

**Red, yellow or green for non-invasive mechanical ventilation**

Mechanical ventilation (MV) can be classified as a supportive treatment modality for hypoxemic respiratory failure/ARDS, as we do not have any data to support MV as a curative treatment modality for ARDS.

The question here is how to manage the supportive treatment period in ARDS. For this aim, we have the possibility of increasing the  $FiO_2$  level by several methods (such as high flow nasal  $O_2$  therapy 'HFNOT' and non-rebreathing masks) or the application of invasive/non-invasive MV for a period to allow time for curative treatments. These supportive treatment modalities may be alternated during the application of curative treatment agents (such as antibiotics). For example, we may start supportive therapy by applying HFNOT and switch to non-invasive ventilation according to patient needs. Later on, we may institute invasive MV if the patients condition deteriorates. We may also use adjunctive treatment options such as positioning the patient during these supportive treatment modalities. The problem is choosing the correct modality of support for the individual patient.

Noninvasive ventilation may be used in the initial period of supportive treatment, following a period of HFNOT or invasive MV. It may also be used as a weaning modality of invasive MV. The application rules of NIN ventilation are the same for its application in the case of several diseases. It may have some indications (green), relative contraindications (yellow) or contraindications (red).

To clarify, non-invasive MV may be contraindicated in a patient with pneumonia caused by gram positive bacteria due to high amount of secretions (red). However, it may be used for a patient with pneumocystis carinii pneumonia (green). While choosing the correct patient to administer MV; mild ARDS can be considered green, moderate ARDS may be considered yellow, and severe ARDS may be deemed red.

During application of non-invasive MV, the most important issue is to monitorize the patient. If goals such as decreasing  $FiO_2$  levels are reached, it may be continued. However, if the patients response is not sufficient, invasive ventilation should be instituted without delay.

A recent study in 50 countries has shown that approximately 15% of 3022 ARDS patients were ventilated with non-invasive MV, whereas 10% of them were ventilated exclusively with non-invasive MV (1). This 10% highlights cases in which non-invasive MV was the sole supportive treatment modality in ARDS. To clarify its usage, we have to study or find the answer to the following questions:

Which ARDS patients should receive non-invasive MV?

When should non-invasive MV be used in ARDS?

Which mode and interface should be used during non-invasive MV in ARDS?

How can we prevent intubation delay in patients with ARDS during usage of non-invasive MV?

By answering these questions, we will be able to decide if the use of non-invasive MV is green, yellow or red for the individual patient.

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1. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. *JAMA* 2016;315:788-800.

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# Noninvasive Ventilation for Acute Hypoxemic Respiratory Failure/ARDS – is There a Role?

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Noninvasive ventilation (NIV) has assumed an important role in the management of acute respiratory failure (ARF) over the past 15 to 20 years. Use of NIV increased substantially during the first decade of the 2000s (1) and it accounts now for approximately 40% of total ventilator starts for ARF and up to 80% of starts in patients with ARF due to exacerbations of COPD or acute cardiogenic pulmonary edema (ACPE) (2). However, the application of NIV in patients with so called de novo acute hypoxemic respiratory failure related to pneumonia or acute respiratory distress syndrome (ARDS) has long been known to be more challenging than in more favorable diagnoses like COPD or ACPE, with NIV failure rates for pneumonia/ARDS exceeding 60% in some studies (3). One epidemiologic study showed that these patients were 3.75 times more likely to fail on NIV than patients with other forms of acute hypoxemic respiratory failure such as chest wall trauma or ACPE (4).

Reasons for the poor track record of NIV for patients with pneumonia/ARDS include the need for higher levels of positive end-expiratory pressure (PEEP) to treat the hypoxemia and higher levels of pressure support to counter the increased stiffness of lungs to alleviate work of breathing and dyspnea. These higher pressures necessitate greater strap tension to control mask leaks, contributing to mask discomfort. In addition, the air leaks, in combination with the high respiratory rates and minute volumes seen in patients with pneumonia/ARDS make it difficult for ventilators to achieve good synchrony, contributing further to patient intolerance.

Other challenges are that patients with pneumonia/ARDS often have progressive underlying processes such as sepsis with evolving multiorgan system dysfunction or problems with secretions, both conditions associated with NIV failure, and might need prolonged ventilatory support. An additional concern raised in recent years is that patients with pneumonia/ARDS often have high and potentially injurious tidal volumes that are hard to control during NIV due to the inability to use high doses of sedation and analgesia

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or paralytics. In one recent study, tidal volumes averaging greater than 9.5 mL kg<sup>-1</sup> predicted body weight were associated with higher rates of NIV failure (5).

