

EDITORIAL

Non-invasive mechanical ventilation in hematology patients with hypoxemic acute respiratory failure: a false belief?

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Acute respiratory failure (ARF) is the most frequent and challenging life-threatening event in patients with hematological malignancies.¹ In patients with prolonged neutropenia, respiratory events occur in up to half the cases, of which half are complicated by ARF.² Although significantly improved over the last two decades^{3–5} survival of hematology patients with ARF remains low, especially when mechanical ventilation is needed.

Non-invasive mechanical ventilation (NIV) successfully treats ARF in patients with hyperbaric chronic obstructive pulmonary disease exacerbation or cardiac pulmonary edema.⁶ NIV is helpful to reduce the need and complications from intubation and invasive mechanical ventilation. In addition, NIV has also been recommended in other clinical conditions such as hypoxemic ARF in immunocompromised patients.⁷ The benefit seems convincing in the postoperative setting of organ transplantation.⁸ However, only very few studies have actually demonstrated benefit in hematology patients. Most of these studies did not control time between ARF onset to NIV implementation, without taking into account ARF etiology, or the presence of associated organ dysfunction at the time of NIV initiation.⁹ As a consequence, prophylactic NIV (in patients with hypoxemia but no respiratory distress) and curative NIV (patients with respiratory distress needing ventilatory support) were lumped together (Table 1). Furthermore, chronic obstructive pulmonary disease and cardiac patients were included, as were patients with various ARF etiologies, some of which may respond better to NIV. These limitations add to safety concerns with the use of NIV in ARF patients who could benefit from early intubation and mechanical ventilation.^{10,11}

A well-designed single center randomized controlled study of prophylactic NIV in hypoxemic immunocompromised patients (including 30 hematology patients) demonstrated highly significant benefit from NIV.¹² As a striking finding in this study published 10 years ago, 90% of the patients intubated and 50% of the patients with NIV success died. Corresponding figures nowadays would be up to 60 and 15%.¹³ Therefore, we are convinced that the current literature has witnessed important advances over the last decades, at a time where most of the hematology patients requiring intubation and mechanical ventilation were dying. However, we also believe that the same studies remain inconclusive now that a substantial number of patients survive to life-sustaining therapies, more particu-

larly mechanical ventilation. Therefore, additional studies are warranted, more particularly in hematology patients, to appraise and update the literature. NIV should be compared with oxygen and early intubation when needed, a therapy that offers nowadays substantial chances of survival.

Table 1 summarizes results from studies that have evaluated NIV in cancer patients. Taken together, these studies suggest benefits from trials of prophylactic intensive care unit (ICU) NIV in patients without extra-respiratory-associated acute organ dysfunctions. They also highlight the risk from late intubation, that is, after NIV failure. However, as shown in Figure 1, compiled data from the current literature does not enable us to draw any sound conclusion.

In the current issue of the Journal, Wermke¹⁴ reported a well-conducted trial of prophylactic NIV in hematology patients outside the ICU, in the BMT unit. This study has the strength of providing valuable information in a homogeneous group of patients with hypoxemia, without significant confounding morbidities, and with an unbiased use of the ICU or of mechanical ventilation. This study shows that NIV performed in the wards is ineffective in hypoxemic hematology patients with ARF. The negative results from this study have several explanations. (1) NIV can be considered as conclusively ineffective in hypoxemic ARF, even in hematology patients. This would be based on the lack of sufficient evidence in the literature and on a doubtful risk/benefit ratio at a time where mechanical ventilation is no longer constantly fatal, more particularly in patients with respiratory distress; (2) prophylactic (as opposed to curative) NIV may be ineffective in hematology patients. This finding needs to be considered as serious information as concerns have been raised about the use of NIV in patients with criteria for mechanical ventilation or associated organ dysfunction.¹⁵ (3) In hypoxemic ARF patients, NIV may be ineffective in the hematology wards. This would be related to the lack of tight monitoring by ICU nurses and availability of intensivists to make adequate and timely decisions at any time of the day or the night. Along this line, an Italian study in the hematology wards where nursing and medical teams had greater NIV experience and with strict intensivist supervision has shown that in patients with respiratory events and early changes in respiratory parameters, continuous positive airway pressure (CPAP) allowed significant reduction in ICU admission, mechanical ventilation and offered survival benefits.¹⁶ (4) When NIV is performed in the wards, timing for ventilatory support and ICU admission may be hampered by NIV itself. For instance, NIV may be

