Noninvasive Oxygen Therapies in Oncologic Patients

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Abstract

Acute hypoxemic respiratory failure (ARF) is the most common cause of critical illness in oncologic patients. Despite significant advancements in survival of oncologic patients who develop critical illness, mortality rates in those requiring invasive mechanical ventilation have improved but remain high. Avoiding intubation is paramount to the management of oncologic patients with ARF. There are important differences between the oncologic patient with ARF compared to the general ICU population that likely underlie the increased mortality once intubated. Noninvasive oxygen modalities have been recognized as an important therapeutic approach to prevent intubation. Continuous low-flow oxygen therapy, noninvasive ventilation, and high-flow nasal cannula are the most commonly used noninvasive oxygen therapies in recent years. They have unique physiologic
properties. The data surrounding their efficacy in the general ICU population and oncologic population has evolved over time reflecting the changes in the oncologic population. This chapter reviews the three different noninvasive oxygen modalities, their physiologic impact, and evidence surrounding their effectiveness.

**Keywords**
High-flow nasal cannula · High-flow oxygen therapy · Low-flow oxygen therapy · Continuous oxygen therapy · Noninvasive ventilation · Acute respiratory failure · Acute respiratory distress syndrome · Oncologic critical care · Immunocompromised

**Introduction**

Acute hypoxemic respiratory failure (ARF) is the most common cause of critical illness in oncologic patients [1–3]. Avoiding intubation is paramount to the management of oncologic patients with ARF. The risks associated with intubation are pronounced in the immunocompromised and oncologic population. These risks include numerous infectious, musculoskeletal, respiratory, and neurologic complications. Oncologic patients may present with a greater frequency of frailty at the time of critical illness, a higher likelihood of succumbing to aggressive or drug-resistant pathogens or they may experience a blunted or dysregulated host response [4–6]. As such, patients who progress to require invasive mechanical ventilation are subject to increased mortality compared to the general ICU population [7].

In hypoxemic oncologic patients, noninvasive oxygen therapy may be delivered via simple face mask (continuous oxygen therapy (COT)), noninvasive ventilation (NIV), or high-flow nasal cannula (HFNC). Earlier studies in immunocompromised patients receiving NIV compared to COT suggested a reduced need for intubation [6, 8]. This resulted in adoption of NIV as a noninvasive strategy to support oncologic patients in an attempt to prevent intubation. However, these results have been called into question in recent years [9]. Furthermore, we have recently seen the development of HFNC with promising preliminary results across the general ICU population. It is unclear whether these promising results with HFNC translate to the oncologic population. With the goal to reserve intubation in those failing noninvasive oxygenation strategies, there remains a need to better understand these therapies in this unique population.

This chapter will focus on the rationale for preventing intubation in the oncologic population, the mechanisms of the various noninvasive oxygen modalities, evidence-to-date of these modalities across the general and oncologic patients, and future areas of consideration.

**Spectrum of ARF in Oncologic Patients**

The number of living patients with cancer has been increasing steadily over the last several years [10]. The spectrum of ARF in oncologic patients varies widely and may be induced by the underlying malignancy or be secondary to treatment-associated toxicities (Fig. 1).

**What Is Unique About ARF in Oncologic Versus Nononcologic Patients**

While mortality across critically ill oncologic patients has decreased significantly in recent decades with advancements in oncologic and critical care, mortality across ARF and acute respiratory distress syndrome (ARDS) remains high [11]. There are a series of factors that are theorized to be underlying this increased mortality. A thorough understanding of these factors is necessary when considering which noninvasive oxygen strategy one may choose.

**Cause of ARF**

ARF in the oncologic patient can broadly be categorized into disease-associated ARF and treatment-associated ARF. Disease associated causes of respiratory failure include tumor infiltration into the airway, pulmonary leukostasis, leukemic infiltrates, and malignant pleural effusions among others. Treatment-associated
toxicities may occur early during treatment (tumor lysis syndrome, cytokine release syndrome, all-transretinoic acid differentiation syndrome), at the height of treatment effect (neutropenic-associated infectious complications), during recovery (neutrophil reconstitution or engraftment syndrome associated with ARDS), or as a late toxicity (cardiomyopathy, pulmonary pneumonitis). These causes are unique to the oncologic population. While infectious etiologies remain the most common culprit, a higher proportion of non-infectious causes are noted in this population. Therefore, an accurate understanding of the differential is imperative to guide early recognition, anticipation of deterioration, and institution of appropriate supportive care and treatment. Recognizing and projecting the reversibility of the underlying cause is an important factor in deciding on the noninvasive or invasive modality one may choose as first line.

Diagnostic Challenge
Undiagnosed ARF is associated with a high mortality [12]. Given this, meticulous attention over previous decades has been dedicated to the optimal approach to diagnostic evaluation of pulmonary infiltrates and ARF in the oncologic population. Diagnostic workup often includes, a series of noninvasive serum and sputum microbiologic tests (sputum cultures, induced sputum for pneumocystic jirovecii pneumonia, cytomegalovirus serum evaluation, serum galactomannan, nasopharyngeal swab for viral polymerase chain reaction, etc.), imaging modalities (CT thorax, echocardiography if hydrostatic pulmonary edema is considered), and possible fiberoptic bronchoscopy for further microbiologic evaluation if no diagnosis has been yielded. This investigative workup is often more invasive and requires more imaging and transportation for the oncologic population compared to the general ICU population.

Frailty
Oncology patients represent a subgroup particularly susceptible to frailty. During intensive treatments, patients may be exposed to transient illnesses, hospitalizations, interruption in normal nutrition regimens, steroids, limited mobility due to toxic side effects, and recovery from surgery. All of these factors potentially put them at higher risk of developing frailty, particularly precritical
illness. Frailty is increasingly being recognized as an important determinant of duration of mechanical ventilation, ICU survival and ICU functional recovery [13–15]. In this population, significant loss of muscle mass that may occur during treatment puts them at higher risk of frailty or prolonged mechanical ventilation due to the development of diaphragmatic dysfunction in the setting of ARF.

**Increased Mortality**

Over the last decade, there has been consistent evidence suggesting that oncologic patients with ARF who undergo invasive mechanical ventilation face a significantly increased risk of poor survival and functional outcomes [2, 16]. Although this association might be explained partially by indication bias, making it challenging to confirm a true causal effect, it is widely accepted that the initial oxygen delivery strategy is a key factor while approaching the management of ARF in this vulnerable population. Mortality across oncologic patients who require invasive mechanical ventilation can range from 40% to 50% and can reach as high as 80% in a certain subset of oncologic patients (i.e., allogeneic hematopoietic stem cell transplant patients, invasive fungal infections) [2, 17]. Risk factors for mortality are outlined in Table 2.

