# Non-invasive Mechanical Ventilation and Prevention of Pneumonia in Patients with Acute Respiratory Failure

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## Introduction

Critically ill patients are at high risk of developing nosocomial infections due to their severity of illness, immunosuppression, and prolonged hospitalization. Among nosocomial infections, pneumonia affects from 20 to 30% of intensive care unit (ICU) patients and is the leading cause of death [1]. The use of the endotracheal (ET) tube to deliver ventilatory support is the single most important predisposing factor for developing nosocomial bacterial pneumonia [2]. Fagon et al. [3] have demonstrated that the risk of pneumonia is incremental in ventilated patients and increases by about 1% per day of continuous invasive ventilation.

Nevertheless, patients with acute respiratory failure often require life-supporting mechanical ventilation. The target points of ventilatory support in patients with acute respiratory failure are reduction in the work of breathing (WOB) and alveolar recruitment to increase the functional residual capacity.

Recently, several authors have demonstrated that non-invasive mechanical ventilation (NIV) may represent a valid, complementary, or alternative approach to conventional ventilation with ET tube in selected groups of patients [4–6].

The application of pressure support ventilation (PSV) and positive end-expiratory pressure (PEEP), delivered by a nasal or a full-face mask, seems to be effective in unloading the respiratory muscles and improving gas-exchange by the recruitment of under-ventilated alveoli [7–9]. This approach may have several advantages in terms of prevention of infections, mainly reducing the rate of ET intubation. Factors involved in reducing the rate of ventilator-associated pneumonia (VAP) may include the maintenance of natural barriers provided by the glottis and the upper respiratory tract, the reduction in need of sedation and the shortening of duration of mechanical ventilation.

Patients with acute on chronic respiratory failure are the most likely to benefit from NIV treatment in term of both additive morbidity and mortality [10–16]. However, clinical evidence exists to propose NIV treatment as first line intervention in early hypoxemic acute respiratory failure [17–24]. Randomized and non-randomized studies on the application of NIV in patients with hypoxemic acute respiratory failure have showed promising results, with reduction of complications, including sinusitis and VAP, and shorter duration of ICU stay [24–36].

NIV can be applied at different phases of the acute respiratory failure (Fig. 1):

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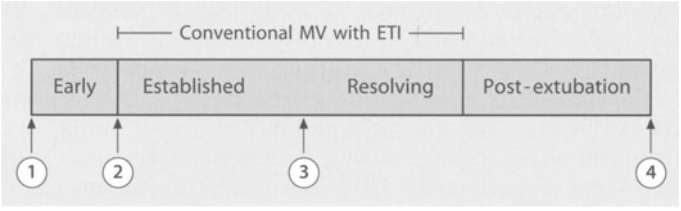


**Fig. 1.** Timing 1–4, see text, of application of non-invasive ventilation (NIV) (reproduced with permission from G. Umberto Meduri MD, University of Tennessee Health Science Center Memphis, TN). ETI: endotracheal intubation

1) during the early phases to prevent ET intubation;
2) when the respiratory failure is already established as a treatment alternative to ET intubation and
3) during the resolution of acute respiratory failure as a means to wean patients from mechanical ventilation or
4) post-extubation, in order to prevent re-intubation.

In the present chapter, the efficacy of NIV in preventing episodes of pneumonia in patients with acute respiratory failure will be discussed through randomized and non-randomized studies where NIV has been adopted as a modulated approach at different times of acute respiratory failure.

## Early NIV: Randomized Trials in Immunocompetent Patients

Several prospective randomized studies have evaluated the usefulness of NIV in avoiding ET intubation and reducing complications related to intubation in patients with hypercapnic and hypoxemic acute respiratory failure.

In a controlled study including 85 patients with chronic obstructive pulmonary disease (COPD), Brochard et al. [16] randomized 43 patients to receive NIV via face mask for at least 6 hours per day and 42 patients to receive standard therapy with oxygen supplementation. The authors found that NIV improved gas-exchange and decreased both the rate of ET intubation and the length of stay in the ICU. There was a trend to reduction of VAP in the NIV group in comparison to patients receiving conventional treatment (5 vs 17%, $p$ = NS). In this study, the crude mortality was significantly decreased in patients receiving NIV treatment.

