Perspective

New puzzles for the use of non-invasive ventilation for immunosuppressed patients

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Abstract: On October 27, 2015, Lemile and colleagues published an article in *JAMA* entitled "Effect of Noninvasive Ventilation *vs.* Oxygen Therapy on Mortality among Immunocompromised Patients with Acute Respiratory Failure: A Randomized Clinical Trial", which investigated the effects of non-invasive ventilation (NIV) in 28-day mortality of 374 critically ill immunosuppressed patients. The authors found that among immunosuppressed patients admitted to the intensive care unit (ICU) with hypoxemic acute respiratory failure, early NIV compared with oxygen therapy alone did not reduce 28-day mortality. Furthermore, different from the previous publications, there were no significant differences in ICU-acquired infections, duration of mechanical ventilation, or lengths of ICU or hospital stays. The study power was limited, median oxygen flow used was higher than used before or 9 L/min, NIV settings provided tidal volumes higher than what is considered protective nowadays or from 7 to 10 mL/kg of ideal body weight and the hypoxemic respiratory failure was moderate to severe (median PaO_2/FIO_2 was around 140), a group prone to failure in noninvasive ventilatory support. Doubts arose regarding the early use of NIV in immunosuppressed critically ill patients with non-hypercapnic hypoxemic respiratory failure that need to be solved in the near future.

Keywords: Non-invasive ventilation (NIV); acute respiratory failure; immunosuppression

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In a landmark trial published in 2001, Hilbert and colleagues (1) showed that in selected patients with immunosuppression, pulmonary infiltrates, fever, and hypoxemic acute respiratory failure, early implementation of non-invasive ventilation (NIV)—was associated with a significant reduction in the rate of endotracheal intubation, serious complications, death in the intensive care unit (ICU), and death in the hospital. Indeed, avoiding intubation should be an important objective in the management of respiratory failure in immunosuppressed patients since it impedes the risk of severe complications such as ventilator associated pneumonia (VAP), barotrauma and ventilator-induced lung injury (2,3).

Subsequently, Antonelli and colleagues (4) showed that the use of NIV in patients undergoing solid organ transplantation with acute hypoxemic respiratory failure compared to oxygen alone decreased the need of endotracheal intubation, the rate of fatal complications, length of ICU stay, ICU mortality but not hospital mortality. Based on these results, a clinical practice guideline suggested that NIV should be used for immunosuppressed patients who have acute respiratory failure, with a grade 2B recommendation (5). Members of this panel, however, questioned the generalizability of the results from centers with highly experienced staff to other centers and this recommendation was debated and remained questioned (6). The major points of debate was that the mortality of immunocompromised patients has improved considerably since the publication of these two trials (7,8), and evidence showing that failure of NIV followed by delayed intubation

may increase mortality (9).

Acute respiratory failures, together with shock are the main reasons for ICU admission in immunosuppressed patients (8). The long-term mortality of this group of patients is high and the presence of acute respiratory failure is independently associated with worse outcomes. The use of mechanical ventilation is associated with a mortality rate of 60%, imposing the need of alternative therapies for patients with acute respiratory failure (8). Based on this, several experts suggest that in immunosuppressed patients, acute respiratory failure should probably be managed initially with NIV (9,10).

The study of Lemiale and colleagues (11) analyzed the relationship between early use of NIV and 28-day mortality in a randomized controlled trial in 374 critically ill immunosuppressed patients. The authors observed that among immunosuppressed patients admitted to the ICU with hypoxemic acute respiratory failure, early NIV compared with oxygen therapy alone did not reduce 28-day mortality. Moreover, there were no significant differences in ICU-acquired infections, duration of mechanical ventilation, or lengths of ICU or hospital stays. In the cohort analyzed, bacterial pneumonia and *Pneumocystis jirovecii* pneumonia account for more than 50% of the causes of acute respiratory failure. As expected, the mortality rate in the Lemiale and colleagues study (11) was much lower than those of the previous randomized controlled trials (26.5% *vs.* 65.4% *vs.* 45.0%) (2,4). An important finding of Lemiale and colleagues study (11) was that among intubated patients, mortality was similar with the use or not of NIV or according to time from start of NIV and intubation confirming the importance of prompt start of invasive mechanical ventilation in patients failing the use of NIV. Also, opposite to what was suggested by previous studies, the use of NIV was not associated with decreased need of intubation and mechanical ventilation.