**Long-Term Outcomes Trajectory**

Despite evidence of a high mortality in the face of ARF, there is a paucity of data on the long-term outcomes of oncologic patients with ARF. What is unique about this population compared to the general population of ARDS survivors is that they have a potentially reversible underlying comorbid condition, and therefore their functional recovery and diseased trajectory could follow a different path. More data is needed to further delineate this dedicated to this population [11, 18].

**Hematologic Malignancy Versus Solid Tumor**

Outcomes of oncologic patients who develop critical illness have improved over the years with reports mirroring, in some studies, mortality rates across the general ICU populations. Critical illness is often associated with a higher severity of illness and, as a result, higher mortality [19, 20]. The more profound and prolonged nature of the immunocompromised state that is achieved, as a consequence of intensive curative therapies, render this vulnerable population to a greater risk of bacterial, viral, and invasive fungal infections. Noninfectious etiologies unique to the hematologic malignancy population include pulmonary leukostasis, pulmonary leukemic infiltrates, lung alveolar proteinosis in the setting of tumor lysis syndrome, alveolar hemorrhage, differentiaion syndrome and capillary leak as a subset of treatment-associated toxicities, cytokine release syndrome-inducing ARDS, immune reconstitution-associated ARDS in the setting of neutrophil recovery, and radiation-associated pneumonitis [21]. In the allogeneic hematopoietic stem cell transplant, additional causes include engraftment syndrome, diffused alveolar hemorrhage, idiopathic pneumonia syndrome, and acute/chronic graft versus host disease [22, 23].

**Noninvasive Oxygen Modalities**

Noninvasive oxygenation strategies in the oncologic patient can be delivered by conventional face-mask oxygen therapy (COT), noninvasive ventilation (NIV), and high-flow nasal oxygen cannula therapy (HFNC). Each of these techniques have unique physiological considerations and important advantages and disadvantages that must be understood so that a clinician can deliver safe, effective, and personalized therapy to this high-risk patient population (Table 1). The following section will discuss the basic physiologic principles, advantages, and possible disadvantages of each.

**Continuous Oxygen Therapy**

Oxygen delivered to spontaneously breathing patients is most commonly delivered by masks. Broadly speaking, oxygen can be delivered by simple, partial rebreathing and non-rebreathing masks. Flow rates range from 6 L/min (simple) to 15 L/min (non-rebreather) with a fraction of
inspired oxygen (FiO2) of approximately 30–90% [24]. The advantages to COT is its noninvasive nature and its portability.

One of the major limitations of conventional face-mask oxygen delivery systems is the limited inspiratory flow rate it can deliver. In the setting of respiratory distress, the inspiratory flow rate of dyspneic patients often greatly exceeds the upper limit of flow rates delivered by these conventional systems and a significant entrainment of ambient air limits the delivery of the targeted FiO2. As a result, oxygen delivery to the alveoli is the resultant fractions of high FiO2 at a fixed delivered rate and ambient air (0.21) at a rate determined by any excessive inspiratory flow generated by a patient in respiratory distress. The greater the entrainment of ambient air, the greater dilution of the alveolar FiO2. Furthermore, an additional shortcoming of COT is its lack of ability to provide any alveolar recruitment in the setting of a consolidated lung. Alveolar recruitment may result in a decreased need for excessive FiO2 delivery through recruitment of additional alveoli to participate in gas exchange. In the absence of this recruitment, a patient on COT may be exposed to unnecessarily high concentrations of inspired oxygen to maintain a sufficient saturation. The resultant negative effect of a prolonged exposure to high oxygen delivery is potentially oxygen toxicity which has been found to be associated with an increased mortality [25]. While we conceptualize oxygen toxicity as having the greatest harm in those with excessive dissolved oxygen content leading to excessive reactive oxygen species, the local toxic effect of the administration of high oxygen concentration of inspired O2 has also been described leading to tracheal and bronchial irritation, impaired mucociliary clearance and surfactant impairment, alterations in microbial flora in the upper airways and alveolar nitrogen washout leading to absorptive atelectasis. Therefore, in critically ill patients, NIV and HFNC may be more attractive options to temporize or reverse acute respiratory failure given some mechanisms described below.

Table 1 Benefits and pitfalls of noninvasive oxygen modalities

| Benefits                                                                 | Pitfalls                                                                 |
|--------------------------------------------------------------------------|--------------------------------------------------------------------------|
| **Continuous low-flow oxygen therapy**                                   | In patients with high work of breathing, they may entrain a high volume of room air dissolving the delivered alveolar oxygen content  |
| Comfortable                                                              | Local toxic effects of high inspired FiO2                                 |
| Ease of application                                                      |                                                                          |
| Amenable for transportation                                              |                                                                          |
| Does not impair cough/secretion management                               |                                                                          |
| **Noninvasive ventilation**                                              | Decrease in preload or increase in right ventricular afterload could precipitate or exacerbate shock  |
| Continuous PEEP to facilitate recruitment to support tidal volumes during poor compliance or fatigue  | Secretion clearance challenging with face mask interface                  |
| Recruitment and decrease work of breathing may facilitate a decreased in FiO2 requirements  | Potential for injurious ventilation particularly in the setting of a high work of breathing |
| Decrease in preload/afterload in the setting of a cardiogenic pulmonary edema  | May delay or impair administration of evidence-based ICU therapies or workup (nutrition, mobility, imaging, bronchoscopy) |
| Amenable for transportation                                              | Facemask interface uncomfortable by some                                   |
| **High-flow nasal cannula**                                              | Cannot transport                                                         |
| Comfortable                                                              | Uncertainty surrounding levels of generated PEEP based upon patient features |
| Heated and humidified oxygen enhances mucociliary clearance              | Highest flows may be considered uncomfortable by some                    |
| Possible generation of PEEP to facilitate recruitment                   |                                                                          |
| High flows help prevent entrainment of room air thus minimizing dilution of administered oxygen  |                                                                          |
| Deadspace washout may contribute to decreasing work of breathing         |                                                                          |
| Can facilitate fiberoptic bronchoscopy                                   |                                                                          |
| **PEEP** positive end expiratory pressure                                 |                                                                          |
Noninvasive Ventilation

NIV refers to the delivery of positive pressure by devices other than an endotracheal tube [26]. In the critical care setting, NIV is most often delivered by application of a full oro-nasal facemask, but can be delivered through a nasal apparatus, or through use of a helmet [27]. When delivering NIV, clinicians will set an appropriate FiO₂, an inspiratory positive airway pressure (IPAP) and an expiratory positive airway pressure (EPAP).

The EPAP is synonymous with positive end-expiratory pressure, commonly referred to as PEEP. This is the positive pressure level (in cmH₂O) that is present at the end of expiration [26]. IPAP refers to the level of inspiratory pressure delivered. The difference between the delivered IPAP and EPAP will determine the amount of pressure support and amount of delivered tidal volume. Nomenclature for NIV settings is best demonstrated with an example: with an IPAP of 10 cmH₂O and an EPAP of 5 cmH₂O, a patient will receive a total inspiratory pressure of 10 cmH₂O with a PEEP of 5 cmH₂O. This patient will receive 5 cmH₂O of pressure support above their baseline pressure of 5 cmH₂O.

