse mortality)* is defined as the death of a patient not caused by the basic disease, but due to a transplant procedure complication. Its incidence varies from 10 to 50% in different series, depending largely on intrinsic factors in transplant technique. Indeed, TRM is generally higher in transplants from alternative donors, in advanced stages of disease and in older patients. Non-relapse mortality can be caused by immunological conflict between donor and recipient, by short- and long-term toxic effects of the conditioning regimen and by the complications of the immunodeficiency and of the immunosuppressive drugs use.

Graft-versus-host disease (GVHD) is the most common and dreaded immunological complication of allogeneic haematopoietic stem cells transplantation. GVHD can occur from 20 to 70% of allogeneic transplants. Clinically is characterized by an *acute* and a *chronic* form, with different clinical features, symptoms, evolution and therapeutic approaches. Classically chronic and acute GVHD are distinguished by the occurrence within or outside of 100 days after transplantation. Recently it has also been recognized as individual categories the *classical acute GVHD*, the *acute persistent*, the *late acute* and the *acute/chronic* (overlap forms) with coexistence of acute and chronic symptoms [10]. There is general agreement in defining the acute or chronic GVHD according to the various clinical manifestations and no longer in function of time interval between transplantation and onset of symptoms.

To date, the pathophysiology of GVHD is not fully known, but recently have been made some progress in understanding the processes that underlie the acute

form, while the chronic form is more hard to be studied, partly because it is more difficult to reproduce in animal models. Briefly, in the case of the acute GVHD, the conditioning regimen leads to a damage of recipient tissues with activation of host antigen presenting cells. One of most involved organs to this damage is the intestinal mucosa, that in this injury state allow the translocation of lipopolysaccharide and other endotoxins from intestinal lumen to the circulation. This transition triggers a host secretion of proinflammatory cytokines, such as interleukin-1 (IL-1) and tumour necrosis factor-alpha (TNF-α), which lead to greater and enhanced antigen presentation by host tissues. This phenomenon leads to activation of mature donor T cells, generating an acute inflammatory response against host tissues.

Chronic GVHD, instead, manifests as an autoimmune disease, sometimes accompanied by signs of chronic inflammation, such as fibrosis, and autoimmune antibodies have been observed chronic GVHD patients, but their clinical meanings and applications are still not clear.

GVHD prophylaxis is performed in every allogeneic transplants, and it bases generally on the early administration of cyclosporine, that is maintained till at least 180 days after the transplant, and five or four low doses of methotrexate; in the case of alternative donor a variety of other drugs are used, especially anti-thymocyte globulin (ATG) and mycophenolate mofetil. Another approach to GVHD prophylaxis is the T-cells depletion of the graft.

Clinically, acute GVHD is characterized by a triad of symptoms: a maculopapular skin rash, a enteritis with nausea and diarrhoea and a cholestatic liver disease. When it's possible, diagnosis of GVHD should be confirmed by a histological exam, but its accuracy depends a lot from pathologist's expertise in this particular field; therefore it remains basically a clinical diagnosis. Because survival is directly correlated with the severity of organ damage, it was created in order to facilitate the study and the prognosis formulation a score for staging organ and overall acute GVHD severity. Both organ involvement and overall scoring have four grades, going from a limited organ damage to an extended acute GVHD, with very poor prognosis. The first-line therapy of acute GVHD (grades II–IV) is prednisone (or an equivalent steroid) at a dose of 2 mg/kg for 5 days. When acute GVHD is refractory to steroids (progression within 3 days or no improvement after 5–7 days of prednisone at 2 mg/kg/day dose) the prognosis is severe. Many agents have been tested for second line or salvage therapy, but there isn't actually a standard protocol. The most common treatments in this setting are extracorporeal photopheresis, anti-TNF-α monoclonal antibodies (infliximab and etanercept), low dose methotrexate, mycophenolate mofetil, alemtuzumab, anti-thymocyte globulin (ATG), tacrolimus, daclizumab, pentostatin, basiliximab and mesenchymal stem cell infusion.

Chronic GVHD may present "de novo" or as an evolution of acute GVHD; in some cases signs and symptoms of acute and chronic GVHD can coexist at the same time (overlap forms). The diagnosis of chronic GVHD requires stringent criteria with the presence of at least one diagnostic symptom (as scleroderma-like lesions of skin, of oesophagus, of joints or as lichenoid lesions of skin or of mucous membranes), or in the case of not diagnostic signs, histological diagnosis is needed. It was created a form guide for evaluating the involvement of chronic GVHD on the

various organs and systems. Once diagnosed with chronic GVHD there must be a staging in mild, moderate or severe. Clinical manifestations of chronic GVHD are similar to those of numerous autoimmune diseases. With regard to the skin there may be melanosis, scleroderma-like injuries, eosinophilic fasciitis, lichen and alopecia. Frequently it can be observed ocular and oral sicca syndrome, liver involvement with hepatitis-like paintings, damage to the gastrointestinal tract malabsorption and anorexia, respiratory patterns with bronchiolitis, cytopenias and a condition of severe combined humoral and cellular immunodeficiency with recurrent infections, impaired quality of life and survival. Chronic GVHD is the leading cause of late transplant procedure failure.

The chronic GVHD treatment of choice is based on prednisone and cyclosporine, in second-line therapy are used extracorporeal photoapheresis, the anti-CD 20 monoclonal antibody rituximab, imatinib in the scleroderma forms, tacrolimus and pentostatin. In chronic GVHD patients remains essential the supportive care for the organs and apparatus involved and the prophylaxis and early therapy of infections with antibiotics, antifungals and antivirals.

Some non-immune complications of BMT are summarized in Table 6.2.

6.6 Conclusions and Major Recommendations

- Allogeneic stem cell transplant is a highly effective immunological therapy with curative potential for several haematologic diseases.
- Graft-versus-leukaemia (GVL) is the immune reaction of the donor lymphocytes against leukemic cells of the recipient; as well as graft-versus-host disease

Table 6.2 A brief overview on the main non-immune BMT complications

Complication	Description
Venous occlusive disease (VOD)	Obstruction with or without occlusion of the central intrahepatic venules resulting in dysfunction of the sinusoidal endothelial cells. Clinically VOD is characterized by jaundice direct hyperbilirubinemia, hepatomegaly mostly painless, fluid retention with ascites and weight gain
Post-transplant thrombotic microangiopathy	It's due to endothelial damage caused by the conditioning regimen, the one related to the use of cyclosporine, to endothelial damage in the course of GVHD and CMV infection. Characterized by microangiopathic anemia, thrombocytopenia, and symptoms secondary to ischemic events in the microcirculation
Viruses reactivation	Immunodeficiency due to transplantation exposes to a variety of opportunistic infections and leads to the reactivation/infection of viruses such as CMV, EBV, HHV6, HZV, JC, BK and adenovirus
Idiopathic interstitial pneumonia	Signs and symptoms of pneumonia with diffuse alveolar damage but in absence of infections, not explained by other organ damage. In most cases there is unstoppable clinical progression and is burdened by very high mortality

VOD venous occlusive disease, *GVHD* graft-versus-host-disease, *CMV* cytomegalovirus, *EBV* epstein-barr virus, *HHV6* human herpesvirus-6

(GVHD), it's due to mismatches between donor and recipient major and minor histocompatibility complex.

– The availability of stem cells from alternative sources, the progress in the understanding of transplant immune mechanisms and the new reduced intensity conditioning protocols implementation in the clinical practice, have currently made allogeneic stem cells available to a growing number of patients.
– Transplant-related mortality (TRM) remains the greatest limiting for a broader BMT application. GVHD is the main cause of TRM. Further studies are needed to improve our understanding of this often fatal disorder.

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Ventilatory Approach in Upper Airway/Neck Cancer Patients with Respiratory Failure

7

Bushra Mina, Khalid Gafoor, and Oki Ishikawa

Head and neck cancers encompass a variety of malignancies arising from the upper aerodigestive tract. There are approximately 500,000 cases annually worldwide and associated with significant mortality in both Europe and the USA at roughly 63,500 and 13,000 per year, respectively [1, 2]. It is divided into five areas—oral cavity, pharynx, larynx, nasal cavity and paranasal sinuses, and the salivary glands. Due to the anatomical areas involved, airway compromise leading to acute respiratory failure is fairly common, and it may occur due to the primary lesion or as a complication of its treatment. It is one of the main reasons for critical care admissions in these patients and contributes significantly to hospital and ICU mortality [3–5]. In this chapter, we discuss our recommendations of how to approach acute respiratory failure in patients with upper airway cancer.

The underlying causes for respiratory failure in head and neck cancer (HNC) patients include, but are not limited to, obstruction, aspiration, thromboembolic disease, infection, effusions, and drug toxicity [6, 7]. In any case, establishment and maintenance of an airway still takes precedence much like any other respiratory emergencies. Oxygenation and ventilation support will proceed afterward, titrated to the patient's need. Noninvasive positive pressure ventilation (NIPPV) and high-flow nasal cannula (HFNC) are often considered in these situations and may be a feasible initial treatment. To our knowledge, there are no studies that specifically look at NIPPV and HFNC use in HNC patients. With regard to NIPPV, they have been studied in patients with hematologic malignancies and solid tumors, which have shown beneficial outcomes in morbidity and mortality, leading to the general acceptance of its use [8–10]. However, there are conflicting data showing negative

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effects of NIPPV for a subset of patients with malignancies, including known pulmonary infection, malignant infiltration, and males [11–13]. This will likely be more clarified and refined as the frequent use of NIPPV in acute respiratory failure continues. Less data is available with regard to HFNC use in acute respiratory failure (ARF). Evidence is accumulating for its use in both hypoxemic and hypercapnic RF, with more for the former. NIPPV is still recommended over HFNC for the latter, among others (COPD exacerbation, cardiac pulmonary edema, etc.) [14]. As far as its use for cancer patients, there have only been benefits shown in the palliative setting according to one retrospective study [15–17]. With these studies in mind, we recommend NIPPV and HFNC use for HNC patients for ARF based on the patient's pathology (hypoxia, hypercapnia, etc.), prior to consideration for intubation. Contraindications to its use will still apply, including copious secretions or inability to protect the airway, which are commonly seen in HNC patients.

If NIPPV and HFNC use are not an option, and the patient has a threatened airway, then one must proceed immediately to establishment of an airway. This may be challenging in HNC patients as the airway may be impeded by the disease or due to previous treatment modalities, including surgery, radiation, or chemotherapy. Although there are some guidelines for intubation of difficult airways in the anesthesia literature, they are more pertinent to the preoperative evaluation of stable and compliant patients, often involving elective intubations [18]. These may not be applicable in emergent situations and may only help to a certain extent. However, there are certain common denominators that apply to both situations. One of these is the importance of identifying the characteristics associated with difficult intubation or ventilation in advance, as they significantly contribute to the development of a failed airway ("cannot intubate, cannot oxygenate"). This identification is primarily based on external observation that encompasses predictors of difficult airway establishment and should be approached systematically in HNC patients. It will start with the evaluation of the airway, then the assessment for difficulty in bag-mask ventilation (BMV), and then an evaluation for extraglottic airway placement and cricothyrotomy difficulty [19].

For the initial evaluation of a difficult laryngoscopic intubation, the commonly used method is the LEMON mnemonic. As listed below, each step is assigned a number of points, with the entire criteria being out of 10. Although there are no strict cutoffs established by the original study, a score of 5 was associated with difficult intubations [20].

7.1 LEMON Criteria

L: Look externally—Clinician's overall impression of the airway with direct observation and is scored out of 4 points. Unusual anatomy, prior surgical scars, body habitus, large incisors, large tongue, and any other abnormalities are included.

E: Evaluate (3-3-2 rule)—The numbers refer to the fingerbreadths of the incisor distance, hyoid to mentum distance, and the thyroid to mouth distance, respectively. Each of these is given 1 point, with the entire category being 3 points. It is important to note that anything less than the 3-3-2 is given 1 point each, as it indicates the ease

of access, the volume of the submandibular space, and the location of the larynx relative to the base of the tongue, respectively. Adjustments to size variations may be made by using the patient's fingers as the standard for measurement. Limitation of mouth opening may be more common in HNC patients, as trismus or lockjaw is reported to occur in up to 35% of HNC patients following radiation and/or surgery.

M: Mallampati score—The Mallampati score system ranges from I to IV and relates the amount of mouth opening to the size of the tongue via the visualization of the oral cavity. This predicts the amount of space available for oral intubation by direct laryngoscopy. Generally, class III and above predict a difficult intubation and is given 1 point [21, 22].

O: Obstruction/obesity—Upper airway obstruction by a mass, abscess, hematoma, or anatomic distortion due to prior surgery and/or radiation can obstruct the view of the airway and thus impede airway access. Obese patients can have excess soft tissue, which also makes the visualization of the glottis difficult. Either of these present will get 1 point.

N: Neck mobility—The ideal position for direct laryngoscopic view and intubation is by flexion of the cervical spine with the extension of the atlanto-occipital joint, known as the sniffing position. Decreased mobility in either of these will get 1 point. As was with mouth opening, neck immobility is one of the more common chronic issues with HNC patients due to fibrotic changes from prior radiation and surgery and may be encountered more often.

Immediately after this evaluation, patients should be assessed for difficulty in bag-mask ventilation (BMV). Regarding HNC patients, airway resistance may occur due to the primary lesion, anatomical distortion due to prior surgery, or radiation changes of the neck (fibrosis, airway edema). All of these can prohibit smooth bag-mask ventilation. In addition, bleeding is also a concern with these patients as mucositis from chemotherapy or radiation is common, and recent surgery may also exacerbate it. Aspiration of this blood or gastric content can certainly interfere with effective bag-mask ventilation. These are all appropriate considerations among others and can be summarized by the mnemonic MOANS [19, 23, 24]. Although there is no clear correlation between each of the aspects and the degree of difficulty of BMV, it is suggested that there is a need for an adjunctive device or maneuver for successful mask seal (oropharyngeal or nasopharyngeal airway and/or position changes) for a score of 2 or higher.

7.2 MOANS

M: Mask seal—Abnormal oral anatomy, facial hair, lack of interfering substance (excessive vomiting, bleeding, etc.), or inability to apply pressure to the face due to trauma will prevent achievement of an effective mask seal.

O: Obstruction/obesity—Similar to LEMON, mechanical obstruction in the airway by soft tissue, tumor, or abscess will contribute to a difficult BMV.

A: Age—Individuals over the age 55 are considered to be at risk for a difficult BMV due to general loss of elasticity of tissues and high incidence of both restrictive and obstructive lung diseases.

N: No teeth—Dentition acts as a scaffold against the mask for an effective mask seal. The lack of this framework can prevent an effective mask seal, which is why dentures are recommended to be left in during BMV and then removed during direct laryngoscopy [25]. This may be more commonly seen in HNC patients as xerostomia and dental complications are very common complications for these patients, especially those who have had radiation therapy.

S: Stiffness—Restriction of lung compliance contributes to resistance with bagging and requires increased inspiratory pressure to ventilate. Patients with asthma, COPD, pneumonia, or pulmonary edema are some of those who may be at risk from this standpoint.

The initial observational evaluation assessment will conclude with an evaluation for extraglottic airway placement and cricothyrotomy difficulty via the RODS and SMART mnemonic, respectively [19]. Both of these have not been clinically validated to our knowledge, but are good additional checklists to go through.

7.3 RODS (Extraglottic Airway Placement Difficulty)

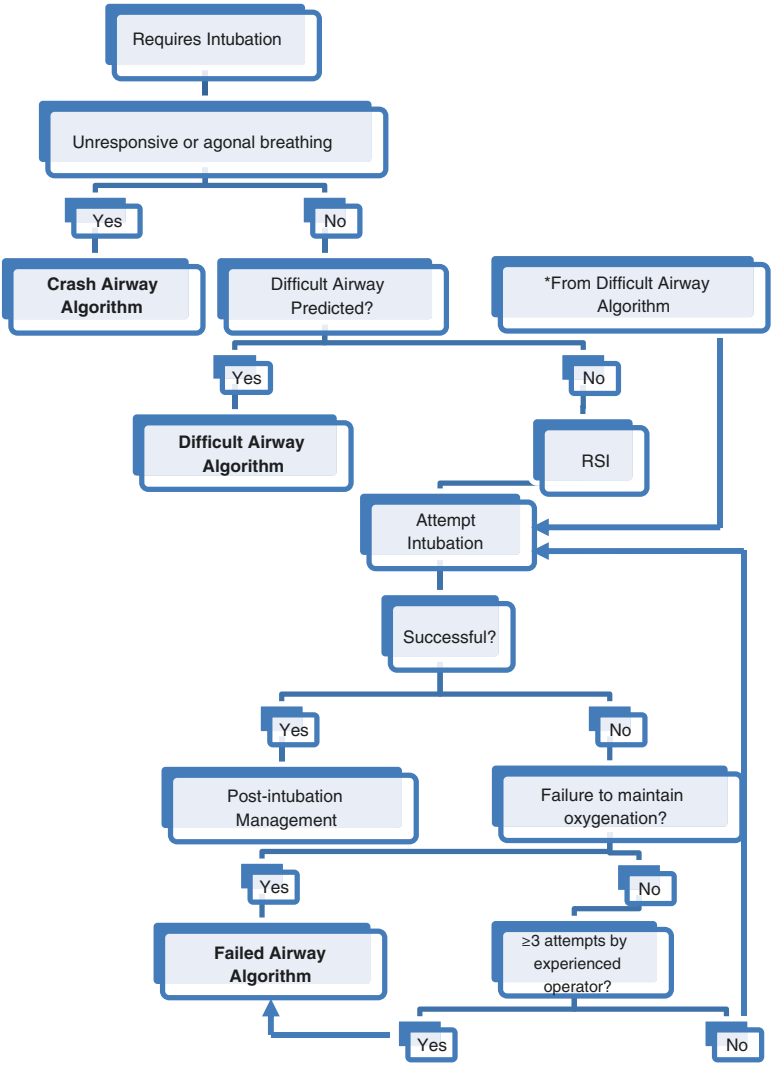
R: Restricted mouth opening
O: Obstruction (foreign objects)
D: Disrupted or distorted airway (by edema, prior surgery, etc.)
S: Stiff lungs or cervical spine

7.4 SMART (Cricothyrotomy Difficulty)

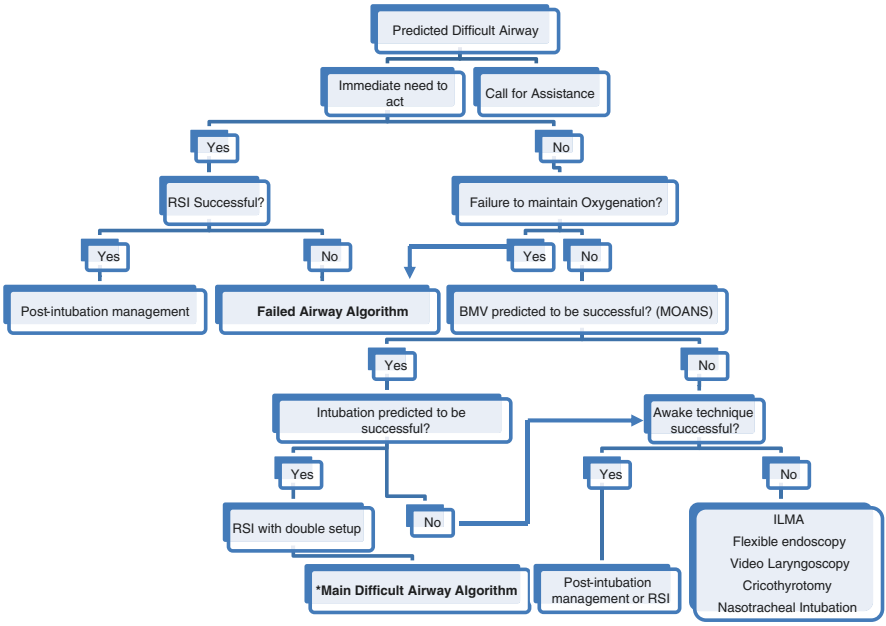
S: Surgery (recent or remote)
M: Mass (hematoma, abscess, etc.)
A: Access or anatomy (obesity, poor landmarks)
R: Radiation (tissue deformity, scarring)
T: Tumor (including intrinsic airway tumors)

While these bedside tools are not specifically tailored for HNC patients, it is a useful approach as these patients often do present with a difficult airway. A similar claim can be mentioned about the actual intubation process as well. Clinically validated algorithms have been developed by the Difficult Airway Society (DAS) on how to approach a difficult airway during an emergency [19]. This can be applied to HNC patients in respiratory failure requiring intubation.

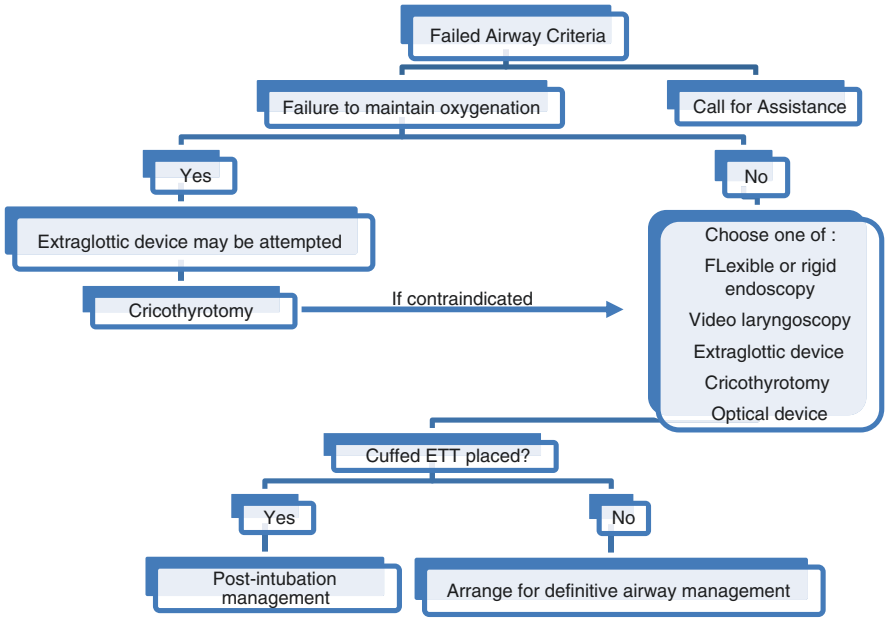
7.5 Main Emergency Airway Management Algorithm



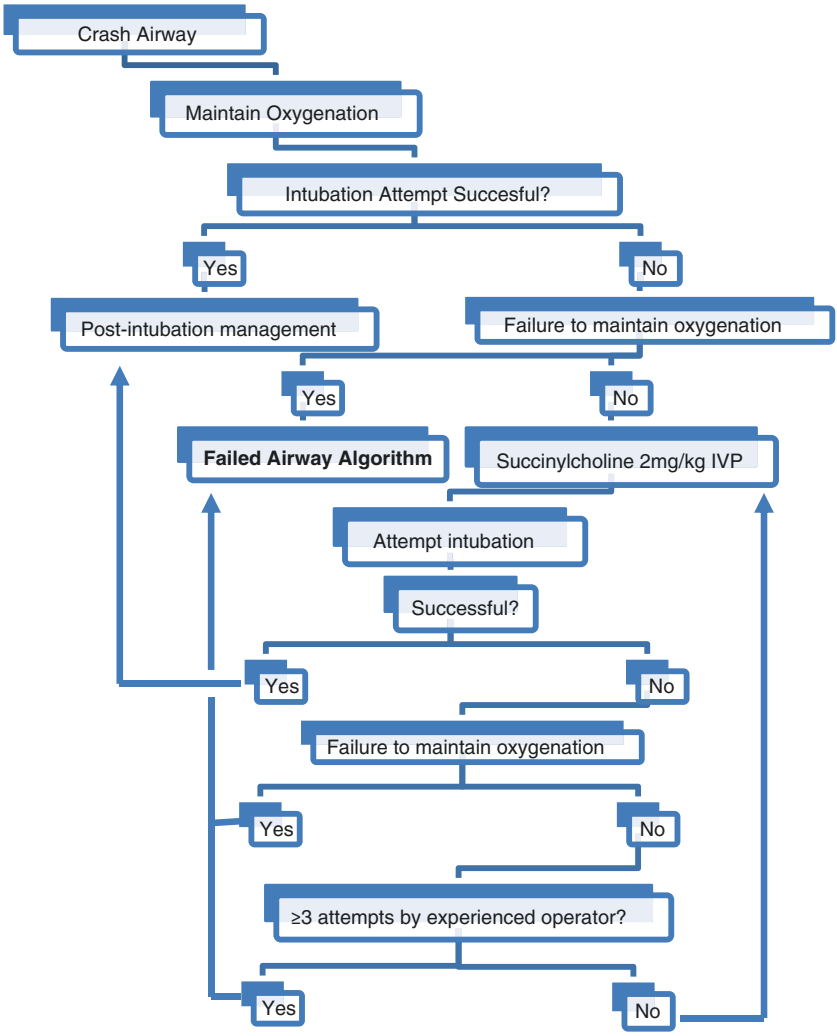
7.6 Difficult Airway Algorithm



7.7 Failed Airway Algorithm



7.8 Crash Airway Algorithm

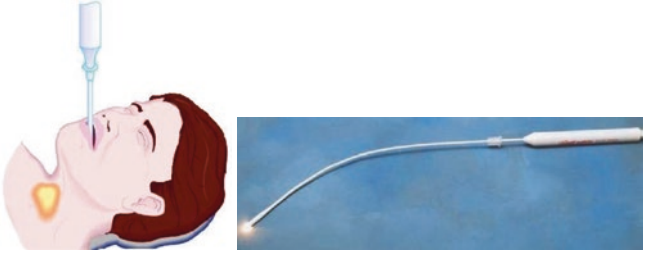


Although not specified in the algorithms above, endotracheal intubation with bedside visualization via video laryngoscopy (GlideScope, etc.) should precede extraglottic devices and cricothyrotomy, as it establishes a definite airway if successful. Also, the use of extraglottic device use should precede cricothyrotomy, as the latter is usually the last resort [26]. The uses of extraglottic devices are somewhat limited in HNC patients due to anatomy distortion, and precautionary measures need to be applied in proceeding with endotracheal intubation. For example, endotracheal tube introducers may exacerbate the current or prior injury or advance outside the airway to adjacent structures [27, 28]. Lighted stylets partially depend on the external visualization of the lighted tip, making

it less reliable in HNC patients as well due to altered anatomy and possible soft tissue abnormalities [29, 30]. Laryngeal mask airways (LMA) are frequently used as a rescue airway, with a previously reported 90% success rate in an emergent failed airway [19, 31, 32]. Though there have not been studies that have demonstrated it, its usefulness may be limited in those with anatomic abnormalities in the supraglottic area, thereby creating an ineffective mask seal and alignment. There is an added benefit of being able to pass an ET tube through the LMA [33]. However, the diameter at maximum is about 6–7 mm, which is less than ideal for the patient. The combitube is another extraglottic device that consists of a dual-lumen, dual-cuff airway with an opening in between the two cuffs to allow for ventilation into the laryngeal outlet. This may be a better choice for HNC patients as it can be inserted without head and neck movement and does not rely on a mask seal with the airway, as well as being effective as a salvage airway [34, 35]. However, its use may be limited by the inability to suction secretions, which also may be a preceding problem in HNC patients who cannot clear them. Flexible endoscopy may be feasible due to its success rate, and there are studies that show that a fiber-optic intubation in oncological head and neck patients has been successful in the surgical and emergency setting [36, 37]. The intubation process itself seems to not take much time; however, the preparation time before that may not make it an optimal choice in emergency situations [38–41]. Retrograde intubation has been periodically studied in with seemingly positive results [42, 43]. While this may be another option for an emergent airway, there have been no studies to show its superiority, and it may be technically limited by inexperience as more and more extraglottic devices and other salvage airways surface. Laryngeal and pharyngeal tubes have shown maintenance of an effective cuff seal in patients with laryngeal and pharyngeal tumors according to one prospective trial [44]. They may gain popularity for HNC patients once more reassuring data becomes available. Anatomically the laryngeal tube is placed in a similar area as the combitube. Thus the combitube may also be effective in creating an effective cuff seal. However, there is another study that showed the laryngeal tube to have a shorter insertion time compared to the combitube, which is an additional advantage [45].

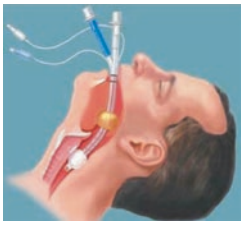
7.8.1 Lighted Stylet

Lighted Stylet

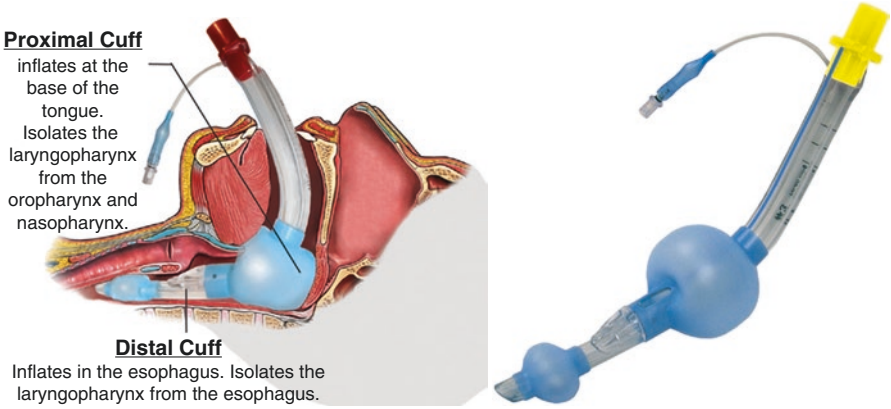


7.8.2 Combitube

Combitube



7.8.3 Laryngeal Tube



Most of the devices mentioned above will result in a cuffed seal in the trachea or in the esophagus and a secured airway. The LMA and other devices such as the Igel rely on a cuffless perilaryngeal seal. If these are used, a protected airway via a cuffed endotracheal tube should be established right after. Although there are many different types of extraglottic airways, currently there is insufficient data to unquestionably favor one over another, especially specific for HNC patients.

If the patient becomes hypoxic and develops a failed airway with any of the above modalities though, cricothyrotomy still remains the first rescue technique. Being the last resort for airway establishment, it is believed that there are no absolute contraindications for emergency cricothyrotomy in adults, although this has been debated [46, 47]. Relative or proposed absolute, the contraindications are related to prior surgeries. Specifically listed are transection of the trachea, laryngotracheal disruption with retraction of the distal trachea into the mediastinum, and prior laryngeal fracture. If a patient fits this group and anatomy distortion does not allow tactile guidance and ascertainment of landmarks, then an emergency tracheostomy via the distal tracheal segment or with fiber-optic scope guidance, followed by direct intubation, is likely the

best approach. There may be delays due to the setup and use of the fiber-optic scope; however, there are very limited options at this point.

Tracheostomies have been studied as an effective and important way to establish an emergent airway for an acute upper airway obstruction. While surgical tracheostomies have been widely accepted for this use, percutaneous methods have not due to possible cannula dislodgement, airway obstruction, tracheal stenosis, or other complications. However, there have been multiple studies showing the latter as an effective method for emergency airway establishment, with comparable or better results against surgical tracheostomies [48–50]. Albeit a current lack of data specific for HNC patients, we believe that both are a plausible method for the initial establishment of an airway. Tracheostomies may also have the benefit of bypassing the complications from affected anatomical sites including the oral cavity, the nasal cavity, and the pharynx.

Once a protected airway is established, oxygenation and ventilation should be managed based on the patient's need. The airway should be assessed periodically for complications including dislodging or obstruction of the ETT, barotrauma (pneumothorax, etc.), and infection. As mentioned above during the discussion of the initial airway evaluation, HNC patients may have increased risk of bleeding. This may be from the primary lesion, mucositis from chemotherapy, or due to post-radiation changes. However, this is thus far a theoretical risk, and complication of ventilation management by increased hemorrhage in HNC patients has not been shown. Whether there are tolerability differences in HNC patients for prolonged transpharyngeal intubation due to these potential risks is also a question unanswered. Along those lines is the consideration of converting these intubated HNC patients to tracheostomies.

The conversion to tracheostomy from oral intubation for HNC patients has not been specifically studied in the setting of an emergent airway inserted in the face of acute respiratory failure. Despite the successful use of tracheostomies as an emergent airway, converting transpharyngeal intubation to tracheostomies has been questioned, and recent studies have not shown benefit [51–56]. Its use has been associated with increased length of hospital stay, increased time to first oral intake, and higher rate of lower respiratory infections. As is with non-HNC patients, the question of early versus late tracheostomy is also ongoing, and mixed results have been yielded across multiple studies. This will have to further be addressed, as most of the studies about the timing of tracheostomy exclude HNC patients altogether. Thus, while there are no formal recommendations against its use, the data obtained so far does not give any compelling evidence for its use, especially if the patients' respiratory status is predicted to improve in about 1 week. It should also be noted that mortality is high among cancer patients with prolonged mechanical ventilation in general [4]. A nationwide study done in Taiwan showed that a majority of cancer patients with prolonged mechanical ventilation (defined as greater than 7 days) had a median survival of 1.37 months and a 1-year survival rate of 14.3% [57]. Prognosis further worsened with the presence metastasis in these patients, and palliative care should be an integral part of HNC patients' care in the face of prolonged need for mechanical ventilation.

While intubation of HNC patients has a readily applicable algorithm with contingency plans for each step, this is not the case with extubation. There is a substantial lack of prospective randomized trials or meta-analyses regarding extubation of HNC patients and difficult airway patients in general. Although we are aware of the possible complications, there are no specialized methods to prevent them and no specified protocol to address them. The Difficult Airway Society does have an algorithm available for the extubation of the difficult airway-based clinical experience and case reports [19, 58]. However, this is more applicable in the surgical setting and not in the context of acute respiratory failure. As was with prior algorithms already discussed, there are aspects that we can adapt though. The core element of this guideline is the importance of planning. The Fourth National Audit Project (NAP4) by the Royal College of Anesthetists and the DAS stated that 30% of all serious complications were associated with extubation or removal of LMA at the end of anesthesia [58, 59]. Poor planning and inadequate risk factor assessment were significant contributors to these adverse events during extubation. Thus the DAS algorithm focuses on thorough preparation with anticipation of complications individualized to the patient, with an overall categorization of whether the patient is low risk or at risk of post-extubation complications. This stratification is based on whether airway risk factors are present such as known airway access difficulty, airway deterioration during clinical/surgical course, and restricted airway access secondary to neck stiffness [60]. Another final evaluation and optimization of these airway factors are also recommended just prior to extubation. This includes direct or indirect visual assessment for potential causes of obstruction including edema and hemorrhage. A cuff-leak test should be done to assess for possible subglottic edema. Chest X-ray should also be considered to assess for lower airway abnormalities including infection. Standard precautions and measured parameters for considering extubation such as ability to protect the airway, cough strength, and fluid balance should of course also be considered and optimized.

As for the extubation process itself, the algorithm allows awake and deep (fully anesthetized) extubation for low-risk patients. We do not recommend the latter as there is risk of upper airway obstruction with this technique. Furthermore, most HNC patients should be considered as at risk unless it is a distant history with minimal resulting anatomy distortion. The awake extubation technique, which is the same for at- and low-risk patients, should be chosen for extubation of HNC patients. As mentioned above, preparation and anticipation of complications remains the mainstay. Other advanced techniques are available for extubation of at-risk patients per the DAS guidelines. One is the exchange method where an LMA is inserted in place of the ETT. However, this is deemed inappropriate for patients with an anticipated difficult reintubation and cannot be recommended for HNC patients. Another technique is a constant remifentanil infusion during extubation to suppress coughing, agitation, and hemodynamic disturbances. This technique is more applicable in the setting of reemergence from anesthesia in the OR and cannot be applied to the extubation of an HNC patient who needed an emergent airway. Suppression of reflexes and the use of sedatives during the latter situation of extubation are unsafe. The last method that the DAS describes is the use of airway exchange catheters

(AECs). This may be more applicable as they can be used as a guide for reintubation. In addition, in emergency situations they can also be used as a source for oxygenation. However, oxygenation via AECs is not recommended, as most of the mortality associated with its use is associated with oxygenation and barotrauma [61, 62]. The AEC has been reported as a lifesaving device during reintubation and should be considered for patients who have difficult intubations or have concerns for post-extubation complications [63].

Although pertaining to the postoperative context, this algorithm also discusses the use of tracheostomies. Its importance is highlighted for patients with laryngeal edema, or if a slow resolution of a problematic airway is anticipated. As mentioned earlier though, the true benefits of converting to tracheostomies for HNC patients in the setting of acute respiratory failure have not been conclusively studied, and its benefits of postoperative conversion from transpharyngeal intubation have also been questioned.

Overall, the DAS algorithm is a good starting point for HNC patients' extubation. However, it is limited in that there are no evidence-based-specific contingency plans and that its applicability is in the postoperative setting rather than those intubated for acute respiratory distress. Unfortunately it is the only guideline currently available, and further studies need to come forward in order to advance our practices.

Despite our limitations due to lack of data, we hope that this chapter has shed some light on how to approach upper acute respiratory failure in upper neck cancer patients. With the current lack of standard procedures and just sparse case reports, there definitely is a need for more prospective randomized trials, particularly on the extubation process of these patients. With an epidemiological impact that head and neck cancer patients have on mortality, it is paramount that we eventually come to a clear solution for this relatively common complication of these patients.

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Psychological Aspects of Critically Ill Cancer

8

Zehra Hatipoğlu, Ayten Bolukbası, and Dilek Ozcengiz

Advanced developments in many areas of medicine allow patients to have a longer life span; however, the number of cancer-related cases grows in today's world. With cancer-related cases becoming ever more frequent, the associated number of critically ill cancer patient numbers has also significantly increased. It may not always be possible to apply curative treatment to critically ill cancer patients; therefore, the aim is to attempt to improve the patients' quality of life through palliative treatment. It's common to apply palliative care with the aim of maintaining or improving the quality of life of critically ill cancer patients, which seems to be rising these days [1]. Quality of life has been defined differently by different authors; nevertheless, authors have reached a consensus about it "being a multi-dimensional concept and including physical, psychological and social well-being" [2, 3].

According to the results of some research, the rate of oncology patients likely to have a mental disorder. Because, many of between 30 and 40% [4]. However, there is a difficulty in attempting to estimate number of percentage of oncology patients that have a mental disorder, for many of the oncology patients may not be diagnosed and, in this way, their conditions may be stable or even get worse in time [5]. To be diagnosed to have a cancer disease is a terrifying diagnosis experienced by patients, and this is likely to psychologically affect more cancer patients compared to non-cancer patients [6]. In this chapter, we would like to focus on psychological aspects of critically ill cancer patients.

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8.1 Risk Factors

Anxiety and depression levels can vary in terms of age, gender and primary cancer site; for example, while depression prevalence with pancreatic and lung cancer patients is quite high, the prevalence of skin cancer patients is relatively less [4]. Piccinelli et al. reported that gender is a variable for anxiety and depression in a healthy population and women have a higher frequency of depression when compared to men [7]. Linden et al. discussed their findings about depression and anxiety levels when comparing women with men, and this suggests that at first, men perceive cancer as being less frightening compared to women. Nevertheless, authors state that they do not have enough knowledge about how men react to cancer, if it gets worse in time. In addition to this, although age is not a significant factor in distress levels suffered by patients, anxiety and depression are more common in younger rather than older adults [4]. The psychological and emotional status of cancer patients is affected by clinicians who impart the diagnosis, patient's personality traits and previous history of psychological morbidity. Also the timing of the diagnosis, medication endpoints and recurrence episodes contribute to this situation [8].

8.2 Psychological Status of Cancer Patients

The feeling that is experienced by patients who are diagnosed with cancer is of demoralization. The meaning and aim of life are questions asked by them, and feelings of hopelessness and helplessness emerge [9]. These patients have more suicidal tendencies compared to the general population [10]. Distress, depression and anxiety may be seen in patients diagnosed with cancer, especially in extended periods of their illness, and consequently, it can be expressed that these disorders lead to reduction in their quality of life, adverse effect on medical treatment and increased mortality [4].

8.3 Treatment Approaches

Treatment of patients who have cancer may be provided with pharmacological and non-pharmacological methods [11]. To manage and assess the psychological condition, cancer patients highlight that there is limited literature in terms of evidence-based guidelines. However, a common view on this subject is that psychosocial therapies provide emotional support. Psychosocial therapies are non-pharmacological methods, and the aim of these therapies is to reduce feelings of isolation, hopelessness and helplessness, with their being four psychosocial aspects to this which are as follows: psychoeducational, psychotherapy, cognitive behavioural therapy and group interventions [12, 13].

Psychoeducational interventions explain how to educate patients on the disease process and how to cope with the disease. Once patients are diagnosed with

cancer, patients and their families or caregivers may wish to collect more information about the illness and the outcomes of it in the future. Yet, it might not always be possible to apply curative treatment, and patients can collect more information about coping strategies they can adopt for their illness. Although "consciously seeking information" seems to be linked to a positive change for patients, patients on the other hand can also be effected by myths, misconceptions, as well as ambiguities which may lead to unnecessary anxiety and inappropriate feedback while seeking information [14].

Most of the cancer patients are seeking as much information as possible about their illness and their medication; nevertheless, there are also a few patients who prefer not to obtain information to keep their hopes of surviving alive, being one of the possible reasons [15, 16]. In fact, there are cancer patients who look for information because it provides them with a coping mechanism and allows them to manage the difficulties of being diagnosed with cancer which include a sense of shock after diagnosis, a sense of responsibility to decide about medication and finally a sense of ambiguity about illness [17]. To sum up, despite the fact that looking for information benefits cancer patients in coping with their illness, as well as in getting more control of their life, increasing self-care ability and adapting to their health condition, cancer patients are still mostly unsatisfied with collected information [18–21].

Hinds et al. stated occasions where information was supplied unclearly, as well incorrectly for cancer patients; nevertheless, authors underlined the fact that they are not sure to which sources patients were referring to [20]. In fact, in a review of literature, there was insufficient information to come to this conclusion which was caused due to a number of different factors: firstly health professionals may not provide sufficient information according to the necessary education level of patients; secondly professionals do not have enough time for that; thirdly patients may not wish to keep the information that they receive as a result of them being most probably in a state of denial; and lastly, the staff think that they already know the information needs of patients; however, it needs to be emphasized that the challenges to those possible reasons can be found through other studies stated in the review of this study [22–27].

Vos et al. highlighted that the coping style after surgery has links to the psychosocial adjustment of patients. When women have an emotional way of coping, they experience more distress and less vitality, as well as there being a significant difference between women who experienced breast-conserving treatment and mastectomy. Breast-conserving treatment is perceived to be less frightening compared to mastectomy by women [28]. A number of studies about coping strategies of breast cancer patients have shown cancer patients with good social adaptation deal with their illness with an active strategy, whereas patients with poor psychosocial adaptation deal with their illness with an avoidant coping strategy [29]. Kershaw et al. found out that active coping is highly correlated to higher quality of life; on the other hand, avoidant coping is highly correlated to a lower quality of life [30]. Hereby, we suggest to examine the coping strategy of cancer patients and supply psychosocial help, if necessary.

Another psychosocial approach is psychotherapy. The aim of psychotherapy in cancer patients is to reduce trouble and help to resolve their emotional difficulties. Patients with cancer can be referred to a clinician or oncologist of their own, if an emotional crisis occurs. Although it is considered that psychological support is presented by a therapist, they take into account illness-related issues such as the threat of an individual suffering from narcissistic integrity, a feeling that they are losing control, dependency, fear of abandonment, loss of identity, treatment-related issues, specific meaning of illness and fear of death [31].

Cognitive behavioural therapy (CBT) is another component of psychological treatment in patients with cancer. Cognitive behavioural therapy aims to help restructure negative thoughts, feeling and behaviour of the patient by behavioural and cognitive techniques, and it is an effective method used to treat depression, anxiety, insomnia and pain of patients diagnosed with cancer [12, 32, 33].

As mentioned above, sleep disturbances, pain and body-image problems are other difficulties observed in cancer patients. Although pharmacological development has improved, most of the critically ill cancer patients suffer from pain and numbness, and they report the decrease in their quality of life, and they are likely to have symptoms such as weakness, pain, anorexia and cachexia [34, 35]. To gain a better cancer pain management, biomedical factors by itself should not be treated, but also psychosocial and spiritual distress levels should be taken into account [36]. Furthermore, Lee et al. suggest that improvement in pain management strategies can be supplied with more psycho-spiritual support [37].

Physical appearance during cancer and its treatment (surgery, chemotherapy or combination) is an important concept for patients. During this illness, they could experience some body alterations such as hair loss, scarring, swelling and loss of appetite. Patients who are undergoing limb, breast, head and neck surgery may suffer more in their body image than other surgery. On the other hand, another issue that worried cancer patients is masculinity and femininity on the basis of their visual appearance, especially for those who suffer from gynaecological, testicular or prostate cancer. Although research studies are limited in this subject, approaches for these patients include CBT, psychosexual therapy and cosmesis-focused, sensate-focused and physical fitness interventions [38].

Sleep disturbances related to cancer are associated with depression and anxiety, and it affects approximately 30–50% of cancer patients [39]. Insomnia can cause the affected in terms of psychological and behavioural outcomes such as fatigue, mood disturbances, cognitive impairments and shorter longevity. Pharmacological and non-pharmacological methods are used in the treatment of insomnia. Pharmacological agents include benzodiazepines, melatonin-receptor agonists and antidepressant medications. These agents have risks and limitations and may cause residual effects, cognitive impairments, delirium in elderly patients and rebound insomnia. Furthermore it has the effects of abuse and dependence in long-term therapy. On the other hand, non-pharmacological methods may also refer to therapy, when these negative factors are taken into account. Interventions for psychological aspects for insomnia are stimulus control therapy, sleep restriction procedures, relation training, CBT and sleep hygiene education [33, 40].

Relatively new research into the psychology of cancer patient is how resilience of patients affects on their psychological well-being. Resilience may help patients with their illness process especially for symptoms [41]. In addition to this, mostly resilience main focuses on personal factors [42]. A study conducted by Matzka et al. concluded that higher resilience amongst cancer patients leads them to having lower psychological distress and being more physically active and that resilience is a key to a more effective psychological symptom management [43].

To be diagnosed as a critically ill cancer patient or to be even a caregiver of cancer patients may lead to some psychological distresses and decrease the quality of life although level of symptoms may vary depending on personal characteristics and coping strategy types and illness differences. Although there are some limited psychological interventions for this population, there is still a great need to test available programmes and struck new intervention programmes with the aim of increasing quality of life. Lastly, collaboration amongst health professionals not only leads to a better physical condition but also a higher level of quality of life for cancer patients and caregivers which is very important.

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Upper Acute Respiratory Failure in Neck Cancer

9

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Respiratory complications are a significant cause of mortality and morbidity in patients with primary or metastatic head and neck cancers [1]. The seriousness of the symptoms differs according to the location of the cancer. For example, a small lesion in the larynx may cause a severe respiratory distress, while a massive lesion in the pharyngeal fossa may cause only minimal respiratory problem. The secondary tumor or metastatic cancer that is found in the upper neck region, pressure of the lesion on the tissue, or sometimes hemorrhage of fragile mass or even little aspiration that adds to the pressure of already existing lesion may also cause respiratory failure. Consequently, the common concern for these cancer types is a respiratory failure [2].

In this section, we will describe upper neck cancer, airway obstruction, post-obstruction negative pressure pulmonary edema, respiratory failure, and treatment approach for ventilatory problems.

9.1 Upper Neck Cancer

Head and neck squamous cell carcinoma is one of the most common types of human cancer, and they include the oral cavity, oropharynx, nasopharynx, hypopharynx, larynx, paranasal sinus, and trachea cancers. Hardly seen cancers such as fibrosarcoma and lymphoma can be counted as upper neck cancers [3]. Upper neck cancers

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generally occur in older men, but in recent years, the incidence has increased both in female and male younger patients.

9.1.1 Risk Factors

The patients, who currently smoke or ever smoked in the past, have a greater risk than never smoked patients. While poor diet or excessive consumption of red meat and fried foods increases the incidence of neck cancer, the diet including fresh fruit, vegetables, olive oil, and fish oil reduces the risk. Human papillomavirus (HPV) infection is associated with these cancers, and, the majority of nasopharyngeal cancers are associated with Epstein-Barr virus (EBV). Excessive alcohol consumption is associated with increased risk of cancers of the oral cavity, hypopharynx, oropharynx, and larynx. Other risk factors include gastroesophageal reflux, poor hygiene in the oral cavity, and dietary and environmental factors [3]. The predisposing risk factors of upper neck cancer are shown in Table 9.1.

9.1.2 Diagnosis

Detailed clinical examination, fiber-optic endoscopy/bronchoscopy, pharyngolaryngoscopy, fine-needle aspiration/biopsy, computerized tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (if primary tumor is unknown) are used for diagnosis and classification of the tumor [4].

9.1.3 Prognosis and Treatment

Treatment for head and neck cancers includes surgical resection, radiotherapy, chemotherapy, and utilization of targeted therapeutic agents. In view of these informations, the standard nonsurgical treatment for patients with head and neck cancers ought to include joined radiation and chemotherapy or their combination. The ideal chemotherapy regimen and fractionation plan and the part of impelling and adjuvant chemotherapy still stay to be characterized [3].

Therapy of upper neck cancers is based on the TNM classification system. TNM is an abbreviation that stands for the tumor size and invasion features (T stage),

Table 9.1 The risk factors for upper neck cancer

1. Smoking
2. Alcohol consumption
3. Diet
4. Gastroesophageal reflux
5. Genetic factors
6. Viruses (HPV, EBV)
7. Environmental factors
8. Poor hygiene

lymph node spread (N stage), and the presence of distant metastasis (M stage). However, patients in the same stage might be treated differently, due to the differences in the molecular characteristics of the tumors [3]. Higher grade, deep invasion (>4 mm) higher T stage with basaloid, spindle cell tumors, vascularperineural infiltration, and severe dysplasia are the criterias of poor prognosis.

In addition, the comorbidities that come with the tumors have an important role on the treatment process and the survey. For example, head and neck cancers and upper aerodigestive tract cancers are usually associated with chronic obstructive lung disease. Also, these cancers accompany other cancer types. When head and neck cancer patients are compared to the patients with other types of cancer, it is seen that patients with head and neck cancer have a 21% rate of moderate or severe comorbidity, while patients with cancers of the prostate, breast, and gynecological sites had lower burdens [5]. The seriousness of comorbidity appeared to be essentially connected with a 2-year survival for the whole associate and for the head and neck cancer patients [5].

The tumors posturing the greater part of the troubles emerge inside the larynx or from adjacent zones, for example, piriform fossa, tongue base, or vallecula. In each of these regions, the tumors embrace distinctive examples in the way they encroach on the airway, and this is why they are managed separately. Patients can encounter upsetting symptoms including stridor and dyspnea as a consequence of upper airway obstruction. Techniques to decrease these symptoms can challenge and will frequently require a blend of surgical and nonsurgical approaches and palliative consideration [6].

9.2 Upper Airway Obstruction

Life-threatening acute respiratory obstruction may occur with bleeding and external or internal compression of primer or metastatic neck tumors. When considering intrinsic obstruction of the upper airway, the vast majority of patients are made up for metastatic or primary tumors of the airway and stricture after endotracheal intubation or mechanical ventilation. Immediately life-threatening or any acute obstruction can be present for weeks and months, and patients especially the ones in sedentary lifestyle are often well adapted for a time, but thick respiratory secretions or tumoral hemorrhage may lead to airway obstruction and asphyxia.

Obstructive symptoms appear at rest, when normal airway passage narrows more than 30%. Upper airway obstruction (fixed obstruction of the larynx and upper trachea) is often associated with inspiratory symptoms, while expiratory symptoms are observed at lower airway obstruction. The most widely recognized symptoms of an obstruction are confusion, panic, swelling of the face and tongue, drooling, unconsciousness, difficulty breathing, choking, agitation, wheezing, and other unusual breathing symptoms. Cyanosis can also appear as a sign of acute upper airway obstruction, depending on the severity of obstruction.

Some examples of airway obstruction are given below.

Primary malignant neoplasms of the trachea take places 0.1–0.4% of all malignancies. They cause late symptoms because when the tracheal lumen is narrowed to less than 7 mm, symptoms or dyspnea occur. At that time, the tracheal lumen occludes nearly 50–75% of the luminary diameter. This situation might have been caused by primary tracheal lymphoma and the symptoms of tracheal mass (caused by lymphoma) mismatch with the symptoms of asthma [7].

Rare seen tumors such as inflammatory pseudotumor are predominantly found in the lung and abdomen, but they may also occur in the head and neck region. Furthermore, they cause upper airway obstruction [8]. On the other hand, even *lipomas* which are found in the head and neck region into laryngeal region cause severe respiratory failure.

The methods of diagnosis of head and neck disease such as fine-needle aspiration may cause respiratory failure due to hemorrhage [9, 10].

In addition, upper airway obstruction may develop due to postoperative airway edema depending on *extensive neck surgery*.

Upper airway obstruction may be related to surgery (such as the obstruction or destruction of major neck vessels/lymphatics or injury to the nerves providing airway control), anesthesia (the prolonged endotracheal intubation period and/or recurrent intubation attempts), or immune-mediated responses [11]. Acute respiratory failure is one of the most dangerous clinical statuses for upper neck cancer. All of these clinical conditions lead to type II respiratory failure, but even if respiratory failure is treated after the obstruction, this situation may cause noncardiogenic pulmonary edema. Namely, respiratory failure turns into type I or mixed type, and so regardless of the type, respiratory failure must be detailed and identified and should be treated.

9.2.1 Assessment and Management of Airway Obstruction

Endoscopy, CT, and MRI are used for the assessment of obstruction. After the patient has been assessed, a management plan can be made for each individual situation. It must be treated with airway stent, endotracheal intubation, flexible fiber-optic balloon dilatation, laser therapy, electrocautery/argon laser coagulation, or tracheotomy. In some cases such as the acute situations, there is a need to use conservative treatments before the intervention. First choice in this situation is usually endotracheal intubation, but nevertheless it should be noted that advanced airway equipment is needed, such as tracheotomy or cricothyroidotomy or jet ventilators [12]. If surgical intervention is considered, the patient is rapidly transferred to the operating room with supplemental 100% oxygen. In the anesthetic strategy, inhalation agents may be preferred for anesthesia induction, and inhalation or total intravenous anesthesia (propofol and fentanyl/remifentanil) may be used for anesthesia maintenance. The use of muscle relaxants is controversial; it is decided according to the patients' clinical condition and desaturation level.

9.2.2 Post-obstruction Negative Pressure Pulmonary Edema

Negative pressure pulmonary edema (NPPE) develops in patients with upper airway obstruction or highly negative intrathoracic pressures. It causes severe hypoxemia and pulmonary edema. Most of these patients are children but also it may be seen in adults. This situation is usually related to laryngospasm especially following surgery and upper airway tumor in addition to obstructive sleep apnea [13, 14].

High negative inspiratory pressures result in high permeability or hydrostatic difference, and the hydrostatic difference in the lung facilitates steady-state fluid filtration from the capillaries into the interstitium; this results in hydrostatic edema in the lung. Pulmonary edema resolves in 24–48 h if there is no continuous persistent hydrostatic stress or patients get positive pressure ventilation by endotracheal intubation [13].

Endotracheal intubation and positive pressure ventilation with supplemental oxygen are usually required in these cases. If necessary, sedation and muscle relaxants should be used for these patients. Several general therapies for acute pulmonary edema could be considered in this setting:

1. Diuretics are the standard of care in heart failure-associated pulmonary edema.
2. Beta agonists are still discussed.
3. If severe and refractory hypoxemia exists, rescue therapies should be considered such as neuromuscular blockade, prone position, and extracorporeal membrane oxygenation [13].

9.3 Respiratory Failure

Acute respiratory failure (ARF) is accompanied with malignancies, and respiratory events happen in 1% (oncology) to 20% (hematology) of patients, and it might reach 40% in neutropenic patients. In addition, nearly half of the patients with respiratory difficulties would require admission in the ICU because of ARF and/or related organ dysfunction and unfortunately in-hospital mortality rises up to half [15].

ARF is characterized as; an oxygen saturation of <90% or PaO_2 of <60 mm Hg on room air, extreme dyspnea at rest with failure to talk in sentences, breathing frequency of >30 breaths/min, or clinical indications of respiratory pain. Respiratory failure occurs when there is an inadequate exchange of O_2 and CO_2. This causes hypoxemia, with or without hypercarbia [16].

9.3.1 Classification of Respiratory Failure

Respiratory failure can be divided into three groups: *type I respiratory failure*, failure of oxygen transfer in the lung that causes hypoxemia (acute or hypoxemic

respiratory failure); *type II respiratory failure*, inadequate ventilation that contributes to retention of CO_2, with hypercarbia and hypoxemia (chronic, ventilatory, or hypercapnic respiratory failure); and *mixed respiratory failure*, a combination of type I and type II respiratory failure (acute on chronic respiratory failure) [16].

9.3.2 Pathophysiology of Type I Respiratory Failure

- Low inspired oxygen partial pressure
- Alveolar hypoventilation
- Diffusion deterioration
- Ventilation/perfusion (V/Q) impairment
- Right-to-left shunt failure of ventilation (hypercapnia, type II failure) [17]

9.3.3 Pathophysiology of Type II Respiratory Failure

Neuromuscular dysfunction and abnormalities of the central respiratory drive, the chest wall, the lungs, and the airways are causes to type II respiratory failure and hypercapnia [16].

9.3.4 Diagnosis of Respiratory Failure

Physical examination and investigations must be included to identify the underlying disease which caused the acute respiratory failure [16]. For this situation, blood gas analysis will assist in identifying the type of respiratory failure and to the examination of the underlying conditions [16].

9.3.5 Treatment of Respiratory Failure

Treatment of respiratory failure should include support of oxygenation because patients may die from hypoxia, and it should maintain SaO_2 of >92%. In acute respiratory failure, $PaO_2 < 8$ kPa (60 mmHg) or $SaO_2 < 90\%$ is an indication for oxygen therapy. Patients with chronic obstructive pulmonary disease or chronic type II respiratory failure, rely on hypoxic drive to stimulate ventilation, there O_2 concentration should be limited to 24–28% PaO_2 and should be maintained at 8–10 kPa (60–75 mmHg). Then the patients must be transferred to an ICU, and mechanical ventilation should be considered [16].

In these cases, tracheal intubation should be considered in the following situations [16]:

- For mechanical ventilation
- Blockage for aspiration
- Facilitation of tracheobronchial suction

- Relief of upper airway obstruction

Indications for mechanical ventilation in these patients [16]:

- Facilitate major surgery
- Support in respiratory failure
- Coma
- Control of intracranial pressure
- Reduction of metabolic demands
- Postoperative ventilation
- Inter/intrahospital transfer of the critically ill patient

Patients with upper aerodigestive tract tumors can have development of airway compromise both before and during chemoradiotherapy (CRT). Tracheotomy is a classic method for securing a safe airway, but tumor debulking may also be used. Type II respiratory failure is less common than hypoxic respiratory failure, and more patients are harmed by the administration of too little O_2.

Conclusion

In conclusion, acute respiratory failure in patients with head and neck cancer is usually life threatening; therefore, the patients must be carefully assessed in terms of respiratory failure classification. Airway must be guaranteed immediately, and difficult airway devices must be prepared.

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Acute Respiratory Failure Before ICU Admission: A Practical Approach

10

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10.1 Introduction

Acute respiratory failure (ARF) occurs in up to half patients with hematologic and solid malignancies and is the leading cause of ICU admission in those patients. It is associated with poor outcome, with an overall mortality of 20–80% depending on the cause, the need for mechanical ventilation, the concomitant organ dysfunctions, the presence of graft-versus-host disease, and the goals of care [1, 2]. Delay in identification of the cause of ARF and the initiation of the appropriate therapy may further increase mortality. The most common cause of ARF in cancer patients is pulmonary infections, as a result of the immunosuppression posed by the underlying disease or the cancer therapy. Other frequent causes include cardiogenic and noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]), antineoplastic therapy (chemotherapy, radiation therapy)-induced lung injury, cancer-related medical disorders (such as venous thromboembolism, transfusion-related acute lung injury), and direct involvement of the respiratory system by malignancy and progression of underlying disease.

In cancer patients with ARF, the diagnostic strategy is to guide the immediate empirical treatment, most notably antimicrobial therapy as well as life-supporting interventions [3]. However, investigations must be obtained very rapidly to confirm or refute the initial diagnoses.

Differential diagnosis of ARF in cancer patients is a challenging process for the clinical physician. The cornerstone in the etiological diagnosis of ARF consists of a

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comprehensive clinical evaluation aimed at identifying the most likely causes and, therefore, at determining the appropriate diagnostic approach. A thorough physical examination provides key information on the respiratory manifestations (bronchial, interstitial, alveolar, vascular, or pleural symptoms), the severity of the ARF, and the time elapsed since respiratory symptom onset.

Both invasive and noninvasive diagnostic strategies can be used to identify the cause of ARF in cancer patients. The invasive strategy relies on fiberoptic bronchoscopy with bronchoalveolar lavage (FO-BAL), and the noninvasive strategy on imaging studies, on microbiological examination of blood and sputum, and on serological test.

It is already established that stable patients presenting with ARF and pulmonary infiltrates should undergo FB-BAL as microbiological and cytological examination of the BAL can be diagnostic in up to 50% of cancer patients with ARF [4]. However, in severely hypoxemic patients, FO-BAL has been described as inadvisable or contraindicated because of the risk of deterioration in respiratory status with a subsequent need for mechanical ventilation [5].

Imaging tests are of importance, in the identification of the cause of ARF. Chest X-ray should be performed in any patient presented with symptoms and signs of ARF, though it is neither specific nor sensitive in providing a specific diagnosis in particular in patients with febrile neutropenia. High-resolution computed tomography (HRCT) with sections at 1-mm intervals and, if needed, sections during expiration is more sensitive than chest radiography even in non-neutropenic patients. However, HRCT provides diagnostic orientation rather than a definitive diagnosis in cancer patients with ARF [6]. HRCT yields an overall sensitivity and negative predictive value of 90%, in identifying the cause of ARF in cancer patients with lung infiltrates, but low specificity and positive predictive value [7]. In some times HRCT may help to select the nature and site of endoscopic sample collection.

Recently lung ultrasound (LUS) has been introduced as diagnostic test in patients with ARF. LUS is a noninvasive and bedside-available imaging test, and many studies have shown that compared to chest X-ray, it has a higher diagnostic accuracy for pleural effusion, consolidation, pneumothorax, and interstitial syndrome and may be used as alternative to CT [8].

This chapter reviews the most common causes of ARF in oncologic patients and discusses the diagnostic and therapeutic approach before ICU admission.

