Editorial

# High-flow nasal cannula oxygen therapy in immunocompromised patients: where? for whom? and when to stop?

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*Comment on:* Kang YS, Choi SM, Lee J, *et al.* Improved oxygenation 48 hours after high-flow nasal cannula oxygen therapy is associated with good outcome in immunocompromised patients with acute respiratory failure. J Thorac Dis 2018;10:6606-15.

Submitted Feb 20, 2019. Accepted for publication Apr 03, 2019.
doi: 10.21037/jtd.2019.04.24
**View this article at:** http://dx.doi.org/10.21037/jtd.2019.04.24

Cancer was diagnosed in 18 million people worldwide last year during which time, almost 10 million patients died from cancer (1). Asia carries a high burden, representing almost half of these newly diagnosed cancers and deaths (1). Although these results are alarming, 10-year survival of patients with cancer has almost doubled in the last 40 years and is currently approaching 50% (2). Hopefully, better understanding of relationships with the microbiome, along with progress in diagnosis, treatment, and follow-up, will continue to improve the prognosis of cancer patients over the coming years (3). Therefore, the proportion of cancer survivors with possibly related impaired immunity requiring hospital admission will continue to grow.

The prognosis of immunocompromised patients admitted to intensive care unit (ICU) depends to a great extent on the reason for admission, with a higher mortality rate in cases of medical rather than surgical admission (41% *vs.* 10% at 30 days, respectively) (4). The leading cause of medical ICU admission is respiratory failure (5). Unfortunately, the mortality rate of immunocompromised patients requiring invasive mechanical ventilation exceeds 50% (5,6). Almost 20 years ago, 2 small sample-sized trials reported dramatically decreased mortality among immunocompromised patients treated with noninvasive mechanical ventilation (7,8). However, the benefits of noninvasive ventilation were recently challenged in a large trial that did not report any difference between noninvasive ventilation and standard oxygen therapy (9). Moreover, in a large trial comparing high-flow nasal cannula oxygen therapy (HFOT) to standard oxygen therapy and noninvasive ventilation in *de novo* acute hypoxemic respiratory failure, mortality was significantly lower in patients treated with HFOT than in the 2 other groups (10), drawing attention to this new oxygen delivery device.

HFOT has interesting physiological effects for patients with acute respiratory failure. As compared to standard oxygen therapy, it decreases patient effort, washes out dead space and decreases minute ventilation through a high flow of heated and humidified gases (11). It can also more precisely deliver higher $FiO_2$ than standard oxygen therapy (12), and subsequently improve patient oxygenation (11). This physiologic rationale is supported by better outcomes with HFOT as compared to standard oxygen therapy in cases of acute hypoxemic respiratory failure (10) and during the post-extubation period in low-risk patients (13). Similarly, HFOT was not inferior to the control treatment in post-cardiac surgery (14), the post-operative (15), or the post-extubation period in high-risk patients (16). As regards immunocompromised patients, whether HFOT is a suitable option is debatable as a recent large multicenter trial did not find any difference in intubation and mortality rates between patients treated with HFOT and standard oxygen therapy (17). Therefore, whether HFOT is the best first-line oxygenation strategy in immunocompromised patients remains unknown. Although none of the above-mentioned trials found harmful effects of HFOT as compared to other oxygenation strategies, late HFOT failure could be

associated with a higher mortality rate than early failure (18).

As a consequence, the identification of factors associated with HFOT failure is of primary importance in order to flag and closely monitor patients bearing the highest risk for failure. Frat and colleagues found that the higher the heart rate after 1 hour of HFOT, the higher the risk of HFOT failure (19). Roca and colleagues developed and recently validated the ROX index ($SpO_2/FiO_2$ to respiratory rate) to predict HFOT failure (20,21). They found that a ROX index lower than 4.88 after 2, 6 or 12 hours was strongly associated with HFOT failure, even after adjustment on immunosuppression (20,21).