From a physiological perspective, the delivery of positive pressure has important implications. Positive pressure may improve arterial oxygenation through re-expansion of collapsed or atelectatic alveoli, redistribution of lung edema, and reducing areas of ventilation-perfusion mismatch [28]. Importantly, this oxygenation improvement is reliant on recruitable lung segments and avoidance of overdistension of normal pulmonary parenchyma [29]. In addition to changes in oxygenation, lung recruitment has important effects of respiratory mechanics. Lung compliance can improve when atelectatic alveoli are recruited or be reduced in situations of overdistension. These mechanisms may also result in the ability to decrease the FiO₂ delivered to the patient minimizing the potential risks associated with direct toxicity related to high inspired oxygen.

Heart–lung interactions must be considered when delivering positive pressure via NIV, and the clinician should appreciate and anticipate the potential hemodynamic alterations. Classically, positive pressure can affect hemodynamic performance through a variety of mechanisms. Positive pressure delivered may result in a decrease in right ventricular preload, a variable impact on right ventricular afterload, augment left ventricular preload through propelling blood volume from the pulmonary capillaries into the left atrium, and decrease left-ventricular afterload. It can both decrease right-ventricular afterload (through improving oxygenation and reversing hypoxic vasoconstriction/decreasing pulmonary vascular resistance) or increase right-ventricular afterload in the setting of alveolar overdistension if excessive PEEP were applied. This may result in a compression in pulmonary capillaries and increasing pulmonary vascular resistance [30].

One may anticipate the potential hemodynamic response to NIV by considering the patients underlying preload status and cardiac function. With normal cardiac function, the main hemodynamic response to an increase in intrathoracic pressure is a reduction in venous return and preload to the heart, which can manifest as a reduction in cardiac output and blood pressure [28]. This phenomenon underscores the need for adequate volume repletion in patients not in cardiogenic pulmonary edema. In contrast, those patients with reduced ventricular function and signs of cardiogenic induced hydrostatic pulmonary edema can greatly benefit from NIV. The physiologic impact of reducing right-ventricular preload and afterload reducing the left ventricle is ideal in the setting of congestive heart failure and an impaired left ventricle. This can result in the redistribution of extravascular lung water [30].

Finally, NIV has an important role in hypercapnic exacerbations of chronic obstructive pulmonary disease (COPD) by decreasing the work of breathing, off-loading the respiratory muscles, counteracting intrinsic PEEP, and preventing dynamic hyperinflation [31].

Despite the potential benefits of NIV, it is important to understand its limitations and relative contraindications. For safe delivery of NIV, patients must be awake and able to protect their airway. Therefore, caution must be employed when patients have a fluctuating level of
consciousness, poor ability to clear secretions, nausea and vomiting, or have a full stomach at risk of pulmonary aspiration [26]. Contraindications may include, but are not limited to, cardiopulmonary arrest, head and neck surgery, upper airway obstruction, fresh esophageal anastomosis, bowel obstruction, hemoptysis, and untreated pneumothorax. Another important concern with NIV is that there is a challenge in measuring the delivered tidal volumes, which, when greater than 6–8 mL/kg of ideal body weight, may precipitate ventilator-associated lung injury [32, 33]. NIV is a modality that has the greatest evidence in rapidly reversible conditions (congestive heart failure, acute exacerbations of chronic obstructive pulmonary disease); however, in more protracted conditions (i.e., pneumonia, checkpoint-associated pulmonary toxicities), NIV may impair one’s ability to proceed with other routine care-objectives, i.e., nutrition, mobility, bronchoscopy, calling into questions its role in longer term management of more complex patients. However, increasingly, evidence have demonstrated the safety of enteral nutrition, mobilization, and bronchoscopy mechanisms with various NIV interfaces [27, 34].

High-Flow Nasal Cannula

HFNC is a novel noninvasive oxygenation device that has rapidly gained popularity. HFNC is a heated, humidified oxygen delivery system that is capable of delivering flows of 40–60 L/min with an FiO₂ of up to a 100% through specialized nasal prongs [35]. One of the major benefits of this system is that the high flow rates can match those of severely dyspneic patients, thereby preventing entrainment of room air (with an FiO₂ of 21%). This mechanism prevents dilution of delivered oxygen [10]. Furthermore, the gas is heated and humidified to avoid mucosal injury and enhance patient comfort, overcoming the key problems of past use of high flow rates [36].

In addition to supplemental oxygen, high flow rates, and humidity, several other mechanisms are hypothesized to play an important role in the clinical benefits associated with HFNC. The use of HFNC is associated with a washout of carbon dioxide from the upper airways [36, 37]. This in turn reduces anatomic dead space fraction, rebreathing of expired, carbon dioxide rich gas, and ultimately making ventilation more efficient.

High inspiratory flow rates delivered by HFNC generate low amounts of PEEP [38]. Both human and benchwork studies have determined that at 60 L/min of flow, at least 2–4 cmH₂O (and perhaps even more) positive pressure can be generated. Through its flow-mediated generation of positive pressure, HFNC can improve oxygenation through recruitment of atelectatic lung regions in a mechanism comparable to NIV [36]. Given that the amount of PEEP is moderate, it may follow that the hemodynamic effects (both positive and negative) may be tempered compared to NIV.

Consistently, HFNC has been demonstrated to reduce respiratory rate, inspiratory effort, and improve oxygenation in patients with acute hypoxic respiratory failure [35, 36, 39] and may play an important role in the mitigation of ventilation-associated lung and diaphragmatic injury [36]. The improved breathing pattern can limit expiratory diaphragm loading [36, 40] and therefore possibly constrain injurious eccentric diaphragm contractions. The above described mechanisms of HFNC ultimately reduce the metabolic cost of breathing and therefore reducing minute ventilation requirements, improve lung compliance, and ventilation-perfusion matching. Importantly, these processes may reduce lung stress and strain and repetitive opening and closing of alveoli (atelectrauma) [36, 41]. Cumulatively, the improved comfort and tolerance, improved oxygenation, and theoretical reduction in diaphragm and ventilation-induced lung injury lead to the improved clinical outcomes observed with HFNC [36].

HFNC has many promising advantages as a highly effective noninvasive oxygenation device. Firstly, it permits patients to be instrumented with nasal prongs and avoids the tight-fitting masks of conventional NIV. This allows patients to eat, sleep, and clear secretions more easily than with NIV. Especially in those patients who have not previously used full face mask NIV, the use of nasal prongs and HFNC may reduce
claustrophobia and improve uptake, compliance, and allows for continuous use of the device. Perhaps as an extension of this, patients with acute hypoxemia have consistently rated HFNC to be more comfortable than NIV [35].