10.2 Acute Respiratory Failure (ARF) in Cancer Patient Causes

10.2.1 Pulmonary Infections

Pulmonary infections are very frequent and represent the most common cause of ARF in oncologic patients, and unless proven otherwise, ARF in cancer patients

must be considered as an infectious emergency. Several factors increase the risk of infection in those patients, including chemotherapy, corticosteroid-induced immunosuppression, multiple hospital admissions, and exposure to broad-spectrum antibiotics [9]. Causative pathogen depends on the underlying immune state. In patients with impaired humoral immunity, such as those with acute and chronic lymphocytic leukemia and multiple myelomas, *Streptococcus pneumoniae* and *Haemophilus influenzae* are the predominantly isolated organisms. In patients with impaired cell-mediated (T-cell) immunity as those with Hodgkin disease or those therapy with corticosteroids, the predominantly isolated organisms are *Pneumocystis jirovecii* pneumonia (PJP), followed by mycobacteria, *Cryptococcus*, *Legionella pneumophila*, and viral infections (mainly herpes virus and *Cytomegalovirus*). Neutropenic patients are usually infected by gram-positive cocci (*Staphylococcus aureus* and *Streptococcus pneumoniae*), gram-negative enteric bacilli (*Pseudomonas aeruginosa* and *Klebsiella pneumoniae*), or opportunistic fungi (mainly *Aspergillus*)—especially in the case of prolonged neutropenia [9, 10] . When evaluating pneumonia in patients with cancer, determining the level and the duration of immunosuppression, the previous exposure to antimicrobials (over the last month), the length of the illness, the presenting symptoms, and the radiographic pattern will better predict the suspected pathogens. Hereby we discuss the most common pulmonary infections in the immunocompromised patients.

10.3 Bacterial Pneumonia

In patients with bacterial pneumonia, clinical manifestation is the typical one occurring in non-oncologic patients with pneumonia, including acute onset of shaking chills, tachypnea, tachycardia, fever (which occurs in virtually all patients with bacterial pneumonia), and productive cough. However, in the setting of neutropenia, clinical diagnosis is often jeopardized by nontypical clinical findings [11] . Sputum production is seen in less than 60% of neutropenic patients, while in severe neutropenia (neutrophils <1000 cells/mm^3), purulent sputum is present in less than 8% of patients. Routine clinical examination often reveals rales and signs of consolidation. To determinate the cause of pneumonia, blood cultures should be performed routinely; however, the results may be of limited value. Similarly, sputum analysis is often low yield, and the results are difficult to interpret. Identifying the exact cause of pneumonia in patients with cancer often requires fiberoptic bronchoscopy with BAL as sputum is seldom produced. The overall diagnostic yield of BAL in neutropenic and non-neutropenic patients with suspected pneumonia is 49% and 63%, respectively [12]. Chest X-ray findings of bacterial pneumonia in cancer patients are nonspecific. The initial chest radiograph may be normal (mainly in neutropenic patients) or demonstrate lobar consolidation (usually missing in neutropenic patients) and diffuse interstitial infiltrates.

10.4 Pulmonary Aspergillosis

Aspergillus lung disease may present in four district clinical syndromes, i.e., allergic bronchopulmonary aspergillosis, aspergilloma, chronic-necrotizing pulmonary aspergillosis, and invasive aspergillosis. Invasive aspergillosis is a rapidly progressive and potentially fatal infection, which typically occurs in the setting of prolonged neutropenia, treatment with corticosteroids and broad-spectrum antibiotics, and underlying leukemia or lymphoma [13]. The clinical features include tachypnea, fever, dyspnea, nonproductive cough, pleuritic chest pain with or without a friction rub, progressive hypoxemia, and sometimes hemoptysis in patients with prolonged neutropenia or immunosuppression.

Often the only evidence of *Aspergillus* pneumonia is fever with pulmonary infiltrates that do not respond to antibiotics. Chest radiographic features are variable and may show patchy bronchopneumonia, multiple nodular densities, and peripheral, wedged-shaped infiltrates. CT scans may demonstrate the characteristic halo (an area of ground-glass infiltrate surrounding nodular densities) or the air-crescent sign [14].

Definitive diagnosis of invasive aspergillosis requires the demonstration of the organism in tissue. Visualization of the specific fungi using Gomori methenamine silver stain or calcofluor or a positive culture from sputum, needle biopsy, or bronchoalveolar lavage (BAL) confirms the diagnosis of invasive aspergillosis. However, a negative result does not exclude pulmonary aspergillosis.

10.5 *Pneumocystis Jirovecii* Pneumonia

The incidence of *Pneumocystis jirovecii* pneumonia (PJP) (formerly known as *Pneumocystis carinii*) is high among patients with lymphoproliferative malignancies and solid tumors and those receiving long-term corticosteroids or immunomodulation agents.

PJP typically presents as an acute or subacute pulmonary process with fever, nonproductive cough, dyspnea, shortness of breath, and severe hypoxemia.

Physical examination is often unrevealing except for fever and tachypnea. Chest examination is commonly normal; however, diffuse rales, and eventually signs of consolidation, may be present as the disease progresses.

Chest X-ray findings are nonspecific consisting of diffuse alveolar or interstitial infiltrates in 80% of the patients. High-resolution computed tomography (HRCT) represents the gold standard imaging modality in detecting parenchymal abnormalities. The most common HRCT finding is bilateral ground-glass opacities with apical predominance and peripheral sparing. The range of other HRCT findings includes a combination of ground glass and consolidative opacities, linear-reticular opacities, cystic abnormalities, multiple nodules, and parenchymal cavities.

The standard method for diagnosis of PJP relies on the microscopic visualization of *P. jirovecii* organisms in respiratory specimens. Bronchoalveolar lavage (BAL) combined with colorimetric and direct or indirect immunofluorescence stain of

BAL fluid is considered the method of choice with sensitivity and specificity more than 95%. An alternative is an examination of material obtained by induced sputum [15]. However, the sensitivity of this method is more dependent on the experience of the personnel performing the procedure and evaluating the samples, with high variation in the diagnostic sensitivity reported (ranged between 50 and 90%). Most recently highly sensitive molecular techniques, using semi- or fully quantitative polymerase chain reaction (PCR) targeting *P. jirovecii*-specific genes, have been introduced. A meta-analysis of PCR studies has shown a pooled sensitivity of 99% and specificity of 92% [16, 17].

10.6 CMV Pneumonia

CMV pneumonia has a high mortality rate of 15–75%, especially in patients that require mechanical ventilation. Cancer patients in risk are the bone-marrow transplant recipients [18]. Fever, nonproductive cough, and dyspnea are common presenting symptoms. Radiographic patterns in CMV pneumonia include lobar consolidation, focal parenchymal haziness, and bilateral reticulonodular infiltrates. CT may reveal ground-glass opacities, bronchial wall thickening, reticular opacities, and nodules.

The diagnosis of CMV pneumonia depends on isolation of the virus from patients with a positive finding on chest radiograph and appropriate clinical signs [19]. CMV may be isolated from the lung with bronchoalveolar lavage (BAL) or open-lung biopsy. In support of the diagnosis, CMV antigen or inclusions are found with histological examination. CMV isolated from clinical samples in the absence of clinical symptoms may represent viral colonization or subclinical replication disease.

10.6.1 Acute Respiratory Distress Syndrome (ARDS)

ARDS is a clinical syndrome characterized by the acute onset (within 7 days) of severe hypoxemia (defined by a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen [PaO_2/FiO_2] of less than 300 despite the application of PEEP or CPAP $\geq$ 5 cm H_2O) and the presence of bilateral alveolar or interstitial infiltrates that cannot be fully attributed to cardiac failure or fluid overload [20].

Even though the incidence of ARDS in the general population is estimated to be 13–24 cases per 100,000, the exact incidence of ARDS in patients with cancer remains unknown. In oncologic patients with or without neutropenia, ARDS may be related to infectious or noninfectious causes. Causes of primary ARDS include bacterial or opportunistic infections such as invasive pulmonary aspergillosis, *Pneumocystis jirovecii* pneumonia, and fungal and severe viral infections. Secondary ARDS is related to a systemic process such as severe sepsis or septic shock from extrapulmonary bacterial or fungal infections. In a recent retrospective study in up to 90% of ARDS, the causative was an infection, including one-third due to invasive fungal disease [21]. Mortality in oncologic patients with ARDS remains high

Table 10.1 The most common chemotherapeutic and immunosuppressive agents associated with pulmonary toxicity

Bevacizumab
Bleomycin
Busulfan
Cyclophosphamide
Docetaxel
Erlotinib
Everolimus
Gefitinib
Gemcitabine
Interferons
Irinotecan
Methotrexate
Mitomycin C
Nitrosourea
Oxaliplatin
Paclitaxel
Topotecan
Trastuzumab
Vinblastine

although a significant decrease has been recorded over the time. Risk factors for higher mortality include the need for mechanical ventilation, allogeneic bone-marrow transplantation, NIV failure, severe ARDS, and invasive fungal infection. ARDS treatment, although supportive, is considered significant, in both identifying and treating—if possible—the underlying cause [22, 23].

10.6.2 Drug-Induced Toxicity

Pulmonary toxicity of antineoplastic agents, known as drug-induced toxicity (DIT), is a common cause of respiratory failure in oncologic patients and should be included in the differential diagnosis of ARF in patients who are on or have been treated with antineoplastic agents. Table 10.1 shows the most common chemotherapeutic and immunosuppressive agents associated with pulmonary toxicity.

Up to 10% of patients treated with chemotherapy will develop DIT. The extent of lung injury depends on both physical and biological factors including the pharmacokinetic properties of the drug and the drug dose and whether it is used as single therapy or as combination with other chemotherapeutics, the prior exposure to radiation and high oxygen concentration, and the presence of preexisting lung disease [24].

DIT may manifest in a broad variety of pulmonary syndromes, including acute interstitial pneumonitis, nonspecific interstitial pneumonia, ARDS, capillary leak syndrome, hypersensitivity pneumonitis (HP), cryptogenic organizing pneumonia (COP), eosinophilic pneumonia (EP), alveolar hemorrhage, and fibrosis [25]. Symptoms are usually nonspecific including low-grade fever, nonproductive cough,

pleural pain, and shortness of breath and can manifest days or even years after the exposure. Routine clinical examination usually reveals rales and/or a pleural friction rub.

The diagnosis of DIT remains an exclusionary process, in particular when considering common or atypical infections, as well as recurrence of the underlying neoplastic process. Diffuse pulmonary infiltrates are the most common findings in chest X-ray, while high-resolution computed tomography (HRCT) findings are mainly dependent on the type of the drug-induced pulmonary syndromes and usually consist of pleural effusions, ground-glass opacities, traction bronchiectasis, and fibrosis. Pulmonary function tests in the majority of DIT cases may reveal a pattern of restrictive abnormality, with decreased values of DLCO. Bronchoscopy can be helpful in determining the presence of pneumonitis and for the differential diagnosis of lymphangitic carcinomatosis, vasculitis, alveolar hemorrhage, or pneumonia from infectious agents. Most drug-induced immunological reactions, such as HP, COP, and EP, may be excluded if BAL cytology is normal. In regard to the management in many instances, DIT may respond to withdrawal of the offending agent and the judicious application of corticosteroid therapy [26].

10.6.3 Acute Pulmonary Embolism

Venous thromboembolic disease (VTD) may be present both in the form of deep venous thrombosis (DVT) or pulmonary embolism (PE) and is one of the leading causes of morbidity and mortality in oncologic patients [27]. It is now well established that the incidence of VTD is higher in patients with cancer than in the general population and that the malignancies that are most frequently associated with thrombotic complications are those of the pancreas, brain, stomach, lung, and pleura [28].

The most common symptoms are shortness of breath, pleuritic or substernal chest pain, palpitations, cough, hemoptysis, and syncope. Even though hypoxemia is considered a typical finding in acute PE, up to 40% of the patients present with normal arterial oxygen saturation.

As the majority of preventable deaths associated with PE can be ascribed to a missed diagnosis and anticoagulation is associated with a risk of bleeding, it is crucial to exclude or confirm the diagnosis of PE to avoid unnecessary anticoagulation or promptly start such treatment if it is appropriate [29].

In patients with suspected PE, both the diagnostic and therapeutic strategies rely on well-established and extensively validated algorithms, which utilize the clinical stratification of severity (assessment of the risk of death), the clinical probability (pretest probability), the plasma D-dimer measurement, and imaging tests [30].

Stratification of severity is based on patient's clinical status at presentation, with high-risk PE being suspected or confirmed in the presence of shock or persistent arterial hypotension.

For patients with suspected PE, the pretest probability is determined by using validated clinical prediction rules, and two alternative classification schemes may

be utilized, i.e., the three category schemes (low, moderate, or high clinical probability of PE) and the two category schemes (PE likely or unlikely) [31].

Regarding the specific for PE diagnostic tests, computed tomography pulmonary angiography (CTPA) remains the gold standard diagnostic method in patients with suspected PE, with 83 and 98% sensitivity and specificity, respectively. Plasma D-dimer testing has a high negative predictive value for excluding PE, though its positive predictive value remains low [32].

Hereby describe the diagnostic and therapeutic workup should be followed in patients with suspected PE, based on the proposed algorithms [30, 33].

In patients with suspected PE and presented with shock or hypotension, bedside transthoracic echocardiography represents the most useful initial diagnostic approach. An echocardiography evidence of right ventricular dysfunction is sufficient to prompt immediate reperfusion without further testing. Following patient's stabilization, a CTPA should be performed to confirm the diagnosis.

In hemodynamically stable patients, the first step in the diagnostic and therapeutic algorithm is the determination of the pretest probability. In patients with a low/intermediate clinical probability, the first-line test is the measurement of plasma D-dimers, and a negative D-dimer test rules out the diagnosis of PE. In the case of a positive D-dimer test, a CTPA should be performed. In patients with high clinical probability, CTPA represents the first-line test.

10.6.4 Transfusion-Related Acute Lung Injury (TRALI)

Patients with cancer, particularly those with hematologic malignancies and those undergoing a major surgical operation, are subjected to multiple transfusions of fresh frozen plasma, platelets, and packed red blood cells, and thus they are at a risk for developing transfusion-related acute lung injury (TRALI). The diagnosis is mainly based on clinical criteria, and several definitions of TRALI have been introduced in the last decades (Table 10.2). Accordingly, the syndrome is characterized by the presence of hypoxemia and bilateral infiltrates occurring during or within 6 h of a transfusion, in the absence of cardiac failure or volume overload [34].

Although any blood component can cause TRALI, plasma-rich units are more likely to be the culprits. The precise mechanisms of the capillary leak syndrome in TRALI have not been fully elucidated, but currently, two main hypotheses have been proposed. The first hypothesis supports the activation of recipient's neutrophils by passively transporting leukoagglutinating antibodies. The activated neutrophils, in turn, are carried to the lungs and activate the complement leading to endothelial damage, capillary leak, and lung injury [35]. The second hypothesis supports that neutrophils accumulate and are primed in the patient's pulmonary microvasculature as a result of preexisting systemic inflammation. Activation of these neutrophils by lipids or other mediators contributes to endothelial damage in susceptible patients.

Signs and symptoms include tachypnea, frothy pulmonary secretions, hypotension (less commonly hypertension), fever, tachycardia, and cyanosis. Routine

Table 10.2 Current criteria for the diagnosis of TRALI

American-European Consensus Conference Definition of ALI
Acute onset
Bilateral pulmonary infiltrates evident on chest radiograph
Hypoxemia, defined as $PaO_2/FiO_2 \leq 300$
No evidence of left atrial hypertension (i.e., no congestive heart failure or PAOP ≤18, if available)
National Heart, Lung, and Blood Institute Definition of TRALI
No ALI before transfusion
Signs or symptoms of TRALI during or within 6 h of transfusion
In patients with an alternative ALI risk factor, TRALI is still possible
Massive transfusion should not exclude the possibility of TRALI
European Haemovigilance Network Definition of TRALI
Respiratory distress during or within 6 h of transfusion
No signs of circulatory overload
Radiographic evidence of bilateral pulmonary infiltrates

clinical examination reveals diffuse rales. The differential diagnosis should include the transfusion-associated circulatory overload (TACO) and respiratory distress due to anaphylactic transfusion reactions.

The mainstay of treatment for TRALI remains supportive care with supplemental oxygen in all reported cases and mechanical ventilator support in up to two-thirds of patients. If the suspected blood product is still being transfused, it should be discontinued immediately. In contrast to ARDS from other causes, the majority of the patients recover completely, with improvement of hypoxia and resolution of pulmonary infiltrates that occur within 96 h of the transfusion.

10.6.5 Cardiogenic Pulmonary Edema

Cardiogenic pulmonary edema (CPE) should always be included in the differential diagnosis of acute respiratory failure in oncologic patients, in particular when chemotherapy with cardiotoxic drugs has been preceded. The etiology of pulmonary edema is multifactorial and includes increased hydrostatic pressure from high-volume infusions and/or multiple transfusions, cardiotoxic effects of chemotherapy, and renal impairment. Anthracyclines (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin), taxanes (paclitaxel and docetaxel), and alkylating agents (cyclophosphamide, ifosfamide, melphalan) are chemotherapeutics drugs with well-established cardiotoxicity [36]. Even though a universally accepted definition does not exist, the American Society of Echocardiography and the European Association of Cardiovascular Imaging define cancer therapeutic-related cardiac dysfunction as a decrease in the left ventricular ejection fraction (LVEF) of >10%, to a value <53% confirmed by repeat imaging [37].

The diagnostic and therapeutic approach in CPE in cancer patients is the same as in any other patients [38]. In most cases, clinical manifestation consists of

hypoxemia, tachycardia, tachypnea, shortness of breath, orthopnea, and profuse diaphoresis. Hypotension may present and indicate severe LV systolic dysfunction and the possibility of cardiogenic shock. Pink, frothy sputum may be present in patients with severe disease. In regard to routine clinical examination, auscultation of the lungs usually reveals fine, crepitant rales (most commonly heard at the lung bases), but rhonchi or wheezes may also be present, while cardiovascular findings are notable for S_3, accentuation of the pulmonic component of S_2, and jugular venous distention.

Apart from clinical examination, laboratory and imaging tests are of great importance for establishing the diagnosis of CPE. Plasma levels of the B-type natriuretic peptide (BNP) and its amino-terminal fragment N-terminal proBNP (NT-proBNP) have been shown to be useful, in addition to clinical judgment, for the etiological diagnosis in patients with acute onset of dyspnea, and should be measured in all patients with ARF and suspected CPE. BNP has a high negative predictive value, and being lower than the recommended cutoff value of 100 pg/mL in patients with suspected CPE makes the diagnosis unlikely [39]. A bedside echocardiogram in a patient with CPE remains the cornerstone in determining the etiology of pulmonary edema. Echocardiography can be used to evaluate LV systolic and diastolic function, as well as valvular function, and to assess for pericardial disease.

Chest X-ray may be proved as a useful diagnostic test for CPE. Pulmonary venous congestion, pleural effusion (particularly bilateral and symmetrical), interstitial or alveolar edema, and cardiomegaly are the most specific findings for CPE. However, it should mention that in up to 20% of patients, chest X-ray maybe nearly normal.

More recently, lung ultrasound (LUS) has been introduced as a simple, non-invasive diagnostic method in patients with suspected CPE. In cases in which there is a moderate to high pretest probability of acute CPE, LUS can be useful in strengthening a working diagnosis. Findings of B-lines on ultrasonography have been reported to have a sensitivity of 94.1% and a specificity of 92.4% for acute CPE [40].

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Acute Myeloid Leukemia and Acute Respiratory Failure: Early Diagnosis and a Practical Approach

11

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Acute leukemia is a group of diseases with high morbidity and mortality, characterized by uncontrolled proliferation of immature lymphoid and myeloid cell lineages in the bone marrow as a result of neoplastic transformation. Acute myeloid leukemia (AML) is the most commonly seen acute leukemia in adulthood (85%) with increasing incidence (3–5: 100,000) with advancing age [1]. The mean age at diagnosis is 60 years in AML and 5-year survival varies from 15 to 30%, with incidence of 8.5: 100,000 in all age groups. In the last few decades, the prognosis has been relatively improved due to advances in supportive care [2].

Acute respiratory failure (ARF) is a rarely seen complication in AML, and mortality can reach up to ≥50% in patients undergoing respiratory support. ARF is the most important and common (50–60%) cause of admission to intensive care unit (ICU) in AML [3, 4]). Conditions such as pneumonia, hyperleukocytosis and leukostasis, pulmonary hemorrhage, and all-trans-retinoic acid (ATRA) syndrome that are associated with pulmonary infiltration are known to constitute a risk for respiratory failure. Male gender, acute promyelocytic leukemia, and increased creatinine levels are predictors of respiratory support [5, 6]. In most cases, respiratory failure is multifactorial and it is difficult to link respiratory failure to a single cause (Table 11.1).

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Table 11.1 Causes of acute respiratory failure in acute myeloid leukemia

Rapidly progressing acute respiratory failure	Pulmonary leukostasis
	Pulmonary leukemic infiltrates
	Leukemic cell lysis pneumopathy
Most common	Pulmonary infections
	Hemorrhage and thrombosis
	ATRA syndrome
	Pulmonary edema

11.1 Causes of Acute Respiratory Failure in Acute Myeloid Leukemia

11.1.1 Pulmonary Infections

Pneumonia is a commonly seen complication that can cause significant mortality and morbidity in patients with acute leukemia. Pulmonary events due to infection are seen in 60% of cases [7].

Several risk factors, particularly neutropenia with neutrophil count less than 0.1×10^9/L lasting >10 days, increase susceptibility to infection in AML patients. In hematological malignancies, febrile neutropenic episodes can occur in 80% during chemotherapy [8]. A diagnosis of febrile neutropenia requires absolute neutrophil count < 500/mm^3 and body temperature of 38.3 °C in a single measurement or 38.0 °C in two measurements within 1 h. It prompts immediate treatment since mortality can be up to 70%. Mortality can be decreased by initiating wide-spectrum antibiotics within the first 60 min. The risk for mortality has been found to increase by 8% for each delay of 1 h in starting antibiotic therapy. Mortality rate related to febrile neutropenia is 14% in patients with leukemia despite appropriate treatment [9, 10].

Clinical and radiological findings can be vague due to impaired inflammatory response; therefore it is difficult to determine the precise incidence of pneumonia [11].

Pneumonias are still associated with high mortality rates (20–69%) despite novel therapeutic and prophylactic approaches in recent years [12, 13]. The risk for mortality can increase sevenfold in patients not receiving appropriate treatment. Advanced age, diffuse infiltration, and prolonged neutropenia are associated with a worse prognosis while young age and remission are positive prognostic predictors. In neutropenia episodes of >3 weeks, there is an increased risk of bacterial or fungal infections [14].

In pneumonia, there may be nonspecific findings. Routine chest radiographs may be used as a screening test in immunocompromised patients with respiratory symptoms, but CT scan allows earlier diagnosis [15]. In routine practice, blood cultures are used to identify the etiological agent, although this is of limited value. Likewise, sputum analysis often yields difficult to interpret results. Thus, microscopic examination of bronchoalveolar lavage (BAL) fluid sampled via bronchoscopy is the standard test to identify the cause of pulmonary infection. This test is minimally invasive, relatively safe, and reproducible, allowing rapid diagnosis in most cases [16].

O_2 supplementation, peripheral venous catheterization, monitorization, empirical antibiotic treatment, and respiratory support with either NIMV or IMV based on patient status are important in the treatment of patients with pulmonary infection.

11.1.2 Pulmonary Leukostasis

Hyperleukocytosis is defined as white blood cell (WBC) count > 100,000/μL in peripheral blood. Leukostasis, tumor lysis syndrome, and disseminated intravascular coagulation are serious problems observed in hyperleukocytosis [17].

Leukostasis is characterized by the occupation of vascular lumen and increased blood viscosity due to intravascular accumulation of blast cells, resulting in vascular stasis. It is present in 10–20% of patients with newly diagnosed AML and more commonly encountered in monocytic (AML-M5) leukemia, myelomonocytic leukemia (AML-M4), or microgranular variant of acute promyelocytic leukemia (AML-M3) [18]. Leukostasis is a medical emergency, which if left untreated, has 1-week mortality of approximately 20–40%. The early high mortality rate is due to pulmonary, renal, and central nervous system complications. Respiratory failure and neurological involvement are clinical conditions with poor prognosis [19]. The following factors play a role in the pathophysiology:

- Microcirculatory hyperviscosity, vascular impedance (stasis), microvascular invasion
- Leukocyte aggregation and leukocyte microthrombi
- Toxic products released from blast cells
- Damage and activation of endothelial cells
- Interaction between blast cells and endothelial cells
- Selectins, VCAM-1, and ICAM-1
- Complement activation
- Oxygen steal and resultant hypoxia

In hyperleukocytosis, pulmonary signs and symptoms include dyspnea and hypoxia with or without diffuse interstitial or alveolar infiltrates on imaging studies. Arterial pO_2 can be misleadingly low in patients with hyperleukocytosis due to utilization of oxygen by WBCs in the test tube. Thus, pulse oximetry can provide a more accurate assessment of oxygen saturation in such patients. However, specific clinical, biological, and radiological features are lacking in hyperleukocytosis [20].

The diagnosis of leukostasis is made empirically in patients presenting with respiratory and neurological symptoms in association with acute leukemia. However, it is difficult to distinguish clinical and radiological manifestations of leukostasis from those of common infections and hemorrhagic complications seen in acute leukemia.

Leukostasis with a mortality rate up to 40% comprises a medical emergency in which management relies on principles similar to hyperleukocytosis. Every effort should be made to decrease WBC count to <100,000/μL and to stabilize the patient.

Leukapheresis, low-dose chemotherapy, or hydroxyurea can be helpful to achieve cytoreduction. Leukapheresis is a method of apheresis proven to be beneficial in cases of WBC > 100,000/μL. L-Leukapheresis should be used in conjunction with cytoreductive agents [21]. There are studies in literature on successful outcomes with pulmonary radiotherapy, but this has not been introduced into routine practice [22]. Supportive care including hydration, transfusion, and oxygen supplementation should be provided to prevent complications.

Supportive care, cytoreductive therapies, and leukapheresis can decrease early mortality (within first week) to <2%. However, there is no clear data regarding long-term outcomes.

11.1.3 Pulmonary Leukemic Infiltrates

Pulmonary leukemic infiltrates (PLI) is an extremely rare complication seen in the course of acute leukemia. PLI in patients with or without hyperleukocytosis suggests that blast type and blast affinity for the pulmonary endothelium may be the cause of pulmonary injury. Infiltrates are typically localized around lymphatic routes along bronchovascular bundles, interlobular septa, and pleural interstitial tissue [23].

The diagnosis of PLI as the cause of ARF relies on pathological or cytological studies after exclusion of other causes. Diagnosis may be made via retrieval of leukemic cells by BAL, particularly in cases of extremely low platelet counts not suitable for biopsy. Leukemic infiltration is considered if blast count in BAL is higher than peripheral blood by 40% in conditions accompanied by pulmonary hemorrhage. PLI is common in AML-M4 and AML-M5 [24].

PLI can have a nonspecific appearance on radiography, and on high-resolution computed tomography (HRCT), thickening of the interlobular septa and bronchovascular bundle is the most notable finding but not specific for PLI [25].

PLI is rarely symptomatic but, if so, generally manifests with nonspecific symptoms such as fever, dyspnea, cough, hemoptysis, and radiographic infiltrates, all of which suggest pneumonia. However, cultures will remain negative and infiltrates will resolve with chemotherapy. Occasionally, PLI may lead to a life-threatening condition, namely, acute respiratory distress syndrome.

11.1.4 Leukemic Cell Lysis Pneumopathy

Leukemic cell lysis pneumopathy (LCLP) is a rare condition that may cause ARF and is characterized by progressive respiratory distress immediately or shortly after chemotherapy (within 4 days of induction) and diffuse alveolar damage [26]. LCLP may also develop in patients with normal baseline pulmonary function. Although generally seen in case of hyperleukocytosis, it may also occur with WBC count < 50,000/μL. Vascular occlusion and tissue hypoxia and local tissue injury caused by oxygen consumption of blast cells are involved in the pathogenesis of

LCLP [27]. Light microscopy findings are similar to those in other hyperleukocytic syndromes:

- Diffuse alveolar damage present in the proliferative phase.
- Endothelial cell hyperplasia, interstitial edema, interstitial lymphocytes, and plasma cells.
- Hyperplasia in Type 1 pneumocytes but no dysplasia.
- Sloughed epithelial cells, macrophages, and varying number of fibroblasts in organizing intra-alveolar exudates.
- The number of leukemic blast variation in vessels, interstitium, and intra-alveolar exudates.
- Blasts and mature granulocytes show signs of degeneration with nuclear pyknosis and cytoplasmic vacuolation.

In LCLP, the diagnosis is made by resolution of respiratory problems by reducing the number of cells with ongoing therapy [27].

Although the central nervous system and lungs are the most frequent areas of vascular occlusion, the extremities, kidneys, heart, and penis can also be involved. Intracerebral stasis can lead to a wide spectrum of clinical presentations, and intracranial bleeding can also be seen secondary to coagulopathy [28].

Pulmonary leukemic infiltrates and LCLP can be seen concurrently, and the need for mechanical ventilation is high in both conditions. Survival rate has been found to be about 50% with aggressive respiratory support, ICU admission, and prompt initiation and continuation of chemotherapy. Dexamethasone is recommended with chemotherapy based on potential preventive effects against LCLP development by reducing the severity of pulmonary involvement and decreasing cytokine and oxidant release [17].

11.2 Treatment in Leukostasis, PLI and LCLP

Leukostasis, PLI, and LCLP lead to rapidly progressing acute respiratory failure. The clinical challenge is to rapidly identify the underlying mechanisms and to decide on the best treatment option for patients developing ARF during the early course of AML. Several mechanisms may be involved in ARF and may occur concomitantly with leukostasis progressing to PLI or LCLP emerging in association to either entity after initiation of induction chemotherapy [26]. It has been suggested that leukapheresis and hydroxyurea improve leukostasis-related organ dysfunction, although the use remains controversial. Recently, steroid therapy has been reported to improve respiratory function and mortality in patients with high-risk AML-M5 [17].

11.2.1 ATRA Syndrome

ATRA syndrome is a complication seen during therapy with differentiation-inducing agents in acute promyelocytic leukemia. The incidence is 2–27% in cases treated

with all-trans-retinoic acid (ATRA) and 7–31% in those treated with arsenic trioxide (ATO), but it is also seen in untreated patients or after other cytotoxic therapies. Early recognition and aggressive management are essential as it can occur within 7–14 days after initiation of treatment [29].

Although the pathogenesis of ATRA syndrome is not fully understood, excessive inflammatory response is assumed to have a significant role. Increased cytokine release from leukemic promyelocytes after treatment with ATRA or ATO is responsible for the majority of effects [30].

In ATRA syndrome, respiratory distress negatively affects the clinical picture, and mechanical ventilation may be needed in 25–30% of patients, more frequently in cases with elevated WBC count (>5 × 10 L) [31].

Dexamethasone is the backbone of treatment of ATRA syndrome, providing a reduction in pulmonary infiltrations. Studies have indicated that early use of dexamethasone decreases mortality from 30 to 5%. Steroid administration allows neutralization of increased adhesion molecules in mature promyelocytes and inhibition of chemokine release. Although the preemptive use of dexamethasone is a part of standard therapy in the presence of early clinical signs, prophylactic use remains controversial [32].

11.2.2 Hemorrhage and Thrombosis

Patients with acute leukemia are at high risk of hemorrhage and thrombosis.

11.3 Pulmonary Hemorrhage

Pulmonary hemorrhage is the most common noninfectious complication in acute leukemia. In a study of AML patients, the rate of pulmonary hemorrhage was found to be 1% at presentation and this may increase up to 9.9% after induction therapy [33]. After consolidation therapy, pulmonary hemorrhage is rarer and mainly develops secondary to myelosuppression related to chemotherapy and autoimmune conditions that may occur during treatment.

Disseminated intravascular coagulation, thrombocytopenia, leukostasis, pulmonary leukemic involvement, and comorbid infections are associated with pulmonary hemorrhage. Viral (CMV, herpes simplex virus), fungal (*Aspergillus*), and bacterial (gram-negative microorganisms) infections are particularly important.

Clinically, patients with pulmonary hemorrhage present with progressive dyspnea with sudden onset, nonproductive cough, fever, and hypoxia [34]. However, hemoptysis is uncommon and clinical signs may be mild despite rapidly progressing imaging abnormalities. Imaging findings are nonspecific, and radiographic changes rapidly progress to diffuse ground-glass opacities and patchy consolidation, which are also the most common findings on CT scan, and reticulation or a crazy-paving appearance is often observed. In pulmonary hemorrhage, the diagnosis is generally based on abnormally high blood content (macrophages with hemosiderin content > 20%) in fluid samples obtained via BAL in the absence of signs of infection.

11.4 Pulmonary Thrombosis

Thrombosis of large vessels is a rarer complication, although recent data indicate that it may represent an important problem at the onset of AML. In a recent, large, retrospective study, the rate of venous thromboembolic events was 2.09% at the onset of disease and the rate of thrombosis was 2.3% in induction in patients with AML (excluding APL) [35].

In AML, clotting system disorders underlying disseminated intravascular coagulation are observed, including hypofibrinogenemia, elevated fibrin degradation products, and prolonged prothrombin and thrombin times. These laboratory parameters worsen with the initiation of cytotoxic chemotherapy, resulting in severe hemorrhagic complications. Novel laboratory tests for markers of hypercoagulation have revealed that thrombin generation is a fixed finding in acute leukemia. The detection of D-dimer, the lysis product of cross-linked fibrin that demonstrates hyperfibrinolysis occurring in response to activation of clotting in leukemia, is an important finding [36].

In coagulopathy observed in acute leukemia, major determinants include (1) factors associated with leukemic cells such as expression of procoagulant, fibrinolytic, and proteolytic properties and secretion of inflammatory cytokines; (2) cytotoxic therapy; and (3) concomitant infectious complications [37].

11.5 Treatment in Hemorrhage and Thrombosis

Prophylactic platelet transfusions are considered an integral part of supportive care in patients with acute leukemia. This has resulted in a considerable decrease in bleeding complications and has prolonged survival, allowing intensification of therapy. Historically, the threshold has been platelet count $< 20 \times 10^9$/L, although clinical settings can dictate changes in indications for prophylactic platelet transfusion. These recommendations are not valid in patients with APL who still have a higher bleeding risk and need platelet transfusion in the retinoic acid era. In patients with APL, the current recommendation is to use platelet transfusion to maintain platelet count $> 20 \times 10^9$/L in those without active bleeding and $>50 \times 10^9$/L in those with active bleeding.

When coagulopathy complicates acute leukemia, the role of heparin therapy is still unclear with no proven benefit in prospective, randomized trials. Therefore, evidence is insufficient to recommend the routine use of heparin in this condition.

11.5.1 Respiratory Support

Respiratory load can be decreased by providing invasive or noninvasive respiratory support in AML patients with acute respiratory distress. Noninvasive ventilation (NIV) has gained popularity as despite advantages, IMV is associated with serious complications and prolonged hospitalization. Primary contraindications for NIV include lack of cooperation, head or facial trauma, organ failure, cardiac or pulmonary

arrest, and high risk for aspiration. Although NIV has a low mortality rate, it is associated with high mortality in cases of failure. Factors predicting poor prognosis include the development of organ failure, vasopressor need, progression of underlying disease, and advanced age. However, there are limited data on factors predicting recovery [38].

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Cardiac Disease in Hematologic Cancer and Acute Respiratory Failure-General Considerations

12

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12.1 Cardiac Complications of Hematologic Cancer

The number of cancer survivors in the United States has exceeded 12 million and is increasing. After secondary malignancies, cardiovascular disease is the leading cause of late morbidity and death among cancer survivors [1]. Due to an aging population in developed countries, it is not uncommon for a patient to have both cancer and cardiovascular disease.

These two diseases have common risk factors other than age. Patients who undergo treatment of a hematological malignancy or any malignancy are at a substantial risk for cardiovascular deterioration. This association was not recognized decades ago simply due to the fact that patients with a metastatic disease usually did not live long enough to manifest cardiovascular complications. However, with the substantial progress that has been made in terms of earlier diagnosis, therapy, and survival along with targeted treatments with combination therapies, cardiotoxicity in hematological malignancies has become a pivotal issue [2].

Cardiac complications could be a result of the cardiotoxicity of chemotherapeutic agents; due to radiation-induced myocardial, coronary, valvular, and pericardial injury; or due to cardiac infiltration from metastatic process. In the first part of this chapter, we will discuss cardiac complications associated with hematologic malignancy.

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12.2 Cardiotoxicity Related to Chemotherapy

Patients exposed to chemotherapeutic agents known to predispose to heart failure—like anthracyclines, trastuzumab, sunitinib, and sorafenib—should be screened for the stage of their heart failure on the basis of the American College of Cardiology/American Heart Association (ACC/AHA) guidelines [3].

The National Cancer Institute defines cardiotoxicity as "toxicity that affects the heart." This broad definition lacks any clear clinical parameters or criteria to quantify toxicity. One of the most encompassing definitions of cardiotoxicity has been developed by the cardiac review and evaluation committee supervising trastuzumab clinical trials.

They define drug-associated cardiotoxicity as one or more of the following:

1. Cardiomyopathy in terms of a reduction in left ventricular ejection fraction (LVEF), either global or more severe in the septum
2. Symptoms associated with heart failure
3. Signs associated with heart failure, such as S3 gallop, tachycardia, or both
4. Reduction in LVEF from baseline that is in the range of less than or equal to 5% to less than 55% with accompanying signs or symptoms of heart failure or a reduction in LVEF in the range of equal to or greater than 10% to less than 55%, without accompanying signs or symptoms [2]

Cardiotoxicity can develop in a subacute, acute, or chronic manner. In order to be characterized by acute or subacute, the manifestations need to occur at any time while initiating chemotherapy and up to 2 weeks after termination. Examples of acute or subacute cardiotoxicity are abnormalities in ventricular repolarization, electrocardiographic changes, supraventricular and ventricular arrhythmias, acute coronary syndrome, pericarditis, or myocarditis. Chronic cardiotoxicity is differentiated into two different subtypes. The first subtype occurs within 1 year after termination of chemotherapy, and the second is more than 1 year after completing chemotherapy. Chronic cardiotoxicity most closely resembles symptoms consistent with congestive heart failure [2].

12.3 Common Anticancer Treatments and Their Cardiac Effect

Anthracyclines are effective anticancer drugs used in the treatment of many hematological malignancies. In patients with lymphoma, anthracyclines have been a mainstay in treatment regimens for over 40 years. These drugs unfortunately are notorious for a having a propensity to cause severe cardiac impairment with development of cardiomyopathy and heart failure [4].

Anthracyclines are a class of drug composed of aglycone, which contains a tetracyclic ring structure and a sugar called daunosamine. The molecular mechanism of how anthracyclines induce cardiotoxicity is still not entirely understood. The

predominant hypothesized molecular mechanism was related to an overproduction of reactive oxygen species; however, more recently the inhibition of topoisomerase II activity now is being considered as playing a role. Topoisomerase is an enzyme that alters the supercoiled form of DNA, and in humans there are two types of topoisomerases. The type present in cardiac myocytes which are quiescent cells is Topo IIB. The inhibition of Topo IIB leads to instability of the double-stranded DNA in the form of breaks which then causes a change in the formation of MRNA molecules produced [4]. Additionally, there is a loss of myofibrils due to increase in proteolytic enzyme activity along with a decreased synthesis of proteins needed to produce sarcomeres. In addition, anthracyclines induce cardiotoxicity via dysfunction of the mitochondria. In particular anthracyclines increase the amount of calcium in the mitochondria leading to irreversible damage to the mitochondrial membrane. In addition, it alters the ability of the mitochondria to produce energy by inducing insult to mitochondrial DNA [4].

The clinical presentation of anthracycline-induced cardiotoxicity varies depending upon if it is acute, subacute, or chronic in nature. The acute form normally presents after an induction of a high dose of the anthracycline, and the subacute will occur a few weeks after administration. Acute form will have signs of myocardial injury in the form of elevated troponin and an acute drop in ejection fraction which is reversible [5]. Both forms share many features in common regarding their clinical presentation. Both can present with ECG changes that can be transient in nature or progress to arrhythmias [4]. The most dreaded complication of their cardiotoxicity however remains left ventricular dysfunction leading clinically to heart failure [6]. Chronic cardiotoxicity is unlike the acute forms because it is dose dependent. The most typical presentation is symptoms of heart failure attributed to a decrease in the left ventricular ejection fraction. The chronic form is unfortunately irreversible [5].

Cyclophosphamide belongs to the antineoplastic class of drugs termed alkylating agents. Cyclophosphamide antineoplastic properties are due to its ability to cause cross-linking of guanine bases in DNA. The disruption of the cross-linking pattern causes an instability of the DNA double helix, thus rendering it incapable of replication [5]. Cyclophosphamide is a pillar in the treatment of hematologic malignancies, most importantly in the treatment of non-Hodgkin's lymphoma. The cardiotoxicity seen with cyclophosphamide presents clinically heterogeneously. It can range from an incidental finding of a pericardial effusion to irreversible heart failure. The cardiovascular complications seen with cyclophosphamide are dose dependent usually with high-dose protocols (>150 mg/kg and 1.5 g/m^2/day) and are seen within 1–10 days after the first dose of the drug. The mechanism of cyclophosphamide-induced cardiotoxicity is still not precisely known; however, it is hypothesized that the drug causes endothelial injury directly leading to extravasation of toxic metabolites. Furthermore, ischemic injury to cardiac myocytes may be due to intracapillary microemboli [5, 7] and through oxidative stress and disruption of the inner mitochondrial membrane.

Cisplatin is an alkylating agent used to treat various types of malignancies including hematologic cancer. It is a platinum-based chemotherapy and was the first of its kind. The cardiotoxicity mechanism is thought to be secondary to its vascular toxicity. In a review of patients with urothelial transitional cell carcinoma receiving

cisplatin, 12.9% of patients had vascular thromboembolic events [5]. A study revealed that survivors of testicular cancer who were treated with cisplatin-based therapy had an increased risk for myocardial infarction. Additionally, cisplatin levels were still measurable in the blood for as long as 20 years. There is a cumulative effect of cisplatin-induced injury on endothelial cells. Biomarkers for endothelial injury can be identified including von Willebrand factor, tissue-type plasminogen activator, and plasminogen activator inhibitor type 1. These markers are higher in patients with cisplatin exposure than in controls.

Bleomycin is widely used in the combination treatments for both Hodgkin's and non-Hodgkin's lymphoma. It has been associated with pericarditis and coronary artery disease. Mucocutaneous toxicity is typical as a form of bleomycin toxicity furthermore serosal inflammation presenting as pleuropericarditis. Bleomycin causes toxic and inflammatory effects on endothelial cells possibly leading to ischemic cardiomyopathy. Furthermore, acute coronary syndrome has been reported to occur after one dose of bleomycin [7].

12.4 Radiation-Related Cardiac Injury

Cardiovascular disease is now the most common nonmalignant cause of death in radiation-treated cancer survivors, most often occurring decades after treatment. Adjuvant radiation therapy in the management of hematology malignancies including Hodgkin's disease, early stage breast cancer, and to a lesser extent other thoracic malignancies has led to a significant improvement in disease-specific survival. The relative risk of coronary artery disease, congestive heart failure, valvular heart disease, pericardial disease, conduction abnormalities, and sudden cardiac death is particularly increased [8].

Radiation exposure to the heart occurs incidentally during treatment of adjacent thoracic, chest wall, or breast neoplasms and as a result may induce damage to the pericardium, myocardium, cardiac valve leaflets, and coronary arteries. The risk of radiation-induced heart disease is thought to be dose dependent, more common with whole-heart radiation exposure above 30 Gy, but doses <5 Gy have also been associated with increased risk of ischemic disease, pericardial disease, and valvular disease.

Cardiac lesions after mediastinal irradiation for Hodgkin's disease are evaluated in patients without risk factors for CAD; it was noted that there is only a low risk of ischemic cardiac events after modern mediastinal radiation for Hodgkin's disease. There is a high incidence of sclerosis of the mitral and/or the aortic valves developing into clinically important lesions in few patients [9].

12.5 Cardiac Complications Due to Infiltration by Malignant Cells

Cardiac involvement in postmortem studies in patients with Hodgkin's and non-Hodgkin's lymphoma has been shown to be as high as 16 and 18% and is normally a late manifestation of the disease process. The vast majority of cardiac malignancies are due to metastatic disease from sites such as the lung, esophagus, and breast as well as lymphoma, leukemia, and melanoma [10].

The clinical presentation and symptomatology of lymphomatous cardiac involvement is quite varied and probably is the likely cause as to why these neoplasms go undetected until autopsy. The presentation of cardiac metastasis is determined by several factors such as the neoplasm size, its location, its speed of growth, its degree of invasion, and its friability. The mechanism of cardiac dysfunction could be related to obstruction of blood flow or secondary to a valvular dysfunction. There might be metastasis and invasion to the conduction pathway presenting as an arrhythmia or involvement of the pericardium presenting as a pericardial effusion or in more severe cases as tamponade. Clinically the patient may complain of dyspnea and chest pain or present with hypotension [10].

A diagnosis of lymphomatous cardiac involvement is a difficult one and requires a high level of clinical suspicion because of the disease processes and variable clinical presentations. Multiple imaging techniques are utilized in aiding the diagnosis such as echocardiography, cardiac CT scan, cardiac MRI, and fluorodeoxyglucose positron emission tomography [3].

The correct pathological diagnosis of cardiac masses in the past required invasive procedure such as a thoracotomy; however, advances in technology techniques such as TEE-guided biopsy, endomyocardial biopsy, or percutaneous intracardiac biopsy with combined fluoroscopy and TEE or pericardial fluid sampling [10]. Due to the rarity of the disease process, there are no definitive guidelines in managing these patients.

12.6 Workup for Cardiac Dysfunction and Resulting Respiratory Failure

Start workup with basic laboratory profiles including CBC, complete metabolic panel, cardiac biomarkers, and arterial blood gas analysis. Electrocardiography and rhythm monitoring may be included in the workup.

Advanced echocardiographic techniques may be useful for earlier detection of cardiac toxicity. Diastolic dysfunction assessed by spectral Doppler echocardiography of mitral valve inflow patterns may be a sensitive method for early detection of cardiac dysfunction. Cardiac MR, to evaluate systolic and diastolic dysfunction, is known to differentiate transient and permanent myocardial injury in various systemic and inflammatory diseases and thus may be able to visualize myocardial tissue changes after chemotherapy before any measurable change in LVEF. MUGA scan has been utilized as well.

Imaging with CXR or CT scan for evaluation of pulmonary abnormality may be required. To evaluate possible infectious cause of respiratory failure, appropriate culture including blood and sputum culture needs to be done. Bronchoscopy evaluation with BAL may be indicated in some instances.

12.7 Acute Respiratory Failure in Hematologic Malignancy

Acute respiratory failure (ARF) is a common cause of morbidity and mortality in patients with hematologic malignancy. This could happen as a result of cardiac failure resulting from cardiac involvement by cancer or related cardiotoxic side effects from treatment or pulmonary involvement from cancer infiltration or an infectious process.

In a prospective multicenter analysis of 380 patients with a hematologic malignancy that included lymphoid (n = 162, 42.6%) or myeloid (n = 141, 37.1%) diseases, the principal causes for acute respiratory failure are pulmonary infections (n = 161, 43%), malignant infiltration (n = 65, 17%), or cardiac pulmonary edema (n = 40, 10%) [11]. In this section we will review the ventilatory approach that included both invasive and noninvasive approaches.

12.8 Ventilatory Approach in Hematologic Malignancy Patients with Acute Respiratory Failure (ARF)

Acute respiratory failure (ARF) is commonly encountered in patients with malignancy in general and in hematologic patients in particular. ARF can happen as a manifestation of the malignant disease process, treatment toxicity, and congestive heart failure or as a consequence of opportunistic infection. Acute respiratory events occur in 20% of patients with a hematologic malignancy and may reach up to 40% in neutropenic and bone marrow transplant recipients [12].

Despite major advances that have been achieved in the care of the critically ill hematological and bone marrow transplant patients over the last two decades, acute respiratory failure requiring intubation and invasive mechanical ventilation still has an associated mortality of approximately 50% [13].

Patients with ARF are generally managed with both invasive with endotracheal intubation and noninvasive means of oxygen therapy depending on their clinical indications. Selection of patients who will qualify for noninvasive ventilation is carefully tailored to individual patients as the use of noninvasive ventilation may have a dual effect: on one side its application results in a significant decrease in mortality, but the failure after a noninvasive ventilation trial increases the risk of death [14]. Noninvasive mechanical ventilation (NIV) by face and nasal mask or helmet is an excellent technique to treat acute episodes in chronic respiratory failure and avoid the need of intubation. In specific clinical conditions, the use of invasive ventilation, both in hypoxemic with and without hypercapnia, is useful, as standard O_2 therapy often shows little benefit in improving the patient's clinical condition. In this case, traditional mechanical ventilation after tracheal intubation is usually the first choice, even though it often has disadvantages which conflict with the clinical condition of patients.

Non-Invasive Mechanical Ventilation (NIV): Noninvasive ventilation is a viable alternative in hematologic malignancy patients with ARF requiring ventilator support. It is preferable and widely utilized in these special set of patients for many reasons; on one hand they exhibit relevant psychological distress due to their primary disease and often refuse to undergo endotracheal intubation and mechanical ventilation. These patients fear spending their final days attached to a machine, deprived of their autonomy in decision-making and communicating with their relatives. Due to the above factors, most patients prefer NIV as an alternative to standard invasive mechanical ventilation, which allowed them to keep their autonomy, gave less anxiety, and required less sedation. Complications related to endotracheal intubation in immunocompromised and thrombocytopenic patients are greatly increased.

There is a high probability of complications related to invasive mechanical ventilator strategy including infections and multiple-organ failure, events that are already common in patients with immunodeficiency states, and exposure to chemotherapy. Trauma to the pharynx and larynx, at the point of contact between the tracheal mucosa and the tube or its cuff; edema; ulceration; or hemorrhage with potential stenosis can complicate the course. The use of noninvasive ventilation reduces the risk of hemorrhage in those thrombocytopenic patients. Nosocomial infections including sinusitis and ventilator-associated events including ventilator-associated pneumonia are very high as endotracheal tube is one of the most important predisposing factors [15].

In a randomized clinical trial on immunocompromised patients, including hematological patients with hypoxemia and diffuse pulmonary infiltrates, therapy with noninvasive ventilation and supportive oxygen reduced rates of intubation and showed better survival in the NIV group, hence providing a strong rationale for the use of NIV in patients with hematologic malignancy presenting with ARF [16].

In hematological patients the use of continuous positive airway pressure (CPAP) delivered by the helmet interface, with standard supplemental oxygen in acute hypoxemic respiratory failure in earlier, or less severe, phase of ARF with PaO_2/FiO_2 levels between 200 and 300 instead of below 200, the intubation rate in the CPAP-treated arm was impressive and is accompanied by a marked decrease of in-hospital mortality [17]. At the same time, and similarly to most of the earlier observational data, patients referred to the intensive care unit with more advanced signs of ARF have fared worse: here NIV failed in half of the cases, and mortality was 90% [18].

Hence, the early use of CPAP on the hematological ward in patients with early changes in respiratory variables prevents evolution to acute lung injury requiring mechanical ventilation and ICU admission.

Invasive mechanical ventilation (IMV): Acute respiratory failure is one of the most prevalent organ failures [13], being the cause of ICU admission in up to 40% [19]. Although mechanical ventilation is the main supportive therapy for those with severe gas-exchange impairment, the need for intubation has been consistently described as one of the most adverse factors in these patients [12, 20].

Though noninvasive ventilation is a preferred first-line ventilator support that works favorably in a certain group of patients with hematologic malignancy presenting with ARF, some patients eventually end up requiring mechanical ventilation. It was noted that subjects receiving NIV were at high risk of invasive mechanical ventilation because 37.6% of them were eventually intubated [21]. One possible explanation for this significant high risk could be due to the fact that a trial of NIV and subsequent NIV failure may delay the onset of optimal respiratory support in these patients. In one prospective, multicenter, observational study, the risk of NIV failure in hematology cancer patients can reach up to 60%. In this study it was noted that those patients with a diagnosis of congestive heart failure and the initial use of NIV significantly improved survival, whereas APACHE II score, allogeneic transplantation, and NIV failure increased the risk of death [14].

In cancer patients with acute respiratory failure, the extent of pulmonary infiltration on chest x-ray and hemodynamic failure at ICU admission are risk factors for requiring invasive mechanical ventilation. Increased severity of the disease, measured by using scores such as SAPS II or by the number of organ failures, has been associated with increased intubation rates [22, 23].

The in-hospital mortality rate in hematologic patients who develop ARF remains high, and the reluctance to intubate and start treatment with invasive MV in this population is unjustified, especially when bacteremia has precipitated ICU admission [18].

Hematologic cancer patients with cardiac failure may have a fast response to therapy, such as diuretics and inotropes for cardiogenic pulmonary edema or directed antibiotic therapy for a documented respiratory infection; they may benefit from noninvasive mechanical ventilation for respiratory support. However, in other causes of lung injury, NIV may not support the ventilatory function for a prolonged time, thus increasing the risk of failure and will require intubation for invasive ventilation.

Decision on the use of invasive and noninvasive ventilation is individualized based on the clinical presentation and considering risk benefit of each modality. Appropriateness of invasive ventilatory support may also be an issue requiring advanced discussion with patients and their families. In the past 10–15 years, the role of noninvasive ventilation has expanded in an attempt to minimize the complications inherent with invasive ventilation strategy.

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Cardiac Diseases in Hematology Cancer and Acute Respiratory Failure: Ventilatory Approach

13

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Abbreviation

ACPE	Acute cardiogenic pulmonary edema
ARF	Acute respiratory failure
CCMP	Chemotherapy-induced cardiomyopathy
CHF	Congestive heart failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPE	Cardiogenic pulmonary edema
EPAP	Expiratory positive airway pressure
ICU	Intensive care unit
IPAP	Inspiratory positive airway pressure
LV	Left ventricular
LVD	Left ventricular dysfunction
MI	Myocardial infarction
NIV	Noninvasive mechanical ventilation
PEEP	Positive end-expiratory pressure

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13.1 Introduction

In the last two decades, the survival of patients with hematological malignancies has improved because of new chemotherapeutic regimens, bone marrow transplantation, peripheral stem cell rescue, and better supportive measures [1]. Hematological neoplasms require aggressive treatments, implying a high risk of adverse events, including severe drug toxicity or the consequences of aplasia. The cardiotoxicity of anticancer agents depends on many factors such as the molecular site of action, the immediate and cumulative dose, the method of administration, and the presence of any underlying cardiac condition. Whereas anthracyclines remain the most common cause of chemotherapy-induced cardiomyopathy (CCMP), recently developed targeted therapies can also cause cardiac dysfunction [2]. From 15 to 20% of the hematological patients require supportive therapy in the ICU and acute respiratory failure (ARF) remains the first reason for admission to ICU in patient with hematological disease [3]. When there is no condition requiring immediate intubation noninvasive mechanical ventilation (NIV) has been advocated as the preferable first-line form of ventilatory support. Over the last decade, the use of NIV in patients with hematological malignancy has increased in everyday practice [4].

13.2 Cardiovascular Complications of Chemotherapeutic and Other Anticancer Agents

Cardiotoxic effects can occur immediately during administration of the drug or they may not manifest themselves until months or years after the patient has been treated. The main effects of cardiotoxic drugs are discussed below.

Anthracyclines (dosage greater than 550 mg/m^2) cause myocyte cell death [5]. Acute anthracycline cardiotoxic effects are rare and can be associated with ventricular arrhythmias and transient left ventricular dysfunction (LVD). The presentation of heart disease due to anthracyclines is one typical of congestive heart failure (CHF). Declines in cardiac function caused by anthracyclines can be irreversible and lead to a cardiomyopathy with poor prognosis. Late cardiotoxic effects can manifest many years after anthracycline administration [5].

Cyclophosphamide (highdose) is associated with myocarditis, pericarditis, LVD, and CHF with considerable morbidity and mortality [6].

Both vincristine and vinblastine have been associated with the development of coronary vasospasm (myocardial ischemia and infaction) [7].

Alemtuzumab has been associated with rare LVD, especially in patients with cutaneous T-cell lymphoma [8].

Most of the side effects of rituximab are infusion related and occur within the first few hours, especially during the first infusion. Less severe reactions such as hypotension, angioedema, hypoxia, or bronchospasm can be seen in up to 10% of cases [9]. Major manifestations of retinoic acid syndrome have included respiratory distress, pulmonary infiltrates, pulmonary edema, and acute renal failure [10]. Approximately 20% of patients also showed substantial decline in the LV ejection

fraction. Fatal MI and thrombosis have also been noted after use of all-*trans* retinoic acid [10].

Imatinib mesylate is associated with a significant incidence of edema, which can progress to severe fluid retention and result in pericardial or pleural effusions or generalized third-space fluid accumulation [11]. Pentostatin has several cardiotoxic effects, including MI, CHF, and arrhythmias [11]. Myocardial ischemia, and occasionally myocardial infarction, is caused by 5fluorouracil (5FU). Although symptoms were transient in most of these patients, 2.2% experienced cardiac death due to arrhythmias or circulatory collapse [12].

Radiation to the thorax can damage the pericardium, myocardium, valves, and coronary vessels, with the pericardium being the most commonly involved. The incidence of radiation-induced heart disease is higher in patients given high doses of radiation or radiation therapy concurrent with doxorubicin. Patients with preexisting coronary artery disease are especially vulnerable. Left-sided valves are more often involved than right valves, and only a minority of patients with radiation-induced valvular disease have clinically moderate or severe dysfunction [13].

13.3 Management of Noninfectious Causes of ARF

Noninfectious etiologies of ARF in patients with hematologic malignancies may result from a diverse range of pulmonary insults, both direct and indirect: cardiogenic pulmonary edema (CPE), pulmonary hemorrhage, aspiration pneumonitis, radiation-induced pneumonitis, venous thromboembolism, transfusion-related acute lung injury, retinoic acid syndrome, leukemic pulmonary leukostasis, leukemic pulmonary infiltrates, and pulmonary lysis syndrome [14]. 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, and parenteral nutrition [15].

Acute cardiogenic pulmonary edema (ACPE) is characterized by an increase in left ventricle filling pressures, causing a rise in pulmonary capillary pressure, and thereafter fluid overload toward the pulmonary interstitial compartment and alveolar spaces [16]. All these factors lead to an increase in airway resistance, a decrease in lung diffusion capacity, a drop in functional residual capacity, and an increased intrapulmonary shunt effect. Hypoxemia develops, associated with an increase in respiratory effort. A large number of patients presenting with ACPE have preserved LV systolic function and as a result are affected by diastolic dysfunction. In ACPE with preserved systolic function the role of NIV is not well known [17].

13.4 Invasive or Noninvasive Mechanical Ventilation?

Fifteen to twenty years ago, hematology patients with acute respiratory failure exhibited mortality rates of about 50% [18], and for those who needed mechanical ventilation mortality reached 90% [19].

Many investigators have emphasized a worsened outcome for granulocytopenic patients undergoing tracheal intubation and mechanical ventilation during ARF [20]. There is a combination of the damage caused by opportunistic infections, the direct interstitial pulmonary toxicity of chemotherapy and complications related to endotracheal intubation [21]. In addition to injury to the pharynx and larynx, at the point of contact between tracheal mucosa and the tube or its cuff, edema, ulceration, or hemorrhage with potential stenosis can occur. The risk of developing nosocomial infections such as sinusitis and ventilator-associated pneumonia is very high [21]. The portion of the trachea between the cuff and the vocal cords becomes a reservoir of colonized secretions by bacteria originating from the sinuses, the nasal passages, pharynx, oral cavity, and the stomach [22]. In this situation, NIV seems to be an interesting alternative because of the low risk of complications.

Tognet et al. [23] were the first to report interesting clinical results with the intermittent application of NIV in patients with hematologic malignancies. Subsequently, Conti et al. [15] evaluated the use of NIV delivered via nasal mask in 16 consecutive patients with hematological malignancies and ARF. Fifteen out of 16 patients showed a clear-cut and sustained improvement in gas exchange after 1 h of treatment. Two patients failed to improve, were intubated, and subsequently died from sepsis. Three other patients died from complications unrelated to ARF.

According to blood gas analyses, one should choose continuous positive airway pressure (CPAP) in hypoxemic patients and NIV in patients who are hypercapnic. For NIV, the initial choice and programming should be guided by physical signs (e.g., breathing pattern, respiratory fatigue signs), comorbidity, patient's physical features and pressure, flow curve analysis, and blood gas analysis.

13.4.1 Continuous Positive Airway Pressure

CPAP is the simplest form of respiratory support and has the greatest evidence base in the treatment of ACPE. CPAP provides constant pressure via facemask, nasal mask, or helmet throughout the respiratory cycle. The continuous positive pressure helps to prevent alveolar collapse and recruits alveoli that have collapsed. Lung compliance is increased and the work of breathing is reduced. Lesser shunting of blood improves oxygenation and the positive intrathoracic pressure reduces venous return, thus reducing cardiac preload. LV transmural pressure is also reduced, with an effective reduction in afterload. The application of intrathoracic positive pressure in patients with ACPE decreases in venous return and in right ventricle preload with a reduction in left ventricle afterload [24]. The choice of initial pressures depends on factors such as personal experience, clinical setting, arterial blood gases, and patient tolerance. Usually, clinicians start with CPAP of 3–5 cmH_2O and inspiratory pressure of 8–12 cmH_2O above CPAP. If necessary, pressure changes are made gradually, depending on the patient's dyspnea, tolerance, and minute ventilation.

13.4.2 Noninvasive Ventilation

This is the mode that should be used in patients with hypercapnia and global respiratory failure and even in patients without hypercapnia but with signs of significant respiratory fatigue. Compared with CPAP, NIV produces greater improvements in oxygenation and CO_2 clearance and a greater reduction in the work of breathing in patients with ACPE [15]. There is an expiratory positive airway pressure (EPAP) that recruits alveoli and prevents their collapse, increasing oxygenation and inspiratory positive airway pressure (IPAP), which reduces the inspiratory effort and diaphragm fatigue, increasing the tidal volume.

Similar to invasive mechanical ventilation, administration of NIV has two major modes of ventilation: pressure-limited and volume-limited. Proportional assist ventilation, which is a relatively new mode that targets patient's effort, can also be used [25].

The choice of the best fitting mask is a crucial point during NIV, as the mask is the only interface between patient and ventilator. Several authors [26, 27] have suggested the use of a face mask in patients with ARF, while others [28] obtained good results in the same kind of patients using a nasal mask. The nasal mask offers several advantages over the full face mask: it allows normal sleep rhythms, oral feeding, and talking, all of which are very important in patients in this particular psychological situation due to their primary disease. It is evident that in all patients in whom there are technical problems with the nasal mask, it must be replaced by a fullface mask before endotracheal intubation is considered.

NIV in patients with hematological malignancy preferably should be treated in an ICU setting, given the relatively high risk of NIV failure [29].

13.5 Risk Factors for NIMV Failure

Several different factors lead to NIV failure. Failure of NIV is associated with increased mortality. The cause of the respiratory failure also plays a key role in predicting the success of NIV. Careful selection of patients is therefore essential, not only with regard to the presence of relative contraindications for NIV, but also estimating the probability that ARF is likely to be reversed within a short period of time [30]. Efforts should be made to improve tolerance of NIV, but one must bear in mind that persisting discomfort or agitation, especially in hypoxemic ARF, may be an early warning sign of inappropriate use of NIV. Positive pressures should by slowly titrated upward to allow patients to accommodate. Careful adjustment of the ventilator settings while observing patient-ventilator synchrony is important, paying attention to inspiratory and expiratory pressures, trigger sensitivity, and inspiratory and expiratory cycling. Different ventilator modes may be tried under the assumption that no mode has been shown to be superior to another. The patient-ventilator interface should be chosen on an individual basis, preferably trying different types, and a compromise must be achieved between permitting a certain amount of

pressure leak and avoiding pressure sores or claustrophobia. Judicious sedation with the use of short-acting agents such as remifentanil and dexmedetomidine may increase the success rate of NIV. If patients remain dependent on NIV for more than 24–36 h, without signs that ARF is resolving, one should consider cessation of NIV and semi-elective intubation to avoid the adverse effects associated with late NIV failure [30].

