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Invited Review

Ventilator Support and Oxygen Therapy in Palliative and End-of-Life Care in the Elderly

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Abstract

Elderly patients suffering from chronic cardio-pulmonary diseases commonly experience acute respiratory failure. As in younger patients, a well-known therapeutic approach of noninvasive mechanical ventilation is able to prevent orotracheal intubation in a large number of severe scenarios in elderly patients. In addition, this type of ventilation is frequently applied in elderly patients who refuse intubation for invasive mechanical ventilation. The rate of failure of noninvasive ventilation may be reduced by means of the integration of new technological devices (i.e., high-flow nasal cannula, extracorporeal CO_2 removal, cough assistance and high-frequency chest wall oscillation, and fiberoptic bronchoscopy). Ethical issues with end-of-life decisions and the choice of the environment are not clearly defined in the treatment of elderly with acute respiratory insufficiency.

KEYWORDS: Acute respiratory failure, bronchoscopy, high-flow nasal cannula, mechanical ventilation, noninvasive ventilation

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INTRODUCTION

Current treatment modalities, such as long-term oxygen therapy and home mechanical ventilation, may be very helpful in patients with chronic respiratory diseases with an aim to prolong survival in a very advanced age [1]. However, a prolonged life expectancy does not necessary mean a better quality of life due to unbearable symptoms that are characteristic for a severe impairment of lung function (i.e., dyspnea, weakness, depressive symptoms) [2-4]. Conversely, in patients with advanced chronic respiratory diseases, palliation of symptoms, "end-of-life" decisions, and good quality of death could be the main issue [5]. The scenario of end-stage pulmonary diseases may be much more difficult to deal with, considering the "nihilism" that characterizes physician's behavior concerning the estimated results of invasive mechanical ventilation (IMV) in chronic obstructive lung disease (COPD) and asthma [6]. Thus, the approach to "terminal stage" cardiac and pulmonary diseases with acute (on chronic) respiratory failure (ARF) may lead to ethical trouble regarding the preference of the stage of the "step-up treatment approach" starting from the medical and oxygen therapy ended with IMV [4]. The risk of developing ARF increases with age as elderly people are more likely to develop chronic respiratory disorders, including cardiac diseases, immune deficiency diseases, and also malignancies (i.e., solid and hematologic malignancies), together with many other diseases [7]. The main reasons of ARF in very elderly patients are acute heart failure, severe pneumonia and exacerbations of COPD, and acute lung injury, including drug-induced lung injury. Worsening of lung function may arise from without any symptoms of an overlying circumstance. This worsening could be thought advance of the underlying diseases course [7].

Non-Pharmacological Treatment Approach for Acute Respiratory Failure in the Elderly

As in younger adult population, standard oxygen therapy via a nasal cannula or facemask represents the first therapeutic choice to support the elderly with ARF with the aim to "buy time" for the etiologic therapy to cancel the ARF cause [8-13]. If oxygen therapy is not enough to correct gas exchange and relieve pulmonary symptoms, noninvasive ventilation (NIV) is the treatment of choice aimed at avoiding IMV and its life-threatening complications [9]. The success of the NIV technique is variable and depends on various factors, such as the experience of the staff applying it, adherence to the scheduled treatment, air leaks, adequate apparatus (mask, circuit), patient-ventilator synchrony and environment, the pathophysiological pattern, and the timing and severity of ARF [9-11]. In the case of the NIV failure, IMV and transfer to intensive care unit (ICU) become the life-saving mandatory choice. The decision to offer mechanical ventilation support in general ICUs and respiratory ICUs (RICU) for very elderly patients is still largely debatable [7]. As a matter of fact, as the previous studies have shown, the elderly patients with IMV have a nearly similar prognosis as younger patients; however, the early usually nonintensive and less expensive approach than the current one has a similar severity of the clinical-pathophysiologic upset.