Although there are many benefits of HFNC, pathophysiological states such as cardiogenic pulmonary edema where increased amounts of PEEP are needed for redistribution of alveolar lung water, NIV may be a better option. Furthermore, more studies are needed to identify those patients who are at risk of HFNC failure requiring intubation and invasive mechanical ventilation. This is of paramount importance because these patients will have little to no oxygenation reserve and are at elevated risk of significant hypoxemia during airway instrumentation.

**Evidence of NIV**

**General Population**

The role of NIV for hydrostatic pulmonary edema or to support a patient with an exacerbation of chronic obstructive pulmonary disease is compelling which recent guidelines have made strong recommendations supporting its use [42]. Its role in ARF remains controversial [31, 42, 43]. However, as a result of its effectiveness for these isolated indications, we have seen a proliferation of use across the general and oncologic population for indications beyond hydrostatic pulmonary edema and chronic obstructive pulmonary disease [44, 45].

In one of the largest, multicenter, international, observational studies evaluating the diagnosis and management patients with ARDS, the Lung Safe Study, NIV was used as a first-line therapy in 15% of patients [46]. There was no major difference across severity of ARDS with reports of its use (mild = 14%, mod = 17%, severe = 13%). NIV failure occurred in a moderate proportion of these patients with failure rates of 22%, 42%, and 47% across mild, moderate, and severe ARDS, respectively. NIV failure was associated with a high mortality (45%) across all cohorts compared to NIV success (15% mortality). In a propensity matched analysis, NIV failure was associated with an increased ICU mortality and was found to have a greater mortality rate than those who were managed with invasive mechanical ventilation as first line with moderate-severe ARDS (i.e., PaO₂/FiO₂ < 150).

**Immunocompromised and Oncologic Patients**

In the immunocompromised and oncologic population, the reported rates of NIV use for ARF has been increasing since 2000 [12, 46]. This increase in use overtime is likely attributable, in part to two seminal studies that hypothesized prevention of intubation would be associated with a decreased mortality.

**Noninvasive Ventilation in Early ARF Versus Conventional Oxygen Therapy to Prevent Intubation**

In a randomized controlled trial evaluating NIV versus COT for immunocompromised patients with early ARF, there was a significant reduction in invasive mechanical ventilation and mortality compared to patients who received COT [6]. Criteria for entry included patients who had evidence of early respiratory failure including pulmonary infiltrates, fever, dyspnea, and a PaO₂/FiO₂ less than 200 on a venturi mask. The majority of these patients were immunocompromised secondary to hematologic malignancies. NIV was applied for a median of 9 h per day in the first 24 h. Of note, the control arm had a very high mortality with an increased incidence of ventilator-associated pneumonia. These results were intriguing to many and led to an increased application of NIV for oncologic patients with ARF [3, 45]. Antonelli and colleagues conducted a randomized controlled trial evaluating a similar question in 40 solid organ transplantation and found a similar reduction in invasive mechanical ventilation and mortality [8]. However, this study was noted to have a high proportion of patients with hydrostatic pulmonary edema as the primary etiology of ARF – for which there is a strong, established evidence base. Squadrone and colleagues randomized 40 patients with hematologic malignancies with bilateral infiltrations, tachypnea, and mild hypoxia (saturation <90% on room air) to CPAP or COT as a means to
prevent the development of acute lung injury and need for ICU admission [47]. Their study found a decreased need for admission to the ICU and need for invasive mechanical ventilation.

Given advancements in oncology and hematologic malignancies, ventilator-associated pneumonia prevention, critical care management, and the small sample sizes of these seminal trials, the generalizability of these trials to current day management of oncologic patients with ARF was called into question, prompting a more recent study evaluating the role of NIV versus COT for early ARF. In the largest RCT to date of NIV versus COT for early ARF, Lemiale and colleagues randomized 374 critically ill immunocompromised patients (85% oncologic patients) to NIV versus COT [9]. ARF was defined the presence of PaO2 < 60 mmHg on room air, tachypnea, or respiratory distress. After 28 days, noninvasive oxygen strategy had failed in 38% of the NIV and 45% of the COT (p = 0.20), and there was no difference in the 28-day mortality (24% in the NIV group vs. 27% in COT group p = 0.47). Study strengths include the large sample size included and the large proportion of oncologic patients allowing its generalizability to our population of interest with ARF. Limitations included the unblinded nature of the trial, low severity of illness across the population, inclusion criteria (although it does address this question in early ARF), and the use of HFNC in the COT group.

The data surrounding NIV compared to COT in the immunocompromised population was recently summarized [56]. Huang and colleagues found 5 RCTs including almost 600 patients. This group found that early NIV significantly reduced short-term mortality (RR 0.62, 95% CI 0.40 – 0.97, p = 0.04) and intubation rate (RR 0.52, 95% CI 0.32 – 0.85, p = 0.01) when compared with COT; however, these results were associated with significant statistical heterogeneity. The controversy and inconsistencies in patient response might be addressed in the evidence summary that follows.

Noninvasive Ventilation in ARDS Versus Invasive Mechanical Ventilation (via Intubation)

Following the publications of trials by Hilbert and Antonelli and colleagues, adoption of noninvasive ventilation beyond early acute respiratory failure was seen in the years that followed [16, 48, 65]. Given historic reports of increased mortality with invasive mechanical ventilation, centers theorized that perhaps a noninvasive approach to management may help mitigate the deleterious consequences associated with invasive mechanical ventilation in this population (ventilator-associated pneumonia/sedation/delirium). What followed were a series of studies that evaluated the impact of NIV versus invasive mechanical ventilation on mortality in oncologic patients with ARDS [56–58].

Reported rates of NIV use for ARDS in oncologic patients are much higher ranging from 32% to 49% [7, 16, 48]. In a post-hoc analysis of the Lung Safe study focusing on the immunocompromised population with ARDS, NIV was used in 21% of patients as the first ventilation modality of choice [65]. The application of NIV has been seen across all severities of ARDS in the setting of oncologic patients [2, 65]. While NIV is associated with a high incidence of failure noted in the Lung Safe study (48%) [65] across patients with ARDS, rates of failure in the oncologic population are even higher than the general ICU population ranging from 38% to 70% [2, 16]. NIV failure is associated with a higher in-hospital and ICU mortality (60–70%) compared to those who experience NIV success (28%) or invasive mechanical ventilation (50–60%) as first-line therapy [2, 16, 48] (Fig. 2). Pulmonary infection, increased severity of illness scores, hematologic malignancies, longer hospitalization prior to ICU admission, and severity of ARDS are consistent factors associated with NIV failure [16, 48] (Table 2). The remaining challenge is the identification of the subset who may benefit from NIV versus those in whom first-line intubation should be pursued. Table 3 outlines the evidence of NIV across oncologic patients across various severities of ARF/ARDS.