Conclusion

ARF represents the most frequent complication in these patients. Noninvasive ventilation is feasible and may be a good choice for the treatment of ARF in a selected population of critically ill patients with hematologic malignancies. Although NIV can avert intubation and thus improve outcome in a significant number of patients, it may also increase mortality in those patients in whom it fails. NIV offers also an important ethical advantage for patients with hematologic malignancies, as it allows treatment of patients who refuse endotracheal intubation but not ventilatory support.

NIV remains then the gold standard for the initial ventilatory strategy in hematological patient.

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14 Oxygen Therapy and Ventilatory Approach in Elderly Cancer Patients: Key Practice Recommendations

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The aging process is defined as a normal and progressive decline in functioning and the ability to respond to intrinsic or extrinsic stimuli. In addition to this normal progression during aging, additional multiple pathological processes lead to comorbidity in the elderly [1].

As a normal part of the process, the respiratory system is unchanged from the end of the third decade of life, although lung function gradually decreases. This decrease is mainly characterized by the loss of alveolar surface changes similar to those that would be observed in a subject with pulmonary emphysema. Muscle mass likewise decreases with age, along with changes in body composition, causing changes in basal oxygen consumption. It becomes very difficult to predict or guess which values to expect in individual patients. Sixty-five percent of those diagnosed with cancer are over 65 years of age [2].

The importance of oxygen for cancer patients has many surrounding dimensions and considerations. The main one, as with all other patients, is the importance of avoiding hypoxemia without reaching hyperoxia. Yet for patients without pathology, both sides of the coin have been seen to signal significant adverse effects and the treatment required to improve blood oxygen levels as well. Toxic effects and damage caused both by positive pressure and by high inspired oxygen fractions are well described, and the level of damage that is acceptable to tolerate is the result of the risk/benefit balance in each patient. The administration of supplemental oxygen inspired fractions greater to 50% causes an indistinguishable lung injury of ARDS caused theoretically by excess production of free radicals which can produce apoptosis, a phenomenon that has been documented in the organ that provides the surface contact with the applied oxygen (the alveolar-capillary membrane).

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Hyperoxemia also has significant side effects, particularly among the geriatric population, given the fact that it primarily affects the cardiovascular system by altering cardiac output, coronary vascular tone and decreasing blood flow to this area; effects would be potentiated if respiratory therapy caused hypocarbia. This has led to the development of such concepts as "permissive hypoxemia" in critically ill patients; however, it is known that cell death can also be triggered in this situation. It is not known whether this term would be acceptable with regard to cancer patients, so a few considerations that have developed around tissue hypoxia in neoplastic cells are in order.

Firstly, it is necessary to define hypoxemia, which is a challenge in itself. Hypoxemia is defined in absolute terms as a PaO_2 less than 80 mmHg when breathing room air at sea level, and less than 94% arterial oxygen saturation (SaO_2) [4]. The same can be put to very different considerations. An elderly oncology patient is usually one for whom oxygen therapy is necessary due to either an acute process or an acute on chronic lung diseasethat lead to a changing oxygen demand. The origin of respiratory failure in a cancer patient includes the same mechanisms as in the rest of the population, intrapulmonary shunt anatomical or physiological (refractory to the use of supplemental oxygen to increase the fraction of inspired oxygen (FiO_2).

The ventilation/perfusion mismatch (one of the most common causes in both critical care patients and cancer patients, usually responds somewhat to increased FiO_2), as well as a decrease in the alveolar ventilation that easily responds to increased hipercapnic respiratory failure [3, 4]. There are two other mechanisms described that are relatively rare in acute critical patients as well as in cancer patients in whom these mechanisms can be triggered by aggregated causes, or by the underlying disease itself. However, taking into account that in a neoplastic illness, basal oxygen consumption may be increased, and therefore, to achieve the contribution balance/consumption, it is necessary to increase arterial oxygen content via oxygen therapy; this raises the possibility that the threshold for developing hypoxemia and hypercapnia in cancer patients is smaller.

The causes of hypercapnia may be further exacerbated in cases of ventilatory failure by muscle wasting in the elderly patient, and even further in the cancer patient who is in a catabolic state. Sarcopenia is an independent factor in the development of hypercapnia respiratory failure.

Using ventilation to determine whether a patient has acute respiratory failure due to hypoxia or hypercapnia, for a patient who has a deterioration in respiratory function that leads to arterial saturation and low oxygen, it should always be approached with arterial blood gas analysis to determine the correct therapy., For hypoxemic failure, only monitoring may be carried out, even with pulse oximetry, if there is no further deterioration.

In these cases, it is better to increase oxygen therapy gradually since sudden administration of oxygen would cause CO_2 retention and turn an hypoxemic respiratory failure into an hypercapnic one. Therefore, the initial goals of arterial oxygen saturation in patients with COPD are 88–92%. The oxygen fraction should be decreased if saturation exceeds this limit. If CO_2 level is normal after oxygen

therapy was started at FiO_2 24–28%, oximetry target could be set to 94–98%, but arterial blood gases should be re-checked in the first hour after this change [5].

Among elderly oncology patients, there are other concomitant alterations that influence blood oxygenation, such as pleural effusion. In such circumstances, therapy can consist of supplemental oxygen via a nasal cannula at 4 L/min and draining the effusion as soon as possible. In most of these cases, the underlying mechanism is hypoventilation with a hypoxemia-perfusion mismatch. While draining the effusion, providing adequate ventilation therapy will avoid increasing the amount of oxygen.

Regarding oxygenation goals in hypoxemic patients in general, a saturation of at least 94% is the target. However, with patients over age 70, if the patient remains hemodynamically stable without biochemical shock signs, it is possible to keep to a blood saturation lower than 94%. An elderly oncology patient will almost always need oxygen therapy, due to a more acute chronic disease process or from chronic (not acute) lung changes leading to a lesser oxygenation requirement. Therefore, patients who have high oxygen levels can be in as bad condition as those with low oxygen levels.

The current concensus concept is the "precise control of blood oxygenation" in these patients. Which then suggests that the lower and upper limits of blood oxygen levels should be set to 60 and 75 mm/Hg, instead of at least 60 mmHg. Such a range contrasts to the contribution patient input/consumption balance showing throughout the curse to avoid tissue hypoxia.

Pilot studies have shown that both biochemical and ventilatory evolution as well as long-term outcomes are not poorer for patients treated with SaO_2 and PaO_2 targets lower than those established conservatively [6]. If a patient does not reach the established goals after giving supplemental oxygen, it is necessary to increase it.

A recent idea showed that cancer patients, including geriatric ones with severe ARDS, may benefit from administrating high-flow oxygen therapy together with non-invasive mechanical ventilation [7]. In assessing this possibility, it should always be taken into account that cancer patients often have complications from bleeding, management of secretions, or having a low threshold for pain. Quite often, the elderly easily experience consciousness alterations and delirium, which means that non-invasive mechanical ventilation is not a feasible option.

14.1 Tumor Metabolism

Tissue hypoxia results from a mismatch between oxygen supply and demand; this condition may be systemic or regional. It is important to note that a patient with an active malignancy will rely on our knowledge of regional delivery and oxygen consumption by tumor cells.

In tumors with local invasion oxygen delivery is decreased or not exist at all. This is the result of abnormal, yet irregularly anatomically shaped circulation. This causes hypoxic tissue in more than half of the tumors of any given origin. Another

contributor to tumor hypoxia is anemia. A high percentage of cancer patients, also elderly ones, develops anemia, which reduces the oxygen being carried in the blood. Hypoxia influences gene expression promoting tumor progression by activating mechanisms that facilitate tumor cells to survive, despite the deprivation of nutrients, leading hypoxic tumors to become more aggressive [8].

Conclusions

- Supplemental oxygen treatment should focus on adjusting the oxygen consumption balance.
- The permissive hypoxemia concept is not applicable to cancer patients.
- The concept of "precise control of arterial oxygenation" is applicable to geriatric cancer patients.
- The use of non-invasive mechanical high-flow oxygen therapy ventilation lacks enough evidence to be applied routinely, as found through testing.
- The use of invasive mechanical ventilation should match the wishes of the patient, his/her family, and the judgment of both the oncologist and critical care physician.

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Part II

Invasive and Non-Invasive Mechanical Ventilation

Rationale and Overview

15

Ravinder Bhanot, Abdulrazak Alchakaki, Jasleen Kaur, and Ayman O. Soubani

15.1 Introduction

Cancer survival has been steadily improving over the last few decades [1]. This improvement correlates with earlier cancer detection, improved diagnosis and staging, better surgical and medical options for treatment, and better supportive care [2]. The advances in cancer treatment and survival have led to more patients requiring intensive care to manage critical illnesses that are either directly or indirectly related cancer. Acute respiratory failure (ARF) requiring mechanical ventilation (MV) is one of the most common causes of intensive care unit (ICU) admission in this patient population. Previous studies have reported mortality exceeding 80–90% and most clinicians and some professional societies recommended against initiating MV in critically ill cancer patients [3]. However, with improvement in ICU care, better diagnostic and therapeutic approaches, and improved ventilatory strategies, the prognosis of these patients has improved in the last two decades. This report provides the rationale of MV in critically ill patients with cancer providing an overview of epidemiology and indications and goals of MV. Also, the main modes of ventilations, complications, and supportive measures during this therapy are presented. Since a significant percentage of critically ill patients with cancer who require MV continue to have high mortality, the predictors of outcome are discussed. We also provide an overview of the role of noninvasive ventilation in this patient population.

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15.2 Epidemiology

Information on the incidence of ARF and need for ventilatory support in patients with cancer are still limited, but seem to vary largely depending on the studied population. Approximately 5% of patients with solid tumors will experience ARF during the course of their disease, while it occurs in 20% of patients with hematological malignancies. The incidence of ARF in recipients of autologous hematopoietic stem cell transplantation (HSCT) recipients similarly is estimated at between 6 and 11%, which is lower than the incidence reported in patients who had undergone allogeneic HSCT (up to 20%) [4].

ARF requiring MV is a leading reason for overall ICU admissions, and many patients will need MV support while in the ICU. Studies in unselected patients with cancer admitted to ICUs demonstrated that MV was provided in 44–69% [5, 6]. In the Sepsis Occurrence in Acutely Ill Patients (SOAP) study, 473 (15%) of 3147 patients admitted to 198 European ICUs over a 2-week period had a diagnosis of malignancy. Of these, 69 (15%) had hematological cancer and 404 (85%) had solid tumors, of which 100 had evidence of metastases. A majority (64%) of these patients received MV [7]. Recently, another large multicenter prospective cohort study conducted in 28 Brazilian ICUs evaluated adult patients with cancer requiring ventilatory support (invasive or noninvasive) during the first 48 h of their ICU stay. Incidence of cancer patients receiving MV was higher (263 of total 717 patients; 37%) than previously reported studies. These mostly consisted of patients with solid tumors (227; 86%), while 36 patients (14%) had hematologic malignancies similar to previous studies. The most frequent types of solid tumors were lower GI (n = 33; 13%) followed by lung (n = 31; 12%), whereas lymphomas (n = 14; 6%) comprised of main hematologic malignancies [8].

15.3 Indications of MV in Patients with Cancer

ARF and the need for MV are the most common reason for ICU admission in patients with cancer [9–12]. There is a wide spectrum of indications for MV in these patients. Table 15.1 provides the most common indications of MV in critically ill cancer patients.

15.4 Diagnostic Strategies of Critically Ill Cancer Patients on Mechanical Ventilation

As the etiology of ARF in these patients is highly variable, appropriate treatment requires timely and accurate diagnosis. However, the available evidence guiding the diagnostic approach in cancer patients with ARF is primarily based on single center, observational studies.

Table 15.1 Main indications of mechanical ventilation in critically ill patients with cancer

Postoperative care—elective or emergency
Acute respiratory failure
• *Infectious*
– Pulmonary—bacterial, viral, fungal
– Extra-pulmonary—severe sepsis/septic shock
• *Noninfectious*
– *Related to cancer*
Airway invasion
Massive malignant pleural effusion
Neuromyopathy—paraneoplastic
Diffuse alveolar hemorrhage
Idiopathic pneumonia syndrome
– *Related to cancer treatment*
Pulmonary drug toxicity
Transfusion-related acute lung injury
– *Not directly related to cancer*
Altered mental status
Pulmonary embolism
Comorbid illnesses—COPD, pulmonary fibrosis, pulmonary edema

Clinical evaluation that takes into account patient presentation, type of immune deficiency, timing of ARF, radiological findings, and provider's clinical experience is useful in determining the etiology of ARF in this patient population [13]. Chest CT scan with high resolution images provides important data that may direct treatment or further diagnostic studies. Early fibro-optic bronchoscopy with bronchoalveolar lavage is currently the cornerstone of the diagnostic workup in these patients. However, the diagnostic yield of this procedure is around 50% and may lead to deterioration of respiratory status in up to 25% of critically ill patients [14]. Furthermore, a prospective, randomized, multicenter study showed no difference in outcome between an approach based noninvasive diagnostic methods and one supplemented by bronchoscopy with BAL [14]. Transbronchial biopsies are associated with high risk of complications and only modest increase in diagnostic yield. Surgical lung biopsy has long been considered as the diagnostic gold standard in cancer patients with pulmonary infiltrates and ARF; however, recent evidence shows that the procedure was not superior to BAL for diagnosis of infections with higher morbidity and mortality [15]. Surgical lung biopsy is currently limited to highly selected situations. There is mounting evidence supporting the role of biomarkers from sputum, blood, urine, and nasopharyngeal aspirates in determining the etiology of ARF in cancer patients [16]. With the current available diagnostic studies, the etiology of ARF is not determined in around 20% of patients, and these patients generally have worse outcome [14].

15.5 Goals of Mechanical Ventilation

The principal objectives of MV in cancer patients during respiratory failure are improved gas exchange and decreased work of breathing while avoiding overstretch and collapse/recruitment ventilator-induced lung injury. This concept, which is illustrated in Fig. 15.1, has gained acceptance because of important empirical and experimental evidence linking high airway pressures and volumes leading to repeat overstretch and collapse of alveoli with poor outcomes.

The majority of causes of ARF in patients with cancer lead to impaired gas exchange ventilation-perfusion (V/Q) match resulting in hypoxemia. MV improves gas exchange by improving ventilation-perfusion (V/Q) matching. This is primarily a consequence of decreased physiologic shunting.

The work of breathing can increase due to altered lung mechanics (e.g., increased airways resistance, decreased compliance) or increased respiratory demand (e.g., metabolic acidemia). The effort required to maintain this elevated work of breathing may result in respiratory muscle fatigue and respiratory failure. These are common problems in patients with cancer. MV can assume some or all of the increased work of breathing, allowing the ventilatory muscles to recover from their fatigue.

Another important goal during MV in these patients is minimizing complications associated with this therapy, including barotrauma, further acute lung injury, and ventilator-associated pneumonia. Also with MV, supportive measures are essential to make the patient comfortable (such as pain control and sedation) and avoid further problems, including malnutrition, venous thromboembolism, and pressure injuries.

Patients with cancer commonly require MV to facilitate diagnostic procedures such as bronchoscopy, or to support the patient during the management of cancer-related respiratory complications, including hemoptysis and endobronchial therapy (laser, stents, or brachytherapy) for airway tumors.

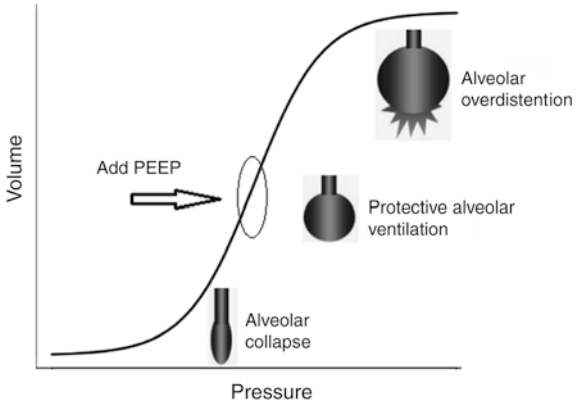

Fig. 15.1 Volume–pressure relationship of the respiratory systems showing the lower (atelectrauma) and upper inflection points (volutrauma). Protective ventilation using lower tidal volume (6 mL/kg of ideal body weight) and maintaining positive end-expiratory pressure (PEEP) can prevent overstretching and collapse/opening of alveoli

Table 15.2 Goals of mechanical ventilation in patients with cancer

1. Improve pulmonary gas exchange thereby relieving hypoxemia
2. Decrease work of breathing thereby relieving respiratory distress
3. Prevent or reverse atelectasis
4. Decrease systemic or myocardial oxygen consumption
5. Stabilize chest wall
6. Minimize ventilator-associated complications
7. Facilitate diagnostic and therapeutic procedures
8. Palliative measure until goals of care are established

MV in patients with cancer may be occasionally necessary during the management of ARF until the goals of care are determined based on the assessment of the cancer status, further treatment options, and building consensus between patient, family, and healthcare providers. Ideally, MV should be avoided in terminally ill patients with cancer or otherwise may be offered NIV to support their respiratory status; however in practice, these two options are not always possible and patients may require MV as a palliative measure and until the goals of care are established. Table 15.2 provides a summary of the goals of MV in critically ill patients with cancer.

15.6 Modes of Mechanical Ventilation

The mode of MV refers to the method or manner in which a breath (inspiratory support) is provided to a patient. This is defined by a combination of following three features:

- What initiates the breath (trigger)?
- What controls the delivery (target volume or pressure)?
- What terminates the breath (cycling)?

Accordingly, there are several different modes of ventilation that are discussed below and summarized in Table 15.3. An important point to mention in this regard is that there is no evidence that critically ill patients with cancer are different from the general population in relation to the choice of mode of ventilation.

Assist Control: During this mode, the clinician determines the minimal minute ventilation by setting the respiratory rate and tidal volume. The patient can increase the minute ventilation by triggering additional breaths. Each patient-initiated breath receives the set tidal volume from the ventilator.

Synchronized Intermittent Mandatory Ventilation: In this mode, the ventilator breaths are synchronized with patient's inspiratory effort. It can be used to titrate the level of ventilatory support over a wide range. Ventilatory support can range from full support (set respiratory rate is high enough that the patient does not overbreathe) to no ventilatory support (set respiratory rate is zero).

Table 15.3 Spectrum of modes of ventilation for patients with acute respiratory failure

Modes	Trigger		Target	Termination (Cycling)	Advantages	Disadvantages
	Ventilator	Patient				
Assist control	Yes	Yes	Volume limited	Volume	Patient control, guaranteed ventilation	Hyperventilation, breath stacking, barotrauma and volutrauma
			Pressure limited	Time		
SIMV	Yes	Yes	Volume limited	Volume	Comfort from spontaneous breaths, guaranteed ventilation	Potential dysynchrony, may result in hypoventilation
			Pressure limited	Time		
PSV	No	Yes	Pressure limited	Flow, pressure or time	Patient control assures synchrony	No timer backup may result in hypoventilation
PCV	Yes	No	Pressure limited	Time	Set inspiratory pressure	Uncomfortable, requires heavy sedation
APRV	Yes	Yes	Pressure limited	Time (very long inspiratory, short expiratory)	Potential for maximal alveolar recruitment	Potential asynchrony, Volutrauma
PRVC	Yes	Yes	Pressure limited with goal tidal volume	Time	Smaller rise in the plateau airway pressure	May cause or worsen auto-PEEP

AC assist control, *SIMV* synchronized intermittent mandatory ventilation, *PSV* pressure support ventilation, *PCV* pressure-controlled ventilation, *APRV* airway pressure release ventilation, *PRVC* pressure-regulated volume control

Pressure Support Ventilation: The patient initiates all breaths. Delivered volume varies from breath to breath. Duration is determined by the patient's inspiratory effort and terminated when inspiratory flow decreases to a preset level, usually 25% of peak flow.

Pressure Controlled ventilation (also called Pressure-Cycled Ventilation)**:** This mode requires the clinician to set the inspiratory pressure level, inspiratory to expiratory (I:E) ratio, respiratory rate, positive end-expiratory pressure (applied PEEP), and fraction of inspired oxygen (FiO_2). Inspiration ends after delivery of the set inspiratory pressure.

Bilevel and Airway Pressure Release Ventilation: During this mode, a high continuous positive airway pressure (P high) is delivered for a longer duration (T high) and then falls to a lower pressure (P low) for a shorter duration (T low). The difference between P high and P low is the driving pressure. Larger differences are associated with greater inflation and deflation, while smaller differences are associated with smaller inflation and deflation. The high continuous positive airway pressure maximizes alveolar recruitment.

Pressure-Regulated Volume Control (also called Volume Control Plus): Clinician sets a goal tidal volume and inspiratory time, and with each breath the ventilator adjusts the pressure to achieve the goal tidal volume, generating a smaller rise in the plateau airway pressure.

Volume-Assured Pressure Support Ventilation: Pressure limited but volume guaranteed. Similar to pressure-regulated volume control, the only difference is that the patient is breathing spontaneously and there is no set mandatory breath.

Proportional-Assist Ventilation: Another spontaneous mode similar to pressure-supported ventilation. However, in this case, there is real-time feedback so that pressure support can be adjusted based on respiratory resistance and compliance breath to breath. No target flow, volume, or pressure is set.

15.7 Weaning from Mechanical Ventilation

Weaning from MV in patients with cancer should be similar to other patients' population. The objective of weaning is the discontinuation of MV or liberation from the mechanical ventilator. It is the process of decreasing the amount of support that the patient receives from the ventilator, so the patient assumes a greater proportion of the ventilatory effort and eventually be successfully discontinued. Weaning may involve either an immediate shift from full ventilatory support to a period of breathing without assistance from the ventilator or a gradual reduction in the amount of ventilator support. It is important to consider discontinuation of MV once the underlying respiratory disease begins to reverse.

Although the predictive capacities of multiple clinical and physiologic variables have been explored, the consensus from a weaning task force includes the following recommendations: (1) lung injury is stable/resolving, (2) gas exchange is adequate with low PEEP (<8 cmH_2O) and FIO_2 (<0.5), (3) hemodynamic variables are stable (patient off vasopressors), and (4) patient is capable of initiating spontaneous breaths. This "screen" should be done at least daily. If the patient is deemed capable of beginning weaning, the recommendation of the task force is to perform a spontaneous breathing trial because several randomized trials support the value of this approach.

The spontaneous breathing trial involves an integrated patient assessment during spontaneous breathing with little or no ventilator support. It is usually implemented with using oxygen delivered by T-piece or 5–7 cmH_2O pressure support from the ventilator to offset the resistance from the endotracheal tube. Once it is determined that the patient can breathe spontaneously, a decision must be made about the removal of the artificial airway; this should be done only when it is concluded that the patient has the ability to protect the airway, is able to cough and clear secretions, and is alert enough to follow commands. Despite the application of all of these methods, ~10–15% of extubated patients require reintubation [17].

Weaning of mechanically ventilated cancer patients is especially challenging despite significant advances in ICU management. This is particularly true for lung cancer patients because these patients have a special condition in which tumor

extension during treatment of reversible problems may preclude successful weaning from MV. Some of the factors affecting weaning include low serum albumin level, high APACHE III score, high FiO_2 and positive end-expiratory pressure and multi-organ failure as shown by LIN YC et al. [18]. Their results suggested that lung cancer patients with ARF will have a better chance to wean if the initial APACHE III score was less than 70, use of FiO_2 never exceeded 0.6, or less than 2 additional organ systems failed during the treatment course. Baseline poor performance status (PS) is another factor that could significantly influence weaning. Advanced cancer patients with respiratory failure usually have extremely poor PS that may affect their respiratory drive and muscle strength. A recent study by Hsia TC et al. showed that only 16 of 83 patients stage IIIb-IV non-small lung cancer (19%) were successfully weaned from MV even after instituting of newer target therapies [19].

15.8 Supportive Care

Amid concern about ARF in patients with cancer requiring MV and emphasis about implementation of various ventilator strategies, it is easy to lose sight of simpler and supportive measures that may also affect patient outcomes. These supportive measures include wise use of sedatives and neuromuscular blockade, careful hemodynamic management, nutritional support, control of blood glucose, expeditious evaluation and treatment of nosocomial pneumonia, and prophylaxis against deep vein thrombosis and gastrointestinal bleeding.

Sedation and analgesia are essential in mechanically ventilated patients with cancer to the extent that they improve tolerance of MV and decrease oxygen consumption [1, 2]. This is particularly important in cancer patients as greater than 60% of these patients experience chronic pain, which is particularly heightened in critical illness. Guidelines, therefore, recommend "analgesia-first sedation" to promote use of analgesic agents over sedatives to treat pain and agitation and reduce undertreating pain in mechanically ventilated cancer patients. These patients are also at increased risk to develop acute brain dysfunction in the form of delirium due to chronic sustained systemic inflammation, older age, high burden of comorbidities, use of steroids, and terminal illness. This can be independently associated with increased hospital mortality as shown by Almeida et al. in a recent study [20]. Of 170 enrolled patients ventilated >48 h with a diagnosis of cancer, acute brain dysfunction was diagnosed in 161 patients (95%). Survivors had more delirium/coma-free days emphasizing the need to address this. However, institution based protocols must be used to prevent overtreatment that might delay liberation from MV.

Occasionally, neuromuscular blockade is required, particularly when asynchrony with the ventilator persists despite adequate sedation. For patients with particularly severe gas exchange abnormalities (e.g., $PaO_2/FiO_2 \leq 120$ mmHg), up to 48 h of neuromuscular blockade is probably safe and potentially beneficial, but this requires additional investigation.

Mortality among many mechanically ventilated cancer patients with ARF is not just from hypoxemia but, instead, as a result of complications that develop during

the course of their ICU stay, including catheter-related blood stream infections, catheter-associated urinary tract infections, venous thromboembolism, ventilator-associated pneumonia, and gastrointestinal bleeding. For these reasons, it is important to institute appropriate prophylactic measures to decrease the risk of these problems. All central venous catheters should be placed with full barrier precautions, and daily assessment made of whether these lines and urinary catheters can be safely removed. All mechanically ventilated patients should undergo daily chlorhexidine oral decontamination and be ventilated with the head of their bed elevated >30°, a measure shown to decrease the risk of ventilator-associated pneumonia. Evidence suggests that use of checklists can increase adherence to these measures [21].

15.9 Outcome of MV in Critically Ill Patients with Cancer

The advances in understanding cancer biology, early cancer diagnosis, and more effective and better tolerated therapeutic modalities have led to increasing number of living patients with cancer. These advances come at a cost of increased therapeutic complications such as infections, drugs toxicity, physical debility, and critical illnesses. These conditions affect organs' functions and increase the need for ICU care. The improvement in the overall cancer outcomes is paralleled by similar improvement in outcome of critically ill patients with cancer. In the case of ARF, this improvement is more modest than other causes of critical illness. The mortality of cancer patients afflicted with ARF has dropped from 72 to 30% over the last two decades. Nevertheless, the need for MV is associated with sixfolds increase in mortality [6, 22]. Table 15.4 provides an overview of the studies of mechanically ventilated patients with cancer and shows that hospital mortality ranges between 60 and 90% and long term (>6 months) 70 and 90%.

Identifying the predictors of poor outcomes in patients with cancer and ARF is essential to avoid potentially harmful and costly therapies and the anxiety and stress for patients and their families. Studies show variability in the predictors of outcome in this patient population. However, several factors that have been traditionally associated with poor outcome have become less significant in the outcome of these patients. Examples include age, cancer characteristics, postoperative MV, initial severity of illness scores, presence of neutropenia, and autologous HSCT [23]. On the other hand, other clinical variables continue to significantly affect the prognosis of patients with cancer requiring MV (Table 15.5). These include poor performance status. Severe debility usually reflects advanced aging, severe comorbidities, or direct cancer effect on organs' function leading to poor outcome with four- to sevenfolds higher mortality [6, 22, 23]. The presence of multiple organ failure, or, more importantly, persistent or progressive multiorgan failure during ICU treatment, is another predictor of poor outcome in mechanically ventilated cancer patients [24]. Patients with allogeneic HSCT who require MV have high mortality, and the outcome is particularly poor if patients have severe, refractory graft versus host disease. The underlying condition leading to ARF plays a role in predicting outcomes as well.

Table 15.4 Major studies addressing short-term and long-term outcome of critically ill patients with cancer and on mechanical ventilation

Author/year	Study type	Malignancy type	MV patient #	Mortality			Predictors of mortality
				ICU	Hospital	≥ 6 Month	
Schuster (1983) [33]	R	HM	52	NR	92%	NR	• Acute respiratory failure due to infection
							• Prolonged MV
Peters (1988) [34]	R	HM on MV	116	NR	82%	NR	• Non-Hodgkin's lymphoma
							• Acute Leukemia
Brunet (1990) [35]	R	HM	111	85%	NR	NR	• High SAPS
							• Multiorgan failure
							• Intractable sepsis
							• Combination of mechanical ventilation and dialysis
Crawford (1992) [36]	R	HSCT on MV	348	NR	96%	97%	• NR
Paz (1993) [37]	R	HSCT	28	96%	NR	NR	• Mechanical ventilation
							• APACHE II score
Faber-Langendoen (1993) [38]	R	HSCT on MV	191	91%	NR	97%	• MV and reason for MV
							• Age > 40
							• HSCT to ICU less than 90 days
Epner (1996) [39]	R	HM on MV	157	NR	83%	NR	• Stage beyond first complete remission
							• Duration of neutropenia greater than 30 days
							• Treatment with HSCT
Ewig (1998) [40]	R	HM	76	NR	68 (90%)	NR	• Severe pulmonary complications
							• MV
							• HSCT
							• Less than 90 days from HSCT to ICU admission

Price (1998) [41]	P	HSCT	48	NR	81%	NR	• MV • Allogeneic HSCT • Infection, respiratory rate, days since transplant, heart rate, and bilirubin level
Jackson (1998) [42]	R	HSCT	92	62%	83%	NR	• Year of HSCT • Hemodynamic support • Bilirubin level
Kress (1999) [43]	R	Predominant HM	153	NR	67%	NR	• MV • Hepatic failure • Cardiovascular failure
Groeger (1999) [44]	P	Predominant HM on MV	782	NR	76%	NR	• Intubation after 24 h, – Leukemia • Progression or recurrence of cancer • Allogeneic HSCT • Cardiac arrhythmias • DIC • Vasopressor therapy
Huaringa (2000) [45]	R	HSCT on MV	60	82%	NR	95%	• Prolonged MV > 15 days • Respiratory failure >30 days after HSCT
Khassawneh (2002) [46]	R	Autologous HSCT on MV	78	NR	74%	83%	• Lung injury with vasopressor use • Hepatic and renal failure
Benoit (2003) [47]	R	HM	88	59%	69%	79%	• Leukopenia • Vasopressor use • Urea >0.75 g/L • MV

(continued)

Table 15.4 (continued)

Author/year	Study type	Malignancy type	MV patient #	Mortality			Predictors of mortality
				ICU	Hospital	≥ 6 Month	
Depuydt (2004) [48]	R	HM	120	NR	70%	NR	• Female sex
							• MV less than 24 h
							• Bacteremia less than 48 h
							• Acute leukemia
							• SAPS of >0.08
Soubani (2004) [49]	R	HSCT	51	63%	NR	NR	• Elevated lactate level
							• MV
							• Failure of more than one organ system
Soares (2005) [9]	P	Predominantly HM on MV	463	50%	64%	NR	• Age > 70
							• Poor performance status
							• $PaO_2/FiO_2 < 150$
							• Cancer status
							• Severity of organ failure
Lamia (2006) [50]	R	HM	58	NR	79%	NR	• SAPS II, LODS and SOFA scores
Pene (2006) [51]	R	Allogeneic HSCT	122	82%	83.4%	86%	• MV
							• Steroids for the treatment of GVHD
							• Elevated bilirubin
							• Multiple organ failure if mechanically ventilated
Reichner (2006) [52]	R	Lung cancer	NR	NR	74%	NR	• MV
							• SOFA
							• Stage IV lung cancer
Trinkaus (2009) [53]	R	Autologous HSCT	11	55%	NR	NR	• Multiorgan failure
							• MV
							• Inotropic support >4 hours
							• Gram negative sepsis

Christodoulou (2007) [54]	R	Solid cancers	44	NR	81.8%	NR	• Performance status
Soares (2007) [55]	P	Head and neck cancer	100	NR	64%	NR	• Performance status
							• Advanced cancer
							• Number of organ failure
Soares (2007) [56]	R	Lung cancer	100	56%	69%	NR	• Airway infiltration by tumor
							• Number of organ failure
							• Cancer progression or recurrence
							• Severity of comorbidities
Mendoza (2008) [57]	R	Solid cancers	93	NR	51%	NR	• Vasopressors
							• Metastatic disease
Adam (2008) [58]	R	Lung cancer	68	38%	53%	NR	• Vasopressor
							• >2 organ failure
Roques (2009) [59]	P	Lung cancer	43	NR	70%	NR	• Performance status
							• MV
							• Cancer progression
McGrath (2010) [60]	Both	Predominant HM	NR	47.3%	NR	NR	• APACHE II and SOFA scores
							• Multiorgan failure
Andrejak (2011) [61]	R	Lung cancer	57	59%	NR	NR	• Vasopressors
							• MV
							• Thrombocytopenia
Chou (2012) [62]	R	Lung cancer	70	NR	58.6%	NR	• SOFA score
Slatore (2012) [63]	R	Lung cancer	10,463	NR	59%	85%	• MV

(continued)

Table 15.4 (continued)

Author/year	Study type	Malignancy type	MV patient #	Mortality			Predictors of mortality
				ICU	Hospital	≥ 6 Month	
Bird (2012) [64]	R	HM	95	NR	64%	NR	• MV
							• Failure of >2 organ systems
Azoulay (2013) [65]	P	HM	484	NR	60.5%	NR	• Poor performance status at admission
							• Charlson comorbidity index
							• Allogeneic HSCT
							• SOFA score
							• Admission for cardiac arrest or acute respiratory failure
							• Invasive pulmonary aspergillosis
							• Organ infiltration by malignancy
Azevedo (2014) [8]	P	Predominant HM on MV	223	NR	72%	NR	• Newly diagnosed malignancy
							• Recurrent or progressive malignancy
							• Performance status
							• NIV followed by MV
							• MV
							• SOFA score
Allareddy (2014) [66]	R	HSCT on MV	6074	NR	50.6%	NR	• MV for more than 96 h
Platon (2016) [67]	R	Allogeneic HSCT	29	62%	NR	NR	• Worsening SOFA from day 1 to day 3
							• MV
							• Active GVHD

Abbreviations: *R* retrospective, *NR* not reported, *HM* hematologic malignancy, *MV* mechanical ventilation, *SAPS* Simplified Acute Physiology Score, *HSCT* hematopoietic stem cell transplantation, *ICU* intensive care unit, *DIC* Disseminated Intravascular Coagulation, *SOFA* Sequential Organ Failure Assessment, *NIV* noninvasive ventilation, *GVHD* graft versus host disease, *APACHE* Acute Physiology and Chronic Health Evaluation

Table 15.5 Clinical variables predicting outcome of mechanically ventilated patients with cancer

Predictors associated with minimal effect on outcome
• Age
• Cancer characteristics
• Neutropenia
• Autologous HSCT
• Chemotherapy in the ICU
• Tumor lysis syndrome
• Initial severity of illness scores
• Postoperative (elective or emergency)
Predictors associated with significant effect on outcome
• Etiology of ARF—including unknown etiology
• Failure of noninvasive ventilation
• Allogeneic HSCT
• Type and number of associated organ failure
Predictors associated with poor outcome
• Poor performance status
• Severe comorbidities
• Refractory cancer with no treatment options
• Persistent multiorgan system failure
• Allogeneic HSCT with severe refractory acute GVHD
• Multiple re-admissions to the ICU
• Following CPR for cardiac arrest

Patients with cardiogenic pulmonary edema, bacterial pneumonia, or diffuse alveolar hemorrhage have better prognosis than those with invasive Aspergillosis, ARDS, idiopathic pulmonary syndrome, cryptogenic organizing pneumonia, or unknown etiology of ARF [5]. Also, failure of noninvasive ventilation is also predictable of high mortality in these patients [6, 25].

15.10 Noninvasive Ventilation (NIV) in Patients with Cancer

In contrast to invasive MV, NIV preserves the integrity of the upper airway functions and defense mechanisms (allowing swallowing, coughing, and vocalization) and decreases the need for sedation. In addition to the use of NIV as a palliative modality in patients with terminal cancer or have decided not to be intubated, this treatment has been increasingly used in the management of ARF in patients with cancer. Some, but not all studies, have shown that NIV has a positive effect on these patients [26]. These encouraging results have prompted clinicians to use NIV as initial ventilatory strategy for ARF in patients with cancer.

Data on the use of NIV in patients with cancer are provided by two small randomized controlled trials as well as a larger set of observational studies [27]. Both interventional studies randomized immunocompromised patients with

hypoxemic ARF (defined as PaO_2/FiO_2 of <200) to treatment with either NIV or with standard supplemental oxygen. Antonelli and colleagues studied 40 solid organ transplant patients; NIV averted intubation in 80% (significantly more than in patients treated with supplemental oxygen only), and was associated with reduced ICU, but not hospital mortality [28]. Hilbert and colleagues included a heterogeneous population of immunocompromised patients (56 patients), 30 of whom were patients with hematological malignancy; intubation was avoided in 54%, and both ICU and hospital mortality were significantly lower in the NIV-treated compared with the control arm [29]. In both studies, the lower ICU mortality in NIV-treated patients was mainly due to the lower rate of fatal complications following intubation.

More recently, a systematic review and meta-analysis assessing the impact of initial ventilatory strategy (NIV vs. MV) in 2380 critically ill hematological patients with ARF was performed. It showed that NIV was associated with a significantly lower risk of death compared with initial invasive support in these patients. Also, NIV failure in such patients with a lower severity of illness significantly worsened their outcome, whereas no detrimental effect was observed for those with a higher predicted mortality [30]. Similar results have been shown in a most recent large retrospective cohort study that included 1614 patients with both hematological malignancies and solid tumors, who received either conventional MV or NIV as first line therapy for hypoxemic respiratory failure. It showed that patients who failed NIV as first line treatment had lower survival rates than those who succeeded or those who were intubated. Younger age, non-Caucasian race, hematological malignancy, and a higher SOFA score were independent predictors of failure. No difference in mortality between early versus late intubation was found [31]. Other risk factors that have been identified to be associated with NIV failure in cancer patients with ARF include factors prior to initiation of NIV such as vasopressor use, multiorgan failure, malignancy involving the airways, ARDS, and delayed onset of ARF. During NIV, factors associated with failure are lack of tolerance, no improvement in arterial blood gases within 6 h, respiratory rate >30/min, NIV dependency 3 days or longer, clinical or respiratory deterioration, and lack of known etiology of ARF [25, 32].

Conclusion

The improvement in the outcome of critically ill patients with cancer is real and promising. ARF remains the most challenging aspect of critical illness in this patient population and the need for MV is associated with higher mortality. Nevertheless, this therapy plays an important role in the management of a significant number of these patients. Identifying the patients who are likely to benefit from MV, initiating therapy in a timely fashion, and choosing the appropriate ventilatory strategy are key factors for successful outcome. Close monitoring and frequent assessments of patients' progress on MV are essential to determine if they are benefiting from this treatment and to avoid continuing futile care.

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Invasive and Interventional Procedures

16

Fayez Kheir and Adnan Majid

Acute respiratory failure represents one of the most common causes of intensive care unit (ICU) admissions in patients with hematologic or solid cancer. Malignant central airway obstruction, massive hemoptysis, and malignant pleural effusion represent common causes of airway compromise, ICU admission, and possible increased need for mechanical ventilation. In this chapter we will discuss potential therapeutic strategies that might provide successful symptomatic relief, possible liberation from mechanical ventilation, and a better opportunity for definitive surgical, radiation, and chemotherapy treatment.

16.1 Malignant Central Airway Obstruction

Malignant central airway obstruction (CAO), defined as obstruction in central airways, the trachea, and/or mainstem bronchi, can cause minimal symptoms until the airway becomes critically narrowed causing dyspnea at rest, significant morbidity, and increased risk of death from suffocation if left untreated. Approximately 30% of patients with lung cancer have associated CAO. Other common malignancies that cause CAO are colon, breast, renal, and metastatic melanoma. Malignant CAO can be classified into three categories: endobronchial, extrinsic compression, and a mixed pattern (Figs. 16.1 and 16.2).

The initial approach should focus on maintaining airway stabilization and reestablishing patency to allow time for more possible definite therapy or palliation. Relief of CAO has been shown to improve symptoms, functional status, quality of life, and possibly survival.

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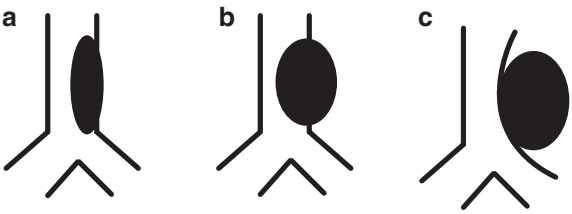

Fig. 16.1 Types of central airway obstruction. (**a**) intrinsic, (**b**) mixed, and (**c**) extrinsic

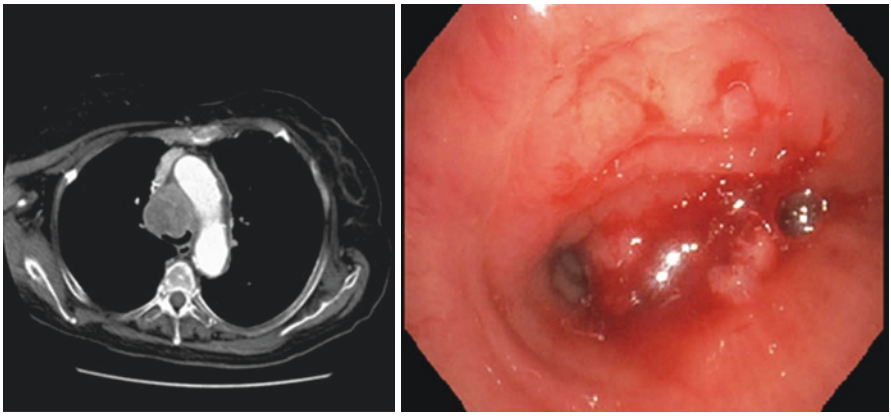

Fig. 16.2 Computed tomography of the chest (*left*) and bronchoscopic view (*right*) for a patient with malignant central airway obstruction

Systemic chemotherapy and/or radiotherapy have showed unsatisfactory results in rapid restoration of airway patency in patients with malignant CAO. Treatment options for immediate relief of CAO include airway dilatation, ablative therapies, and mechanical techniques. Maintaining patency can be achieved with stents (silicone, metal or hybrid). The choice of treatment depends on patient clinical status, underlying process, type of lesion, equipment availability, and operator experience. So far, no strong data exist about prospective randomized studies comparing the effectiveness of one approach over another and no modality has proven to be superior. It is important to emphasize that any treatment modality should involve a multidisciplinary team comprising of interventional pulmonologist, intensivist, medical oncologist, radiation oncologist, and thoracic surgeon.

16.1.1 Bronchoscopy

Rigid bronchoscope might be the preferred modality over flexible bronchoscope in such setting. Unlike the flexible bronchoscope, the rigid bronchoscope requires general anesthesia for insertion. However, it allows better airway protection and ventilation while re-establishing airway patency, selective intubation of one of the main stem bronchi, mechanical debridement of the affected airway, tamponading any

bleeding and permitting the use of flexible bronchoscope through the rigid barrel to evaluate any distal obstruction. Furthermore, the wider operating channel permits passage of instruments, such as lasers, ablation devices, suction catheters, and forceps, as well as facilitates the deployment of stents.

16.1.2 Airway Dilatation

Dilating the obstructed airway can be achieved either mechanically using a rigid bronchoscope barrel, a semirigid Jackson dilator, or a non-conformal balloon which are available in different sizes (Fig. 16.3). Although immediate airway patency can be achieved in 80% of cases, it is not sustained unless combined with other modalities such as endobronchial debridement, airway stenting, and/or ablative therapy. Complications are rare and include airway rupture leading to pneumothorax or pneumomediastinum, mediastinitis, chest pain, and hemorrhage.

16.1.3 Ablation Therapies

The ablative techniques are classified according to their effect (immediate versus delayed), mechanism of action, and depth of tissue. In the following section, we will discuss electrocautery, argon plasma coagulation, laser, and cryotherapy. Brachytherapy and photodynamic therapy are beyond the scope of this chapter and will not be discussed here.

1. Electrocautery

   Electrocautery (ECT) is a contact thermal ablative technique that uses an electric current conducted by an insulated metal wire probe to generate heat and eventually burn the tissue. ECT cauterizes vessels to achieve hemostasis and helps in tumor debulking along with debridement. It should not be used with extrinsic compression CAO and when oxygen concentration is not below 40%. Different ECT

Fig. 16.3 (*Left* to *right*) Rigid bronchoscope barrel, semirigid Jackson dilator, and balloon dilator

devices are available, including probes, snare, knife, and forceps (Fig. 16.4). Complications include bleeding, airway perforation, damage to the bronchoscope, and airway fire (if FiO_2 is above 40%). ECT has been shown to attain endoscopic and radiographic improvement and decrease the need for further laser therapy.

2. Argon Plasma Coagulation

   Argon Plasma Coagulation (APC) is a noncontact electrocoagulation using high frequency current by means of ionized argon gas (plasma). APC is effective in achieving hemostasis from bleeding endobronchial lesions and tumor debridement of CAO (Fig. 16.5). As in the case of ECT, APC should not be used in patients with extrinsic compression CAO or when oxygen concentration is above

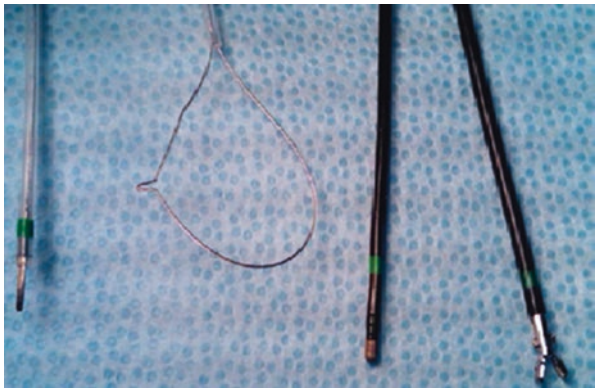

Fig. 16.4 Electrocautery devices (*left* to *right*)—knife, snare, probe, and forceps

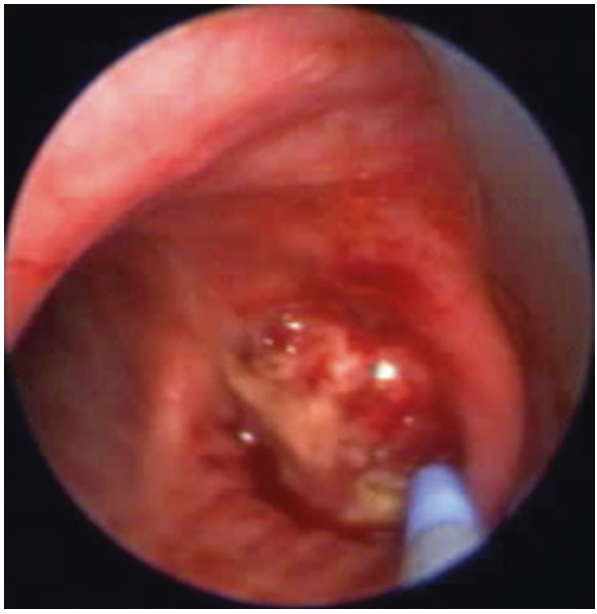

Fig. 16.5 Argon plasma coagulation probe for endobronchial lesion

40%. Complications of APC include gas embolism besides similar adverse events of ECT. APC and ECT are less effective than laser in achieving large tumor debulking but have limited risk of airway damage and perforation due to less tissue penetration compared to laser therapy.

3. Laser

   Endoscopic laser (light amplification by stimulated emission of radiation) produce a beam of monochromatic, coherent light that focuses thermal energy onto tissues causing vaporization, coagulation, devascularization, hemostasis, and necrosis. It is one of the most important techniques used for bronchial debulking of endobronchial tumor. Several laser types have been used in the airway, including carbon dioxide laser (CO2), potassium titanyl phosphate (KTP), neodymium:yttrium-aluminum-garnet (Nd:YAG) and neodymium:yttrium-aluminum-perovskite (Nd:YAP). Nd:YAG is the most commonly used laser in the airways. Comparing Nd:YAG laser to other modalities: (1) CO2 has a poor coagulation property; (2) Nd:YAP has a better coagulation and devascularization but decreased vaporization and cutting ability; (3) KTP is preferentially absorbed by hemoglobin which makes it well suited for vascular lesions but has less tissue penetration. The volume of ablation is determined by target tissue, power setting, and pulse duration. Tissue penetration of Nd:YAG is up to 10 mm, which is deeper that ECT and APC, with power settings between 20 and 40 W and pulse duration of 0.5–1.0 s. Laser can be used for endobronchial CAO as an adjunct to debridement. As in the case of other ablative therapies, laser should not be used in patients with extrinsic compression CAO or when oxygen concentration is above 40%. Complications include bleeding, airway perforation, airway fire, death, and cardiac and cerebrovascular gas embolism.

   The effectiveness of the Nd:YAG laser has been assessed in several large case series studies that showed radiographic and endoscopic improvement in 85–94% of cases with reported complications less than 17%. The success was higher in central rather than peripheral airways and when there was no associated extrinsic compression. Moreover, Nd:YAG therapy has been shown to improve quality of life, symptoms, performance status, and probably survival when combined with chemo and radiation therapy.

4. Cryotherapy

   Cryotherapy induces tumor destruction by causing hypothermic cellular crystallization and microthrombosis through repeated cycles of extreme cold (below −40 ° C) followed by slow thawing. The absolute effects depend on the rapidity of the freezing and thawing, the lowest temperature achieved, the number of freeze–thaw cycles, and the water content of the tissue causing both physical and vascular tissue injury. The Joule–Thomson effect describes the decrease in temperature that is observed during the expansion of gas from a high- to a low-pressure environment. Nitrous oxide which is stored at room temperature under high pressure is the most commonly used cryogen. When it is released at the tip of the cryoprobe, the temperature falls to −89 ° C within several seconds and placed in direct contact with the endobronchial tumor and pulled back after having frozen the tumor.

Recently, cryodebridement (CD) techniques (also called cryosurgery) (Fig. 16.6), in which the cryoprobe uses cryoadhesion to achieve immediate recanalization, remove airway obstruction more expeditiously, thus reducing the need for repeat endoscopic procedures. CD requires the use of a secure airway via the laryngeal mask, endotracheal intubation, or rigid bronchoscopy with total intravenous anesthesia. Case series have shown that CD, when used alone or in combination with other endoscopic treatment modalities such as APC and ECT, is safe and effective in improving symptoms as well as achieving airway patency in patients with malignant CAO. The most common complication reported in CD case series is bleeding which is often minor and resolves with conservative measures.

Spray cryotherapy (SCT) (Fig. 16.6) in malignant CAO has also been reported in case series, but to a lesser extent than CD. SCT uses liquid nitrogen via a non-contact delivery with a maximal negative temperatures (−196 °C) achieved after 1–2 min. An open circuit rigid bronchoscope or deflating of the endotracheal tube cuff along with holding ventilation as well as low-flow, repeat-freezing cycles are required to prevent gas reexpansion and barotrauma.. Complications of SCT include bleeding, pneumothorax, hypoxemia, bronchospasm, arrhythmias, and death. Another drawback of SCT is the delayed effect on the tissue which requires delayed repeat bronchoscopy (minimum 3–4 weeks) to remove necrotic debris. Thus, more rigorously studies using SCT are needed before widespread use of such therapy be recommended.

16.1.4 Mechanical Debridement

Endobronchial lesions causing CAO can be effectively removed using a forceps biopsy (rigid or flexible), the bevel tip of the rigid bronchoscope (coring out), or a microdebrider (Fig. 16.7).

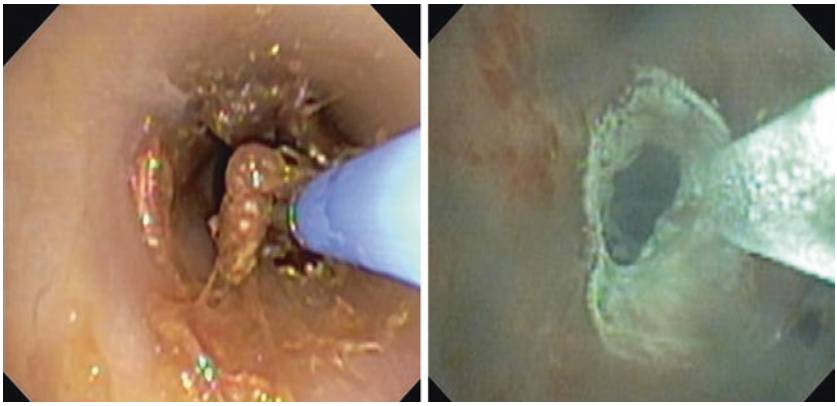

Fig. 16.6 Cryodebridement (*left*) and Spraycryotherapy (*right*)

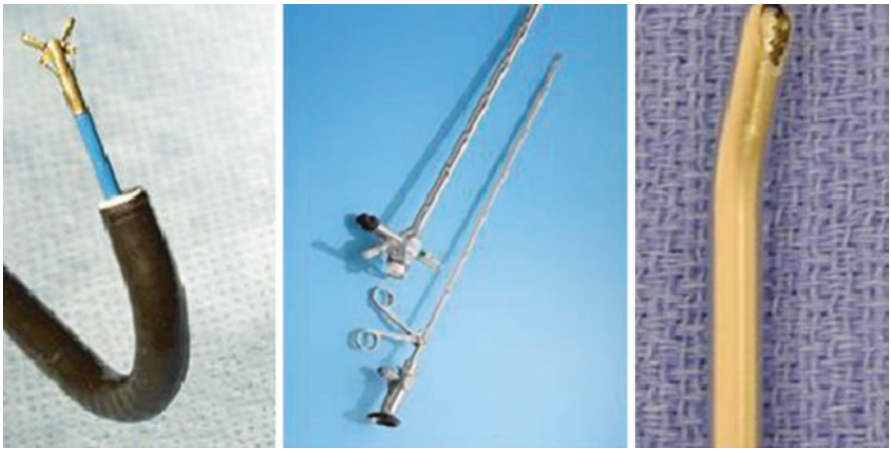

Fig. 16.7 Mechanical debridement devices (*left* to *right*)—flexible forceps, rigid bronchoscope, rigid forceps, and microdebrider

Under direct visualization, the interventionalist can gently remove endobronchial or endotracheal tumor by placing the beveled edge of the rigid bronchoscope against the base of lesion and gently rotating with forward pressure to bluntly dissect it away from the wall. Fragments from the tumor can be removed with a suction catheter, forceps, or other devices. It is crucial to emphasize that this technique requires careful attention to maintain spatial orientation and ascertain the origin and extent of endoluminal obstruction. Additional benefits of the rigid scope is the ability to provide adequate suctioning while maintaining a patent lumen for adjunctive instruments and maintain ventilation throughout the procedure.

Debulking of an endoluminal tumor can also be achieved using a microdebrider to morselize and aspirate the lesion. The microdebrider is a tool that has been used by orthopedics and ENT surgeons before being adapted by interventional pulmonologists in the management of CAO. It is a hollow metal tube with an internal rotary blade that can rotate in a 360° angle. The microdebrider should always be deployed under direct visualization with the blade parallel to the airway wall axis avoiding putting any pressure on the airway. Perhaps the most common but avoidable complications are accidental normal airway resection or perforation when the technique is not applied adequately.

16.1.5 Airway Stents

The main purpose of an airway stent in malignant CAO is to restore airway patency (Fig. 16.8), alleviate symptoms, and improve quality of life, functional status, and possibly survival. Stents should be regarded as a palliative option or as a bridge to therapies such as chemoradiation or surgery. Purely endobronchial CAO is often managed with debulking/ablative therapy with a stent placement if necessary

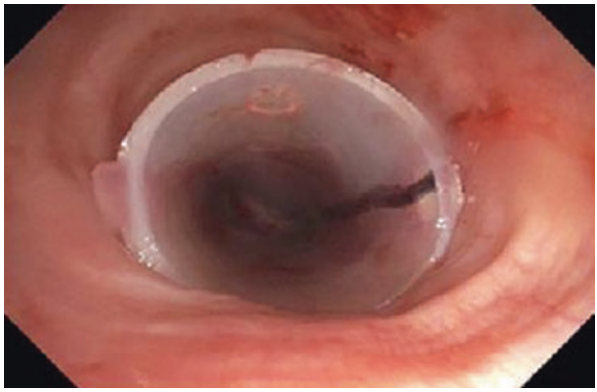

Fig. 16.8 Bronchoscopic view after a stent placement and restoration of airway patency in a patient with malignant central airway obstruction

whereas an extrinsic compression without endoluminal disease is usually treated with dilatation followed by stenting. The treatment of mixed pattern (intrinsic and extrinsic) CAO requires a multimodality approach of debulking/ablative therapy and stent insertion.

The proper sizing and choice of stent depends on airway anatomy, length, and diameter of the obstruction. Although airway measurements can be done quantitatively based on computed tomography (CT) or multidetector CT with virtual bronchoscopy reconstruction; it is only during bronchoscopy that secretions, necrotic tissues, and blood clots can be distinguished from tumor causing CAO as well as airway diameter can be measured accurately for proper stent placement.

Stents are usually placed in the trachea, main stem bronchi, and bronchus intermedius. A special attention should be made when placing stents in the right mainstem bronchi as the right upper lobe should not be covered if it is still patent. The length of the stent should extend about 5 mm proximal and 5 mm distal to the lesion of interest. Although stents should fit firmly to avoid migration but oversized stents may induce excessive granulation tissue or mucosal ischemia.

Airway stents are generally divided into two types: silicone stents (tubular and Y-shaped) and metallic stents (fully covered, partially covered and uncovered). Table 16.1 lists the comparison between the two types.

1. Silicone Stents

   Silicone stents remains the most commonly used stents for the treatment of benign and malignant airway obstruction. It has two specific designs: straight (tubular) and Y-shaped (for disease involving the carina). These stents are covered with little studs on their surface to theoretically prevent stent dislocation accompanied with a smooth inner surface to minimize plugging of secretions. Compared with metal stents, silicone stents are cheaper, can be easily removed or repositioned, and can undergo on-site customization for aeration of patent lobar bronchus. However, silicon stents require insertion through a rigid bronchoscope under general anesthesia and does not conform well to the airway.

Table 16.1 Comparison of silicone stent and self-expanding metal stent (SEMS)

Silicone	SEMS
Rigid bronchoscopy for insertion	Rigid of flexible bronchoscopy for insertion
Does not conform well to tortuous airways	Conform to tortuous airways
Can be customized on-site	Cannot be customized on-site
Removed and adjusted easily	More difficult to remove/adjust
Requires more expertise to deploy	Deployed easily
Low internal to external diameter ratio	High internal to external diameter ratio
Higher incidence of migration	Less incidence of migration
No tumor in-growth	Tumor in-growth with uncovered SEMS
Impairs mucociliary clearance	Preserves mucociliary clearance
Low incidence of granulation tissue formation	Higher incidence of granulation tissue formation
No wall perforation	Risk of airway wall perforation

Several large case series have suggested that airway patency can be readily established with immediate relief of respiratory symptoms and improvement in quality of life among majority of patients with malignant CAO.

2. Metallic Stents

There has been considerable improvement in metallic stent technology since their early development. Earlier designs were made of steel and required balloon dilation after deployment in order to expand. In addition, they do not re-expand following deforming forces such as coughing. These were replaced by the newer generation of self-expanding metallic stents (SEMS). SEMS are made from metal alloys such as nitinol (nickel and titanium).

Nitinol exhibits shape memory, a property allowing stent expansion to its intended size following deployment. Also, nitinol displays an elastic property that prevents damage to the mucosa, regains its shape after deforming forces such as coughing, and exhibits adequate resistance to airway compression by the tumor. SEMS exert an outward radial force and migrate less than silicon stents. SEMS may be covered with plastic (polyurethane or silastic) or uncovered (Fig. 16.9). Uncovered stents allow mucocilliary clearance and neo-epithelialization of stent walls but are prone to tumor and granulation tissue in-growth. Partially covered stents are used in the presence of endobronchial tumor in order to avoid tumor in-growth but the proximal and distal ends of the stents are not covered allowing granulation tissue and tumor to grow through the stents' mesh. In addition, these stents conform well to the tortuous airways occurring with the presence of tumors. The main disadvantage of metal stents is that they are difficult to be removed and are usually avoided in long-term use such as benign airway diseases. Fully covered SEMS, although they prevent tumor in-growth and are easily removed, they have increased rigidity and may not conform well in tortuous airways.

As in the case of silicone stents, several retrospective studies have showed immediate symptomatic improvement and airway patency in patients with malignant CAO undergoing SEMS placement.

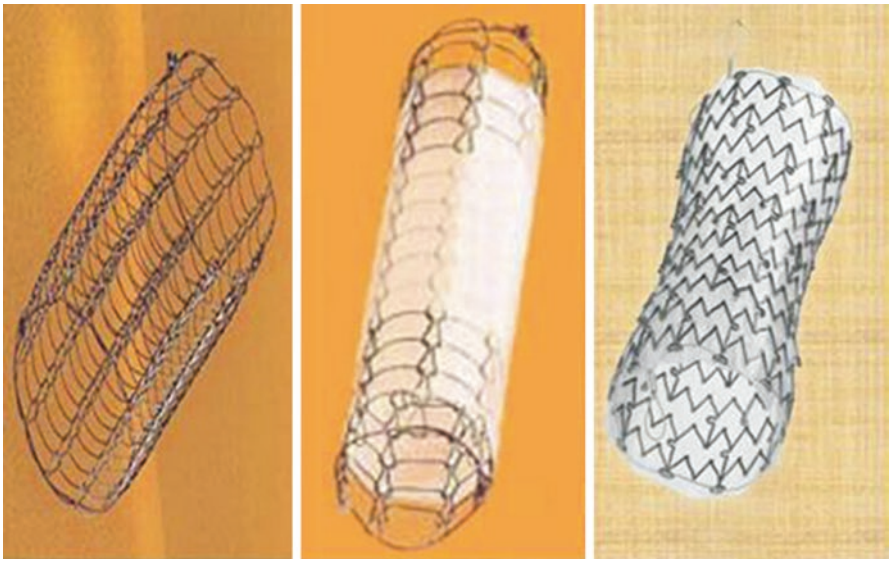

Fig. 16.9 Metallic stents (*left* to *right*)—uncovered, partially covered, and fully covered

3. Complications of airway stents
   (a) Silicone Stents

   The most common complication of silicone stents are migration that occurs in around 10% of the cases. It usually present as increased cough, hoarseness (if tracheal or subglottic location), and shortness of breath. It occurs due to inappropriate size or tumor shrinkage after treatment. It is managed by stent removal with rigid bronchoscopy and possible replacement of a new stent or percutaneous external fixation in selected cases. Granuloma tissue formation occurs in around 8% of the cases and can obstruct the stent at the distal and proximal end. Mechanical and ablative therapy as well as replacement of the stent might be considered in such cases. Other complications include mucous plugging and bacterial overgrowth which can be reduced by maintaining humidification of the stent through nebulized solution and taking mucolytic therapy.

