

# Supporting respiratory function in the immunocompromised critically ill patient: new perspectives for an old paradigm

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Delivering care to patients suffering from a severe depression of the immune system is a challenge for the intensivist. Such patients pose relevant issues in terms of choice of the appropriate treatment and resource allocation, as well as relevant ethical issues in both clinical practice and research. Especially in the past, the poor prognosis improvement achieved with intensive treatment among these patients lead critical care givers to be reluctant in admitting them to the intensive care unit (ICU) for two main reasons: the willingness to avoid relentless treatment and the perception of ICU as a high-risk setting for contracting multiresistant microorganisms (1). Acute respiratory failure (ARF) is a common complication in these patients, and the leading reason requiring admission to the ICU (1-3). For many caregivers the idea that immunocompromised patients are unlikely to benefit from ICU admission has been a paradigm for long time.

The last decade was characterised by several changes in epidemiology, prognosis and treatment of immunocompromised patients admitted to the ICU. First, the proportion of individuals in the general population living with different degrees of suppression of the immune response due to haematological malignancies, solid tumour, chemotherapy and immunosuppressive treatments for chronic non-oncological conditions is steadily increasing (4). Second, the observed outcome after unplanned admission to the ICU of oncologic patients is higher than that of non-immunocompromised ones, but is better than that observed in previous studies (1,3,5). As a result, the admission to the ICU of this subpopulation of patients is increasing (3), and the attitude of intensivists is slowly changing accordingly (6). In a recent observational study in Netherlands, the proportion

of haematological patients admission increased by 6% per year from 2004 to 2012 (3), and this is likely to reflect the tendency of many other high-income countries. In another retrospective study, immunocompromised patients were not found to be more prone than matched controls to develop infections by multidrug resistant bacterial strains during the ICU stay (7).

It is matter of intense debate whether the higher survival rates are due to specific changes in care delivery (8), or merely reflect the general improvement of ICU mortality (9).

Intubation and invasive mechanical ventilation was earlier identified as an independent predictor of mortality among immunocompromised patients, and this provided the rationale for few small-sampled randomized trials investigating the role of non-invasive positive pressure ventilation (NPPV) as a tool to avoid intubation, thus potentially improving outcome (10,11). The encouraging findings of these trials lead to a widespread acceptance of NPPV as a first-choice tool for early treatment of ARF among haematological and oncological patients (12).

In a randomized trial recently published on *JAMA* by the French-Belgian network “*Groupe de Recherche Respiratoire en Réanimation Onco-Hématologique*”, Lemiale and colleagues compared early intermittent NPPV to oxygen therapy in immunocompromised patients, hypothesizing that the former could reduce mortality at 28 days in patients developing ARF (13). This study was rigorously conducted, and its protocol was registered and published before the end of patients enrolment (14). The authors screened for inclusion 680 subjects in the 28 participating hospitals, randomizing a total of 374 patients with a 1:1 ratio. In the

intention-to-treat analysis testing the superiority hypothesis, the trial found no differences between NPPV and oxygen therapy in any of the pre-defined primary and secondary outcomes, including all cause 28-days mortality, need and duration of invasive mechanical ventilation, changes in sequential organ failure assessment (SOFA) score, ICU-acquired infections, length of ICU and hospital stay as well as mortality and performance status at 6 months. It is opinion of the authors of the present editorial that several peculiarity of this study makes the interpretation and generalization of the results particularly complex.

Immune system deficiency was defined as the presence of haematological or solid malignancies, regardless of the timing of last chemotherapy course, or long term high dose immunosuppressive therapy. Patients with a recent onset of hypoxemic ARF were screened for inclusion, excluding those with hypercapnia, heart failure, need for high dose vasopressors, or other contraindications for NPPV. The study found no differences between immunodeficiency due to haemato-oncological conditions and immunosuppressive treatment. Differences between solid tumours and haematological disease were not investigated, but predicted mortality should have been similar according to a previous observational study (3). Half of the patients in both arms had received chemotherapy shortly prior to ICU admission, but it was not planned to analyse whether this subgroup had a higher mortality.

As observed by the authors themselves, this study's power was lower than expected. A priori sample size calculation was rigorously based on previous studies: a 28-days mortality as high as 35% was expected in the control arm, but observed mortality in both arms was significantly lower (27% and 24%). Most of the outcomes show a slight trend favouring NPPV: this might suggest that further studies are warranted before concluding that NPPV should be abandoned in these patients. Moreover, caregivers were given the option to choose humidified high flow nasal cannulas (HHFNC) as an alternative to conventional oxygen delivery in the control arm, and in the intervention group between NPPV courses. This could have contributed to the unexpectedly low mortality in the control arm. A recent large randomized trial study found that HHFNC in ARF can halve 90-days mortality in the general population compared to both standard oxygen and NPPV, with an unclear mechanism apparently not mediated by the reduction of the intubation rate, that was found to be comparable (15). Lemiale *et al.* also conducted a separate pilot study investigating HHFNC in immunocompromised

