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Citation for final published version:

Szakmany, Tamas 2020. Noninvasive ventilatory support in COVID-19: operating in the evidence free zone. *Minerva Anesthesiologica* 86 (11) , pp. 1126-1128. 10.23736/S0375-9393.20.15158-7

Publishers page: <http://dx.doi.org/10.23736/S0375-9393.20.15158-7>

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Non-invasive ventilation in COVID-19: operating in the evidence free zone

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Keywords: COVID-19, non-invasive ventilation

The COVID-19 pandemic is continue to threaten to overwhelm the critical care capacities of healthcare systems, especially in the low and middle income countries where strict social distancing measures are unsustainable due to the knock-on effects of underlying economic issues ¹². Invasive mechanical ventilation, although the mainstay of management of severe acute hypoxaemic respiratory failure (AHRF) secondary to SARS-CoV-2 infection, has been associated with significant mortality in various healthcare settings ³. Since the early reports of the pandemic taking foothold in China, healthcare providers looked at non-invasive respiratory support (NRS) options, including continuous positive airway pressure (CPAP),

bilevel positive airway pressure (BiPAP) ventilation and the use of high-flow-nasal oxygen (HFNO). Despite considerable efforts to gather data from diverse populations, it is still unclear if NRS is beneficial or harmful for patients with COVID-19. In the current issue of *Minerva Anesthesiologica*, Dr Crimi and her colleagues present a rapid narrative review on the role of NRS in COVID-19 and other viral illnesses leading to AHRF⁴. The authors summarised 58 reports, 11 in COVID-19 whilst the rest in other viral illnesses. Importantly, they not only concentrated on patient outcomes, but also on the effect of NRS treatment options on the environment, as contamination of healthcare staff and nosocomial spread of SARS-CoV-2 has been a significant concern. Their findings paint a varied picture. NRS has been utilised in a wide percentage of patients in both the pandemic and non-pandemic influenza settings, ranging from 11% to over 90%. Most of the cohorts were small, retrospective single centre cohort studies, with a few exceptions from the various pandemic influenza infections. Notably, they were unable to find a well-conducted randomised controlled trial to evaluate the benefits or harms of NRS in viral AHRF. The results of this review should generate further thoughts and should encourage researchers to design and conduct rigorous studies to evaluate the effect of NRS on patient-centred outcomes, as there continues to be a physiological rationale to use this modality⁴. The review by *Crimi et al.* was not able to elucidate if there is any mortality benefit, due to the lack of granular and high-quality data available at this time⁴. In the context of the COVID-19 pandemic, we have since learnt that failure to progress using NRS alone is common in approximately 50-70% of patients, however recent data indicates that those, who need invasive mechanical ventilation after failing NRS techniques have similar mortality to those, in whom the initial respiratory support was invasive mechanical ventilation⁵⁶. Hopefully, the actively recruiting

RECOVERY-RS trial (ISRCTN16912075) will help us to elucidate if either NIV or HFNO use is superior to standard care in COVID-19 patients with AHRF.

A welcome contribution of the paper is the in-depth review of the available evidence on the safety of providing NRS in various healthcare settings. The findings are reassuring. The ten papers reviewed by *Crimi et al.* describe potential strategies to reduce viral transmission, such as the preferential use of helmets with neck-seal and hint the lack of spread via exhaled air using HFNO devices. These findings, together with the accumulating operational evidence, that the appropriate use of personal protective equipment can drastically reduce, if not eliminate patient-to-provider transmission of droplets containing significant viral load, could pave the way for more widespread adoption of NRS support even in the pandemic era.

It is clear from the review, that much needs to be done to understand the best use of NRS not just in COVID-19 but also in other aetiologies of AHRF. It is unclear if by phenotyping either by clinical characteristics or biomarkers, we could highlight patient populations who might be more amenable for NRS support ⁶⁷. There is no information on whether concomitant disease modifying therapies, such as dexamethasone could produce synergistic effects in milder hypoxia with NRS, leading to avoidance of invasive mechanical ventilation and its associated complications ⁸. Interestingly, the sole prospective trial with patient allocation reported in the review, has shown a dramatic mortality reduction in the group receiving steroids and CPAP in patients infected with SARS ⁹. Whether this can be replicated in COVID-19 remains to be seen. There is a continued uncertainty about the best methods to protect staff and patients in contact with other COVID-19 patients on NRS and it is clear that further multidisciplinary research efforts are needed to determine how the human cough propagates virus particles in these settings. Recent data indicates that this is indeed

governed by the propagation of viscous vortex rings, which can be simulated in wind tunnels
10.

In summary, the review of NRS techniques by *Crimi et al.* highlights, that much of our clinical practice in COVID-19 is currently in the “evidence free zone” where rigorous data collection, careful data interpretation and most importantly, the generation of definitive evidence by randomised controlled trials will be paramount to combat the pandemic.

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