   (b) Metallic Stent

   The frequency of complications of metallic stents depends on stent type and survival after stent placement. Granulation tissue formation occurs at the ends of the stents due to frequent contact of the mucosa with stent causing chronic inflammation and can be treated with mechanical/ablative therapy. Tumor stent in-growth can occur with uncovered or partially covered SEMS and usually treated with mechanical/ablative therapy. Stent migration occurs much more commonly in covered SEMS and can be treated with repositioning or removal (if occurred >30 post placement). Mucous impaction and infection can also occur in SEMS and incidence can be usually reduced by nebulized

saline and mucolytics. Other reported complications such as stent fracture and bronchovascular and tracheobronchial fistulas can occur and usually require multidisciplinary team and expertise to manage such adverse events.

16.2 Massive Hemoptysis

Although there is no universal acceptable definition, volumes of 100–1000 mL over a 24-h-period have been used in the medical literature to define massive hemoptysis. It comprises around 5% of all hemoptysis cases with a mortality rate exceeding 50%. It is believed that the amount of blood that threatens patient's condition rather than volume of blood itself be used to define massive hemoptysis.

1. Anatomy

   The lungs have two arterial vascular supplies: the pulmonary arteries and the bronchial arteries. The pulmonary arteries originate from the right ventricle, branch into lobar arteries, and then form small alveolar capillary interface. They provide around 99% of arterial blood supply to the lungs and participate in gas exchange. They are regarded as a low pressure and resistance system capable of accommodating increased blood flow without remarkable increase in pressure. The bronchial arteries (right and left bronchial artery) usually arise from the upper portion of the descending thoracic aorta or from right intercostal arteries (right bronchial artery). Ectopic bronchial arteries occur in around 30% of cases and commonly arise from the inferior aspect of the aortic arch, subclavian artery, brachiocephalic trunk, thyrocervical trunk, internal mammary artery, costocervical trunk, pericardiophrenic artery, inferior phrenic artery, abdominal aorta, and coronary arteries. The bronchial arteries are regarded as high pressure system and thus massive hemoptysis can be more rapid and life-threatening when arising from such blood supply rather than from pulmonary arteries. Furthermore, the pulmonary parenchymal nutrient supply is provided by bronchial arteries.
2. Causes

   Around 90% of massive hemoptysis originates from bronchial arteries, 5% from pulmonary arteries, and the remaining 5% from other sites such as pulmonary, bronchial veins and capillaries. Some authors classify massive airway hemorrhage according to location: proximal airways (trachea, mainstem, and proximal lobar bronchi) and distal airways. Others classify hemoptysis broadly according to its origin: immunologic, infectious, neoplastic, autoimmune, cardiovascular, coagulopathic, trauma, and iatrogenic. For the purpose of this chapter, the three common causes requiring cancer patients to be admitted to the intensive care unit for massive hemoptysis are (a) neoplasm, (b) infectious cavitary lung disease, and (c) coagulopathic diseases.

   (a) Neoplasm

   Although any type of lung cancer can cause hemoptysis, squamous cell lung cancer is the most common type that leads to massive hemoptysis due to its central location and tendency to cavitate. Chemotherapeutic agents

such as bevacizumab can cause bleeding in patients with cavitary lung lesions. Furthermore, any endobronchial or intraparenchymal metastatic tumor to the lung can cause massive hemoptysis.

(b) Fungal Infection

Immunocompromised patients secondary to chemotherapy and hematopoietic stem cells transplant can predispose patients to invasive fungal infections such as aspergillosis forming a cavitary lung lesion. However, massive hemoptysis is usually uncommon until neutrophil recovery begins. The neutrophil infiltration promotes a rapid and brisk inflammatory response leading to vascular disruption and massive airway hemorrhage.

(c) Coagulopathic Diseases

Due to prolonged bone marrow suppression in patients receiving chemotherapy or stem cell transplant, patients are prone to have diffuse intraparenchymal hemorrhage. The treatment in this situation is usually supportive with blood, platelet and plasma transfusion as well as other medications to enhance bone marrow activity. Other agents such as tranexamic acid, thrombin and fibrin endobronchial therapy have been reported in case reports and small case series.

3. Diagnostic Workup

(a) Laboratory Studies

Complete blood count, coagulation profile, calcium, blood urea nitrogen, and creatinine should be sent and attempt to correct any abnormalities should be done. Also, sputum culture should be sent to assess any underlying fungal infection for instance.

(b) Chest Radiography

CXR is a quick, inexpensive, and readily available imaging that can be used as initial screening tool to help localize or lateralize source of bleeding. It can also help detect any cavitary lung lesions, masses, or lobar/alveolar infiltrates. However, CXR sensitivity is around 50–75% and negative CXR warrants further workup.

(c) Computed Tomography

Multidetector computed tomography (MDCT) represents an important imaging tool to guide therapy. Contrast enhancement allows comprehensive evaluation of the lung parenchyma, airways, and thoracic vessels. MDCT has the ability to visualize distal airways that might be beyond the reach of bronchoscopy. It can identify bleeding site in >60% of the case. Importantly, MDCT angiography can help carefully evaluate bronchial arteries, nonbronchial arteries, and pulmonary arteries circulation supply to the bleeding lesion in order to choose which vessels might be amenable for embolization. The ability to trace vessels from their origin to the hilum rather than detecting vessels diameter dilatation alone is important to identify cause of hemoptysis. The major limitations of MDCT are (1) inability to differentiate between a blood clot and endobronchial lesion, (2) time required to obtain study, and (3) ability for the patient to lie supine without compromising airway clearance. Urgent intervention should not be delayed for a MDCT in the event of acute rapidly progressing life-threatening hemoptysis.

4. Management

The management of massive hemoptysis should always involve a multidisciplinary team comprising of intensivist, interventional pulmonologist, thoracic surgeon, and interventional radiologist. Table 16.2 summarizes steps taken in patients presenting with massive airway hemoptysis.

(a) Airway Stabilization

The first step in the management of massive hemoptysis is securing the airway. If the site of the bleeding is known, patient should be placed in the lateral decubitus position with the affected side down and allowed to clear his/her own airway secretions. Endotracheal intubation should be considered if patient cannot clear the bleeding, develops respiratory distress and/or hypoxemia secondary to hemoptysis. It is recommended that large bore endotracheal tube (ETT >8.5 mm) be placed to facilitate further management, suctioning and bronchoscopic insertion. Bronchoscopic endotracheal intubation is recommended in an attempt to isolate unaffected lung, inflate ETT balloon in the main stem, and prevent blood spillage to the unaffected site. Double-lumen ETT is usually not recommended since its placement is technically difficult, time consuming and often inaccurate. Besides, the narrow lumens predispose to blockage from blood clots and patients will require neuromuscular blockade for paralysis.

(b) Interventional Pulmonary Approach

Rigid bronchoscopy is an essential skill needed in patients with hemoptysis. It provides large volume suction as well as large conduit to introduce different tools while maintaining airway patency, adequate oxygenation and ventilation. In the case of proximal airway hemorrhage rigid bronchoscopy can tamponade the site to form a clot while other therapeutic measures are administered.

Mechanical approaches to control bleeding are balloon-occlusion devices. In general, bronchial bleeding can be halted by tamponading the segment of the airway using a Fogarty catheter, pulmonary artery catheter, or a bronchial blocker. A 6 or 7 French Fogarty arterial embolectomy catheter can be introduced to the right or left main stem airway to occlude the area on interest. Fogarty balloon can be introduced through a bronchoscopy working channel

Table 16.2 Approach to patients with massive airway hemoptysis

1. Massive hemoptysis identified
2. Remember ABC (airway, breathing, circulation)
3. Coagulation profile, hemoglobin, chest radiography
4. Patient in lateral decubitus position (if bleeding site is known)
5. Multidetector computed tomography angiography in stable patients to identify vessels
6. Bronchoscopy to localize and identify any endobronchial causes
7. Assess with a multidisciplinary team best approach to control bleeding (endobronchial therapy or bronchial artery embolization)
8. Assess with a multidisciplinary team for definitive therapy (radiation therapy, delayed or emergent surgery)

but cannot be left in the desired site. Another way is to introduce this catheter by rotating the head of the patient to the opposite direction of the desired mainstem. Although this approach is cumbersome and balloon is prone to migration, it might provide enough time for clot formation and initiation of definitive procedure. Alternatively, a specialized bronchial balloon catheter (Arndt endobronchial blocker set, Cook Medical, Bloomington, IN, USA) can be used that has the additional advantage of being fixated in the desired site for prolonged time period (Fig. 16.10). This can be achieved via a specialized three ports ETT adaptor: (1) ventilation port, (2) bronchoscopy access port, and (3) bronchial blocker balloon access port (Fig. 16.10). Regardless of the catheter being used, the balloon should be inflated to the minimum, deflated periodically to prevent mucosal ischemia, and bronchoscopy done frequently to assess any brisk bleeding. Others devices such as silicone spigots, surgical packing, stents, or mesh have also been described in the literature.

Endobronchial cold saline lavages, epinephrine, vasopressin, and thrombin/fibrin therapy can be attempted to control bleeding by inducing vasoconstriction and hemostasis. Ablative therapy can be applied endobronchially as well. They are especially useful when an endobronchial lesion is identified as the source of bleeding. ECT, APC, and laser can be applied effectively to control bleeding. However, laser requires a dry field in order to work. Cryodebridment is also very effective for removing life-threatening clots occluding the central airways without the need to lower FiO_2.

(c) Interventional Radiology Approach

Bronchial artery embolization (BAE) has become the most used nonsurgical approach to control bleeding. It has been shown to be effective in >90% of carefully selected patients and in experienced hands. The success of BAE depends on the ability to identify the bleeding vessel and collaterals. It is especially useful in distal airways bleeding such as tumor invasion but is not the method of choice for proximal airways. Complications are usually rare and minor and include vascular access site (femoral artery), minor risk of stroke, risk of rebleeding, bronchial wall ischemia, and ischemic myelopathy from inadvertent spinal artery embolization.

(d) Palliative Thoracic Radiation Therapy and Surgery

The overall 30-day rate of rebleeding is 30% and thus definite therapy should be planned ahead following temporizing measures such as BAE or rigid bronchoscopy therapy. Unfortunately, most patients presenting with massive hemoptysis are not surgical candidates and therefore radiation therapy might be offered as a palliative treatment. Palliative thoracic radiation therapy has been shown to be well tolerated in >90% of cases and was able to control hemoptysis in around 60–80%. Even if the patients are deemed to be surgical candidates, the surgical mortality from emergent cases of massive hemoptysis is >25%. Recent case series have suggested that the mortality can be reduced or even approach a routine elective resection if less invasive measures (as described earlier) can be done initially to temporize bleeding while optimizing patient's medical condition.

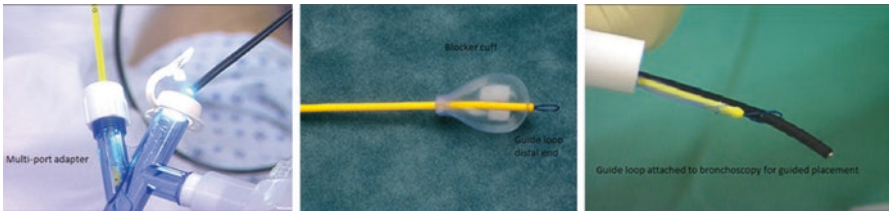

Fig. 16.10 Arndt endobronchial blocker set for massive hemoptysis

16.3 Malignant Pleural Effusion

Malignant pleural effusion (MPE) is common with an estimated incidence of more than 150,000 new cases in the United States each year from a data collected 10 years ago. This incidence is expected to be even higher nowadays as the global burden of malignancy continues to increase. About 30% of patients with breast and lung cancer and 90% of patients with malignant pleural mesothelioma have MPE. The average life expectancy for patients with MPE is 3 month for metastatic carcinomas and 9 months for mesothelioma, although prognosis varies by malignancy type and performance status of patients. MPE causes increased dyspnea requiring hospital and intensive care unit admission. The goal of treatment for such population with limited life expectancy is to alleviate symptoms effectively, prevent recurrence of effusion, and minimize patient's length of hospital stay.

The management of MPE depends on several factors: (1) symptoms are caused by MPE, (2) re-accumulation of effusion after thoracentesis, (3) degree of lung expansion after initial pleural drainage, and (4) prognosis. It is important to assess whether dyspnea is caused by MPE. This can be achieved simply by observing whether patient's symptoms improve after thoracentesis. In several studies, the need for definitive treatment ranged between 40 and 50% over the course of the disease. Moreover, many patients have no to slow re-accumulation of fluids when chemo and radiation therapy is initiated and can be managed more conservatively with observation or simple thoracentesis if needed. Another very important factor to consider is the ability to predict patient prognosis as well as fluid recurrence. A newly developed system called the LENT prognostic score (pleural fluid lactate dehydrogenase, Eastern Cooperative Oncology Group (ECOG) performance score (PS), neutrophil-to-lymphocyte ratio and tumor type) was able to predict survival with significantly better accuracy than ECOG and PS alone. Another study showed that MPE with an effusion of low pleural fluid pH and large size on radiographs at first presentation are more likely to be treated with definitive therapy rather than observation or simple thoracentesis.

Although ultrasound guided thoracentesis is safe and provide rapid relief of symptoms, it does not prevent the recurrence of effusion and eventually symptoms leading to multiple hospital admissions and repeated thoracenteses. Therefore, definitive control of recurrent MPE is needed to achieve better quality of life and

maximize out of hospital stay. Currently, this could be achieved by chemical pleurodesis or indwelling pleural catheter (IPC).

The ideal timing for definite therapy remains unknown. Although most physicians defer intervention until at least one symptomatic recurrence effusion, others advocate for early therapy in appropriate candidates due to inevitable re-accumulation, declining functional status, and risk of trapped lung (inability of the lung to expand due to a restricting fibrous visceral pleural peel).

1. Indwelling pleural catheter

   IPC is ideally placed in an ambulatory setting under local anesthesia. It is a 15.5-French soft silicone catheter (Fig. 16.11) that has distal fenestrations positioned in the pleural space, a proximal polyester cuff that reduces inadvertent migration and a one-way safety valve that prohibits air as well as fluid flow toward the pleural cavity. It can be connected to a vacuum bottle which allows patients and caregivers to drain fluids intermittently after adequate education about proper catheter care and function. A systematic review of 19 cohort studies showed that IPC attained symptomatic improvement in 96%. IPC has been shown to achieve symptomatic control through repeated drainage even in patients with trapped lung. Spontaneous pleurodesis can be achieved via IPC in approximately 50% of patients at a median of 52 days. The frequency (daily vs. less frequently) of IPC drainage to achieve pleurodesis is unclear and is currently being addressed in a multi-central trial. IPC are especially suitable for patients who have adequate social support and able to take good care of IPC. Complications secondary to IPC are usually not immediate post placement and often delayed. Pleural infections occur in around 5% of cases and are often mild and resolve with antibiotics treatment and continuous IPC drainage. Occasionally, IPC removal might be necessary. Also, chemotherapy did not affect the rate of infection in patients with IPC. Tumor metastasis can complicate IPC placement occurring in 10% of cases especially in mesothelioma and can be controlled with local radiation therapy. Other complications include cellulitis, catheter fracture, dislodgement, and blockage.
2. Chemical pleurodesis

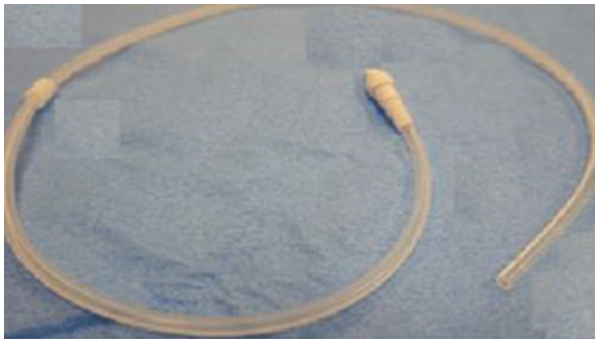

Fig. 16.11 Indwelling pleural catheter

Chemical pleurodesis have been traditionally considered the main treatment for patients with symptomatic recurrent MPE. It can be achieved through injecting a sclerosant into the pleural cavity through a chest tube or during thoracoscopy (medical or surgical (VATS)) in patients without trapped lung. The rate of successful pleurodesis varies considerably in the reported literature between 60 and 100% due to different sclerosants, route of administration (slurry vs. poudrage), duration of follow-up, size of chest tube, study designs, definition of outcomes, and population of interest. Although many substances have been shown to induce successful pleurodesis, talc is the most commonly used sclerosing agent and has been shown to be superior to others in a 2004 Cochrane meta-analysis review of comparative trials. However, the route of administration of talc is still debatable. Talc slurry via chest tube is universally available, less expensive, and relatively easy to perform but may require prolonged hospital stay. An alternative approach is the application of sterile talc powder under direct vision during thoracoscopy (poudrage). However, this approach requires access to thoracoscopy, specialized training, and increased cost. The 2004 Cochrane meta-analysis review suggested a slightly improved rate of successful pleurodesis in the talc poudrage group. However, subsequent randomized trial showed a similar rate of pleurodesis when both groups (slurry vs. poudrage) were compared but post hoc subgroup analysis showed higher successful pleurodesis rate with talc poudrage with lung and breast cancer when trapped lung patients were excluded. A randomized multicenter study is currently undergoing to evaluate the efficacy of thoracoscopy and talc poudrage versus pleurodesis using talc slurry (TAPPS trial) and will hopefully allow clinicians to make the most appropriate and best informed decisions to such patient population. Common complications of talc pleurodesis include pain, fever, and transient hypoxemia. Other rare reported adverse effects include systematic inflammatory response syndrome, arrhythmia, hypotension, and myocardial infarction. It is now well recognized that acute respiratory distress syndrome is caused by nongraded (<15 μm) talc and in patients receiving >5 grams of talc.

3. Indwelling pleural catheter versus chemical pleurodesis

The optimal approach for patient with MPE who have limited life expectancy should focus on effective long-term symptoms relief with minimal need for hospitalization and least adverse effects from treatment. Talc pleurodesis (talc slurry and poudrage) achieved successful pleurodesis only in about 71–78% of patients, required hospitalization for 4–6 days in reported series, and around 22% required further pleural interventions. Besides, talc has known immediate side effects (pain, fever and transient hypoxemia). On the other hand, IPC can be placed as an outpatient procedure without need of hospitalization or immediate side effects. However, IPC requires subsequent care of the catheter inserted, further pleural procedures in about 9% of patients and associated with delayed complications such as infection, blockage, pleural infection, catheter track metastases, etc. necessitating possible hospital admission. So far two randomized studies compared IPC with talc and one randomized study compared IPC with doxycy-

cline. Both IPC and pleurodesis showed equal effective symptomatic control and quality of life but with longer initial hospital stay in the pleurodesis group. The AMPLE (Australasian Malignant Pleural Effusion) is a multicenter randomized trial designed to investigate whether the use of IPC or pleurodesis impacts the need for further hospitalization, adverse events and need for subsequent pleural interventions in the patients with MPE.

An interesting approach that combines both IPC and talc pleurodesis the so-called "Rapid pleurodesis protocol" has been reported in small case series. It consists of IPC insertion and talc poudrage during medical thoracoscopy followed by a large bore chest tube under suction for total of 24 hours. After that IPC was drained daily until low output achieved (<150 mL) on two consecutive attempts and then removed. This has potential to reduce hospital days, catheter days, and time to pleurodesis but remains poorly studied. A multicenter trial is ongoing to address a similar approach of IPC alone versus IPC with talc through IPC in an outpatient setting. Another approach that is being tested in clinical trial is the addition of silver nitrate coating on the intrapleural aspect of the IPC to enhance rates of auto-pleurodesis.

Conclusion

Life-threatening central airway obstruction often requires a multimodality approach which includes a combination of mechanical debridement, an ablative endoscopic procedure, and insertion of a stent. The type of procedure is often dictated by the location/type of lesion and local expertise. These procedures when performed by an experienced operator are safe and effective improving patients' symptoms, quality of life, functional status, and survival.

There are different techniques to manage hemoptysis in cancer patients. The use of bronchoscopic interventions along with BAE and/or palliative thoracic radiotherapy provides symptomatic control with subsequent improvement of the patient's quality of life.

Symptomatic MPE requires a multimodality approach with the goal of palliating the symptoms, preventing fluid recurrence, and minimizing subsequent hospital admissions. Therapeutic modalities for recurrent MPE include pleurodesis and/or insertion of IPC. In patients presenting with a good performance status and life expectancy of >3 month, pleurodesis can be performed either talc slurry or poudrage depending on local expertise, equipment availability, patient preference, and center experience. For patients with a very poor general condition and limited life expectancy or trapped lung following initial thoracentesis, an IPC providing outpatient management can be considered.

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Modes of Mechanical Ventilation

17

Eduardo Mireles-Cabodevila, Abhijit Duggal, and Robert L. Chatburn

Abbreviations

CMV	Continuous mandatory ventilation
CSV	Continuous spontaneous ventilation
IMV	Intermittent mandatory ventilation
PC	Pressure control
PEEP	Positive end expiratory pressure
RR	Respiratory rate
VC	Volume control
VT	Tidal volume

17.1 Modes of Mechanical Ventilation

A mode of mechanical ventilation is a preset pattern of interaction between a patient and a ventilator. There is plethora of modes of mechanical ventilation available for the practitioner; however, these are just names. In reality, many modes, although with different names, do the same thing. We present in method to classify all modes of mechanical ventilation and describe what they do and on which patients to apply.

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17.2 Understanding Modes

All current critical care mechanical ventilators use computer software to control the hardware. Thus, all current mechanical ventilators have an effector (e.g., a form of a blower, flow and pressure regulators) and a computer program that measures the machine and the patient's activity. Thus, it is fair to say that all ventilators have the same basic components. As such, modes of mechanical ventilation in all ventilators have the same three components: (1) the breath control variable, (2) the breath sequence, and (3) the targeting scheme. These three components can be used to describe and classify all the modes of mechanical ventilation [1].

17.2.1 The Breath Control Variable

For practical purposes, the breath control variable refers mainly to the inspiratory portion of the breath. (The expiratory phase is passive and the ventilator maintains a constant expiratory pressure (PEEP)). During inspiration, the ventilator can only control the pressure or flow (volume) that is delivered to the patient. It cannot control both. This is based on the equation of motion, and is described in detail elsewhere [1].

Volume control means that both the tidal volume and inspiratory flow are preset. Flow delivery will not change with changes in respiratory system mechanics (compliance and resistance), but airway pressure does change. Pressure control means either that the inspiratory pressure is preset or it is proportional to the patient's inspiratory effort. Flow delivery changes with changes in respiratory system mechanics. There are unconventional modes of ventilation (e.g., HFO) for which neither pressure, volume, nor flow is preset. Only the inspiratory and expiratory times are preset. Hence the control variable is time.

In summary, most modes of mechanical ventilation can be divided into those that control volume (VC) and those that control pressure (PC). See Fig. 17.1.

17.2.2 The Breath Sequence

A mechanical ventilator also interacts with the patient according to the type of breath delivered. There are two types of breaths that exist when a patient interacts with a ventilator. A mandatory breath is one where the ventilator starts (triggers) or ends (cycles) inspiration (or both), hence the patient has lost some or all control of the timing of the breath. In contrast, a spontaneous breath is one for which the patient both triggers and cycles inspiration, thus retaining control of the timing of the breath.

It follows that only three breath sequences can exist. See Table 17.1.

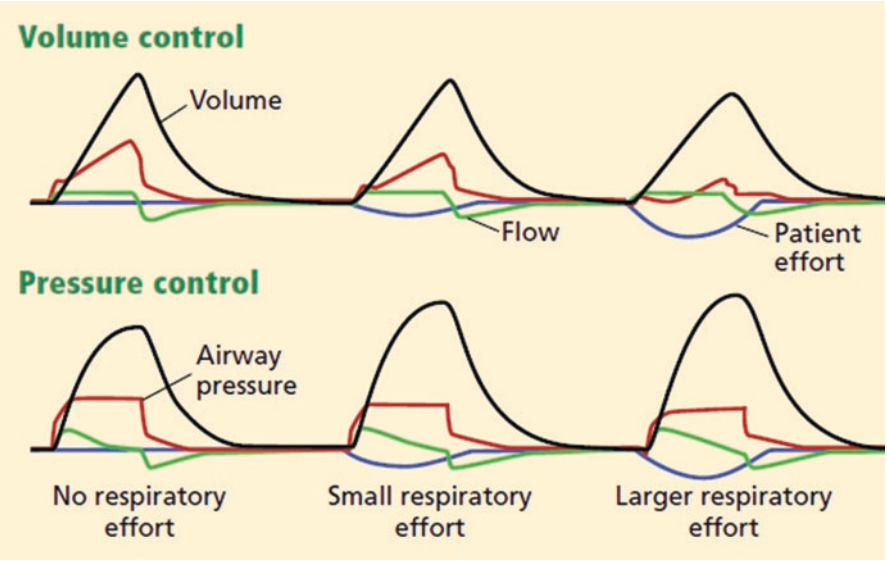

Fig. 17.1 Volume control (*top*) and pressure control (*bottom*) are modes of continuous mandatory ventilation. Each mode is depicted as patient effort increases. Notice that the mode's control variable (volume or pressure) remains constant as patient effort increases. (Permission solicited from Cleveland Clinic Journal of Medicine, from Cleve Clin J Med. 2009 Jul;76(7):417–30.)

Table 17.1 Breath sequences

Breath sequence	Description
Continuous mandatory ventilation (CMV)	All breaths are mandatory
Intermittent mandatory ventilation (IMV)	Mandatory and spontaneous breaths occur
Continuous spontaneous ventilation (CSV)	All breaths are spontaneous

17.2.3 The Targeting Scheme

The computer software obtains signals from the ventilator and from the patient. The ventilator uses these signals to regulate the interaction with the patient. This is called closed loop control. To date, there have been seven different patterns (schemes) that regulate the patient–ventilator interaction [2]. They differ on the method and targets that are used. We call these targeting schemes. See Table 17.2.

17.3 Putting It All Together

A mode of mechanical ventilation is the result of a combination of a breath control variable, a breath sequence, and one (or more) of the targeting schemes. We now can describe a mode of mechanical ventilation, regardless of the brand or brand name, with a simple acronym (e.g., VC-CMVs, refers to a volume control, continuous

Table 17.2 Targeting schemes

Targeting scheme	Description
Set-point (s)	The clinician sets all the targets. The machine delivers, regardless of changes in patient respiratory characteristics or effort
Dual (d)	The ventilator changes from pressure control to volume control (or vice versa) during a single inspiration. The change occurs if a target V_T or a pressure limit is reached
Servo (r)	The ventilator gives pressure proportional to the patient's inspiratory effort
Bio-variable (b)	The ventilator varies support randomly to a deliver V_T pattern similar to normal breathing
Adaptive (a)	The ventilator adjusts inspiratory pressure to deliver an average target V_T with changes in respiratory system mechanics and inspiratory effort
Optimal (o)	The ventilator adjusts targets to minimize or maximize a target (e.g., work of breathing)
Intelligent (i)	The ventilator uses tools of artificial intelligence to adjust targets

mandatory ventilation that uses a set-point targeting). We will now use these definitions to describe some of the most common modes of mechanical ventilation available in clinical practice as well as their interactions with patients and most common indications. Note that each of the ventilators listed has many more modes than mentioned in this brief summary.

17.4 Common Modes of Mechanical Ventilation

In almost all modes, PEEP and FiO_2 are set by the clinician, thus we will not comment on them.

17.4.1 Volume Control Modes (VC-CMV, VC-IMV)

17.4.1.1 Set-Point and Dual Targeting

Commercial names:

- Covidien: A/C Volume Control, SIMV Volume Control (offers only set-point targeting).
- Dräger: Volume Control A/C, Volume Control CMV, Volume Control SIMV (offers both set-point and dual targeting).
- Hamilton: Synchronized Controlled Mandatory Ventilation, SIMV (offers only set-point targeting).
- Maquet: Volume Control, SIMV (offers both set-point and dual targeting).
- Philips/Respironics: Volume Control A/C, Volume Control IMV (offers both set-point and dual targeting).

What the clinician sets: The clinician sets the respiratory rate, tidal volume, inspiratory flow waveform (usually square or descending ramp), and the peak inspiratory flow (this will determine the inspiratory time).

What the ventilator does if patient is passive: The ventilator will deliver the clinician set tidal volume at the set flow rate and given respiratory rate. The minute ventilation is the result of the clinician set rate and tidal volume. The tidal volume will be delivered unless a pressure alarm is reached. Changes in the patient's compliance and resistance lead to changes in the pressure the ventilator delivers.

What the ventilator does if the patient is actively breathing: The patient will trigger the breath as long his breath rate is faster than the set rate. There is a minimum minute ventilation that the patient will receive (rate x tidal volume), so all patient triggered breaths add to the actual minute ventilation.

For set-point targeting, as the patient effort increases, the contribution of the ventilator to the total work of breathing will decrease (need less pressure to deliver the set tidal volume), thus the work of breathing is shifted to the patient. For dual targeting, as patient effort increases, inspiration switches from VC to PC and the tidal volume can be as large as the patient wants.

Type of Patient-Ventilator Interactions: The most common types in VC-CMVs are

- Double triggering: The patient effort is so large that he triggers a second ventilator breath after the first one is over. This leads to breath stacking, the patient gets up to double the size tidal volume. Dual targeting tends to reduce double triggering [3].
- Cycle dyssynchrony: The patient effort ends earlier or later than the set inspiratory time. This can lead to discomfort.
- Flow dyssynchrony: As the patient's demand for flow is not constant, nor in a descending ramp pattern, the preset ventilator flow will frequently not match demand. This can lead to discomfort and perhaps to wasted energy on the part of the patient. Dual targeting minimizes flow asynchrony [3].
- Unsupported Work of Breathing: As the patient effort increases, the ventilator will need less pressure to deliver the set tidal volume. Work output of the ventilator is a function of pressure and volume. Thus, for set-point targeting, the work output per breath of the ventilator decreases while the total work remains constant, so the work of breathing is shifted to the patient.

Indications of VC-CMVs in an oncologic patient: This mode is indicated when the clinician is concerned about ensuring gas exchange and when attempting to prevent VILI by limiting tidal volumes. A classic condition could be alveolar hemorrhage in the setting of bone marrow transplant. These patients have rapidly changing lung compliance, where volume control would ensure minute ventilation. It would also ensure a controlled tidal volume to minimize the risk of VILI.

17.5 Pressure Control Modes with Mandatory Breaths (PC-CMV, PC-IMV)

17.5.1 Set-Point Targeting

Commercial names:

- Covidien: A/C Pressure Control, SIMV Pressure Control
- Dräger: Pressure Control CMV, Pressure Control SIMV
- Hamilton: Pressure Controlled CMV, Pressure SIMV
- Maquet: Pressure Control, Pressure Control SIMV
- Philips/Respironics: Pressure Control A/C, Pressure Control IMV

What the clinician sets: The clinician sets the respiratory rate, inspiratory pressure, and inspiratory time.

What the ventilator does if patient is passive: The ventilator will deliver the clinician set inspiratory pressure for the set inspiratory time and set respiratory rate. The minute ventilation is the result of the clinician set rate and the patient resultant tidal volume. The tidal volume is dependent on the patient's lung respiratory characteristics (compliance and resistance). That is, changes in the patient's compliance and resistance lead to changes in the volume the ventilator delivers.

What the ventilator does if the patient is actively breathing: The patient will trigger the breath as long his breath rate is faster than the set rate. There is no minimum minute ventilation, as the tidal volume is dependent on the patient respiratory characteristics. As the patient effort increases, the ventilator will deliver larger tidal volumes. The contribution of the ventilator to the total work of breathing remains constant as the patient effort increases.

Type of Patient-Ventilator Interactions: The most common types of asynchrony in PC-CMVs are

- Double triggering: The patient effort is so large that he triggers a second ventilator breath after the first one is over. In contrast to VC-CMVs, the patient will get a second breath that is determined by the respiratory system characteristics (compliance and resistance) and a PEEP. Thus breath stacking is less injurious in VC-CMVs.
- Cycle dyssynchrony: The patient effort ends early or late than the set inspiratory time. This can lead to patient discomfort.

Indications of PC-CMVs in an oncologic patient: This mode is indicated when the clinician is concerned about keeping a constant level of pressure, maintaining a level of ventilator support, or when variable flow is required. A common patient would be one recovering from pneumonia, in which the level of sedation is being decreased, and we want to maintain ventilator support while allowing some comfort.

17.6 Airway Pressure Release Ventilation, BiVent, and DuoPAP (PC-IMVs,s)

17.6.1 Set-Point Targeting

- Covidien: Bilevel
- Dräger: Airway Pressure Release Ventilation
- Hamilton: Airway Pressure Release Ventilation, DuoPAP
- Maquet: Bi-Vent

What the clinician sets: The clinician sets two levels of pressure corresponding to inspiratory and expiratory pressure (P-high and P-low) and two times corresponding to inspiratory and expiratory time (T-high and T-low, in seconds). An inverse Inspiration:Expiration ratio is characteristic of APRV (4:1 or greater). The I:E ranges from 1:1 to 1:4 in the other modes.

What the ventilator does if patient is passive: The ventilator will deliver the clinician set inspiratory pressure for the set inspiratory time. The minute ventilation is the result of the clinician set rate (rate in bpm = 60 s/[T-high + T-low]) and the resultant tidal volume. The tidal volume is dependent on the patient's lung respiratory characteristics (compliance and resistance). That is, changes in the patient's compliance, resistance, and autoPEEP lead to changes in the volume the ventilator delivers. This would be a form of pressure controlled inverse ratio ventilation.

What the ventilator does if the patient is actively breathing: This mode allows spontaneous breathes at any point during T-high or T-low. On some ventilators, the T-high is synchronized with the patient's inspiratory effort and T-low with spontaneous exhalation, which may affect the duration of each period. The spontaneous breaths classically do not receive any type of pressure assistance (although some manufacturers do). There is no minimum minute ventilation, but there is an amount of the minute ventilation that comes from the patient effort, and other that comes from the intermittent mandatory breaths. Because this is a pressure control breath, the tidal volume is dependent on the patient respiratory characteristics. As the patient effort increases, the ventilator will deliver larger tidal volumes. The contribution of the ventilator to the total work of breathing remains constant as the patient effort increases.

Type of Patient-Ventilator Interactions: There are multiple types of asynchrony and dyssynchronies in inverse ratio PC-IMVs,s. The interaction between the patient and the ventilator may be independent, thus predisposing to dyssynchrony between patient and ventilator [4]. Proponents state that it is more comfortable, although evidence to that respect is lacking.

Indications of inverse ratio PC-IMVs,s in an oncologic patient: There is currently no indication for use of PV-IMVs,s as it does not serve any goal of mechanical ventilation and may lead to conditions that promote ventilator induced lung injury [5].

17.7 Adaptive Pressure Control (PC-CMVa, PC-IMVa,s)

17.7.1 Adaptive Targeting

Commercial names:

- Covidien: A/C Volume Control Plus, SIMV Volume Control Plus
- Dräger: Volume Control A/C with AutoFlow, Volume Control SIMV with AutoFlow
- Hamilton: Adaptive Pressure Ventilation CMV, Adaptive Pressure Ventilation SIMV
- Maquet: Pressure Regulated Volume Control, SIMV Pressure Regulated Volume Control
- Philips/Respironics: not available

What the clinician sets: The clinician sets the respiratory rate, target tidal volume, and inspiratory time.

What the ventilator does if patient is passive: The ventilator uses pressure control breaths to deliver the target tidal volume. The ventilator will adjust the inspiratory pressure to achieve the target tidal volume based on the prior breaths' tidal volumes. The minimum minute ventilation is the result of the clinician set rate and the target tidal volume. Changes in the patient's compliance, resistance, and inspiratory effort lead to changes in the inspiratory pressure such that the average tidal volume delivered is equal to the set tidal volume.

What the ventilator does if the patient is actively breathing: The patient will trigger the breath as long his breath rate is faster than the set rate; thus, there is a minimum minute ventilation. As the patient effort increases, the ventilator will start decreasing the inspiratory pressure to maintain the tidal volume within target. The ventilator will decrease the inspiratory pressure as low as its algorithm allows (some down to 0 cm H_2O) [6]. If the patient effort is large enough, the tidal volume can be larger than the target. Like volume control with set-point targeting, the contribution of the ventilator to the total work of breathing decreases as the patient effort increases.

Type of Patient-Ventilator Interactions: The most common types in PC-CMVa are:

- Double triggering: The patient effort is so large that he triggers a second ventilator breath after the first one is over. In contrast to VC-CMVs, the patient will get a second breath that is determined by the respiratory system characteristics (compliance and resistance) and aPEEP. Thus breath stacking is less injurious than VC-CMVs.
- Cycle dyssynchrony: The patient effort ends early or late than the set inspiratory time. This can lead to patient discomfort.
- Unsupported Work of Breathing: As the patient effort increases, the ventilator will decrease the inspiratory pressure to deliver the target tidal volume, thus the work of breathing is shifted to the patient.

Indications of PC-CMVa in an oncologic patient: This mode is indicated when the clinician is concerned about keeping a minimum level of minute ventilation in the face of changing lung mechanics, while wanting to avoid a preset flow (i.e., allowing some patient comfort). The common patient would be one recovering from pneumonia, in which the level of sedation is being decreased, and we want to maintain ventilator support while allowing some comfort.

17.8 Pressure Control Modes with All Spontaneous Breaths (PC-CSV)

17.8.1 Set-Point Targeting (PC-CSVs)

Commercial names: A manufacturers call this Pressure Support.

What the clinician sets: The clinician sets the inspiratory pressure and possibly the flow cycle threshold (i.e., the percent of peak inspiratory flow at which inspiration is terminated).

What the ventilator does if patient is passive: This is not a mode for patients that are passive (not breathing). The ventilator will not deliver any breaths. The apnea alarm will sound and apnea ventilation starts.

What the ventilator does if the patient is actively breathing: The patient will trigger and cycle every breath. The respiratory rate and minute ventilation are determined by the patient. There is no minimum minute ventilation. Tidal volume is dependent on the level of inspiratory pressure, and respiratory system mechanics (including inspiratory effort). As the patient effort increases, the ventilator will deliver larger tidal volumes. The ventilator work output per breath remains constant, but the total work of breathing increases as the patient effort increases.

Type of Patient-Ventilator Interactions: The most common in PC-CSVs is ineffective trigger efforts (e.g., a patient with cancer and chronic lung disease). Other types are rare and mostly dependent of the clinician settings for trigger and cycling ventilator thresholds.

Indications of PC-CSVs in an oncologic patient: This mode is commonly used to allow spontaneous breathing trials to assess readiness to liberate from mechanical ventilation. It is also used to provide ventilator support to patients that have spontaneous breaths, and comfort (synchrony) is the main goal.

17.9 Volume Support (*PC-CSVa*)

17.9.1 Adaptive Targeting

Commercial names:

- Covidien: Spont Volume Support
- Dräger: Spontaneous CPAP/Volume Support

- Hamilton: not available (not needed because of Adaptive Support Ventilation mode)
- Maquet: Volume Support
- Philips/Respironics: not available

What the clinician sets: The clinician sets the target tidal volume.

What the ventilator does if patient is passive: This is not a mode for patients that are passive (not breathing). The ventilator will not deliver any breaths. The apnea alarm will sound and apnea ventilation starts.

What the ventilator does if the patient is actively breathing: The patient will trigger and cycle the breaths; thus, there is no minimum minute ventilation. There is a target tidal volume that is set by the clinician, the ventilator will measure the last breaths size of the tidal volume and adjust the next breath inspiratory pressure according to an algorithm. The goal is to maintain the target tidal volume. As the patient effort increases, the ventilator will start decreasing the inspiratory pressure to maintain the tidal volume within target. The ventilator will decrease the inspiratory pressure as low as its algorithm allows (some down to 0 cm H_2O). If the patient effort is large enough, the tidal volume can be larger than the target. The contribution of the ventilator to the total work of breathing decreases as the patient effort increases.

Type of Patient-Ventilator Interactions: The most common types in PC-CSVa are

- Unsupported Work of Breathing: As the patient effort increases, the ventilator will decrease the inspiratory pressure to deliver the target tidal volume, thus the work of breathing is shifted to the patient.

Indications of PC-CSVa in an oncologic patient: This mode is commonly used to allow spontaneous breathing trials while ensuring that a minimum target tidal volume is achieved. This would be a good mode for a patient that is recovering from sedation or is weak to achieve the set tidal volume.

17.10 Proportional Assist Ventilation and Neurally Adjusted Ventilatory Assist (*PC-CSVr*)

17.10.1 Servo Targeting

- Covidien: Proportional Assist Plus
- Dräger: Spontaneous Proportional Pressure Support
- Hamilton: not available
- Maquet: Neurally Adjusted Ventilatory Assist
- Philips/Respironics: not available

17.10.1.1 Proportional Assist Ventilation (PAV)

What the clinician sets: On Covidien ventilators, the clinician sets the type and size of the airway, the percent of work supported by the ventilator. The ventilator

automatically determines respiratory system elastance and resistance. On Dräger ventilators, the operator must determine the mechanical properties of the patient's respiratory system and then enter the amount of respiratory system elastance and resistance the mode should support.

What the ventilator does if patient is passive: This is not a mode for patients that are passive (not breathing). The ventilator will not deliver any breaths. The apnea alarm will sound and apnea ventilation starts.

What the ventilator does if the patient is actively breathing: The patient will trigger and cycle the breaths; thus, there is no minimum minute ventilation. The ventilator applies inspiratory pressure in proportion to the patient respiratory effort. The greater the patient's inspiratory effort, the greater the increase in applied pressure. The contribution of the ventilator to the total work of breathing increases as the patient effort increases. The ventilator uses an algorithm to estimate the patients muscle effort, so the pressure waveform mimics that of a diaphragm pressure contraction [7].

Type of Patient-Ventilator Interactions: The most common in PC-CSVr is

- Runaway phenomena: It occurs when the ventilator overestimates the patient's effort or respiratory mechanics. It is a type of delayed cycling where the ventilator continues to provide support. The clinician sets limits to tidal volume and pressure to avoid this asynchrony.

Indications of PAV in an oncologic patient: This mode is commonly used to allow spontaneous breathing while ensuring that the work of breathing is balanced. This mode is appropriate for any patient where pressure support would be indicated.

17.10.1.2 Neurally Adjusted Ventilatory Assist (NAVA)

What the clinician sets: The clinician sets the amount of pressure to be given in proportion (called the NAVA level) to the electrical diaphragmatic signal (Edi). The clinician must insert an esophageal catheter that has sensors which detect the diaphragmatic electromyography. The ventilator processes the EMG into a simplified and usable waveform [7].

What the ventilator does if patient is passive: This is not a mode for patients that are passive (not breathing). If the Edi signal is lost, the ventilator provides backup Pressure Support with pressure of flow triggering. If the patient becomes apneic, the ventilator switches to PC-IMVs.

What the ventilator does if the patient is actively breathing: The patient will trigger and cycle the breaths according to the electrical diaphragmatic signal. The ventilator applies inspiratory pressure in proportion to the patient respiratory effort as interpreted from the Edi signal. The greater the patient's inspiratory effort, and the higher the NAVA setting, the greater the increase in applied pressure. The contribution of the ventilator to the total work of breathing increases as the patient effort increases.

Type of Patient-Ventilator Interactions: When applied properly, this should be the mode of ventilation that offers the best level of synchrony with the patient.

Indications of NAVA in an oncologic patient: This mode would be indicated on a patient in which achieving synchrony with conventional modes has not been possible. Underlying diseases, such as COPD or other obstructive lung diseases, are common indications.

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Continuous Positive Airway Pressure (CPAP) for Critically Ill Cancer Patients

18

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Abbreviations

AML	Acute myeloid leukemia
ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
CPAP	Continuous positive airway pressure
ICU	Intensive care unit
NIV	Noninvasive ventilation
RCT	Randomized control trials
SAPS	Simplified acute physiology score

18.1 Introduction

Critically ill cancer patients can be difficult to manage for many reasons [1]. The majority of critical care cancer patients die with cancer, not from cancer in the intensive care unit (ICU). Cancer patients are often extremely ill, requiring extensive therapeutic measures. Cancer patients may be accustomed to dealing with poor odds and are in fact often viewed as "fighters" not easily willing to give up [2]. Critically ill cancer patients are associated with increased mortality rate. A review of the literature reveals mortality rates between 72 and 98% for mechanical ventilation oncology patients. Studies that include hematologic malignancies [3–5] reported mortalities in the 80% to upper 90% range, with 70% mortalities commonly reported for solid tumor malignancies. The reported 67% mortality rate for

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mechanical ventilation patients included a population in who nearly half of them had hematologic malignancies and/or bone marrow transplant. Respiratory failure condition was consistently associated with mortality in the whole group, in addition to the evaluated subgroups.

CPAP is a common noninvasive ventilation treatment modality for acute respiratory failure (ARF) in critical care settings. Historically, CPAP has been administered using a tight-fitting mask to the face. The face mask is light in its weight and comprises a soft adjustable seal in order to reduce gas leakage and trauma [6, 7].

The CPAP and noninvasive ventilation (NIV) terms are constantly used interchangeably. However, they are distinctly different. With noninvasive CPAP, a face mask or any other interface is used to apply a pressure greater than atmospheric to the proximal airway. This results in splinting and opening the upper airway, an increase in lung volume, and an increase in intrathoracic pressure. With CPAP application, there is no unloading to inspiratory muscles; in fact, tidal ventilation is completely dependent on the respiratory muscles with CPAP. On the other hand, NIV works by applying a pressure during the inspiratory phase greater than the pressure applied during exhalation phase. Thus, NIV works by unloading the respiratory muscles and can provide complete respiratory support.

This chapter will summarize the evidence on noninvasive ventilation in cancer critically patients.

18.2 Clinical Outcomes of Critically Ill Patients

Clinical outcomes in critically ill patients with cancer disease have clearly improved over the last decade [8, 9]. This is probably associated with a better selection of patients with cancer for intensive care units and vast advances in antitumor management in critical care have led to vast improvement in survival rates. In addition, early referral, better management, and noninvasive ventilation have also played a significant role [10]. Selection of patients for NIV is critical; early recognition of respiratory failure is of great help. It is also crucial to realize the limitations of NIV, as well as recognize failure of NIV early and avoid unnecessary delay in intubation [11]. For critically cancer patients, CPAP can be helpful to avoid invasive treatment, and in recent years it has been linked to improve survival rate [12, 13].

In fact, the mortality rates in critically cancer patients are now comparable with other population of non-cancer patients requiring ICU care [14]. It appears that other factors than the diagnosis of cancer influence the critical care management outcome. Many studies have failed to show that cancer as a diagnosis is an independent predicator of ICU mortality [15]. A study of 773 cancer patients (85%) has showed cancer diagnosis was not an independent risk factor for ICU mortality [16]. In total study of 3147 patients, involving 198 European intensive care units, patients with solid cancers had similar outcomes to non-cancer patients [17]. Although cancer may not be independent risk factor, there are data showing that increasing severity of active cancer is detrimental to prognosis [18], but would this contribute to definitive outcome prediction is not known [19].

18.3 CPAP Application

CPAP is a supportive, positive pressure throughout the entire respiratory cycle (inspiration and expiration), when breathing spontaneously [20]. The CPAP system is delivered using a tight-fitting face or nasal mask and a valve, usually at a pressure of 5–10 cm H_2O, against which the patient exhales [21]. The CPAP valve should be a low resistance type [22]. Noninvasive ventilation (NIV) has been one of the major advances in the field of mechanical ventilation in the last 20 years and its application has special significance in cancer patients [8, 23]. The use of noninvasive application of CPAP in the acute care settings has increased in recent years because of continued development of new and improved patient interfaces, noninvasive ventilators, enhancements on ICU ventilators, and reports of success in the literature [24].

18.4 CPAP for Immunosuppressed Patients

With the increased number of immunosuppressed patients, respiratory complications are the main contributor to mortality [25] and often require invasive mechanical ventilation which is associated with significant risk of death [26].

Immunocompromised often suffer from acute respiratory failure that signal a serious underline phase of the disease, with decreased survival rate and increased costs to the ICU admission [27]. Early use of NIV could lead to better help as shown by ICU randomized studies that compared NIV therapy with standard therapy. Patients with a received solid-organ transplant and who suffered with hypoxemic acute respiratory failure, NIV had reduced intubation rate, complications, mortality rate, and ICU duration of stay [28]. In view of the risk of ICU admitting patients with immunosuppressed, at current, NIV is used in some institutions at early phase in hematology wards, either via a helmet or face mask, to prevent transfer to intensive care [29].

NIV benefit in immunocompromised patients has been evaluated in two randomized control trials (RCTs) who also had acute respiratory failure or distress [23, 28]. The first RCT evaluated 40 patients who received NIV or oxygen therapy with solid-organ transplantation and suffered hypoxemic respiratory failure [28]. Patients treated with NIV had improved oxygenation and less rate of endotracheal intubation and mortality. The second RCT evaluated 52 immunosuppressed with hypoxemic respiratory failure and pneumonia who received NIV or oxygen therapy [23]. Patients with NIV showed lower rate of endotracheal intubation, mortality when compared with the other therapy.

18.5 CPAP for ARF in Critically Cancer Ill Patients

ARF is the most common indication for ICU admission with critical cancer patients with a high rate of mortality [30]. Azoulay has demonstrated the impact of using NIV in this population with a better outcome compared to those groups needed

invasive mechanical ventilation [8]. The mortality of invasive mechanical ventilation was 75% when compared to 50% with those using NIV [31].

NIV has physiological benefits with hypoxemic ARF such as recruiting underventilated alveoli, prevention of atelectasis, and reduction of increased work of breathing. However, NIV can rapidly lead to worsening gas exchange if interrupted, thus NIV Failure and endotracheal intubation becomes a definitive intervention. In a case-controlled study, Rocco [32] has shown that the use of helmet is a better interface when compared to a facemask in hypoxemic ARF. Currently, it is possible to predict NIV success with hypercapnic respiratory failure but in case of hypoxemic respiratory failure, it is necessary to set definite criteria to when to invasively ventilate the patient. Hypoxemic RF patients with delay of invasive mechanical ventilation have shown with a poor prognosis [33] and such NIV failure showed a 93% mortality [12].

18.6 Risk Factors for NIV Failure

Few studies have evaluated risk factors for NIV failure in critically cancer patients. First study by Azoulay et al. [12], a prospective cohort study, evaluated 203 patients and with 57% observed NIV failure. Authors showed the risk factors for NIV failure as follow: longer NIV duration and acute respiratory distress syndrome (ARDS). The study findings were the NIV use had led to endotracheal intubation and suboptimal management to ARDS patients.

The second study by Azevedo et al. [34], a prospective study, evaluated 85 cancer patients with ARF treated with NIV which reported 53% NIV failure. Authors showed the risk factors for NIV failure as follow: septic shock, ARDS, and high respiratory rate during the first day of NIV initiation.

Ferreira et al. [35], a retrospective cohort study, evaluated 114 with ARF and 41% observed NIV failure. Authors showed the risk factors for NIV failure as follow: infection, male sex, and Simplified Acute Physiology Score (SAPS) of 3.

18.7 CPAP in Patients with Hematology Patients

Hematological malignancy patients seem to have higher rate of mortality [9], although some reports showed same mortality rate as with lung cancer [36, 37]. Even though, ICU patients showed improved survival rate over the last decade [38], Table 18.1, the evidence is still conflicting due to illness severity. Among other leukemias, acute myeloid leukemia (AML) has the lowest prognosis outcome [11].

Mechanical ventilation for hematological malignancy patients is the most robust predictor of a poor ICU outcome [39]. Although NIV showed advantage over invasive MV [8], Depuydt et al. showed the similar outcome of NIV when compared with invasive MV in 166 patients with hematological malignancies within 24 h of ICU admission [11]. It is questionable data because of less known about the severity degree of lung injury. In another data, Gristina et al. showed in 1302 hematological

Table 18.1 shows the differential diagnosis of ARF in cancer population [31]

ARF in cancer
Progression or spread of underlying cancer
Acute respiratory distress syndrome
Infection
Chemotherapy/radiation induced lung injury
Pulmonary thromboembolism
Tumor emboli
Diffuse alveolar hemorrhage
Pulmonary leukostasis
Lymphangitic carcinomatosis
Transfusion related lung injury
Airway obstruction
Paraneoplastic syndromes

cancer patients that even with better NIV outcome, mortality was significantly higher once invasive ventilation required after NIV failure [40]. It is crucial to early identify patients whom can be benefit from NIV to avoid increased risk of failure. In out-side ICU settings, nasal CPAP with helmet in selected 17 hematological malignancy patients showed improved oxygenation with hypoxemic acute respiratory failure and reduced endotracheal intubation [29].

In hematological malignancy patients, ARF is the most common life-threatening condition [41]. Few studies have shown limited benefit with those patients but failed to control the time between ARF occurrence and initiation of NIV [42].

Hilbert et al. evaluated the tolerance and the efficacy of using CPAP therapy administered by face mask on 64 patients with in severe ARF occurring in ICU neutropenic patients with hematologic malignancies [43]. Respiratory rate was improved by 53% with a 25% CPAP efficiency of the ICU neutropenic patients with acute respiratory distress.

Benefits of NIV with hematological malignancy patients remain inconclusive and additional well-designed studies are needed.

18.8 Conclusions

The management of critically ill cancer patients in ICUs is a complex matter and using noninvasive ventilation should be with caution. Clinical reports revealed general improvement in the outcomes of critically ill cancer patients but not consistent due to diversity of conditions that require specific knowledge and clinical experience to maximize the benefit of treatment in particular with noninvasive ventilation. Noninvasive ventilation is a feasible therapeutic option to avoid invasive ventilation in specific groups of cancer patients who develop respiratory failure. However, the time to initiate noninvasive ventilation is a crucial aspect of management in acute care settings.

18.9 Recommendations

- CPAP is a form of noninvasive ventilation that can be effectively used in the management of critically ill cancer patients.
- It has shown several benefits, including decreased rate of endotracheal intubation, invasive mechanical ventilation, decreased mortality, and hospital length of stay.
- Well-knowledge and highly experienced team with noninvasive ventilation are crucial for a successful application.
- Early identification for NIV failure risk factors in cancer patients, using a detailed diagnostic approach and close monitoring of NIV, is the main key to a successful NIV initiation.
- Well-designed clinical trials are required to identify clinical indicators of NIV success or failure with critically ill cancer patients.

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Airway Pressure Release Ventilation

19

Jennifer C. Cabot and Stephen M. Pastores

19.1 Introduction

Airway pressure release ventilation (APRV) was first described in 1987 by Stock and Downs [1]. It became available on commercial ventilators in the 1990s, and depending upon the brand, it may have any of the following names: APRV (Drager), BiLevel (Covidien), Bi-Vent (Maquet), Biphasic (CareFusion), and DuoPAP (Hamilton). APRV is based on the "open lung concept" and is a form of pressure-controlled intermittent mandatory ventilation using extreme inverse inspiratory–expiratory (I:E) ratios [1]. It can be most easily understood as a type of continuous positive airway pressure (CPAP) mode modified to apply two alternating levels of pressure. The majority of the respiratory cycle (T_{high}) is spent at a high pressure (P_{high}) to maximize alveolar recruitment, while a short period (T_{low}) is spent at a low pressure (P_{low}) to allow CO_2 clearance. Mandatory breaths are time-triggered, pressure-targeted, and time-cycled. The patient may breathe at any time during the respiratory cycle, though due to the extreme I:E time ratio, most spontaneous breathing takes place during T_{high} (Fig. 19.1).

The purported benefits of APRV are twofold: (1) minimization of peak airway pressures (P_{aw}), and (2) maintenance of spontaneous breathing. By minimizing peak P_{aw}, ventilator-induced lung injury (VILI) theoretically may be avoided and hemodynamics improved. Spontaneous breathing by the patient leads to several advantages, including increased patient comfort, decreased patient-ventilator asynchrony, reduced need for sedation, and improved aeration of basilar lung segments [2].

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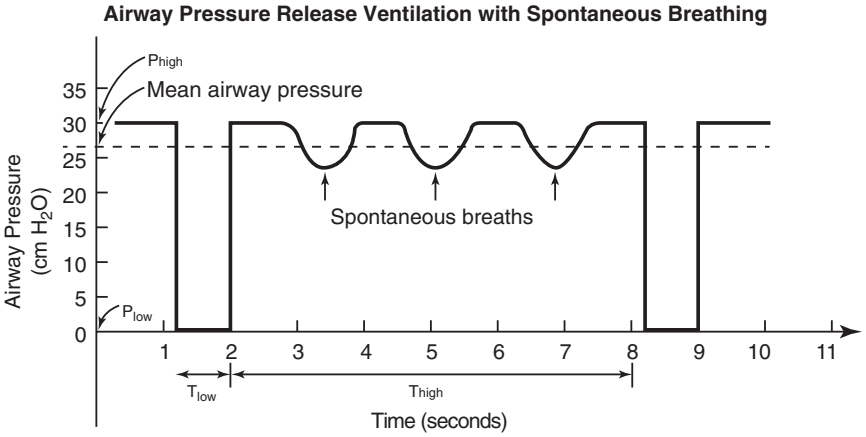

Fig. 19.1 Two ventilator cycles with P_{high} and P_{low} labeled, as well as a mandatory breath and a spontaneous breath. Reprinted with permission from the publisher

Unfortunately, there are few human studies comparing APRV to conventional modes of ventilation, and those that exist do not show a mortality benefit [2]. Thus, despite the intuitive advantages of APRV, it is infrequently used in the United States other than as a rescue strategy.

19.2 Indications for APRV

APRV has been used in multiple clinical settings over the past three decades, including trauma-associated respiratory failure, cardiac surgery, and pediatrics [4–9]. The most common indication for APRV to date, however, is acute respiratory distress syndrome (ARDS) [2]. In ARDS, multiple areas of the lung undergo collapse, particularly in the dependent portions. This leads to significant pulmonary shunt and hypoxemia. Conventional ventilator strategies can compound this problem by causing VILI through volutrauma (overdistension of normal alveoli), barotrauma (damage from excessive peak inspiratory pressures), and atelectrauma (shear stress from repeated opening and closing of under-recruited alveoli) [3]. APRV purports to minimize VILI in patients with ARDS by recruiting both healthy and diseased alveoli at lower peak pressures and preventing cyclic alveolar collapse and reopening with intrinsic PEEP [1, 2].

19.3 Pathophysiology of Mechanical Ventilation with APRV

The goal of APRV is to ventilate the patient on the steep portion of the pressure–volume curve, where lung compliance, venous admixture, and arterial oxygenation are optimized, and risk from lung stretch and alveolar collapse is minimized [2]. The difference between APRV and most other modes of ventilation, however, is that

APRV accomplishes this task while maintaining long inflation times, low peak airway pressures, and spontaneous breathing throughout the ventilatory cycle.

APRV divides the respiratory cycle into two time periods, a long T_{high} at a high pressure (P_{high}) and a very short T_{low} at a low pressure (P_{low}). Eighty to ninety-five percent of the respiratory cycle is typically spent at P_{high}, which allows a higher mean airway pressure to be generated at a substantially lower peak airway pressure than with conventional ventilation modes [10–12]. Additionally, the long T_{high} allows progressive recruitment of both healthy and diseased alveoli during inflation. Diseased lung units have decreased compliance and tend to inflate and deflate rapidly, as opposed to healthy lung units with normal compliance. Therefore, a long inflation time is required to achieve inflation of the maximum number of alveolar units and to minimize shunt [2]. The release times (T_{low}) in APRV are typically only 0.4–0.8 s, which is long enough to allow ventilation but short enough to create significant intrinsic PEEP. Intrinsic PEEP prevents alveolar collapse and minimizes shear stress to alveolar units.

Spontaneous breathing is another crucial aspect of APRV. An active exhalation valve allows spontaneous breathing with CO_2 elimination during both T_{high} and T_{low}. Studies have shown that spontaneous breathing accounts for up to 30% of the minute ventilation in APRV [2]. Perhaps even more importantly, spontaneous breathing decreases shunt by increasing recruitment of basilar lung segments [13, 14]. These actions decrease ventilation-perfusion mismatch and improve oxygenation. Spontaneous breathing also increases lung compliance, cardiac index, and oxygen delivery, compared to ventilator strategies that require deep sedation or paralysis [4]. Finally, spontaneous breathing increases patient comfort, as shown by the significantly reduced requirements for sedation and analgesia in APRV as compared to conventional modes of ventilation [15].

19.4 Nuts and Bolts: How to Choose the Settings

APRV improves oxygenation through progressive recruitment of lung segments during long inflation times and prevention of collapse through intrinsic PEEP, while ventilation occurs via release times with a large pressure differential. It can be difficult to strike a balance between these two needs, and various methods exist for setting APRV parameters [2]. A bedside guide to choosing APRV settings is shown in Table 19.1.

19.5 Setting the Pressures: P_{high}/P_{low}

1. Pressure–Volume Curve (PVC) Method

One method to set P_{high} and P_{low} involves the creation of a patient's pressure–volume curve during a short period of paralysis. P_{high} is then set to just below the upper inflection point (UIP) on the curve and P_{low} to just above the lower inflection point (LIP) [2].

Table 19.1 Bedside guide to choosing APRV settings—adapted from Modrykamien et al. [11]

Bedside guide to APRV settings	
Initial settings	
• P_{high}	• Set as plateau pressure on volume-control mode OR the peak P_{aw} of pressure-control ventilation
	• Maximum P_{high} of 30 cm H_2O
• P_{low}	• 0 cm H_2O
• T_{high}	• (60/desired RR)—T_{low}
• T_{low}	• 50% of peak expiratory flow
	• Should be in the range of 0.2–0.8 s
Adjustments	
Hypoxemia	
• Increase T_{high} by up to 1 s	
• Increase P_{high} by 5 cm H_2O	
Hypercarbia with pH < 7.2	
• Increase frequency of pressure releases—reduce T_{high} by 0.5 s	
• Cautiously increase T_{low} by 0.1 s—may worsen oxygenation	
Weaning	
• Decrease P_{high} by 2 cm H_2O at a time	
• Increase T_{high} by 0.5 s at a time	
• At P_{high} of <16 cm H_2O and T_{high} of >15 s, convert the mode to CPAP	
• May add pressure support as needed	

2. Plateau/Peak Airway Pressure (PAP) Method

An alternative method is to set the P_{high} at the level of the plateau pressure of volume-control ventilation or the peak P_{aw} of pressure-control ventilation, with a maximum P_{high} of 30 cm H_2O. In contrast to the PVC method, P_{low} in the current strategy is always set at 0 cm H_2O. This combination of settings allows efficient CO_2 release due to a large pressure gradient while creating intentional intrinsic PEEP to prevent collapse of alveoli [2, 11].

There is no consensus on which of these two methods is superior. In the PVC method, a passive breath is required to create an accurate pressure–volume curve, and therefore the patient must be completely sedated and/or paralyzed. Aside from the disadvantages of deep sedation in a critically ill patient who may not be able to clear medications efficiently, there is also a controversy regarding interpretation of the curve and how accurately this method determines the ideal level of PEEP [2, 16].

The PAP method also has intrinsic flaws. While this method attempts to limit inflating pressures (and thus tidal volumes), the patient's spontaneous efforts at P_{high} may result in extremely variable tidal volumes, at times larger than 6–8 mL/kg. Furthermore, lung mechanics change rapidly during the course of critical illness, and even small changes in lung compliance and elastance can lead to large changes in tidal volume and intrinsic PEEP. The level of intrinsic PEEP generated by the short T_{low} is unpredictable and may be insufficient to prevent alveolar collapse [2, 17].

19.6 Setting the Times: T_{high}/T_{low}

APRV is a form of extreme inverse ratio mechanical ventilation. Ratios are often greater than 2:1 and can be as high as 5:1. The method for setting the exact T_{high} and T_{low}, however, remains controversial.