Theories of Harm Associated with NIV

1. Injurious ventilation

It is theorized that NIV could be associated with harm secondary to the pressure levels generated in NIV compared to pressure transmitted via low- or high-flow oxygen. During NIV, patients may generate tidal volumes that are above those considered lung protective (>8 mL/kg tidal volume based upon ideal body
Injurious tidal volumes could be exacerbated in the setting of spontaneous breathing facilitating further ventilator-induced lung injury [33, 50, 51]. This, in turn, could worsen hypoxemia and generate conditions requiring invasive mechanical ventilation and multisystem organ failure. Immunocompromised patients typically present to ICU with higher illness weight) [68].

Table 2: Risk factors associated with an increased morality in oncologic patients with acute respiratory failure and noninvasive oxygen failure

| Risk factors associated with an increased mortality in oncologic patients with ARF | Risk factors for noninvasive oxygen therapy failure |
|----------------------------------------------------------------------------------|---------------------------------------------------|
| **Demographic and clinical characteristics**                                     | Hematologic malignancy                             |
| Hematologic malignancy, allogeneic hematopoietic stem cell transplantation         | Hematologic malignancy                             |
| Cause of respiratory failure (infectious, PJP, invasive fungal infection, unclear etiology) | Pulmonary infection                                |
| Prolonged duration of hospitalization prior to admission to ICU                   | Prolonged duration of hospitalization prior to admission to ICU |
| **Critical illness-associated features**                                        |                                                   |
| Greater severity of illness                                                      | Greater severity of illness                        |
| Worsened severity of ARDS                                                        | Worsened severity of ARDS                         |
| NIV failure as first line oxygen therapy                                         | Lack of physiologic response to noninvasive ventilatory therapies (i.e., drop in respiratory rate, heart rate, improvement in oxygenation) evaluated early after initiation (1–4 h) |
| Vasopressors/renal failure                                                       | Vasopressors/renal failure                         |
| Tidal volume greater than 9 mL/kg 1 h after initiation of NIV                    | Tidal volume greater than 9 mL/kg 1 h after initiation of NIV |

ARDS acute respiratory distress syndrome, ICU intensive care unit, NIV noninvasive ventilation, PJP pneumocystis jiroveci pneumonia

Fig. 2: Noninvasive ventilation mortality across successes and failures. Figure depicts overall survival difference in mortality across NIV success, NIV failure, and IMV. NIV noninvasive ventilation, IMV invasive ventilation.
| Year     | Design                          | N       | Location | Population                  | Intervention | Control | Outcomes reported | Study outcomes          | Limitations                           |
|----------|---------------------------------|---------|----------|------------------------------|--------------|---------|-------------------|--------------------------|---------------------------------------|
| Azoulay 2017 | Prospective cohort study       | (915)   | ICU      | IC patients with ARF         | HFNC         | COT NIV | 90-day mortality, in-hospital mortality, ICU mortality, IMV | After propensity score matching, HFNC but not NIV had an effect on IMV rate | Observational                          |
| Frat 2016     | Post hoc analysis of randomized controlled trial | 82      | ICU      | IC patients with ARF         | HFNC         | COT NIV | 90-day mortality, ICU mortality | Odds ratios for intubation were higher in NIV versus HFNC or COT. NIV failure was associated with IMV and mortality | Post hoc analysis of RCT, exclusion of profound neutropenia |
| Coudroy 2016  | Matched cohort study           | 115     | ICU      | IC patients with ARF         | HFNC         | NIV     | 28-day mortality, IMV | After PS score matching, NIV was associated with an increased mortality compared to HFNC | Observational                          |
| Mokart 2015   | Retrospective cohort study; PS matching | 178**   | ICU      | Oncologic patients with ARF | HFNC         | COT or NIV | 28-day mortality, IMV | Lower mortality at 28 days; however, HFNC group was exposed to intermittent NIV | Observational, cohorts contained a combination of modalities (i.e., HFNC with intermittent NIV) |
| Hui 2013      | Randomized controlled trial    | 30      | Acute care units | Advanced cancer and dyspnea | HFNC         | NIV     | Symptom resolution | Both modalities improved dyspnea compared but no significant difference existed between groups | End stage cancer, small sample size |

(continued)
| Year       | Design                        | N    | Location | Population                     | Intervention | Control | Outcomes reported                  | Study outcomes                                      | Limitations                                                                 |
|------------|-------------------------------|------|----------|--------------------------------|--------------|---------|------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------|
| Lemiale 2015 | Randomized controlled trial  | 374  | ICU      | IC patients with ARF (85% oncology) | NIV          | COT     | 28 day mortality and IMV          | No difference in rates of IMV or mortality            | COT arm included HFNC                                                        |
| Hilbert 2001 | Randomized controlled trial  | 52   | ICU      | IC patients with ARF            | NIV          | COT     | In-hospital mortality, ICU mortality, IMV | Lower in-hospital mortality (50% vs. 81%), lower ICU mortality (38% vs. 69%), lower IMV rates (46% vs. 77%) with NIV versus COT | Unblinded, small sample size, high mortality in control arm, possible outdated practices compared to recent years |
| Squadrone 2010 | Randomized controlled trial  | 40   | Ward     | HM patients with early ARF      | CPAP         | COT     | In-hospital mortality, CPAP       | Lower in-hospital mortality in those admitted to ICU (15% vs. 75%) Lower IMV (20% vs. 80%) | Unblinded, small sample size                                                                                   |

**Noninvasive ventilation for acute respiratory distress syndrome**

| Year       | Design                        | N    | Location | Population                     | Intervention | Control | Outcomes reported                  | Study outcomes                                      | Limitations                                                                 |
|------------|-------------------------------|------|----------|--------------------------------|--------------|---------|------------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------|
| Rathi 2017 | Retrospective cohort study    | 1614 | ICU      | Hematologic malignancy and solid tumor | NIV failure  | IMV     | Overall survival (NIV vs. NIV failure vs. IMV) | 38% NIV failure 80% hospital mortality in NIV failure group 28% hospital mortality in NIV success group 69% hospital mortality in IMV group | Observational                                                                 |

