Editorial Commentary

Improving survival in immunocompromised patients with hypoxemic acute respiratory failure

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Over the last two decades, the number of patients living with immune deficiency has steadily increased (1). Even though a greater life expectancy could be achieved (2), immunocompromised patients still experience life-threatening complications warranting admission to the intensive care unit (ICU), chiefly for hypoxemic acute respiratory failure (ARF). Case fatality is high in ARF patients, especially when endotracheal intubation (ETI) is needed (3). Hence, oxygenation and ventilation strategies to avoid invasive mechanical ventilation have been widely evaluated in this setting. The single center trial from Hilbert *et al.* (4) which reported a significant reduction in intubation and mortality rates associated with noninvasive ventilation (NIV) has been challenged by larger and multicenter data (5,6).

In a paper published recently in Annals of Intensive Care, Coudroy *et al.* (7) investigated whether immunosuppression was a determinant of NIV failure. They used pooled data from a prospective randomized trial of oxygenation strategies in unselected patients combined to those from a single center retrospective study (8) and applied a propensity-score matching approach leaving only 108 of the 208 patients for the final analysis.

Using this set of pooled data, they found that immunosuppression status was not associated with NIV failure but only with mortality rate. This finding, if confirmed in studies adequately powered for this endpoint, is an important one as it suggests that discrepancies across studies may either be ascribable to different patient's severity or to differences in criteria for intubation. Along this line, authors identified the degree of hypoxemia (PaO_2/FiO_2 after 1 hour of NIV trial) as associated with NIV failure. The finding that expired tidal volume (ETV) was associated with NIV failure on the entire cohort but not on the matched sample also suggests that this sound and valid hypothesis should be validated in larger prospective studies. These results taken together with previously published data (5,9) raise awareness that NIV should not be used anymore in patients with criteria of ARDS, especially in patients remaining with a high respiratory drive despite optimal pressure support. ETV in these high risk patients with hypoxemic ARF could be used to risk-stratify patients unlikely to benefit from NIV, if not those in whom NIV is an actual harm because of the high respiratory drive exposing them to self-inflected lung injury (9,10). All of these factors have been already reported and summarized in a easy to use mnemonic, namely, the HACOR score for Heart rate, Acidosis, Consciousness, Oxygenation and