T_{high} will be set automatically as a function of the desired mandatory respiratory rate, which is typically 8–12 breaths per minute. The crucial aspect of setting times in APRV is choosing an appropriate T_{low}, which is typically between 0.4 and 0.8 s [2, 11]. However, as with setting pressures, there are a variety of methods used to set this parameter.

1. Percent Flow (PF) Method

In the PF method, T_{low} is set as the time required to reach 50% peak expiratory flow. The goal is to create an intrinsic PEEP within a small range that will prevent alveolar collapse. However, as discussed previously, intrinsic PEEP depends upon a combination of the set pressures, lung elastance, lung compliance, and ventilator variables and can be extremely hard to predict [2].

2. Expiratory Time Constant (ETC) Method

In the ETC method, T_{low} is set according to the expiratory time constant. This variable is the product of the static respiratory compliance and resistance. During each time constant, the variables of pressure, volume, and flow change by 63.3%, and it is thought that intrinsic PEEP reaches zero after 4–5 time constants. Therefore, T_{low} is set to the number of time constants required to reach the desired intrinsic PEEP at end-expiration. For instance, if the ventilator is set with a P_{high} of 30 cm H_2O and P_{low} of 0 cm H_2O, T_{low} could be set to two time constants to achieve an intrinsic PEEP of 4 cm H_2O. Similarly, if one would prefer a higher intrinsic PEEP of 11 cm H_2O, T_{low} would be set to only one time constant [2, 11]. This method is attractive, given its ease and simplicity; however, multiple studies have shown that the ETC method is inaccurate and that the expiratory time constant does not remain static during mechanical ventilation [2, 17]. As there is no method that provides a perfect strategy for setting T_{low}, many clinicians simply start with a time between 0.6 and 0.8 s and adjust from there [2, 11].

19.7 APRV Weaning

APRV is generally weaned in a "drop and stretch" method [2, 11]. P_{high} is gradually decreased and T_{high} increased until the patient is on one continuous level of pressure support and the mode of ventilation is converted to CPAP. From there, the patient may undergo spontaneous breathing trials prior to extubation.

19.8 Comparison to BIPAP

A common source of confusion is the difference between APRV and biphasic positive airway pressure (BIPAP) ventilation. Both are modes of pressure-controlled intermittent mandatory ventilation along the same spectrum. Each has mandatory

breaths that are time-triggered, pressure-targeted, and time-cycled, and each allows the patient to breathe spontaneously during any part of the respiratory cycle. One major difference, however, is the I:E ratio, which tends to be less extreme in BIPAP than in APRV. A review of 50 studies describing both modes showed that none of the BIPAP studies used an I:E ratio greater than 2:1, compared to 46% of the APRV studies. In contrast, very few APRV studies used an I:E ratio less than 1:1, whereas a quarter of the BIPAP studies did [18].

The second important difference, which is related to the I:E ratio, is the duration of T_{low}. As mentioned previously, T_{low} in APRV is kept very short, generally 0.2–0.8 s, in order to prevent de-recruitment of alveolar segments. In contrast, T_{low} in BIPAP is generally 2–3 times longer than in APRV. The effect of these differences is that compared to BIPAP, APRV supplies a higher mean airway pressure with a lower minute ventilation [2, 11, 18].

19.9 APRV and Patient Outcomes

There are few human trials comparing APRV to conventional modes of ventilation, and those that exist are generally observational studies with small numbers of subjects. Nonetheless, studies investigating APRV in ARDS and trauma have demonstrated that APRV improves oxygenation but does not decrease mortality [2, 4, 5, 11].

Results are rather mixed regarding other indicators of morbidity. For instance, one randomized study comparing APRV to pressure-controlled continuous mandatory ventilation in trauma patients found fewer ventilator days and shorter ICU stays in the APRV group [4]. In contrast, a second randomized study showed increased ventilator days, ICU stay, and incidence of ventilator-associated pneumonia in the APRV group as compared to the low tidal-volume ventilation group [6]. Both studies, however, were limited by the small numbers of patients and differences in illness severity of the two groups.

Conclusions

APRV is an alternative mode of pressure-controlled intermittent mandatory ventilation. Animal, human, and mechanical model studies are providing an increasing body of evidence that APRV improves oxygenation, alveolar recruitment, hemodynamics, and patient comfort compared to conventional modes of ventilation. Due to a lack of proven mortality benefit, however, APRV is still a rarely used technique of mechanical ventilation, mostly confined to salvage therapies in ARDS. Future investigations will clarify the role of APRV and determine the most appropriate groups of patients to receive it.

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Non-Invasive Ventilation: Determinants of Success or Failure

20

Mario Albani Pérez, Patricia Iranzo Gómez, and Antonio Esquinas

20.1 Introduction

The respiratory failure is a common cause of admission to intensive and respiratory care units in patients with hemato-oncology malignancies. The use of Non-invasive Mechanical Ventilation (NIV) is expanding rapidly with promising results and has been a breakthrough in ventilatory support [1]. The access of patients to acute units must be individualized because of heterogeneity in prognosis. The admission to receive acute ventilation and its application can be determined by aspects like the stage of oncologic disease, clinical condition, comorbidities, and life expectancy [2].

20.2 General Considerations

The lung is the most usual organ involved in medical complications of hemato-oncological patients. Acute respiratory failure (ARF) is common in advanced stages of the disease, and occurs in almost 30% of patients [3] being the most important cause of admission in intensive care units [4].

NIV has been shown to be useful to treat acute respiratory failure according to its indication. The two presentations of ARF are the hypoxemic (type 1) and the hypoxemic-hyperbaric (type 2). The first one is usually related to a ventilation-perfusion mismatch, diffusion impairment, and shunting; and the second one, with a depressed central respiratory drive, mechanical defect, or neuromuscular dysfunction [4].

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The types of hematologic neoplasm most commonly reported involving NIV as a ventilatory support are acute leukemia, lymphomas and myelomas, followed by solid tumors [5]. Some patients are characterized by a higher incidence of comorbidities that could be an independent cause or contribute to respiratory failure, requiring a complex management (this kind of situations are more common in patients with solid tumors). Infections, especially pneumonias, are the most common cause of admission in ICU in 50%, followed by acute heart failure, pneumonitis, and acute distress respiratory syndrome.

Survival rate is increasing in the last few years due to new therapies and technologic advances, achieving 50–80% according to different series [6]. A decrease in mortality was reported in patients who require invasive mechanical ventilation (IMV), but this is not out of risks. Infections associated with IMV (including VAP), iatrogenic effects as barotrauma, tracheal acute lesions and dysphagia, are commonly reported complications. For these reasons, the use of non-invasive ventilation has been considered as a beneficial resource in these patients, allowing airway integrity, normal physiological and immunological response, communication with the outside, and the ability to swallow, cough, and expectorate [4].

Some studies have shown endotracheal intubation increases the risk of developing new infections. NIV seems to be an effective alternative in the management of these patients (usually immunosuppressed), decreasing the rate of infectious complications. The impact of the use of NIV in cancer was demonstrated [7]. Compared with IMV, NIV showed better outcomes and a mortality rate less than 50% [8].

It is important to be careful in the management of patients with hematopoietic cell transplantation. During the different phases of treatment (pre-graft and post-transplantation), they could develop lung infiltrates usually due to viral or bacterial infections. The etiology of ARF in this case is related with survival, and mortality rate is over 90% when mechanical ventilation is required. The correct management needs a prompt diagnosis and treatment with knowledge of patient's immune state [9, 10].

20.3 Determinants of Success and Failure

A systematic evaluation before starting NIV is recommended. It is important to make a correct selection of patients, identify the etiology of respiratory failure, and an early assessment of clinical response. These three steps for general evaluation determine in a big proportion the success rate.

On the other hand, it is essential to identify the patients which initially benefit from invasive mechanical ventilation, in order not to delay its indication.

20.3.1 General Assessment and Selection of Patients

Firstly, assessing the indications and contraindications is fundamental, and usually are not too far from classic NIV premises. The most common indications are acute respiratory failure that does not meet criteria for adult respiratory distress syndrome,

chronic respiratory failure, acute pulmonary edema, and the refusal of the patient to be intubated. Other indication is the use of prophylactic NIV to improve oxygenation and decrease the respiratory effort, in order to perform diagnostic procedures through the airway (bronchial aspirates, bronchoalveolar lavage, etc.). NIV should be contraindicated especially in those cases with failure of two or more systems (multiple organ dysfunction), acute respiratory failure associated with septic shock, non-hypercapnic decreased level of consciousness, hemodynamic instability, need for vasoactive drugs, clinical or analytical failure of NIV after 1 hour (desaturation, non-adaptation, blood gas deterioration, decreased level of consciousness, persistence of tachypnea, etc.). In these cases would be necessary start invasive mechanical ventilation [1, 11].

20.3.2 Clinical Indicators in Acute Situations

Considering success and failure indicators is necessary to select patients and start invasive or non-invasive therapies. Failure in NIV is determined with main risk factors like PaO_2/FiO_2 index, vasopressors use, renal failure, respiratory rate, and delay of NIV. The scoring systems could be helpful to determine prognosis and potential benefits.

Several studies show rates of failure in patients with acute respiratory distress syndrome (ARDS) (PaO_2/FiO_2 < 200 mmHg), higher than in controls (PaO_2/FiO_2 > 200 mmHg). There is a lack of evidence for NIV in ARDS because tracheal intubation is usually performed at first [5, 12].

Maintain respiratory rate less than 25 bpm (breaths per minute) is a goal in NIV. If after 1 h it is higher than 35 bpm, NIV failure must be suspected, implicating anxiety or intolerance as a result of organic dysfunction. Adjusting NIV parameters and early consideration of IMV is necessary [13].

Despite the use of vasopressors is the standard treatment in hemodynamic instability, it is also considered as a predictor of NIV failure. Doses employed are not well established and clinic outcomes are unknown.

Patients with renal failure requiring dialysis, particularly in those with hematological neoplasms, have more risk of NIV failure. The decrease in glomerular filtration is another factor to be considered to suspend NIV [14].

Scales to predict mortality are usually employed when a patient is admitted to ICU unit to evaluate its general status, including clinical objective variables. In a study with 1302 hemato-oncological patients treated with invasive and non-invasive mechanical ventilation, high scores of the *Simplified Acute Physiology Score II* (*SAPS II score*) were risk predictors for mortality, with an odds ratio of 4.66. The Acute Physiology and Chronic Health Evaluation (*APACHE II)* score was also studied as a prognostic factor in admission [14].

In contrast, a successful NIV was associated with shorter mechanical ventilation periods and ICU stays, less severe postadmission infections, and lower ICU and hospital mortality [15].

Maybe the most important factor is not to delay the NIV when it is indicated. The delay of correct ventilatory treatment increases the mortality in 15%. In the same way, a poor response of NIV after 1 h of treatment should be considered as a risk factor that

increases mortality. It can rise from 93 to 100% in cases that require intubation after a period of time (hours or days) of non-response to NIV. This is the main reason because a prompt detection of noninvasive treatment failure must be assessed [11].

A study comparing oxygen therapy and non-invasive ventilated patients has been published. In a prospective randomized trial, intermittent NIV was compared with standard oxygen therapy without any ventilator support in patients with hematologic malignancies and neutropenia, achieving a significant reduction in the rate of intubation, serious complications, and death in ICU and hospitalization [16]. Otherwise, in cases of solid tumors, it has been shown that NIV compared with standard oxygen therapy improves the quality of life, reduce dyspnea, respiratory rate, use of opioids, and oxygen [7].

Early identification of respiratory failure etiology and its potential reversibility allows the use of NIV with a greater assurance of success. Appropriate diagnostic tests are necessary to identify the specific cause of acute respiratory failure (tests employed in routine clinical practice can be confounding factors when analyzing survival in immunocompromised patients) [2].

Hemato-oncological patients could benefit of NIV especially in circumstances such as COPD exacerbations, immunosuppression, and cardiogenic pulmonary edema due to cardiotoxicity or hyperhydration during treatments [11].

Recent studies support its efficacy and benefits in terms of prognosis, but the dilemma for the indication and its effect on mortality is still unknown if it is compared with tracheal intubation. In a cohort of 114 cancer patients with acute respiratory failure, NIV was a successful treatment in nearly 60% of treated patients, and the risk factors associated with failure were: male sex, severe acute disease at admission, and respiratory infections as the cause of ARF. In other series of hematologic cancer patients, the higher respiratory rate was also included as an independent risk factor [13, 17].

Other clinical situations with bad prognosis, like septic shock and acute respiratory distress syndrome, are related with the failure of NIV. Septic shock has a worse response compared with a non-complicated infection. Hemodynamic instability is considered as a relative contraindication for NIV, and usually requires vasopressors and orotracheal intubation to ensure the optimal treatment [11, 15].

In order to choose the right respiratory therapy, the type of ARF has to be considered. Patients with hypoxemic-hyperbaric respiratory failure (type 2) need a ventilatory support with a bilevel device. In contrast, those with partial respiratory failure (type 1) could be benefited only with CPAP. At the present time, according to clinical evidence, the ability to predict success using NIV is better for hypoxemic-hyperbaric respiratory failure [1].

20.4 Technical and Environmental Aspects

A correct ventilatory programming is necessary to ensure an optimal respiratory support. An appropriate IPAP and EPAP benefit patient-ventilator dynamic ensures a right tidal volume. The use of low tidal volume could act in reducing the

mortality rate. Aspects related with patient-ventilator circuit must be considered as other NIV technical situations. It has been demonstrated that a basic consideration like checking leaks through the interface during therapy is an independent factor of success. Choosing the correct interface could be a challenge in these patients because of high skin fragility. The perfect mask should be comfortable, light, and soft.

Differences between the places where NIV is performed were studied, showing that ICU admission was a protective factor for prognosis in hematology patients with mild to moderate ARF, compared with patients treated in wards or units without trained personal (physicians and nurses) and constant monitoring of NIV [4].

20.5 Considerations in Palliative Care

In patients with advanced cancer under palliative care should determine the risks and benefits of NIV application. It is necessary to ensure comfort, an optimal pharmacotherapy treatment and assess their individual clinical and psychosocial circumstances. In some situations, this alternative is used as a temporary measure to improve symptoms.

NIV has shown to be effective improving dyspnea, oxygenation and sometimes reversing the acute respiratory situation [18]. In a randomized study performed by Nava and colleagues comparing patients with end-stage solid tumors (with a life expectancy less than 6 months, admitted for acute respiratory failure), the improvement of dyspnea and lower use of morphine was demonstrated in the NIV group versus standard oxygen therapy group. Moreover, these findings are not enough to assess the effectiveness of NIV in general practice or determining other clinical outcomes [7].

The success in palliative care is restricted to several small studies, and the results cannot be generalized to usual clinical practice.

From the ethical point of view, its palliative indication in terminally ill patients remains under discussion. In this moment, there is no consensus to determine the clinical significance and benefits of NIV at the end of life.

Conclusion

Due to the high risk associated with tracheal intubation, NIV is a well-tolerated therapy with proved results, which should be considered to treat hemato-oncological patients with acute respiratory failure, always under supervision in a specialized unit with trained clinicians. A prompt and right indication of NIV permits to avoid the intubation, but if it meets criteria IMV must not be delayed. Factors of failure and success are dependent on each patient and ventilatory therapy should be individualized. The challenge for a successful treatment in acute or palliative landscape will be given by new and well-designed trials in the future.

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Part III

Postoperative Mechanical Ventilation

General Postoperative Complications

21

Gulsah Karaoren

Abbreviations

ADH	Antidiuretic hormone
ASA	American Society of Anesthesiologists
COPD	Chronic obstructive pulmonary disease
DTR	Deep tendon reflexes
OSAS	Obstructive sleep apnea
PONV	Postoperative nausea and vomiting
TUR	Transuretheral resection

21.1 Introduction

In patients undergoing anesthesia, it has been suggested that postoperative complications develop in approximately 25% of cases, although the actual rates cannot be verified as no consensus on definitions has been reached. The complication rate varies according to the surgery applied, the anesthesia technique, and preexisting comorbidities. Further treatment may be required for postoperative complications and hospital discharge may be delayed. With correct perioperative evaluation, risks can be minimized and medical treatment can be optimized, with early identification saving lives, time, and money. Patients with suspected complications must be questioned as to what type of surgery has been applied and for what purpose, if they have any comorbidities and what medication is being used, and what applications have been made since the onset of the suspected complication [1].

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A total incidence of 23% postoperative complications was determined in a retrospective review of 18,473 patients. Postoperative nausea and vomiting (PONV) at reported rates of 10–30% was determined to be the most common postoperative complication, followed by upper airway problems (6.9%), hypotension (2.7%), dysrhythmias (1.4%), hypertension (1.1%), altered mental status (0.6%), and suspected or major cardiac events (0.6%) [2].

The ability to preoperatively predict complications which may develop is important in respect of preventative measures. However, even if it is known that a complication may develop, some patient-related risk factors, such as age, cannot be eliminated. In a previous study it was shown that the 37 risk factors determined in the preoperative period that were related to postoperative mortality were effective in only 12% of deaths and thus it was reported that the effect of postoperative care was just as important as the preoperative factors [3].

There are various ways to approach the management of postoperative complications, the most practical of which is to consider the frequency of different complications (Table 21.1).

Table 21.1 General postoperative complications

Postoperative cardiovascular complications	Postoperative hypotension
	Hypovolemia
	Ventricular dysfunction
	Postoperative hypertension
	Myocardial ischemia
	Cardiac dysrhythmias
	Bradycardia
	Tachycardia
	Premature contractions
Postoperative pulmonary complications	Hypoxemia
	Hypoventilation
	Increased airway resistance
	Laryingospasm
	Bronchospasm
	Reduced compliance
	Neuromuscular and skeletal problems
	Impaired oxygen exchange
	Intrapulmonary shunting
	Pulmonary embolism
	Pulmoner edema
	Pneumonia
	Atelectasis
	Aspiration
	Anemia
Renal complications	Urinary retention
	Oliguria
	Polyuria

Table 21.1 (continued)

Fluid electrolyte disorders:	*Hyponatremia, Hyperkalemia, Hypokalemia, Hypocalcemia, Hypermagnesemia*
Pain	
Postoperative nausea/vomiting	
Hypothermia/shivering	
Fever	
Neuropsychiatric complications	*Delirium*
	Prolonged sedation
	Visual disturbance
Reduced bowel function	
Pressure sores and peripheral nerve damage	

21.2 General Postoperative Complications

21.2.1 Postoperative Cardiovascular Complications

The cardiovascular complications which may develop postoperatively include hypotension, hypertension, cardiac dysrhythmias, cardiac ischemia, and infarct. A 2012 study of vascular complications in non-cardiac surgery patients (VISION) demonstrated that patients with cTp-I levels ≥0.02 ng mL had an increased risk of postoperative death [4]. Therefore, there should be immediate investigation of any new cardiovascular change, including angina or dysrhythmias.

21.2.1.1 Postoperative Hypotension

Hypoperfusion of vital organs and systems can be caused by the common postoperative complication of systemic hypotension. This generally occurs because of hypovolemia, arterial hypoxemia, reduced myocardial contractility, reduced systemic vascular resistance (neuraxial anesthesia, sepsis), cardiac arrhythmia, pulmonary emboli, pneumothorax or cardiac tamponade. Inefficient anabolic metabolism is promoted by tissue hypoxia and lactic acid accumulation may result in unexplained metabolic acidemia. A decrease in the venous flow rate increases the risk of deep vein thrombosis and pulmonary embolism. The risk of systemic hypotension has been determined to be high in patients with atherosclerotic heart disease and those with chronic hypertension and elevated intracranial pressure with stenotic vascular diseases.

(a) *Hypovolemia*: Hypotension is the most common cause. Ventricular filling and cardiac output are decreased by a reduction of >15–20% of circulating intravascular volume. Unnoticed haemorrhage and third space losses can exacerbate hypovolemia. Postoperative severe pain or vasovagal responses may cause an increase in venous capacity with the activation of the sympathetic system. In patients applied with mechanical ventilation, compression of thoracic veins and reduced venous return associated with positive intrathoracic pressure is another effect.

(b) *Ventricular dysfunction*: This is generally seen in patients with known cardiac disorders. These patients often have increased left ventricle end diastolic pressure and increased sympathetic activity with sufficient cardiac output. However, fluid accumulation in these patients may cause ventricular dilatation, reduced cardiac output, hypotension, and frequently hydrostatic pulmonary edema. Deep acidosis and reduced blood ionized Ca can reduce ventricular contractility. Right ventricle dysfunction, which may be seen associated with pulmonary thromboembolism, often presents with systemic hypotension.

21.2.1.2 Postoperative Hypertension

A slight increase in blood pressure is expected in the postoperative period, but when there is an increase of 20–30% compared to the baseline value of systolic or diastolic pressure, this may cause headache, bleeding, third space losses, cardiac ischemia or dysrhythmias. Generally, when there is known hypertensive disease, anxiety, pain, stomach, and bladder distension, hypervolemia, hypoxemia, and increased intracranial pressure are observed.

21.2.1.3 Myocardial Ischemia

Postoperative myocardial ischemia is often determined in patients with coronary disease and congestive heart failure, a history of smoking and hypertension and in those who have undergone emergency surgery. Tachycardia associated with postoperative pain, hypotension, acidemia, anxiety, and some medications may lead to ischemia by shortening the diastolic filling time. Insufficient diastolic blood pressure is a cause of ischemia. Anginal chest pain, which is the most important symptom, may be suppressed by incision pain, gastric distension, or the residual effect of anesthetics or narcotic analgesics and the risk of morbidity in the early period for these patients is extremely high.

21.2.1.4 Cardiac Dysrythmias

Arterial hypoxemia, hypercarbia, hypovolemia, hypothermia, pain, electrolyte and acid base imbalance, myocardial ischemia, elevated intracranial pressure, drug toxicity (digoxin), and anticholinesterase medication seen in the postoperative period may cause the formation of cardiac dysrhythmia. However, axis, intraventricular conduction, p-t wave morphology, and ST segment alterations seen on ECG in the early period associated with the application of general anesthesia are not accepted as cardiac dysrhythmia. These changes which cause an imbalance in hypotherthermia, inhalation agents, and the autonomous nerve system and a mild electrolyte imbalance are electrophysiological effects which spontaneously correct within 3–6 h. If these changes persist, cardiac ischemia must be considered and by providing oxygen support together with monitorization of the patient, serial ECG and enzyme monitorization must be applied. The most commonly encountered dysrhythmias are bradycardia, tachycardia, and premature contractions.

(a) *Bradycardia*: In the postoperative period, increased parasympathetic nervous system activity and the reduced sympathetic nervous system effect promote sinus bradycardia. Sick sinus syndrome, ischemia, and hypoxemia reduce the

sinus rate in sinoatrial node. Bradycardia is generally harmless but when heart rate falls below 40–45 bpm, this may cause hypotension.

(b) *Tachycardia*: Postoperative sinus tachycardia is generally harmless, but in cases of coronary artery disease may cause myocardial ischemia. Tachycardia may exacerbate hypertension and acidosis and hypoxemia may be markers. It is generally corrected with treatment of the underlying cause such as pain management, hydration, and voiding of a full bladder. Following thoracic surgical procedures, if ventricle rate exceeds 150 in patients with mitral valve disease or pulmonary embolism, rapid ventricular response atrial fibrillation may develop. Ventricular filling and cardiac output reduce at a high rate and may be a cause of hypotension. Atrial flutter, paroxysmal atrial tachycardia, and re-entry rhythms are rarely seen postoperatively in patients. Postoperative ventricular tachycardia or fibrillation is encountered in severe myocardial ischemia, systemic acidemia or hypoxemia.

(c) *Premature contractions*: Atrial premature contractions seen in the postoperative patient are generally caused by sympathetic system activation. Premature ventricular contractions usually have a benign course. However, when there is high amplitude, wide or bizarre QRS complexes, damage is seen in ventricular communication.

21.2.2 Postoperative Pulmonary Complications

The vast majority of complications which occur after surgery comprise pulmonary complications formed as a result of respiratory muscle dysfunction and impaired chest wall mechanics. These complications are a significant cause of postoperative morbidity and)mortality, prolong hospital stay, and increase costs. In a study of patients in which postoperative pulmonary complications developed, the likelihood of mortality was shown to be increased 14.9-fold compared to patients who did not develop those complications [1, 5]. The most important risk factors are smoking, obesity, obstructive sleep apnea syndrome (OSAS), severe asthma and chronic obstructive pulmonary disease (COPD), steroid use and thoracic-upper abdominal surgery.

In clinical practice, microatelectasis-related fever, cough, dyspnea, bronchospasm, hypoxemia, hypercapnia, aspiration, atelectasis, pneumonia, pulmonary edema, acute respiratory distress syndrome, pulmonary embolism, and pleural effusion are the most commonly encountered complications and may cause acute respiratory failure in patients [5].

21.2.2.1 Hypoxemia

Intrapulmonary shunts which form secondary to reduced functional residual capacity are the basis of postoperative hypoxemia. Other causes are ventilation perfusion imbalance, reduced cardiac flow, alveolar hypoventilation, obstruction of the upper airway, bronchospasm, gastric aspiration, pulmonary edema, pulmonary embolism, pneumothorax, obesity, and senility. Pain, abdominal distension, diaphragm dysfunction, and a supine position worsen this condition. Hypoxemia in the

postoperative period can be easily and quickly diagnosed with pulse oxymetry. Hypoxemia findings are nonspecific and may be confused with hypercapnea. In the early stage, tachycardia, tachypnea, hypertension, hypotension, agitation, and changes in mental status may be observed. In the late stage, there may be hypotension, bradycardia, and cardiac arrest.

21.2.2.2 Hypoventilation

The most common causes are the residual depressant effects on hypoxic drive of anesthetic agents and insufficient neuromuscular blockage antagonism. Insufficient analgesia and bronchospasm are other causes. Increased PaCO2 alone in the postoperative period is not an indicator of hypoventilation. To be able to be defined as hypoventilation, there must be tachypnea, anxiety, dyspnea, and increased sympathetic system activation together with respiratory acidosis (pH < 7.25) or increased CO2 correlated with a decrease in arterial pH. Hypoventilation may often be a cause of hypoxemia in obese patients with OSAS and advanced COPD.

21.2.2.3 Increased Airway Resistance

High resistance to the gas flow in the airways may be a cause of high resistance respiratory function. If sufficient pressure exceeds the resistance of the inspiratory muscles, a gradient cannot form, so alveolar ventilation decreases and progressive respiratory acidosis may occur. Upper airway resistance may be seen associated with posterior tongue displacement, laryngospasm and laryngeal edema, tracheal stenosis or extrinsic pressure associated with a tumour or haematoma in expanded airways.

(a) *Laryngospasm*: In the early postoperative period, as a result of sensory stimulation by foreign body or secretion of the pharynx or the superior laryngeal nerve, which innervates the vocal cords, there may be a strong and involuntary spasm of the laryngeal muscles. This is often encountered in smokers and those with a reactive airway. Strong negative intrathoracic pressures in laryngospasm may cause pulmonary edema.
(b) *Bronchospasm*: Patients who smoke and have a bronchospastic status are at risk of bronchospasm. In the preoperative period, prolonged expiration, the use of accessory respiratory muscles and spirometric evidence of increased airway resistance together with high peak airway pressures during perioperative mechanical ventilation predict an increased risk of postoperative bronchospasm.

21.2.2.4 Reduced Compliance

Extrinsic factors which reduce pulmonary compliance (a high level of gas in the stomach and intestines, tight chest cage or tight abdominal dressings) may cause fatigue in the respiratory muscles, hypoventilation, and respiratory acidosis. Of parenchymal factors, a reduction in FRC causes the closure of small airways and distal lung collapse and the patient needs more strength to keep these open. Obesity, large intra-abdominal tumours, intra-abdominal haemorrhage, acid, ileus or term pregnancy may cause a reduction in compliance by restricting diaphragmatic movement.

21.2.2.5 Neuromuscular and Skeletal Problems

Postoperative airway obstruction or hypoventilation may sometimes be seen because of incomplete neuromuscular block reversal. In this condition, coughing makes respiratory effort to overcome airway resistance and airway reliability more difficult. In addition, patients with Myasthenia Gravis, Eaton Lambert, periodic paralysis, and muscular dystrophy give exaggerated, prolonged responses to muscle-relaxant medication and as these patients do not have sufficient muscle reserve, even with the administration of muscle relaxants, respiratory failure may develop. Abnormal motor function, flail chest, severe kyphoscoliosis or scoliosis may cause postoperative ventilation failure.

21.2.2.6 Impaired Oxygen Exchange

As a result of intrapulmonary shunting, pulmonary edema, and pulmonary embolism, impaired oxygen exchange may develop in the postoperative period.

(a) *Intrapulmonary shunting*: In conditions causing pulmonary collapse, such as atelectasis and pneumothorax, areas may form in the lungs, which are perfused but not ventilated. This condition, which is known as intrapulmonary shunt, may cause severe hypoxemia if there is no ventilation and an excessive amount of blood.
(b) *Pulmonary embolism*: This complication is not often encountered but is life threatening. It generally occurs because of venous thromboembolism and, less often, due to fat or air embolism. Precipitating factors of pulmonary embolism are obesity, hypercoagulopathy, use of contraceptives, varicose veins in the lower extremities, advanced age, immobility, pelvic fracture, and malignancies. Clinically, a table of tachypnea, hyperventilation, hypoxemia, and shock may be seen. A definitive diagnosis can be made from CT pulmonary angiogram or a ventilation-perfusion isotope scan.
(c) *Pulmoner edema*: The common complication of pulmonary edema develops as a result of various etiological factors, which can be easily detected in the postoperative period. In patients with preexisting cardiac diseases, the most common and significant cause is cardiogenic pulmonary edema. Myocardial infarction is generally the underlying cause, which results in left ventricular dysfunction and elevated hydrostatic pressure in the pulmonary circulation of these patients. Subsequently, fluid leaks into the interstitium. Other causes include cardiac dysrhythmias and congestive cardiac failure. In patients with no known cardiac disease and no underlying pathology, non-cardiogenic pulmonary edema can develop. In the etiology, there is an impairment in the filtration and absorption mechanisms between the pulmonary capillaries and the lymphatics. Other causes include fluid overload, anaphylaxis, pulmonary injury, negative pressure pulmonary edema, and neurogenic pulmonary edema. If not diagnosed early, pulmonary edema can be fatal.

21.2.2.7 Pneumonia

Pneumonia, which is a significant cause of postoperative morbidity and mortality, is a complication often encountered after non-thoracic surgery. The incidence has been reported as approximately 10% [6]. Generally secretion retention can develop

secondary to colonization of the microatelectasis area and gastric aspiration. Those with a prolonged need for respiratory support or patients, who cannot clear tracheobronchial secretions because pain has not been well managed, constitute a risk group.

21.2.2.8 Atelectasis

The collapse of areas of the lungs is known as atelectasis and this can lead to postoperative pulmonary complications such as hypoxemia. Even if subclinical microatelectasis generally develops in postoperative patients, extensive atelectasis may be encountered at a not uncommon rate. Although the overall incidence is not fully known, it was determined at 13.7% in non-thoracic surgery in a previous study [7]. As severe atelectasis facilitates pneumonia which is a complication related to mortality, the development of atelectasis must be prevented. It generally develops related to superficial respiration because of pain management, secretion retention, and bronchial narrowing which can develop following thoracic surgery. Although most patients are clinically asymptomatic, the most common complaint is shortness of breath. There may also be tachypnea, tachycardia, and sudden increase in temperature.

21.2.2.9 Aspiration

Although it is observed less than in the perioperative period, postoperative aspiration occurs more often than is estimated. Gastric content aspiration of >0.4–1.0 mL/kg and <pH 2.0–2.5 constitutes the most severe clinical table. Partially digested food particles within the aspirate or foreign bodies worsen the clinical table, while persistent cough, diffuse reflex bronchospasm, distal atelectasis, and airway obstruction may cause severe pneumonia. Postoperative hypoxemia, hypercarbia, and acidemia are factors increasing the risk of nausea, regurgitation, and aspiration. In addition, the airway protective reflexes are suppressed in the postoperative period by the residual effect of anesthetics and the depressant effects of analgesic opioids.

21.2.2.10 Anemia

The oxygen carrying capacity of the patient in the postoperative period is defined by the preoperative haematocrit values and perioperative haemorrhage. Lowness in these values is a cause of hypoxemia and may cause ischemia in vital organs of patients at risk.

21.2.3 Renal Complications

21.2.3.1 Urinary Retention

This is often seen after urogenital and inguinal surgery and may delay discharge from hospital. The risk factors may be patient-related (older age, male, preexisting neurological disease [e.g., cerebral palsy, neuropathy, multiple sclerosis]), procedure-related (anorectal surgery, joint arthroplasty, hernia repair) or anesthesia-related (prolonged surgery, excessive fluid administration, beta-blockers,

sympathomimetics, and anticholinergic agents). Postoperative urinary retention is more likely to be seen after neuraxial anesthesia rather than general anesthesia.

21.2.3.2 Oliguria

Low urine output (<0.5 mL/kg/h) often develops secondary to hypotension and hypovolemia in the recovery period. Strict assessment of urine output may be appropriate with an initial fluid challenge. If distended bladder is determined on abdominal examination, postrenal causes are likely and a urethral catheter should be applied. Intrinsic renal disease should be considered only when pre- and postrenal failure have been excluded.

21.2.3.3 Polyuria

Although usually secondary to hypervolemia, polyuria may be seen associated with hyperglycemia or osmotic diuretic use. If a rate of 4–5 mL/kg/h continues, inappropriate ADH secretion, diabetes incipitus, and high output renal failure must be considered and serum-urine osmolarity and electrolytes must be evaluated.

21.2.4 Fluid Electrolyte Disorders

Hyponatremia, hyperkalemia, hypokalemia, hypocalcemia, and hypermagnesemia may be observed following prolonged surgery or in geriatric, hypertensive or diabetic patients or those using diuretic medication.

Hiponatremia is seen most often in hypophyseal malignancies and inappropriate ADH, stress, general anesthesia, positive pressure ventilation, and small cell lung cancer. It may also be seen in cerebral salt-wasting syndrome following head trauma and in TUR syndrome.

Hypokalemia may be seen in patients receiving chronic diuretic treatment, those applied with insulin infusion and those with excessive vomiting.

Hyperkalemia may be seen in patients with cronic renal failure and acidemia.

Hypocalcemia is an anticipated finding in cases of liver failure, massive transfusion, acute pancreatitis, and hypoparathyroidism and end-stage renal failure. Confusion, seizures, hypotension, long QT syndrome, and muscle spasms may be observed.

Hypermagnesemia is seen in pre-eclamptic patients treated with Mg sulphate and in those with end-stage renal failure. Findings may be seen of DTR loss, sedation, and coma.

21.2.5 Pain

There must be serious assessment and management of postoperative pain. Chronic pain from preexisting conditions (e.g. regular analgesia use before surgery) can make the management of postoperative pain more difficult. In cases of sudden and new onset of pain or when pain is disproportionate to the clinical situation, there must be consideration of surgical complications (e.g. bleeding or perforation).

21.2.6 Postoperative Nausea/Vomiting

The most common complication in the postoperative period is postoperative nausea and vomiting. It is most often observed within 24–48 h. Control of PONV is an absolute criterion for hospital discharge as in patients with insufficient airway reflexes or who cannot clear secretions. Increased heart rate and blood pressure values associated with gastric aspiration and sympathetic system activation may cause myocardial ischemia and dysrhythmias [8].

Postoperative PONV is generally associated with a short preoperative fasting period, anxiety, a young age, female gender, obesity, gastroparesis, pain, motion sickness, no history of smoking, prior PONV, and prolonged surgery (laparoscopy, laparotomy, breast, strabismus, plastic, maxillofacial, gynecological, abdominal, neurological, ophthalmological and urological surgery). It is seen at rates threefold more in females than in males and decreases by 13% per decade.

There is an increased risk of PONV following anesthesia with opioid analgesics, volatile anesthetics, (sevoflurane desflurane nitrous oxide, ketamin, etomidat), and anticholinesterase reversal drugs. Other factors increasing the incidence include stomach distension, mask ventilation, postoperative pain, vertigo, early mobilization, and early oral intake. When the PONV risk is assessed as high, pharmacological prophylaxis can be administered and non-emetogenic anesthetic techniques can be used [8].

21.2.7 Hypothermia

Hypothermia and shivering are complications which can occur in almost every postoperative patient. It generally develops secondary to the low environmental temperature of the operating theatre and recovery room, impaired regulation of core temperature with the anesthetic effect, exposure of body cavities to room temperature air, or administration of room temperature IV fluids. A large observational study reported that hypothermia (core temperature < 36 °C) developed in 46% of ICU patients after elective non-cardiac surgery, and in 1.2%, this continued for more than 24 h.

Hypothermia is more severe in cases of cachexia, trauma or burns. Postoperative hypothermia increases vascular resistance, reduces venous capacity, and may lead to myocardial ischemia. Immune suppression, coagulopathy, and slow drug metabolization may develop in patients related to hypothermia. In patients applied with neuraxial anesthesia, warming in the postoperative period may be delayed because of residual vasodilation and paralysis.

21.2.8 Shivering

Although shivering is most often seen in hypothermia, it may also be observed in postoperative hyperthermic and normothermic patients. Increased myocardial oxygen consumption occurs associated with shivering and this may cause ischemia in high risk patients.

21.2.9 Fever

Fever of >38 °C may be seen within the first few days after major surgery and is usually caused by the release of inflammatory mediators (IL-6) as a response to the surgery. When fever persists, the cause is usually surgical site infection, nosocomial pneumonia, urinary tract infection or pulmonary embolism. A hypermetabolic state may result from excessively elevated body temperature, which then leads to increased respiratory rate and heart rate thereby exacerbating underlying medical conditions.

21.2.10 Neuropsychiatric Complications

Excessive sedation or agitation may be seen in postoperative patients. Risk factors include cognitive impairment, advanced age, dementia, comorbidities such as renal failure, infection, various medications, metabolite disorders, hypoxia, hypercarbia, urinary retention, electrolyte imbalance (especially hyponatremia), drug-induced anticholinergic activity, and pain. There is an increased risk of incidental trauma for these patients, including contusion or fracture as a result of collision with equipment or side rails.

Delirium: Delirium is defined as an alteration in mental status characterized by a dissociated state of consciousness in which the patient is irritable, uncooperative, uncompromising, incoherent, or crying.

Emergent delirium observed immediately after surgery is a temporary condition and may be seen in almost all age groups. Interval delirium is observed between the 2nd and 7th day postoperatively, generally in adults at a rate of <5% and is most common in geriatrics following major orthopaedic surgery.

Prolonged sedation: Patients generally respond to stimuli given 30–45 min after the application of general anesthesia. When prolonged sedation is observed, before holding the persistence of anesthesia responsible, other reasons must be discounted, such as hypotension, hypoxia, hypercarbia, hypoglycemia, and electrolyte abnormalities. This condition may be observed particularly in obese patients on whom volatile anesthetics have been used at high concentrations for a long period. In addition to the anesthetic effect, paradoxal embolism in patients with right to left intracardiac shunt, and cerebral thromboembolism in patients to whom catheterization has been applied in cardiac, proximal major vascular or invasive neck surgery should also be kept in mind. Patients with AF, carotid flutter or hypercoagulopathy are at risk of these kinds of thromboembolism. In cases of suspected cerebrovascular injury, head CT should be taken.

Visual disturbance: The most common cause of postoperative eye pain with or without visual disturbance is corneal abrasion. Occasionally, a patient may experience partial or complete visual loss (with or without pain) on awakening from anesthesia and in these cases, urgent ophthalmological consultation must be applied. Ischemic optic neuropathy, retinal artery occlusion, damage to the intracranial visual pathways, acute angle-closure glaucoma, retrobulbar hematoma, pituitary

apoplexy, or posterior reversible encephalopathy syndrome (PRES) all require urgent treatment [9].

21.2.11 Reduced Bowel Function

Constipation may develop in the postoperative period as a result of the effects of opioids and anticholinergics. The problem can be resolved with sufficient hydration, appropriate nutrition, and laxatives. A more serious condition is postoperative ileus, which may be related to perioperative bowel manipulation, pain, immobility, hypokalemia, or opioids and can cause abdominal bloating, nausea, vomiting, and impaired absorption of oral medication. Postoperative ileus generally spontaneously clears within 24–36 h. Abdominal compartment syndrome, anastomosis leakage, and stoma-related complications may also be observed.

21.2.12 Pressure Sores and Peripheral Nerve Damage

For the prevention of pressure sores, it is recommended that the patient is turned every 2 h. Injuries, which are neural-mediated such as peripheral nerve damage, may be severe, with the likelihood and severity of the injury affected by both patient-related and surgery-related factors.

Peripheral nerve damage is generally seen in diabetic, obese or advanced cachetic patients, those with peripheral vascular disease, those who have undergone a lengthy surgical intervention or related to a difficult operating position such as lithotomy, steep Trendelenburg or jack-knife.

In open surgery, postoperative peripheral nerve complications have been reported at an incidence rate of 0.14%. However, in the American Society of Anesthesiologists Closed Claims Study, 16% of all claims were found to be related to nerve injury [10]. In cases where nerve damage cannot be prevented, prompt recognition and treatment is essential for a good outcome, and other etiologies should be excluded.

21.3 Key Topics

1. Postoperative complications are estimated to develop in approximately 25% of patients following anesthesia.
2. Complications may increase morbidity and mortality by mostly affecting the cardiovascular and pulmonary systems and therefore can delay hospital discharge and increase costs.
3. Complications vary depending on the surgery applied, the anesthesia technique, and any preoperative comorbidities. However, postoperative care and follow-up has been found to be just as important as preoperative factors.
4. The risk of complications can be reduced with proper preoperative evaluation and medical optimization.

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Mechanical Ventilation After Neurosurgery

22

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Abbreviations

ALI	Acute lung injury
ARDS	Acute respiratory distress syndrome
CBF	Cerebral blood flow
$CMRO_2$	Cerebral metabolic rate of oxygen
CO	Cardiac output
DO_2	Oxygen delivery
GCS	Glasgow Coma Scale
ICH	Intracranial hemorrhage
ICP	Intracranial pressure
MAP	Mean arterial blood pressure
MV	Mechanical ventilation
NCCU	Neurocritical care unit
P_aCO_2	Arterial partial pressure of carbon dioxide
P_aO_2	Arterial partial pressure of oxygen
PEEP	Positive end-expiratory pressure

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SAH Subarachnoid hemorrhage
TBI Traumatic brain injury
VILI Ventilator induced lung injury

22.1 Introduction

There is no single universal approach to mechanical ventilation in critically ill neurosurgical patients or patients with acute neurologic injury; mechanical ventilation (MV) must be individualized to each patient's comorbidities, physiology, and acute illness. Acute respiratory failure can occur in four different contexts: (1) hypoxemic; (2) hypercapneic; (3) airway obstruction; or (4) hypopnea, diminished respiratory drive, or inability to protect airway. Respiratory failure can be chronic, acute, or acute on chronic. Indications for MV in the neurocritical care unit (NCCU) include airway protection in the setting of mechanical or physiologic airway compromise, hypoxemia, hypercapnia, or as an adjunct intervention in the management of intracranial pressure.

Neurosurgical patients comprise patients with traumatic brain injury, perioperative brain mass lesion, acute intracranial bleeding, spinal cord injury, spinal lesions and tumors, subarachnoid hemorrhages, and, increasingly, peri-neurointerventional procedure. Risks for MV in the critically ill include aspiration pneumonitis, pneumonia, traumatic pulmonary contusions, neurogenic or cardiogenic pulmonary edema, neuromuscular failure, and forms of noncardiogenic pulmonary edema or acute respiratory distress syndrome (ARDS). The goal of MV in the NCCU is to minimize the risk of secondary brain ischemia or injury though optimization of oxygenation and ventilation while minimizing impact on the cerebrovasculature which may adversely affect intracranial pressure (ICP), cerebral blood flow (CBF), and global oxygen delivery (DO_2).

Increases in P_aCO_2 (hypercapnia) or reductions in P_aO_2 (hypoxemia) will increase CBF and, consequently, cerebral blood volume which will then cause ICP elevation as a function of cranial vault compliance and any intracranial mass effect from brain, cerebrospinal fluid and edema volume. Blood oxygen levels are essential to tissue oxygen delivery. Mathematically $DO_2 = [(Hg \times SpO_2 \times 1.34) + PaO_2 \times 0.0031] \times CO$, where the delivery of oxygen to tissues is the sum of the oxygen bound to hemoglobin and the amount of oxygen dissolved in the plasma multiplied by the cardiac output. Without oxygen, the brain's cerebral metabolic rate of oxygen ($CMRO_2$) needs may be inadequate causing ischemic neurologic injury, especially in vulnerable edematous or injured tissues. Where oxygen delivery is severely compromised, $CMRO_2$ can be decreased through sedation, and more controversially, with targeted temperature management. Hyperoxia, on the other hand, may precipitate oxygen toxicity and damage to cell membranes and subcellular metabolic pathways throughout the body, but may have maximal impact on the more vulnerable brain and lung. Hypercapnia causes vasodilation of the cerebral vasculature, leading to hyperemia and potentially increased ICP, especially in patients with compromised intracranial compliance. Conversely, acute hypocapnia is implicated in cerebral vasoconstriction and metabolic crises,

especially in areas with compromised autoregulation, and subsequently increased volumes of ischemic brain.

22.2 Sedation, Anxiolysis, and Analgesia

The anesthesiologist's goal at the conclusion of a neurosurgical procedure is to achieve a rapid and smooth emergence with early extubation to facilitate early reliable neurological assessment and diagnosis of postoperative neurological complications; this is not always possible.

In the NCCU, sedation of a neurosurgical patient will require an optimal mix of anxiolysis and analgesia. Rarely is chemical paralysis through neuromuscular blockade necessary. Sedation should be titrated to quantifiable endpoints. The Bispectral Index (BIS) monitor has never been validated in the neurocritical care population. Commonly used sedation scoring systems in non-verbal or intubated patients include the Ramsay Sedation Scale (RSS), Richmond Agitation Sedation Scale (RASS), and the Sedation-Agitation scale (SAS); similarly, analgesia may be titrated to the Behavioral Pain Score (BPS), the Critical Care Pain Observation Tool (CPOT), or the Nonverbal Pain Assessment Tool (NPAT). The PAIN algorithm consists of three parts (pain assessment, assessment of patient ability to tolerate opioids, guideline-based management) and has been proposed as one of many objective assessment and intervention tools to optimize analgesic dosing. Regular interruption and reinstitution of any sedation at the lowest necessary level has been demonstrated to result in more reliable patient assessment, decreased utilization of imaging, shorter duration of ventilator days and ICU stay, and also decreased incidence of ICU delirium. However, sedation weaning trials should be undertaken with extreme caution in patients with elevated ICP.

Anesthetics affect various indicia of cerebral function including $CMRO_2$, CBF, cerebral blood flow-metabolism coupling, ICP, autoregulation, vascular response to CO_2, and brain electrical activity. Commonly used anesthetic agents all decrease $CMRO_2$ in a dose-dependent manner, but their potency varies with individual agents. Analgesic and anxiolytic agents generally decrease $CMRO_2$; however, they also have variable effects on MAP and therefore CBF, which must be calculated into the choice of agent and the dose. No single best sedation regimen has been identified. Propofol is widely used due to its short duration of action, but its use can be limited by hypotension. Midazolam and fentanyl (or its shorter-acting analog remifentanil) are also widely used either individually or in combination for intermediate duration sedation and confer better hemodynamic stability but at the cost of prolonged sedation after discontinuation. Increasingly, dexmedetomidine is emerging as a combination sedative and analgesic which meets the needs of short duration of effect, titratability, and relative hemodynamic stability—it is also the only agent which does not suppress respiratory drive at usual doses. In a comparison of dexmedetomidine, propofol, and midazolam for post-neurosurgical sedation in mechanical ventilated patients, dexmedetomidine allowed for similar level of sedation and time to extubation as propofol, but patients required less fentanyl (analgesia) administration and had improved ease of neurologic assessment during use [1].

22.3 Monitoring the Adequacy of Oxygenation and Ventilation

Ventilator management is traditionally guided by arterial blood gas (ABG) data and chest radiographic imaging findings. Newer anesthesia machines and ICU ventilators are now equipped with sophisticated graphics which allow real-time spirometric monitoring of pressure-volume loops, trends in static and dynamic pulmonary compliance, are capable of objectively determining optimal positive end-expiratory pressure (PEEP), and have in-line Open Lung tools.

The application of PEEP in neurosurgical patients has been controversial because of theoretical concerns about compromised venous drainage, transmission of elevated intrathoracic pressures to the brain, and decreases in cardiac output as a consequence of decreased preload. Controversy regarding PEEP in brain-injured patients has increasingly become settled; PEEP is now widely considered both safe and effective in neurosurgical patients, particularly if the PEEP level is set below the level of ICP, when patients have poor pulmonary compliance [2], and when PEEP is necessary for lung volume recruitment [3]. Data strongly suggests that modest PEEP (PEEP $\leq$8) significantly increases compliance of the respiratory system (Crs) without deleterious effects on MAP as long as intravascular volume is within normal limits. Evolving PEEP theory suggests that because the cerebral circulation functions as a Starling Resistor, CBF is primarily a function of MAP, and PEEP-related increases in ICP only become relevant if the central venous pressure (CVP) exceeds the ICP. Safe application of PEEP therefore requires avoidance of hypotension and maintenance of cardiac output; when PEEP affects MAP, multimodality monitoring has demonstrated adverse effects on brain tissue oxygen tension and regional cerebral blood flow [4]. Adjunct elevation of the head of the bed both increases cerebral venous drainage and decreases the transmission of airway pressures to the brain, blunting potentially deleterious effects of PEEP. The Open Lung approach to MV [5] is now widely accepted and consists of low tidal volume, elevated PEEP level, and early use of lung recruitment maneuvers to recruit atelectatic lung thereby minimizing shunt and increasing pulmonary compliance; multimodality monitoring, specifically brain tissue oxygen monitoring provides a useful tool to optimize ventilator settings in neurosurgical patients [6]. Permissive hypercapnia, a strategy frequently employed in the management of ARDS is not recommended in neurosurgical patients with elevated ICP.

22.4 Multimodality Brain Monitoring and Mechanical Ventilation

Multimodality neuromonitoring consists of the integration of cerebral physiological data allowing continuous assessment of the impact of pathophysiologic or therapeutic interventions. Multimodality brain monitoring represents an evolving field and is comprised of both traditional monitoring such as ICP, transcranial duplex, and continuous electroencephalographic (EEG) in combination with more innovative

monitoring techniques, like brain oxygenation (PbtO2), brain oximetry using near infrared spectrometry (NIRS), jugular venous bulb oximetry, and cerebral microdialysis, and are increasingly guiding the titration of mechanical ventilation and hemodynamic interventions [7]. Recommendations regarding the use of multimodality monitoring are based mainly from studies performed in patients with severe brain injury (TBI, SAH, ICH, stroke), a GCS <9 and an abnormal brain CT scan (intra-parenchymal contusions/hemorrhages) in whom clinical examination is not reliable and who are at high risk for secondary brain injury, particularly elevated ICP, cerebral ischemia/hypoxia, energy dysfunction and non-convulsive seizures. Whereas the effects of ventilator modality, PEEP, and cardiac output have been argued in the past, multimodality monitoring promises to quantify the effects of interventions.

22.5 Classification of Mechanical Ventilation Modes

Mechanical ventilation modalities can be classified in a number of ways; given the explosion of new modes of mechanical ventilation, many such modes are proprietary and available only on specific ventilators. On a most basic level, mechanical ventilatory support can be noninvasive (such as BiPAP and traditional CPAP by mask) or invasive via an artificial airway such as an endotracheal tube or tracheostomy. Invasive mechanical ventilation can then be sub-classified based on the level of support as either continuous mechanical ventilation (CMV), intermittent mandatory ventilation (IMV), or continuous spontaneous ventilation (CSV). Where ventilation is controlled, it can be targeted to either a preset tidal volume (volume-controlled ventilation; VCV) or pressure (pressure controlled ventilation; PCV). In VCV, both volume and flow are preset prior to inspiration. In PCV, inspiratory pressure is predetermined as a function of time. Time controlled ventilation represents a category of ventilator modes for which inspiratory flow, inspiratory volume, and inspiratory pressure are all dependent on respiratory system mechanics and examples of time controlled ventilation are high-frequency oscillatory ventilation (HFOV) and volumetric diffusive respiration (VDR). A spontaneous breath is a breath for which the patient controls timing. A mandatory breath is a breath for which the ventilator has assumed control over timing. With controlled modes, each breath that a patient triggers will deliver the entire preset breath as limited by volume or pressure; in such modes agitation, pain, or neural triggers such as neurogenic hyperventilation can result in severe over-ventilation and hypocapnia. IMV represents a ventilator mode and breathing sequence where spontaneous breaths are possible between mandatory breaths and where the spontaneous breaths, unlike in CMV, are controlled by patient effort and the preset inspiratory flow. IMV can decrease the risk of over-ventilation caused by inappropriate physiologic triggers but it can also impose a significant work or breathing. Synchronized IMV (SIMV) is a mode where spontaneous breaths suppress mandatory breaths as long as the minute ventilation and time presets allow. Spontaneous invasive ventilation modes range from airway pressure release ventilation (APRV) which uses both expiratory and inspiratory synchronization windows

in a time-cycled fashion and is most commonly used for management of ARDS; whereas CPAP is a spontaneous breathing mode that is used in spontaneous breathing trials and is a combination of a continuous positive airway pressure, as set by PEEP, with a manually adjusted flow to augment spontaneous patient breaths. A promising new mode of ventilation, neurally adjusted ventilatory assist (NAVA) is a form of partial ventilatory support wherein continuous positive pressure is applied throughout inspiration and triggers the ventilator cycle based on an analysis of diaphragmatic activity. With NAVA, diaphragmatic electrical activity (Edi) controls the timing and the magnitude of pressure delivered, and thereby purports to improve patient–ventilator interaction in two dimensions: achievement of optimal timing between the beginning and end of the patient's effort and the start and end of the ventilator-delivered breath; and the delivery of assistance in proportion to the patient's respiratory drive. No mode of mechanical ventilation has been persuasively demonstrated to be superior over any other mode in the management of neurosurgical and neurocritical care patients.

22.6 Ventilator Induced Lung Injury (VILI)

Brain lung cross-talk represents a complex series of interactions from brain to lung and lung to brain. Although the pathophysiology of lung injuries after an acute brain injury remains unclear, it is postulated that the sympathetic storm accompanying acute brain injury in the form of neuro-cardiac and neuro-hemodynamic paradigms, such as those implicated in Takatsubo's cardiomyopathy, precipitate a hydrostatic form of pulmonary (neurogenic pulmonary) edema. Simultaneously, brain injury causes an intracranial inflammatory response with production and release of pro-inflammatory cytokines [interleukin 1 (IL-1), IL-6, tumor necrosis factor (TNF), IL-8] from microglia and astrocytes are the principal source of inflammatory mediators [8]. Lung injury also affects the brain: VILI represents a form of biotrauma [9] whereby injury to the lung parenchyma precipitates a local and then a more systemic inflammatory response culminating in multi-organ failure as a result of pulmonary injury [10]. About one-third of patients with acute brain injury will also develop acute lung injury.

Animal and human studies have attempted to better define the brain–lung link. Both the blood–brain and blood–lung barriers become more permeable in the pathophysiologic state, which may lead to increased susceptibility to pro-inflammatory mediators. In a rodent model, mechanical ventilation alone was shown to increase inflammatory cytokine production in the lungs and plasma while simultaneously increasing *c-fos gene* expression, a marker of neuronal activation, in multiple brain regions, with larger tidal volumes associated greater *c-fos* expression in the brain [11] thus demonstrating a link between lung and brain physiology. A porcine study of lung density and extravascular lung water (ELW), animals had induced ARDS, elevated ICP, or ARDS + ICP; isolated ICP elevation lead to increased lung density and ELW which were further increased in pigs with ARDS + ICP [12]. This cross-talk is further demonstrated in severe traumatic brain injury patients where the

presence of ALI is associated increased levels of neuron specific enolase and S100B, markers of neuronal damage, and with worse outcome; but lung-protective ventilation strategies have been shown to achieve better cerebral oxygenation while decreasing presence of VILI [13]. The brain–lung interaction underscores the importance of appropriate mechanical ventilator support in neurosurgical patients and the need to ensure protective ventilation strategies for lung and brain.

22.7 Specific Mechanical Ventilation Considerations by Type of Neurosurgical Intervention

Perioperative neurosurgical patients are susceptible to cerebral edema, elevated ICP, seizures, intracranial hemorrhage, ischemic infarction, and cranial nerve palsies which require specific ventilator management considerations.

The most complex class of neurosurgical patient and the one most likely to require protracted mechanical ventilation is the patient with traumatic brain injury (TBI) because of the brain–lung interactions that perpetuate local and systemic inflammatory response. Hypotension at admission and respiratory failure requiring mechanical ventilation are associated with increased in-hospital mortality after TBI. TBI frequently results in the development of ALI or ARDS which are associated with worse long-term neurologic outcome in survivors; however, the risk of developing ALI/ARDS is not associated with any specific anatomic lesion on CT scan. The mode of mechanical ventilation in TBI patients has not been demonstrated to be associated with outcome and either controlled modes or spontaneous supported breathing modes are equally acceptable, as long as work of breathing and synchrony are optimized. Airway Pressure Release Ventilation (APRV) represents an alternative to the Open-Lung strategy and data suggest that APRV may also increase cerebral blood flow without increasing intracranial pressure. If elevated intracranial pressure is present, it is important to closely monitor P_aCO_2 and adjust settings to avoid hypercapnia as this will exacerbate ICP.

Pituitary surgery via the transsphenoidal approach can pose intubation challenges during the induction of anesthesia, particularly in acromegalic patients, who are three times more likely to have a difficult airway than in patients with other pituitary tumors; but in whom intubation with the assistance of a bougie is generally successful [14]. Intra-operatively, venous bleeding from the cavernous sinus is associated with the central venous pressure (CVP). Intrathoracic pressure may affect CVP and may therefore impair venous return and increase the risk of venous bleeding in the pituitary bed. Nasal packing can occlude the airway after surgery and negative pressure pulmonary edema has occurred after airway occlusion followed by strong inspiratory efforts against a closed glottis. Postoperatively, the nasal route should be avoided for oxygenation or ventilation purposes, as should nasal trumpets, CPAP or BiPAP masks, and nasal intubations of any sort.

Infratentorial neurosurgery is an independent risk factor for respiratory failure and death in patients undergoing intracranial tumor resection. Brainstem handling, especially in the sitting position, during neurosurgery correlates with prolonged

postoperative mechanical ventilation. Many of these procedures utilize a modified park bench patient position which can constrict venous outflow and cause facial edema. Patients with facial edema can be presumed to have airway edema and therefore extubation should be delayed until facial swelling begins to resolve. An air leak around the endotracheal cuff can help predict but is not strictly predictive of laryngeal compromise from edema. Risks for stridor post-extubation or need for reintubation in this group include facial edema, weak cough, upper extremity weakness, and dysphagia [15]. Central apnea is a relatively rare complication but one that may also be encountered following infratentorial procedures for resection of large tumors or medullary based masses; it may be transient and resolve as brainstem edema and surgical bed trauma improve or it may persist due to damage to the respiratory centers. Patients with central apnea require a controlled mode of ventilation as they have no respiratory drive. For those postoperative patients who remain intubated due to inability to protect their airway or airway edema but who are otherwise cognitively intact with intact respiratory drive, a spontaneous ventilation mode is often most comfortable, such as APRV or pressure support ventilation, and such modes can also be maintained with minimal sedation.

Following supratentorial surgery, protracted mechanical ventilation is an independent predictor of mortality but best correlates with preoperative comorbidities and American Society of Anesthesiologists physical status.

Neurosurgical patients undergoing spine procedures are at lower risk for postoperative respiratory failure and need for reintubation after the early postoperative period. However, some issues, potentially more prevalent in spine patients, should be considered: spine operations are typically performed in prone position, which places the patient at increased risk of facial and laryngeal edema, particularly with longer duration procedures. Special attention should be paid to airway patency prior to and immediately following extubation in these cases. The spinal levels involved should be noted as they may directly affect the function of respiratory musculature, especially with intradural or intramedullary involvement. Lesions and procedures involving the cervical and upper thoracic cord can significantly impair the innervation of muscles necessary for inspiration, forced expiration, and effective cough including the diaphragm (C3–C5), intercostals (T1–T6), and scalenes (C2–C7).

22.8 Ventilator Weaning and Tracheostomy

Weaning the neurosurgical or neurocritically ill patient from mechanical ventilation is largely a matter of judgment and experience. There are no specific weaning protocols or extubation criteria that can be applied to this population. More importantly, the decision to extubate the neurologic patient must not only account for pulmonary mechanics which are frequently adequate, but also for uncertain post-extubation airway patency, ability to manage secretions, and protect the airway. Conventionally, airway protection is advocated for all patients with a Glasgow Coma scale (GCS) ≤ 8; a multivariate analysis revealed that a GCS ≥ 8 was associated with an extubation success rate of 75% versus a 33% success rate for a GCS < 8

but that the probability of successful extubation increased by 39% for each incremental improvement in the GCS [16]. The neurosurgical patient is likely to have a higher incidence of problems with airway patency; cervical spine procedures performed in the prone position can result in facial and laryngeal edema; although demonstration of a cuff leak around an existing endotracheal tube is a common practice, its validity is controversial. Pulsed steroids, such as dexamethasone or methylprednisolone, for 24 h before extubation can help ameliorate a compromised airway secondary to laryngeal or glottic edema.

Where there is no neuromuscular impairment, spontaneous breathing trials (SBTs) with monitoring of the rapid shallow breathing index (RSBI) are standard. The RSBI is the ratio of respiratory frequency divided by the tidal volume in liters (f/V_T) and can be problematic in instances where there is a central neurogenic breathing pattern; however, as long as the time-averaged RSBI is within normal limits, a trial of extubation may be reasonable. Failed extubation, especially when reintubation is delayed in the presence of increased work of breathing or hypoxemia, even when aggressive respiratory and nursing pulmonary interventions are in progress, is especially detrimental in the neurosurgical patient with compromised ICP; these patients must be closely observed after extubation and early reintubation should not be considered a failure. The risk of reintubation in neurosurgical patients correlates more closely with functional status and renal, pulmonary, cardiovascular, or neurologic comorbidities than neurosurgical intervention per se [17].

There is increasing support for early tracheostomy in otherwise stable neurocritical care patients; tracheostomy as early as 4 days after initiation of mechanical ventilation is associated with improved short- and long-term outcomes, decreased pneumonia, more ventilator-free days, earlier mobilization, shorter ICU stays, less needs for sedation, decreased incidence of delirium, and reduced long-term mortality [18].

22.9 Key Recommendations

1. Understand that there is no single best approach to mechanical ventilation that is applicable to all neurosurgical patients. Mechanical ventilation must be individualized to patient comorbidities, pathology, physiology, and response to acute illness.
2. Optimize sedation so as to allow more accurate neurologic assessment, decrease reliance on imaging, and decrease the risk for delirium, but maintain adequate analgesia.
3. Utilize lung-protective mechanical ventilation strategies and the Open Lung concept whenever possible.
4. Consider multimodality monitoring as a means to titrate mechanical ventilation and hemodynamic support to more objective measures of cerebral metabolic needs.
5. In the event of a difficult weaning process, consider early tracheostomy where warranted by long-term prognosis and patient or family directives as a bridge to ventilator weaning.