Wysocki et al. [25] compared NIV delivered through a face mask versus conventional therapy in a group of 41 patients with acute respiratory failure. A reduction in ET intubation (36 vs 100%, $p = 0.02$), duration of ICU length of stay ($13 \pm 15$ vs $32 \pm 30$ days, $p = 0.04$), and in mortality rate (9 vs 66%, $p = 0.06$) was observed only in hypercapnic patients. The authors concluded that NIV may not be effective in all forms of acute respiratory failure not related to COPD, but the incidence of pneumonia and severe sepsis was not reported.

In a randomized, controlled, prospective trial, Wood et al. [27] evaluated the effects of early NIV in 27 patients with hypoxemic acute respiratory failure requiring admission to the emergency department. Sixteen patients (59.3%) were randomly assigned to receive conventional medical therapy plus NIV and 11 patients (40.7%) to receive conventional medical therapy alone. NIV was delivered by a nasal mask

with biphasic positive airway pressure (BiPAP) ventilator. The rate of pneumonia was higher in the group receiving conventional medical therapy than in the NIV group (18 vs 0%, $p < 0.05$).

Confalonieri et al. [28] conducted a multicenter, prospective, randomized study comparing standard treatment plus NIV delivered through a face mask to standard treatment alone, in patients with acute respiratory failure caused by severe community-acquired pneumonia. Fifty-six consecutive patients (28 in each arm) were enrolled, and the two groups were similar at study entry. Patients randomized to NIV had a significantly lower rate of ET intubation (21 vs 50%, $p = 0.03$) and a shorter duration of ICU stay ($1.8 \pm 0.7$ vs $6 \pm 1.8$ days, $p = 0.04$). Among patients with COPD, those randomized to NIV had a lower intensity of nursing care workload ($p = 0.04$) and improved 2-month survival (88.9 vs 37.5%, $p = 0.05$). Timing to ET intubation was similar in both groups, and rate of complications developing during intubation was not increased in patients failing NIV and requiring intubation. Complications associated with conventional mechanical ventilation included two cases of bronchoalveolar lavage (BAL)-proven VAP, one case of otitis and mastoiditis, and one of pneumothorax. All these complications occurred in patients originally randomized to standard treatment.

In a prospective randomized trial, Martin et al. [29] compared non-invasive positive pressure ventilation (NPPV) with usual medical care in the treatment of patients with acute respiratory failure of various origins. Thirty-two patients were randomized to receive NPPV and 29 to receive usual medical care (UMC). NPPV was delivered through a BiPAP system, using initial inspiratory (IPAP) and expiratory (EPAP) positive airway pressure levels of 5 $cmH_2O$. A significantly lower rate of ET intubation was observed in the NPPV group than in the usual medical care group (6.38 intubations vs 21.25 intubations per 100 ICU days; $p = 0.002$). Mortality rates in the ICU were similar for the two treatment groups (2.39 [NPPV group] vs 4.27 deaths [UMC group] per 100 ICU days, $p = 0.21$). Patients with hypoxemic acute respiratory failure in the NPPV group had a significantly lower ET intubation rate than those in the usual medical care group (7.46 intubations vs 22.64 intubations per 100 ICU days, $p = 0.026$); a similar trend was reported also in patients with hypercapnic acute respiratory failure (5.41 intubations [NPPV group] vs 18.52 intubations [UMC group] per 100 ICU days, $p = 0.064$). No infectious complications were evidenced in the two groups.