Table 1 Studies that have evaluated benefit from NIV in cancer patients with acute respiratory failure

Author ^{a,d}	No. of patients	Design	ICU	NIV timing	Results	Comment
Antonelli ⁸	40, Transplant	RCT	Yes	Curative NIV	Reduction in intubation rate (20 vs 70%) and ICU length of stay. Survival benefits from NIV (80 vs 50% of ICU survival) but no significant survival benefit on hospital mortality NIV (35 vs 55%, $P=0.17$)	No difference in hospital mortality
Hilbert ¹⁸	64, Neutropenia	Prospective	Yes	Curative CPAP	CPAP helped to avoid intubation in 16 (25%) patients who all survived	Only (8.3%) patients needing intubation survived
Azoulay ⁴	48, Cancer	Retrospective case/control study	Yes	Curative NIV	Survival benefits from NIV (44 vs 71%, OR = 0.343, $P<0.001$)	Only patients who required NIV or MV were included
Hilbert ¹²	52, Immunosuppressed	RCT	Yes	Prophylactic NIV	Survival benefits from NIV on both ICU and hospital mortality (50 vs 81% of hospital mortality, $P=0.02$)	All but one intubated patients died
Principi ¹⁹	34, Hematology	Prospective	No	Prophylactic NIV, Helmet CPAP vs mask	Increased success rate and comfort using Helmet Hospital mortality of 35%	Patients were treated in the wards with PaO ₂ /FiO ₂ < 200
Azoulay ²⁰	79, Cancer	Retrospective	Yes	Curative NIV	Late NIV failure independently associated with reduced survival	Only one patient with late NIV failure survived
Depuydt ²¹	27, Hematology	Retrospective	Yes	Curative NIV	No survival benefit from NIV: (hospital survival of 35% in both NIV patients and matched controls immediately intubated)	Increased survival in patients early intubated
Adda ⁹	99, Hematology	Retrospective	Yes	Curative NIV	Hospital survival of 38% reduced survival in case of failure of NIV	Reduced survival in ARDS patients and those with associated organ dysfunction
Depuydt ²¹	24, Hematology	Retrospective	Yes	Curative NIV	No survival benefit from NIV. Hospital survival of 25% in NIV patients compared with 34% in patients with O ₂ or first intubated)	Patients receiving oxygen only had 47% mortality rate
Azoulay ¹³	219, Receiving NIV or oxygen	RCT	Yes	Both	No survival benefit from NIV compared with O ₂ (hospital mortality 42 vs 33%, OR = 1.50, $P=0.20$)	Part of RCT on diagnostic strategy
Squadrone ¹⁶	40 Hematology	RCT	No	Prophylactic CPAP	Benefits from CPAP in terms of ICU admission, need for intubation and development of acute lung injury	Study in the hematology wards
Meert ²²	41 Cancer	Retrospective	Yes	Curative NIV	Reduced survival from NIV in patients requiring MV (24 vs 10%, OR 0.30, $P=0.04$)	
Gristina ²³	270, Hematology patients, NIV used in 21% of ARF cases	Retrospective	Yes	Both	NIV failure in 46%. Mortality of ALI/ARDS patients with NIV failure was 77%. Trend of benefit from early intubation. NIV was associated with survival benefit	Survival benefit from NIV after propensity score adjustment
Present study, 2011	86, Allo-BMT	RCT	No	Prophylactic NIV	No significant benefit from NIV in terms of oxygenation, ICU admission, intubation or survival	None of the intubated patients survived

Abbreviations: ALI = acute lung injury; ARF = acute respiratory failure; CPAP = continuous positive airway pressure; ICU = intensive care unit; NIV = non-invasive mechanical ventilation; OR = odds ratio; RCT = randomized clinical trials.