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Mechanical Ventilation After Lung Cancer Resection

23

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Abbreviations

ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
EPAP	Expiratory positive airway pressure
IPAP	Inspiratory positive airway pressure
NIV	Noninvasive ventilation
PPCs	Postoperative pulmonary complications

23.1 Introduction

Lung cancer is the leading cause of cancer related death worldwide and is expected to exceed cardiovascular diseases as the top cause of death in the next few years [1]. Approximately 85% of all diagnoses of lung cancer correspond to non-small-cell lung cancer [2]. For early stages of the disease (Stages I and II), lung resection surgery is the treatment of choice [3]. Unfortunately, only ~20–25% of all cases are considered eligible to undergo surgery at the time of diagnosis [3]. On top of that, individuals with lung cancer are frequently old, had a smoking history, exhibit low cardiorespiratory fitness, and suffer from cardiovascular and respiratory

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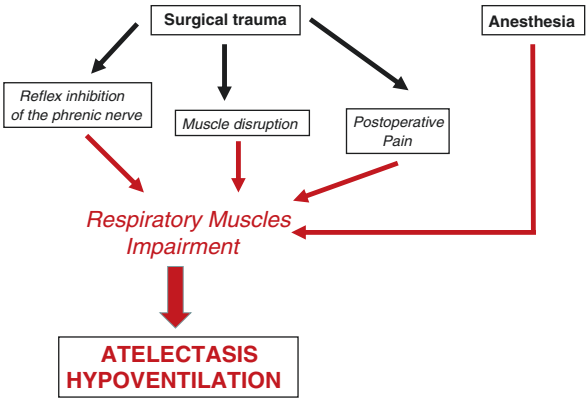

Fig. 23.1 Factors producing respiratory muscle dysfunction after thoracic surgery

comorbidities, which are known to negatively impact surgical tolerability and increase perioperative risk [4]. Postoperative pulmonary complications (PPCs) still are a significant problem in modern practice. PPCs mainly include atelectasis, pneumonia, respiratory failure requiring mechanical ventilation, and bronchospasm [5]. Many PPCs are related to the intra- and postoperative respiratory function impairment. Among main causes, anesthetics, surgical trauma (incision of intercostal muscles, reflex inhibition of the phrenic nerve), and postoperative pain lead to respiratory muscle dysfunction, producing a decrease of vital capacity and functional residual capacity. As a result, atelectasis and pulmonary gas exchange impairment occur (Fig. 23.1) [6, 7]. These modifications of the respiratory function appear early after surgery, and diaphragm dysfunction may last up to 7 days, with important deterioration in arterial oxygenation [5]. PPCs remain the leading cause of death occurring in between 60 and 80% of the patients [8–10]. This mortality is often linked to complications of postoperative re-intubation and invasive mechanical ventilation [5, 7]. Considering patient related risk factors, such as chronic obstructive pulmonary disease (COPD), age older than 60 years, American Society of Anesthesiologists class of II or higher and congestive heart failure, prevention of PPCs is of major importance. The more commonly applied strategies to prevent PPCs include stop smoking, perioperative lung function optimization with medications, oxygen therapy and physiotherapy tailored to the needs of the individual patient, good analgesia, and early mobilization [5, 11]. Also, noninvasive ventilation (NIV) and continuous positive airway pressure (CPAP) may play a role to prevent PPCs.

23.2 Analysis Main Topic

23.2.1 Rationale for Perioperative NIV or CPAP Use

NIV is a mechanical ventilation modality that does not require any artificial airway (endotracheal tube or tracheostomy) and, compared to invasive ventilation,

requires lower sedation, improves the comfort, and reduces the nosocomial infection rate [12, 13]. NIV has primarily been applied in patients with acute exacerbations of COPD, cardiogenic pulmonary edema, and acute respiratory failure in immunocompromised patients [14, 15]. In recent years, NIV has been used to treat (curative approach), and NIV or CPAP have also been used to prevent (prophylactic approach) PPCs in different settings [7, 16–18]. Although NIV and CPAP may be defined as noninvasive ventilator support, they propose different modes of delivering positive pressure. CPAP delivers a constant airway pressure during all the respiratory cycle while NIV delivers intermittent inspiratory positive airway pressure (IPAP). CPAP is a spontaneous breathing modality where the pressure applied to the respiratory system is only generated by the respiratory muscles, whereas during NIV the pressure applied to the respiratory system may be generated only by the ventilator (controlled mode) or by the ventilator and the respiratory muscles (assisted mode). Furthermore, NIV may be delivered as pressure support ventilation with or without expiratory positive airway pressure (EPAP).

The main expected benefits from applying NIV in the perioperative period are an increase in tidal volume, an improvement in gas exchange, a reduction of atelectasis, and work of breathing, thus trying to avoid invasive mechanical ventilation and its risk [17, 18].

23.2.2 Curative Approach

In a randomized controlled trial, Auriant et al. were the first to compare the efficacy of nasal NIV with standard therapy in patients with acute respiratory failure (ARF) after lung resection [19]. Patients were enrolled if they presented at least three of the following criteria: respiratory rate higher than 25 breaths per minute, active contraction of the accessory respiratory muscles, arterial oxygen ratio lower than 200 mmHg, and chest X-ray abnormalities. Two hours after the initiation of treatment, NIV significantly improved the arterial oxygenation and respiratory rate. Twelve of the 24 patients (50%) randomly assigned to the standard therapy required endotracheal mechanical ventilation, versus only five of the 24 subjects (20.8%) in the NIV group, the difference was statistically significant. Mortality was significantly higher in the no-NIV group (37.5%) compared to the NIV group (12.5%).

In another randomized controlled study, Lefebvre et al. [20] assessed early NIV use for ARF after lung resection during a 4-year period. Among 690 patients, 113 (16.3%) experienced ARF, which was initially treated with NIV in 89 subjects (78.7%), including 59 with hypoxemic ARF (66.3%) and 30 with hypercapnic ARF (33.7%). The overall success rate of NIV was 85.3%, while NIV failure occurred in 14% without any difference between hypoxemic or hypercapnic ARF. The mortality rate following NIV failure was 46.1%. The two independent factors significantly associated with NIV failure were the presence of cardiac comorbidities and no initial response to NIV.

23.2.3 Prophylactic Approach

23.2.3.1 CPAP Use

In an unselected and non-hypoxemic population, Barbagallo et al. have assessed the prophylactic use of Helmet CPAP after pulmonary lobectomy [21]. The authors have randomly allocated 50 subjects to receive continuous oxygen therapy or two cycles of helmet CPAP for 120 min, alternating with analog oxygen therapy for 4 h. At the end of the second Helmet CPAP treatment, the patients had a significantly higher PaO_2/FiO_2 ratio, compared with the control group, but the improvement did not continue beyond 24 h. The postoperative preventive Helmet CPAP was associated with a significantly shorter stay. However, minor or major PPCs, ICU readmission, and mortality were similar between the two groups.

After lung resection, Garutti et al. randomized 110 patients to receive CPAP during the first 6 h after surgery or oxygen therapy through a Venturi mask [22]. Patients who received CPAP had significantly PaO_2/FiO_2 at 24 h. On subgroup analysis, the authors found that the benefits of CPAP in the same field were interestingly greater in higher risk patients. Nevertheless, the incidence of PPCs and stay in the post-anesthesia unit were similar in both groups.

In another study by Nery et al. [23], 30 patients in the postoperative period of lung resection were allocated into two groups: an experimental group of 15 patients who underwent CPAP and a 15 patient control group who performed breathing exercises. Although, significant increases were observed in peak expiratory flow, muscle strength, and FEV1 between the first and seventh postoperative day in both groups, FVC and PaO_2 increased significantly in the same period only in the experimental group. The average loss in 6-min walk distance from preoperative to postoperative day 7 was significantly lower in patients who underwent CPAP. No air leakage increase through the drain was observed with the early use of CPAP.

23.2.3.2 NIV Use

In a randomized controlled and physiological trial, Aguilo et al. investigated the short-term effects of NIV on pulmonary gas exchange, ventilator pattern, systemic hemodynamics, and pleural air leaks in patients extubated after elective lung resection [24]. Patients received NIV during 1 h. NIV significantly increased the arterial oxygenation and this latter effect was still remained 1 hour after withdrawing NIV. By contrast, the carbon dioxide level did not change significantly, but importantly, NIV did not affect hemodynamics parameters, dead space to tidal volume ratio or worsen pleural air leaks.

Liao et al. conducted a randomized controlled trial to explore the effects and safety of prophylactic use of NIV in post-thoracic surgery of different types (mainly lung resection cancer, but also lung biopsies and esophageal resection) on the lung re-expansion, lung function change, and PPCs [25]. Fifty patients were enrolled and randomly divided into conventional treatment (control) group and NIV group. The average IPAP was set at 13 ± 3.2 cm H_2O and EPAP was set at 4 cm H_2O. Total ventilation time was 13.5 ± 4.9 h. Compared with the control group, NIV therapy reduced inadequate lung expansion rate and volume of residual cavity calculated

with CT scan. Nevertheless, there were no significant difference in the change of lung function parameters or PPCs rate after operation between the two groups. Anyway, it is important to specify that patient lung function was close to normal at baseline.

In our experience, we studied whether prophylactic use of NIV administered pre- and postoperatively might reduce the postoperative pulmonary function impairment [26]. In a randomized controlled study, 39 patients with a preoperative FEV1 < 70% of the predicted value and scheduled for elective lobectomy related to lung cancer were enrolled. Seven patients were excluded. Patients were required to follow standard treatment without (n = 18, control group) or with NIV (n = 14, study group) during 7 days at home before surgery, and during 3 days postoperatively. NIV was applied for at least five 1-h period per day. Two hours after surgery, PaO_2, FVC, and FEV1 values were significantly better in the NIV group. Also, gas exchange and the spirometric values were significantly better in the NIV group compared to the control group from day 1 to day 3. The hospital length of stay was significantly shorter in the NIV group (12 ± 1 days) than in the control group (19 ± 3 days). The incidence of major atelectasis was 14.2% in the NIV group and 38.9% in the control group but the difference was not significant.

Lorut et al. [27], in a recent multicenter randomized controlled study, investigated whether prophylactic postoperative NIV might prevent PPCs following lung resection surgery in COPD patients (GOLD II to IV). In seven thoracic surgery departments, 360 COPD patients were randomly assigned to two groups: conventional postoperative treatment without (n = 179) or with (n = 181) prophylactic NIV, applied intermittently during 6 h per day for 48 h following surgery. Acute respiratory events did not differ between groups. ARF, re-intubation rates, and mortality were, respectively, 18.8%, 5.5%, and 2.2% in the prophylactic NIV group, and 24.5%, 7.2%, and 5% in controls. Although a trend towards a lower incidence, the difference was not statistically significant. Infectious and noninfectious complications rates, and duration of intensive care unit and hospital stays were similar between groups.

23.3 Discussion and Conclusions

Anesthesia and pulmonary resection in patients with lung cancer can profoundly impair respiratory function for several days resulting in PPCs leading to respiratory failure.

Beside conventional medical strategies (medications and physiotherapy), NIV or CPAP have been proposed to prevent (prophylactic approach) or to treat (curative approach) PPCs in patients undergoing lung resection surgery. Despite some limited data [19, 20], NIV should be considered as an efficient therapeutic tool for improving gas exchange, reducing endotracheal mechanical ventilation requirement and mortality in patients with ARF after lung resection.

However, the role of NIV to prevent PPCs after pulmonary resection remains unclear. Studies remain very few, with small sample size and low frequency of

outcomes [28]. Although some studies support NIV as efficient to improve functional respiratory parameters after lung resection in selected patients with higher risk [22, 24, 26], the largest multicenter randomized controlled study conducted in patients with COPD reports negative results [27]. In their work, the authors showed that early postoperative prophylactic noninvasive ventilation after lung resection in COPD patients did not reduce acute respiratory events, ARF episodes, re-intubation rates, and mortality. Infectious and noninfectious complications rates, and duration of intensive care unit or hospital stays were not improved. However, the authors [27] reported several hypotheses that may explain these negative results. The endpoints used in this trial to measure the benefit of preventive NIV need comment. Acute respiratory events is a composite endpoint that included clinical, biological, and radiological signs of pulmonary complications. Re-intubation rate was rather low with NIV (5.5%). This confirms once again that, in patients with ARF after pulmonary resection surgery, NIV is able to avoid intubation in many cases. This point suggests that preventive NIV could be more effective in better selected severe patients at risk in future studies [29]. The selection of the appropriate patients who may benefit from postoperative prophylactic NIV is a key issue. Another hypothesis may be linked to NIV application methods. Prophylactic NIV was not applied immediately after extubation, as the mean time between extubation and NIV initiation was more than 4 h, this would have decreased its efficiency. Furthermore, prophylactic NIV was only applied during 48 h following surgery, whereas respiratory function impairment after surgery may last up to 7 days with important deterioration in arterial oxygenation [30]. Part of the negative results may also be explained by the discrepancies in skills of both medical and paramedical staff of the different centers involved in the study. Indeed, new well-designed and well-conducted randomized trials are still needed to answer the question of the real role of NIV for prevention of PPCs after pulmonary resection in lung cancer [28].

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Postoperative Pulmonary Management After Esophagectomy for Cancer

24

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24.1 Postoperative Pulmonary Management After Esophagectomy for Cancer

Esophageal cancer is the sixth most common cause of cancer-related deaths around the world, and the incidence has been increasing in recent years [1, 2]. The two most common types of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (AC). The use of alcohol and tobacco are primary risk factors for SCC, while gastro-esophageal reflux disease is held responsible for the etiology of AC [3]. The prognosis of these patients is poor, and the five-year survival rate is approximately 10–13% [4]. The main treatment for esophageal cancer is surgical resection, which has high morbidity and mortality in the perioperative period [5].

Esophageal resection for cancer is a complex surgical procedure. The overall survival rate 5 years after esophagectomy is 15–40% [4]. Several serious postoperative complications can occur in patients undergoing esophagectomy for cancer. These complications include anatomic leak, esophageal stricture, hemorrhage, injury of the recurrent laryngeal nerve, tracheobronchial injury, delayed gastric emptying, dumping, and cardiovascular and pulmonary complications [6, 7].

Postoperative pulmonary complications (PPCs) following esophagectomy occur at a rate of about 15.9–30%. PPCs include chylothorax, atelectasis, pleural effusion, pneumonia, pulmonary embolism, and acute respiratory failure (acute lung injury and acute respiratory distress) [8, 9]. Such complications may lead to the need for mechanical ventilation support and intensive care for these patients. Additionally, these complications have an adverse effect on tumor recurrence, increased postoperative mortality and morbidity, and length of stay in hospital [7, 8, 10].

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Respiratory muscle weakness, surgically induced pulmonary changes, and deficiency in pain management are formative mechanism of PPCs. As a result of these complications, respectively, atelectasis, postoperative hypoxemia, pneumonia, and acute respiratory failure may be unavoidable if the process is not well managed [11].

24.1.1 Risk Factors for Postoperative Respiratory Impairments

Risk factors for PPCs can be divided into two categories: patient-related factors and procedure-related factors. Patient-related risk factors involve advanced age, poor physical and nutritional status, impaired oral hygiene, preoperative pulmonary dysfunction, and induction therapy before surgery. On the other hand, procedure-related factors are associated with surgical techniques, the use of one lung ventilation (OLV), and anastomotic leak, pain, and swallowing disorders following esophagectomy [12, 13]. Other risk factors except the two risk factors explained below will be discussed in other parts of this book.

24.1.1.1 Preoperative Pulmonary Status

Patient preexisting pulmonary conditions effect the development of PPCs. Therefore, measurement of pulmonary function prior to surgery [forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1)] can help to predict the occurrence of pulmonary complications after esophagectomy. A retrospective study reported that the patients with $FEV_1 < 65\%$ may require prolonged mechanical ventilation support postoperatively [8]. Reduced FEV_1 and FVC measures are associated with pulmonary complications [14]. However, proscriptive spirometric values for esophagectomy are not mentioned in the literature.

24.1.1.2 Induction Therapy

Neoadjuvant chemotherapy or chemoradiotherapy for resectable esophageal cancer also affects the occurrence of PPCs. Induction therapy is performed according to histological type and localization of tumor [15]. Treatment protocols for esophageal cancer are as follows: chemotherapy, radiation therapy, and surgery. These methods can be also used in combination [16]. The rate of multimodal treatment has increased in recent years. A meta-analysis indicated that neoadjuvant chemoradiotherapy or chemotherapy have a more favorable impact on survival than surgery alone for resectable esophageal cancer [17]. However, both chemotherapy and radiotherapy have poor effect on the pulmonary system. Radiotherapy causes an acute inflammatory response on lung tissue, resulting in fibrosis [18]. Chemotherapy depresses the immune system and appetite of patients, resulting in delayed wound healing and increased infection risk [19]. Hence, multimodal treatment of patients with esophageal cancer should be planned considering all risk factors.

24.1.2 Pathophysiology of Pulmonary Complications

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are suggested to be responsible for the development of pulmonary complications after esophagectomy. It has been shown that serum and pulmonary cytokines and inflammatory mediators increase in patients undergoing esophagectomy [20, 21]. Furthermore, OLV during transthoracic esophagectomy is reported to be associated with the development of ALI in postoperatively. The possible mechanisms of lung injury following esophagectomy are as follows: ischemia reperfusion injury, use of high oxygen fraction, barotrauma during surgery, and pulmonary capillary stress failure [22].

24.1.3 Treatment Approaches to Pulmonary Complications

Postoperative care is important in reducing pulmonary complications, and a multidisciplinary approach is required. However, preoperative and intraoperative implementations should not be ignored as these may also affect postoperative respiratory outcomes. Especially, applied anesthesia and analgesia techniques during esophagectomy are directly related to postoperative pulmonary management. In light of the above, postoperative pulmonary management mainly includes mechanical ventilation and treatment of pain [11]. Other essential preoperative and intraoperative implementations in order to reduce pulmonary impairments will be mentioned below.

24.1.3.1 Preoperative Approaches

While some preoperative approaches may not directly reduce a patient's pulmonary impairments, they may favorably contribute to the healing process. These approaches are as follows:

Nutrition support: Long-standing dysphagia in patients with esophageal cancer is the most important cause of malnutrition, which has a negative effect on respiratory and immune systems. A prospective controlled cohort study reported that malnutrition leads to respiratory muscles weakness and reduced chest wall expansion after upper abdominal surgery, and it is known that malnourished patients have high risk of PPCs [23]. Therefore, although there is insufficient evidence, preoperative nutrition support in patients with inadequate oral intake may help to decrease PPCs. Moreover, nutrition support is also an important component of postoperative treatment due to reduce morbidity and mortality [11, 24].

Respiratory rehabilitation: Respiratory muscle weakness is another factor affecting postoperative risk of PPCs. Insufficient respiratory muscle strength can lead to a reduction in ventilatory capacity and to coughing. Several clinical studies reported that preoperative respiratory muscle exercises prevent PPCs in patients undergoing esophagectomy. These strengthening programs include deep inspirations,

respiratory muscle and thoracic cage stretching, and upper and lower limb and abdominal muscles strengthening exercises [9, 25]. A multicenter randomized controlled trial demonstrated that inspiratory muscle training reduces pneumonia and other PPCs [25].

24.1.3.2 Intraoperative Approaches

Surgical procedure: Esophagectomy is applied through transthoracic and transhiatal. Although transthoracic esophagectomy may be more influential on long-term survival than transhiatal esophagectomy, in this procedure, postoperative mortality and morbidity are higher [26]. In this topic, it is considered that the duration of OLV may be effective [13]. Additionally, these operations can be performed both open and laparoscopically. The notion that minimally invasive esophagectomy (thoracoscopy and/or laparoscopy assisted esophagectomy) is superior to traditional open surgery, concerning complications, is contentious [27]. Although recent reviews have expressed that minimally invasive esophagectomy (MIE) reduces PPCs, they also reported that long-term outcomes and pulmonary complication rates of MIE are still not clear [1, 5, 27].

Steroids, neutrophil elastase inhibitors, and prostaglandin E_1: Surgical trauma causes the activation of pathways resulting in inflammatory cytokines. The inflammatory process is closely related to PPCs. Hence, corticosteroids and prostaglandin E_1 (PGE_1) are used to suppress inflammatory cytokines such as interleukin 6 and interleukin 8. Several studies have indicated that the use of corticosteroids in the pre- and intraoperative period diminished inflammation and the risk of developing respiratory failure after esophagectomy [28, 29]. Neutrophil elastase inhibitors are also efficient agents. These suppress the release of both neutrophil elastase and inflammatory cytokines. Furthermore, intra- and postoperative administration of neutrophil elastase inhibitors improves respiratory function after thoracic esophagectomy [30]. On the other hand, a randomized double-blind clinical trial showed that PGE_1 reduces interleukin 6 levels and improves the alveolar-arterial oxygen gradient [31].

Fluid management: Excessive fluid therapy leads to adverse changes in pulmonary functions. Most studies encourage restrictive fluid therapy, which improves pulmonary functions, shortens gastrointestinal recovery time, and reduces morbidity [11]. Therefore, restrictive fluid therapy is commonly recommended in the perioperative period. However, the preferred fluid in the intraoperative period is controversial. While crystalloids have fewer side effects, colloids increase intestinal blood flow, oxygen tension, and anastomotic healing [24].

24.1.3.3 Postoperative Approaches

In patients with postoperative pulmonary disorders after esophagectomy, it should first be investigated whether the disorder is linked to the surgery. Then, targeted treatment strategies should be performed for patients with a diagnosis. Particularly, anastomotic leakage is associated with pulmonary complications following esophagectomy. Several diagnostic procedures to exclude this may be performed with the cooperation of a surgeon. These procedures include control of the chest tube

drainage, computed tomography to determine possible mediastinitis and empyema, and fiberoptic endoscopy. Treatment options are conservative, percutaneous drainage, and exploration [6, 32]. On the other hand, chylothorax may be identified by chest radiographs and inspection of the chest drainage content. Recurrent laryngeal nerve injury is also an important postoperative complication because it can cause life-threatening aspiration and lead to fatal pneumonitis. Diagnosis is made in the postoperative period. Cessation of oral intake to prevent aspiration is the basis of treatment in these patients [7].

The routine use of nasogastric (NG) tube is controversial. Widespread opinion favors the use of NG tubes for protection against aspiration. However, several trials reported that use of NG tubes does not contribute to reduced pulmonary impairments, and the NG tube itself may lead to patient discomfort, and hypopharyngeal dysfunction, as well as being a source of upper respiratory tract infections and pneumonia. It is recommended that NG decompression for esophagectomy is applied selectively [33, 34].

Pain management is another important aspect of preventing atelectasis and pulmonary infections. Systemic analgesia and regional techniques such as thoracic epidural analgesia can be used to reduce postoperative pain. Both methods can be performed as patient-controlled or on-demand. A meta-analysis reported that the use of epidural analgesia following abdominal and thoracic surgery is more efficient in reducing PPCs, the risk of prolonged ventilation, and reintubation than systemic analgesia [35].

Noninvasive mechanical ventilation: Acute respiratory failure (ARF) is described as dyspnea, increased breathing rate (>25 breaths/min), asynchronous breathing movements, the participation of accessory inspiratory muscles, and peripheral (SpO_2) and arterial oxygen (PaO_2) desaturation ($SpO_2 < 92\%$, $PaO_2 < 60$ mmHg on room air or $PaO_2 < 80$ mmHg with oxygen therapy) [36]. In recent years, noninvasive positive-pressure ventilation (NPPV) has emerged as a treatment for acute respiratory failure after esophagectomy. Several studies have suggested that poor pulmonary function, increased morbidity and mortality, and prolonged hospital stay are linked to reintubation and mechanical ventilation [8, 37].

Basically, NPPV is applied using a face mask for pressure support ventilation (PSV) and positive end expiratory pressure (PEEP), and the aims of usage are alleviated respiratory load and improved gas exchange [36]. Furthermore, NPPV reduces the formation of atelectasis and increases functional residual capacity and tidal volume in patients after upper abdominal surgery. Forms of noninvasive pressure ventilation are continuous positive airway pressure (CPAP) and bilevel positive airway pressure (bilevel NPPV) [38]. Continuous positive airway pressure presents positive pressure to the airway during inspiration and expiration, and it may be applied by nasal, oral, oronasal, or full face mask, or helmet [39, 40]. Bilevel NPPV is a combination of inspiratory positive airway pressure and expiratory positive airway pressure [41]. In this context, systematic reviews have reported that CPAP and bilevel NPPV are effective and safe interventions for treatment of ARF after upper abdominal surgery, but the quality of the evidence is low [38].

Nevertheless, despite increasing NPPV applications, practitioners have doubts associated with its implementation after esophagectomy based on the following disadvantages of NPPV: NPPV in the early postoperative period may lead to loss of integrity of esophageal sutures, and subsequently, secondary esophageal perforation may occur. In this case, the applied airway pressures should be examined. Inspiratory pressure support of ≤15 cmH_2O is considered safe to avoid gastric insufflation. However, the pressure can be adjusted up to 15–20 cmH_2O [42, 43]. Compression on the lungs and, consequently, reduction of pulmonary compliance are among the possible effects of gastric insufflation. Moreover, escape of gas into the esophagus may increase transient upper esophageal sphincter relaxation; and this may result in aspiration of gastric content [43–45].

In summary, not only pulmonary management after esophagectomy for cancer consists of postoperative approaches, but it is also related to pre- and intraoperative approaches. Therefore, patients with esophageal cancer should be carefully followed. Particularly, these patients should be assessed in collaboration with surgeon to exclude surgical complications, postoperatively. Noninvasive mechanical ventilation following esophagectomy is ranked first in pulmonary management. Noninvasive positive-pressure ventilation is an effective method unless high pressures are applied. Furthermore, pain management and gastric decompression contribute to treatment process.

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Part IV

Withdrawal from Mechanical Ventilation Support

Tracheostomy: Indications

25

George Eapen and Macarena R. Vial

25.1 Introduction

Tracheostomy is a common surgical procedure in patients admitted to intensive care units (ICU), and is most commonly utilized in patients with persistent respiratory failure expected to require prolonged mechanical ventilation. Up to 10–24% of patients will undergo this procedure during their ICU admission [1, 2] and given the increasing use of mechanical ventilation, such tracheostomies are also likely to increase [3]. It is therefore important for clinicians to clearly understand the indications, contraindications, optimal timing, and different placement techniques available. In this chapter, we will mainly focus on the indications for tracheostomy with a brief discussion on techniques.

25.2 What Are the Benefits of a Tracheostomy?

The advantages of a tracheostomy are reasonably clear in patients with upper airway obstruction, or those with severe neurologic injury or severe maxillofacial trauma [4, 5], where tracheostomy provides a secure airway, permitting adequate ventilation and long-term secretion management. In the majority of other ICU patients, who present with acute respiratory failure, the decision is not straightforward and the possible benefits are more controversial.

Tracheostomy is typically recommended in patients who are expected to require long-term mechanical ventilation due to the risks associated with prolonged

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translaryngeal intubation. There are several potential advantages of tracheostomy in such patients, including possibly preventing airway injury, facilitating weaning, decreasing the risk of ventilator-associated pneumonia (VAP), and facilitating nursing care. Another claimed benefit of tracheostomy includes improved patient comfort, permitting patients to resume oral intake, communicate, and decrease sedation requirements. The evidence supporting some of these benefits is variable and since tracheostomies can have serious and sometimes lethal complications, such as stoma infection, tracheo-innominate artery fistulas, pneumomediastinum, and pneumothorax [6, 7], it is important to review such evidence. Furthermore, many of the risks of prolonged translaryngeal intubation were described with old endotracheal tubes but as with many medical devices, the endotracheal tube's design and materials have changed in order to minimize associated complications [8]. Understanding the benefits we can reasonably expect in individual patients and accurately identifying those in whom the risk-benefit ratio may not favor a tracheostomy, is essential for clinicians dealing with these critically ill patients. In this chapter, we will therefore review the evidence supporting some of the potential benefits mentioned above. It is important to note that the majority of studies evaluating the benefits of tracheostomy in these patients have compared early tracheostomy versus late tracheostomy, but data comparing tracheostomy versus prolonged translaryngeal intubation is scarce.

25.3 Does Tracheostomy Reduce Airway Injury in Patients Requiring Prolonged Ventilatory Support?

Upper airway injury can occur with both tracheostomy and translaryngeal intubation, with rates of post intubation tracheal stenosis ranging between 0.6–21% and 6–21% for post tracheostomy stenosis [9, 10]. Although the site of stenosis varies, there is no evidence to suggest that either one is less or more likely to induce airway injury. Only one study randomized patients to early tracheostomy versus no tracheostomy, i.e., prolonged translaryngeal intubation [11]. It included 123 patients and assessed airway injury with both laryngeal symptoms (swallowing and dysphonia) and bronchoscopic airway examination. This study failed to demonstrate any difference in terms of laryngotracheal complications. Whether an early versus late tracheostomy reduces laryngotracheal complications is a slightly different question, but so far, the answer seems to be the same. Performing a tracheostomy earlier during the patient's hospitalization has not been demonstrated to prevent airway injury [12, 13]. In a study by Rumbak et al. [13] 120 patients were evaluated for laryngotracheal damage at the time of admission and at week 10 after intubation, using bronchoscopy and linear radiographic tomography, but no significant differences were observed.

25.4 Does Tracheostomy Decrease Patient Discomfort?

Increased patient comfort and consequently decreased sedation requirements are often cited among the benefits of tracheostomy. The evidence for this statement is contradictory and scarce, with few studies designed to assess this as a primary

outcome. Patient comfort measured by a visual analog score of anxiety has not shown to be different before and after placement of a tracheostomy [14]. A retrospective study by Veelo et al. [15] did not observe any difference in sedation requirements among 129 patients who underwent a tracheostomy. The only study to date that demonstrated decreased sedation requirements was a retrospective study by Nieszkowska et al. [16] Unfortunately, due to deficiencies in the study design and the fact that there was already decreased sedation requirements in the week preceding the tracheostomy, it is difficult to conclude that the procedure was responsible for the reduced sedation requirements.

The use of sedatives was also evaluated as a secondary outcome in the TracMan trial [17], the largest early versus late tracheostomy trial. The number of days during which any sedatives were received was five in the early group and eight in the late group ($P < 0.001$). This difference was not significant when the analysis was restricted to patients surviving less than 30 days. Other studies have also reported decreased sedation requirements but none of them designed for this specific purpose. Despite the limitations of the data regarding sedation requirements, it is very likely that being able to communicate and eat are reasons for patients to feel more comfortable, but additional studies are needed.

25.5 Does Tracheostomy Reduce the Risk of Ventilator-Associated Pneumonia (VAP)?

Removing the endotracheal tube is thought to allow laryngeal competence and therefore prevent microaspiration. Since microaspiration has been associated with pneumonia, one should expect a reduction of ventilator-associated pneumonia (VAP) after a tracheostomy. However, the available evidence is contradictory with some studies demonstrating a decreased risk [13, 18, 19] and others an increased risk of VAP with early tracheostomy [20–22]. The risk of pneumonia in patients with a tracheostomy compared to prolonged translaryngeal intubation was the main outcome of a case control study, where the rate of VAP was found to be significantly higher in patients with endotracheal tube (22 versus 14 VAP episodes·1000 mechanical ventilation days − 1 [23]. At least three meta-analyses have examined the effect of early tracheostomy on the risk of VAP [24–26]. Due to significant methodological and statistical heterogeneity no pooled estimate could be reported in two of them, including a Cochrane meta-analysis [26]. The only meta-analysis reporting a pooled estimate found the incidence of VAP to be lower in patients assigned to early tracheostomy versus late or no tracheostomy (OR 0.6, 95% CI: 0.41–0.90, $p = 0.01$) [25].

25.6 Does Tracheostomy Facilitate Earlier Liberation from Mechanical Ventilation?

Decreased dead space, decreased airway resistance, and decreased work of breath have all been described with tracheostomy cannulas as compared to endotracheal tubes [27]. However, the clinical significance of these observations on liberation

from mechanical ventilation is not clearly defined. There is evidence supporting decreased length of mechanical ventilation as one of the benefits of tracheostomy, but this has always been reported as a secondary outcome [5, 13, 17–19, 21, 22, 28]. The majority of these studies have found a trend [17] or a significant reduction in the length of mechanical ventilation with early tracheostomy compared to late tracheostomy [13, 18, 19, 28] with differences ranging from 9.8 [13] to 2.1 [18] days. It is important to keep in mind that clinician's behavior towards ventilatory liberation may be different when a secure airway is in place and since blinding is not possible, the benefits may not be attributable to the tracheostomy itself.

25.7 Decreased Mortality

Several randomized controlled trials [5, 13, 17–19, 21, 28] and a few meta-analyses [24–26] have evaluated the effects of tracheostomy in mortality. In one of the first randomized trials comparing early (within 48 h) versus late tracheostomy (>14 days), Rumbak et al. [13] reported a 50% mortality risk reduction in the early tracheostomy group ($p < 0.005$). Although definitions of early and late vary significantly, none of the other randomized trials that followed reported similar findings [17, 19, 21, 28] except for one study that was only limited to neurocritical patients [5]. The TracMan trial is the largest randomized study assessing 30-day mortality as the primary outcome [17]. Early tracheostomy was defined as ≤4 days of orotracheal intubation and late as after 10 days of intubation, with no significant differences in mortality between the groups.

At least three meta-analyses have attempted to derive a pooled estimate, with inconsistent results. A Cochrane review [26] included the longest follow-up time available for each of the seven studies and reported a significant reduction in mortality with early tracheostomy (risk ratio = 0.83; 95% CI: 0.7–0.8) [26]. These results were not reproduced in two recent meta-analyses; one measured mortality at 1 year in 13 randomized trials with no mortality benefit, relative risk of early versus late tracheostomy of 0.93 (95% CI: 0.85–1.02) [24]. Similar finding were reported by Liu et al. with a relative risk of 0.84 (95% CI: 0.67–1.04) [25].

To summarize, the clearest evidence-based benefit of tracheostomy in critically ill patients with respiratory failure seems to be a reduction in the length of mechanical ventilation. Tracheostomy might also increase patient comfort, since it enables the patients to communicate, eat, and transfer to chair, but qualitative studies are lacking.

25.8 If We Believe a Tracheostomy Is Indicated, When Is the Most Appropriate Time to Do It?

Several trials have evaluated the best time to perform a tracheostomy. Unfortunately, the definitions of what is considered early and late tracheostomy and the outcomes measured in each study vary widely, making comparisons and pooled estimates

very difficult. The majority of trials evaluating the effect of early tracheostomy on mortality have failed to prove any difference [17–19, 21, 28] with only two showing a mortality reduction with early tracheostomy. It is worth mentioning the TracMan study [17], in which patients were identified within 4 days of admission; if the patient was believed to require at least 7 more days of mechanical ventilation, the patient was included in the study and randomized to either early (within 4 days of admission) or late (after day 10 of admission) tracheostomy. There was no difference in mortality at day 30. Interestingly, when patients randomized to a late tracheostomy where reassessed, the procedure was considered unnecessary in 55% of them, highlighting the difficulty in predicting the length of ventilator support.

Two meta-analyses have summarized the evidence, with conflicting results. In a Cochrane review, results favored early versus late tracheostomy with mortality rates of 47.1 and 53.2%, respectively ($p = 0.03$). These results were not reproduced in a more recent meta-analysis that included 13 RCTs with no difference in mortality at 1-year. These studies have also assessed other outcomes including length of ICU admission [5, 13, 18, 19, 21, 22], risk of VAP, and duration of mechanical ventilation. The effects of early tracheostomy on the length of admission and risk of VAP are inconsistent across studies. It appears, however, that early tracheostomy reduces the duration of mechanical ventilation [13, 18, 19] with differences ranging from 9.8 days [13] to 2.1 [18].

Given the above data, if a tracheostomy is indicated in a patient with respiratory failure, then performing an early tracheostomy may reduce the duration of mechanical ventilation but possibly at the cost of performing unnecessary tracheostomies in up to half of the patients if done before 10 days of mechanical ventilation.

25.9 How Good Are We at Predicting Prolonged Mechanical Ventilation?

To optimize the benefits of a tracheostomy, clinicians need to assess the probability of prolonged mechanical ventilation early on the course of the patients ICU admission. Traditionally, this assessment is based on clinical judgement but unfortunately it can be very inaccurate. This was one of the most important lessons from the Tracman trial [17], a randomized study with 909 patients comparing early versus late tracheostomy. The estimated time of mechanical ventilation was assessed on day 4 and only those who were believed to require mechanical ventilation longer than 10 days were enrolled on the trial. Surprisingly, only 45% of those enrolled and subsequently randomized to late tracheostomy still required mechanical ventilation at day 10, highlighting the poor ability of clinicians to estimate the length of mechanical ventilation. Several predictive models have been used [29, 30], all with poor to moderate accuracy. This suggests that until we improve our ability to predict prolonged mechanical ventilation, decisions regarding tracheostomy should be deferred for 7–10 days after initiation of mechanical ventilation to avoid a large number of unnecessary procedures.

25.10 Techniques and Additional Equipment

Tracheostomy can be performed by an open surgical technique, or percutaneously with a modified Seldinger technique initially described by Ciaglia in 1985 [31]. Surgical tracheostomy (ST) is usually performed in the operating room, but it can also be performed as a bedside procedure in the ICU. During surgical tracheostomy an incision is made in the skin, subcutaneous tissue, and trachea, allowing for direct visualization of the trachea while inserting the tracheostomy tube. It is the preferred option in patients with a difficult neck anatomy. Percutaneous tracheostomy (PT) involves needle puncturing the trachea and inserting a guidewire, followed by dilation of the trachea and placement of the tracheostomy cannula. Several studies have compared surgical and percutaneous methods, and while reviewing these results it is important to keep in mind that "percutaneous tracheostomy" involves multiple techniques with different dilation methods, some of which have largely been abandoned. Furthermore, some studies were carried out shortly after percutaneous tracheostomy was introduced at a particular institution, at a time when the operators experience was limited.

Percutaneous tracheostomy is usually performed as a bedside procedure, potentially saving the costs of the operating room and complications associated with patient transport. Studies comparing PT performed at the bedside to ST in the OR demonstrated significant cost differences [32, 33]. Freeman estimated the total costs of PT at the bedside compared with ST in the operating room to be $1569 ± $157 versus $3172 ± $114, respectively. Interestingly, PT opened the way for surgical tracheostomies to be performed as a bedside procedure, so savings related to the operating room is no longer a unique advantage of percutaneous tracheostomies. Two randomized trials have compared costs of ST and PT when both are performed at the bedside, with conflicting results [34, 35]. It is very likely that total cost varies in different institutions according to the local costs of operating rooms, type of tracheostomy kit, anesthesia support, the use of bronchoscopy and/or ultrasound, among others.

At least four meta-analyses have compared the risks of mortality and complications of PT and ST [36–39]. All these studies have failed to show any difference in mortality. Regarding complications, the most consistent finding is a lower risk of infection with PT compared to ST with OR from 0.22 to 0.37. This was also confirmed in a RCT by Silvester [40, 41] who also described an additional benefit of PT; he observed that time from randomization to execution of the tracheostomy was shorter in patients assigned to PT, probably reflecting a logistical advantage.

If the choice is to perform a percutaneous tracheostomy, multiple techniques are available and probably the best option is the one that the operator feels more comfortable with. There are several RCTs, generally small trials and with important methodological differences that have compared two or three different PT techniques. Most have shown minimal differences or findings that have not been reproduced later. A recent meta-analysis that included 14 RCT comparing at least two percutaneous techniques described no differences among them in terms of complications [42]. They reported Ciaglia Blue Rhino to be technically easier according to the operators, but they did not calculate pooled estimates for the other techniques reviewed.

25.10.1 Bronchoscopy Guidance

Bronchoscopy has been used for visual guidance during percutaneous tracheostomy. It allows the operator to directly visualize the needle entering the airway as well as the dilators and finally the tracheostomy tube. It is used in an attempt to decrease the risk of serious complications such as perforation of the tracheal wall, false lumen, and possible associated tension pneumothorax. Despite the limited to almost no data supporting this approach, it is widely used with a recent European survey showing that 97.7% routinely used bronchoscopy to perform PT in the ICU [43].

The benefits of bronchoscopy guidance have not been evaluated in a randomized trial. Few retrospective studies [41, 44] have attempted to compare complications of PT with and without bronchoscopy guidance but failed to demonstrate any difference. Unfortunately a retrospective design is problematic because physicians performing a procedure are more likely to use bronchoscopy when they expect a higher risk of complications, for example, in patients with poor anatomic landmarks. This might partially explain the findings of a more retrospective recent trial [45] that reported a significantly increased risk of complications in bronchoscopy guided procedures (11.9% versus 1.9%, $p = 0.58$). Although the benefits are likely small, the use of bronchoscopy seems reasonable if it increases the operator confidence, particularly for physicians in training. The main disadvantage is the added cost and the risk of equipment damage.

25.10.2 Ultrasound Assistance

Ultrasound allows more accurate identification of the tracheal midline, as demonstrated by a randomized trial where real-time US guidance was used [46]. The proportion of appropriate punctures, defined as $0 \pm 30°$ from midline, evaluated by still bronchoscopy images, was 87% versus 50% ($p = 0.06$). However, this did not translate into fewer complication rates.

The largest study assessing the utility of ultrasound for bronchoscopy included 341 patients [47]. Ultrasound was used prior to the procedure to identify abnormalities that might increase the risk of PT. In 23% of patients who underwent an US examination, a vascular, thyroid, or tracheal abnormality potentially complicating the procedure was identified. Perioperative complication rates were lower with the use of US, although the difference did not achieve statistical significance (7.8% versus 15%, $p = 0.051$).

Conclusions

The principal benefit of tracheostomy in critically ill patients with persistent respiratory failure appears to be an overall reduction in the duration of mechanical ventilation. Additionally, it might be helpful in decreasing the patient's discomfort. Other benefits such as decreased mortality, decreased VAP, and decreased airway injury have not been consistently found in clinical studies. The

magnitude of the benefit varies with the timing of the tracheostomy. Tracheostomy should be considered early on in the patient's ICU admission, but only performed when there is reasonable certainty that the patient will need prolonged mechanical ventilation after 7–10 days of respiratory failure. Reliable methods to prospectively identify those patients who will need prolonged ventilatory support are sorely lacking.

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Nutrition in Critically Ill Cancer Patients

26

Laura D. Ciobanu

26.1 Introduction

Despite being a highly preventable disease, lung cancer remains the most common cancer in the world in terms of new cases, 1.8 million in 2012 (12.9% in total), and mortality (World Cancer Research Fund/American Institute for Cancer Research Second Report WCRF/AICR 2007; [1–3]). It accounts for 19.4% of all cancer deaths, being the main cancer-related cause of mortality regardless of the gender [2]. In both men and women the incidence of lung cancer is low in young people under 40 years old and increases up to 75–80 years as reported in most populations [4]. This incidence depends on the pattern of smoking in population [4] and on the long period of time of 20–30 years required for lung carcinogenesis to develop [5].

The idea that human diet might influence cancer risk and that appropriate diet could reduce it has opened a new research era, offering new resources for prevention. After two decades of work, researchers have found that the diet–cancer relationship is complex, meeting difficulties in measuring usual diets over time, in estimating nutrients intake at different life stages, together with a long time for cancer to develop. Would it be possible for the diet as a whole to exert a greater influence than the sum of its ingredients [6]?

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26.2 The Risky Diet and Lifestyle

Lifestyle is a term used to characterize individual behaviors, such as tobacco smoking, alcohol consumption, poor diet, and physical inactivity; it implies individual volition in order to make positive changes [7]. As estimated by Doll and Peto in 1981 (cited by White et al. 2013) [7], 25–40% of lung cancer-related deaths could be attributed to tobacco use (with a mean of 30%), 10–70% could be attributed to poor diet (with a mean of 35%), 4% to occupation, and 2% to pollution. Consistent work of researchers worldwide has focused over the identifiable risk factors in lung cancer and the possibility to influence some of them. Genetic factors, tobacco smoking, diet and alcohol, chronic pulmonary inflammation, ionizing radiation, occupational exposure, environmental pollution (mainly due to tobacco smoke, radon, and asbestos), and other risk factors (hormones, underweight) have been largely discussed [3, 5]. Moreover, the World Cancer Research Fund/American Institute for Cancer Research Second Expert Report Panel [1] judged that arsenic in drinking water and β-carotene supplements have increased the risk of lung cancer.

Tobacco smoking is the most avoidable risk factor and it is the main risk factor for all major histological types of lung cancer [3]. Because cigarette smoking accounts for 80% of the worldwide lung cancer burden in men and at least 50% of the burden in women, preventing the onset of smoking and a successful smoking cessation in current smokers will be the first effective measure in primary prevention of lung cancer [1, 5]. Not smoking is the first strategy in preventing lung cancer [8].

About 25% of cancers globally are due to excess weight and to a sedentary lifestyle [9]. *Physical activity* is defined as any bodily movement produced by skeletal muscle contraction leading to increased energy expenditure above the resting energy expenditure; it is conventionally divided into four types, occupational, transport, recreational, and household settings [10]. Regular moderate physical activity is associated with a significantly lower risk of cancer mortality, potentially through improving insulin sensitivity and immune function, and reducing sex hormones, metabolic hormones (e.g., adipokine level), oxidative stress, and systemic inflammation [9–11]; it is recommended a moderate physical activity of 30 min daily, with increasing at 60 min as fitness improves [1].

Epidemiological evidences suggest an increased lung cancer risk associated with *alcohol* consumption, especially with beer and liquor, after controlling for cigarette smoking [12]. In addition to ethanol, alcoholic beverages contain antioxidants such as sulfites, flavonoids, and resveratrol, as well as chemicals with carcinogenic potential like nitrosamines, asbestos fibers, and polycyclic aromatic hydrocarbons [12]. Alcoholic beverages mediate carcinogenesis through multiple mechanisms: pro-carcinogenic effects of acetaldehyde, redox changes, formation of free radicals, liver injury, elevation of sex hormones levels, folate deficiency, and interactions with tobacco smoking [10]. Wine may apparently be a protector up to a certain level where its potential antioxidant effects are outweighed by the detrimental effects of high levels of ethanol exposure [12]. Because of the high caloric content of alcoholic beverages, heavy drinkers tend to displace other elements of a diet, having an

increased fat intake and eating less fruits and vegetables. The relationship between alcohol and lung cancer has been reported to be stronger or even limited to individuals who eat less vegetables, vitamin A, and carotenoids [12].

A meta-analysis published in 2011 [13] reported no association between alcohol consumption and lung cancer risk in never smokers; seemingly, alcohol does not play an independent role in lung cancer etiology in this category of people. Authors cannot conclude that alcohol is not associated with lung cancer in smokers; alcohol may enhance the carcinogenic effect of cigarette smoke on lung tissue by inducing the activity of cytochrome P-450 enzymes, which in turn can activate procarcinogens present in alcoholic beverages [14]. Experimental studies have shown that alcohol acts in the later stages of carcinogenesis as a co-carcinogenic or promoter, and not as an initiator [14]. It is therefore recommended to limit alcohol consumption to no more than two drinks a day in men and one drink a day in women [1].

A limited number of studies have proven that *coffee* drinkers had a higher risk for lung cancer, but they are far more likely to smoke than nondrinkers; these results are debatable if considering the chemopreventive mechanisms of action of some coffee components. Guertin et al. [15] found that coffee drinking was positively associated with lung cancer, although the association is obviously attenuated after adjustment for tobacco smoking; drinkers of more than six cups a day have a hazard of 30% comparing to nondrinkers. Coffee drinkers are more likely to be men, smokers, and to have a low level of education. Greater smoking intensity was strongly correlated with heavier coffee consumption, probably through the shared CYP1A2 metabolic pathway [15]. The majority of coffee consumed in the USA is filtered coffee, so the aforementioned findings reflect the association between coffee filtered and lung cancer; it is possible that associations may differ for other types of coffee (unfiltered, percolated, espresso) due to different proportion of caffeine and other constituents [15]. A meta-analysis conducted by Tang et al. [16] indicated that high or an increased consumption of coffee may increase the risk of lung cancer; because the residual confounding effects of smoking and other factors may still exist, these results should be interpreted with caution.

As demonstrated by Sinha et al. [17], consumption of *red meat*, mainly fried and/or well-done, was associated with an increased risk of lung cancer, most probably due to the formation of heterocyclic amines during cooking at high temperatures, especially by pan-frying and grilling [18]. The effect on cancer might be linked to mutagenic compounds generated in red meat and processed meat such as heterocyclic amines, polycyclic aromatic hydrocarbons, and N-nitroso compounds [10]. As reported by Okubo et al. [19], *processed meat* consumption was negatively associated with the lung function in both males and females; it was a stronger association among males with low fruit and vegetable consumption, low dietary total antioxidant capacity and current smoking. Men and women with a high consumption of processed meat, participants at the European Prospective Investigation into Cancer and Nutrition (EPIC) study, followed-up for a median time of 12.7 years, with a maximum of 17.8 years, were at increased risk of death, in particular due to cardiovascular diseases and cancer [20]. If processed meat intake would be reduced at less than 20 g/day, this action would prevent 3.3% of all deaths [20].

Processed meat (i.e., bacon, gammon, ham, corned beef, spam and luncheon meal, sausages, and meat pies) is associated with a worse lung function in both males and females [19]. Processed meat is treated by salting, curing, smoking, has added nitrites as preservatives, antimicrobial agents, taste improvers, and color fixatives [19–21]. Dietary nitrites generate reactive nitrogen species that amplify inflammatory processes in the lung parenchyma and airways, leading to DNA damage, inhibition of mitochondrial respiration, protein dysfunction and cell damage through oxidative and nitrosative damage [19]. Processed meat is also rich in advanced glycation end-products, which can increase oxidative stress and inflammation [19]. As meat intake is a modifiable risk factor, a healthy diet should contain a low, still not a zero daily amount, as it is an important source of proteins, iron, zinc, vitamins A and B, and essential fatty acids (linoleic, eicosapentaenoic, and docosahexaenoic acids) [20, 21]. Meat consumption should be, as a population target, not more than 300 g red meat per capita per week, while the personal target for meat-eaters should be less than 500 g red meat per week, very little if any of which to be processed [1].

A pooled analysis on eight prospective cohort studies could not identify any statistically significant association between intakes of total or specific types of *dietary fat* (saturated, monounsaturated, or polyunsaturated) and lung cancer among never, past, and current smokers, in both males and females. Dietary cholesterol was not associated with lung cancer risk in a multivariate analysis made by Smith-Warner et al. [22].

According to WCRF/AICR 2007 [1], the population average consumption of *salt* from all sources should be less than 5 g (2 g of sodium) a day. Experimental and in vivo data have shown that a high intake of salt is a risk factor for acute lung inflammation and edema, and acts through M(Na), a novel macrophage activation state salt-induced [23].

There are important debates around *β-carotene supplements*, an antioxidant naturally present in many fruits and vegetables and designated by the US Food and Drug Administration as "generally recognized as safe" to be used as a dietary supplement and as an additive in foods [24]. β-Carotene has been the subject to one of the most intensive chemoprevention research, but there have been registered important differences in results between observational studies and preventive trials [3]. The Expert Panel of the 2007 WCRF/AICR Second Report concluded as convincing evidence that high doses of β-carotene supplements (in smokers) increase the risk of lung cancer; fruits and foods containing carotenoids probably decrease the risk of lung cancer. For cancer prevention people should not rely on dietary supplements, excepting severe illnesses or dietary inadequacy, where supplements might be valuable [1].

26.3 Chemoprevention in Lung Cancer

Chemoprevention means the use of specific agents to reverse, suppress, or prevent the process of carcinogenesis; the ultimate goal is to reduce disease incidence and mortality. It involves the use of dietary or pharmaceutical interventions to slow or

reverse the progression of premalignancy to invasive cancer [5]. Natural products originated in marine and terrestrial organisms feature a large number of chemical structures that modulate a wide range of biological effects. They have been used in traditional medicine for thousands of years without having a complete understanding of their mechanism of action [25]. Phytochemicals or phytonutrients are bioactive food constituents derived from a plant source; they intervene as inducers of important mechanisms related to antioxidant defense, longevity, cell maintenance, gene expression modulation, and DNA repair [26]. Plant-based food introduces significantly more antioxidants into human diet than non-plant food based on meat, fish, and other products originated from the animal kingdom. There is no linear relationship between the antioxidant content of a food sample and the antioxidant activity in the target cell; the bioavailability of the antioxidants depends on the food matrix, absorption through action of the gut microbiota, and metabolism [26].

Thousands of *fruits and vegetables* constituents manifest protective effects mainly by reducing oxidative damage of DNA, increasing the activity of enzymes able to detoxify carcinogens, stimulation of immunologic response, modulation of hormonal level, and antiproliferative activities [27, 28]. Because of the overwhelming confounding effect of smoking, the true relationship between fruits, vegetables, and lung cancer might be better clarified by studying a never smoking population, but lung cancer is a rare disease in never smoking people and data gathered so far are insufficient to draw a sound conclusion [27]. Tens of case-control and cohort studies conducted over many years in various populations have indicated that people who eat more vegetables and fruits, foods rich in β-carotene and carotenoids, and those with higher blood β-carotene concentrations have a lower risk of lung cancer [29]. A recent meta-analysis from 2016 has concluded that the current evidence from prospective studies is consistent with a protective role of fruits and vegetables in lung cancer etiology. A healthy diet with plenty of whole grains, pulses (legumes), non-starchy vegetables and fruits, with a high content in vitamins, antioxidants and phytonutrients apart from β-carotene, in balanced doses, may benefit in reducing lung cancer risk [8]. Significant inverse dose-response associations were observed for each increase of 100 g/day for fruits and vegetables. The risk for lung cancer decreases by 27% with increasing intake up to 400 g/day; no benefit was obtained with increasing consumption above 400 g, which mean five portions per day [8]. The population average consumption of non-starchy vegetables and of fruits should be at least 600 g daily; the personal intake should be at least 400 g or five portions a day of non-starchy vegetables and fruits [1].

A cup of *coffee* is a complex mixture containing more than a thousand molecules, heterogeneous bioactive compounds able to act on different cancer hallmarks, helping to prevent its appearance and development [25]. It has been demonstrated that daily drinking of 4–6 cups of regular black coffee, meaning up to 750 mL, is sufficient to prevent carcinogenesis and slow the progression of different types of cancer [30]. The current body of evidence recommends coffee consumption to be included into a healthy lifestyle [25].

Green tea, with its high level of flavonoids, has strong chemopreventive effects against lung tumorigenesis in most animal studies through multiple mechanisms,

especially by inducing cell cycle arrest and apoptosis. Still, epidemiological studies on the cancer-preventive effects of tea have produced inconsistent results [31]. Whereas majority of studies have focused over antineoplastic effects of green tea, the potential health benefits of white tea become increasingly recognized [5]. Mao et al. have found that the white tea extract is capable of inducing apoptosis in non-small cell lung cancer (NSCLC) cell lines through upregulation of the peroxisome proliferator-activated receptor-gamma and 15-lipoxygenase signaling pathways, with enhanced activation of caspase 3 that plays a central role in the execution-phase of cell apoptosis [32].

Dietary fibers intake might be beneficial in smoking-related lung diseases as COPD and lung cancer, where systemic inflammation is highly prevalent and linked to poor outcomes [33]. Dietary fibers are not absorbed in the small intestine; they exert a protective effect in several cancers through prevention of insulin-resistance, decrease of insulin-like growth factor-1, decrease systemic inflammation via production of short-chain fatty acids by gut microbiota, and optimization of the colonic microbiota reinforcing the intestinal barrier [10]. Short-chain fatty acids have anti-inflammatory (by inhibition of 3-hydroxy-3-methyglutaryl-coenzyme A reductase), antiproliferative, and pro-apoptosis effects [10]. High fiber intake might partly explain the lower rates of COPD and lung cancer in Mexican (the Hispanic paradox) and Asian population, with a traditionally increased consumption of legumes, mainly beans, lentils, and soybeans products, respectively [34]. The daily intake of soluble and insoluble fibers originating in fruits, vegetables, and cereals should be over 25 g [10].

Dairy products comprise milk (whole or skim), cheese (fresh, cottage, and hard cheese), and yoghurt. They can have positive and negative effects on carcinogenesis in the same time, so the level of evidence concerning lung cancer is "not conclusive" [10]. The possible protective effect acts through the calcium content and to a lesser extent through vitamin D, lactoferrin, and fermentation products; new data concluded that dairy products have the ability to modulate inflammatory processes. Milk is a source of cholesterol and saturated fatty acids that might increase cancer risk, but it also contains conjugated linoleic acid, sphingolipids, and butyric acid, with hypolipidaemic and antioxidant properties [10].

Experimental studies have observed that *vitamin D* inhibits metastasis, angiogenesis, and lung carcinoma progression [11], while higher vitamin D receptor expression in lung tumors is associated with improved survival through lower proliferative status and G1 arrest [35]. Still, higher serum concentration of 25-hydroxyvitamin D (25(OH)D) and vitamin D binding protein did not influence lung cancer survival in a population of male smokers [11]; moreover, TaqI polymorphism of vitamin D receptor gene appears to be a risk factor for lung cancer [36]. Although there is no overall association between 25(OH)D level and lung cancer risk, Kilkkinen et al. [37] have observed that women and younger participants with higher serum levels of 25(OH)D have a lower risk for lung cancer. Vitamin D has two origins in humans, nutrition and photosynthesis in the skin when exposed to ultraviolet B radiation; Weinstein et al. [38] have found an inverse association between 25(OH)D status and lung cancer risk when blood was collected during the

darker months of the year November–April, a time when skin synthesis of vitamin D is reduced. The ability of 1,25 dihydroxycholecalciferol (or calcitriol) to induce cell cycle arrest, apoptosis and differentiation at doses without toxicity makes it an attractive lung cancer chemopreventive agent [5].

26.4 Other Dietary Sources in Chemoprevention of Lung Cancer

Curcumin, a yellow spice that enters in the composition of curry, is a polyphenolic molecule extracted from the rhizome of the plant Curcuma longa. Used for thousands of years in Ayurvedic, Chinese, and Hindu traditional medicine, it is considered nowadays as a promising chemopreventive compound able to reverse, inhibit, or prevent the development of cancer by inhibiting the molecular signaling pathways involved in carcinogenesis [39]. The chemopreventive effect is mainly based on the ability to decrease cancer cell proliferation through disruption of the cell cycle and death of cell by apoptosis, mitotic catastrophe and autophagy; the antiproliferative effect was observed in several cancer cell types (lung, prostate, breast, head and neck, lymphoma, and leukemia) [39].

Ginger (Zingiber officinale), a common condiment, has long been used in oriental medicine for the anti-inflammatory and chemopreventive activities of its major pungent constituents including gingerols, shogaols, and paradols. These ginger poliphenols have been attributed with anticancer effects through antioxidant, anti-inflammatory, antiproliferative, antiangiogenic, anti-invasive, and antimetastatic activities. [6]-Shogaol seems to be the most potential candidate for the prevention and treatment of NSCLC. Shogaol suppresses the proliferation of NSCLC cells by inducing cycle arrest (G1 and G2/M) and apoptosis [40]. Despite being more common and spreading more slowly than SCLC, the majority of NSCLC is diagnosed only when it has metastasized; also, primary and secondary resistance limits therapeutic success. Adopting appropriate preventing strategies might reduce the incidence and mortality from NSCLC [40].

Seaweeds are very rich in beneficial bioactive compounds like proteins, carbohydrates, lipids and fatty acids, polysaccharides, phenols, phytosterols, antioxidants, minerals, vitamins, and dietary fibers. Marina algae have a high content in polyunsaturated fatty acids (PUFAs), especially in α-linoleic, octadecatetraenoic, arachidonic, and eicosapentaenoic acids, playing an important role in the prevention of cardiovascular disease, osteoarthritis, and diabetes; they also exhibit antiviral, antimicrobial, anti-inflammatory, and antitumoral properties [41]. Monogalactosyldiacylglycerols (MGDG) and digalactosyldiglycerols (DGDG), the major glycolipids from Ulva armoricana and Solieria chordalis, were shown to inhibit in vitro the growth of NSCLC-N6 cell lines derived from a human NSCLC [41].

Maslinic acid (MA) is a pentacyclic triterpenic acid naturally occurring in many plant foods such as hawthorn fruit, basil, brown mustard, and olive. Treatment with MA caused A549 cells apoptosis via mediating mitochondrial apoptoic pathway

and HIF-1α pathway under normoxic and hypoxic conditions. These findings support that MA is a potent agent against lung cancer (A549—a lung adenocarcinoma cell line; HIF-1α-hypoxic inducible factor-1α) [42].

Siberian ginseng (Eleutherococcus senticosus) used in herbal Western medicine as tea or roots extract for its immune stimulant properties also displays anticancer properties. These may affect tumor growth and provide an anti-fatigue effect for cancer patients, in particular for those suffering from lung cancer. The anticarcinogenic, anti-inflammatory, and antioxidant activity of E senticosus and Acanthopanax senticosus used in East Asian medicine are seen in cell cultures, animal studies, and also in humans [43].

Perilla frutescens Britton leaves are a commonly consumed vegetable in different Asian countries. Ethanol extract of Perilla leaf (PLE) have been shown to inhibit growth, anchorage-independent colony formation, adhesion and migration in human lung cancer cells, indicating the anticancer of PLE in vitro [44].

Due to its bioavailability and acceptable toxicity, valeric acid (2-propylpentanoic acid), a short-chain fatty acid extracted from *Valeriana officinalis* roots (used for more than 2000 years in traditional medicine as tea or tincture) has become one of the most promising compounds for cancer prevention and treatment. They are already ongoing clinical trials in phase I or II using 2-propylpentanoic acid in combination with Camptothecin, Irinotecan, Karenitecin, Doxorubicine, Vindesine (targeting topoisomerase inhibitors) and also with azacitidine and decitabine (targeting DNA methyltransferase inhibitors) for the treatment of lung cancer [45].

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Prolonged Mechanical Ventilation in the Cancer Patient

27

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27.1 Introduction

Although acute respiratory failure remains a dangerous and frequent complication in the cancer patient, the mortality of these patients has declined in the intensive care unit (ICU). This is due to a combination of improved aggressive cancer therapies, earlier and more accurate diagnostic strategies, and an enhanced knowledge of supportive treatments in the critically ill. The improvement in mortality, however, has also led to an increase in the number of patients who remain dependent on the ventilator despite overcoming their acute illness. The definition of "prolonged mechanical ventilation (PMV)" has been set forth by a consensus statement by the former National Association for Medical Direction of Respiratory Care (NAMDRC) in 2004, and it is defined as the need for 21 or more days of mechanical ventilation for 6 or more hours per day [1]. Other authors describe the "chronically critically ill (CCI)" patient. Generally, the chronically critically ill population includes patients who require the ICU setting for weeks to months, typically due to the need for prolonged mechanical ventilation [2]. Definitions have been variable, however, and this is reflected in the heterogeneity of clinical, medicolegal, financial, and epidemiologic data collection. In this chapter, the terms PMV and CCI will be used interchangeably.

Data specific to patients with solid and hematologic malignancies is lacking, but a 2011 retrospective cohort study in the UK found that 4.4 of 100 ICU admissions and 6.4 of 100 ventilated ICU admissions became PMV patients [3]. Few other incidence studies have been reported using the consensus definition of PMV. An Argentinean study estimated a 12% incidence of chronic critical illness in their ICU population, defined as the placement of a tracheostomy for prolonged ventilator

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support. These patients were found to have higher APACHE II and SOFA scores, and acute respiratory distress syndrome (ARDS) and shock occurred more frequently compared with the non-CCI population [4]. In another retrospective cohort study, 104 of 765 ICU patients on mechanical ventilation for >7 days would go on to require 29 days or more of ventilatory support.