## Randomized Trials in Immunocompromised Patients

Avoiding intubation is a major goal in the treatment of acute respiratory failure in immunosuppressed patients. However, few clinical data are available on the efficacy of NIV in these high risk patients. Two different randomized studies suggest that early NIV application is a therapeutic challenge in patients after transplantation or with immunosuppression of various origins. In a prospective randomized study, Antonelli et al. [30] compared the use of NIV delivered through a face mask with standard treatment using oxygen supplementation to avoid ET intubation, in 40 patients with hypoxemic acute respiratory failure after solid organ transplantation. Twenty patients were randomly assigned to each group and the two groups were similar for baseline characteristics at study entry. All COPD patients were excluded.

Within the first hour of treatment, 14 (70%) of the 20 patients in the NIV group improved their $PaO_2/FiO_2$ ratio vs five (25%) in the standard treatment group. The improvement of gas-exchange over time was more prolonged in the NIV group than in the standard treatment group (60 vs 25%; $p = 0.03$). The use of NIV was well tolerated, safe, and associated with a significant reduction in ET intubation (20 vs 70%, $p = 0.05$) and in severe sepsis and septic shock rates, including VAP (20 vs 50%, $p = 0.047$). Patients in the NIV group had lower durations of ICU stay (mean [SD] days, 5.5 [3] vs 9 [4], $p = 0.03$) and lower rates of ICU mortality (20 vs 50%, $p = 0.05$) than those in the standard treatment group. Hospital mortality did not differ in the two groups.

Hilbert et al. [31] investigated the ability of NIV to prevent ET intubation and serious complications in patients with hematological malignancies, immunosuppression, bone marrow transplantation or human immunodeficiency virus (HIV). Fifty-two patients were enrolled into the study and randomized (26 in each arm) to receive standard treatment with oxygen therapy through a Venturi mask or standard treatment plus intermittent face mask NIV. The authors found that patients in the NIV group required less ET intubation (46 vs 77%, $p = 0.03$) and had fewer serious complications (50 vs 81%, $p = 0.02$) than patients in the standard treatment group. The early application of NIV was associated with a decrease in the rate of VAP (12 vs 35%, $p = 0.05$), and in ICU and hospital mortality (10 vs 18 patients, $p = 0.03$ and 13 vs 21 patients, $p = 0.02$, respectively).

These results confirm that the early application of NIV to immunosuppressed patients with hypoxemic acute respiratory failure may be effective in preventing episodes of VAP, by avoiding ET intubation. Moreover, the reduction in additive morbidity may improve patient survival.

## NIV as a Means of Treating Established Acute Respiratory Failure: Randomized Trials

Recently, Antonelli et al. [24] conducted a prospective, randomized trial comparing NIV via face mask to ET intubation with conventional ventilation in hypoxemic acute respiratory failure patients who met well defined criteria for mechanical ventilation. Sixty-four consecutive patients were enrolled (32 in each arm) and randomly assigned to each group. The study had a true 'intention to treat' approach and represents the first trial that used NIV as an alternative to conventional mechanical ventilation with ET intubation when the acute respiratory failure is already established. After 1 hour of mechanical ventilation, 20 out of the 32 patients (62%) in the NIV group and 15 of the 32 patients (47%) in the conventional ventilation group improved their ratio of $PaO_2$ to $FiO_2$ ($PaO_2/FiO_2$) ($p < 0.05$). Patients in the conventional ventilation group had more serious complications (66 vs 38%, $p = 0.02$) and ET intubation-related complications, including pneumonia and sinusitis (31 vs 3%, $p = 0.003$), than patients in the NIV group. Among patients who failed NIV and required ET intubation, 12 patients (38%) developed serious complications. One of these 12 patients had pneumonia after 6 days of ET intubation. Among survivors, patients in the NIV group had a shorter duration of mechanical ventilation ($3 \pm 3$ vs $6 \pm 5$ days, $p = 0.006$) and a shorter stay in the ICU ($6.6 \pm 5$ vs $14 \pm 13$ days, $p = 0.002$) than those in the conventional ventilation group.