patients with negative results (16), but the outcome was the need for respiratory assistance in a short time window. Therefore, we agree with the authors that further studies comparing conventional oxygen, NPPV and HHFNC are needed to provide the clinicians with a definitive answer on how to manage ARF in the immunocompromised patient. However, this need raises some ethical problem. As often occurs in evaluating rescue therapies, for patients enrolled in the control arm of randomized trials that have mortality as primary endpoint, it is hard to deny the access to treatments whose efficacy is proven or at least alleged. Lemiale and co-workers seem to have considered these aspects, and found a fair and reasonable compromise between scientific robustness and quality of care. Nonetheless, this could have played a role in reducing the achieved statistical power. This issue has to be addressed carefully in the design of future trials in the field.

Concerning the type of intervention, all the randomized trials published so far have investigated the efficacy of early intermittent NPPV: short cycles of around one hour were alternated with few hours of spontaneous breathing under oxygen therapy, immediately after the onset of specific criteria defining ARF (10,11,13). Other indications, timing and course duration could affect the clinical outcome, therefore they could be considered for investigation.

NPPV is a valid option when respiratory failure occurs because of a reversible underlying cause, and when it does not represent only a delay to an unavoidable intubation (17). Among immunocompromised patients it is particularly difficult to predict NPPV efficacy identifying patients who can benefit from its application. Efforts should be made to identify specific subgroups of patients in which NPPV can effectively modify the course of the respiratory failure.

Despite the solidity of this new randomized controlled trial, we do not believe that the available evidence should be interpreted as a definitive indication to discontinue the recourse to NPPV to relief ARF in immunocompromised patients. Rather, the clinicians should be aware that short courses of NPPV alone does not seem to provide benefits that surpass those that can be achieved by oxygen therapy, including HHFNC. This does not exclude that in specific cases NPPV could improve outcome.

At the moment further studies are necessary to provide an answer on how one should treat ARF in an immunocompromised patients: pending more definitive data, a meticulous clinical judgement that takes into account the conflicting results of the most recent studies should be the guidance to the management of these conditions.

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## Footnote

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## References

- Bird GT, Farquhar-Smith P, Wigmore T, et al. Outcomes and prognostic factors in patients with haematological malignancy admitted to a specialist cancer intensive care unit: a 5 yr study. *Br J Anaesth* 2012;108:452-9.
- Azoulay E, Lemiale V, Mokart D, et al. Acute respiratory distress syndrome in patients with malignancies. *Intensive Care Med* 2014;40:1106-14.
- van Vliet M, Verburg IW, van den Boogaard M, et al. Trends in admission prevalence, illness severity and survival of haematological patients treated in Dutch intensive care units. *Intensive Care Med* 2014;40:1275-84.
- Soerjomataram I, Lortet-Tieulent J, Parkin DM, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012;380:1840-50.
- Bos MM, de Keizer NF, Meynaar IA, et al. Outcomes of cancer patients after unplanned admission to general intensive care units. *Acta Oncol* 2012;51:897-905.
- Hill QA. Intensify, resuscitate or palliate: decision making in the critically ill patient with haematological malignancy. *Blood Rev* 2010;24:17-25.
- Nseir S, Di Pompeo C, Diarra M, et al. Relationship between immunosuppression and intensive care unit-acquired multidrug-resistant bacteria: a case-control study. *Crit Care Med* 2007;35:1318-23.
- Mokart D, Pastores SM, Darmon M. Has survival increased in cancer patients admitted to the ICU? Yes. *Intensive Care Med* 2014;40:1570-2.
- Pène F, Salluh JI, Staudinger T. Has survival increased in cancer patients admitted to the ICU? No. *Intensive Care Med* 2014;40:1573-5.
- Antonelli M, Conti G, Bufi M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA* 2000;283:235-41.
- Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med* 2001;344:481-7.
- Keenan SP, Sinuff T, Burns KE, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ* 2011;183:E195-214.
- Lemiale V, Mokart D, Resche-Rigon M, et al. Effect of Noninvasive Ventilation vs Oxygen Therapy on Mortality Among Immunocompromised Patients With Acute Respiratory Failure: A Randomized Clinical Trial. *JAMA* 2015;314:1711-9.
- Lemiale V, Resche-Rigon M, Azoulay E, et al. Early non-invasive ventilation for acute respiratory failure in immunocompromised patients (IVNIctus): study protocol for a multicenter randomized controlled trial. *Trials* 2014;15:372.
- Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015;372:2185-96.
- Lemiale V, Mokart D, Mayaux J, et al. The effects of a 2-h trial of high-flow oxygen by nasal cannula versus Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. *Crit Care* 2015;19:380.
- Tobin MJ. Principles and practice of mechanical ventilation. New York: McGraw-Hill Medical, 2013.

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