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In the elderly, the refusal of ICU access is often emphasized by an unjustified physician pessimistic perspective [6]. In majority of ICUs, the label of "do-not-intubate" (DNI) order can be usually applied to patients of an advanced age with chronic advanced pulmonary disease [14]. There is not a definite distinction among the terms "curative," "palliative," and "end-of-life" approach in patients with end-stage respiratory diseases, which makes the clinical situation more difficult [4,5,11]. In the elderly showing severe acute respiratory distress syndrome (ARDS), a more advanced respiratory, such extracorporeal membrane oxygenation (ECMO), and/or extra-pulmonary support, such as renal replacement therapy, is less likely to be offered [12]. New therapeutic tools could be applied as either alternative or integrative supportive strategy to NIV and IMV, such as high-flow nasal cannula (HFNC) [13], non-invasive cough assist devices -such as mechanical insufflator-exsufflator (MI-E) [14], high frequency chest wall oscillation (HFCWO) [15], fiberoptic bronchoscopy (FOB) [16], extracorporeal CO_2 removal ($ECCO_2R$) [17] both in patients who are failing NIV and in those who have to be intubated and are at risk of developing extubation failure. Palliation care and terminal sedation are the "end-of-life" therapeutic option which has to be considered when invasive or noninvasive ventilator support are considered either inappropriate [4,11,18]. In Figures 1 and 2, therapeutic options available in the elderly with ARF and a flowchart of the different supportive ventilator and non-ventilator measures are depicted.

Noninvasive Ventilation in the Elderly

The majority of elderly patients with COPD, cardiogenic pulmonary edema, immunosuppression of different origin, neuromuscular disease without severe bulbar impairment, obesity hypoventilation syndrome, and chest wall deformity require NIV as the first choice treatment when ARF is developed [9]. NIV has similar physiologic effects to those in patients mechanically ventilated via the intubation tube or tracheostomy cannula (i.e., unloading respiratory muscles, improvement gas exchange, and augment alveolar ventilation) and keep away from ventilator-associated pneumonia in patients with advanced age patients [19]. An early application of NIV together with optimum medical therapy and oxygen support in patients with ARF, including those at an advanced age, successfully prevents unnecessary intubation and a prolonged hospital stay, and reduces the hospital mortality rate, particularly in hypercapnic acidotic patients; in addition, if patients with ARF present with lack of airway protection, inadequate cooperation, and cough reflex, then NIV should be switched off, and intubation for IMV should be considered [9]. The main ventilator management in elderly DNI patients with cardio-pulmonary diseases is NIV [11,19,20]. NIV may be also useful in the management of different palliative clinical situations, for example, patients with terminal stage solid tumors and acute-on-chronic respiratory failure [4,21].

The best hospital management of NIV in patients at an advanced age should require well-trained staff and a 24 h observation with an adequate monitoring of patients' condition severity during the NIV application in case a quick move to IMV is required, acceptable costs, and an organized discharge plan, including end-of-life options [9,22,23].

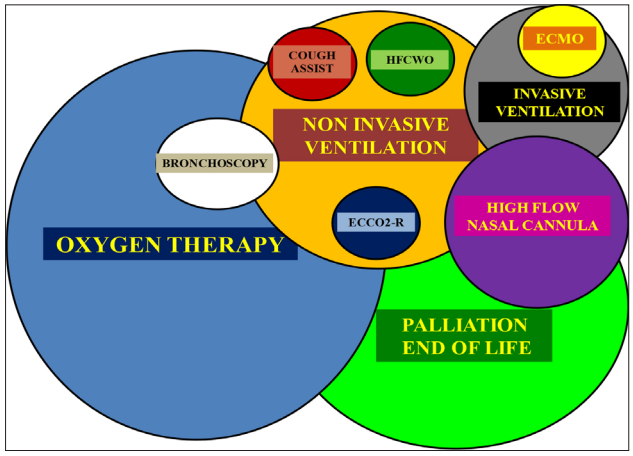

Figure 1. Therapeutic non-pharmacologic options in the elderly with acute respiratory failure. $ECCO_2R$: extracorporeal CO_2 removal; ECMO: extracorporeal membrane oxygenation; HFCWO: high-frequency chest wall oscillation

