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WHAT'S NEW IN INTENSIVE CARE

My paper 20 years later: NIV in immunocompromized patients

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Introduction, historical background

Twenty years ago we designed a trial, the first patients were included in May 1998, and in 2001 we published in *the New England Journal of Medicine* the study entitled 'Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure' [1].

Pulmonary complications were an important cause of illness in immunocompromised patients and invasive mechanical ventilation (MV) was associated with a significant risk of death [2, 3]. Thus, avoiding intubation should be an important objective in the management of hypoxemic acute respiratory failure (ARF) in immunosuppressed patients.

There were only limited data on the efficacy of NIV in high-risk immunocompromized patients [4, 5].

Summary of original study

In a prospective, randomized, controlled study, we compared the efficacy of NIV delivered intermittently through a mask with that of standard medical treatment with supplemental oxygen and no ventilatory support in patients with immunosuppression of various causes in whom hypoxemic ARF had been precipitated by pulmonary infiltrates and fever [1]. It is important to underline that randomization was done well before the patients were even headed for intubation. Fifty-two patients were included (26 in each group), the immunosuppression could have been caused by neutropenia after chemotherapy or bone marrow transplantation in patients with hematological cancers (15 in each group), drug-induced immunosuppression in organ-transplant recipients, or as a result of corticosteroid or cytotoxic therapy for a non-malignant disease, or AIDS. In the NIV group, as compared with standard therapy, fewer patients required endotracheal intubation (12 vs. 20, RR 0.60, 95% CI 0.38–0.96; $p=0.03$). Serious complications and complications resulting in death in ICU were significantly higher in the standard treatment group than in the NIV group (81 vs. 50%, $p=0.02$ and 69 vs. 38%, $p=0.03$, respectively). Overall, with NIV, there were improvements in mortality in the ICU (10 vs. 18, RR 0.56, 95% CI 0.32–0.96; $p=0.03$), and in total in-hospital mortality (13 vs. 21, RR 0.62, 95% CI 0.40–0.95; $p=0.02$).

The main limitation of our study was certainly the small number of patients included. Nevertheless, our study was in agreement with publication standards in our field. To our knowledge, two important randomized controlled studies had been published by Antonelli et al. [5] on NIV in hypoxemic ARF, before our contribution: the first where immunocompromised patients were excluded (64 patients) and the second with 40 patients.

Implications of this original study

Over the last years, overall survival rates of immunocompromised patients admitted to the ICU are improving [6, 7]. Nevertheless, the negative impact of intubation and MV has been confirmed in recent studies [6, 8]. Hospital mortality was 45.3% in critically ill hematologic patients with neutropenia, and need for MV was associated with a poor outcome (OR 6.57; 95% CI 3.51–12.32) [6]. In a very recent study, the need for intubation was associated with mortality with higher odds for mortality in case of NIV or high flow oxygen (HFO) failure [8].

It is also important to well know the limits of NIV and the criteria predictive for failure that must push towards

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an invasive strategy. Indeed, if the methods can represent an alternative to intubation, conversely a delay to perform a necessary intubation can be very detrimental to the patient.

ARF in immunocompromised patients is a recognized indication of NIV [9]. ATS 2005 guidelines on the management of adults with nosocomial pneumonia recommended (with a Level I) that "Noninvasive ventilation should be used whenever possible in selected patients with respiratory failure" in order to prevent ventilator induced pneumonia [10].

Subsequent studies

To our knowledge, since the publication of our original paper, a single large prospective controlled study has been published on NIV in immunocompromised patients. The primary outcome was day-28 mortality in this multicenter randomized study on patients receiving treatment for hematologic malignancies or solid tumors [11]. No mortality benefit was demonstrated at day 28, with 24.1% mortality in the group NIV vs 27.3% in the group receiving oxygen alone ($p=0.47$). Furthermore, intubation rates were not different between the groups (38.2 vs 44.8%, $p=0$ 0.25).

This study has much strength. It was well designed, with excellent compliance to the protocol and 100% long-term follow-up. The end points of 28-day mortality and need for endotracheal intubation are objective with a low risk of bias likely to affect the results.

Nevertheless, as underlined in the editorial of the paper [12], the patients enrolled in the earlier trials by Hilbert et al. [1] and Antonelli et al. [5] had greater degrees of tachypnea compared with patients in the current study (35–38 vs. 25/min), suggesting a greater severity of respiratory failure in the previous trials. In addition to the lesser severity of ARF in this study [11] than in previous studies [1, 5], a severity of illness score of the disease was not reported unlike previous studies.

A post hoc subgroup analysis of the FLORALI study was performed in the 82 immunocompromised subjects included in the princeps study [13]. In this last trial, patients were randomly assigned to receive either standard oxygen, HFO alone, or NIV interspaced with HFO between NIV sessions. The lack of stratification for immunocompromised status in the princeps study of Frat et al. may have led to unbalances between randomization groups in the post hoc analysis. It seems very important to stress that in this last study, patients with neutrophil count < 500 neutrophils per mm3 were excluded. The proportion of intubated patients was lower for patients treated with HFO than in those treated with the combination of HFO and NIV (31 vs. 65%, $p=0.04$).