**Table 3** (continued)
| Year | Study Type | Study Design | Sample Size | Setting | NIV Success | NIV Failure | Hospital Mortality | Mortality Comparison | Mortality Details |
|------|------------|--------------|-------------|---------|-------------|-------------|-------------------|---------------------|------------------|
| Neuschwander 2017 | Post hoc analysis | prospective cohort study | 1004 ICU Hematologic malignancy and solid tumor | NIV success | NIV failure | Hospital mortality | 71% NIV failure | 63% hospital mortality in NIV failure group | Risk factors for NIV failure see Table 2 |
| Azevedo 2014 | Prospective cohort study | 717 ICU Hematologic malignancy and solid tumor | NIV IMV | Hospital mortality | 53% NIV failure | 69% hospital mortality in NIV failure group | 40% hospital mortality in NIV success group | 73% hospital mortality in IMV group |
| Adda 2008 | Retrospective cohort study | 99 ICU Hematologic malignancy | NIV success | NIV failure | Factors predictive of NIV success or failure Hospital mortality | 54% NIV failure | 79% hospital mortality in NIV failures | 41% hospital mortality in NIV success | Risk factors for NIV failure see Table 2 |

* - 915 included, only 859 analyzed
** - retrospective study that utilized propensity score matching

**ARF** acute respiratory failure, **ARDS** acute respiratory distress syndrome, **COT** conventional oxygen therapy, **CPAP** continuous positive airway pressure, **HFNC** high-flow nasal cannula, **IC** immunocompromised, **ICU** intensive care unit, **IMV** invasive mechanical ventilation, **NIV** noninvasive ventilation
severity and multiple organ dysfunction [2] and are therefore at higher risk of ventilation-associated lung injury, potentially exacerbated by injurious tidal volumes during NIV.

2. Delay in intubation

It is further theorized that prolonged NIV without evidence of respiratory improvement may lead to a delay in intubation. In previous studies of patients with ARDS, there is a suggestion that a longer duration of NIV in those requiring intubation, the greater the mortality compared to those intubated sooner [51]; however, this was not found across a retrospective studies focused specifically on oncologic patients [16]. A delay in intubation or prolonged NIV prior to intubation potentially creates a setting of lower respiratory reserve, risk of aspiration pneumonitis, or potential greater instability around induction for intubation.

3. ICU evidence-based care

NIV may prevent ongoing evidence-based ICU care including mobilization, transport for imaging, enteral nutrition, and invasive diagnostic tests such as bronchoalveolar lavage. Sufficient recruitment to achieve adequate oxygenation may not be possible due to the facemask interface or discomfort by the patient.

Is There a Role for NIV in Oncologic Patients with ARDS?
The subset of those who experience NIV success consistently have been found to have the lowest mortality rate compared to those who undergo first-line invasive mechanical ventilation or fail NIV [16, 48]. Rates of NIV success have varied from reports across different institutions which may reflect important differences in patient selection and practice. Accurate identification of those who are at highest risk of NIV failure versus success is paramount to potentially defining any role for NIV in the setting of ARDS for oncologic patients. Data-to-date is limited by its retrospective nature subjecting it to selection bias – those who experience NIV failure are patients that the intensivist may not be keen to intubate given poor overall prognostic factors and therefore turned to NIV first line. Until further research clarifies its role in ARDS in oncologic patients, it should be reserved for those patients in which one suspects underlying hydrostatic pulmonary edema as a plausible cause of ARF or contributor, or be applied for a time limited trial (1 or 4 h) in those with a low severity of illness with an early evaluation of physiologic improvement (decrease in respiratory rate, drop in FiO₂ requirements – Fig. 3). In the study by Rathi and colleagues, they evaluated improvement in respiratory rate, Glasgow coma score, oxygenation parameters, and acid-base status as markers of NIV success (and thus continuation) or NIV failure (potential indication to consider intubation) [16]. Frat and colleagues also evaluated factors associated with NIV failure. At 1 h following initiation, a persistent PaO₂/FiO₂ < 200 and tidal volumes greater than 9 mL/kg of predicted body weight were independently associated with the need for invasive mechanical ventilation and mortality [52]. It would be important that the intensivist considers (1) tidal volumes generated, (2) need for other invasive tests or imaging (CT/fiberoptic bronchoscopy), and (3) immediate response to its application with a projected rapid wean-off of NIV (i.e., drop in respiratory rate/oxygenation response). Furthermore, Patel and colleagues recently evaluated the interface of helmet versus face mask for NIV and found a decreased need for invasive mechanical ventilation and mortality [27]. These findings are intriguing for which its role needs to be further elucidated in this population compared to alternative noninvasive oxygen strategies outlined below.

Evidence for HFNC

General Population

HFNC has recently emerged as a safe and comfortable device with a means to effectively administer high-flow oxygen to patients with ARF. Emerging data has demonstrated promising results compared to alternative noninvasive oxygen strategies (Table 4). In one of the largest RCTs to date, Frat and colleagues randomized 310 patients with ARF to HFNC versus COT versus NIV [32]. HFNC was associated with a lower incidence of 90-day mortality compared to the COT and NIV. In the subgroup of patients with a PaO₂/FiO₂ < 200,
Non-Invasive Oxygen Strategies in Acute Respiratory Failure for Oncology Patients

Severity of Acute Respiratory Failure

Dyspnea, Hypoxia, PaO₂/FiO₂ 300

Early Acute Respiratory Failure

COT  HFNC  NIV

HFNC

If high, consider switching to HFNC

Evaluate FiO₂ delivered

Evaluate tidal volumes in NIV

Consider COT or HFNC with a frequent and early re-evaluation of RR, FiO₂

Consider HFNC or NIV with a frequent and early re-evaluation of RR, FiO₂ to ensure drop in RR, FiO₂

If tidal volumes are high with NIV, consider HFNC or IMV if increased severity of illness

Hypoxia with extensive pulmonary infiltrates but no tachypnea

Hypoxia, tachypnea, or possible pulmonary edema and no contraindications to NIV or failing COT

PaO₂/FiO₂ 300

Acute Respiratory Distress Syndrome

Mild ARDS

Moderate ARDS

Severe ARDS

Risk factors associated with NIV failure include hematologic malignancy, prolonged duration of hospitalization prior to admission, lack of physiologic response after a time limited trial, higher severity of illness score on admission, the need for vasopressors, high tidal volumes 1 hour after NIV initiation, low PaO₂/FiO₂ at 1 hour

Delay in intubation creating unsuitable conditions for induction or introduction of an endotracheal tube, injurious ventilation and lack of control over pressure and volume limited ventilation and prevention of proceeding with evidence based ICU care (nutrition, imaging) may explain the increased mortality associated with NIV failure

Extrapolating from a series of studies, there is a greater risk of NIV failure in moderate-severe ARDS. NIV failure is associated with the highest mortality compared to other cohorts. In the Lung Safe study evaluating all patients receiving NIV, the use of NIV as first line in patients with a PaO₂/FiO₂ <150 was an independent risk factor for death compared to first line application of IMV (Bellani 2016).

While this was not restricted to oncology patients, observational data suggest a high risk of NIV failure in oncology patients with higher severity of illness.