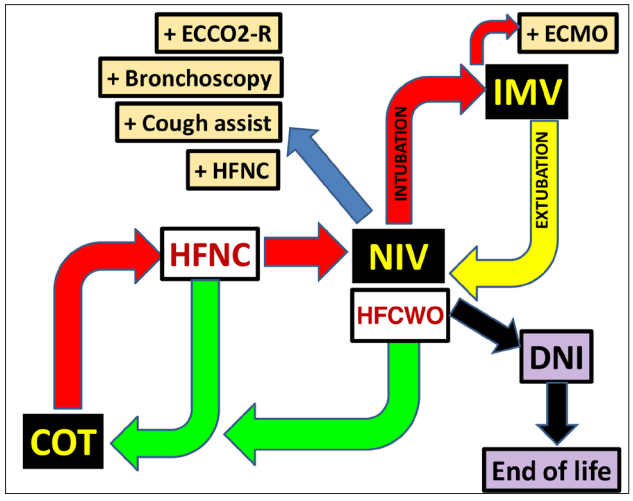

Figure 2. Flow chart for the management of acute respiratory failure in the elderly. $ECCO_2R$: extracorporeal CO_2 removal; ECMO: extracorporeal membrane oxygenation; HFCWO: high-frequency chest wall oscillation; HFNC: high-flow nasal cannula; IMV: invasive mechanical ventilation; DNI: do-not-intubate; NIV: noninvasive ventilation

MAIN POINTS

- In elderly patients with acute respiratory failure the rate of limitations of ICU care (ie endotracheal intubation) is higher than in younger patients.
- NIV is widely used with success in the elderly with acute respiratory failure aiming at either preventing endotracheal intubation and death as supportive care or relieving symptoms as palliative care.
- The integration of NIV with other supportive devices (such as HFNC, ECCO2-R, HFCWO, bronchoscopy) is likely to decrease the rate of treatment failure in the elderly.
- HFNC provides an effective non invasive respiratory assistance as alternative or integrative tool to NIV in the elderly.
- Ethical issues and end of life decisions may challenge the management of acute respiratory failure in the elderly with advanced chronic respiratory diseases.

ICU is not the best setting for NIV because of the costs that are not proportional to the severity of the illness and a limited number of beds. Initiation of NIV outside ICUs provides an opportunity to treat less difficult patients with a similar rate of success at a lower cost [22] and preventing the disturbing experience of a technological environment. Conversely, treating patients in unprotected settings such as wards might increase the risk of deterioration in patients receiving NIV that will not be promptly recognized and managed [24]. RICUs represent a well-organized setting with an expertise in NIV, cost effectiveness, knowledge of the history of chronic respiratory patients, and awareness of end-of-life issues [25-27]. RICU are units organized for patients who need an intermediate level of care, which is between the ICU and the ward, where monitoring and ventilation are mainly noninvasive, even if not entirely, performed. RICU is accepted as the "step-down unit," which is used basically in weaning and decannulation of stabilized patients and patients who may still be unstable after medical management in wards or emergency units [25,27]. These step-down units supply well-organized and trained staff care to optimize the health resources (decreased nurse-to-patients ratio) and to prevent the over- and under-care environments (ICU and wards respectively) [25]. Other advantages of RICU are privacy and an easy family access, which contribute to remedial activities and earlier discharge [25]. However, a large heterogeneity on RICU features emerges also within the same country in terms of human resources, organization models, and practical skills [27].

Hypoxemic ARF, such as ARDS, pneumonia, and obstructive larger airway diseases (i.e., asthma), are less responsive to NIV, and these patients should be treated in RICU or ICU in case of a high intubation risk. However, in DNI/DNR patients, NIV can be applied to relieve the respiratory symptom [4,5]. The condition that shows a very quick response to NIV applications in an ambulance or emergency department is acute cardio-pulmonary edema [9,22,23]. The goals of NIV may be very different and should be identified before starting ventilation [4,5,8,11,28], e.g.,

1) To avoid the development of (but not observed) ARF or after extubation failure,
2) To anticipate patients' clinical progression and intubation when mechanical ventilation is not really necessary,
3) When mechanical ventilation is necessary, it will be another IMV option or a choice to promote the weaning from IMV,
4) In patients with a DNI/DNR ordered due to terminal stage (i.e., chronic respiratory or malignancy related respiratory failure).

NIV should be applied as early as possible to avoid further deterioration and decrease the failure. Meanwhile there is no point in applying NIV to ARF patients with mild hypercapnia without acidosis [28].