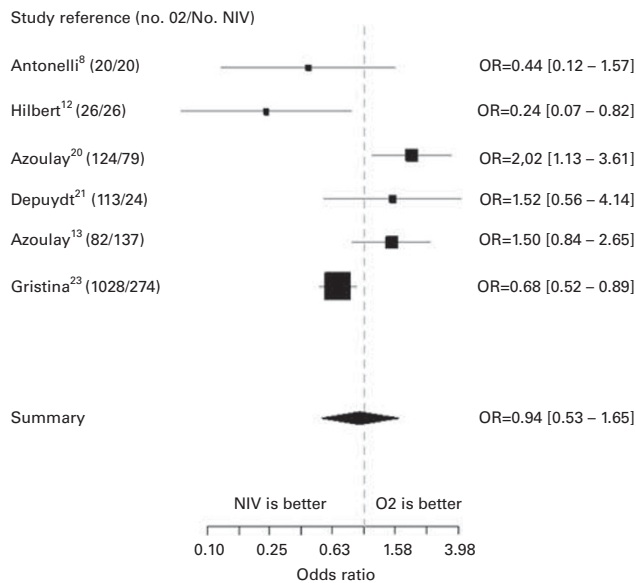


Figure 1 Outcomes associated with the in-ICU use of non-invasive mechanical ventilation in immunocompromized patients. Only cohort studies or trials reporting both patients receiving oxygen or NIV are reported. The authors are indebted to Dr Gerome Lambert (statistician) for devising this figure.

administered in control patients at a time where they would benefit from ICU admission and intubation. Along this line, studies in Table 1 report the frequent use of NIV in the wards, in patients with $\text{PaO}_2/\text{FiO}_2$ ratio <200 . (5) Last, endpoints of such interventions can be considered as inaccurate. Indeed, ICU admission sometimes can be protective in hematology patients with mild to moderate organ dysfunction. Also, in-ICU prophylactic NIV could be a way to safely perform non-invasive or invasive diagnostic strategy.^{5,13,17}

In summary, we believe that the following 10 reasons warrant additional randomized trials of prophylactic NIV in hematology patients with respiratory events. (1) No controlled trial on NIV use in only hematology patients is available; (2) no trial of prophylactic NIV in hematology patients is available; (3) only one randomized controlled trial from a single ICU has evaluated prophylactic NIV in 30 hematology patients; (4) benefit from NIV comes from studies with high mortality rates of intubated patients; (5) no study has formally distinguished prophylactic from curative NIV; (6) data from cohort studies suggest that early intubation offers survival benefits to hematology patients; (7) data from cohort studies raise concerns about late failure from NIV in hematology patients with ARF; (8) according to each hospital, technical requirements as well as nurse/physician to patient ratio may be insufficient to safely use NIV in patients with ARF; (9) conflicting results come from two studies on NIV outside of the ICU in hematology patients with respiratory events but no respiratory distress; (10) in patients who receive palliative NIV, cancer patients are the least likely to benefit. The study from Wermke is convincing about the lack of benefit from NIV in the hematology wards. In ICU patients, NIV should be evaluated in patients with hypoxemia but no respiratory distress. We believe that there is no place for

NIV in patients with hypoxemic ARF, respiratory distress, failure of oxygen and need for a ventilatory support. These patients should merely be intubated. The same is true for patients with criteria of acute respiratory distress syndrome or associated-organ dysfunction. Early (or prophylactic) NIV will need to demonstrate survival benefits at a time where ICU admission and mechanical ventilation are far from being futile interventions. In such a trial, great care should be taken to undertake appropriate diagnostic tests so as to identify the precise cause of the ARF, which can be a major confounding factor when analysing survival in immunocompromized patients with pulmonary involvement.^{12,13}

Conflict of interest

The authors declare no conflict of interest.

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