Factors that may have been involved in shortening the duration of mechanical ventilation in the NIV group included avoidance of sedation, lower rate of VAP,

elimination of the extra-work imposed by the ET tube and earlier removal from MV. The authors concluded that NIV is as effective as conventional ventilation in improving gas-exchange in patients with hypoxemic acute respiratory failure and that when ET intubation is avoided the development of VAP is unlikely.

## NIV as a Weaning Strategy or to Avoid Re-Intubation: Randomized Trials

The rationale for NIV as a weaning strategy may be related to the ability of NIV to decrease the workload of respiratory muscles, and the development of rapid and shallow breathing associated with unsuccessful weaning from mechanical ventilation.

Nava et al. [12] conducted a prospective randomized controlled study to evaluate the use of non-invasive PSV in the weaning of COPD patients with acute respiratory failure. Fifty patients who had failed a T-piece trial were randomized (25 in each group) to extubation with immediate application of NIV with pressure support or to weaning with ET intubation in pressure support mode. Twenty-two out of the 25 patients (88%) in the NIV group were successfully weaned vs 17 in the invasively ventilated group (68%). None of the patients (0%) in the NIV group developed VAP whereas 7 patients (28%) in the invasive weaning group did ($p = 0.005$). The use of NIV significantly decreased the duration of ICU stay ($15 \pm 5$ vs $24 \pm 13$ days; $p < 0.05$) and increased the 60-day-survival rate (92 vs 72%, $p = 0.009$).

This study showed that by using NIV as a weaning strategy, the likelihood of weaning success increases, with a decrease in the additive morbidity and the overall mortality.

The effect of NIV during persistent weaning failure was evaluated in another randomized clinical trial [13] including 43 patients who had failed a spontaneous breathing trial for three consecutive days. Thirty-three of these patients had underlying chronic obstructive failure. Patients were randomly assigned to be extubated with NIV or to follow a conventional weaning approach. In this study, the authors found that NIV was effective in facilitating the weaning process, reducing the duration of mechanical ventilation and need for tracheostomy. NIV was associated with a decrease in additive morbidity, including the incidence of VAP, septic shock and multiple organ failure (MOF), and with improvement in the ICU and 90-day cumulative mortality.

## NIV: Non-randomized Studies

The ability of NIV to prevent nosocomial pneumonia was also demonstrated in a prospective epidemiological survey on a cohort of 320 consecutive patients with acute respiratory failure on more than 48 hours of mechanical ventilation [32]. The authors reported a lower ($p = 0.004$) rate of VAP in non-invasively supported patients (0.16 per 100 days of NIV) versus those on conventional ventilation (0.85 per 100 days of ET intubation).

Similar results were reported by Nourdine et al. [33] in a prospective study comparing a group of 159 patients with acute respiratory failure of various origins, treated with NIV and 607 patients with ET intubation and mechanical ventilation. The authors described a significantly lower incidence of VAP (4.4 vs 13.2 per 1000 patients/days, $p < 0.05$) and other nosocomial infections in the NIV group in comparison to the conventional ventilation group.

Recently, Girou et al. [34] conducted a matched-case control study that described the application of NIV in everyday clinical practice on 100 patients with acute exacerbation of COPD or hypercapnic cardiogenic pulmonary edema, to evaluate whether the use of NIV was associated with a decreased risk of nosocomial infection and improvement of survival. NIV was delivered in 134 out of 1040 patients. Only 50 of these patients were eligible as cases and treated with NIV for at least two hours. Fifty control patients receiving conventional ventilation with ET intubation were matched for diagnosis, age, simplified acute physiology score II (SAPS II), logistic organ dysfunction (LOD) score and absence of contraindications to NIV treatment.

The 50 patients treated with NIV developed significantly fewer complications ($p=0.006$) during their ICU stay and received fewer antibiotics for nosocomial infection (8 vs 26%, $p=0.01$) than controls. Rates of nosocomial infection (18 [NIV group] vs 60% [ET group], $p<0.001$) and pneumonia (8 [NIV group] vs 22% [ET group]; $p=0.04$) were significantly decreased when NIV was applied. Interestingly, the authors also observed that the mean duration of ventilation (mean [SD]; 6 [6] vs 10 [12] days, $p=0.01$), mean duration of ICU stay (9 [7] vs 15 [14] days, $p=0.02$), and crude mortality (4 vs 26%; $p=0.002$) were lower in the NIV group than in the ET intubation group.