One earlier study argued that NIV might be more successfully used if limited to a selected sub-population (6). In this study, NIV was used as a “first line” therapy in approximately 30% of patients who hadn’t been intubated by the time they arrived in the ICU. A trial of NIV averted intubation in 54% of these patients and, not surprisingly, NIV success was associated with much better outcomes than NIV failure. Ventilator associated pneumonia occurred in 2% of successes and 20% of failures and mortality in 6% vs. 53%, respectively. Successes were characterized by SAPS II ≤34 and PaO<sub>2</sub>/FiO<sub>2</sub> > 175 after the first hour of NIV. Thus, one could hypothesize that candidates for NIV with pneumonia/ARDS could be offered a trial if initial SAPS II was 34 or less and continued if PaO<sub>2</sub>/FiO<sub>2</sub> rose to more than 175 during the first hour. Of course, a randomized controlled trial would be necessary to determine if this improves outcomes, and this has not yet been done.

Several recent studies have raised further questions about the efficacy of NIV to treat pneumonia/ARDS. Frat et al. (7) randomized over 300 patients with ARDS, 75% with pneumonia, to receive standard oxygen, high-flow nasal therapy (HFNT) or NIV. Although the major outcome variable, need for intubation, showed only a strong trend favoring the HFNT group, the HFNT group had significantly lower ICU and 90 day mortalities than the NIV and standard oxygen therapy groups. Patients in the NIV group used it for only 8 hours daily for 2 days, whereas the rest of the time they used HFNT. Average tidal volume in the NIV group was 9.2 mL kg<sup>-1</sup>, thought to have contributed to greater volutrauma and thereby heightened mortality, but tidal volume was measured in neither the standard oxygen nor HFNT group.

A more recent large observational database on ARDS, the LUNG SAFE study (8), comprised of centers in Europe and North America, showed that NIV failure rates ranged from 22% in mild, 42% in moderate and 47% in severe ARDS and that mortality rates in mild and severe patients were 16% and 45%, respectively. Of particular concern, however, was that the mortality rate of patients with a PaO<sub>2</sub>/FiO<sub>2</sub> <150 was actually greater in patients treated with NIV than in those treated with invasive mechanical ventilation. This raises the concern that NIV may be more hazardous to use in patients with more severe ARDS than proceeding directly to invasive mechanical ventilation. It is important to acknowledge, however, that this was not a randomized controlled study and thus was hypothesis-generating only.

Given the unfavorable results from a long history of studies on NIV to treat pneumonia/ARDS one might question whether NIV should be used at all for this indication, especially when there is an option like HFNT to treat pneumonia/ARDS that showed superior results in the Frat study (7). However, recent experience has taught us that we must be careful accepting the results of a single

RCT, even if it included multiple centers. Why, for example, did Frat et al. (7) target a tidal volume of 7 to 10 mL kg<sup>-1</sup> in the NIV group, clearly excessive in the age of lung protective strategies? Also, why were there so many deaths due to refractory shock in the NIV group (17%) compared to 6% in the HFNT group? The authors argue that this was related to more intubations and ventilator associated pneumonias leading to sepsis in the NIV group, but could there have been a problem with randomization?

Before we abandon NIV altogether, we should consider another recent study suggesting that the particular interface used for NIV might be important for success. Patel et al. (9) randomized 80 patients at a single center to receive NIV using a full-face mask versus a helmet-type interface. The major outcome variable, rate of intubation, was significantly less (18%) with the helmet compared to a full-face mask (62%). Acknowledging all the caveats surrounding relatively small, single center studies, it is conceivable that attributes of helmet NIV, such as delivery of higher PEEP, contributed to the better outcomes.

Presently, we are in flux regarding recommendations on use of non-invasive ventilatory techniques to treat ARF due to pneumonia/ARDS. HFNT clearly has comfort and tolerability advantages over NIV or even standard oxygen and most patients can tolerate 24/7 use, something that is difficult to achieve with NIV. The Frat study suggests that HFNT yields better outcomes, even survival, than either standard oxygen or NIV, with the effect more pronounced in sicker patients. Thus, it could be argued that HFNT should be used whenever oxygen needs exceed what can be delivered using standard nasal prongs. On the other hand, the Patel et al. (9) favors the idea that the interface makes a big difference when NIV is used and that the helmet may effect an even greater reduction in need for intubation than HFNT when compared to face mask NIV.

Clearly, more studies are needed and helmet NIV needs to be compared to directly to HFNT. Until then, we recommend, by virtue of its effectiveness at oxygenation and greater tolerability, that HFNT be used initially when oxygen needs exceed what can be attained with standard nasal prongs at 6 L min<sup>-1</sup>. A trial of NIV, perhaps using a helmet where it is available and caregivers are experienced, might be considered if HFNT fails to improve oxygenation. But we also strongly caution against persisting with noninvasive approaches if the patient’s underlying process is progressing and oxygenation is not improving. Invasive mechanical ventilation should still be considered the mainstay for management of pneumonia/ARDS and we should continue to vigilantly avoid unnecessary delays of needed intubation.

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