The overall mortality in the immunosuppressed critically ill population has declined in recent years due to advances in targeted chemotherapy, prophylactic use of antibiotics, and improved supportive care (12). In their study, Lemiale and colleagues (11) anticipated a higher baseline mortality of 35% in the Oxygen alone group to 20% in the NIV group. The lower than expected mortality with oxygen alone limited the power of their study to detect a significant between-group difference in mortality.

Recently, Frat and colleagues (13) showed that in patients with non-hypercapnic acute hypoxemic respiratory failure, treatment with high-flow nasal cannula (HFNC) was associated with a lower 90-day mortality compared to standard oxygen therapy, or NIV. In the Lemiale and colleagues trial (11), a greater proportion of patients in the oxygen alone group received a higher than usual oxygen through the nasal cannula and perhaps because of this median flow of 9 L/min, the benefits of NIV was diluted. Few studies assessed the impact of HFNC in immunosuppressed patients. Recently, Lemiale and colleagues reported that a 2-hour trial with HFNC improved neither mechanical ventilatory assistance nor patient comfort compared with oxygen delivered via a Venturi mask in immunosuppressed patients with hypoxemic acute respiratory failure (14). Indeed, as with NIV, failure of HFNC might cause delayed intubation and worse clinical outcomes in patients with respiratory failure (15).

As stated above, the delayed intubation in critically ill patients is associated with worse outcomes (16). In immunosuppressed patients, mortality was highest in patients needing intubation and invasive mechanical ventilation, particularly when started after the first three days in the ICU (12), thus, patients should be intubated as soon as necessary. Respiratory disease severity and hemodynamic failure at ICU admission were risk factors for invasive mechanical ventilation in subjects with malignancies admitted for acute respiratory failure, and patients with these risk factors should be considered for invasive mechanical ventilation (17).

A big observational study by Lemiale and colleagues (18) confirmed that in hematologic patients with acute respiratory failure, initial treatment with NIV did not improve survival compared to oxygen only. Wermke and colleagues (19) also showed that early NIV performed in the wards is ineffective in hypoxemic hematologic patients with acute respiratory failure. Finally, several experts suggest that NIV should be used with caution in this group of patients (6).

Another important point not addressed in the study by Lemaile and colleagues was the ventilatory parameters used in the patients undergoing NIV. The authors described in the Methods section of their study that "the pressure support level was adjusted to obtain an expired tidal volume of 7 to 10 mL/kg of ideal body weight". Several animal and clinical studies demonstrated that ventilation with high tidal volumes could induce VILI (3,20-22). Thus, the use of higher tidal volumes during NIV in the study by Lemiale and colleagues (11) could be associated with higher degrees of lung injury and worse outcomes, as suggested in a recent trial comparing HFNC to NIV and oxygen (12,23).

In conclusion, new puzzles were introduced in the evaluation of NIV use in immunosuppressed patients with

acute hypoxemic respiratory failure: the innovative use of high flow oxygen via nasal cannula therapy , the use of NIV with non-protective or protective ventilation and algorithms to better evaluate the failure of both therapies leading to prompt early intubation and invasive protective mechanical ventilation. Further research, preferentially by means of a new multicentric randomized controlled trial, is needed to delineate the role of NIV versus other strategies of initial respiratory support in hypoxemic ARF in immunosuppressed patients. Severity and type of immunosuppression , type and severity of acute hypoxemic respiratory failure, number of organ failures, time between onset of acute respiratory failure and ICU admission, clear indications and contra-indications for NIV and or high flow oxygen therapy , type of interface and equipment use, strict NIV and high flow oxygen use protocol, early recognition of NIV or high flow oxygen failure , clear indications of intubation and invasive protective mechanical ventilation should be part of the prospective randomized protocol to answer the important clinical question if early NIV or high flow oxygen use will really improve outcome in immunosuppressed critically ill patients with acute hypoxemic respiratory failure.