Predictors of difficulty weaning from mechanical ventilation have been extensively studied, but applicability to the PMV population is plagued by the same definition heterogeneity. Independent predictors of CCI in one model included ARDS on admission, APACHE II and McCabe scores with an area under the receiver operating curve of 0.74. Interesting, underlying comorbidities were more common in those ICU patients who were subsequently weaned off of the ventilator, and mortality was similar. This led authors to surmise that less underlying disease and greater physiological reserve led the CCI patients not to succumb to critical illness but instead develop a chronic course of disease with a multitude of complications [4].

27.2 Causes of PMV in the Cancer Patient

The causes of PMV in the cancer patient are diverse (Table 27.1). Similar conditions that predispose to PMV in the noncancer patient can occur in the cancer patient. Also, similar conditions leading to acute respiratory failure can eventually lead to PMV under certain circumstances. The burden of underlying comorbidities, the sometimes deleterious effects of cancer treatments, and poor nutritional or functional status may weaken the ability of the cancer patient to wean from the ventilator.

Table 27.1 Causes of prolonged mechanical ventilation in cancer patients

Cancer related causes
• Direct involvement of the respiratory tract
– Airway involvement by cancer
– Lymphangitic spread
– Massive and recurrent pleural effusions
• Indirect causes related to cancer
– Paraneoplastic syndromes
– Respiratory muscle weakness due to spinal cord compression
– Altered mental status due to CNS involvement
– Complications of lung involvement by GVHD (idiopathic pneumonia syndrome, bronchiolitis obliterans syndrome
– Poor performance status
– Toxicity of cancer treatment (drug or radiation induced pneumonitis
– Postoperative respiratory failure (thoracic or extrathoracic surgery)
– Complications of pneumonia, sepsis or pulmonary thromboembolic disease
Independent of cancer
– Comorbid illnesses (COPD, cardiac, CNS)
– Critical care myopathy or delirium
Combinations of above causes

Specifically, in the critically ill cancer patient with respiratory involvement of their malignancy, PMV may be caused by the cancer process itself. The classic example is overwhelming involvement of the pulmonary parenchyma or respiratory tree with tumor; however, less common examples have been reported. Cases of respiratory failure due to Lambert-Eaton myasthenic syndrome due to small cell lung cancer [5] and breast cancer associated polymyositis [6] are examples. Additionally, catheter-associated thrombus leading to an atrial mass, intracardiac shunt, and respiratory failure has been reported in a patient with colon cancer [7].

Often malignancy-associated causes of acute respiratory failure can be reversed so as to allow weaning of the patient from the ventilator. Such is the case with bulky airway obstruction caused by tumor. Debulking and endobronchial stenting with rigid bronchoscopy has been shown to be successful in relieving the obstruction and facilitating extubation in such patients [8]. Thus, in eligible candidates, patients and their loved ones can be educated that brief intubation can be expected, and prolonged mechanical ventilation may be avoided. Patients who are ineligible for rigid bronchoscopy for various reasons may have worse chances of avoiding PMV. They may be offered radiotherapy with similar goals in mind. However, in such patients there is only a 27% rate of successful extubation and a dismal 6-month overall survival of only 11% [9]. Of note, the single patient in this analysis who was found to have lymphoma rather than primary lung cancer was successfully extubated, which allowed treatment with chemotherapy and long-term survival. Thus, the availability of treatment options and likelihood of ventilator weaning may influence the initial decision to intubate a patient.

27.3 Patient Selection

The junction at which a critically ill patient is transitioned to prolonged mechanical ventilation is marked by the tracheostomy. Recent studies indicate that tracheostomy rates have been rising. A large study using a national database of hospital discharges indicated an increase from 6.7 to 8.5% of mechanically ventilated patients in 1993 versus 2012. This was excluding patients for whom tracheostomy was placed due to a head, face, or neck condition. The median time to tracheostomy placement decreased from 11 days in 1998 to 10 days in 2012. Patients who were more likely to receive tracheostomy were male, younger, nonwhite, and had less comorbidities [10].

The benefits of tracheostomy are purported to be improved comfort allowing for less sedation, faster weaning, improved oral care and secretion control, easier mobility and rehabilitation, facilitation of transfer to a lower level of care, and the facilitation of communication and oral nutrition. The ideal PMV patient, thus, is mobile, alert and communicative, weanable, able to participate in self-care and rehabilitation, and willing to transition to assisted living facility or home on the ventilator with the proper social support. Tracheostomy should be performed in patients whose quantity and quality of life may be improved by transition from acute MV to PMV. Many PMV patients are less than ideal candidates by these criteria, and it is likely that not all patients would benefit from tracheostomy placement.

There is a growing body of evidence that patients and families are unaware of the heavy physical and psychological burden of the CCI patient. Interviews of patients receiving a tracheostomy revealed that information given prior to the procedure was not sufficient to prepare them, and patients cited fear, anxiety, frustration, and physical discomfort [11]. In an interview study of 126 PMV patients following tracheostomy placement, only 26% of surrogates reported that physicians discussed what to expect for the patients' likely future survival, general health, and caregiving needs. Most surrogates expected the patients to survive, have no major functional limitations, and a good quality of life at 1 year; in actuality, only 9% were alive and functionally independent [12]. This discrepancy between surrogate expectations and published outcomes for PMV patients suggests that communication at the time of tracheostomy placement needs improvement. Furthermore, cancer patients who are recovering from critical illness should be counseled about the outcomes of PMV in the context of their cancer diagnosis before being considered candidates for PMV.

27.4 Sites for PMV Patients

There exist a range of options for the chronically mechanically ventilated patient. PMV patients may certainly continue to require an intensive level of care, especially in light of their propensity to adverse health outcomes. Complications such as recurrent infections with multidrug-resistant bacteria, pressure ulcers, recurrent shock, and nutritional deficiencies may preclude discharge from the ICU. However, most PMV patients have already been discharged from the ICU to one of a number of ventilator facilities, outlined in Table 27.2. The trend toward early ICU discharge is likely driven by pressure to both save on costs and open beds for other critically ill patients. Although patient safety is paramount in the decision to discharge a patient from the ICU, transfer protocols specific to a particular ICU, regional availability of weaning facilities, patient and family preferences, and individual physician practices all affect timing of transfer of ventilated patients.

The number of long-term acute care (LTAC) facilities has risen 11.3% per year between 1992 and 2005 [13]. In parallel, the proportion of ventilated ICU patients who were discharged to a LTAC increased from 3.3% in 1997 to 8.7% in 2006 [14]. Aside from aggressive weaning protocols, LTACs offer initiation of hemodialysis, wound care expertise, specialty consultation, antibiotics for active infection, and other patient care needs which might have previously kept a patient kept in an ICU setting. Although attractive for obvious financial reasons, the safety of earlier ICU discharge and success of weaning in such acute patients is called into question. The time mechanically ventilated in the ICU prior to transfer to a large California LTAC declined from 1988 to 1999, with a coincident rise in Acute Physiology Score (APS) from 32 to 40. Such a score is on par with patients in 28 ICUs in Cleveland during the same time [15]. Facility-specific guidelines on the appropriate acuity level and time for transfer are significantly heterogeneous. Data from Medicare Payment Advisory Commission (MedPAC) suggest that risk-adjusted rates of deaths in LTACs and readmission

Table 27.2 Options for post-intensive care mechanical ventilation

	Distinguishing characteristics	Nursing intensity	Specialized rehabilitation	Cost comparison
Noninvasive ICU or step-down unit	Within same hospital as ICU, shares DRG payment with ICU	+++	+	$$$$
Long-term acute care (LTAC)/regional weaning center (RWC)	DRG exempt, early transfer from ICU possible. Active weaning and respiratory care protocols	++	+++	$$$
Subacute/extended care facility	Limited weaning and acute care needs met (e.g., IV antibiotics)	++	++	$$
Home mechanical ventilation	Extensive support and training required in home environment. Typically no weaning attempts made	+	+	$$
Group home for mechanical ventilation	Rare in United States. No weaning attempts made	+	+	$$

to acute care hospitals has fallen [13]. Yet 1 year mortality remains high in this population, up to 69.1% in elderly Medicare beneficiaries who were discharged mechanically ventilated to a LTAC [14].

The cancer patient undergoing continued chemotherapy and radiotherapy would need to consider the costs and feasibility of transport between the ventilator facility and the treatment facility. While many treatments are placed on hold during the intensive care stay for obvious reasons, the PMV patient may be forced to forgo treatment even beyond the acute phase due to the facility's constraints. For example, the step-down unit and LTAC facility attached to a hospital are examples of relatively easy administration of intravenous chemotherapy or transport to radiation therapy suite by gurney. In contrast, an ambulance or transport service equipped to manage ventilated patients is necessary for those in off-site facilities, and arranging such transportation would need to accommodate treatment sessions often several times per week. Costs associated with these transfers are variably reimbursed by insurance.

Transport between and within hospitals itself poses several risks to a patient as complex as the ventilator-dependent cancer patient. Weakened by critical illness and malignancy and travelling with tracheostomy, ventilator, monitors, intravenous lines, and other connections, the patient is at risk for falls, disconnections, inappropriate bagging, equipment problems, and even accidental decannulation. In a retrospective review of 1782 mechanically ventilated patients in a French ICU, respiratory events such as ventilator associated pneumonia, pneumothorax, and atelectasis were reported with higher frequency in transported patients. Deep venous thrombosis and

metabolic derangements such as hypernatremia, hyperglycemia, and hypoglycemia were also more prevalent. Decreased availability of tracheal suctioning, inadequate bagging or transport ventilator settings, discontinuation of insulin therapy or nutritional support, and a number of other factors were cited as possible factors [16]. Death was a complication of transport in 4 of 176 reports to an Australian Incident Monitoring Study in Intensive Care study [17]. Guidelines from various professional societies about improving the safety of intrahospital transport have been published [18, 19]. By extrapolation, *inter*-hospital transport likely subjects mechanically ventilated patients to similar if not more dangerous risks.

27.5 Preparation for the Home Mechanical Ventilation

The home setting has been considered by some to offer the best opportunity for improved quality of life in a PMV patient. The cancer patient can be considered for home mechanical ventilation following medical stabilization and a stable ventilator requirement. A fractional inspired oxygen requirement of less than 40%, positive end-expiratory pressure of less than 10 cm of water, and a mature tracheostomy have been recommended measures of readiness [20]. Optimization of the patient's communication, mobilization, and nutritional status should be established. Being removed from the healthcare setting and the expertise of respiratory specialists, adequate home support and social-psychologic stability are paramount. Early involvement of caregivers in patient care can facilitate the extensive training and preparedness required to manage the needs of a long-term mechanically ventilated patient. An inadequate physical environment in the home for monitoring and infection control, inadequate financial and psychosocial resources, lack of medical follow-up, and unwillingness to abide by the medical team plan are all considered contraindications. At least two willing caregivers are recommended.

Many types of compact and even portable positive-pressure ventilators are available. The assist/control mode using volume-cycled breaths is typically used, and the simplest settings with minimal monitoring requirements should be selected. A back-up ventilator and power source should be available for patients who cannot maintain spontaneous ventilation and/or live in a remote area, with detailed action plans regarding ventilator alarming, power failures, and other common problems. An oxygen source and suction equipment must be provided, and a home healthcare agency with 24-hour call and expertise on home ventilation is necessary. The home ventilated patient requires a team-oriented approach with continued medical and ancillary follow-up, including physical and occupational therapists, nurses and aides, case managers, nutritionists and speech therapists, and physicians. Detailed recommendations about home procedures and equipment, and a checklist for caregiver preparation have been detailed elsewhere [20, 21].

A web-based decision aid for family members of patients receiving prolonged mechanical ventilation addressing goals of care preferences for surrogate decision-makers of patients was recently tested in ICU with excellent usability and acceptability [22]. Such a tool could be used in the future to assist in decision-making

processes—including cancer treatment, ventilator management, and goals of care—in cancer patients with PMV whether they are at home or in an LTAC. Further studies are needed in this regard.

27.6 Weaning and Decannulation

The reversal of the physiologic derangements of critical illness and concurrent strengthening of the respiratory capacity is the crux of weaning from PMV. It is likely that failure to wean in the ICU setting is associated with different challenges compared with failure to wean in the PMV patient. Protocol driven weaning practices are most widely used at LTAC and other weaning facilities. Typically, some combination of assist control, synchronized intermittent mandatory ventilation, and pressure support ventilation is used, and the support is incrementally decreased. Spontaneous breathing trials are then introduced via tracheostomy mask or T-piece, and these trials are progressively increased in length. Respiratory therapists and pulmonary physicians implement the protocols, and the median time to weaning in a review of the largest series of weaning center publications was 40 days [15].

A therapist-implemented patient-specific (TIPS) weaning protocol for 271 ventilator-dependent patients at a LTAC facility was described using historical controls. The protocol includes a daily safety evaluation and weaning assessment, then a step-wise reduction in SIMV and PSV. When a "half-ventilator-supported" point is reached, a SBT is undertaken. Various "acceleration steps" were incorporated, allowing the patient to progress faster than one step daily. Although similar overall weaning rates and mortality were reported, the TIPS protocol was associated with a significantly shorter time to weaning, from 29 days in historical control subjects to 17 days for TIPS protocol patients [23]. This translated to shorter length of stays at the LTAC.

A randomized trial at a single LTAC hospital in Illinois found that tracheostomy collar protocol was associated with higher success rates and shorter time to weaning when compared with a pressure support protocol. Patients were eligible after 21 days of mechanical ventilation after failing a screening process of spontaneous breathing off of the ventilator for up to 5 days [24]. In contrast, there was no difference between the two protocols in weaning success rates or time to weaning in 57 COPD patients admitted to three Italian LTAC facilities [25]. While the ideal protocol for weaning from PMV is not yet elucidated, the close adherence to a well-defined protocol alone may be tied to success. Interestingly, in both trials, over 30 percent passed the screening procedure and were considered weaned at the time of LTAC transfer, suggesting that the patients' ability to be weaned may be underestimated at the transferring ICU [24].

No guidelines exist as to when a patient should be decannulated. Surveys of 22 respiratory ICUs in Italy revealed five major criteria for decannulation used by these centers: stability of respiratory conditions, effective cough, slowly progressive underlying disease, effective swallowing, and no or mild hypercapnia [26]. Prior to decannulation, some recommend evaluation for airway obstruction with fiberoptic endoscopy and consideration of a stoma stent to maintain patency of the tracheostomy tract [15].

Noninvasive ventilation (NIV) may offer an alternative to invasive mechanical ventilation in select patients, especially when the etiology of ventilator dependency is primarily due to irreversible neuromuscular diseases. Theoretically, patients who can be weaned to at least part-time off the ventilator may be considered for NIV with the goal of improving quality of life, although tolerance and compliance may become an issue. NIV may indeed be attractive in the cancer patient who may have limited life expectancy, as it may facilitate discharge to home and avoid infectious complications associated with invasive PMV.

27.7 Complications and Prevention

Ventilated patients are subject to complications involving every organ system. Both new and worsening existing medical problems can occur, and the patient who is further weakened by malignancy and its treatments is particularly vulnerable.

Airway-associated complications culminate in the loss of an airway and imminent respiratory arrest. If possible, a mature tracheostomy at the time of transfer would help to prevent potentially fatal outcomes in the case of accidental decannulation. Loss of the artificial airway will be more disastrous if compression by tumor or adenopathy contribute to a difficult airway. Bleeding complications, such as life-threatening innominate artery fistula, can be limited by careful monitoring of cuff pressures and avoidance of aggressive manipulation and suctioning. A spare tracheostomy and inner cannula must be present at the bedside at all times.

Infectious complications are frequent and may occur with increasingly drug-resistant organisms over time spent ventilated. In a large cohort of LTAC patients, 7 of the 10 most frequent complications at the LTAC were infectious, including respiratory tract infection, Clostridium difficile colitis, and sepsis [27]. The majority of PMV patients are invasively cannulated; intravenous and bladder catheters are frequent sources of nosocomial infection. In addition, patients are at increased risk due to advanced age, organ dysfunction and comorbidities, ICU exposure to broad-spectrum antibiotics, aspiration, and other insults to immunoregulation. Cancer patients tend to be older and are more likely to have frequent healthcare exposures, indwelling central venous lines, and immunologic insults, such as chemotherapy.

The respiratory tract in a tracheotomized patient is frequently colonized. In the setting of a clinical ventilator associated respiratory infection, the flora of the transferring ICU, the patterns of the accepting facility, and the previous cultures of the individual patient should guide empiric antibiotic choices while awaiting respiratory cultures. Antimicrobials should be aggressively de-escalated to reduce drug resistance, avoid over-treatment, and control costs.

27.8 Financial/Legal Considerations

The provision of PMV is associated with $20 billion in annual inpatient costs [2]. The average daily cost of an ICU stay for a mechanically ventilated patient is $3968 in 2002 dollars [28]. Any measure targeting the ICU LOS would significantly

reduce healthcare spending, and for the PMV patient, a push toward early discharge is certainly underway. This may include early discharge to an LTAC facility or ECF; however, clinicians must also explore an individual patient's care goals early in the course of treatment, preferably before the decision is made to tracheotomize.

Reflecting the increase in long-term acute care admissions in the U.S., the annual costs of such care increased from $484 million to $1.325 billion from 1997 to 2006. Also underlying this increase is the fact that patients have significantly more comorbidities upon arrival to the LTAC, likely due to pressure for earlier transfer from ICUs [14]. Although associated with lower daily costs, if more frequent readmissions to hospitals and occurrence of associated complications are the result of earlier and more frequent LTAC transfer, overall healthcare expenditures may increase.

Costs per one-year survivor of PMV were $423,596 in one prospective study of 114 PMV patients [29]. These authors identified patients who received "potentially ineffective care," or greater than $100,000 in hospitalization costs associated with early death (survival less than 100 days). Forty-one percent of their cohort of PMV patients could be classified as such, compared with fewer than 10% of the short-term ventilation patients. This is despite the 36% hospital mortality of the short-term ventilation patients. They concluded that PMV defined by ventilation for more than 21 days specifically identifies patients who are "outliers in resource consumption."

On the other hand, a recent study from Taiwan comparing the cost-effectiveness of treating cancer patients who required PMV compared to other chronic illnesses found that the cost was less than one gross domestic product (GDP) per capita per quality-adjusted life year (QALY). This was less than patients with end stage renal disease and was considered to be cost-effective [30].

27.9 Outcomes

Meaningful outcomes when counseling families about the prognosis of PMV include survival, weaning success rates, functional debility, and quality of life. Because of multiple transfers of care across the spectrum of healthcare facilities, 1-year mortality may be a more useful measure than hospital mortality. Successful weaning was defined in a recent consensus report as complete liberation from mechanical ventilation or a requirement for only nocturnal NIV for 7 consecutive days [1]. Additionally, because successfully weaned individuals may continue to suffer from other organ failure and functional decline necessitating specialized long-term care, discharge to home is an important indicator of quality of life, especially for the cancer patient. To meet these goals, the "ideal" patient with cancer who should be considered for PMV is proposed in Table 27.3.

The survival rates of PMV patients are historically low, with 1-year mortality of at least 50% overall. Much of the data is limited to single center experience, but a national database of LTAC admissions found that 69.1% LTAC patients who were mechanically ventilated in ICUs then LTACs had died in 1 year [14]. A large observational study by Scheinhorn et al. included 1419 patients at 23 U.S. LTAC facilities. They demonstrated a 1-year mortality of at least 52%, evenly split between

Table 27.3 The ideal patient for prolonged mechanical ventilation

Controlled or treatable cancer
No renal failure or dialysis
Few other comorbidities
Able to participate in physical/occupational therapy
Alert and communicative
Sufficient education regarding expectations and alternatives
Willing to transfer to appropriate facility or home with adequate support
Reversible cause of ventilatory failure
Good weaning potential
Good or improving nutritional status

deaths prior to discharge from the LTAC and deaths following discharge. While 54.1% were successfully weaned, only about 4.2% of the original cohort were found to have "good functional status" at 12 months after admission, and about 21.5% were discharged to home or assisted living [27]. These data reflect the often unsurmountable burden of illness these patients face that is independent of ventilator liberation.

These odds may be even more stacked against patients with cancer. In Scheinhorn's study above, 5.5% of the patients in the cohort were admitted with cancer, but mortality data on this subset was not available. A large national database study in Taiwan described 5138 cancer patients who required more than 21 days of mechanical ventilation. Because the withdrawal of mechanical ventilation was not legally allowed in Taiwan prior to 2011, the database offers a unique perspective on the natural history of such patients. The median survival in these patients was 1.37 months with overall 1-year survival of 14.3%. Improved life expectancy was seen in head and neck cancer, and the worst prognosis was in patients with liver and lung cancer. Patients with metastatic cancer had a dismal 1-year survival rate of 5.9%. Due to the significant financial burden and low quality-adjusted life years (QALYs), the authors suggested early palliation, especially in patients with metastatic disease [31].

Newly diagnosed malignancy, recurrent or progressive malignancy, cancer as a direct reason for mechanical ventilation, and poor performance status were associated with hospital mortality in a prospective cohort of 263 mechanically ventilated Brazilian patients admitted to the ICU with cancer [32]. Other factors associated with particularly worse outcomes in the general PMV population were hemodialysis and severe kidney failure [33], medical versus surgical/trauma reasons for ventilator dependence, and age [34]. The ProVent score was developed recently to predict 1-year mortality in PMV patients with an area under the receiver operating characteristic curve of 0.82. This model used age of at least 50, platelet count of less than 150×10^9/L, need for vasopressors, and need for hemodialysis at 21 days of ventilation [35]. This has not been validated in the cancer population.

Conclusions

The cancer patient, the patient's family and caregivers, and the treatment team must consider a host of factors along the path toward tracheostomy and prolonged mechanical ventilation. Associated mortality and morbidity are high, with significant physical, emotional, and socioeconomic burdens. While individual patient values and experiences should be considered, evidence suggests that expectations very often do not reflect reality. If it is expected to reasonably improve quality and quantity of life and allow independence and physical/emotional well-being, certain patients may benefit from prolonged invasive ventilation. Certain cancer therapies may even be continued while ventilated, but transport from a ventilator facility should be arranged. For other patients, it is the clinicians' task to educate about the option for hospice care and palliation as alternatives to imposing lifestyle changes, likelihood of early death, and accumulating medical illnesses.

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Part V

Palliative Ventilatory Support in Cancer Critical Care

Avoidance of Endotracheal Intubation

28

Pieter Depuydt

Abbreviations

ARDS	Acute respiratory distress syndrome
ARF	Acute respiratory failure
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CPE	Cardiac pulmonary edema
DNI	Do-not-intubate
HFOT	High-frequency oxygen therapy
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
NIRS	Noninvasive respiratory support
NIV	Noninvasive ventilation
RCT	Randomized controlled trial

28.1 Avoiding Endotracheal Intubation in Cancer Patients with Acute Respiratory Failure: Why Is It Important?

Acute respiratory failure (ARF) is a frequent and often fatal complication in cancer patients. Until the 1990s, the Intensive Care Unit (ICU) was considered a "no go area" for cancer patients and endotracheal intubation and invasive mechanical ventilation (IMV) for ARF perceived as futile. With long-term prognosis markedly improving for many forms of malignancy and with better ICU-survival of cancer

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patients resulting from overall progress in intensive care, this pessimistic view has thoroughly changed. It is now commonly accepted that a predicate of "cancer patient" should not be used to forgo endotracheal intubation as a life-saving intervention [1, 2], as ICU-survival in these patients is nowadays not dissimilar from that of non-cancer patients with major comorbidities as congestive cardiac failure, advanced kidney disease, or liver cirrhosis. However, endotracheal intubation is still a predictor of high mortality and morbidity in cancer patients: mortality rates of 70% and more are still common in recent publications [3–5]. Although this poor outcome is probably mainly due to limited reversibility of pulmonary and extrapulmonary organ injury in ARF, it may be partially attributable to complications associated with IMV [6]. Endotracheal intubation itself may impose a risk for aspiration of gastric content, hemodynamic instability, cardiac arrhythmia, and hypoxia. IMV may cause or exacerbate lung injury and be complicated by ventilator-associated pneumonia and noninfectious ventilator-associated events [7]; it usually requires sedation which predisposes to delirium and neuromuscular weakness. IMV in cancer patients often results in an extended ICU stay, imposing major emotional distress and suffering on patients and their relatives. Difficult and prolonged weaning from IMV may leave ICU survivors in a debilitated state, which then thwarts ongoing or planned oncological treatments or reduces quality of the patient's remaining life [8].

Ideally, for a cancer patient with potentially reversible ARF, the time with need for respiratory support in the ICU should be as short as possible, carry a minimal risk for iatrogenic complications, and consume little physiological reserves. In this respect, techniques for noninvasive respiratory support (NIRS) have received interest as these may help avoid endotracheal intubation and its complications. In addition, NIRS may offer the possibility to overcome a reversible episode of ARF in cancer patients who refuse intubation or who are judged to be poor candidates for IMV due to advanced cancer status, poor general health, or major comorbidity. Finally, NIRS could, at least from a theoretical point of view, alleviate respiratory distress and provide palliation in terminal cancer stages. Since the initial reports of the use of continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) for ARF in the 1980s, there has been an expansion of noninvasive ventilator modes on standard ICU-ventilators as well as development of ventilators specifically designed for noninvasive use [9]. Apart from CPAP and NIV, NIRS may consist of the more recently introduced technique of high-flow oxygen therapy (HFOT) provided through nasal prongs, which overcomes the drawbacks of standard oxygen therapy through Venturi mask: unpredictable oxygen delivery by drawing in surrounding room air and inadequate heating and moisturing of inspired air. HFOT provides flows up to 60 L/min with adequate heating and complete humidification. As such, a constant FiO_2 titrated between 0.21 and 100% can be provided and the humidification may improve mucociliary clearance and mobilization of airway secretions. In addition, the high flows, overcoming expiratory flow, result in a moderate level of positive airway pressure and lead to increased washing out of alveolar CO_2 and thus a reduction in alveolar dead space [10]. Apart from mechanical ventilation and oxygen therapy, NIRS in the ICU may also

include intensive airway management with the use of physiotherapy and suctioning, which may help to clear excessive secretions, remove airway obstruction and lower airway resistance, or reduce atelectasis. Mechanical support to increase mucus clearance may consist of judicious application of positive end-expiratory pressure or of the use of intrapulmonary percussive ventilation. The latter technique consists of delivering short bursts of high-flow gas at high frequency through a face mask; the associated percussive effects lead to a continuous increase of airway pressure and to airway opening, while airway wall vibrations enhance mucus mobilization [11]. Patient tolerance of NIRS is critical to its success: in the ICU, use of continuous medication, titrated under constant monitoring, may optimize anxiolysis and analgesia and relieve respiratory distress while keeping the patient awake and cooperative [12, 13].

28.2 Avoiding Intubation and Mortality in Cancer Patients with ARF by NIRS: What Is the Evidence?

The use of NIV to avoid intubation in ARF is best documented in hypercapnic failure exemplified by exacerbation of chronic obstructive pulmonary disease (COPD) and in hypoxemic ARF due to acute cardiac pulmonary edema (CPE). NIV has proven to reduce intubation rates, mortality and hospital stay in patients with ARF due to COPD exacerbation [14] and, to a more limited extent, in CPE [15]. NIV for hypoxemic ARF not due to CPE is more controversial as no consistent benefit has been observed [16]. Immunocompromised patients with ARF, including hematological patients, have been recommended as candidates for NIV based on two randomized controlled trials (RCT) showing lower intubation rates and mortality in patients assigned to NIV [17, 18]. However, both trials were small, included a heterogeneous case mix, and had mortality rates in patients requiring intubation that were much higher than what is nowadays observed. Two more recent RCTs including only hematological cancer patients arrived at different conclusions. An Italian study comparing CPAP with standard oxygen in hematologic patients at the ward observed less intubation in the CPAP arm [19], while a German RCT comparing NIV with standard oxygen in allogeneic bone marrow transplant patients did not find a difference in intubation rates between both arms [20]. In the largest RCT to date (the INVICTUS trial), 374 immunocompromised patients with ARF, of whom 84% were cancer patients, were randomized between NIV or oxygen [21]. Only patients with ARF present for less than 72 h were included; patients with need for immediate intubation, with hypercapnic ARF or CPE were excluded. Pneumonia was the cause of ARF in 65%. NIV was applied as pressure support ventilation intermittently as 60 min sessions every 4 h. HFOT was allowed in the study at the discretion of the treating physician and was significantly more applied in the oxygen group as compared to the NIV group (44% vs. 31%). Intubation occurred at the discretion of the treating physician and was required in 41% of patients; no differences were found between treatment arms in terms of mortality, rate, or timing of intubation.

Two recent RCTs, one in a mixed ICU population and one in a predominantly cancer population, tested HFOT to avoid intubation in hypoxemic ARF. The FLORALI trial randomized 313 hypoxemic patients between three treatment arms, respectively, providing NIV, standard oxygen therapy delivered through a nonrebreather mask, and HFOT [22]. Hypercapnic patients, patients with CPE, COPD, or urgent need for intubation were excluded. Immunodeficiency was present in 26% of patients and pneumonia was the underlying cause of ARF in 74%. Rescue NIV was permitted in the HFOT and standard oxygen treatment groups and strict criteria for determining the need for intubation were applied. Intubation was required in 50%, 47%, and 38% of patients treated with NIV, standard oxygen, and HFOT, respectively, and time of intubation was not different between the three treatment arms. ICU mortality and 90-days mortality were significantly lower in HFOT-treated patients (11% respectively 12%) than in patients treated with NIV (25% respectively 31%) or standard oxygen (19% respectively 23%). In a post hoc analysis of the subgroup of patients with $PaO_2/FiO_2 < 200$, the authors observed a significantly lower intubation rate in patients treated with HFOT (35%) than in patients treated with NIV (58%) or standard oxygen (53%). Lemiale et al. randomized 100 immunocompromised patients with hypoxemic ARF, of whom 84 had cancer, between 2 h of HFOT or standard oxygen therapy [23]. No differences were found between both arms in terms of need for NIV, intubation rate, and patient comfort.

Both the INVICTUS and the FLORALI studies failed to show that early application of NIV prevents intubation or mortality in cancer (INVICTUS) or unselected (FLORALI) patients with hypoxemic ARF not due to CPE, although both studies may have been underpowered [21, 22]. In addition, NIV did not postpone intubation, whether or not a strict protocol for intubation was applied. On the other hand, the FLORALI study showed a protective effect of HFOT on mortality, which the authors ascribed to a lower risk for intubation in HFOT-treated patients with more severe hypoxemia, and a lower mortality in patients requiring intubation following HFOT. In the INVICTUS trial, HFOT was applied more frequently in the oxygen-only arm: whether the effect of HFOT was indifferent or HFOT may have masked a potential protective effect of NIV cannot be deduced from the study. In the study by Lemiale et al., HFOT did not prevent intubation although the duration of the intervention may have been too short to observe a difference. Patients treated with HFOT showed a better subjective tolerance and rapid resolution of dyspnea in the FLORALI study, but not in the study by Lemiale et al. [23].

Additional evidence for NIV in cancer patients with ARF has been provided by a large number of observational studies. Most of these reported an association between the use of NIV, as compared to IMV, and lower mortality [3, 5]. However, these studies demonstrate essentially a protective effect of avoidance of endotracheal intubation rather than of the use of NIV as such; failure of NIV has been associated with increased mortality in many of these studies [4, 5] (see below). In addition to NIV studies, there is an increasing number of observational studies of HFOT in adult patients with hypoxemic ARF. Most of these focused on immediate endpoints such as oxygenation and patient comfort, showing the potential of HFOT to reverse hypoxemia and relieve respiratory distress [10]. An analysis of 183 cancer patients treated with HFOT at the Memorial Sloan-Kettering Cancer Center showed patient improvement or

stabilization in 85% and deterioration in 15% [24]. Tolerance was mostly good, with only two patients requesting HFOT stop because of nasal discomfort. Similar to the studies in NIV, HFOT has been associated with a lower need for intubation but HFOT failure has been associated with increased mortality [25]. Interestingly, in a propensity-score-adjusted retrospective analysis of the use of HFOT, NIV, and standard oxygen in 178 cancer patients with hypoxemic ARF, Mokart et al. observed a protective effect of the alternating application of HFOT and NIV on 28 days mortality, although no effect on the rate of intubation was found [26]. A caveat in interpreting these studies is the fact that observational data cannot unambiguously show a causal link between mortality and choice of initial ventilator support. The association between improved outcome and NIV may be biased by numerous factors favoring patient selection for NIV, and it may be impossible to adjust for all of these.

28.3 NIRS in Cancer Patients: What Are the Dangers?

NIV in cancer patients with ARF has a high risk of failure. Observational studies in ARF patients with hematological malignancies and treated with NIV showed a median intubation rate of 61% [27] and even in the recent INVICTUS trial, 41% of patients receiving NIV required intubation despite their careful selection in early-onset ARF. In addition, the frequently observed association between failure of NIV and increased mortality raises the question whether exposure to an unsuccessful trial of NIV or HFOT may cause harm. If so, this would likely occur through undue postponement of endotracheal intubation in patients in whom this is ultimately unavoidable, leading to further depletion of physiologic reserves. This is suggested by the observation that ARF patients have a higher risk for intubation-related complications such as desaturation, hypotension, or aspiration when intubated following a trial of NIV [28]. NIV may also induce more ventilator-induced lung injury by its inability to control tidal volumes [29]. On the other hand, the association between NIV failure and increased mortality may be confounded by the fact that NIV failure is a marker for a more insidious but less reversible type of ARF. A more slowly deteriorating ARF, as indicated by a need for intubation after a few days instead of at presentation of ARF was associated with increased mortality in a retrospective cohort study in acute respiratory distress syndrome (ARDS) patients [30]: the authors did not find an interaction between the use of NIV, delays in intubation, and mortality. Similarly, the INVICTUS trial observed no difference in outcome in patients intubated after NIV or oxygen with a similar duration between study inclusion and intubation in both groups. Finally, the impact of a failed NIV trial may differ among patient categories. A recent meta-analysis of studies in hematological patients found no overall association between NIV failure and mortality; however, a meta-regression, correcting for the large heterogeneity found in the studies, suggested increased mortality associated with NIV failure in the subset of less severely ill patients [27].

Taking all this into account, NIV should be applied cautiously, especially in patients with a decision for full ICU support. Its potential adverse effects should be recognized and limited through careful patient selection and close monitoring of the

response to NIV. In the absence of unambiguous signs of resolution of ARF within 1 or 2 days, intubation should not be further delayed. In this respect, it may be helpful to define strict criteria for intubation a priori and adhere to these. Predictors for NIV failure have been identified, which should raise further awareness with the physician: in patients with hematological malignancy, these risk factors were more profound hypoxemia in the presence of bilateral infiltrates (fulfilling the criteria of ARDS), a longer delay between diagnosis of ARF and initiation of NIV, persistent tachypnea under NIV and development of additional organ failure under NIV [31].

28.4 NIRS as the Upper Limit of Care: How Useful Is It?

Most of the evidence about NIRS has been derived from patients with a full therapy code. However, NIV has increasingly been used to support patients with ARF and a decision to forego intubation. In 2010–2011, 20% of patients treated with NIV in French hospitals had a do-not-intubate (DNI) code, as compared to 13% in 2002 [32]. In a survey of Canadian and US ICU physicians and respiratory therapists, 56% of respondents reported that they at least sometimes used NIV in patients with ARF and a DNI code [33]. Data about the outcome of NIV in DNI patients are limited and observational only, with acute CPE, COPD exacerbation and pneumonia as main causes of ARF. In these mixed populations, NIV as upper limit of therapy may reverse ARF in 40–60% of patients, but this depends upon underlying indication [34–36]. In these studies, a diagnosis of cancer was associated with poor outcome: hospital survival rates of the subgroup of NIV-treated DNI patients with cancer were variable, ranging from 15 to 48% [34–38]. Physicians reported that they were less likely to consider NIV in DNI patients with cancer than in patients with COPD or CPE [33].

Subjective tolerance of NIV in DNI patients was assessed in a French prospective study: tolerance of NIV was good to excellent in 34%, sleep was qualified as good at least one time under NIV in 38%, and oral intake was possible in 66% [37]. In survivors, functional status after hospital discharge was not significantly decreased in comparison with pre-ICU status. As such, the presumption that NIRS offers a reasonable chance of surviving ARF without the adverse effects of a prolonged and debilitating ICU stay appears to be confirmed. Judicious use of sedation may help to improve tolerance of NIV: in a Japanese retrospective study, 5% of patients treated with NIV required sedation; over 90% of these patients, including those with a DNI code, could be continued on NIV [13]. In the future, it is likely that some of the use of NIV, especially in hypoxemic ARF, will be replaced by HFOT, given its overall good tolerance. Hospital survival in the thus far only published series of DNI patients treated with HFOT was 40% [39].

28.5 Deciding for NIRS in Cancer Patients with ARF: Considering the Patient and the Cause of ARF

Cancer patients constitute a heterogeneous population with a very variable prognosis. ARF may occur at various stages of the disease course, and its causes and triggers are varied. ARF may be part of the presentation of malignancy, may herald a terminal

phase of disease progression, or may be caused by drug toxicity or infection and thus represent a major complication of treatment aimed at cure or cancer remission. Finally, ARF may not be due to malignancy itself but instead to comorbidities such as COPD or CPE which are prevalent in an aging and smoking cancer population. The cause of ARF and its timing in the cancer disease course, the prognosis of the malignancy and the available treatment options, and, most importantly, patient performance, comorbidities, and personal wishes all have major impact on the therapeutic approach to ARF and the choice of ventilator support. When selecting cancer patients with ARF for ventilator support, it is important to delineate what goals are to be achieved. Recently, a task force has developed a document to guide decisions on the use of NIRS in patients with and without a DNI decision [40]. Based on this document, cancer patients with ARF may be divided in three categories and the following recommendations may be given, taking into account the advantages and limitations of NIRS.

28.6 First Category: Patients Who Are Still Candidates for IMV (Full Curative Intent)

The cause of ARF is potentially reversible and the medium to long-term prognosis is good as there are effective treatment options for the underlying malignancy. The patient is in good general condition and is willing to receive full treatment. To this category belong patients with ARF as presentation of malignant disease with good susceptibility to chemotherapy (e.g., pulmonary leukostasis in acute myelogenous leukemia or pulmonary involvement due to lymphoma) and patients with ARF as a complication of therapy (e.g., fluid overload, toxicity, or opportunistic infection) given with curative intent. It may be considered to offer NIRS as a preventive therapy in an earlier stage of ARF, with the hope to avert intubation. The potential benefit of NIRS must be balanced against the potential harm caused by NIRS failure. Attention must be given to avoid undue prolongation of NIRS if intubation is more appropriate. Patients with a high risk of NIRS failure, such as ARDS patients, should be considered for immediate intubation instead of NIRS.

28.7 Second Category: Patients Who Are Still Candidates for Intensive Care, But with a DNI-Code (Limited Curative Intent)

The cause of ARF is potentially reversible, but the medium- to long-term prognosis is poor due to lack of cancer treatment, major comorbidities, or debilitated state. The patient has acceptable quality-of-life and is willing to receive a limited amount of organ support but no intubation. To this category belong patients with ARF due to COPD exacerbation, acute CPE, or pneumonia but who are not considered to be candidates for intubation. Here NIRS may be considered as a bridge to overcome an acute life-threatening event and thus to prolong life, however without the morbidity associated with intubation and a long ICU stay. NIRS is offered as a potentially curative treatment rather than a preventive treatment. The potential success of NIRS must be balanced against the discomfort and disadvantages associated with it; it

may be justified to withdraw NIRS if this is poorly tolerated, even if this decreases the chances that patients survive the acute event. As such, early recognition of impending failure of NIV has less therapeutic consequences as intubation is no remaining option. Attention for patient comfort and well-being takes a central place however.

28.8 Third Category: Patients in Whom Intensive Care Is Only Used as Palliation or to "Buy Time" (Palliative Intent)

The cause of ARF is probably irreversible and/or the short-term prognosis is poor due to cancer extensiveness with lack of treatment options or generally poor condition. The patient requires some more time to come at terms with impending death. To this category belong patients with ARF due to pulmonary or cardiac involvement as a presentation of malignant disease which is unlikely to respond rapidly to chemotherapy; in addition, selected patients with ARF heralding a terminal phase of cancer may be considered (although as a rule these patients should receive adequate advance care planning and palliation instead of life-prolonging therapy). Here NIRS may be considered as a temporary measure to alleviate dyspnea and avoid immediate death but without hope for reversal. NIRS should only offered for a limited time, which may be used for patients settling financial or relational issues, coming at terms with impending death or saying goodbye to relatives and friends. Attention to patient comfort is pivotal whereas monitoring for signs of failure may only be used to try to predict "time left" to patients and relatives and decide to start palliative sedation. Explicit communication of these goals of therapy is essential, as well as regular evaluations whether therapy still matches with these goals.

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Ventilator Withdrawal at the End of Life

29

Margaret L. Campbell

Some mechanically ventilated cancer patients will not be restored to a desirable baseline function after a trial of critical care. Decisions with these patients and/or their surrogates may be made to withdraw mechanical ventilation (MV) and allow a natural, comfortable death. Withdrawal of MV leads to patient suffering and distress and to high levels of psychological distress among family members if not performed correctly [1]. The focus of this chapter is the process of withdrawing MV to ensure patient respiratory comfort.

Withdrawal of invasive mechanical ventilation consists of reduction in mechanical ventilatory support until the patient is breathing spontaneously. This may be accomplished in one-step by turning off the ventilator and removing the endotracheal tube, an approach commonly referred to as "terminal extubation." An alternative multistep process, described as "terminal weaning" or "rapid terminal weaning," is completed using a stepwise incremental reduction of oxygen and ventilation over a period of several minutes to hours. Terminal weaning is concluded by turning off the ventilator; a subsequent decision to remove or maintain the endotracheal tube follows [2]. Currently, there are limited *evidence-based* guidelines for withdrawal of MV.

Ventilator withdrawal processes are not standardized. Small samples and largely retrospective chart reviews characterize the body of evidence about processes for ventilator withdrawal. Available evidence suggests there is (a) a lack of a common measure for detecting respiratory distress to guide the process, (b) high variability in initiation and escalation of opioids across studies of ventilator withdrawal, and (c) an inability to predict the method that best ensures patient comfort without hastening death [1]. Only one pilot study has compared methods for terminal ventilator withdrawal [3]. Thus, the recommendations in this chapter are derived from the small evidence base and the large clinical experience of the author.

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29.1 Characteristics of Patients Undergoing Ventilator Withdrawal

Cognitive impairment or unconsciousness typifies the period before death in the ICU. Thus, most patients are unable to reliably report any distress. Patients undergoing ventilator withdrawal are at risk for respiratory distress in response to respiratory failure. Patients who cannot self-report symptom distress can be at risk for undertreatment [4]. Conversely, mechanically ventilated patients may be vulnerable to over treatment of anticipated distress [1].

Patients undergoing ventilator withdrawal are heterogeneous. For example, patients choosing ventilator withdrawal for themselves are awake and aware and often completely dependent on the ventilator. However, a majority are critically ill and cognitively impaired or unconscious. Some patients have been intubated for only a short time and subsequent extubation of the endotracheal tube is not expected to produce airway complications. In other cases the patient has had an endotracheal tube for more than a few days or has other airway conditions, such as self-extubation laryngeal edema, that predict complications such as stridor or complete airway obstruction. Thus, the anticipated experience of the patient will vary greatly. A patient-centered algorithm that accounts for differences in patient characteristics, such as the one suggested in this chapter, is essential for improving the practice of withdrawal of mechanical ventilation. The ideal best practice process for conducting ventilator withdrawal across a heterogeneous population must account for the variance in patient experience and a patient-centered algorithm will provide the best guide [3].

Families are at risk for high levels of distress when mechanical ventilation is withdrawn since they are intimately involved in this process in a number of ways. Patients are usually unable to make the decision to withdraw ventilation and family members serve in a surrogate capacity. Patient death often occurs shortly after withdrawal and many families want to be with the patient at the time of death. Weigand reported that family members' experiences involved a variety of dimensions [5]. Lack of clear, timely, comprehensive communication from healthcare providers can contribute to the anxiety and distress reported by patients' families after a patient's death in the intensive care unit [6]. Uncertainty about the prognosis of the patient, concern about decisions that need to be made, what to expect during dying, and the extent of a patient's suffering pervade families' end-of-life experiences [7]. Family counseling, information and support provided by the nurse are integral to the patient/family-centered algorithmic approach.

29.2 Interventions and Procedures

29.2.1 Assessment

The gold standard for measuring symptom distress is the patient's report. When the patient is severely cognitively impaired or unconscious self-report becomes

impossible. The Respiratory Distress Observation Scale (RDOS) is the only known tool for assessing respiratory distress when the adult patient cannot self-report dyspnea. The RDOS has undergone rigorous clinical testing to establish scale reliability, inter-rater reliability, convergent validity, construct validity, discriminant validity, and intensity cut-points [8–11]. The RDOS is an eight-item ordinal tool to measure the presence and intensity of respiratory distress; each item is scored from 0 to 2 points and the points are summed. Higher scores suggest higher intensity respiratory distress (Appendix). The instrument is not valid for use in children, when the patient is undergoing neuromuscular blockade or has bulbar amyotrophic lateral sclerosis. Scores of 3 or higher signify respiratory distress [11].

29.2.2 Ventilator-Withdrawal Algorithm

Complete the Following Pre-withdrawal

- Cease Neuromuscular Blocking Agents, if any, proceed with withdrawal after return of motor function
- Family preparation
  - Identify where family prefers to be during withdrawal, bedside or other
  - Identify family preference for chaplain support
  - Permit family private time with patient for last rituals, traditions if desired
  - Secure chairs, water, tissues wherever family will be in the hospital
  - Describe the process to family in lay terms
  - Describe expected patient behaviors
  - Describe permissible family behaviors
  - Answer family questions
- Patient preparation
  - Consider diuresing if evidence of pulmonary interstitial edema
  - Consider dexamethasone 4 mg intravenously every 6 h prior to MV withdrawal
  - Ascertain consciousness
- Conduct a cuff-leak test

Ceasing neuromuscular blocking agents, also known as paralytics, is a standard through expert consensus so that patient signs of distress are not masked [2]. Reducing pulmonary interstitial edema as early as possible when MV withdrawal is planned will decrease the patient's risk for respiratory distress. Likewise, a dexamethasone regimen begun early may reduce the risk for post-extubation stridor. Patients who are comatose with no response to deep pain and those with stereotypical responses such as flexion or extension posturing are unlikely to experience respiratory distress during MV withdrawal [12]. Patients with higher levels of consciousness are at risk for respiratory distress and will benefit from anticipatory premedication. Cuff-leak testing that yields a leak of <180 cm^3 (Preset tidal volume—spontaneous tidal volume with cuff deflated) predicts post-extubation stridor [13].

Premedication

- Premedicate patients with higher levels of consciousness
- Premedicate patients who have respiratory distress while ventilated (RDOS ≥3)
- Administer morphine 5 mg IV and lorazepam 1 mg IV (adjust doses for patient tolerance)
- Repeat doses every 10 min if needed to achieve pre-withdrawal respiratory comfort (RDOS ≤3)
- Proceed to ventilator withdrawal when patient displays respiratory comfort

Premedication is recommended if respiratory distress can be anticipated [2]. Some patients undergoing ventilator withdrawal are comatose and not expected to be able to experience distress. Morphine and benzodiazepines are the most commonly used medications for this purpose, although reported doses in other investigations have been highly variable [1]. Morphine or Fentanyl are the drugs of choice for the treatment of dyspnea [14]. Benzodiazepines have utility in adjunct to opioids [15].

Select a Withdrawal Method

- *One-step*
  1. Turn off ventilator, place room air t-piece and assess RDOS
- *Rapid wean*
  1. Decrease PEEP to 0, wait 2 min if no distress (RDOS ≤3) proceed
  2. Reduce FiO_2 by 0.20 every 1 min until 0.21, if no distress proceed
  3. Change mode to SIMV/PSV, wait 2 min, if no distress proceed
     (a) Maintain Vt
     (b) Set frequency to 10 breaths/minute
     (c) Set PSV to 5 cm
  4. Reduce SIMV frequency by two breaths every 2 min until four breaths, if no distress proceed
  5. Change mode to CPAP 0 cm, PSV 5 cm, wait 2 min, if no distress proceed
  6. Turn off ventilator, place humidified room air t-piece
- *Respond to distress*
  1. Assess RDOS immediately after every ventilator change and after ventilator is turned off
  2. Cease wean progress whenever RDOS ≥3
  3. Bolus with morphine 5 mg, wait 10 min for peak effectiveness, if no distress proceed with rapid wean
  4. Re-bolus with morphine 5 mg and lorazepam 1 mg if distress persists and repeat every 10 min if needed until RDOS ≤3.
- *Continuous morphine infusion*
  1. Begin infusion at conclusion of rapid wean, if premedication or medication administered during wean
  2. Initial dose = 50% of total bolus doses, e.g., bolus with 5 mg × 3 = 15 mg, begin infusion at 7.5 mg/h.
  3. Titrate infusion to maintain RDOS ≤3 by administering morphine 5 mg bolus, increase infusion by 2.5 mg after each bolus

Rapid weaning and turning the ventilator off without weaning (one step) are conventional withdrawal methods [2]. Rapid weaning is suggested in cases where the patient may experience distress since this process affords an opportunity to restore the patient to a previous ventilator setting while their distress is relieved. The one-step method is reserved for unconscious patients who are unlikely to experience distress.

A prospective, 2-group, repeated measures, observation design was used with nurses from one medical ICU (MICU) conducting this algorithm and nurses from a second MICU providing unstandardized usual care. Patient respiratory comfort/distress was measured with the RDOS. Fourteen patients evenly distributed by ethnicity and gender were enrolled, 8 in the control ICU and 6 in the intervention unit. No significant differences in age, consciousness, illness severity, or baseline RDOS were found. All control patients underwent a one-step terminal extubation process. Patients in the intervention group had greater respiratory comfort compared to control patients ($p < 0.05$). Differences in medication use were found with lorazepam favored in the control unit; morphine is recommended in the algorithm [3].

Make an Extubation Decision

- Extubate patients who passed the cuff-leak test and do not have a swollen, protuberant tongue
- Extubation process
  1. Drape the distal end of the endotracheal tube
  2. Cut tube ties and release air from the cuff
  3. Suction until cough is elicited, if any
  4. Withdraw the suction catheter and tube simultaneously while applying suction
  5. Wrap catheter and tube in drape and discard out of sight of patient's family
  6. Clean patient's mouth and face
  7. Monitor patient for post-extubation stridor
- Treat stridor
  - Dilute racemic epinephrine 2.25% (22.5 mg/mL) 0.5 cm^3 in 3 cm^3 normal saline as an aerosol treatment, repeat 1× after first treatment if stridor persists

Maintaining the endotracheal tube in the face of a swollen or protuberant tongue or a failed cuff-leak test will minimize the occurrence of partial or complete airway obstruction which will be a source of patient and/or family distress. When a patient is withdrawn from the ventilator in the context of brain death there is no expectation of spontaneous breathing or coughing/gagging, hence the endotracheal tube can always be removed in that context. Stridor typically occurs within the first hour after extubation and is effectively treated with racemic epinephrine [16–18].

In the afore-cited clinical comparison trial [3] all patients in the intervention group passed the cuff-leak test and were extubated with no incidences of stridor. No cuff-leak testing was performed in the control arm and three patients developed

stridor. Furthermore, the patients with stridor had the most severe respiratory distress compared to those without stridor.

Post-withdrawal

- Determine need for supplemental oxygen
  - $SpO_2 < 86\%$ and RDOS >3
- Determine need for continuous morphine infusion
  - Is there ongoing respiratory distress?
  - Is duration of survival predicted to be longer than minutes?

Oxygen is useful to treat dyspnea in the face of hypoxemia [19]. Oxygen is not needed even in the face of hypoxemia if there is no evidence of respiratory distress [20].

Triage Considerations

Estimating the duration of survival after MV withdrawal will contribute to triage decision-making. As expected, the sickest patients will die more rapidly than less sick patients [21]. High FiO_2 and a requirement for vasopressors was associated with a shorter time to death [22, 23]. The majority of patients die within 24 h [22].

29.3 Take Away Points

- Ventilator withdrawal is a commonly performed ICU procedure to afford a natural death.
- The process is not standardized and only a single pilot study has compared methods.
- A patient-centered algorithmic approach is suggested.

Appendix: Respiratory Distress Observation Scale©

Variable	0 points	1 point	2 points	Total
Heart rate per minute	<90 beats	90–109 beats	≥110 beats	
Respiratory rate per minute	≤18 breaths	19–30 breaths	>30 breaths	
Restlessness: non-purposeful movements	None	Occasional, slight movements	Frequent movements	
Accessory muscle use: rise in clavicle during inspiration	None	Slight rise	Pronounced rise	

Variable	0 points	1 point	2 points	Total
Paradoxical breathing pattern	None		Present	
Grunting at end-expiration: guttural sound	None		Present	
Nasal fearing: involuntary movement of nares	None		Present	
Look of fear	None		Eyes wide open, facial muscles tense, brow furrowed, mouth open	

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Outcome: Prognosis Determinants

30

Thierry Hernández-Gilsoul

30.1 Introduction

Prognosis is the simple probability or risk of future conditions and mainly tries to estimate the specific time of an outcome or particular health state; usually, in order to defend this forecast, we require certain clinical elements that allow us to estimate the risk [1]. To give a better idea of what this chapter intends to cover, it should be understood that palliative care is support to improve the quality of life of patients and their companions with such life-threatening illnesses as cancer [2]. Ventilatory support can be seen as a palliative measure that provides relief from dyspnea—not necessarily as a terminal event, but rather as main organ, non-palliative supportive therapy in a critically ill cancer patient. Ventilatory support usually opens the discussion on establishing the need for advance directive, since mechanical ventilation (MV) is seen as a life-sustaining practice [3].

The aim of this chapter is to provide the information necessary to estimate the risk of death associated with ventilatory support in palliative-care cancer patients, since MV is one of the main reasons for ICU admission—from 41.1 to 69% in all cancer patients [4–13] (with higher proportions, even up to 88% in some hematological malignancy cohorts [14–20]).

Prognostic estimates, especially of terminally ill patients, are often optimistic and rely on intuition. In a prospective cohort study, doctors tended to be "overoptimistic" or "overpessimistic," considering as an accurate prediction 0.67–1.33 times the actual survival rate; multivariate modelling showed a tendency towards better prognostic accuracy among experienced doctors, and more prognostic errors in

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those with stronger doctor-patient relationships [21]. Because a prognosis should be determined using clear information, the first step in the assessment of cancer patients is to remove all intuition-based estimates and establish the exact reason why the patient requires ventilatory support.

30.2 What Causes Lead to the Need for Ventilatory Support?

Ventilatory support is for a major organ that requires critical care support in cancer patients owing to a wide range of reasons: severe sepsis, septic shock, acute respiratory distress syndrome (ARDS), lung infiltration, coma, cardiogenic pulmonary edema, capillary leak syndrome, transfusion-related acute lung injury, drug-induced toxicity, radiation-induced lung damage, cardiopulmonary arrest, pulmonary embolism, hemoptysis, alveolar hemorrhage, bronchiolitis, chronic obstructive pulmonary disease (COPD) exacerbation, or cryptogenic organizing pneumonia, among others. All these causes can be grouped into infection-related, direct tumoral involvement of the respiratory system, cancer-related medical disorders, or anticancer drug-induced respiratory distress [22, 23].

The need for MV remains a major outcome predictor in critically ill cancer patients who still have a relatively high mortality; the main independent mortality predictors are listed in Table 30.1. Vasopressor therapy and several organ dysfunction parameters are the principal factors associated with increased mortality risk.

Table 30.1 Independent mortality predictors for critically ill cancer patients

Independent predictor	Mortality odds ratio (95% interval confidence)	*p*
Vallot et al. [24]		
Leucopenia	0.23 (0.06–0.83)	0.03
Azoulay et al. [25]		
Respiratory failure		
Congestive heart failure	0.16 (0.03–0.72)	0.01
Invasive aspergillosis	3.78 (1.05–14.24)	0.049
No definite diagnosis	3.85 (1.26–11.70)	0.01
Vasopressor therapy	3.19 (1.28–7.95)	0.01
Respiratory support		
NIV followed by MV	17.46 (5.04–60.52)	<0.0001
MV	8.75 (2.35–32.54)	0.001
Late NIV failure (after 2 days)	10.64 (1.05–107.83)	0.04
Depuydt et al. [26]		
Females	0.36 (0.16–0.82)	0.014
Intubation before 24 h	0.29 (0.11–0.78)	0.015
Bacteremia before 48 h	0.22 (0.08–0.61)	0.003
AML	2.73 (1.05–7.11)	0.04
SAPS II	1.07 (1.04–1.11)	<0.001
Soares et al. [27]		
Age 40-70	3.09 (1.61–5.93)	0.001
>70 years	9.26 (4.16–20.58)	<0.001

Table 30.1 (continued)

Independent predictor	Mortality odds ratio (95% interval confidence)	*p*
$PaO_2/FiO_2 < 150$	2.64 (1.40–4.99)	0.003
ECOG PS 3-4	2.51 (1.40–4.51)	0.002
Disease progression/recurrence	3.43 (1.81–6.53)	<0.001
SOFA excluding respiratory point (each 4 points change)	2.34 (1.7–3.24)	<0.001
Airway/pulmonary tumor ARF cause	5.73 (1.92–17.08)	0.002
Azoulay et al. [28]		
Allogenic BMT	5.95 (1.48–23.90)	0.01
Respiratory failure		
+Neutropenia recovery	0.13 (0.03–0.57)	0.006
+Undetermined diagnosis	8.65 (1.39–53.56)	0.02
MV	8.18 (1.16–57.36)	0.03
Vasopressor therapy	5.09 (1.07–24.18)	0.04
Lecuyer et al. [29]		
SAPS II	1.02 (1.01–1.03)	<0.0001
MV	7.17 (5.03–10.20)	<0.0001
ARDS	2.66 (1.73–4.1)	<0.0001
Shock	2.43 (1.77–3.33)	<0.0001
Vasopressors therapy	2.94 (2.15–4.02)	<0.0001
Coma	2.36 (2.15–4.02)	<0.0001
RPT	2.07 (1.42–3.01)	<0.0001
Length of MV days	0.98 (0.96–0.99)	<0.0001
Taccone et al. [12]		
SAPS II	1.07 (1.05–1.08)	<0.001
Sepsis	2.1 (1.2–3.7)	0.01
ARDS	2.5 (1.2–5.3)	0.014
MV	2.4 (1.2–4.7)	0.015
Azevedo et al. [23]		
Medical ward admission	4.64 (2.22–9.71)	<0.001
New cancer diagnosis	3.59 (1.28–10.10)	0.015
Disease recurrence/progressive	3.67 (1.25–10.81)	0.018
ECOG PS 2-4	2.39 (1.24–4.59)	0.009
MV	3.53 (1.45–8.6)	0.006
NIV followed by MV	3.00 (1.09–8.18)	0.034
SOFA, excluding respiratory point	1.15 (1.03–1.29)	0.015
Hawari et al. [4]		
APACHE II	1.12 (1.1–1.13)	<0.05
Neutropenia at admission	1.77 (1.42–2.2)	<0.05
MV	2.01 (1.54–2.63)	<0.05
ICU length of stay	1.023 (1.01–1.04)	<0.05
Multiple ICU admissions	1.42 (1.18–1.7)	<0.05

ARDS acute respiratory distress syndrome; *AML* acute myeloid leukemia; *BMT* bone marrow transplant; *CV* cardiovascular; *DIC* disseminated intravascular coagulation; *ECOG PS* Eastern Cooperative Oncology Group Performance Status; *MV* mechanical ventilation; *NIV* non-invasive ventilation; *RRT* renal replacement therapy; *SAPS II* Simplified Acute Physiology Score; *SOFA* Sequential Organ Failure Assessment

30.3 Ventilator Support Among Palliative-care Cancer Patients

More recently, Azevedo et al (2014) reported the highest mortality rates in relapsed cancer with poor performance status and other organ failure, with almost 90% hospital mortality and more than 90% mortality in the infrequent group of relapsed cancer with poor performance status and tumoral acute respiratory failure (ARF). On the other hand, with controlled cancer with good performance status with non-tumoral ARF, or other organ failure or sepsis, ICU and hospital mortality rates were less than 30% and 53%, respectively, so they suggest full intensive care support for the latter groups, and palliative support for the first two groups [23]. As in these groups, in a retrospective study of stage III B-IV lung cancer patients admitted to the ICU, a multivariate analysis showed that in a PaO_2/FiO_2, less than 150 was independently associated with ICU mortality [OR 5.51, 95% CI 2.10–14.48, $p = 0.001$] as an Eastern Cooperative Oncology Group (ECOG) PS $\geq$ 2 [OR 9.53, 95% CI 2038–44.85, $p = 0.004$], and as well as the need for vasoactive support [OR 6.94, 95% CI 1.61–29.84, $p = 0.009$] [30].

30.4 Ventilatory Support Among "Do-not-Intubate" (DNI) Patients

Regardless of the cause that leads to respiratory failure, the use of NIV in palliative-care patients who have decided to forego endotracheal intubation is an option currently under discussion, although some consider it to be a life-sustaining method [3, 31]. The palliation of dyspnea can be seen as a comfort measure that is required to minimize the adverse effects of opiates and maintain the NIV while the patient remains conscious and able to communicate; others consider it a failure to palliate when a patient wants to stop NIV or comfort is not achieved (some patients outweighed discomfort due the tight facial mask for dyspnea relief). Limited communication has to be weighed by the patient, since it is restricted during the NIV periods, and failure has to be considered also when the patient becomes unable to communicate [3]. In the context of the NIV requirement for hypoxemic DNI patients, some had proposed a high-flow oxygen nasal cannula; these included seven cancer patients and seven hematologic malignancy patients who showed a respiratory rate decrease from 30.6 to 24.7 bpm ($p < 0.001$). Of them, only 18% needed further NIV support, and a hospital mortality rate of 60% was reported [32].

Studies on the outcome and predictors in patients with DNI are less common. The outcomes, as previously mentioned, are avoiding intubation and death, and for comfort measures only (CMO), decreasing dyspnea, and avoiding opiates, including for those who wish to have more time when family members visit [31].

Fernandez et al, in a retrospective cohort study in a single center of 233 patients treated with NIV, showed that after multivariate analysis, the same factors associated with hospital mortality and six months (the latter factors associated in cancer patients needing critical care), authors described vasoactive drugs, acute renal failure, and age as the independent predictors [33].

According to Levy et al (2004), in a prospective multiple-center cohort of 114 DNI patients were 43% survived to discharge, multivariate analysis was made and favorable odds ratio for surivival to discharge were seen. Being awake [OD 0.18, 95% IC 0.05–0.62, $p = 0.007$] and stronger coughing [OD 0.16, 95% IC 0.05–0.51, $p = 0.001$] as well as, higher baseline $PaCO_2$ (>80 mmHg) [OD 0.01, 95% IC 0.01–0.93, $p = 0.04$] were associated with greater probability of survival. Diagnosis of the DNI patients with better survival rates were congestive heart failure over chronic obstructive pulmonary disease, cancer and pneumonia [34]. Additionally, Schettino et al (2005), in a single-center prospective study, looked at 137 ARFs of 131 DNI patients, for whom of the 40 patients who had advanced cancer versus non-cancer patientes, the mortality rate was 85 vs. 15%, $p = 0.002$. Independent predictive factors for death were albumin ≤ 2.5 g/dL, and SAPS II above 35 points [OD (95% IC) 11.25 (3.72–33.99) and 3.04 (1.11–8.34), respectively]; researchers proposed a predictive score for death based on the independent predictors, divided among a total score rank of 0 to 3. Two points were given for albumin, and one for SAPS II of more than 35 points; the mortality rate was 61, 83, and 94%, for each point gain [35].