When NIV is considered a valuable option in the elderly, the physician should first differentiate the hypercapnic ARF with underlying chronic respiratory diseases (i.e., kyphoscoliosis, COPD, neuromuscular diseases) from hypoxemic ARF without underlying cardio-pulmonary diseases (i.e., ARDS), which is important for NIV response; hypercapnic ARF is more responsive to NIV than hypoxemic ARF. Among progressive neuromuscular diseases, such as amyotrophic lateral sclerosis (ALS) with intact bulbar function, shows a very good response to NIV when hypercapnia developed due to pump failure [29]. Meanwhile, a close follow-up and exclusion of NIV contraindications are important such as cardio-respiratory arrest and need for immediate intubation to protect airways. According to the RCTs for exclusion criteria of NIV, contraindications are defined, and it is eventually accepted that NIV is not to be applied in these situations [9,22]. As an example, NIV is an accepted contraindication in patients with encephalopathy, which would lead to a higher risk of aspiration pneumonia and lack of patients' adaptation to NIV. Meanwhile this is incorrect when the reason of encephalopathy is hypercapnia, which is generally reversed safely by NIV [30].

A study that included mainly elderly patients with acute exacerbation of COPD in moderate-to-severe hypercapnic encephalopathy showed that NIV versus IMV had a similar short and long-term survival and fewer nosocomial infections [31]. NIV is also used for improving airway clearance to treat the episodes of ARF due to secretion retention and/or inappropriate cough reflex [14,32]. Meanwhile, patients tolerate NIV well, even when they have a severely depressed sensorium; however, NIV application is nearly almost prevented in agitate-awake patients. Elderly patients with ARF are in a nearly agitated state and/or delirium. Low-doses of sedatives (i.e.,., opioids or alfa-2 agonists) use can supply NIV tolerance in a close monitoring place with a caution in mildly agitated patients with ARF [33]. When patients are intolerant to NIV, a "safe" sedation can accomplish for patients comfort and improve patient-ventilator synchrony [32]. However, even with a good sedation effect during NIV, physicians should be aware of the sedation overdose risk [9,34]. Considering of the predictive factors can be helpful in the selection-making process, although patients with a higher rate predictive value (i.e., clinical-physiological parameters after a trial of NIV) are not present before the NIV application. However, present of severe acidosis (i.e., pH<7.25), new onset severe hypoxemia (i.e., PaO_2/FiO_2<200) and organ failure other than pulmonary are nearly well-defined risks associated NIV failure [9,34,35]. Considering all defined NIV application procedures and diseases states, there is no a "magic formula for NIV success" that should be remembered [11,22]. This is also true for elderly patients with ARF. Still, physicians should consider these elements when applying NIV to DNI patients, because NIV sometimes can be an "intrusive therapy," and it can increase patients' burden and stress, and in these circumstances for the sake of patients comfort, physicians should apply an alternative palliation strategy.

The NIV failure rate ranges from 5% to 60%; the severity of ARF, the expertise of the team, and the intensity of the level of care are the main determinants of the NIV outcome [34]. Given the fact that the delay of intubation may worsen hospital mortality, it is crucial to identify the early signs of NIV failure.

The NIV failure may be classified into three different time-frame scenarios: 1) immediate failure (within minutes to <1 hour) due to a weak cough reflex, abundant secretions, hypercapnic encephalopathy syndrome, discomfort/agitation, and patient-ventilator asynchrony; 2) early failure (from 1 to 48 hours), due to severe lung gas exchanges derangement and the inability of ventilation to promptly correct them, severe acute illness, and the persistence of tachypnea with signs of overload of respiratory muscles; and 3) late failure (after 48 hours), which can occur after an initial positive quick response to NIV and may be related to sleep disturbances and/or severe comorbidities [34,35].

The strategy based on the combination of NIV with other minimally invasive or noninvasive procedures of support (e.g.,., HFNC, mechanical cough assistance devices, FOB with toilette of abundant secretion, low-flow CO_2-removal systems) with the aim of increasing the success of NIV may be a good viable and favorable option in the elderly, in who IMV is frequently not desirable or appropriate [11,36-46].