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Footnote

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References

1. 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.
2. Razlaf P, Pabst D, Mohr M, et al. Non-invasive ventilation in immunosuppressed patients with pneumonia and extrapulmonary sepsis. Respir Med 2012;106:1509-16.
3. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. N Engl J Med 2013;369:2126-36.
4. 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.
5. 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.
6. Azoulay E, Lemiale V. Non-invasive mechanical ventilation in hematology patients with hypoxemic acute respiratory failure: a false belief? Bone Marrow Transplant 2012;47:469-72.
7. Azoulay E, Lemiale V, Mokart D, et al. Acute respiratory distress syndrome in patients with malignancies. Intensive Care Med 2014;40:1106-14.
8. Azoulay E, Mokart D, Pène F, et al. Outcomes of critically ill patients with hematologic malignancies: prospective multicenter data from France and Belgium--a groupe de recherche respiratoire en réanimation onco-hématologique study. J Clin Oncol 2013;31:2810-8.
9. Gristina GR, Antonelli M, Conti G, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. Crit Care Med 2011;39:2232-9.
10. Barbas CS, Couto LP, Kawano-Dourado LB. Noninvasive ventilation for acute respiratory failure in patients with hematologic malignancies: what an Italian 5-year multicenter survey tells us. Crit Care Med 2011;39:2358-9.
11. 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.
12. Azoulay E, Soares M, Darmon M, et al. Intensive care of the cancer patient: recent achievements and remaining challenges. Ann Intensive Care 2011;1:5.
13. 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.
14. 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.
15. Kang BJ, Koh Y, Lim CM, et al. Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. Intensive Care Med 2015;41:623-32.

16. Corrêa TD, Sanches PR, de Morais LC, et al. Performance of noninvasive ventilation in acute respiratory failure in critically ill patients: a prospective, observational, cohort study. BMC Pulm Med 2015;15:144.
17. Lemiale V, Lambert J, Canet E, et al. Identifying cancer subjects with acute respiratory failure at high risk for intubation and mechanical ventilation. Respir Care 2014;59:1517-23.
18. Lemiale V, Resche-Rigon M, Mokart D, et al. Acute respiratory failure in patients with hematological malignancies: outcomes according to initial ventilation strategy. A groupe de recherche respiratoire en réanimation onco-hématologique (Grrr-OH) study. Ann Intensive Care 2015;5:28.
19. Wermke M, Schiemanck S, Höffken G, et al. Respiratory failure in patients undergoing allogeneic hematopoietic SCT--a randomized trial on early non-invasive ventilation based on standard care hematology wards. Bone Marrow Transplant 2012;47:574-80.
20. Neto AS, Simonis FD, Barbas CS, et al. Lung-Protective Ventilation With Low Tidal Volumes and the Occurrence of Pulmonary Complications in Patients Without Acute Respiratory Distress Syndrome: A Systematic Review and Individual Patient Data Analysis. Crit Care Med 2015;43:2155-63.
21. Serpa Neto A, Schultz MJ, Slutsky AS. Current concepts of protective ventilation during general anaesthesia. Swiss Med Wkly 2015;145:w14211.
22. Serpa Neto A, Simonis FD, Barbas CS, et al. Association between tidal volume size, duration of ventilation, and sedation needs in patients without acute respiratory distress syndrome: an individual patient data meta-analysis. Intensive Care Med 2014;40:950-7.
23. Matthay MA. Saving lives with high-flow nasal oxygen. N Engl J Med 2015;372:2225-6.

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