However, from our point of view, some intubation criteria used in this last study were questionable, such as intolerance to NIV. For us, intolerance to NIV is not systematically an intubation criterion but more a message to try to optimize NIV [14]. Intubation led to more nosocomial pneumonia, septic shocks, and higher mortality at day 90 in patients treated with the combination of HFO and NIV than in patients in the HFO group (15 vs. 46%, $p=0.046$) [13]. The authors hypothesized that NIV could have increased the incidence of ventilator-induced lung injury due to increased tidal volumes (> 9 ml/kg) [13]. This hypothesis was argued in other trials and reminds us that any ventilation, including NIV, must improve gas exchange, support the work of breathing, but must also be protective.

On the other hand, the randomized trial by Lemiale et al. [11] found no benefit but also no harm from NIV; in a post hoc analysis of this last princeps study, HFO was neither associated with a lower intubation rate nor day-28 mortality [15]. In a large multinational observational prospective cohort study, NIV did not influence the need for intubation or mortality rates; in addition, the association of HFO + NIV was not associated with increased intubation or hospital mortality [8]. In an additional trial, among 178 patients with solid cancer or hematological disease and hypoxemic ARF, 43% received HFO associated with NIV, 42% NIV associated with conventional oxygen therapy, 11% HFO alone, and 5% conventional oxygen therapy alone. Patients receiving NIV-HFO had lower mortality than the other patients (37 vs. 52%, $p=0.045$) [16]; in a propensity analysis, after adjustment for the propensity score, the combination of HFO and NIV was independently associated with improved survival.

The American Thoracic Society and the European Respiratory Society published this year their clinical practice guidelines on NIV for ARF [17]. Pooled analysis of relevant studies demonstrated that NIV use led to a decrease in mortality (RR 0.68, 95% CI 0.53–0.88; moderate certainty), the need for intubation (RR 0.71, 95% CI 0.58–0.87; moderate certainty) and the rates of nosocomial pneumonia (RR 0.39, 95% CI 0.20–0.76; low certainty) in immunocompromised patients. The guideline committee suggested early NIV for immunocompromised patients with ARF (conditional recommendation, moderate certainty of evidence) [17].

Table 1 reports prospective, randomized, and controlled studies on NIV in immunosuppressed patients with ARF, and discussed in this paper.

Table 1 Main prospective, randomized, controlled studies on NIV in immunocompromised patients with hypoxemic acute respiratory failure (ARF)

Study, year [references]	Arms	Patient number	Underlying conditions	Severity of ARF: RR/min	Primary outcome	Main results
Antonelli et al., 2010 [5]	NIV/Oxygen therapy alone	20/20	Recent organ transplant	38 ± 3/37 ± 1	Need of intubation	Intubation rate was lower in the NIV group than in the oxygen group (20 vs 70%; $p = 0.002$) Hospital mortality did not differ
Hilbert et al., 2011 [1]	NIV/Oxygen therapy alone	26/26	Various immunocompromised	35 ± 3/36 ± 3	Need of intubation	Intubation rate was lower in the NIV group than in the oxygen group (12 vs. 20, $p = 0.03$) With NIV, there were improvements in total in-hospital mortality (13 vs. 21, $p = 0.02$)
Lemiale et al., 2015 [11]	NIV/Oxygen therapy alone	191/183	Various immunocompromised	27 (21–31)/25 (21–30)	day-28 mortality	No mortality benefit with NIV at day 28 (NIV: 24.1% vs oxygen: 27.3%; $p = 0.47$) Intubation rates were not different
Frat et al., 2016 [13][a]	HFO alone/NIV + HFO/standard Oxygen	26/26/30	Various immunocompromised Patients with neutrophil count < 500 neutrophils per mm3 were excluded	32 ± 5/33 ± 8/32 ± 6	Need of intubation within 28 days	Intubation rate was lower in the HFO group than in the NIV + HFO group (31 vs 65%, $p = 0.04$) Mortality rate at day 90 was higher in NIV + HFO group than in HFO group (15 vs 46%, $p = 0.046$)

NIV noninvasive ventilation, *RR* respiratory rate, *HFO* high flow oxygen

[a] Post-hoc analysis of a randomized trial

Conclusions

Intensive care management of ARF in immunocompromised patients has progressed in the last two decades.

In our opinion, while acknowledging concerns raised by recent trials, NIV must be part of the standard of care in immunocompromised patients with pulmonary infiltrates, fever, ARF and without criteria of ARDS.

Studies to appraise oxygenation and ventilation strategies in immunosuppressed patients with hypoxemic ARF (tachypnea > 30/min) are still warranted.

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Compliance with ethical standards

Conflicts of interest
The authors do not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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