Furthermore, Schortgen et al (2012) observed a small sample of patients, divided into groups of those needing ventilator support who were older or younger than 80; among them, 40 and 8% for each group had DNI orders and were associated with high mortality rates, compared with those categorized as full critical-care patients, but they found that there was no difference among the younger and more elderly patients (DNI 56 vs. 73%) [36]. Additionally, Nava et al (2011) showed that among 82 patients who were older than 75, and who met the criteria for intubation, 21 of the 25 who received standard medical treatment had DNIs; 17 of them recovered successfully with NIV, showing a mortality odds ratio of 0.6 (IC 95%, 0.18–1.92) against 4.03 (2.35–6.94) of the endotracheal intubation group. This study also noted a respiratory rate and dyspnea score improvement in the NIV group ($p < 0.01$ and $p < 0.05$, respectively) [37]. Furthermore, Cuomo et al (2004) described palliative NIV in 23 patients with solid malignancies; thirteen were discharged, and seven died after NIV failed, PaO_2/FiO_2 increased, the Borg dyspnea score decreased, and predictors for mortality findings were higher using SAPS II and lower with PaO_2/FiO_2 at admission [38].

NIV may fail in cancer patients due to a delay in beginning ventilatory support, ARDS, vasopressor therapy, and RRT, the obvious logic here being that the increasing respiratory rate was associated with NIV failure [39].

The argument about which location is best suited for ventilator supports needs to be based on facility capabilities, availability of the ventilator operator's expertise, patient-family comfort, and if limited critical care resources allocating to those patients most likely to benefit. Further randomized trials are needed for optimal NIV indications [40].

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Part VI

Outcome, Healthcare Resource Utilization and Organizational Support in Cancer Critical Care

Outcome of Critically Ill Allogeneic Hematopoietic Stem-Cell Transplantation Recipients

31

Darius Seidler and Alex H. Gifford

31.1 Introduction

Hematopoietic stem-cell transplant (HSCT) recipients present a special challenge when they are admitted to the intensive care unit. Mortality is typically high, particularly in those who need mechanical ventilation [1]. Even among HSCT recipients not receiving mechanical ventilation, mortality rates range from 4 to 34% [2–4], which are comparable to rates for general ICU patients. Although outcomes for allogeneic HSCT patients have improved significantly over the past decades [5], HSCT patients that require mechanical ventilation (MV) have hospital mortality rates on the order of 44–100%. Recent studies, such as that of Lengline et al. [6], report a significant improvement in survival for allogeneic HSCT patients admitted to the ICU from 2004 to 2011 compared to those admitted from 1997 to 2003. ICU, 90-day, and 1-year mortality are reported as 52%, 69%, and 67% in the 1997–2003 cohort and 30%, 51%, and 48%, respectively, in the 2004–2011 cohort.

31.2 Causes of Critical Illness After Bone Marrow Transplant

Complications related to HCST can involve a variety of organs with different conditions developing with respect to the stage of transplantation. During the pretransplant or conditioning phase, one may expect acute toxicities related to chemotherapy. This is followed by the establishment of donor hematopoietic cells during the engraftment phase. Peripheral blood-derived stem cells tend to engraft more rapidly

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Table 31.1 Pulmonary complications following allogeneic SCT

	Neutropenic phase	Early engraftment phase	Late phase
Typical latency (days)	<30	30–100	>100
Non-infectious complications	DAH	Spontaneous air leak	GVHD
	PERDS	IPS	PTLD
	Pulmonary edema	PCT	IPS
	Chemotherapy toxicity		Spontaneous air leak
	Spontaneous air leak		
	IPS		
Infectious complications	Bacterial pneumonia	Pulmonary aspergillosis	PJP
	Invasive aspergillosis	CMV pneumonia	
	Candida pneumonia	PJP	

DAH diffuse alveolar hemorrhage, *IPS* idiopathic pneumonia syndrome, *PERDS* peri-engraftment respiratory distress syndrome, *PCT* pulmonary cytolytic thrombi, *CMV* cytomegalovirus, *PJP Pneumocystis jiroveci* pneumonia, *GVHD* graft-versus-host disease, and *PTLD* posttransplant lymphoproliferative disorder

than bone marrow-derived stem cells (median: 14 days versus 21 days) [4, 7]. This fact generally leads to shorter periods of neutropenia and a lesser need for transfusion of blood products. Although cell counts may quantitatively normalize following engraftment, lymphocyte function can remain limited for months, thus imparting a relative form of immunodeficiency. The posttransplant period can be divided into three phases as well (Table 31.1). The first phase (30 days posttransplant) has complications related to toxicities from chemotherapy and neutropenia. During the second phase (up to 100 days posttransplant) a deficiency in cell-mediated and humoral immunity ensues, while the third phase (after 100 days) is dominated by complications related to GVHD, chronic chemotherapy toxicity, and relapse [8].

31.3 Common Reasons for ICU Admission

By far, the most common reason for ICU admission among allogeneic HSCT patients is acute respiratory failure (ARF), which occurs in more than 60% of patients. This is followed by hemodynamic instability due to sepsis (18%), cardiac dysrhythmias (8–17%), neurologic complications (11%), gastrointestinal bleeding (5%), and acute renal failure (5%). Acute renal failure is very common in this population, but only 5% were noted to be the primary cause for ICU admission [4, 9, 10]. Thrombocytopenia and GVHD predispose to hemorrhagic complications, while intracranial hemorrhage (ICH) is reported in 2–5% of HSCT recipients [9, 11, 12]. One study found 32% of HSCT patients had evidence of ICH at autopsy [13]. Common causes of ARF in this population are ARDS related to sepsis, pulmonary edema, DAH, infectious pneumonia, IPS, pulmonary GVHD (bronchiolitis obliterans/organizing pneumonia), and PERDS [9].

31.4 ICU Course and Diagnostic Interventions

Afessa and Azoulay [9] have summarized the ICU course of HSCT recipients and reported single or multi-organ failure in 64–94%. Respiratory failure is most common at 62%, while ARDS and interstitial pneumonia are the most common causes of death. Acute renal failure is reported in approximately 80% of patients, while 52% of patients have hepatic failure.

Aside from standard blood tests and cultures, more aggressive interventions have been reviewed in the literature. Pulmonary artery catheterization in the critically ill does not have an effect on patient outcome, length of stay, and mortality, though its use should be reserved for highly selected patients [14].

Given the underlying immunosuppression and high rate of pulmonary complications, bronchoscopy is often considered for diagnosis. However in a patient who already has compromised respiratory function this could lead to mechanical ventilation and poor outcomes. In an observational study, Azoulay et al. [15] found that respiratory decompensation developed after bronchoscopy in 22 out of 45 (49%) of patients and 16 (36%) required mechanical ventilation. Furthermore, Azoulay et al. [15] examined noninvasive testing (sputum and blood cultures, serology for *Aspergillus* antigen, sputum staining for *Pneumocystis jiroveci*, urine Legionella and *Streptococcus pneumoniae* antigens, CMV antigenemia, nasopharyngeal aspirates, and echocardiography) versus bronchoscopy and found that 60% of diagnoses established were made by noninvasive tests only, 28% by bronchoscopy only, and 12% by both methods. This shows that most diagnoses can be made using noninvasive testing, while bronchoscopy has a complementary role in selected patients. Empiric treatment could be considered if the risk of worsening respiratory failure and subsequent intubation is deemed to outweigh the benefit of obtaining a specific diagnosis.

Transfusion of blood products is associated with lung injury [16]. Granulocyte transfusion has not shown benefit for neutropenic patients [9, 17, 18]. Practice guidelines from the American Society of Clinical Oncology recommend a platelet transfusion threshold of 10,000/μL in the absence of active bleeding [19, 20]. With regard to erythrocyte transfusion, a threshold of 7.0 g/dL seems adequate in the absence of active bleeding and hemodynamic instability [21].

31.5 Predictors of Prognosis

In the early 1990s, prognosis for allogeneic HSCT patients admitted to the ICU was quite poor with mortality close to 100%, especially when MV was needed [22]. However, over the past two decades improvements in hematologic and critical care decreased the hospital mortality, 90-day and 1-year mortality to 39%, 48%, and 57% according to Azoulay et al. [23]. In their cohort of patients, 75% required MV, renal replacement therapy, or vasoactive drugs.

Patient age, gender, donor type, HLA match, stem cell source, and disease status at transplantation have not been found to be associated with ICU outcomes [24, 25].

The type of HSCT and conditioning regimen affect the risk for critical illness, with allogeneic HSCT and high intensity conditioning regimen conferring the highest risk. Whether these factors influence ICU outcomes is unclear [26]. In terms of patient-related factors, only pretransplant comorbidities and patient functional status prior to ICU admission have been correlated with increased hospital mortality [24, 27]. Critical care severity scores such as APACHE II, APACHE III, SOFA, and SAPS II have not been validated in the allogeneic HSCT population and might underestimate mortality [4, 11, 12, 24, 25].

Factors associated with poor prognosis in critically ill allogeneic HSCT patients include mechanical ventilation, renal replacement therapy, vasopressor use, gastrointestinal bleed, disseminated intravascular coagulation (DIC), hepatic dysfunction, multisystem organ failure, active GVHD requiring corticosteroids, and ICU admission >10 days after hospital admission [4, 12, 24, 25]. Of all these factors, the number of failed organs appears to have the greatest impact on survival [23]. In acute respiratory failure, the need for ventilator support arises in 28–76% of patients, and ICU mortality ranges from 63–85% [11, 12, 23]. If mechanical ventilation is required and multiple organ failure is present, mortality approaches 100% [12]. Need for MV during the engraftment period is associated with a better prognosis, while patients admitted 30 days or more after HSCT tend to fair worse. Comparing patients undergoing MV during the engraftment period to those undergoing MV during the post-engraftment period, Pene et al. found that 26% versus 13% are discharged from the ICU, 22% versus 12% are discharged from the hospital, and 17% versus 7% are alive at 6 months [12]. The presence of GVHD is associated with a 1-year survival of 10%, while MV in patients with active GVHD does not seem to provide a survival benefit [6, 11]. Acute kidney injury (AKI) at ICU admission also portends poor prognosis. As few as 19% of patients with HSCT and stage 3 AKI are alive at hospital discharge [28].

31.6 Mechanical Ventilation and Noninvasive Ventilation (NIV)

ARDS develops in 5% of HSCT recipients (16% in allogeneic-HSCT and 3% in autologous-HSCT), and this is associated with a 67% mortality [29]. In patients that required mechanical ventilation it was found that 3-month mortality in HSCT recipients dropped from 84% (1997–2003 cohort) to 70% (2004–2011 cohort), which can likely be attributed to the common acceptance to low tidal volume ventilation in patients with ARDS when comparing cohorts before and after low tidal volume ventilation protocols became the standard of care [6, 11]. Duration of mechanical ventilation is an uncertain predictor of outcomes [22], though longer time of mechanical ventilation appears to portend higher mortality [30]. Prolonged MV suggests more severe respiratory failure at the onset of illness and poor response to therapy, validating the dictum that sicker patients tend to do worse and have poorer outcomes.

Recent advances in NIV and the use of high flow nasal cannula (HFNC) are promising alternatives to avoid the need for MV in some patients. Use of HFNC in cancer patients demonstrated encouraging results with improvement of 28-day mortality and reduced need for invasive MV [31]. Failing NIV does not appear to confer a poor prognosis [32]. Among allogeneic HSCT patients in the early posttransplant period, Wermke et al. found that NIV improved oxygenation during early treatment of respiratory failure, but it failed to demonstrate improvements in ICU admission rate, need for intubation, and survival [33]. Prospective studies in this specific patient population are still lacking and we have to await further study to optimize the use of NIV in allogeneic HSCT patients.

31.7 ICU Admission

Currently there are no guidelines to assist clinicians in decision-making when to limit support for critically ill allogeneic HSCT patients. These patients will invariably require a significant amount of ICU resources and both ethical concerns and cost may persuade the clinician to initiate palliative care in favor of aggressive ICU therapy. In light of recent data, Saillard et al. [11] propose to initiate aggressive, unlimited critical care, including mechanical ventilation for allogeneic HSCT patients if they are admitted early in the ICU with isolated organ dysfunction. However, patients with known poor prognostic factors such as multisystem organ failure, bedridden patients with uncontrolled or refractory disease and uncontrolled GVHD requiring MV should be considered for palliative care over aggressive ICU care. Between these two extremes of illness severity, there is a large zone of uncertainty, and every patient should be considered individually. Treatment limitations between admission and ICU days 5–7 should be discussed based on the clinical course and the development of organ dysfunction [11, 34, 35].

Conclusions

Mortality of critically ill allogeneic HSCT patients is high, though over the past decades improvements in hematologic and critical care have yielded outcomes that justify aggressive critical care in this patient population. Mechanical ventilation, active GVHD, and multi-organ failure remain poor prognostic factors and they should be taken into consideration when caring for critically ill allogeneic HSCT patients to allow for thoughtful resource allocation and perhaps improve end-of-life care for these patients and their families. Traditional indices of severity of illness underestimate the outcomes in this population, and each patient should be assessed on a case-by-case basis in collaboration with members of the hematology, palliative care, and critical care teams.

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Clinical Utility of Prognostic Scoring Systems in Patients with Hematological Malignancies Who Require Mechanical Ventilation

32

Elliot D. Backer and Alex H. Gifford

Hematological malignancies account for approximately 10–20% of all cancers [1, 2] and include acute and chronic leukemia, Hodgkin's and non-Hodgkin's lymphoma, and rare dyscrasias of specific cell lineages. As the sophistication and efficacy of therapies evolve, patients are living longer with their conditions. However, some patients develop complications that lead to treatment in the intensive care unit (ICU). Acute respiratory failure requiring invasive mechanical ventilation is one of the most common problems that arises in this population [3–6]. Whereas an estimated 15–38% of all patients admitted to the ICU die from their illnesses [7, 8], those with hematological malignancies experience hospital mortality rates between 45 and 60% [5, 9, 10]. Mortality can exceed 75% when invasive mechanical ventilation is required [11]. Practitioners caring for this population of patients must weigh the benefits of implementing these services against their potential futility. Unfortunately, this decision-making process is usually fraught with nuances and idiosyncrasies.

Patients with hematological malignancies can develop acute respiratory failure for multiple reasons, including chemotherapy-related lung toxicity, transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), pneumonia, profound muscle weakness, and syndromes associated with allogeneic stem cell transplant (SCT), such as alveolar hemorrhage and pulmonary graft-versus-host disease (bronchiolitis obliterans). Although TRALI occurs in 0.08–15% of patients who receive a blood transfusion [12], at least half of affected patients require invasive mechanical ventilation [13, 14]. The suspected pathogenesis of TRALI has been discussed by others [12], but we should mention that data from a murine model of TRALI has suggested that mechanical ventilation, even at low-tidal volumes, augments lung injury [15] and that methylprednisolone does not

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prevent the development of TRALI [16]. Transfusion of fresh frozen plasma (FFP), particularly from female donors, confers a greater risk of developing TRALI than transfusion of packed red blood cells in critically ill patients [17]. To date, no human studies have demonstrated a specific ventilatory strategy that favorably modifies the natural history of TRALI or TACO, although several authors have reported on the use of prone positioning during mechanical ventilation in patients with suspected TRALI [18, 19].

Approximately 10–20% of patients treated with chemotherapy experience some type of pulmonary complication [20]. In categorical terms, these include bronchospasm, hypersensitivity reaction, infusion reaction, pneumonitis, capillary leak syndrome, eosinophilic pneumonia, and acute respiratory distress syndrome (ARDS) [21]. Certain drugs like methotrexate, bleomycin, busulfan, oxaliplatin, and anthracyclines are notorious for their potential to cause lung toxicity, but some members of newer drug classes (tyrosine kinase inhibitors, proteosome inhibitors, and monoclonal antibodies) can also precipitate respiratory failure [20]. Despite their widespread use and reputations for causing lung damage, specific chemotherapeutic agents have not been studied as predictors of ICU mortality using a formal scoring system. This line of inquiry could help to identify patients with hematological malignancies who are at high risk for acute respiratory failure.

Acute respiratory failure frequently occurs contemporaneously with other problems that mandate ICU admission. In one study [22], patients who had undergone hematopoietic stem cell transplant (HSCT) and developed cardiac arrhythmias were more likely to require ICU admission (52% vs. 7%) and to die in the hospital (28% vs. 3%) than patients who had undergone HSCT but had not developed cardiac arrhythmias. Infection and congestive heart failure complicate 29% and 12% of cases of acute respiratory failure, respectively, in patients with cancer [23]. Extracorporeal membrane oxygenation (ECMO) has been used in small cohorts of patients with hematological malignancies for support of acute respiratory failure with some success [24].

Due to the high mortality associated with ICU admission in patients with hematological malignancies, attempts have been made to better identify those who stand to benefit from intensive care. Independent risk factors for death in the ICU have been elucidated by multivariate analyses that incorporate data from various scoring systems for critical illness severity (Table 32.1).

32.1 Mortality Prediction: SAPS II Score vs. Need for Mechanical Ventilation Alone

Introduced in 1993, the Simplified Acute Physiology Score (SAPS) II was designed to predict the probability of hospital mortality [25]. It includes twelve physiologic parameters and four additional attributes (Table 32.1). Importantly, a need for mechanical ventilation is not one of these criteria. In a single-center retrospective study of patients with hematological malignancies, Kroschinsky et al. found that ICU mortality was higher among those with a SAPS II score >50 and that

Table 32.1 Comparison common critical illness severity scores by included variables

	SAPS II [25]	SOFA [26]	APACHE II [27]
Variables	Age Heart rate Systolic blood pressure Body temperature PaO_2/FiO_2 Urine output BUN White blood count Serum potassium Serum sodium Serum bicarbonate Serum total bilirubin GCS Type of admission AIDS Hematological malignancy Metastatic cancer	PaO_2/FiO_2 Platelets ($\times 10^3/mm^3$) Serum bilirubin Hypotension GCS Serum creatinine or urine output	Body temperature Heart rate Respiratory rate PaO2 (or A-aDO_2) Arterial pH (or serum bicarbonate) Serum sodium Serum potassium Serum creatinine Hematocrit White blood count GCS

SAPS Simplified Acute Physiology Score, *SOFA* Sequential Organ Failure Assessment, *APACHE* Acute Physiology and Chronic Health Evaluation, *PaO_2* arterial partial pressure of oxygen, *FiO_2* fraction of inspired oxygen, *GCS* Glasgow Coma Scale, *BUN* blood urea nitrogen, *AIDS* acquired immunodeficiency syndrome, *MAP* mean arterial pressure

mechanical ventilation did not significantly predict mortality in multivariate logistic regression analyses. Medeiros et al. [28] recently reported in an abstract that neither the SAPS II score nor the SOFA score showed robust discriminative power to predict hospital mortality in immunocompromised patients. However, the study by Medeiros et al. [28] included 91 patients (only 15% of whom had hematological malignancies), while the study by Kroschinsky et al. [4] included 104 patients (all of whom had hematological malignancies). These distinctions probably explain the discordant conclusions of these authors regarding the SAPS II score, but it might also indicate that a cohort size of at least 14 (and perhaps closer to 100) patients is needed for adequate power to conclude that the SAPS II score is useful in predicting ICU mortality in this population.

Sawicka et al. [29] recently evaluated the utility of APACHE II, SAPS II, and SOFA scores for predicting mortality among patients with hematological malignancies in the ICU. These authors studied 24 patients who survived to ICU discharge and 75 patients who died in the ICU, and they applied the scoring systems during the first 24 h of ICU admission. In univariate analyses, Sawicka et al. [29] determined that hemodynamic parameters, kidney injury, neutrophil and platelet counts in peripheral blood, and scores from each system were independent risk factors for death. However, in multivariate logistic regression calculations, only the SAPS II score emerged as a significant predictor of mortality (OR 1.052, 95% CI: 1.022–1.082, $p = 0.0004$).

32.2 Mortality Prediction: SOFA Score vs. Need for Mechanical Ventilation Alone

The Sequential Organ Failure Assessment (SOFA) score was designed to describe the temporal evolution of morbidity in critically ill patients but not to predict ICU mortality [26]. The SOFA score is generated by grading the severity of dysfunction in the respiratory, coagulation, hepatic, cardiovascular, central nervous, and renal systems using a 1–4 scale on a daily basis (Table 32.1). Notably, a need for mechanical ventilation is not part of the SOFA score. The severity of lung dysfunction in the SOFA score is described by a reduction in the ratio of arterial partial pressure of oxygen (PaO_2) to fraction of inspired oxygen (FiO_2), the so-called P/F ratio.

Despite its original purpose as a means of characterizing the severity of organ dysfunction over time, the SOFA score has been used to predict mortality among patients with hematological malignancies admitted to the ICU. Geerse et al. [30] compared SOFA scores and many additional variables between two patient cohorts, one consisting of 48 ICU non-survivors and one comprised of 38 ICU survivors, all of whom had hematological malignancies. A higher proportion of ICU non-survivors required invasive mechanical ventilation within 24 h of admission (71% vs. 29%, $p < 0.001$); in multivariate analyses, patients with this outcome were 5.16 times more likely to die in the ICU (95 CI: 1.31–20.38, $p = 0.019$) than those who did not require early initiation of invasive mechanical ventilation. In multivariate analyses, patients with an increasing SOFA score were 7.01 times more likely (95% CI: 1.09–45.01, $p = 0.04$) than those with a decreasing SOFA, and 9.24 times more likely (95% CI: 1.67–50.95, $p = 0.011$) than those with an unchanged SOFA score, to die in the ICU. More recently, Duayer et al. [31] reported that a higher SOFA score was associated with ICU mortality (OR 1.69, 95% CI: 1.38–2.06, $p < 0.001$) in a comparable population.

A number of risk factors for ICU mortality in patients with hematological malignancies have been identified that do not fit discretely into a scoring system (Table 32.2). These include certain types of infection and neutropenia. Prospective studies should be performed in which these clinical attributes, along with a history of exposure to chemotherapeutic agents associated with lung toxicity, are added to traditional scoring systems to quantify any additional predictive utility.

32.3 Which Patients with Hematological Malignancies Are at High Risk for Invasive Ventilation?

Several studies have focused on identifying risk factors for endotracheal intubation and mechanical ventilation in patients with hematological malignancies who develop acute respiratory failure [32–35] (Table 32.3). These studies vary in terms of setting, cohort size, and design. Despite these distinctions, fulfillment of ARDS criteria at the time of ICU admission was more common in patients who required intubation. Gristina et al. [33] found that the SAPS II score was helpful in distinguishing patients who were and were not intubated, but Adda et al. [32] did not

Table 32.2 Studies evaluating mortality in patients with hematological malignancies who are admitted to the ICU

Author	Year	Study type	Patients (*n*)	In-hospital mortality (%)	Risk factors for mortality
Blot et al.	1997	Retrospective, single-center	57	61	Number of organ system failures, acute respiratory failure
Benoit et al.	2001	Retrospective (case-control)	124	54	Leukopenia, vasopressor, BUN >12 mmol/L
Massion et al.	2002	Retrospective, single-center	84	61	Respiratory failure, serum creatinine, fungemia
Hampshire et al.	2009	Retrospective, database analysis	7689	59	Longer time from hospital admission to ICU transfer, hematocrit 20–29%, systolic hypotension <50 mmHg, GCS = 3, arterial pH, serum sodium, PaO_2, BUN, urine output, heart rate, respiratory rate
Geerse et al.	2010	Retrospective, single-center	86	65	Inotrope/vasopressor, invasive mechanical ventilation within 24 h, higher SOFA score
Bird et al.	2012	Retrospective, single-center	199	46	Failure of ≥2 organ systems, invasive mechanical ventilation
Azoulay et al.	2013	Prospective, multicenter	1011	39	Poor performance status, Charlson comorbidity index, allogeneic HSCT, organ dysfunction score, cardiac arrest, acute respiratory failure, malignant organ infiltration, invasive aspergillosis
Sawicka et al.	2014	Retrospective, single-center	99	NR	SAPS II score
van Beers et al.	2015	Retrospective, single-center	234	38	Neutropenia, positive blood culture during ICU admission
Duayer et al.	2015	Retrospective, single-center	277	36	RRT, SOFA score, RDW, serum lactate, colonization by MDR agent, hospital stay prior to ICU admission >4 days

BUN blood urea nitrogen, *MDR* multi-drug resistant, *NR* not reported, *RDW* red blood cell distribution width, *RRT* renal replacement therapy

Table 32.3 Summary of studies evaluating factors associated with an increased risk of invasive mechanical ventilation in critically ill patients with hematological malignancies

Author	Year	Study type	Patients (*n*)		Risk factors for invasive ventilation
			Non-intubated	Intubated	
Adda et al.	2008	Single-center, retrospective	46	53	Respiratory rate, delay from ICU admission to initiation of noninvasive ventilation, need for vasopressors, need for RRT, satisfy ARDS criteria at beginning of noninvasive ventilation
Gristina et al.	2011	Multi-center, retrospective	147	127	ALI/ARDS at ICU admission, baseline illness severity (SAPS II score)
Molina et al.	2012	Multi-center, prospective	52	79	Younger age, lower incidence of CHF or bacteremia at ICU admission
Lemiale et al.	2014	Multi-center, randomized controlled trial	130	81	Oxygen requirement at ICU admission, number of quadrants involved on chest X-ray, hemodynamic dysfunction

ALI acute lung injury

observe similar utility of the SAPS II score in their population. Lemiale et al. [35] noted that fewer patients who survived to hospital discharge had received mechanical ventilation than those who died during the hospital stay (12.4% vs. 50.4%).

32.4 Which Patients with Hematological Malignancies May Benefit from Noninvasive Ventilation?

High-quality research has confirmed that noninvasive ventilation benefits patients with acutely decompensated chronic obstructive pulmonary disease (COPD) and systolic heart failure [36, 37]. Studies of noninvasive ventilation in patients with hematological malignancies are much fewer in number and offer data that are more difficult to interpret. Schell et al. [38] have succinctly discussed factors that have led to discordant findings in studies of noninvasive ventilation in this population: lack of control for timing of noninvasive ventilation implementation, lack of control for prophylactic use of noninvasive ventilation, variation in the location (ICU vs. ward) where noninvasive ventilation is delivered, and heterogeneity of the causes of acute respiratory failure. These authors [38] also offered strategies that may improve the efficacy of noninvasive ventilation in patients with hematological malignancies: improved patient selection, careful identification of the etiology for acute respiratory failure, and early assessment of the efficacy of noninvasive ventilation. Until steps of this nature are routinely incorporated into the design of clinical studies on

this topic, it will be difficult to create a useful scoring system by which noninvasive ventilation is optimally leveraged in the care of critically ill patients with hematological malignancies.

32.5 Palliative Care for Patients with Hematological Malignancies and Acute Respiratory Failure

Compared to patients with solid cancers, those with hematological malignancies receive more aggressive care at the end of life [39, 40]. The prudence of this approach in the latter group of patients has come into question [41]. In the last month of life, patients with hematological malignancies are nearly five-times more likely to be admitted to the ICU and approximately eight-times more likely to die in the ICU than those with solid cancers [40]. A single-center study from a German teaching hospital revealed that 83% of patients with a hematological malignancy who were admitted to the ICU during the last week of life were treated with invasive mechanical ventilation [39]. Odejide et al. [42] sought a more granular understanding of why this and other heroic practices transpire when death is imminent. These authors [42] found that hematologist-oncologists are often unsure about a patient's prognosis (59% of respondents), do not want to take away hope (71% of respondents), and believe that their patients have unrealistic expectations (97% of respondents). Some institutions have embedded palliative care providers with ICU care teams [43], but it remains to be seen how this practice will impact the care of those with hematological malignancies who are admitted to the ICU with acute respiratory failure.

In summary, patients with hematologic malignancies are frequently admitted to the ICU for acute respiratory failure, and the development of this complication carries a guarded prognosis. Of the three critical illness severity scoring systems discussed here, the SAPS II and SOFA scores perform reasonably well in identifying patients with these types of cancer who are likely to die in the ICU. A striking number of heroic interventions are performed in this population in the last days of life, and it remains difficult to determine which patients will benefit and which ones will not.

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Organization of Ventilatory Support

33

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33.1 Introduction

Mechanical ventilation, invasive or noninvasive, is a potentially life-saving intervention in acutely critically ill patients. It has also been applied less extensively in stable patients with chronic ventilatory failure, sometimes in the home setting. We shall discuss the organizational framework of ventilatory support in the hospital environment.

33.2 Organization of Invasive Ventilatory Support for the Acutely Ill Patient

The optimal application of invasive mechanical ventilation in acutely ill patients requires:

- Healthcare professionals specially trained in the treatment of the critically ill patients and working as a multidisciplinary team (Table 33.1).
- Facilities with appropriate structure and with well-defined policies and procedures.
- Treatment space with sophisticated monitoring equipment, mechanical ventilators with complex modes of ventilation and possibly the availability of other forms of life-sustaining treatments like techniques of extracorporeal clearance.

These conditions are met in full in the Intensive Care Unit (ICU) environment, which is the ideal place for the treatment of mechanically ventilated patients [1–3].

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Table 33.1 Personnel involved in the ICU

• Physicians qualified in critical care
• Medical trainees
• Nurses
• Respiratory therapists
• Physical therapists
• Speech and language therapists
• Occupational therapists
• Clinical pharmacists
• Dieticians
• Psychologists
• Technicians
• Cleaning personnel

There are major differences regarding the provision of critical care services and ICU organization across different countries. These are likely to reflect in addition to population characteristics and financial resources available, the structure and character of the Health Care System or even factors like specialty status [4]. Nevertheless, regardless of such differences, some organizational models seem to be preferable: "closed" ICUs seem to be superior to "open" ICUs, while the presence of a dedicated fully qualified ICU physician on a 24-h basis seems also desirable [5–7].

The level of care (LOC) provided to patients in the ICU varies according to patient complexity and severity of critical illness. The highest LOC (LOC III) is reserved for patients with two or more acute vital organ failures, while patients with only one acutely failing organ system are in need of less intensive care (LOC II). The lowest level of care (LOC I) is suitable for patients at risk for developing acute organ failure, who require for this reason intensive monitoring, timely interventions, and possibly minor device-related support (for example, noninvasive positive pressure ventilation—NIPPV) [1].

LOCs are defined on the basis of the intensity of nurse staffing (Table 33.2) [1]. Mechanically ventilated patients in the ICU require by definition a LOC of II–III, corresponding to a nurse-to-patient ratio of 1:1 to 1:2. The nurse-to-patient ratio is an important quality indicator for intensive care and has been associated with patient outcomes and complications [8, 9]. Nurse staffing has also a large impact on ICU cost which is determined to a large degree by the salaries of personnel (while the impact of bedside equipment is by comparison less important). Bedside equipment on the other hand is not taken into account in the definition of LOCs as it is deemed desirable to have all critical care beds regardless of LOC equipped to the highest possible level. This approach provides a higher flexibility in bed utilization: the same bed can be used for patients requiring different levels of care, as need arises. Furthermore, in case of deterioration, a patient who initially requires a lower LOC may continue to be treated in the same bed with more intensive personnel allocation, maintaining in this way the continuity of care [1]. Ideally several LOCs should be integrated into the same ICU, enabling maximal exploitation of staff and equipment resources, and permitting flexibility in satisfying varying clinical demands [1, 10].

Table 33.2 Definition of LOCs in the critical care environment

LOC	Patient characteristics	Nurse/patient ratio	Nurse/bed ratio
III	Two or more acute organ failures	1/1	6
II	One organ failure	1/2	3
I	At risk, requiring monitoring	1/3	2

Table 33.3 Options of ICU care for critically ill patients with cancer

A. No restriction in ICU treatment:
• Newly diagnosed cancer and first line therapy
• Patients with cancer in complete remission
B. Consideration of ICU trial: in this case, repetitive reassessment of patient response with possible limitations in ICU therapy:
• Patients with basically unfavorable prognosis but cannot exclude benefit from ICU stay
• Palliation of symptoms that cannot be controlled outside the ICU
C. No ICU admission:
• Patient and family reject aggressive treatment
• Patient with very serious functional impairment
• Recurring/progressive disease without further treatment options

Many hospital facilities do not adopt this model, but have developed instead in addition to the ICU, separate structures variously characterized as high dependency units (HDU), intermediate care units or step-down units which provide a lower intensity of care, usually corresponding to LOC I. Their LOC is generally suboptimal for patients undergoing invasive mechanical ventilation, but they may care for patients with isolated respiratory failure who need only monitoring or NIPPV, for post-ICU patients, or possibly for relatively stable chronically ventilator-dependent patients. There is no conclusive evidence that separate HDUs have a positive effect in improving patient outcomes and reducing costs compared to the integration of LOC I beds in the ICU. This latter model might permit greater flexibility in bed use and staffing and better utilization of healthcare resources [1, 11–13].

Regardless of the model of ICU care, important aspects in the organization of invasive mechanical ventilation relate to decision-making in two fields: (a) admission and discharge in the ICU and (b) withdrawing/withholding treatment in already admitted patients [14–18]. Such decisions should be taken on an individualized basis, as there are no accurate bedside tools to guide clinical judgment. In every case effort should be made to reach a consensus between the ICU physician, the referring physician, and the patient and family [18–20]. Great differences may be observed in these fields among different countries, because of cultural, religious, and social factors [21, 22] which are often reflected in the legal framework [23]. Economic constraints and a relative dearth of intensive care unit beds in many countries can make such decisions even more complex [14, 15, 24].

As a general rule, a rather broad ICU admission policy should be favored, to avoid inappropriate rejection of patients likely to benefit from life-sustaining treatments. In critically ill cancer patients for example, policies regarding ICU admission can be summarized briefly in Table 33.3. It is emphasized that in these patients,

the number and severity of organ dysfunctions on admission and after 3–5 days of ICU treatment is an important determinant of ICU mortality and should influence decisions regarding withholding/withdrawal of treatment [18, 19].

33.3 Organization of Prolonged Invasive Mechanical Ventilation

A substantial number of patients surviving acute critical illness fails to be weaned off the ventilator, becoming dependent on prolonged mechanical ventilation support (usually defined as mechanical ventilation dependency ≥21 days, ≥6 h/24 h) [25, 26]. Such patients often constitute part of the distinct population of "chronically critically ill" [27, 28].

The approach to such patients is not uniform. Many of them, especially in Europe, continue to be treated in the ICU, with a lower LOC if appropriate. An alternative, mainly practiced in the USA, is treatment in specialized post-acute care facilities, often separate from the acute care hospital, in an effort to reduce costs. These facilities, often without full coverage on site by an attending physician, continue the effort to wean the patient and offer long-term mechanical ventilation and continuing rehabilitation. In case of acute deterioration the patient may have to be transferred for treatment in an acute-care hospital. The financial incentives behind these health structures and the variability and mix in patient population make assessment of the effectiveness of this model of care problematic [25, 27–29].

33.4 Invasive Mechanical Ventilation of Acutely Ill Patients in General Wards

Because of limited ICU bed availability, patients fitting ICU admission criteria have sometimes to be hospitalized for a varying period of time in general wards. The level of care provided in this setting is suboptimal for many reasons: nurse-to-patient ratios ranging from 1:8 to 1:15, (which are very low for mechanically ventilated patients), lack of equipment and technical infrastructure, and lack of skilled personnel [30–32]. These shortcomings result in increased hospital mortality [31–35]. Thus Hersch et al. report an in-hospital mortality of 38% for medical patients ventilated in the ward vs. 20% for patients ventilated in the ICU. In this study, a more active ventilatory management concerning respiratory monitoring and weaning process was observed in the ICU environment, with far less inadvertent events related to the endotracheal tube (20% vs. 62%), owing to close observation and monitoring by the critical care nursing staff [31]. Even limited periods of stay in the ward may have undesirable consequences: delayed (≥6 h) admission to ICU for critically ill surgical patients has been associated with increased mortality [36]. It seems that for mechanically ventilated patients there is an early "critical window of time" during which appropriate management in an ICU setting offers a survival advantage [30].

Table 33.4 Basic requirements for the provision of invasive mechanical ventilation outside the ICU

• Oxygen supply
• Ventilators not requiring compressed air
• Suction
• Monitoring of basic cardiorespiratory parameters (SpO_2, blood pressure, EKG)
• Infusion pumps

In order to bridge the gap between the ICU environment and the wards, various interventions and strategies have been proposed, so as to provide appropriate care to eligible critically ill who have to remain in the wards because of ICU bed unavailability. These strategies are based on the notion of "critical care without walls" which underlines the importance of the level of care required for the patient, rather than the location where this care is provided [37].

To this purpose, rooms with up-graded equipment (Table 33.4) and with higher nurse-to-patient ratio may be provided for mechanically ventilated patients treated in the wards. The use of more basic ventilators requiring only an oxygen supply and not compressed air makes such provisions more feasible. Additionally, ward nurses should acquire basic knowledge and skills necessary to care for mechanically ventilated patients, like suctioning techniques, central iv line care, awareness of endotracheal tube complications, and ability to recognize and respond to any sudden clinical deterioration [38].

The implementation of Rapid Response Teams (RRT) is a complementary approach. RRTs are multidisciplinary in nature and offer critical care services in the wards both to critically ill patients and to clinically deteriorating unstable patients with the aim of preventing their further destabilization [39–42]. Such RRTs may also serve as active surveillance teams performing periodic assessments and problem-solving interventions in mechanically ventilated patients kept on general wards [43]. Besides, RRTs may have a role in the provision of nosocomial end-of-life care in cases deemed futile and in the therapeutic transition toward palliative care [44, 45]. RRTs are activated by the ward staff, and their performance and efficacy are dependent on the staff's competency to anticipate and detect signs of physiological instability and life-threatening conditions [37, 40–42]. It seems that effective deployment of these critical care outreach services has indeed started to improve healthcare delivery and patient outcomes [46–48].

33.5 Surge Capacity Mechanical Ventilation

Surge is defined as an unexpected increase in the demand of services—in our case services of mechanical ventilation, leading to a situation where demand outstrips supply. Such situations are typically observed in mass-casualty events or in the setting of an infectious disease pandemic.

Surge capacity is the ability of the healthcare system to respond to such a crisis. This response relies upon contingency plans aimed to address the need for medical equipment, facility space, and sufficient specialized staff, in order to provide timely, adequate care for the large influx of additional patients.

The optimal initial response should be an escalation in resource utilization, so as to cover increased needs with minimal disruption to normal standards of patient care. Yet, as the capacity of the system becomes exhausted in the context of exceptional circumstances, a reallocation of priorities may become necessary, with a relative degradation of services and shifting of efforts in order to provide limited but essential critical care with basic life-sustaining interventions (Table 33.5) to the maximum possible number of patients [49–51].

The following measures may be considered:

- Critical care capacity can be increased several-fold through the recruitment of available beds with monitoring equipment (intermediate or post-anesthesia care beds, emergency care beds) and finally through the recruitment of general ward beds that could be outfitted with the minimum functional requirements needed to provide ventilation care with safety (Table 33.4) [50–52].
- Canceling elective surgical operations, diversion of patients to neighboring facilities thus freeing up local resources.
- In order to address the short supply of qualified critical care personnel, personnel with appropriate credentials currently employed in non-ICU settings can be reallocated to the ICU [50, 53]. Policies involving an extension of working hours, modification of patient-to-provider ratios (i.e., more patients per provider), and postponing of vacations may also be implemented [50, 53]. Mobilization of healthcare professionals from outside the affected area, who are willing to volunteer their assistance in an emergency, is another option [53]. Finally, when a very large surge of mechanically ventilated patients is anticipated, as it may happen during the initial phase of a developing infectious disaster, patient care may have to rely on "just-in-time" training of staff to assist in the management of patients who require mechanical ventilation [53].

Planning and preparedness efforts of institutions' authorities may involve the acquisition and stockpiling of limited-feature, less expensive mechanical ventilators (Table 33.6), as well as consumable ancillary equipment and supplies [51, 54–57].

Particular emphasis should be placed on the need for communication and coordination between healthcare institutions during a pandemic in order to enhance and facilitate planning, interaction, optimal sharing of medical resources, and distribution of patient load between individual hospitals [50, 57, 58].

Table 33.5 Life-sustaining therapeutics and interventions during mass critical care events

• Mechanical ventilation
• Iv fluid resuscitation
• Sedatives and analgesics
• Vasopressors/inotropes administration
• Antibiotics or antidotes administration for specific diseases
• Nutritional support
• Renal replacement therapy

Table 33.6 Recommended ventilator performance characteristics for mass casualty respiratory failure

• Portable, rugged, light weight (<10 kg)
• Inexpensive to purchase and maintain
• User-friendly
• Ability to adequately oxygenate and ventilate adult and pediatric patients
• Ability to operate with low-flow oxygen and not requiring compressed air
• Battery life ≥4 h to allow for transportations and supply during intermittent power failure
• Volume control ventilation with optional pressure control ventilation
• Operator control of minimum respiratory rate, tidal volume, PEEP, and FiO_2
• Monitoring of airway pressure and tidal volume
• Appropriate alarms recognizing high airway pressure, low airway pressure (leak), low source gas pressure, patient apnea, and circuit disconnection

Regional and local government authorities and public health officials should cooperate with healthcare experts and leadership, to develop formal legal disaster activation mechanisms in order to implement, and support surge response plans and standards of care [58].

33.6 Organization of Noninvasive Mechanical Ventilation in the Acutely Ill Patient

In recent decades, noninvasive positive pressure ventilation (NIPPV) has become an established approach for selected patients with isolated respiratory failure, especially in the context of chronic obstructive pulmonary disease (COPD) exacerbations, cardiogenic pulmonary edema, or neuromuscular disease. NIPPV is also an option in hematology-oncology patients with acute hypoxemic respiratory failure in the context of severe immunosuppression [59–63], as in these patients, invasive mechanical ventilation is associated with very high mortality.

NIPPV can be delivered in a number of different locations, including ICU, high dependency units (HDU), emergency departments, and general (mainly respiratory) wards. The selection of location depends on the patient's acuity of respiratory compromise and the risk of NIPPV failure and subsequent emergent intubation.

There are some concerns when NIPPV is applied in the wards, especially as regards detection of NIPPV-related adverse events (air leakage, accidental breathing circuit disconnection, patient-ventilator asynchrony, mask intolerance) and timely detection of NIPPV failure requiring intubation [64]. Thus more severely compromised patients (in particular patients with acute hypoxemic respiratory failure) are best managed in critical care beds with a LOC of at least I (HDUs or ICUs) in order to ensure more intensive care, continuous observation, and early identification of sudden deterioration [65–69].

Nevertheless NIPPV has been implemented successfully in some categories of appropriately selected patients in the wards (Table 33.7). Success of NIPPV in this setting depends on the involvement of skilled professionals (a critical care outreach team, a multidisciplinary dedicated NIPPV team, or even an eager clinician committed to developing NIPPV) [68, 70]. These persons will have to identify the appropriate clinical area where NIPPV is to be based, matching the patient's need for monitoring with the unit's capabilities and also ensuring the provision, maintenance, and safety of suitable equipment (Table 33.8). They will also be responsible for the adoption, implementation, and update of specific protocols as regards indications, method of delivery, and patient monitoring. Finally, they must also organize training for staff (Table 33.9) [68, 70].

NIPPV has been increasingly used as a palliative strategy in patients with end-stage disease, when endotracheal intubation is deemed futile. In these patients, NIPPV can either be administered to reverse the acute deterioration and offer a chance for survival, or to alleviate the symptoms of respiratory distress, relieve patient's suffering and offer the best possible quality of life for patients and their families [19, 63, 71, 72]. NIPPV for palliative reasons may also be performed either in a critical care setting or in the wards by appropriately trained staff [19, 63, 71, 72].

Table 33.7 NIPPV application in the wards

• Hypercapnic COPD exacerbations
• Cardiogenic pulmonary edema
• Obesity-hypoventilation syndrome
• Ventilatory failure due to neuromuscular disease or chest wall deformity

Table 33.8 Minimum equipment requirements for NIPPV delivery in the wards

• Portable NIPPV ventilators
• Different sizes and models of interfaces
• Pulse oximetry
• EKG
• Noninvasive blood pressure monitoring
• Arterial blood gas sample analysis

Table 33.9 Minimum staff requirements for NIPPV delivery in the wards

• Clinical evaluation of patient and ability to recognize signs of NIPPV failure
• Ability to adjust the mask in order to achieve comfort with minimum air-leak
• Identification of air leaks and patient–ventilator asynchrony
• Modification and adjustment of ventilator parameters according to the patient's clinical response

Conclusion

Invasive mechanical ventilation is one of the most demanding and widely used supportive techniques in the critically ill patient. Balancing patients' needs for appropriate level of care with the available healthcare resources is a great challenge. The growing demand of ICU beds and limitations of bed availability place pressure on healthcare systems and resources and emphasize the need for flexible responses of the healthcare system.

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Acute Respiratory Failure After Hematopoietic Stem Cell Transplantation

34

Meaghen Finan and Stephen M. Pastores

Key Points

1. Pulmonary complications occur in up to 60% of HSCT recipients and are the leading cause of respiratory failure requiring mechanical ventilation and ICU admission.
2. Infectious complications are time dependent, with bacterial pneumonias and invasive fungal infections common during the pre-engraftment period and viral pneumonias (especially cytomegalovirus) and other opportunistic infections during the early and post-engraftment phases.
3. Unique noninfectious pulmonary complications include peri-engraftment respiratory distress syndrome, diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome.
4. Risk factors for respiratory failure include older age, active malignancy, donor-recipient marrow HLA mismatch, and pretransplant abnormal pulmonary function tests.
5. HSCT recipients requiring invasive mechanical ventilation continue to have high mortality rates (80–90%).

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34.1 Introduction

Hematopoietic stem cell transplantation (HSCT) is used to treat over 50,000 patients with malignancies every year worldwide [1]. In 2014, >40,000 HSCT in 36,469 patients (15,765 allogeneic (43%), 20,704 autologous (57%)) were reported by 656 centers in 47 countries in Europe [2]. Patients may receive autologous HSCT, wherein hematopoietic stem cells are collected from the patient prior to the administration of high dose chemotherapy to treat the underlying malignancy followed by reinfusion of these cells, or allogeneic HSCT, where stem cells are harvested from the bone marrow or peripheral blood of matched or unmatched, related or unrelated donors or from umbilical cord blood. The most common indications for autologous HSCT are multiple myeloma and non-Hodgkin lymphoma and the vast majority of allogeneic transplants are performed for acute myeloid and lymphoid leukemias and myelodysplastic syndrome [2].

Improved conditioning regimens, human leukocyte antigen (HLA) typing, supportive care, and prevention and treatment of serious infections have significantly reduced transplantation-related mortality and morbidity [3]. Nevertheless, HSCT recipients can face multiple complications relating to the underlying malignancy, the conditioning received prior to transplant, as well as posttransplant infections.

Traditionally, the posttransplant course is divided into three phases reflecting the recovery of immune system: pre-engraftment phase (0–30 days), early posttransplant (days 30–100), and late posttransplant (>100 days). Pulmonary infectious and noninfectious complications are common, occurring in up to 60% of HSCT recipients and are the leading cause for ICU admission and respiratory failure requiring initiation of mechanical ventilation [4–6].

Specific infectious and noninfectious pulmonary complications occur depending on the phase of recovery (Fig. 34.1). This chapter will provide a brief overview of the causes of respiratory failure among HSCT patients, risk factors for mechanical ventilation, treatment strategies, and prognosis.

34.2 Risk Factors for Respiratory Failure and Need for Mechanical Ventilation

A recent report showed that among HSCT recipients admitted to the ICU, 42–88% of HSCT patients received mechanical ventilation for respiratory failure [7]. Risk factors for the development of respiratory failure include older age, active malignancy, and donor-recipient marrow HLA mismatch. Patients who were found to have pretransplant abnormal pulmonary function tests (e.g., restrictive physiology, total lung capacity <80%) had twice the risk for respiratory failure [8].

34.3 Infectious Causes of Respiratory Failure

Infection is more common in allogeneic than in autologous HSCT patients due to prolonged immunosuppressive therapy and graft-versus-host disease (GVHD). Although the timing of infections may suggest a diagnosis, some presentations are

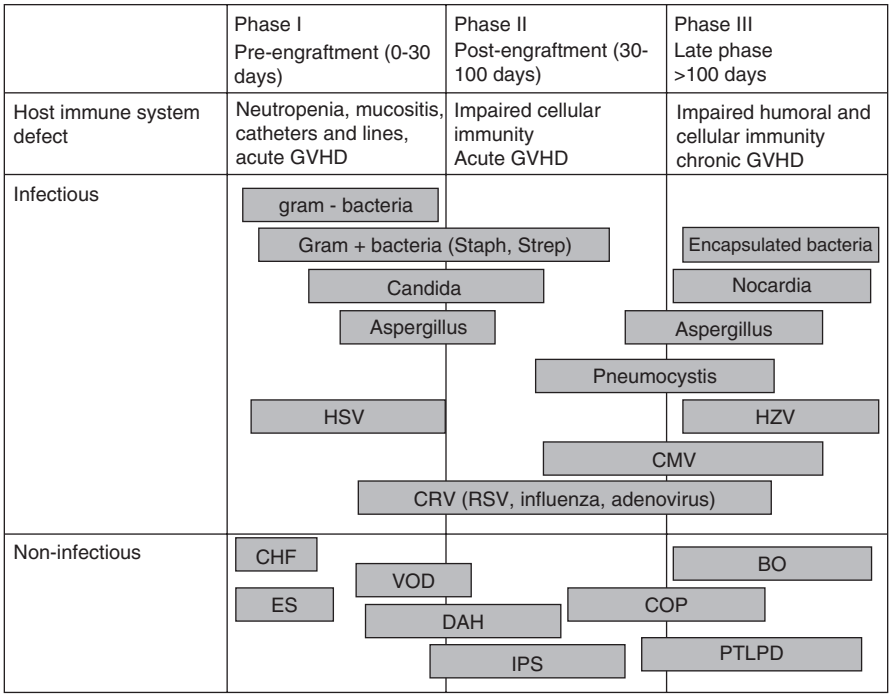

Fig. 34.1 The timeline of pulmonary complications following hematopoietic stem cell transplantation (HSCT). *BO* bronchiolitis obliterans, *CHF* congestive heart failure, *CMV* cytomegalovirus, *COP* cryptogenic-organizing pneumonia, *DAH* diffuse alveolar hemorrhage. Amy K. Chi, Ayman O. Soubani, Alexander C. White, Kenneth B. Miller. An Update on Pulmonary Complications of Hematopoietic Stem Cell Transplantation. Chest, Volume 144, Issue 6, 2013, 1913–1922

atypical. Fiberoptic bronchoscopy can be valuable especially if performed early, yielding a diagnostic pathogen in 55% of patients [4]. However, because bronchoscopy may cause respiratory deterioration with less than half of them revealing definitive diagnoses, other modalities should be considered for diagnosis of pulmonary infection in HSCT patients. These include noninvasive strategies such as nasopharyngeal washings or swabs sent for immunofluorescence antibody or multiplex polymerase chain reaction (PCR) testing for respiratory viruses and culture, blood cultures, sputum studies, and imaging studies (chest radiography and computed tomography (CT)).

During the pre-engraftment phase (0–30 days post-HSCT), the transplant recipient develops defects in mucocutaneous barriers as well as neutropenia, which predisposes to bacterial and fungal (especially Candida) infections. In a study of 427 consecutive allogeneic HSCT recipients, bacterial pneumonia developed in the first post-HCT month in 4%, fungal pneumonia in 9%, and viral pneumonia in 2%; 4% percent of patients who had suspected pneumonia had no specific organism identified [9]. The most common bacterial organisms causing pneumonia were *Escherichia coli*, *Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*.

Community acquired respiratory viruses including respiratory syncytial virus (RSV), influenza, and parainfluenza may also cause pulmonary infections, with RSV the most common. Untreated RSV pneumonia is associated with a high mortality (up to 80%). Treatment consists of aerosolized ribavirin and IV immunoglobulin. More recently, influenza A subtype H1N1 infection in HSCT patients was associated with a 28-day mortality rate of 7 and 19% at 4 months post diagnosis [10].

Among the fungal infections, invasive pulmonary aspergillosis is the most common with a reported incidence of 5–30% in allogeneic and 1–5% in autologous HSCT [4]. Prophylaxis with voriconazole or posaconazole is recommended for HSCT patients who remain neutropenic for >14 days and those on immunosuppressive treatment for GVHD. Screening measures in high risk patients include pretransplant ferritin level >1000 ng/mL, Aspergillus galactomannan, serum beta-D-glucan, or serum Aspergillus PCR testing. Imaging with high resolution chest CT is recommended with radiographic findings such as halo sign (nodule surrounded by ground-glass attenuation), hypodense sign (low density within nodules), and cavitation in late stages suggestive for aspergillosis. Treatment of choice is voriconazole, although there is increased risk of secondary infection with mucormycosis. Failure with voriconazole alone may require treatment with liposomal amphotericin B, combination therapy (echinocandins with voriconazole), or surgical intervention. Despite therapy, survival at 1 year is 20%. Other fungal species such as Zygomycetes (Mucor, Rhizopus), Fusarium, and Scedosporium require surgical resection of localized lesions. The diagnosis and treatment of *Pneumocystis jiroveci* pneumonia is identical to nontransplant patients.

In the early post-engraftment phase (30–100 days), impaired cellular and humoral immunity are the main factors contributing to pulmonary infection with cytomegalovirus (CMV) pneumonitis being a major concern. Older patients, positive CMV serology, allogeneic grafts, and GVHD are risk factors. Although ganciclovir has been used for CMV prophylaxis, it causes myelosuppression. Recent studies have shown comparable viral clearance with valganciclovir [4]. The gold standard for diagnosis of CMV pneumonitis is by lung tissue biopsy demonstrating viral inclusion bodies. However, CMV may be diagnosed presumptively by PCR testing of blood or bronchoalveolar fluid, clinical symptoms (fever, nonproductive cough, dyspnea, and hypoxemia), and CT imaging demonstrating ground glass attenuation, parenchymal opacification, or innumerable small (<5 mm) nodules. Treatment requires ganciclovir and CMV immunoglobulin. Treatment failure is associated with high mortality (>90%) particularly for those patients who progress to respiratory failure.

34.4 Noninfectious Causes of Respiratory Failure

The noninfectious causes of respiratory failure in HSCT patients include pulmonary edema of cardiogenic or noncardiogenic etiology and lung parenchymal damage secondary to the preparative conditioning regimen and/or radiation. Although

capillary leak syndrome may be the culprit, pulmonary edema in HSCT recipients is most commonly secondary to the volume of blood and blood products given during the pre-engraftment phase and immediate posttransplant period. Plasma B-type natriuretic peptide is usually elevated and the echocardiogram reveals left ventricular dysfunction.

There are unique acute pulmonary syndromes that are described following HSCT. These include peri-engraftment respiratory distress syndrome (PERDS), diffuse alveolar hemorrhage, and idiopathic pneumonia syndrome.

34.4.1 Peri-engraftment Respiratory Distress Syndrome (PERDS)

Engraftment syndrome is more common in autologous HSCT patients, with an incidence of up to 11% [4]. Clinical characteristics include fever, non-drug induced erythematous rash, noncardiogenic pulmonary edema, and hypoxemia occurring within 96 h of engraftment. PERDS is attributed to the release of proinflammatory cytokines, such as interleukin (IL)-2, tumor necrosis factor-α, interferon-γ, IL-8 and IL-6, macrophage colony-stimulating factor, and erythropoietin that precedes neutrophil engraftment. Use of granulocyte colony-stimulating factor (G-CSF) has been identified as a risk factor. Major criteria for diagnosis include fever without infectious etiology, rash involving more than 25% total body surface area and pulmonary edema. Minor criteria include hepatic dysfunction, renal insufficiency, weight gain of 2.5% of baseline body weight, and transient encephalopathy. Three major criteria or two major criteria and one minor criterion are typically required for diagnosis. Discontinuation of G-CSF is recommended as well as corticosteroids (methylprednisolone 1–1.5 mg/kg/day) for severe cases. Up to one-third of patients require ICU admission and mechanical ventilation [4, 7].

34.4.2 Diffuse Alveolar Hemorrhage (DAH)

Diffuse alveolar hemorrhage may occur in the pre-engraftment or early post-engraftment phases. It occurs equally in autologous and allogeneic recipients, with an overall incidence of 4%. Patients at greatest risk include those over 40 years old, those that underwent total body irradiation, presence of fever, severe mucositis, acute GVHD, renal insufficiency, and HSCT for solid tumors. Neither platelet level nor type of conditioning appears to play a role in the development of DAH. It is hypothesized that DAH is induced by neutrophil infiltration of the lung accentuating alveolar hemorrhage induced by chemotherapy/radiation or occult infection. The diagnosis of DAH is suggested by dyspnea, nonproductive cough, fever, diffuse interstitial infiltrates of the middle and lower lung zones, and confirmed by progressively bloody BAL fluid samples from three separate lung subsegments [4]. Treatment with corticosteroids is recommended given the high mortality associated with this syndrome. Platelet transfusion is of limited value. Mortality is commonly due to superimposed multiorgan system failure or sepsis.

34.4.3 Idiopathic Pneumonia Syndrome (IPS)

Idiopathic pneumonia syndrome represents a pattern of diffuse lung injury for which no pathogens are identified and is considered to be the result of intensive chemotherapy and radiation. It usually occurs in the early post-engraftment phase. It has been hypothesized that TNF-α and donor T cell effectors play a role in lung injury. Risk factors include old age, low performance status, transplantation for solid tumors, high intensity conditioning, total body irradiation, GVHD, and positive donor CMV serology. IPS is less common in autologous than in allogeneic recipients (5.7% vs. 7.6%, respectively). Diagnosis is made by radiologic evidence of diffuse alveolar injury, negative infectious workup including BAL, lung biopsy (if performed) demonstrating alveolar damage or interstitial pneumonitis, and the absence of iatrogenic volume overload or cardiac or renal dysfunction. Chest radiograph may show non-lobar infiltrates. Small studies have shown improvement with etanercept (TNF-α binding protein) as well as etanercept and corticosteroids [4]. High dose steroids alone do not appear to be effective. Progression of disease is rapid with nearly two-thirds of patients requiring mechanical ventilation. Mortality rates with IPS ranges from 60 to 86% with 1 year survival rate less than 15%.

34.4.4 Late Noninfectious Complications

Noninfectious pulmonary complications in the late posttransplant phase include bronchiolitis obliterans (BO) and cryptogenic organizing pneumonia (COP) especially in those patients with chronic GVHD [4]. Bronchiolitis obliterans occurs mainly in allogeneic transplant recipients, with an average incidence of 8%. Risk factors for BO include progressive chronic GVHD, age >20 years, prior evidence of airflow obstruction, respiratory infections, unrelated donor, total body irradiation >12 Gy, low pretransplant serum surfactant D protein level, and NOD2/CARD15 genetic polymorphism. Several pathogenetic mechanisms have been suggested including lung injury caused by conditioning regimens, injury secondary to infectious etiology, recurrent aspirations-microaspirations or due to esophagitis-associated GVHD, or donor T cells targeting epithelial cells of bronchioles, leading to inflammation and damage. The majority of patients report dry cough and wheezing. Up to 25% experience upper respiratory tract symptoms; conversely, 20% of patients are initially asymptomatic. Diagnosis is made based on clinical characteristics, chest CT findings (air trapping, hyperinflation, ground-glass opacities), pulmonary function tests (PFTs) demonstrating new onset airflow obstruction, and no evidence of infection (including negative BAL). Biopsy is generally discouraged as the disease is patchy and peripheral, and samples may not show pathology. Patients may experience slow progression with occasional exacerbations. Some patients may develop recurrent respiratory infections and colonization with Pseudomonas, Staphylococcus aureus, and Aspergillus, while others may progress rapidly to respiratory failure within a few months. Treatment is aimed at slowing and stabilizing the disease with recommendations based on small trials and expert opinions. Generally,

high dose corticosteroids are given; adjunctive therapies include augmentation of immunosuppressive therapy with cyclosporine A or tacrolimus, and potentially macrolides. Promising new directions include use of inhaled corticosteroids, extracorporeal photodynamic therapy, and anti-TNF-α monoclonal antibodies. Lung transplantation has been successful in a minority of patients. Mortality is 18% at 10 years, whereas attributable mortality in those with GVHD is 40% at 10 years. Age over 60 years, progressive chronic GVHD, disease relapse, respiratory viral infections, and rapid deterioration of PFTs are associated with higher mortality [5, 6].

Cryptogenic organizing pneumonia (formerly known as bronchiolitis obliterans organizing pneumonia) occurs in the early posttransplant period and is more common in allogeneic recipients with an incidence of 2%. It usually occurs within the first 100 days. Patients at risk for COP include those with leukemia, radiation exposure, and presence of GVHD. Clinical presentation includes fever, nonproductive cough, and dyspnea. Diagnosis is made by clinical characteristics, radiography showing patchy peripheral consolidations/ground glass opacities, PFTs with restrictive pattern with no airflow obstruction, decreased diffusing capacity, and negative infectious workup including negative BAL. Biopsy is required for definitive diagnosis. Patients generally respond well to systemic corticosteroids with up to 78% resolving or remaining stable. Case fatality rate approaches 20% [4, 5, 7].

34.5 Ventilatory Support and Supportive Care Measures

Despite advances in the treatment of infectious and noninfectious causes of respiratory insufficiency in HSCT patients, HSCT recipients who end up requiring intubation and invasive mechanical ventilation have extremely high mortality (80–90%) [7]. Noninvasive positive pressure ventilation (NIPPV) has been shown to reduce endotracheal intubation rates in HSCT patients. Thus, early application of NIPPV in HSCT patients with reversible causes of respiratory failure should be strongly considered.

In general, ventilator management strategies for HSCT patients with respiratory failure are similar to non-HSCT patients. The use of lower tidal volumes and conservative fluid management for patients with ARDS, early and appropriate antibiotics and fluid and vasopressor therapy for sepsis, and use of corticosteroids for DAH and PERDS are integral to the management of the critically ill HSCT recipient.

34.6 Prognosis and Outcomes

Mortality for HSCT patients requiring mechanical ventilation in the 1990s approached 100%. With advances in ventilation strategies, supportive therapies, early diagnosis, and prophylaxis for varying opportunistic infections, it would seem that mortality rates would decrease. However, mortality for the intubated HSCT patient remains high ranging from 80 to 90% and is 94–100% with the onset of multiorgan failure [7]. Risk factors for poor prognosis include advanced age,

coexisting comorbidities, lower functional status, allogeneic transplant, progression of underlying disease, and high dose conditioning. Although there are multiple scoring systems to calculate mortality on intensive care unit (ICU) admission (e.g., Acute Physiology and Chronic Health Evaluation II, III, IV, Mortality Probability Model II, III), there is limited data evaluating these models in HSCT patients.

Despite the high mortality of HSCT patients requiring intubation, there are no validated criteria for admission to the ICU for these patients. Because the HSCT physicians are extremely familiar with the patient's entire course, their input is needed when deciding to institute a trial of ICU care in clinically deteriorating HSCT patients. In the event an unfavorable outcome is expected, transition to palliative care measures should be discussed with these patients and their families early in the ICU course. These discussions should be held in conjunction with the transplant teams to ensure that the most appropriate goals of care and therapeutic interventions are provided to this high-risk patient population.

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