In a prospective survey among 42 ICUs, Carlucci et al. [35] enrolled 689 patients with acute respiratory failure who required ventilatory support. In 108 of these patients, NIV treatment was delivered through a face mask. Among the 581 patients receiving conventional treatment with ET intubation, 382 were intubated before ICU admission. SAPS II score was significantly higher in patients receiving conventional treatment with ET intubation (mean [SD]; 47 [21] vs 36 [20]; $p<0.001$) than in patients receiving NIV treatment. Eleven patients (10%) in the NIV group and 72 patients (19%) in the ET intubation group developed nosocomial pneumonia ($p=0.03$). Overall mortality was significantly decreased in the NIV group (22 vs 41%; $p<0.001$). The authors concluded that NIV may be successful in selected patients and is associated with a decreased risk of pneumonia and death.

In a prospective multicenter cohort study [36], Antonelli et al. prospectively investigated outcome descriptors for NIV in a population of 354 hypoxemic patients with acute respiratory failure of various origins. The authors found that NIV was successful in 264 (70%) patients whereas 108 (30%) patients failed NIV treatment and required ET intubation. A multivariate analysis identified age >40 years (OR=1.72, 95% CI: 0.92–3.23), SAPS II score ≥35 (OR=1.81, 95% CI: 1.07–3.06), the presence of ARDS or community-acquired pneumonia (OR=3.75, 95% CI: 2.25–6.24), and a $PaO_2:FiO_2 \leq 146$ mmHg after 1 hour of NPPV (OR=2.51, 95% CI: 1.45–4.35), as factors independently associated with NPPV failure. Throughout the study period, patients avoiding ET intubation had shorter duration of mechanical ventilation (median [range], 48 [1–216] vs 24 [1–192] days, $p=0.06$) and ICU length of stay (median [range], 5 [3–31] vs 9 [1–72] days, $p<0.001$) than those requiring ET intubation. Successful NIV was associated with a significant decrease in the rate of VAP (0.4 [NIV success] vs 28% [NIV failure], $p<0.01$), severe sepsis and septic shock (3 [NIV success] vs 65% [NIV failure], $p<0.01$).

## Future Perspectives

During the early phases of hypoxemic acute respiratory failure, if disconnection from mechanical ventilation occurs, patients can rapidly deteriorate gas exchange with potential life threatening consequences. Thus, the improvement of patient-ventilator interface seems crucial to achieve a prolonged application of NIV.

NIV can fail due to: a) conditions related to the disease (inability to correct hypoxia, manage copious secretions, etc.) or b) technical causes (intolerance, skin necrosis).

Attempting to improve tolerance of patients we adopted a transparent Helmet® (Starmed, Mirandola, Italy) (Fig. 2) made in latex-free PVC as an interface during non-invasive PSV. The device allows patients to see, read and speak, and actively interact with the environment.

We conducted a prospective clinical pilot investigation [37], on 33 consecutive non-COPD patients with hypoxemic acute respiratory failure treated by pressure support delivered by helmet and 66 matched controls treated with pressure support delivered by facial mask. Eight patients (33%) in the helmet group and 21 patients (32%) in the facial mask group ($p = 0.3$) failed non-invasive PSV and were intubated. No patients failed non-invasive PSV due to intolerance of the technique in the helmet group in comparison with 8 patients (38%) in the mask group ($p = 0.047$). Complications related to the technique (skin necrosis, gastric distension and eye irritation) were fewer in the helmet group compared to the mask group (no patients vs 14 patients; $p = 0.002$). Four patients (12%) in the helmet group and 10 patients (20%) in the mask group developed nosocomial pneumonia after the study entry ($p = 0.3$).