In a recent issue of the journal, Kang and colleagues reported the outcomes of 91 immunocompromised patients admitted to hospital and treated with HFOT for more than 48 hours (22). In this retrospective monocenter observational study, patients were analyzed according to their oxygenation response which was assessed using $SpO_2/FiO_2$ ratio 48 hours after HFOT initiation. Responders were defined as having a higher $SpO_2/FiO_2$ ratio after 48 hours of HFOT than at HFOT initiation. At HFOT initiation, respiratory rate was 27 and 26 breaths/min, and $SpO_2/FiO_2$ ratio 142 and 157 in responders and non-responders, respectively. In responders, respiratory rate decreased to 24 breaths/min after 12 hours of HFOT, and $SpO_2/FiO_2$ ratio increased to 156 after 24 hours of HFOT as compared to HFOT initiation. Conversely, in non-responders, respiratory rate remained unchanged during the first 48 hours of HFOT and $SpO_2/FiO_2$ ratio decreased to 144 after 12 hours of HFOT as compared to HFOT initiation. All in all, only 19 out of the 91 patients (21%) required intubation. Overall mortality at day 28 was 57% (52 out of the 91 patients) and hospital mortality was 63% (57 out of the 91 patients). Improved $SpO_2/FiO_2$ ratio 48 hours after HFOT initiation was associated with lower mortality using univariate analysis, but not after adjustment. The existence of a do-not-intubate order was the only factor associated with mortality at day 28 using multivariate analysis (22). Importantly, this study differs from the previous ones in various aspects. First, patients were treated with HFOT outside the ICU whereas in all of the above-mentioned studies, all patients were admitted to ICU for HFOT treatment (17,20,21,23). Indeed, HFOT failure rate in immunocompromised patients ranged from 31% to 39%, which could justify the need for ICU or intermediate care unit admission to closely monitor these patients (17,23). Second, in the study, 50 out of the 91 patients included (55%) had a do-not-intubate order (22). By mixing patients with do-not-intubate order with the others, interpreting outcomes might be misleading. In patients with do-not-intubate order, HFOT failure was defined as death, whereas in the others it was defined as the need for intubation. Therefore, mixing these 2 subpopulations may markedly underestimate intubation rates. As an example, in the present study the overall intubation rate was 21% (19 out of the 91 patients included), whereas it was 46% in the subgroup of patients without do-not-intubate order (19 out of the 41 patients without treatment limitation) (22). Reporting the rate of HFOT failure may have been more informative than the rate of intubation, given the high proportion of do-not-intubate orders. Importantly, in these patients noninvasive ventilation was associated with better outcomes than standard oxygen therapy (24). Data on the use of HFOT for this indication is scarce and a prospective multicenter cohort study comparing outcomes of patients with a do-not-intubate order treated with HFOT and/or noninvasive ventilation is ongoing (NCT03673631). Third, the authors excluded patients treated with HFOT for less than 48 hours. However, nearly three-fourths of patients treated with HFOT who fail the technique and need mechanical ventilation are intubated within the first 48 hours after HFOT initiation (10,17). Likewise, mean HFOT duration was much longer in Kang and colleagues' study than in the HIGH trial (almost 6 *vs.* 2 days, respectively) (17,22). Notably, the lack of weaning criteria for HFOT may have contributed to unnecessarily prolongation of the treatment. In focusing on a subgroup of patients remaining under HFOT for more than 48 hours, Kang and colleagues excluded both patients who responded enough to be weaned from HFOT within the first 48 hours, and patients with early HFOT failure. Therefore, the outcomes reported in Kang and colleagues' study may not be compared with previous studies. Fourth, Kang and colleagues used $SpO_2/FiO_2$ ratio under HFOT as a surrogate of $PaO_2/FiO_2$ based on the results of a post-hoc analysis of 2 trials on acute respiratory distress syndrome (25). Of note, Rice and colleagues excluded patients with $SpO_2$ >97% because flattening of the dissociation curve of hemoglobin above this point could artificially underestimate $PaO_2/FiO_2$ (25). However, the accuracy of $SpO_2/FiO_2$ ratio as a means of estimating $PaO_2/FiO_2$ under HFOT has never been tested. Moreover, the proportion of patients with $SpO_2$ >97% in the present study is unknown.

Despite these limitations, the study by Kang and colleagues demonstrated that in immunocompromised patients treated with HFOT for more than 48 hours,

 

improvement in $SpO_2/FiO_2$ ratio after 48 hours of HFOT was not independently associated with survival. More studies are needed to evaluate factors associated with outcome in patients remaining under HFOT for more than 48 hours. Furthermore, this study raises additional interesting questions on the suitability of HFOT outside the ICU in a subset of patients with high rate of failure, on the appropriateness of HFOT in patients with do-not-intubate order, and most importantly, on the weaning criteria for HFOT.

## Acknowledgements

We gratefully thank Jeffrey Arsham for editing the original manuscript.

## Footnote

*Conflicts of Interest:* R Coudroy reports travel expense coverage to attend scientific meetings from Fisher & Paykel and MSD, outside the submitted work. JP Frat reports travel expense coverage to attend scientific meetings and personal fees from Fisher & Paykel and SOS Oxygène, outside the submitted work. AW Thille reports travel expense coverage to attend scientific meetings and payment for lectures from Fisher & Paykel, Covidien, Maquet-Getinge, General Electric Healthcare, outside the submitted work.

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**Cite this article as:** Coudroy R, Frat JP, Thille AW. High-flow nasal cannula oxygen therapy in immunocompromised patients: where? for whom? and when to stop? J Thorac Dis 2019;11(Suppl 9):S1157-S1160. doi: 10.21037/jtd.2019.04.24

 