HFNC is a new noninvasive tool for providing non-invasive respiratory assistance to patients with ARF thanks to its capability of delivering up to 100% of heated and humidified oxygen at a maximum flow of 60 L/min of air via a comfort interface, represented by nasal cannula [13]. Literature data have demonstrated that HFNC has several physiological advantages over conventional oxygen therapy and in part also over NIV, e.g., 1) capability of delivering reliable values of FiO_2 in the range from 21% to 100%; 2) efficient wash out of CO_2 from upper airways with a reduction of pharyngeal physiologic dead space; 3) great humidification and heating of the delivered oxygen-air mixture associated with enhanced secretion clearance; 4) good comfort and adherence to the scheduled treatment without the interference with eating, drinking, and speaking; 5) flow-dependent unloading of respiratory muscles based in part on the match between patient's inspiratory needs and the amount of the flow rate provided by the system; 6) lung alveolar recruitment due to the generation of flow-dependent low positive end expiratory pressure (PEEP) levels (up to a median of 7.4 cmH_2O at 60 L/min) [13]. HFNC has been shown to be feasible and effective in a large variety of patterns with ARF to achieve a good comfort, relief in dyspnea, and reduction in the need of escalating ventilatory therapy (i.e., NIV and IMV), in DNI patients, during FOB in high-risk patients with ARF, including a large series of the elderly [36-38].

Incapability to spontaneously manage respiratory secretions is a relative contraindication for NIV in ARF; this is particularly true in patients with a depressed sensorium and cough reflex [7-10,34]. In this clinical situation, the application of noninvasive and mini-invasive integrated strategies may be successful at attempting to reduce the secretion burden-induced risk of NIV failure.

There is a high level of evidence highlighting that a combined application of NIV with MI-E may reduce the need for ETI and tracheostomy in patients with neuromuscular disorders in ARF with preserved bulbar function, complaining of an accumulation of secretions due to a severely impaired cough [14,34]. However, according to a recent RCT, the "breath-stacking" technique using a lung volume recruitment bag may be a successful and an easier alternative to the MI-E technique to actively enhance secretion clearance in ALS patients with ARF [39].

On contrary, only a few published data suggest that noninvasive physiotherapeutic techniques may be effectively integrated with NIV in acute exacerbations of chronic lung diseases with impaired mucous clearance. Some papers demonstrated that the addition of HFCWO to NIV is likely to improve arterial blood gases in acute-on-chronic respiratory failure with bronchial hypersecretions of different etiology [40,41]. However, a systematic review does not routinely recommend the use of HFCWO in hospitalized COPD patients in acute exacerbations as clinical outcomes may be not much more improved compared to the only usual medical care; consequently, the role of this technique in these patients remains controversial [42], especially for the application of HFCWO in neuromuscular diseases.

FOB may play a therapeutic role during NIV in chronic respiratory diseases with mucous accumulation [34,43,44]. In a matched case-control study, Scala et al. [16] compared 15 acutely decompensated COPD patients with copious secretion retention and hypercapnic encephalopathy due to pneumonia, who were undergoing early FBO plus BAL during NIV in RICU with 15 controls receiving IMV in ICU. An improvement in $PaCO_2$ and pH, as well as hospital mortality, the length of hospital stay, and ventilation duration were not different with NIV plus FOB as compared to the IMV plus FBO strategy. NIV significantly reduced the rate of life-threatening infections and the need for tracheostomy as compared to IMV.

$ECCO_2R$ is a technique developed from the traditional ECMO [17]. ECMO is a "total extracorporeal support" that is able to oxygenate severely hypoxemic ARDS patients and remove up to 50% of the total body CO_2 production; conversely, $ECCO_2R$ is a "partial extracorporeal support" that is able to remove a lower amount of CO_2 while it has no substantial impact on the blood oxygenation due to a lower percentage of cardiac output submitted to artificial lung extracorporeal exchange. The latter has been recently proposed as an alternative or an integrated therapeutic option in patients with acute hypercapnic acidotic respiratory failure who are likely to fail after a NIV trial [45,46]. The advantage of using $ECCO_2R$ in place of ECMO as non-ventilatory tool to wash out an excessive burden of CO_2 is due to the lower rate of severe complications correlated with its less "invasiveness" in terms of a smaller cannula diameter and lower doses of heparin required [17]. Briefly, the fields of application of $ECCO_2R$ are the ultra-protective ventilator strategy in patients with severe ARDS, the bridge to transplant in severely chronically ill patients, and severe hypercapnic respiratory failure due to COPD exacerbations not solving under NIV, mostly occurring in elderly subjects [17,46]. In a matched study with historical controls, the addition of $ECCO_2R$ to NIV in 25 COPD elderly patients with severe acidotic exacerbation and at risk of NIV failure was associated with a significant improvement in pH, $PaCO_2$, and respiratory rate with a significant reduction in the ETI rate as compared to the control