PaO₂/FiO₂ 100

Time period of re-evaluation 1hr and 4hr

Evaluate FiO₂ delivered

Evaluate tidal volumes in NIV

Consider HFNC or NIV with a frequent and early re-evaluation of RR, FiO₂ to ensure drop in RR, FiO₂

If tidal volumes are high with NIV, consider HFNC or IMV if increased severity of illness

Consider time limited trial of NIV in select patients instead of IMV if results in improved dyspnea, decrease in RR <35 bpm, improved GCS, and 2/3 gas exchange parameters: PaO₂ >85, PaO₂ >60 on FiO₂ 0.60, pH >7.3.

Evaluate at 1 and 4 hours (Rathi 2017). OR if PaO₂/FiO₂ <200 and/or TV >9ml/kg at 1 hour consider intubation (Frat 2018)

It remains unclear whether one oxygen modality is superior to another in the oncologic population. While one large trial and its post hoc analysis (Frat 2013/2017) demonstrated benefit of HFNC compared to COT/NIV (general population) and HFNC/COT compared to NIV (immunocompromised population), two recent trials comparing NIV to COT (Lemiale 2015) and HFNC to COT (Azoulay 2018) did not demonstrate benefit of either modality over COT. Posing the data to date restricted to oncologic studies does not confirm nor refute the superiority of one modality over another.

High severity of illness, shock, vasopressors, renal failure, high tidal volumes on NIV

Hypoxia with extensive pulmonary infiltrates but no tachypnea

Hypoxia, tachypnea, or possible pulmonary edema and no contraindications to NIV or failing COT

It remains unclear whether one oxygen modality is superior to another in the oncologic population. While one large trial and its post hoc analysis (Frat 2013/2017) demonstrated benefit of HFNC compared to COT/NIV (general population) and HFNC/COT compared to NIV (immunocompromised population), two recent trials comparing NIV to COT (Lemiale 2015) and HFNC to COT (Azoulay 2018) did not demonstrate benefit of either modality over COT. Posing the data to date restricted to oncologic studies does not confirm nor refute the superiority of one modality over another.

ARDS acute respiratory distress syndrome, ARF acute respiratory failure, COT conventional oxygen therapy, GCS Glasgow coma scale, HFNC high flow nasal cannula, IMV invasive mechanical ventilation, NIV non invasive ventilation, RR respiratory rate

Fig. 3 Noninvasive oxygen strategy decision algorithm
| Year       | Design                  | Sample size | Location | Population | Entry criteria                                                                 | Intervention | Control | Outcomes                                                                 | HFNC intubation rate | HFNC mortality<sup>a</sup> |
|------------|-------------------------|-------------|----------|------------|--------------------------------------------------------------------------------|--------------|---------|--------------------------------------------------------------------------|----------------------|-----------------------------|
| Azoulay    | Prospective cohort study| 859         | ICU      | IC patients with ARF | RR > 30/min or saturation <90% room air or P<sub>O</sub><sub>2</sub> ≤ 60 mmHg and requiring >6 L/min and respiratory symptoms less than 72 h | HFNC         | COT COT | NIV 90-day mortality, in-hospital mortality, ICU mortality, IMV          | 39%                  | 42% (90-day)                |
| Azoulay    | RCT                     | 778         | ICU      | IC patients with ARF | RR > 30/min or saturation <90% room air or P<sub>O</sub><sub>2</sub> ≤ 60 mmHg and requiring >6 L/min | HFNC         | COT COT | 28-day mortality, IMV, P/F over 3 days, respiratory rate, ICU and hospital LOS, comfort, dyspnea | 38.7%                | 35.6% (28-day)              |
| Kim        | Retrospective cohort study | 52         | General ward, ICU | Non-HIV patients with PJP and ARF | Acute respiratory failure and PJP | HFNC | None | 60-day mortality, IMV                                                   | 56%                  | 35% (60-day)                |
| Lemiale    | Post hoc analysis of RCT; PS matching | 353 | ICU      | IC patients with ARF | PaO₂ < 60 mmHg on room air or tachypnea >30/min or respiratory distress <72 h | HFNC | COT COT | 28-day mortality, IMV                                                   | 49%                  | 24% (28-day)                |
| Durey      | Retrospective cohort study | 11         | ER       | Oncologic patients with ARF | Any adult patient with solid malignancy | HFNC | None | Mortality, IMV                                                          | 18%                  | 36% (In-hospital)           |
| Frat       | Post hoc analysis of RCT | 82         | ICU      | IC patients with ARF | RR > 25 and P<sub>O</sub><sub>2</sub>/FiO₂ < 300 and P<sub>CO</sub><sub>2</sub> ≤ 45 mmHg | HFNC | COT COT | 90-day mortality, ICU mortality                                         | 46%                  | 29% (90-day)                |
| First Name | Study Type | N | Setting | Patients | Criteria | Treatment | Outcomes | Mortality | Duration |
|------------|------------|---|---------|----------|----------|-----------|----------|-----------|----------|
| Coudroy 2016 | Matched cohort study | 115 | ICU | IC patients with ARF | RR ≥ 25 breaths/min or clinical signs of respiratory distress, PaO2/FiO2 < 300 | HFNC | NIV | 28-day mortality, IMV | 44% | 30% (28-day) |
| Harada 2016 | Retrospective cohort study | 56 | ICU | Hematologic malignancy with ARF | 4 L/min oxygen for SpO2 < 90%, RR > 25, Clinical signs of respiratory distress | HFNC | None | IMV | 15% (64% palliated after HFNC failure) |
| Lemiale 2015 | RCT | 100 | ICU | IC patients with ARF | <72 h from admission, 6 L/min oxygen for SpO2 > 95%, RR > 30 and signs of respiratory distress | HFNC | COT | Invasive or Non-IMV | 9% (evaluated on day 1 only) |
| Mokart 2015 | Retrospective cohort study; PS matching | 178 | ICU | Oncologic patients with ARF | O2 > 9 L/min | HFNC+ | COT or NIV | 28-day mortality, IMV | 50% | 45% (28-day) |
| Lee 2015 | Retrospective cohort study | 45 | ICU | Hematologic malignancy patients with ARF | Acute respiratory failure with hematological malignancy | HFNC | None | Mortality, IMV | 58% | 62% (In-hospital) |
| Hui 2013 | RCT | 30 | Acute care units | Advanced cancer and dyspnea | Locally advanced cancer, Dyspnea at least 3/10 (NRS) despite O2, Life expectancy > 1 week | HFNC | NIV | Symptom resolution | 30% |

*ABG* arterial blood gas, *ARF* acute respiratory failure, *ARDS* acute respiratory distress syndrome, *BP* blood pressure, *CHF* congestive heart failure, *COT* conventional oxygen therapy, *ER* emergency department, *GVHD* graft versus host disease, *HIV* human immunodeficiency virus, *HR* heart rate, *ICU* intensive care unit, *IMV* invasive mechanical ventilation, *LOS* length of stay, *MOF* multiorgan failure, *NIV* noninvasive ventilation, *NRS* numeric rating scale, *PaCO2* partial pressure of arterial carbon dioxide, *PaO2/FiO2* ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen, *PJP* pneumocystis jiroveci pneumonia, *PNA* pneumonia, *ROS* retrospective observational study, *RCT* randomized controlled trial, *RR* respiratory rate, *SpO2* oxygen saturation

*Mortality at longest follow-up*
HFNC was associated with a lower incidence of invasive mechanical ventilation. However, the signal of benefit has not been consistent across all studies. A Cochrane review by Corley and colleagues evaluated the use of HFNC compared to COT or NIV for ARF or postextubation across 11 RCTs [53]. HFNC compared to COT was not associated with lower rates of invasive mechanical ventilation (reported in six studies) or mortality (reported in three studies). Confidence in the results using GRADE criteria [54] was downgraded to low given the risk of bias across these studies and different participant indications. Data comparing HFNC to NIV was not pooled given the low number of studies and their heterogeneity.