Interestingly, three of the four pneumonias in the helmet group and six of the 10 nosocomial pneumonia in the mask group developed only after the failure of non-invasive PSV and ET intubation. Helmets allowed the continuous application of non-invasive PSV for a longer period of time ($p = 0.05$). Length of stay in the ICU, intensive care, and hospital mortality were not different in the two groups. We showed that non-invasive PSV by helmet successfully treated hypoxemic acute respiratory failure, with better tolerance and fewer complications than facial mask non-invasive PSV.

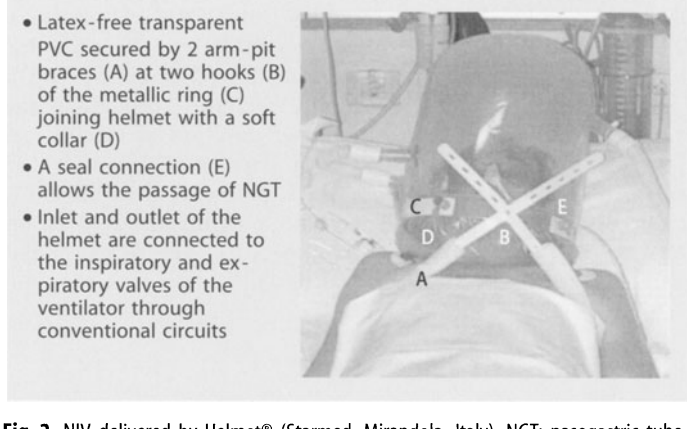


**Fig. 2.** NIV delivered by Helmet® (Starmed, Mirandola, Italy). NGT: nasogastric tube

If larger studies confirm these preliminary data, the helmet could become another valid therapeutic option to deliver non-invasive PSV to patients with hypoxemic acute respiratory failure.

## Conclusion

Randomized and non-randomized clinical studies [17–36] conducted on more than 2000 patients have demonstrated that NIV is really effective in the clinical management of patients with acute respiratory failure.

When NIV is successful, and ET intubation is avoided, the development of nosocomial pneumonia is unlikely (Table 1). Recent studies [24–37] have also reported that NIV treatment may be attempted as a first line intervention for hypoxemic acute respiratory failure with significant reductions in nosocomial infection, including VAP, as well as in antibiotic use, duration in ICU stay, and overall mortality. However, large prospective randomized multicenter trials are needed to obtain a definitive consensus.

**Table 1.** Randomized studies evaluating the usefulness of early non-invasive ventilation (NIV) as a means of preventing nosocomial pneumonia

| Author | Year | N. of pts NIV vs ETI | Episodes of PNEU in CT group (%) | Episodes of PNEU in NIV group (%) | p-value | Mortality in CT group (%) | Mortality in NIV group (%) | p-value |
|---|---|---|---|---|---|---|---|---|
| Brochard [16] | 1995 | 43 vs 42 | 17 | 5 | NS | 29 | 9 | 0.02 |
| Wysocki [25] | 1995 | 21 vs 20 | NR | NR | NR | 66 | 9 | NS |
| Antonelli [24] | 1998 | 32 vs 32 | 25 | 3 | 0.003 | 47 | 28 | NS |
| Wood [27] | 1998 | 16 vs 11 | 18 | 0 | <0.05 | 0 | 25 | NS |
| Confalonieri [28] | 1999 | 28 vs 28 | 7 | 0 | <0.05 | 88.9* | 37.5* | 0.05* |
| Martin [29] | 2000 | 14 vs 11 | 0 | 0 | NS | 34 | 16 | NS |
| Antonelli [30] | 2000 | 20 vs 20 | 20 | 10 | 0.047 | 50 | 20 | 0.05 |
| Hilbert [31] | 2001 | 26 vs 26 | 35 | 12 | 0.05 | 69 | 38 | 0.03 |

PNEU = pneumonia; Pts = patients; ETI = endotracheal intubation; CT = conventional treatment; NR = not reported; NS = not significant.

* Refers only to patients with chronic obstructive pulmonary disease

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