group of 21 patients receiving only NIV [47]. However, about half of patients treated with $ECCO_2R$ plus NIV developed complications, some of them of severe degree (i.e., bleeding episodes and malfunctioning of the system). A subsequent systematic review examined the safety and effectiveness of $ECCO_2R$ to avoid intubation, and its capability to reduce the need and the length of IMV in hypercapnic respiratory failure due to COPD exacerbations both to prevent ETI and extubation failure. According to the included studies, the review concludes that this technique should be still considered experimental; as a matter of fact, higher-quality studies are required to better clarify the risk-benefit ratio of $ECCO_2R$ [46]. This concept is applicable specifically to fragile elderly patients with comorbidities, who are at a higher risk of hemorrhagic complications.

NIV and Palliative Care

The choice of applying NIV to elderly patients responding poorly to ARF (e.g.,., hypoxemia *de novo* or interstitial lung diseases) with the DNI status should be carefully contextualized taking in account the balance between the favorable symptomatic effects of NIV and the risk of a useless prolongation of the interface and ventilator-correlated complications [4,5,11,19,26]. As expected, this issue is still largely controversial. Some authors claim that the palliative use of NIV in this scenario may relieve respiratory symptoms and/or to allow the communication and/or to provide additional time to finalize personal affairs and to come to the acceptance of death [48]. Conversely, other authors considered the use of NIV inappropriate in this context as it may cause discomfort and may prolong uselessly the dying process, while diverting critical care resources away from other patients who are more likely to take clinical advantage from NIV [4,49-51].

A Task Force on the Palliative Use of NIV of the Society of Critical Care Medicine [5] suggested to classify the use of NIV for patients with ARF into three categories: 1) NIV as life support with no preset limitations on life-sustaining pulmonary and non-pulmonary treatments (i.e., ETI, renal support, etc.); 2) NIV as life support when ETI is not considered appropriate by the patient and/or its family; 3) NIV as a palliative measure when patients and families have chosen to forego all life support, receiving only palliative measures. Transition from one category to another may occur due the possible quick variation in the goals of the care or the risk-benefit balance of NIV, as well as patient decisions [4,5]. For subjects refusing ETI as escalating treatment, NIV will be withdrawn, and comfort measures will only be intensified if NIV fails and/or could not be tolerated any longer. Conversely, from the first two categories of candidates for NIV, patients who receive ventilation as the only comfort measure should not be encouraged to tolerate the NIV-associated discomfort because the goal of the chosen therapy is to only relieve the symptoms [52]. In this scenario, there is no point in providing NIV to patients who could not benefit from the effects of ventilation on dyspnea because of severe sensorium alteration or even comatose status [4,5]. This palliative use of NIV may be a feasible symptomatic option also for patients who desire to be transferred home to spend the end of their life in their own home/bed [4,48,49]. The use of anticipated doses of opiates before withdrawing NIV by the end-of-life may be a possible effective strategy to achieve the higher level of patient comfort, similarly to what was already reported with IMV [53]. The transition from mechanical support to an oxygen mask looks much simpler both ethically and technically with NIV than with IMV. In this context, the role of HFNC should also be considered, due to a greater comfort as compared to NIV and the higher physiologic respiratory effects as compared to conventional oxygen therapy.

Another goal of the palliative use of NIV is to integrate its effect on dyspnea with those provided by analgo-sedation pharmacological therapy. Results of a recent multicenter RCT [21] performed in patients with advanced solid cancer showed that compared to the only oxygen and medical therapy, the addiction of NIV may reduce the amount of the needed doses of opiates and therefore their side effects, keeping the sensorium much more preserved. Thus, this may mean a better capability of communication for the patient at the end-of-life with a reliable control of symptoms.

CONCLUSION

The management of ARF in the elderly should include care not only from the technical aspects of ventilatory and non-ventilatory strategies, but also considering the ethical and economic issues. All these points must be contextualized taking into consideration the type of disease, the degree of patient awareness, the achievement of the shared goals, local health resources, and the team's expertise in ventilation and intensive care treatment [54]. NIV together with HFNT remains the ventilatory support of choice in the elderly, provided that the physician carefully analyses the correct selection of the case and the appropriate choice of the setting and of the timing of application. The NIV/HFNC failure management should be done also depending on the will of the patients to either escalate the therapy or to apply palliative and end-of-life care.

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