**Immunocompromised and Oncologic Population**

Given the important differences in the oncologic population and the general ICU population and evolving evidence of potential harm associated with NIV failure, HFNC has emerged as a promising modality in this population. High quality data evaluating use of HFNC compared to COT or NIV in this population is unfortunately limited. In a multinational, prospective observational study across 16 countries of immunocompromised patients with ARF (87% oncologic), noninvasive oxygen strategies were evaluated in 915 patients [12]. Fifty-three percent received COT, 17% received NIV, 20% received HFNC, and 9% received a combination of HFNC and NIV. After propensity score matching, HFNC had an impact on invasive mechanical ventilation but not NIV. HFNC was not independently associated with a lower mortality.

In a post hoc analysis of the RCT by Frat and colleagues evaluating HFNC versus COT and NIV, outcomes across the cohort of 82 immunocompromised patients (44% oncology) were evaluated [68]. NIV was associated with an increased need for invasive mechanical ventilation compared to HFNC or COT.

Finally, in a post hoc propensity score-matched analysis by Lemiale and colleagues of their prior RCT (NIV vs. COT) [9], they compared 90 patients who received HFNC in their control group matched to 90 patients who received COT in their control group [55]. They found no difference in the rates of invasive mechanical ventilation or mortality.

Sklar and colleagues recently described the role of HFNC compared to any noninvasive oxygen control (COT or NIV) across immunocompromised patients (13 studies) [66]. Data from RCTs and observational studies that used matching techniques were meta-analyzed (8 studies). Mortality was found to be lower at the longest available follow-up with HFNC compared to the oxygen control groups (NIV or COT – 7 studies; 1429 patients, relative risk of 0.72, 95% CI 0.56–0.93, p=0.01). There was a lower rate of invasive mechanical ventilation with HFNC compared to the oxygen therapy controls across 8 studies (8 studies, 1529 patients, relative risk of 0.81, 95% CI 0.67–0.96, p=0.02). However, one of the limitations of this analysis was the pooling of the two control arm techniques and the inclusion of observational studies in the analysis.

Eleven studies have evaluated the use of HFNC specifically in oncologic patients (Table 4) reporting on 1,881 patients.

These studies included 6 retrospective, cohort studies [59, 60, 62–64], 1 prospective observational study [12], and 4 RCTs, 2 of which were post hoc analyses of previous RCTs outlined above [9, 55, 61, 68]. Eight studies compared HFNC to an oxygen therapy control (NIV or COT). Oncologic diagnosis or treatment associated effect was the leading cause of immunosuppression with a predominance of hematologic malignancy (9/11 studies). HFNC was initiated in the emergency department, acute care ward, or intensive care unit with the latter being the most common site of initiation. Various indications for the application of HFNC existed ranging from tachypnea or hypoxia on room air to more formalized PaO2/FiO2 thresholds. The median PaO2/FiO2 across the studies was 145 (IQR 115–175). The need for invasive mechanical ventilation, evaluated at 28-day intubation or hospital discharge, was 46% (IQR 25–67%). The longest follow-up mortality time points are reported in Table 3 with a median mortality of 36% (IQR 14–58%).

Mortality at longest available follow-up and the need for invasive mechanical ventilation was reported in 7 and 8 studies, respectively (Table 4).
Using a random effects model, HFNC compared to NIV or COT was not associated with a decreased mortality or need for invasive mechanical ventilation. Data are pooled using an inverse variance random effects model. Results are summarized as risk ratios. (Oncologic subgroup of studies extrapolated from a systematic review evaluating HFNC compared to other modalities—unpublished data.)

These findings are primarily meant to be exploratory given the heterogeneous nature of the populations and low quality of evidence (observational studies, post hoc analyses of RCTs).
Most recently, Azoulay and colleagues performed the largest RCT to date of immunocompromised patients with ARF and randomized the approximately 800 patients to COT or HFNC [67]. These patients were mainly immunocompromised secondary to hematologic malignancy or its treatments. The primary outcome of 28-day survival was not different between the two groups (35.6% HFNC vs. 36.1% COT), nor were a number of secondary outcomes including intubation rates, ICU and hospital length of stay, or ICU-related complications. This trial therefore suggests that HFNC in all immunocompromised patients may not be better than COT and further subgroups of HFNC “responders” must be sought. Future directions would necessitate larger, randomized controlled trials specifically enrolling oncologic patients comparing COT, NIV, and HFNC head-to-head. In addition, there could exist a differential impact across varying severities and indications for ARF.

In deciding optimal noninvasive oxygen therapy, one needs to consider the etiology, timing of reversal, severity of illness, impact of the modality on tidal volumes, and immediate response of respiratory physiology variables and tidal volumes to the modality chosen [16, 52]. Figure 3 represents a proposed algorithm for consideration of noninvasive oxygen therapies and factors to consider in deciding upon first-line and second-line modalities. The figure attempts to capture some important factors that should be considered in deciding upon modality of choice.

Conclusions

COT, NIV, and HFNC are multimodal techniques to administer oxygen noninvasively in critically ill patients with ARF. Each has unique mechanisms, advantages, and disadvantages. Until further research is available, individual patient characteristics, severity of illness, and early response to each modality is imperative to guide selection of which strategy is most applicable. Most importantly, the physician needs to pay meticulous attention to the rapidity of reversibility of the underlying condition and reevaluate the impact of the strategy chosen at an early time points (e.g., 1 and 4 h). An improved physiologic response to the modality of choice has been consistently found to be associated with success. While HFNC is a unique oxygen delivery modality that holds theoretical promise for the treatment of ARF in oncologic patients, the current body of literature demonstrates that there is a paucity of high-quality data in this specific population to guide evidence-based therapy. This chapter underscores the need for further research with clinical and physiological studies, including larger randomized controlled trials specifically of oncologic patients to more clearly elucidate the potential benefits of one modality over another.

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