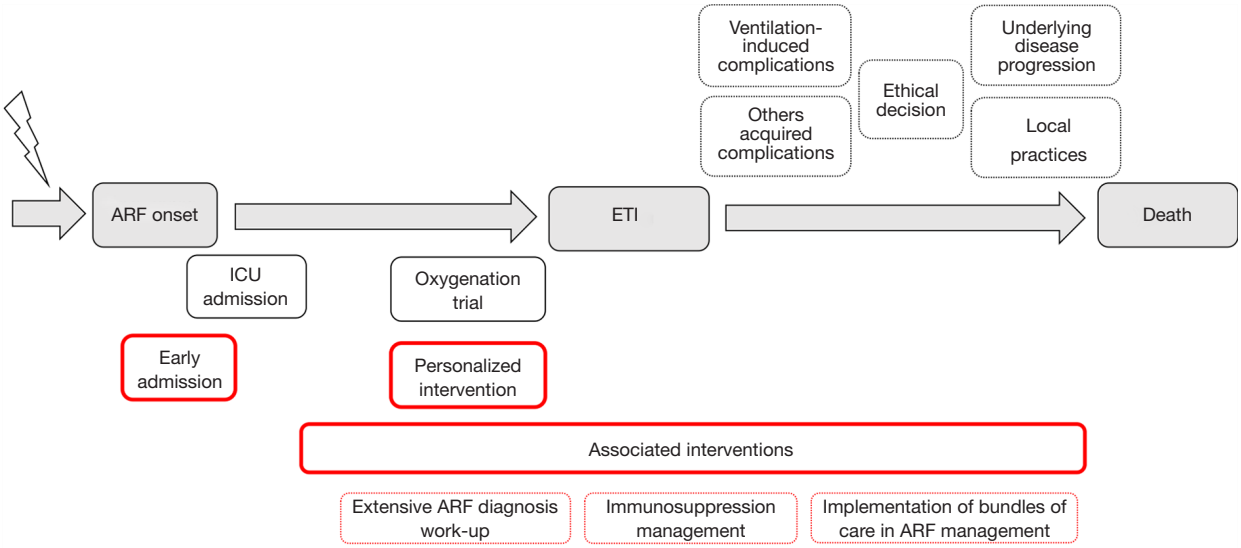

Figure 1 Schematic representation of causal pathway from acute respiratory failure onset to death with traditional and new proposed concepts in its management. Grey boxes show representation of causal pathway with classical intervention (Black boxes). Red boxes show potential targets for prognosis improvement. ARF, acute respiratory failure; ETI, endotracheal intubation.

Respiratory rate, to identify patients at high risk for NIV failure (11). Noteworthy, immunocompromised patients of the present cohort have a significant higher severity score at ICU admission as well as more severe clinical respiratory presentation than non-immunocompromised ones. These features are suggestive of delayed admission to the ICU. Studies to compare immunocompromised and non-immunocompromised patients should address the specific issue of timing of ICU admission as it has been associated with mortality (12).

This study also raises the question of the causal pathway between initial oxygenation therapy, need for intubation and death (*Figure 1*). Over the past two decades, studies have primarily focused on the initial oxygenation strategy, with various devices (CPAP, NIV with mask or helmet, high-flow nasal canula, standard oxygen therapy) in order to avoid ETI (4,5,13-17). However, based on large number of patients, data are now convincing to ascertain that strategies to improve survival should not target oxygenation and ventilation strategies (5,6,17-19). Most importantly, as mortality in intubated patients remains high (*Table 1*), we suggest the use of another agenda to further reduce case fatality in hypoxemic patients with ARF. For instance, three major targets should better be evaluated: (I) optimal timing of ICU admission; (II) clinician's ability to personalize the appropriate oxygenation strategy for a given patient; and (III) selecting the most appropriate diagnostic strategy to avoid leaving the patient with an undetermined ARF etiology, a situation at risk for increased mortality (6,20). In addition, preventing ICU acquired events from both invasive mechanical ventilation and underlying impairment of immunological functions will also be challenging (3,12,21). Future research agenda will have to address these unanswered questions. Large prospective cohorts and clinical trials with adaptive design have the potential to identify which patient could benefit from a given diagnostic or therapeutic strategy, as well as a better stratification of specific risks through machine learning advances (22,23).

That immunocompromised and non-immunocompromised patients can be managed the same way with regard to oxygenation and ventilation strategy is very likely. However, it is time now to understand that survival benefits will not come from this research. Studies to improve global medical management based on updated strategies and newly developed diagnostic tools are warranted.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Table 1 Randomized controlled trial of oxygenation/ventilation strategies specifically dedicated to immunocompromised patients with hypoxemic acute respiratory failure

Authors, review, year of publication	N	Intervention/control	No. of centers	IMV rate, %	In-ICU Mortality rate in IMV patients, %
Antonelli *et al*., *JAMA*, 2000	40	NIV/O_2	1	45	78
Hilbert *et al.*, *NEJM*, 2001	52	NIV/O_2	1	61.5	88
Squadrone *et al*., *Intensive care Med*, 2010*	40	CPAP/O_2	1	40	100
Wermke *et al.*, *Bone Marrow Transpl*, 2012*	90	NIV/O_2	1	20	100
Lemiale *et al*., *Critical Care*, 2015	100	HFNC/O_2	4	39	46
Lemiale *et al*., *JAMA*, 2015	374	NIV/O_2**	28	42	52
Azoulay *et al*., *JAMA*, 2018	776	HFNC/O_2	31	41	56
Total	1,472	–	–	41.2	74.3

Only studies published in English from Jan 01, 2000, to March 31, 2019, were taken into account. *, patients included in ward; **, 127 patients received HFNC therapy. NIV, non-invasive ventilation; O_2, standard oxygen therapy; HFNC, high-flow nasal cannula oxygen therapy; IMV, invasive mechanical ventilation.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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